SCIENTIFIC ADVICE

Zika virus and safety of substances of human origin

A guide for preparedness activities in Europe

First update

www.ecdc.europa.eu

ECDC SCIENTIFIC ADVICE

Zika virus and safety of substances of human origin

A guide for preparedness activities in Europe

First update

This report of the European Centre for Disease Prevention and Control (ECDC) guide was coordinated by Dragoslav Domanović and written by the working group:

Kari Aranko (European Blood Alliance), Alina Mirella Dobrota (Regional Blood Transfusion Center, Romania), Dragoslav Domanović (ECDC), Beatriz Domínguez-Gil (ONT, Spain), Deirdre Fehily (Directorate-General for Health and Food Safety – European Commission), Patricia Galea (Ministry of Energy and Health, Malta), Pierre Gallian (European Blood Alliance); Ryanne Lieshout-Krikke (European Blood Alliance); Giancarlo Liumbruno (National Blood Centre, Italy), Sophie Lucas-Samuel (Agence Biomedicine, France), Wolfgang Mayr (European Blood Alliance), Didier Musso (Institut Louis Malarde, Tahiti, French Polynesia), Cristina Pintus (Italian National Transplant Center), Constatina Politis (Hellenic Coordinating Haemovigilance Centre, Greece), Ingrida Pucinskaite-Kubik (Directorate-General for Health and Food Safety – European Commission), Imad Sandid (ANSM, France), Undine Samuel (Eurotransplant, the Netherlands), Jan Styczynski (European Society for Blood and Marrow Transplantation), Gracinda Sousa (Portuguese Institute for Blood and Transplantation), Stefaan Van der Spiegel (Directorate-General for Health and Food Safety – European Commission).

Any information on the use of commercial laboratory tests in this guide has been retrieved from the cited sources. The fact that ECDC has included the information in the guide does not constitute an endorsement of products and services on the part of ECDC.

Suggested citation: European Centre for Disease Prevention and Control. Zika virus and safety of substances of human origin: a guide for preparedness activities in Europe – first update. Stockholm: ECDC; 2017.

Stockholm, August 2017

ISBN 978-92-9498-081-6
doi: 10.2900/450662
Catalogue number TQ-01-17-859-EN-N

Contents

Tables

Abbreviations

BE	Blood establishments
BM	Bone marrow
CDTR	Communicable disease threats report
CNS	Central nervous system
DG SANTE	Directorate-General for Health and Food Safety, European Commission
EATB	European Association of Tissue Banks
EBMT	European Society for Blood and Marrow Transplantation
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European Medicines Agency
EDQM	European Directorate for the Quality of Medicines and Healthcare
ESoHO	Establishments for substances of human origin
ESHRE	European Society of Human Reproduction and Embryology
EUAL	Emergency use assessment and listing
EUFRAT	European up-front risk assessment tool
GBS	Guillain–Barré syndrome
HLA	Human leukocyte antigen
ID-NAT	Individual donation nucleic acid testing
IHR	International health regulations
IVDs	In-vitro diagnostics
NAT	Nucleic acid testing
NCA	National competent authorities
NUTS	Nomenclature of territorial units for statistics
PBHSC	Peripheral blood haematopoietic stem cell
PHEIC	Public Health Emergency of International Concern
RAB	Rapid alert platform for blood
RATC	Rapid alert platform for tissues and cells
RT-PCR	Reverse transcription polymerase chain reaction
RNA	Ribonucleic acid
SAR	Serious adverse reaction
SoHO	Substances of human origin (blood, tissues and cells, organs)
TC	Transmission category
TESSy	The European Surveillance System
WHO	World Health Organization

Executive summary

This first update of the original guide was prompted by the evolution of the Zika virus epidemic, a new classification of countries and areas based on their epidemiological profile, and recent scientific developments since the first edition of this guide. This summary contains only main changes that have been introduced into the update.

Despite a dramatic global decrease in the incidence of Zika virus infections in 2017, there is still need to be vigilant and use risk reduction measures in EU Member States. Introduction and spread of the imported virus is possible during the mosquito season in all Member States that have permissive climate conditions and competent vectors.

Data, though limited, indicate that there is a risk of Zika virus transmission through substances of human origin (SoHO), especially by blood transfusion. The high proportion of asymptomatic cases, documented occurrence of Zika RNA-positive blood donations and reports of probable transfusion-transmitted (TT) cases indicate that Zika-positive blood, donated by asymptomatic infectious donors, may enter the blood supply and henceforth could be transfused to a patient. However, the low number of TT cases, all without clinical consequences in recipients, preclude a more accurate risk assessment. Cases of donor-derived Zika-virus associated Guillain–Barré syndrome (GBS) have not been reported. Moreover, the likelihood of maternal and foetal exposure to blood products and presumably to other SoHO is very small. Data on Zika virus infection in donors of cells, tissues and organs and transmission of the virus to the transplant recipients are lacking. Nevertheless, the clear association between Zika virus infection and congenital malformations and GBS justifies the implementation of preventive measures to reduce the risk of transmission via the SoHO supply.

A revised scheme has been developed by WHO, in collaboration with the US CDC and ECDC, to categorise the epidemiological profile of vector-borne Zika virus transmission in countries and territories: Category 1 (area with new introduction or re-introduction with ongoing transmission); Category 2 (area either with evidence of virus circulation before 2015 or area with ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption); Category 3 (area with interrupted transmission and with potential for future transmission); Category 4 (area with established competent vector but no known documented past or current transmission). A map depicting these categories of countries and areas is regularly updated by ECDC and may be used for applying SoHO safety measures[1]. In the C1 and C2 areas, the Zika virus transmission is active, while in the C3 and C4 areas, active transmission of Zika virus is absent. The working group behind this guide agreed that only areas with active transmission of Zika virus are relevant for the implementation of SoHO safety measures. Thus, for the purpose of this guide, C1 and C2 areas are considered as 'areas with active transmission' while in C3 and C4 areas, and areas not at risk of ongoing vector-borne transmission, are considered as 'areas without active transmission'.

In the areas without active transmission, a temporary deferral from the donation of blood and/or non-reproductive cells and tissues for 28 days is suggested after cessation of disease symptoms, return from an area with active transmission and sexual contact with a Zika-infectious person. In order to harmonise this guide with the CDC's and ECDC's advice for sexual precaution against Zika virus transmission and to avoid unnecessary donor loss in areas without active transmission risk, a temporary deferral from donation of blood and/or non-reproductive cells and tissues for 28 days is suggested for donors after sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact.

In the areas without active transmission, a temporary deferral from sperm donation for six months is also recommended for donors after cessation of disease symptoms, return from an area with active transmission, or sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact.

The deferral periods due to the sexual exposure are applied as a precautionary measure because the duration of infectivity in sperm and vaginal fluid is currently unknown. Suggested periods will be revised if new evidence becomes available. The risk of Zika virus-positive blood donation after sexual contact with travellers returning from areas with active transmission has been estimated to be extremely low. Implementation of these measures, including a temporary deferral after sexual exposure to diagnosed persons or travellers returning from area with active transmission, may be adapted to the local conditions in a given country, but changes should be explained in a risk assessment and outlined in the national preparedness plan.

Commercial NAT (nucleic acid testing) screening for blood donations on fully and semi-automated high-throughput platforms using CE-marked kits is available.

[1] http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx

Introduction

The objective of this document is to support the operational preparation and implementation of national preparedness plans for the safety of substances of human origin (SoHO)[2] during outbreaks of Zika virus infection.

This document includes key elements to be considered in the risk-based decision-making process of mitigating the threats to the safety of SoHO posed by Zika virus. It also identifies supporting tools and additional information available at the EU level, either from ECDC or the European Commission's Directorate-General for Health and Food Safety. The purpose of guide is to offer the EU/EEA Member States and their national health authorities a tool that may be useful in dealing with Zika outbreaks.

Available data indicate that there is a potential risk of Zika virus transmission through SoHO that may have consequences for the health of recipients. Zika virus poses a threat to the SoHO safety in Europe because asymptomatic residents or travellers returning from areas with active transmission may donate SoHO infected with Zika virus. Furthermore, the possibility of autochthonous Zika virus transmission in Europe upsurges the threat. The risk of transmission of Zika virus by transfusion, transplantation or assisted reproduction technologies has not been sufficiently quantified yet, but cannot be ignored. On the other hand, the implementation of safety measures can also lead to a negative impact on the supply of SoHO, which has to be assessed and, if needed, addressed.

To further explore the SoHO aspects of human-to-human Zika transmission, the SoHO team at the European Commission's Directorate-General Health and Food Safety established a multi-country working group of experts from the blood, tissues and cells, and organs sectors in March 2016 to support ECDC in the preparation of a guide for preparedness activities for Zika virus outbreaks in the EU. The conclusions of an expert meeting organised by ECDC in May 2017 have also been incorporated in this update. Additional input on the guide from national competent authorities (NCA) on SoHO was also considered.

This document is based on previous preparedness plans for Europe, e.g. on West Nile Virus and blood safety [1]. This is the first update of a 2016 ECDC guide entitled *Zika virus and safety of substances of human origin* [2]; it reflects the currently available knowledge on Zika virus infection in humans and will be reviewed and updated as new relevant information becomes available.

[2] Substances of human origin (SoHO) are human blood, blood components, tissue, cells or organs as defined in Directive 2002/98/EC, Directive 2004/23/EC and Directive 2010/53/EU.

Background

Disease background information

Zika virus disease is caused by an RNA virus (Flavivirus genus, Flaviviridae family) transmitted to humans mainly by *Aedes* mosquitoes, in particular by the *Aedes aegypti* species. The virus can also be transmitted by sexual contact with an infected person [3-6], via blood transfusion and possibly by other SoHO donated by infectious donors. To date, three probable cases of Zika virus transmission through blood transfusion have been reported [7,8] while transmission through cells, tissues and organs remains unknown. Zika virus can also be transmitted vertically from an infected mother to the foetus during pregnancy and is responsible for foetal loss, microcephaly, and other congenital neurological syndromes [9].

The incubation period ranges from 3.5 days in a human volunteer [10] to 6 to 10 days in returning travellers and blood donors [3,11,12]. Although previous reports state that 80% of Zika virus infection cases are asymptomatic [13], it seems that the ratio of asymptomatic to symptomatic infections varies according to local conditions, as demonstrated among blood donors in French Polynesia, Martinique and the USA [14-18]. Symptomatic infections are characterised by a self-limiting febrile illness of 4 to 7 days' duration, accompanied by rash, arthralgia, myalgia and non-purulent conjunctivitis. Symptoms of Zika virus infection can be similar to other arboviral diseases, especially dengue, which makes laboratory testing necessary to confirm a diagnosis [6,19-21].

Zika virus infection was linked to Guillain–Barré syndrome (GBS) for the first time in 2014 during an outbreak in French Polynesia [22,23]. A case-control study in French Polynesia and recent observations confirm the role of Zika virus infection as a presumptive disease preceding GBS [24]. During the outbreak in Brazil, the higher frequency of microcephaly after Zika virus infection in pregnant women was recognised [9,25,26]. A growing body of research later confirmed that Zika virus is a cause of microcephaly and other congenital CNS malformations [27].

Zika virus infection can be confirmed by direct detection of Zika virus RNA or specific viral antigens in clinical samples. Virus-specific antibodies can usually be detected from day 4 or 5 of illness, but serological results should be interpreted with caution due to cross-reactivity with other flaviviruses and according to the vaccination status against flaviviruses. More information on Zika virus disease can be found in several ECDC risk assessments [26,28-35] and the ECDC factsheet for health professionals [13]. So far, neither Zika virus latency (the dormant virus is present within a cell in a lysogenic life cycle and can be reactivated) nor a chronic clinical course of infection have been observed.

To date, there is neither a vaccine to prevent Zika virus infections nor is there a specific antiviral treatment. The first Phase I trials, evaluating the safety, tolerability and immunogenicity of two Zika virus DNA vaccine candidates in healthy adult volunteers, are underway in the US and Canada [36]. Although several compounds show in vitro activity against Zika virus, there is no currently approved drug to prevent or treat Zika virus infection in humans.

While Zika virus is considered a mild disease for the general population, the severity of foetal impairment indicates the need to reduce the risk of infection, especially during pregnancy and in women of childbearing age. The first international recommendation to prevent transfusion-transmitted Zika virus infection was issued by ECDC in 2014 [37].

Epidemiological situation

Zika virus was discovered in 1947 in Uganda [38]. From the 1960s to 1980s, human infections were found across Africa and Asia, typically accompanied by mild illness. The first large outbreak of disease caused by Zika infection was reported from the Island of Yap (Micronesia) in 2007 [39], as the virus moved from south-east Asia across the Pacific. Genetic analyses revealed that Zika virus evolved from a common ancestor in East Africa into three distinct genetic clades: East African, West African and Asian [40]. Cases of Zika virus infection that were detected in Brazil and the Americas are most closely related to a 2013 isolate from French Polynesia, which is in the Asian clade [6,41].

The second Zika virus outbreak took place in French Polynesia in 2013–14, followed by an outbreak in Brazil in 2015. In February 2016, as Zika moved rapidly through the range occupied by *Aedes* mosquitoes in the Americas, a potential association between microcephaly/other neurological disorders and Zika virus was established. This caused WHO to declare that the cluster of microcephaly cases and other neurological disorders reported in Brazil – which followed a similar cluster in French Polynesia in 2014 – constituted a Public Health Emergency of International Concern (PHEIC)[42]. In November 2016, the WHO Emergency Committee stated that Zika virus and its associated consequences remained a significant enduring public health challenge but no longer constituted a PHEIC as defined under the International Health Regulations (IHR). Based on this advice, the Director-General declared the end of the PHEIC for Zika virus disease [43].

ECDC provides regular updates on the Zika virus epidemic through its Zika outbreak webpage and a monthly epidemiological update [44] (also available in the ECDC Communicable Disease Threats Report [45]). Since October 2016, the Zika virus epidemic appears to have been slowing down in the Americas and the Caribbean regions. New information about Zika virus circulation has been documented in south-east Asia. Between 26 October 2016 and 9 March 2017 [46,47], the main developments can be summarised as follows:

- Seventy countries have reported evidence of mosquito-borne Zika virus transmission since 2015, including three new countries (26 October 2016 and later): Palau, Montserrat and Angola.
- The United Kingdom reported one case of sexual transmission of Zika virus. Overall, 13 countries reported evidence of person-to-person sexual transmission.
- Thirty-one countries and territories reported cases of microcephaly and other central nervous system (CNS) malformations potentially associated with Zika virus infection to WHO, including eight since 26 October 2016 (Argentina, Bolivia, Guadeloupe, Mexico, Nicaragua, Saint Martin, Trinidad and Tobago, and Vietnam).
- Four additional countries (Bolivia, Curaçao, Trinidad and Tobago, and Saint Martin) reported at least one case of Guillain–Barré (GBS) syndrome potentially associated with Zika virus infection.

No locally acquired cases by vector-borne transmission have been reported by EU/EEA countries in continental Europe as of week 10/2017. Since week 26/2015, 21 countries have reported 2 130 travel-associated Zika virus infections through The European Surveillance System (TESSy). The latest week of exposure reported was week 50/2016. France reported 54%, Spain 14%, and the UK 9% of the cases. During the same period, eight countries reported 108 Zika cases among pregnant women.

In cases where gender was reported, 20 sexual transmission events were recorded in TESSy (all male to female, as of 7 March 2017): France (12), Italy (2), the Netherlands (2), Spain (2), Portugal (1) and the United Kingdom (1). Reported exposures took place in Brazil (2), Guatemala (1), the Maldives (2), Martinique (1), Puerto Rico (1) and Thailand (1) [48,49].

The importation of the virus into the EU is most likely through infected travellers returning from affected countries. Several factors might facilitate the spread of Zika virus infection from affected countries to the continental EU: an immunologically naïve population, a frequent occurrence of asymptomatic cases, the presence of a competent vector, increasingly permissive climate conditions in some Member States, and highly mobile populations. There is no evidence of airplane transportation of Zika-infected mosquitoes similar to airport malaria to date [50]. The risk of importation of Zika-infected mosquitoes or the transmission of arbovirus infections inside aircraft cabins is low. WHO has issued specific recommendations for aircraft disinfection [51].

The risk of autochthonous transmission of Zika virus infection in the EU is variable across geographic areas and depends on several local co-factors. The main vector of Zika virus transmission to humans is the mosquito *Aedes aegypti*, which was previously found sporadically in the Mediterranean in the first half of the 20th century but disappeared from this region after the Second World War [52]. It has since re-colonised Madeira [53] and parts of southern Russia and Georgia [54] and has been recently imported to the Netherlands, but is not established there [55].

A potential mosquito vector of Zika virus is *Aedes albopictus*, which is established in most places around the Mediterranean coast [56]. However, the capacity of this species to transmit Zika virus has not yet been determined for European mosquito populations [57,58]. A recent study suggests that although susceptible to infection, *Ae. aegypti* and *Ae. albopictus* were unexpectedly low competent vectors for Zika virus [59]. Moreover, *Ae. albopictus* had a lower competence than *Ae. aegypti* when tested in parallel in Italy [60].

The risk of autochthonous transmission of Zika virus infection is extremely low in the EU during the winter season, because the climatic conditions are not suitable for the activity of the *Ae. albopictus*. Nevertheless, during the summer season, autochthonous transmission in the EU – after the introduction of the virus by a viraemic traveller – is possible in areas where *Ae. albopictus* is established [56]. Despite the current decrease in the incidence of Zika virus infections and a growing number of countries expecting the interruption of transmission, EU/EEA Member States should be vigilant and persistent in the use of risk reduction measures.

EU legislation

This update is in line with the EU Directives that lay down the standards for the quality and safety of blood and blood components [61][62], tissues and cells [63], and organs [64,65]. In addition, Commission Implementing Directive 2012/25/EU lays down information procedures for the exchange of human organs intended for transplantation in the EU Member States [66]. A website, established with the support of the international organ-

exchange organisation Eurotransplant International Foundation (or Eurotransplant for short) provides a list of authorities appointed as contact points by each Member State for cross-border organ exchange[3].

[3] Eurotransplant International Foundation. Transplantation contact list [internet]. Luxembourg and Brussels: Eurotransplant; 2017 [cited 20 July 2017]. Available from: http://txcontactlist.eu

1 Key elements of a preparedness plan

Member States should adopt a set of appropriate measures in their national preparedness plans in order to be able to provide a rapid response to a potential Zika virus outbreak. Such plans, once established, should be evaluated and updated annually. Addressing an epidemic of Zika virus disease requires a broad multidisciplinary approach and should include public health, animal health expertise, entomological expertise, collaboration with NCA for SoHO (substances of human origin), ESoHO (establishments for substances of human origin), and related vigilance services. Such a multidisciplinary approach allows for continuous risk assessments at the national and European levels and also facilitates appropriate and timely decision-making in several health areas, including transfusion and transplantation medicine.

Key elements of a national preparedness plan entail affected areas, risk assessment, safety measures, SoHO supply, and communication among all parties. For each of these elements, activities can be undertaken at the EU, national and local levels (Table 1).

Proposed activities at the national and local levels are discretionary and include a range of options that the Member States may expand upon in their national preparedness plans. While it is important that each key element is appropriately addressed, the actual responsibilities and competences for specified activities depend on the organisational structure of the national SoHO supply system and can, therefore, vary between the Member States.

This guide does not cover possible activities outside the area of SoHO.

Table 1. Summary of key elements and activities at the EU, national and local levels

	Commission/ECDC	NCA for SoHO	ESoHO
1. Areas with active transmission	• Guidance for defining affected areas • Continuous surveillance and assessment of the epidemiological situation • Maps or lists of vector distribution, affected areas and countries.	• Monitor maps/lists of relevant vector distribution, affected areas and countries • Define geographical areas where safety measures need to be considered.	• Monitor and use maps/lists of relevant vector distribution, affected areas and countries in donor selection process.
2. Risk assessment	• Rapid risk assessment for Zika virus outbreaks • Risk assessments of Zika virus transmission through SoHO • Guidance on the use of risk assessment tools.	• Ensure that a national/regional risk assessment of Zika virus transmission is prepared, according to type of SoHO.	• Cooperate in assessing and reassessing the risk*.
3. Safety measures	• Mitigation options for risks posed by Zika virus to the safety of SoHO • Guidance/tools for assessing cost-efficiency of possible national measures • Information on test kits and protocols that may be considered in national preparedness plans.	• Define appropriate SoHO safety measures and include them in the national preparedness plan • Declare the start and end date of SoHO safety measures • Analyse safety impact and cost-effectiveness of measures • Evaluate feedback from ESoHO on applied measures and analyse effectiveness of the measures.	• Apply SoHO safety measures and, where needed, change the SoHO safety protocols in line with adopted measures.
4. SoHO supply	• Share contact details of EU NCAs for potential cross-border communication • Share national experiences to ensure the safe supply of SoHO in areas with active transmission • Identify the Zika screening capacity and capability of ESoHO in EU Member States to assist affected Member States that lack the capacity to independently screen SoHO donors.	• Evaluate the impact of implemented measures on SoHO supplies, while taking into account ESoHO input • Prepare and coordinate measures with ESoHO to ensure sufficient and sustainable SoHO supplies in different areas.	• Monitor and manage the use of SoHO.
5. Communication	• Run rapid alert platforms • Ensure communication with other authorities at the EU level, including surveillance authorities for animal health and medicines.	• Develop information leaflets** • Communicate changes in national guidelines to ESoHO • Inform the ministry of health and other authorities about the implemented measures • Communicate messages from RAB, RATC, and organ alerts to ESoHO • Inform NCAs in other Member States • Assess effectiveness of communication channels and adjust as needed.	• Cooperate with NCA in the development and dissemination of information leaflets** • Monitor new information from EU rapid alert platforms RAB and RATC, as communicated by NCA • Inform the responsible NCA on changes in the SoHO supply.

** In addition to general national/regional risk assessments on Zika virus transmission through SoHO, the risk of infection should be assessed individually for each organ transplantation procedure.*
*** The involvement of ESoHO and NCAs in the provision of information (e.g. leaflets) for donors, clinicians and patients depends on the situation in the individual Member States.*

2 EU-level support activities for the safety of SoHO

2.1. Case definition of Zika virus infection transmitted via SoHO

The declaration of local Zika virus transmission in a country or territory is based on a laboratory confirmation of at least one autochthonous case reported by a competent health authority. For the purpose of this document, the EU case definition proposed by ECDC for the surveillance of Zika virus infection is used [67]. This case definition is regularly reviewed and updated by ECDC and approved by the EU Health Security Committee. The current definition is currently under revision. To define a case of Zika virus transmission through SoHO, the following case definition is proposed:

The case of Zika virus infection transmitted through SoHO is considered when:

- The patient had evidence of Zika virus infection after receiving SoHO;

and

- there was no evidence of infection prior to SoHO therapy and no evidence of an alternative source of infection;

and either

- at least one SoHO product received by the infected recipient was donated by a donor who had evidence of the Zika virus infection;

or

- at least one SoHO product received by the infected recipient was shown to contain the Zika virus.

2.2. Country classification scheme

In contrast to the first preparedness plan, this guide uses a revised scheme developed by WHO, in collaboration with the US CDC and ECDC, to categorise the epidemiological profile of vector-borne Zika virus transmission in countries and territories.

ECDC's publishes lists and maps of transmission risk areas in accordance with the WHO classification (including areas in the EU at the NUTS 3 level) online at http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx.

The following four categories were defined by WHO [68]:

`**Category 1 (C1):** Area with new introduction or re-introduction with ongoing transmission

a. A laboratory-confirmed autochthonous, vector-borne case of ZIKV infection in a country/territory/subnational area where there is no evidence of virus circulation before 2015, whether it is detected and reported by the country/territory/subnational area where infection occurred, or by another country by diagnosis of a returning traveller; or

b. A laboratory-confirmed autochthonous, vector-borne case of ZIKV infection in a country/territory/subnational area where transmission has been previously interrupted, whether it is detected and reported by the country where infection occurred, or by another country by diagnosis of a returning traveller.

Category 2 (C2): Area either with evidence of virus circulation before 2015 or area with ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption

This category takes into account those countries with known historical laboratory evidence of ZIKV circulation prior to 2015, based on the literature as well as all ZIKV surveillance data whether detected and reported by the country where infection occurred or by another country reporting a confirmed case in a returning traveller. Countries in this category may have seasonal variations in transmission. These countries may also experience outbreaks of ZIKV disease.

Category 3 (C3): Area with interrupted transmission and with potential for future transmission

Some countries – particularly those that are geographically isolated and have small populations – may be classified as countries where transmission has been interrupted (Category 3). Historical evidence exists that,

in some instances, such as in Yap (the Federated States of Micronesia) or French Polynesia, ZIKV transmission may be interrupted after first introduction; however, the potential for re-introduction remains.

The minimum timeline for determining transition to an interrupted state is 12 months after the last confirmed case, and no cases identified in travellers. For countries with a high capacity for diagnostic testing, consistent timely reporting of diagnostic results, a comprehensive arboviral surveillance system and/or a temperate climate or island setting, the interruption of vector-borne transmission is defined as the absence of ZIKV infection 3 months after the last confirmed case. Countries where interruption is epidemiologically likely to have occurred should provide surveillance data to WHO to support the assessment by expert review.

Category 4 (C4): Area with established competent vector but no known documented past or current transmission

All countries/territories/subnational areas where the main competent vector (*Ae. aegypti)* is established, but which have not had a documented, autochthonous, vector-borne case of ZIKV infection. This category also includes a subgroup of countries/territories/subnational areas where ZIKV transmission may occur because of a shared border with a neighbouring Category 2 country, by belonging to the same ecological zone and having evidence of dengue virus transmission. In this subgroup, a first laboratory-confirmed, autochthonous vector-borne case of ZIKV infection may not necessarily indicate new introduction (Category 1), but rather previously unknown and undetected transmission (Category 2), and these countries/territories/subnational areas will be reclassified accordingly.'

Countries and territories classified into these categories are presented on the ECDC maps with the following adjustments which were made to reflect the risk to travellers more accurately [49]:

- While WHO lists countries or territories as one entity, ECDC uses subnational level areas for some large countries.
- A red hatching pattern is used for all areas of countries in Category 2 that experience new (and documented) intense transmission. The hatching pattern highlights areas where ten or more confirmed/probable/suspected cases were documented over the last three months, or where two or more confirmed/probable/suspected cases were documented in at least two locations over the last three months.
- Countries and areas in Category 4, which show a potential for transmission because of the presence of a suitable vector and have a common border with a Category 2 area, are listed as Category 4a. Category 4a indicates a higher risk of transmission because of the proximity to a category 2 area as both areas share the same ecological characteristics or experience virus transmission following past virus circulation (endemic areas). Other countries and areas are listed as Category 4b.

Some countries/territories/subnational areas are currently not at risk of ongoing vector-borne Zika virus transmission because of the absence of a competent vector and a climate unfavourable to mosquitoes and are not included in this classification scheme.

The working group agreed that only a risk resulting from active transmission in an area is relevant for the implementation of SoHO safety measures. Thus, for the purpose of this guide, areas classified as C1 and C2 are considered as 'areas with active transmission', while areas classified as C3, C4 or 'No risk' are considered 'areas without active transmission' (Table 2).

Table 2. Categories of country classification scheme and relevance for SoHO transmission

Transmission category	Definition	SoHO-relevant transmission areas
C1	Area with new introduction or re-introduction with ongoing transmission	Areas with active transmission
C2	Area either with evidence of virus circulation before 2015 or area with ongoing transmission that is no longer in the new or re-introduction phase, but where there is no evidence of interruption.	
C3	Area with interrupted transmission and with potential for future transmission.	Areas without active transmission
C4	Area with established competent vector (*Ae. aegypti)* but no known documented past or current transmission. Areas where *Ae. albopictus* mosquitoes are the only potential vectors are not included as there is no evidence that they can maintain sustained Zika virus transmission on their own (ECDC subcategories).	
No risk	Countries/territories/subnational areas currently not at risk of ongoing vector-borne Zika virus transmission because of the absence of a competent vector and a climate unfavourable to mosquitoes.	

The geographical area of the reporting unit should be of a size that allows for meaningful characterisation of the transmission dynamics and the application of SoHO safety measures. If an EU Member State is affected by autochthonous vector-borne Zika virus transmission, the geographic boundaries of areas applying blood safety measures should be consistent with local geographic specificities, vector distribution, and administrative borders. However, for the purpose of applying travel-related SoHO safety measures within the EU, transmission risk areas are notified at the NUTS-3 level (Nomenclature of Territorial Units for Statistics, level 3). Using the NUTS-3 level ensures the concise communication of geographical information in an international setting and avoids difficulties in recognising areas below the NUTS-3 level.

2.2.1 Initiation and discontinuation of SoHO safety measures

SoHO safety measures are initiated and discontinued by NCAs for SoHO, based on an assessment of the risk of Zika virus transmission within the country and information about the status of Zika infection in foreign countries.

Areas with active transmission

The first case of a confirmed autochonous vector-berne Zika virus infection in the EU/EEA triggers activities to assess the outbreak situation and initiate adequate SoHO safety measures. Blood and tissue establishments in the EU/EEA should consider the immediate interruption of donations as soon as they receive reports of the first confirmed autochthonous case of Zika virus infection. The interruption of donations should initially be restricted to donations from the smallest geographic administrative area that reported a vector-transmitted case. Within seven days after the first case, Member States should – based on cooperation between NCAs, ESoHOs and national public health bodies – assess the risk of Zika virus transmission through SoHO and decide on the initiation of SoHO safety measures at the local and national level. Measures can be discontinued when an interruption of active transmission is declared in the area. According to the WHO definition, an interruption of transmission is declared 3 to 12 months after the last case was reported. This timeframe depends mainly on a country's laboratory testing capacity and its surveillance system.

Areas without active transmission

In areas without active transmission, SoHO safety measures should be applied to residents or travellers returning from areas with active transmission. Information on the status of Zika virus transmission may be obtained from ECDC's maps of affected countries.

If safety measures are modified or not applied, the reasons behind this decision should be documented in a risk assessment study.

2.3 Risk assessment

2.3.1 Risk of Zika virus transmission via SoHO

The frequency of positive Zika RNA donations that were tested by reverse transcription-polymerase chain reaction (RT-PCR) was 2.8% (42/1 505) in French Polynesia [11], 0.89% (190/21 468) in Puerto Rico [69,70] and 2.0% (1.84% (76/4 129) in Martinique [16]. The occurrence of Zika-positive donations was lower in the contiguous US. Galel et al. [17] reported 14 (0.004%) repeatedly positive Zika virus-infected donations among 358 786 blood donations, mostly in southern US states (confirmed by alternate NAT (nucleic acid testing) and serology). Also, Williamson et al. [18] reported five (0.001%) reactive RNA donations in the US in 466 834 donations screened and collected in areas without active transmission, and all five donors had travel exposures.

Data obtained by the follow-up of RNA-positive blood donors suggest that the ratio of symptomatic/asymptomatic infected cases may vary according to local conditions. During the outbreak in French Polynesia, Aubry et al. found the proportion of symptomatic and asymptomatic RNA-positive blood donors to be approximately 1:1 [15]. Musso et al. [14] reported higher Zika virus RNA loads in asymptomatic infected blood donors compared with symptomatic patients. A follow-up of 75 viraemic blood donors in Martinique showed that 34 (45.3%) remained asymptomatic and 41 (54.7%) reported symptoms [16]. The first two reports on the universal screening of blood donations in the US show that 43% (6/14) and 60% (3/5) of RNA-positive donors developed symptoms during a post-donation follow-up [17,18]. As the proportion of asymptomatic but viraemic donors entering the selection process may significantly affect the risk of Zika infections through the donation of SoHO, the ratio of asymptomatic/symptomatic RNA-positive donors requires further investigation [16].

The Brazilian news media reported possible cases of transfusion-transmitted (TT) Zika virus in March 2015 and February 2016 [71,72]. Following these reports, three cases of probable TT Zika virus infection in Brazil were published in the literature [7,8]. In all three cases, the recipients of blood components, donated by Zika-infected donors who developed symptoms after donation, did not develop symptoms compatible with Zika virus infection although they all tested positive. The fact that only three cases were reported although the frequency of Zika RNA positive donations may be up to 2.8% suggests that TT Zika virus infection might occur unrecognized [11,69,73]. It is also possible that transmission through blood transfusion is a less efficient route of transmission [74]. The

consequences of a TT Zika virus infection in pregnant women or the foetus are not yet ascertained. Nevertheless, congenital malformations associated with vector-borne transmission of the virus call upon the use of Zika-virus-negative SoHO in pregnant patients.

A mounting number of reports of sexual transmission of Zika virus from infected males or females to a partner and the presence of the virus in semen and vaginal swabs provide indirect evidence of Zika virus gonadotropism and indicate a possible virus transmission route through donated reproductive cells [3,75-78].

There are no documented transmissions of Zika virus via saliva, urine or breastfeeding. However, the virus was detected in the breast milk of three symptomatic breastfeeding mothers. Although two of their newborns were infected with Zika virus, the evidence was not sufficient to distinguish breastfeeding transmission from other perinatal transmission routes [79]. No cases of Zika virus transmission through donated cells, tissues and organs have been reported, but transmission cannot be excluded due to the confirmed presence of the virus in human blood and body fluids. Zika virus RNA was found in several organs of infected animals during a modelling study of disease pathogenesis [80]. There is one report of virus RNA presence in the aqueous humour of a Zika-virus-infected patient with uveitis [81]. Lately, Heck et al. found that vitreous humour of an asymptomatic cornea donor tested positive for Zika virus while the serum was negative for viral RNA. Two recipients of these corneas did not develop symptoms; data on the laboratory evidence of infection were not available [82]. The first four cases of vector-borne Zika virus infection in immunosuppressed patients were reported in two kidney and two liver transplant recipients in Brazil [83]. All patients presented with a bacterial infection and required hospitalisation. Besides symptoms of acute infection, the patients also had thrombocytopenia and worsening allograft function but no typical Zika symptoms like skin rash, conjunctivitis or neurological signs. The small number of cases is, however, insufficient to draw any conclusions about the effect of immunosuppression on the clinical course of Zika virus infection in solid organ transplant patients and the impact of Zika virus on allograft function. Vector-borne Zika virus infection was also reported in haematopoietic stem cell transplant recipients and onco-heamatological patients who survived without sequelae; thrombocytopenia is the most frequent complication [84]. One patient, who acquired Zika virus infection 25 days before transplantation, had a delayed engraftment.

After the onset of symptoms, Zika virus RNA is usually detectable in serum for 14 days [85]. However, prolonged persistence the viral RNA has been reported up to 105 days post symptom onset in pregnant women [86] and up to 60 days after birth in a Zika-virus-infected neonate [87]. A systematic review and pooled analysis of 22 symptomatic Zika cases projected RNA clearance in 95 percent of affected patients in 19 days, with a 95 percent confidence interval of 13–80 days [88]. The screening of blood donors in the US indicates the clearance of Zika RNA from plasma within 28 days. The same study also reports the detection of Zika virus RNA after appearance of IGM antibodies in red blood cell (RBC) samples over a period longer than 28 days [17]. Recent findings show that Zika virus RNA can be detected in whole blood up to 81 days post-symptom onset even though the virus was not isolated [89,90]. In another study, the viral RNA was detected in the whole blood 101 days post symptom onset [91]. Detection of Zika virus RNA in whole blood for a longer period than in serum or plasma is consistent with similar findings for both West Nile virus [92,93] and dengue viruses [94]. Longer periods of detection of the virus RNA have been attributed to the erythrocyte component of whole blood. Infectivity of Zika virus-RNA-positive whole blood samples has not been proven and requires further investigation [90]. These data call into question the effectiveness of testing using plasma-based NATs in detecting Zika virus infection in humans. The impact of transfusion of blood that is positive for Zika virus RNA – based on whole blood (WB) or RBC testing but negative in plasma testing – to the recipients is currently being investigated [95]. The transfusion of platelets donated 90 days after returning from an area with active transmission by donors with low levels of Zika virus RNA in the plasma and moderate levels of Zika virus RNA associated with RBCs, did not result in infection [18].

Data, though limited, indicate that there is a risk of Zika virus transmission through SoHO, especially by blood transfusion [96,97]. The high proportion of asymptomatic cases [15-18], the documented occurrence of Zika RNA-positive blood donations [11,69,98], and the reports of probable TT cases [7,8] indicate that Zika-positive blood, donated by an asymptomatic infectious donor, may enter the blood supply and henceforth could be transfused to a patient. However, the low number of TT cases, all without clinical consequences in recipients, preclude a more accurate risk assessment. Cases of donor-derived Zika virus-associated GBS have not been reported, and the likelihood of maternal and foetal exposure to blood products and presumably to other SoHO is very low [99].

Cases of Zika virus transmission through infectious non-reproductive tissues and cells, and reproductive cells such as donated semen and oocytes have not been reported. Since the risk of Zika virus transmission cannot be excluded, precautionary measures should be undertaken in order to prevent possible transmission with potential consequences to recipient's health. The tissue and cell recipients may be immunosuppressed and are more likely to develop serious disease symptoms after Zika virus infection.

Nevertheless, the clear association between Zika virus infection and congenital malformations and GBS justifies preventive measures to reduce the risk of transmission via SoHO supply [54].

2.3.2 Risk of sexual transmission and the donation of SoHO

The presence of Zika virus within reproductive tissues may pose a significant threat to couples planning pregnancy and patients using assisted reproductive technology services. The presence of Zika virus in sperm and proven cases of Zika virus transmission through sexual contact with infected male indicate that an infectious asymptomatic male may donate Zika positive sperm.

Several cases of sexual transmission from symptomatic persons in the early phase of infection have been described in the literature [3,5,76,100-103], with the longest interval being 44 days between sexual contact and the onset of symptoms in a man and his female partner [102]. Two cases of transmission from asymptomatic male partners have been described [104,105]. The two longest reported durations of Zika virus RNA persistence in the semen of symptomatic men are 181 and 188 days [106,107], but there are indications that this period could even be longer than 12 months [Luisa Barzon, personal communication]. In one case, infectious virus particles were detected through semen culture 69 days after onset [108]. Zika viral RNA was documented in the semen of an asymptomatic male 39 days after returning from an area with active transmission [104]. Zika virus antigens were identified inside the spermatozoa of a symptomatic man 56 days after onset (with 3.5% of the cells infected) [109]. Sexual transmission was documented from a vasectomised man with Zika virus RNA identified in semen [108] and from a man with azoospermia, with Zika virus RNA present in semen plasma [104]. A follow-up study of five Zika-virus-infected women showed the virus RNA disappearing from genital tract three weeks after symptom onset [110]. Zika virus RNA was detected in a vaginal swab up to days 13 and 14 after onset, respectively [90,111]. In addition, a study from France [112] reported for the first time the isolation through cell culture of infectious Zika virus from vaginal samples of a woman with well controlled HIV-infection on day three post onset of Zika symptoms while a second swab on day 10 was negative. A study on 50 symptomatic women found that only one woman (2%) had Zika virus-RNA in vaginal secretions (at day 3 after onset) [113]. These findings indicate a short duration of the infectivity (through genital secretions) of women with acute Zika virus infection.

On 6 September 2016, WHO increased the duration for sexual precautions from eight weeks to six months for males and females exposed to Zika virus infections, whether they were symptomatic or not [114]. On 30 September, the US CDC extended the period for sexual precaution for couples planning to conceive to up to six months for exposed males, symptomatic or not, but it kept the eight-week period for sexual precaution for females exposed to Zika virus infections [115]. Both advices are based on a precautionary principle because a period of sexual infectivity during Zika virus infection is not fully established. Based on the low transmissibility and frequencies of reported sexually transmitted cases in areas without active transmission [49] and several national risk assessments, it appears that the risk of Zika-positive donation by sexually exposed donors is very low. Risk assessments from Australia [116], the Netherlands [117] and France [118] show that the risk of blood donations by persons infected after sexual contact with travellers returning from areas with active transmission is extremely low or negligible. A survey by the European Commission in October 2016 showed that only 38% of the Member States implemented a deferral of donors who had sexual contacts with persons returning from affected areas. In May 2016, France implemented a 28-day deferral of donors who had sexual contact with an asymptomatic man who had returned from an area with active transmission within three months preceding sexual contact.

Zika virus genome has also been detected in saliva during and after the acute phase of the disease. Viral isolation was reported on day six after symptom onset [119,120]. Comprehensive data about the presence of the viable virus, viral load or kinetics are lacking, and at this point the risk of transmission via saliva cannot be further assessed.

2.3.3 Use of the EUFRAT tool

The European Up-Front Risk Assessment Tool (EUFRAT) may be used to assess and quantify the risk of transfusion-transmitted Zika virus infection in an area with active transmission, or, alternatively, assess the risk posed by a donor returning from an area with active transmission. EUFRAT is not designed and validated for cells, tissues and organs, and cannot be used for the risk assessment of Zika virus transmission through SoHOs other than blood. The tool is available from: http://eufrattool.ecdc.europa.eu.

2.4 Safety measures

NCAs, ESoHOs and clinicians dealing with SoHO need to be vigilant and aware of the risk of donor-derived Zika virus transmission through transfusion and transplantation. Measures to prevent Zika virus transmission through SoHO should be taken in areas with and without active risk of transmission. Implementation of SoHO safety measures should be defined by a risk assessment at the national level.

2.4.1 Possible measures

Experiences in French Polynesia have shown that mitigation strategies that consisted of medical history taking, medical check-ups, post-donation information, discardingand quarantine of blood products failed to prevent transfusion of Zika virus RNA-positive blood products in areas with active transmission. However, NAT screening of blood donors effectively prevented the use of Zika virus-contaminated blood products [121]. During chikungunya outbreaks in Italy [122] and La Reunion [123], the complete or partial suspension of blood donations, combined with blood supply from areas without active transmission, and pathogen inactivation of locally collected plasma and platelets was applied.

In areas without active transmission, a temporary deferral from the donation of blood, non-reproductive cells and tissues for 28 days after cessation of disease symptoms or exposure to the Zika virus has been suggested. The period of 28 days covers double period of the viraemic phase in plasma, which may last up to 14 days [98,124,125]. Zika virus RNA positivity in whole blood samples up to 101 days post symptom onset is not considered a reason for donor deferral because infectivity during the period of prolonged RNA positivity has not been proven.

The working group for this document finds that travelling to areas with active transmission and sexual contact with a person diagnosed with Zika virus infection are relevant risk exposures for SoHO donors. The risk of Zika virus transmission through sexual contact of a potential donor with a person who travelled or lived in an area of active transmission is estimated to be extremely low or even negligible. All implemented measures, including a temporary donor deferral for 28 days after sexual exposure, should be assessed/reassessed in accordance with the local conditions in a given country, supported by a risk assessment, and outlined in the national preparedness plan.

The introduction of new safety measures requires a robust, evidence-based evaluation of associated benefits, both clinical and economical. A cost-effectiveness analysis of possible preventive measures should, therefore, be performed within the national context, taking into account the nature of the proposed measures and country-specific costs. The recommended methodologies are WHO's guide to cost-effectiveness analysis [126] and the Alliance of Blood Operators' risk-based decision-making framework for blood safety [127]. All approaches, including those that infer cost-effectiveness from the other mosquito-borne disease outbreaks in Europe, are highly complex and require a sufficient amount of data and a high level of expertise [122,128,129].

2.4.2 Availability of laboratory tests

Zika virus is a risk-group-2 pathogen which requires biocontainment precautions at biosafety level 2 (BSL-2) in Europe, the USA and Canada [130-132]. Laboratory evidence of Zika virus infection is generally established by the detection of viral RNA and/or specific anti-viral antibodies in biological samples.

Laboratory tests for the diagnostic of Zika virus infection

Several laboratory tests for the qualitative detection of Zika virus infection (in vitro diagnostics, based on real-time PCR technology) are available but not yet registered/approved for marketing by the national regulatory bodies in the EU. So far, two PCR kits received a EU declaration of conformity (CE marking): RealStar Zika virus RT-PCR kit 1.0 (Altona Diagnostics) and Aptima Zika Virus assay (Hologic, Inc.). Also CE-marked are the serologic anti-Zika virus ELISA and IIFT tests (Euroimmun) [133]. However, to facilitate the timely access to diagnostic tools, national regulatory bodies may authorise the emergency use of validated commercial or in-house diagnostic tests. As of January 2017, the US Food and Drug Administration (FDA) has authorised the emergency use of several tests in order to ensure timely access to diagnostic tools [134] [135]:

- CDC Zika immunoglobulin M (IgM) (MAC-ELISA)
- CDC Trioplex Real-time RT-PCR Assay (Trioplex rRT-PCR)
- Zika Virus RNA Qualitative Real-Time RT-PCR (Focus Diagnostics)
- RealStar Zika Virus RT-PCR Kit U.S. (Altona Diagnostics)
- Aptima Zika Virus assay (Hologic)
- Zika Virus Real-time RT-PCR Test (Viracor-IBT Laboratories)
- VERSANT Zika RNA 1.0 Assay (kPCR) Kit (Siemens Healthcare Diagnostics)
- xMAP MultiFLEX Zika RNA Assay (Luminex Corporation)
- LightMix Zika rRT-PCR Test (Roche Molecular Systems)
- Sentosa SA ZIKV RT-PCR Test (Vela Diagnostics USA)
- Zika Virus Detection by RT-PCR Test (ARUP Laboratories)
- Abbott RealTime ZIKA (Abbott Molecular Inc.)
- Zika ELITe MGB Kit U.S. (ELITechGroup Molecular Diagnostics).

A number of commercial laboratory tests for the in vitro diagnostics of Zika virus infection have been submitted to WHO for an emergency use assessment and listing (EUAL). As of 18 December 2016, the following IVD tests have been recognised by WHO as suitable for emergency use [136]:

- AccuPower ZIKV (DENV, CHIKV) Multiplex Real-Time RT-PCR Kit, EUAL number: EAZ 0006-004-00
- RealStar Zika Virus RT-PCR Kit 1.0, EUAL number: EAZ 0003-002-00

Laboratory tests for the screening of SoHO donors/donations

Ideally, only test kits that are registered and approved should be used to screen SoHO donors and donations. Commercial Zika tests for the screening of blood donations have recently been developed and approved for investigational use by the US FDA and WHO. ESoHOs and laboratories may develop in-house tests or adapt commercial diagnostic tests for screening purposes. The investigational use of screening tests in a Zika virus outbreak should be validated and approved by a competent national body. Quality control material for validation is available from the global European virus archive [137]. Some blood establishments are gaining experience with in-house testing or using adapted commercial tests. Semi-automated platforms for the NAT screening of blood donations using CE-marked kits for diagnostics were employed in the French West Indies during the 2014 outbreak of chikungunya [138] and Zika virus screenings in the French Antilles (RealStar RT-PCR Zika Kit 1.0, Altona Diagnostics). In the US, the FDA, in close collaboration with the product manufacturer (Roche Molecular Systems, Branchburg, New Jersey), approved the use of an investigational screening test for blood donations to screen blood donors in Puerto Rico [139]. The report from the US shows a high specificity of the employed test (99.997%) and demonstrates the value of individual donations over mini-pool testing in the screening of donated blood for the presence of Zika virus RNA in plasma and RBCs [17]. A recent study also showed that the investigational Zika virus NAT assays for the screening of blood donations have excellent sensitivities, comparable to the assays used to screen for established TT viruses [140].

The Procleix Zika virus assay (Grifolds/Hologic) is available on a fully automated platform (Procelix Panther system) and has obtained the CE mark on 22 December 2016; the company is in the process of completing product registration for all EU countries.

On 26 August 2016, the FDA issued a revised guidance which recommended the universal screening of donated whole blood and blood components for the presence of Zika virus by NAT. The FDA also advised pathogen reduction technology with an FDA-approved device in the USA and its territories [141]. These recommendations do not apply to the collection of source plasma for the production of plasma-derived medicinal products.

In the light of the revised FDA guidance, ECDC suggests screening of blood donations but only in areas with active transmission in the EU, as proposed in this document. This is based on the assumption that the Zika virus will not rapidly spread in EU Member States with areas with permissive conditions for vector-borne transmission. The likelihood of local vector-borne transmission in the EU is considered to be low to moderate due to the low vector competence of the studied European populations of *Ae. albopictus* [60,142,143]. The risk of local transmission is higher only in Madeira island where *Ae. aegypti* mosquitoes are present. Also, according to an interim risk assessment issued by the WHO Regional Office for Europe, the capacity to contain Zika virus transmission at an early stage is considered 'good' for the countries of the WHO European Region [144].

2.4.3 Pathogen inactivation

Pathogen inactivation of platelets has successfully been used as a preventive measure in response to the chickungunya outbreak in La Reunion [123]. Currently available pathogen inactivation treatments of platelets and plasma (amotosalen–UVA light, riboflavin–UV light, methylene blue–UV light, and UV–C light) are effective in the inactivation of flaviviruses, including dengue virus, West Nile virus, chikungunya virus and Zika virus [145-150]. The amotosalen–UVA light method has been demonstrated to inactivate Zika virus in plasma. The mean Zika virus titres and RNA loads in plasma before inactivation were 6.57 log TCID50/mL and 10.25 log copies/mL, respectively. After inactivation, the mean Zika virus RNA loads was 9.51 log copies/mL, but cell cultures inoculated with inactivated plasma did not result in infected cells and did not produce any replicative virus after one passage, nor was there any detectable viral RNA from the second passage, confirming the high level of Zika virus inactivation [151]. The amotosalen–UVA light method also inactivates Zika virus in platelets. The mean Zika virus titres and RNA loads in platelets before inactivation were 4.4 log $TCID_{50}$/mL and 7.5 log_{10} genome equivalents per millilitre, respectively. No infectivity was detected immediately after amotosalen–UVA treatment. No replicative virus remained after treatment, as demonstrated by multiple passages on Vero cell cultures [152]. A chemical method employing amustaline (S-303) and glutathione (GSH) has lately been reported [153]. This method effectively inactivates Zika virus in red blood cell components of more than 7.75 log genomic equivalents of Zika virus RNA and 5.99 log of infectivity relative to sham treatment using a cell culture assay. The method is in the advanced developmental stage of obtaining approval for use in the preparation of red blood cell components for clinical use. The data above show that high levels of Zika virus can be inactivated in all blood components.

Tissue allografts are typically disinfected with irradiation or chemical methods that might be effective against Zika virus. Pathogen inactivation methods for musculoskeletal allografts are subdivided into 'disinfection methods,' and

'terminal sterilization methods' [154]. Disinfection methods include chemical and antibiotic treatments that target microorganisms, whereas terminal sterilisation methods typically include irradiation, ethylene oxide, or heat treatments and eliminate all living microorganisms to a particular level of assurance after treatment. A combination of radioprotectants and optimised, high-dose gamma irradiation has been effectively used in pathogen inactivation of cancellous bone grafts [155,156]. Pasteurisation of breast milk has been shown to be effective in the inactivation of Zika virus [157].

2.5 Supply management

The SoHO supply is vulnerable to incidents affecting the health of donors. A large Zika virus outbreak may temporarily decrease the number of SoHO donors and staff in ESoHOs, making it difficult to treat patients timely and adequately. In order to maintain the SoHO inventory and supply chain, ESoHOs should evaluate their current supply management policy and strengthen their contingency plans [70]. Member States may decide to stop the collection of blood in areas with active transmission and instead supply blood from parts of the country not affected by active transmission. For instance, at the beginning of the Zika virus outbreak in Puerto Rico, blood collection was halted, and blood components were shipped from the US mainland to areas with active transmission; the screening of blood donations was introduced at a later stage [158]. By maintaining regular contacts, NCAs would be able to help with cross-border shipments of SoHO supplies to areas where the local collection is limited or impossible due to the high intensity of Zika virus transmission.

Countries that do not have adequate laboratory capacities may consider to contract out NAT laboratory services to providers in other EU countries. The European Blood Alliance has therefore informed the European Commission and ECDC that blood establishments from France, Germany, Ireland and the UK have capacities to screen blood donations. Although this capacity is somewhat limited at the moment, the blood establishments mentioned above could be approached for testing support [159].

Blood, tissues and cells should not be imported from area with active transmission. However, countries and territories with active Zika virus infection are not always identified and reported [160]. In special circumstances or for life-saving procedures, blood, tissues and cells may be imported from areas with active transmission, but only if they tested negative for the presence of Zika virus. The importation of organs from areas with active transmission should be based on an individual risk assessment which should weigh factors such as infection transmission to any potential recipient, the possibility to perform NAT testing for Zika virus, and the balance between risks and benefits for the patient.

2.6 Communication

Communication strategies that ensure accurate and timely information at all levels are an important component of responding to infectious disease outbreaks. Communication strategies should provide a meaningful response to unwanted and unexpected events and help to keep negative economic consequences to a minimum while maximising the desired outcome of all public health measures [161].

National preparedness plans for SoHO safety should outline a communication strategy which addresses all levels. The communication strategy should cover the exchange of information with international organisations while at the same time ensuring that the public health sector, the healthcare sector and the wider population are all kept informed on the latest scientific and epidemiological developments and the impact of the measures taken to ensure the safety of the SoHo supply.

NCAs for SoHO use a web-based rapid alert system for blood (RAB) and a rapid alert system for tissues and cells (RATC) to exchange essential information between the Member States and ensure that cross-border incidents are prevented or contained, with immediate measures taken to ensure the safety of patients. RAB/RATC are used in parallel with national vigilance systems and ESoHOs, which collect and manage alerts on products donated and used in the Member States.

Alerts should be communicated to relevant ESoHOs, professional associations (European Blood Alliance, the European Association of Tissue Banks, the European Society of Human Reproduction and Embryology) and other stakeholders such as ECDC, the European Medicines Agency, and the European Directorate for the Quality of Medicines and Healthcare. Regular contacts and exchange of information between all stakeholders and the EU Commission (Directorate-General for Health and Food Safety – Unit B4-SoHO) can ensure the consistency of information across Europe.

3 Safety measures by type of SoHO

The working group behind the production of this guide agreed that the implementation of safety measures for donors who have had sexual contact with potentially infected needs to be reassessed and justified by risk assessments conducted within the framework of national preparedness plans. This has to be done by taking into account the type of SoHO whose safety level has to be assessed and the travel frequency of donors. Table 3 summarises the proposed safety measures for the main types of SoHO.

Table 3. Summary of proposed safety measures by type of SoHO and area affected by Zika infection

Type of SoHO	Area without active transmission	Area with active transmission
Whole blood and blood components	Deferral of donors for at least 28 days (i) after cessation of symptoms in case of confirmed Zika virus infection, and (ii) after return from areas with active transmission, and (iii) after sexual contact with a man diagnosed with Zika virus infection in the six months preceding sexual contact or with a woman diagnosed with Zika virus in the eight weeks preceding the sexual contact* OR NAT screening if available AND/OR application of plasma and platelet pathogen inactivation techniques. (Inactivation of red blood cells or whole blood may also be applied if technique is available).	NAT screening of donations OR temporary suspension of local blood donations and import blood components from areas without active transmission, AND/OR application of plasma and platelets pathogen inactivation techniques. (Inactivation of red blood cells or whole blood may also be applied if technique is available).
Plasma for fractionation	It is not essential to exclude blood donors who have returned from active transmission areas from donating plasma for fractionation. It is also not essential to screen plasma for fractionation which was collected in areas with active Zika virus transmission.	It is not essential to exclude blood donors who have returned from active transmission areas from donating plasma for fractionation. It is also not essential to screen plasma for fractionation which was collected in areas with active Zika virus transmission..
Sperm	Deferral of donors for six months (i) after cessation of symptoms in case of confirmed Zika virus infection, and (ii) after return from active transmission risk areas, and (iii) after sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or (iv) after sexual contact with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact OR NAT screening of sperm donation if available	NAT screening of sperm donation if available OR temporary suspension of local donation and importation of sperm donated from an area/country without active transmission.
Non-reproductive tissues and cells	Deferral of donors for at least 28 days (i) after cessation of symptoms in case of confirmed Zika virus infection, and (ii) after return from areas with active transmission, and (iii) after sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact or with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact* OR NAT screening if available OR/AND pathogen inactivation if applicable	NAT screening of donors OR suspension of local donation and importation of tissue and cell materials from areas without active transmission OR/AND pathogen inactivation if applicable
Organs	Individual assessment of organ donors, while carefully weighing the benefits against the risks for the potential organ recipient; final decision lies with the transplant team.	Individual assessment of organ donors, while carefully weighing the benefits against the risks for the potential organ recipient. NAT testing may be used in donors to identify the pathogen.

* Member States may, according to the risk assessment and local conditions in the country, adapt eligibility criteria for donors who had sexual contact with potentially exposed person.

3.1 Blood safety measures

3.1.1 Areas without active transmission

3.1.1.1 Donor information

Blood establishments should update donor information materials and add information on Zika virus infection, including information on transmission routes, clinical signs and the risk of being infected. The information should also include advice on donor self-deferral for 28 days after:

- a medical diagnosis of Zika virus infection;
- returning from an area with active transmission;
- having sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or after sexual contact with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact.

3.1.1.2 Donor questionnaire

Donor history questionnaires contain a question about travelling abroad. Donors with a history of travelling to areas with active transmission should be asked questions about the length of their stay in the area, Zika symptoms, and if there was a Zika diagnosis. Questions about sexual contacts with men diagnosed with Zika virus infection in the six months preceding the sexual contact, or with women diagnosed with Zika virus infection in the eight weeks preceding the sexual contact, could be included in the questionnaire if warranted by a risk assessment conducted within the framework of the national preparedness plan. The risk of infectious donation by donor having sexual contact with person returning from an area with active transmission is assessed to be extremely low. In accordance with national risk assessments, Member States should decide on the type of intervention and eligibility criteria for the deferral of donors at risk of being infected with Zika virus.

3.1.1.3 Donor eligibility

Deferral for at least 28 days after is required after:

- a medical diagnosis of Zika virus infection;
- returning from an active transmission risk area;
- sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or sexual contact with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact[4].

The deferral period for travellers returning form the area with active transmission already affected by another vector-borne disease (e.g. malaria) should be extended to whichever deferral period is longer.

Member States may consider a longer deferral of donors (i.e. more than 28 days after cessation of symptoms) as a precautionary measure to prevent possible infectivity due to prolonged RNA positivity of whole blood and erythrocytes.

3.1.2 Areas with active transmission

Depending on the level of risk posed by Zika virus infection to the safety of blood and blood components in areas with active transmission, the blood establishment can either temporarily suspend blood donations or continue blood collections and screen them using Zika RNA NAT.

Temporary suspension of blood donation

Blood establishments might temporary suspend blood donation in areas with active transmission and source all necessary blood components from parts of the country without active transmission. The criteria for this measure should be defined in the risk assessment. This measure should be coordinated at the national level among blood establishments and the NCA for blood and blood components in order to ensure an adequate and timely supply of blood components from areas without active transmission to areas with temporarily suspended donations. Blood donors must be informed of the measures. Affected Member States may establish an international cooperation to compensate for the losses in the blood supply due to the temporary suspension of blood donations. This cooperation should be coordinated by the Directorate-General for Health and Food Safety – Unit B4-SoHO.

Continuation of blood donation

Blood establishments may decide to continue with blood donations in areas with active transmission if the suspension of blood collection jeopardises the blood supply, but only if laboratory screening tests and pathogen inactivation procedures are available.

Partial continuation of blood donation

- Continue with the apheresis collection of platelets and plasma; platelets and plasma should later be pathogen inactivated
- Import only red blood cells from parts of the country without active transmission
- If possible, use recovered fresh frozen plasma collected before the outbreak
- People diagnosed with Zika virus infection, after cessation of symptoms, should be deferred for 28 days.

Complete continuation of blood donation

- Continue with all types of blood donations
- Screen donated blood using a validated NAT screening test
- Defer for the following groups for 28 days:
  - People diagnosed with Zika virus infection after cessation of symptoms
  - Donors whose blood donation tested positive for Zika virus infection.

3.1.3 Donation of plasma for fractionation

The European Medicines Agency (EMA) and competent authorities in the EU Member States have confirmed that there is no increased risk of Zika virus infection for recipients of plasma-derived or urine-derived medicines [162]. EMA's Committee for Medicinal Products for Human Use Biologics Working Party (CHMP's BWP) assessed the

manufacturing processes for these products and concluded that they successfully inactivate or remove the virus. Thus, additional safety measures such as the screening of plasma and urine donors/donations or the deferral of donors returning from areas with active transmission are not considered necessary [163]. Recent studies also confirm that Zika virus is sensitive to solvent-detergent and heat treatments and thus does not pose a risk of transmission through plasma products that include such treatments in their manufacturing process [164-166].

It is not essential to exclude blood donors who have returned from areas with active transmission areas from donating plasma for fractionation. It is also not essential to screen plasma for fractionation which was collected in areas with active transmission.

3.1.4 Post-donation information and haemovigilance

Post-donation information

Blood donors should be encouraged to inform blood establishments if they develop symptoms compatible with Zika virus infection within two weeks after donation.

For collected blood or blood components from a donor who has provided post-donation information as noted above, undistributed in-date blood or blood components should immediately be quarantined. Blood establishments should investigate the nature of the disease in the donor. If the donor is infected with the Zika virus, all blood components from this donor should be destroyed except components intended for pathogen inactivation and plasma for fractionation. Separate storage and appropriate labelling of infected blood components may be allowed for investigational or research purposes only. The collection facility should evaluate all in-date current, prior, or subsequent donations from donors who should have self-deferred, or who were deferred, to determine whether the donation was collected during a time interval that placed the donor at risk of Zika exposure. If so, the quarantine policy should apply.

Haemovigilance

Hospitals should immediately report any case of post-transfusion Zika virus infection to the blood establishments that issued the blood components associated with the case. Blood establishments should perform a look-back procedure to trace the recipients of blood components from a potentially infectious blood donation and notify these recipients, through their treating physicians, for further investigation. Blood establishments should withdraw all blood components in stock and recall issued blood or blood components that are linked to the possibly infected donation material.

3.2 Tissue and cell safety measures

Characteristics of tissues and cells and possible Zika virus inactivation during processing and storage should be evaluated and considered when assessing the risk of virus transmission through cells and tissues. If validation shows that the virus has been inactivated, or if inactivation can be assumed based on the results obtained in the inactivation of similar model viruses, no other safety measures related to donor selection or screening have to be taken.

3.2.1 Living donation

Donor information and selection

Tissue establishments should update their donor information material by including basic information on Zika virus infection, including information on the clinical signs of the disease and the risk of getting infected. Information should also include advice on donor self-deferral (28 days for non-reproductive tissues and cells, and six months for sperm donation). Deferral is required:

- after a medical diagnosis of Zika virus infection;
- after returning from an area with active transmission; or
- if the donor had sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or after sexual contact with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact.

The donor history questionnaire should contain questions about the history of medical diagnosis of Zika virus disease within the last 28 days and travel to areas with active transmission. Questions about sexual contacts can be included in the questionnaire if warranted by a risk assessment conducted within the framework of the national preparedness plan The risk of infectious donation by donor having sexual contact with person returning from an area with active transmission is assessed to be extremely low. In accordance with national risk assessments, Member States should decide on the type of intervention and eligibility criteria for the deferral of donors at risk of being infected with Zika virus.

Reproductive tissues and cells

Assisted reproductive technology

Assisted reproductive technology (ART) procedures such as in vitro fertilization should be temporarily postponed in areas with active Zika virus transmission. Under specific conditions, reproductive tissue establishments can continue with fertility preservation, for example when postponing an assisted reproductive technology procedure would significantly worsen a couple's chances to conceive. In this case, all donors/partners should be screened by NAT.

There is accumulating evidence that Zika virus is present in sperm for a longer period than in whole blood, saliva or urine. Thus, validated NAT testing for sperm samples is recommended for fertility preservation. When using NAT, negative results should be interpreted with caution because they may reflect a temporary absence of the virus in the sperm due to intermittent shedding. Serological testing such as enzyme immunoassays and immunofluorescence assays for the presence of anti-Zika IgM antibodies in the blood sample may be used to exclude false negatives.

Sperm donation

Areas with active transmission. Tissue establishment should temporary interrupt sperm donation during active transmission in an area and reinstate donation six months after the last case has been reported.

Areas without active transmission. Continue with sperm donation, but apply the following selection measures for donors:

- Deferral of donors for six months (i) after cessation of symptoms in case of confirmed Zika virus infection, and (ii) after return from active transmission risk areas, and (iii) after sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or (iv) after sexual contact with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact
- NAT screening of donors who are at risk of being infected if donation cannot be postponed; accept donors whose semen tested negative for Zika virus by NAT and whose serological tests for Zika virus disease were also negative [94].

Donation of other reproductive tissues and cells: oocytes and embryos (in vitro fertilisation), and ovarian and testicular tissues (fertility preservation)

Areas with active transmission. Tissue establishments in areas with active transmission should temporarily interrupt in vitro fertilisation and fertility preservation, except under specific conditions. For children, fertility preservation should not be postponed, but the use of preserved tissues will depend on NAT test results and the available technology. Fertility preservation or in vitro fertilisation may also be performed when suspending would significantly worsen a couple's chances to conceive. NAT testing on sperm and serological test on blood samples should be performed [94]. Tissue establishments may reinstate procedures for fertility preservation and in vitro fertilisation, two to six months after the last case has been reported in an area.

Areas without active transmission. Female donations (fertility preservation and assisted reproductive technology procedure): deferral for at least 28 days after diagnosed illness, return from areas with active transmission, or sexual contact with a male diagnosed with Zika virus infection.

Male donations (fertility preservation): the sperm of all donors who were diagnosed with Zika virus infection or who returned from an area with active transmission six months or less before donation, should be tested using NAT.

According to the WHO interim guide on laboratory testing for Zika virus infection, NAT testing on blood or urine samples in areas with active transmission may be used in the donor selection process [94].

Non-reproductive tissues and cells

Cord blood and placental tissues

- Pregnant women with a diagnosis of Zika virus infection are not eligible to donate cord blood or placental tissues.
- Pregnant women returning from the areas with active transmission may donate cord blood and placental tissues if tested negative for Zika virus by NAT.
- Donation of cord blood and placental tissues should be suspended in areas with active transmission and reinstated nine months after the end of the outbreak has been declared. This may prevent the donation of infected cord blood by women who were exposed to Zika virus in early pregnancy at the end of the outbreak.

Bone marrow and peripheral blood haematopoietic stem cells

The risk of Zika virus transmission through bone marrow (BM) or peripheral blood haematopoietic stem cell (PBHSC) transplants is the same as via blood transfusion. However, the life of the recipient of allogeneic BM/PBHSC transplantation may depend on the timely selection of an acceptable human leukocyte antigen (HLA)-matched donor. Only a limited number of HLA-matched donors might be identified. Hence, the transplant physician may

have to accept a higher risk for transmission of the pathogen through BM/PBHSCT or perform laboratory testing of the donor beyond the standard tests for blood donors.

Area without active transmission

For the following donor groups, the donation of BM/PBHSC should be postponed for 28 days:

- After a medical diagnosis of Zika virus infection
- After returning from an area with active transmission
- If the donor had sexual contact with a man diagnosed with Zika virus infection in the six months preceding the sexual contact, or after sexual contact with a woman diagnosed with Zika virus infection in the eight weeks preceding the sexual contact.

If donation cannot be postponed, donors at risk should be screened by NAT (blood and/or urine) and accepted if they tested negative.

Areas with active transmission

Due to the high proportion of asymptomatic cases of Zika virus infection, deferral policies might be ineffective in the active transmission risk areas. Thus the transplantation should be performed, provided that BM/PBHSC donors tested negative by Zika NAT RNA testing.

3.2.2 Post-mortem donation

Areas without active transmission. The presence of risk factors for Zika virus infection should be identified by reviewing the medical, behavioural and travel history as well as the post-mortem examination of a donor. Deceased donors who were diagnosed with Zika virus disease in the last 28 days, or returned from areas with active transmission, should not be used as tissue or cell donors.

Areas with active transmission. Using only a donor's medical and behavioural history in the selection of deceased donors may be insufficient in areas with active transmission because of the high proportion of asymptomatic infections. Based on the level of risk determined by a risk assessment on the safety of tissues, tissue establishments can temporarily suspend or resume tissue donations in areas with active transmission under specific conditions.

If tissue donation was temporarily suspended in areas with active transmission, needed tissue products should be supplied from parts of the country that report no active transmission. If tissue donation in area with active transmission continues, all tissue donors/donations have to be laboratory screened, and, if possible, tissue products should be inactivated using appropriate pathogen inactivation technology.

3.3 Organ safety measures

The risk of Zika virus transmission through solid organ transplantation remains unknown. The virus may have infected deceased organ donors prior or during their terminal illness. It can also affect living organ donors before the transplantation procedure. An asymptomatic viraemia in infected individuals might result in organ infection. Zika virus RNA has been detected in brain, liver, spleen, kidney, lung and heart samples from a fatal adult case with underlying chronic health conditions [95]. It is, however, unknown whether organs infected with Zika virus transmit the disease. It appears that Zika virus transmission through organ transplantation is possible, but no cases have been reported to date.

Thus, the organ transplant community should be aware of the threat posed by Zika virus to solid organ transplant donors and recipients. Particular attention must be paid to the travel history of the donor. A possible Zika virus infection in an organ donor should not automatically lead to exclusion from the donation, except when the organ recipient is a pregnant woman [96].

The risk of infection through living or deceased donation should be assessed during a pre-donation evaluation and balanced against the risk of losing the opportunity of solid organ transplantation. Transplant clinicians have a key role in the risk–benefit analysis (this includes life-threatening emergencies) and in the decision whether to perform a transplant, even when part of the data on organ and donor characterisation might still be incomplete at the moment of the transplant decision; this might be the case if tests results on infectious diseases are not yet available, as organs cannot be preserved for a long time [97].

Information on the severity of Zika virus infection in immunosuppressed patients is limited to a small number of cases. No conclusions can be drawn about the effect of immunosuppression on the clinical course of Zika virus infection in solid organ transplant patients and the impact of Zika virus on allograft function [83].

3.3.1 Areas with and without active transmission

Solid organ transplantation is a life-saving procedure dependent on organ supply. Organ availability is the primary limiting factor affecting the number of transplant procedures that can be performed. Therefore, it is crucial to

proceed with the transplantation of organs in both areas with and without active transmission. An accurate and timely assessment of the infection risk, both for the solid organ transplant donor and the recipient, based on epidemiologic exposure and medical examination, could lower the risk of disease transmission. The risk of Zika virus infection should be balanced against the benefits of transplantation.

3.3.2 Living and post-mortem donation

Living donation

The risk of Zika virus transmission from a living donor should be assessed during a pre-donation evaluation and balanced against the benefits of the transplantation for each potential recipient. If indicated, donations from living donors at risk of Zika virus infection can be postponed for 28 days after possible exposure or cessation of Zika virus disease symptoms. In symptomatic donors, targeted NAT testing may be used to identify pathogens. Viraemic donors should not be used without prior consultation with a transplant infectious disease expert.

Post-mortem donation

Routine laboratory screening of deceased organ donors at risk for the presence of Zika virus infection is not recommended because there is not enough time for an exhaustive investigation, except for tests for which results are likely to be available within a few hours. NAT testing may be performed if a deceased donor was exposed to Zika virus. The results of the test should be communicated to the transplanting clinician so that a follow-up can be arranged if the test results were positive.

3.4 Post-donation information and biovigilance for organs, tissues, and cell

3.4.1 Donors

Living donors of organs, tissues and cells should be encouraged to inform the tissue establishment or procurement centre if they develop symptoms compatible with Zika virus infection within 28 days after donation. Upon this information, the centre should investigate the case. If a donor (living or deceased) is diagnosed with Zika virus infection after the transplantation of the donated material, the tissue establishment/procurement centre should report the incident to the relevant authority as a serious adverse event and provide information on the outcome. At the same time, the tissue establishment/procurement centre should inform the transplant centres that performed the transplantations about the incident. If tissues, cells or organs were supplied cross-border, information should be provided to all involved parties, i.e. from tissue establishment/procurement centre to the transplant centres.

3.4.2 Recipients

If a recipient of an organ is diagnosed with Zika virus infection, the transplant centre should investigate the incident and inform the tissue establishment/procurement centre. Findings of possible, probable or confirmed donor-derived infections should be reported to the relevant authority as serious adverse reactions and the national biovigilance system. If the donor-derived infection can be excluded, Zika virus infection of other origins in an organ recipient should also be reported to the relevant authority. The transplant centre should also initiate a clinical and laboratory follow-up for recipients of tissue, cells, or organs with a confirmed Zika virus infection. The presence of the virus in blood and urine should be checked weekly until negative results are obtained.

References

1. European Commission. West Nile virus and blood safety introduction to a preparedness plan in Europe Brussels: European Commission; 2012 [cited 2016]. Available from: http://ec.europa.eu/health/blood_tissues_organs/docs/wnv_preparedness_plan_2012.pdf.
2. European Centre for Disease Prevention and Control. Zika virus and safety of substances of human origin - A guide for preparedness activities in Europe. Stockholm: ECDC; 2016. Available from: https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/Zika-virus-safety-of-substances-of-human-origin.pdf.
3. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. Emerg Infect Dis. 2011 May;17(5):880-2.
4. Davidson A, Slavinski S, Komoto K, Rakeman J, Weiss D. Suspected female-to-male sexual transmission of Zika virus - New York City, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(28):716-7.
5. D'Ortenzio E, Matheron S, Yazdanpanah Y, de Lamballerie X, Hubert B, Piorkowski G, et al. Evidence of sexual transmission of Zika virus. N Engl J Med. 2016;374(22):2195-8.
6. Musso D, Gubler DJ. Zika Virus. Clin Microbiol Rev. 2016 Jul;29(3):487-524.
7. Barjas-Castro ML, Angerami RN, Cunha MS, Suzuki A, Nogueira JS, Rocco IM, et al. Probable transfusion-transmitted Zika virus in Brazil. Transfusion. 2016;56(7):1684-8.
8. Motta IJ, Spencer BR, Cordeiro da Silva SG, Arruda MB, Dobbin JA, Gonzaga YB, et al. Evidence for transmission of Zika virus by platelet transfusion. N Engl J Med. Epub 2016 Aug 17.
9. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika virus and birth defects - Reviewing the evidence for causality. N Engl J Med. 2016;374(20):1981-7.
10. Bearcroft WG. Zika virus infection experimentally induced in a human volunteer. Trans R Soc Trop Med Hyg. 1956 Sep;50(5):442-8.
11. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill [Internet]. 2014; 19(14). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20761.
12. Kutsuna S KY, Takasaki T, Moi ML, Kotaki A, Uemura H, Matono T, Fujiya Y, Mawatari M, Takeshita N, Hayakawa K, Kanagawa S, Ohmagari N. . Two cases of Zika fever imported from French Polynesia to Japan, December 2013 to January 2014. Euro Surveill [Internet]. 2014; 19(4):[pii=20683 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20683.
13. European Centre for Disease Prevention and Control. Factsheet for health professionals: Zika virus infection. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx.
14. Musso D, Rouault E, Teissier A, Lanteri MC, Zisou K, Broult J, et al. Molecular detection of Zika virus in blood and RNA load determination during the French Polynesian outbreak. J Med Virol. Epub 2016 Nov 14.
15. Aubry M, Teissier A, Huart M, Merceron S, Vanhomwegen J, Roche C, et al. Zika virus seroprevalence, French Polynesia, 2014-2015. Emerg Infect Dis. Epub 2017 Jan 13;23(4).
16. Gallian P, Cabie A, Richard P, Paturel L, Charrel RN, Pastorino B, et al. Zika virus in asymptomatic blood donors in Martinique. Blood. 2017;129(2):263-6.
17. Galel SA, Williamson PC, Busch MP, Stanek D, Bakkour S, Stone M, et al. First Zika-positive donations in the continental United States. Transfusion. 2017 Feb 05.
18. Williamson PC, Linnen JM, Kessler DA, Shaz BH, Kamel H, Vassallo RR, et al. First cases of Zika virus-infected US blood donors outside states with areas of active transmission. Transfusion. 2017 Feb 23.
19. Moulin E, Selby K, Cherpillod P, Kaiser L, Boillat-Blanco N. Simultaneous outbreaks of dengue, chikungunya and Zika virus infections: diagnosis challenge in a returning traveller with nonspecific febrile illness. New microbes and new infections. 2016 May;11:6-7.

20. Villamil-Gomez WE, Gonzalez-Camargo O, Rodriguez-Ayubi J, Zapata-Serpa D, Rodriguez-Morales AJ. Dengue, chikungunya and Zika co-infection in a patient from Colombia. Journal of infection and public health. 2016 Jan 2.

21. Centers for Disease Control and Prevention. Zika Virus — What Clinicians Need to Know [Internet]. Atlanta: CDC; 2016. Available from: http://emergency.cdc.gov/coca/calls/2016/callinfo_012616.asp.

22. Mallet H, Vial A, Musso D. Bilan de l'épidemie à virus Zika en Polynesie française, 2013-2014. BISES - Bulletin d'information sanitaires, épidémiologiques et statistiques [Internet]. 2015; 13. Available from: http://www.hygiene-publique.gov.pf/IMG/pdf/no13_-_mai_2015_-_zika.pdf.

23. Oehler E, Watrin L, Larre P, Leparc-Goffart I, Lastere S, Valour F, et al. Zika virus infection complicated by Guillain-Barre syndrome - case report, French Polynesia, December 2013. Euro Surveill [Internet]. 2014; 19(9):[pii=20720 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20720.

24. Cao-Lormeau V-M, Blake A, Mons S, Lastère S, Roche C, Vanhomwegen J, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. Lancet. 2016 (ePub: 29 February 2016).

25. World Health Organization. Zika situation report: Neurological syndrome and congenital anomalies, 5 February 2016 [Internet]. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204348/1/zikasitrep_5Feb2016_eng.pdf?ua=1.

26. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic. Eighth update, 30 August 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/01-08-2016-RRA-eighth-update-Zika%20virus-Americas,%20Caribbean,%20Oceania.pdf.

27. Wu KY, Zuo GL, Li XF, Ye Q, Deng YQ, Huang XY, et al. Vertical transmission of Zika virus targeting the radial glial cells affects cortex development of offspring mice. Cell Res. 2016 Jun;26(6):645-54.

28. European Centre for Disease Prevention and Control. Rapid risk assesment - Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome. Second update, 8 February 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-8-february-2016.pdf.

29. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic. Seventh update, 8 July 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/RRA-Zika-virus%20epidemic-seventh-update-final.pdf.

30. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic. Sixth update, 20 May 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika%20virus%20rapid%20risk%20assessment%2010-05-2016.pdf.

31. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic: potential association with microcephaly and Guillain-Barre syndrome. Fifth update, 11 April 2016. [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-11-april-2016.docx.pdf

32. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome. Fourth update, 9 March 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-9-march-2016.pdf.

33. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome. Third update, 23 February 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-23-february-2016.pdf.

34. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome. 10 December 2015 [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf.

35. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome. First update, 21 January 2016 [Internet]. Stockholm: ECDC; 2016. Available from:

http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-zika-virus-first-update-jan-2016.pdf.

36. National Institutes of Health, National Institute of Allergy and Infectious Diseases. Zika virus vaccine research [Internet]. NIH; 2016 [updated 2016 Aug 18]. Available from: https://www.niaid.nih.gov/topics/Zika/ResearchApproach/Pages/vaccineResearch.aspx.
37. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus infection outbreak, French Polynesia. 14 February 2014 [Internet]. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf.
38. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg. 1952 Sep;46(5):509-20.
39. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun 11;360(24):2536-43.
40. Faye O, Freire CC, Iamarino A, Faye O, de Oliveira JV, Diallo M, et al. Molecular Evolution of Zika Virus during Its Emergence in the 20(th) Century. PLoS Negl Trop Dis. 2014;8(1):e2636.
41. Zanluca C, de Melo VC, Mosimann AL, Dos Santos GI, Dos Santos CN, Luz K. First report of autochthonous transmission of Zika virus in Brazil. Mem Inst Oswaldo Cruz. 2015 Jun;110(4):569-72.
42. World Health Organization. WHO statement on the first meeting of the International Health Regulations (2005) Emergency Committee on Zika virus and observed increase in neurological disorders and neonatal malformations, 1 February 2016 [Internet]. Geneva: WHO; 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/1st-emergency-committee-zika/en/.
43. World Health Organization. WHO Statement on the Fifth meeting of the Emergency Committee under the International Health Regulations (2005) regarding microcephaly, other neurological disorders and Zika virus 2016 [cited 2016]. Available from: http://apps.who.int/ihr/eventinformation/announcement/34468-who-statement-fifth-meeting-emergency-committee-under-international-health.
44. European Centre for Disease Prevention and Control. Zika epidemics 2014 onwards [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/zika-outbreak.aspx.
45. European Centre for Disease Prevention and Control. Communicable Disease Threats Report (CDTR) [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/surveillance_reports/Communicable-Disease-Threats-Report/Pages/cdtr.aspx.
46. World Health Organization. Zika situation report: Zika virus, microcephaly, Guillain-Barré syndrome, 27 October 2016 [Internet]. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/250633/1/zikasitrep27Oct16-eng.pdf?ua=1.
47. World Health Organization. Zika situation report: Zika virus, microcephaly, Guillain-Barré syndrome, 10 March 2017 [Internet]. Geneva: WHO; 2017. Available from: http://apps.who.int/iris/bitstream/10665/254714/1/zikasitrep10Mar17-eng.pdf?ua=1.
48. European Centre for Disease Prevention and Control. Communicable disease threats report, 11-17 December 2016, week 50 2016 [cited 2016]. Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1616.
49. European Centre for Disease Prevention and Control. Rapid risk Assessment - Zika virus disease epidemic, Tenth update, 4 April 2017 2017. Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1671.
50. Gratz NG, Steffen R, Cocksedge W. Why aircraft disinsection? Bull World Health Organ. 2000;78(8):995-1004.
51. International Programme on Chemical Safety (IPCS), IOMC (Inter-Organization Programme for the sound Management of Chemicals). Aircraft disinsection insecticides. Geneva: WHO; 2013. Available from: http://www.who.int/ipcs/publications/ehc/ehc243.pdf?ua=1.
52. Reiter P. Yellow fever and dengue: a threat to Europe? Euro Surveill. 2010 Mar 11;15(10):19509.
53. Margarita Y GA, Lencastre I, Silva AC, Novo MT, Sousa CA. First record of Aedes (Stegomyia) aegypti (Linnaeus, 1762) (Diptera, Culicidae) in Madeira Island - Portugal,. Acta Parasitol Port 2006;13:59-61.

54. Yunicheva YU RT, Markovich NY, Bezzhonova OV, Ganushkina LA, Semenov VB, et al., . First data on the presence of breeding populations of the Aedes aegypti L. mosquito in Greater Sochi and various cities of Abkhazia. . Med Parazitol (Mosk). 2008;3:40-3.

55. Scholte E, Den Hartog W, Dik M, Schoelitsz B, Brooks M, Schaffner F, et al. Introduction and control of three invasive mosquito species in the Netherlands, July-October 2010. Euro Surveill. 2010;15(45).

56. European Centre for Disease Prevention and Control. Mosquito maps: Current known distribution as of July 2016 [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx.

57. Grard G, Caron M, Mombo IM, Nkoghe D, Mboui Ondo S, Jiolle D, et al. Zika virus in Gabon (Central Africa)--2007: a new threat from Aedes albopictus? PLoS Negl Trop Dis. 2014 Feb;8(2):e2681.

58. Wong PS, Li MZ, Chong CS, Ng LC, Tan CH. *Aedes (Stegomyia) albopictus* (Skuse): a potential vector of Zika virus in Singapore. PLoS Negl Trop Dis. 2013 Aug;7(8):e2348.

59. Chouin-Carneiro T, Vega-Rua A, Vazeille M, Yebakima A, Girod R, Goindin D, et al. Differential susceptibilities of Aedes aegypti and Aedes albopictus from the Americas to Zika Virus. PLoS Negl Trop Dis. 2016;10(3):e0004543.

60. Di Luca M, Severini F, Toma L, Boccolini D, Romi R, Remoli ME, et al. Experimental studies of susceptibility of Italian Aedes albopictus to Zika virus. Euro Surveill [Internet]. 2016; 21(18). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22468.

61. European Commission. DIRECTIVE 2002/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 January 2003, 2003 [cited 2016]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:033:0030:0040:EN:PDF.

62. Commission Directive 2004/33/EC of 22 March 2004 implementing Directive 2002/98/EC of the European Parliament and of the Council as regards certain technical requirements for blood and blood components. OJ [Internet]. 2004; L91/25. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:091:0025:0039:EN:PDF.

63. Commission E. COMMISSION DIRECTIVE 2006/17/EC of 8 February 2006, implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, 2006 [cited 2016]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:038:0040:0052:EN:PDF.

64. European Commission. DIRECTIVE 2010/45/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 7 July 2010 on standards of quality and safety of human organs intended for transplantation, 2010. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32010L0053&from=EN.

65. European Commission. Corrigendum to Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation 2010. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32010L0053R(01).

66. European Commission. COMMISSION IMPLEMENTING DIRECTIVE 2012/25/EU of 9 October 2012 laying down information procedures for the exchange, between Member States, of human organs intended for transplantation 2012 [cited 2016]. Available from: https://www.google.se/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=COMMISSION+IMPLEMENTING+DIRECTIVE+2012%2F25%2FEU+of+9+October+2012+laying+down+information+procedures+for+the+exchange%2C+between+Member+States%2C+of+human+organs+intended+for+transplantation.

67. European Centre for Disease Prevention and Control. Interim case definition for surveillance of Zika virus infection [internet]. ; 2016 [cited 7 Aug 2017]. Stockholm: : ECDC; 2016 [cited 2017 7 Aug 2017]. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/patient-case-management/Pages/case-definition.aspx. .

68. World Health Organization. Zika virus country classification scheme, Interim guidance [Internet]. Geneva: WHO; 2017 [cited 2017 Mar 10]. Available from: http://www.who.int/csr/resources/publications/zika/classification/en/.

69. Vasquez AM, Sapiano MR, Basavaraju SV, Kuehnert MJ, Rivera-Garcia B. Survey of blood collection centers and implementation of guidance for prevention of transfusion-transmitted Zika virus infection - Puerto Rico, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(14):375-8.

70. Chevalier MS, Biggerstaff BJ, Basavaraju SV, Ocfemia MC, Alsina JO, Climent-Peris C, et al. Use of Blood Donor Screening Data to Estimate Zika Virus Incidence, Puerto Rico, April-August 2016. Emerg Infect Dis. 2017 May 15;23(5).

71. Herriman R. Transfusion-associated Zika virus reported in Brazil. 18 December 2015 [Internet]. Outbreak News Today; 2015. Available from: http://outbreaknewstoday.com/transfusion-associated-zika-virus-reported-in-brazil-76935/.

72. Souto L. São Paulo registra segundo caso de transmissão de zika por transfusão. 3 February 2016 [Internet]. O Globo; 2016. Available from: http://oglobo.globo.com/brasil/sao-paulo-registra-segundo-caso-de-transmissao-de-zika-por-transfusao-18601427#ixzz3zBOmp9Nn

73. Kuehnert MJ, Basavaraju SV, Moseley RR, Pate LL, Galel SA, Williamson PC, et al. Screening of Blood Donations for Zika Virus Infection - Puerto Rico, April 3-June 11, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(24):627-8.

74. Coffey LL, Pesavento PA, Keesler RI, Singapuri A, Watanabe J, Watanabe R, et al. Zika Virus Tissue and Blood Compartmentalization in Acute Infection of Rhesus Macaques. PLoS One. 2017;12(1):e0171148.

75. Ministry of Health (New Zealand). Media release: Possible case of sexual transmission of Zika virus. 3 March 2016 [Internet]. Wellington: MoH (New Zealand); 2016. Available from: http://www.health.govt.nz/news-media/media-releases/possible-case-sexual-transmission-zika-virus.

76. Venturi G, Zammarchi L, Fortuna C, Remoli M, Benedetti E, Fiorentini C, et al. An autochthonous case of Zika due to possible sexual transmission, Florence, Italy, 2014. Euro Surveill [Internet]. 2016; 21(8):[pii=30148 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21395.

77. Gobierno de la Provincia de Cordoba (Argentina). Confirman primer caso autóctono de zika en Córdoba [Internet]. [Cordoba]: Gobierno de la Provincia de Cordoba; 2016. Available from: http://prensa.cba.gov.ar/salud/confirman-primer-caso-autoctono-de-zika-por-probable-contagio-por-via-sexual/.

78. France detects first sexually transmitted case of Zika virus [Internet]. [Paris]: France 24; 2016 [updated 2016 Feb 28]. Available from: http://www.france24.com/en/20160227-france-zika-first-sexually-transmitted-case.

79. Colt S, Garcia-Casal MN, Pena-Rosas JP, Finkelstein JL, Rayco-Solon P, Weise Prinzo Z, et al. Transmission of Zika virus through breast milk and other breastfeeding-related bodily-fluids: a systematic review. Bull World Healt Organ [Internet]. 2016. Available from: http://www.who.int/bulletin/online_first/16-176677.pdf.

80. Morrison TE, Diamond MS. Animal Models of Zika Virus Infection, Pathogenesis, and Immunity. J Virol. 2017 Feb 01.

81. Furtado JM, Esposito DL, Klein TM, Teixeira-Pinto T, da Fonseca BA. Uveitis Associated with Zika Virus Infection. N Engl J Med. 2016 Jun 22.

82. Heck E, Cavanagh HD, Robertson DM. Zika Virus RNA in an Asymptomatic Donor's Vitreous: Risk for Transmission? Am J Transplant. 2017 Apr 27.

83. Nogueira ML, Estofolete CF, Terzian AC, Mascarin do Vale EP, da Silva RC, da Silva RF, et al. Zika virus infection and solid organ transplantation: a new challenge. Am J Transplant. Epub 2016 Sep 15.

84. Machado CM, Pereira BBdS, Felix AC, Oliveira MC, Darrigo LG, de Souza MP, et al. Zika and chikungunya virus infections in hematopoietic stem cell transplant recipients and oncohematological patients. Blood Advances. 2017;1(10):624-7.

85. Bingham AM, Cone M, Mock V, Heberlein-Larson L, Stanek D, Blackmore C, et al. Comparison of test results for Zika virus RNA in urine, serum, and saliva specimens from person with travel-associated Zika virus disease - Florida, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(18).

86. Suy A, Sulleiro E, Rodo C, Vazquez E, Bocanegra C, Molina I, et al. Prolonged Zika Virus Viremia during pregnancy. N Engl J Med. 2016;375(26):2611-3.

87. Oliveira DB, Almeida FJ, Durigon EL, Mendes EA, Braconi CT, Marchetti I, et al. Prolonged shedding of Zika virus associated with congenital infection. N Engl J Med. 2016 Sep 22;375(12):1202-4.

88. Lessler J, Ott C, Carcelen A, Konikoff J, Williamson J, Bi Q, et al. Times to key events in the course of Zika infection and their implications: a systematic review and pooled analysis [Submitted]. Bull World Health Organ [Internet]. Epub 2016 Apr 1. Available from: http://www.who.int/bulletin/online_first/BLT.16.174540.pdf.

89. Lustig Y, Mendelson E, Paran N, Melamed S, Schwartz E. Detection of Zika virus RNA in whole blood of imported Zika virus disease cases up to 2 months after symptom onset, Israel, December 2015 to April 2016. Euro Surveill [Internet]. 2016; 21(26). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22515.

90. Murray KO, Gorchakov R, Carlson AR, Berry R, Lai L, Natrajan M, et al. Prolonged detection of Zika virus in vaginal secretions and whole blood. Emerg Infect Dis. Epub 2016 Oct 17;23(1).

91. Froeschl G, Huber K, von Sonnenburg F, Nothdurft HD, Bretzel G, Hoelscher M, et al. Long-term kinetics of Zika virus RNA and antibodies in body fluids of a vasectomized traveller returning from Martinique: a case report. BMC Infect Dis. 2017;17(1):55.

92. Lustig Y, Mannasse B, Koren R, Katz-Likvornik S, Hindiyeh M, Mandelboim M, et al. Superiority of West Nile Virus RNA Detection in Whole Blood for Diagnosis of Acute Infection. J Clin Microbiol. 2016 Sep;54(9):2294-7.

93. Lanteri MC, Lee TH, Wen L, Kaidarova Z, Bravo MD, Kiely NE, et al. West Nile virus nucleic acid persistence in whole blood months after clearance in plasma: implication for transfusion and transplantation safety. Transfusion. 2014 Dec;54(12):3232-41.

94. Klungthong C, Gibbons RV, Thaisomboonsuk B, Nisalak A, Kalayanarooj S, Thirawuth V, et al. Dengue virus detection using whole blood for reverse transcriptase PCR and virus isolation. J Clin Microbiol. 2007 Aug;45(8):2480-5.

95. Benjamin RJ. Zika virus in the blood supply. Blood. 2017 Jan 12;129(2):144-5.

96. Musso D, Stramer SL, Busch MP. Zika virus: a new challenge for blood transfusion. Lancet. 2016 May 14;387(10032):1993-4.

97. Lanteri MC, Kleinman SH, Glynn SA, Musso D, Keith Hoots W, Custer BS, et al. Zika virus: a new threat to the safety of the blood supply with worldwide impact and implications. Transfusion. 2016 Jul;56(7):1907-14.

98. Aubry M, Finke J, Teissier A, Roche C, Broult J, Paulous S, et al. Seroprevalence of arboviruses among blood donors in French Polynesia, 2011-2013. Int J Infect Dis. 2015 Oct 23;41:11-2.

99. Murphy MS, Shehata N, Colas JA, Chasse M, Fergusson DA, O'Brien SF, et al. Risk of exposure to blood products during pregnancy: guidance for Zika and other donor deferral policies. Transfusion. 2017 Feb 05.

100. Hills SL, Russell K, Hennessey M, Williams C, Oster AM, Fischer M, et al. Transmission of Zika virus through sexual contact with travelers to areas of ongoing transmission: continental United States, 2016. MMWR Morb Mortal Wkly Report. 2016;65(8):215-6.

101. Frank C, Cadar D, Schlaphof A, Neddersen N, Gunther S, Schmidt-Chanasit J, et al. Sexual transmission of Zika virus in Germany, April 2016. Euro Surveill [Internet]. 2016; 21(23). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22498.

102. Turmel JM, Abgueguen P, Hubert B, Vandamme YM, Maquart M, Le Guillou-Guillemette H, et al. Late sexual transmission of Zika virus related to persistence in the semen. Lancet. 2016;387(10037):2501.

103. Harrower J, Kiedrzynski T, Baker S, Upton A, Rahnama F, Sherwood J, et al. Sexual transmission of Zika virus and persistence in semen, New Zealand, 2016 [Letter]. Emerg Infect Dis. 2016;22(10).

104. Freour T, Mirallie S, Hubert B, Splingart C, Barriere P, Maquart M, et al. Sexual transmission of Zika virus in an entirely asymptomatic couple returning from a Zika epidemic area, France, April 2016. Euro Surveill [Internet]. 2016; 21(23). Available from: http://www.eurosurveillance.org/images/dynamic/EE/V21N23/art22500.pdf.

105. Brooks R, Carlos M, Myers R, White M, Bobo-Lenoci T, Aplan D, et al. Likely sexual transmission of Zika virus from a man with no symptoms of infection — Maryland, 2016. MMWR Morb Mortal Wkly Rep. 2016;Early Release

106. Barzon L, Pacenti M, Franchin E, Lavezzo E, Trevisan M, Sgarabotto D, et al. Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016. Euro Surveill [Internet]. 2016; 21(32). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22556.

107. Nicastri E, Castilletti C, Liuzzi G, Iannetta M, Capobianchi M, Ippolito G. Persistent detection of Zika virus RNA in semen for six months after symptom onset in a traveller returning from Haiti to Italy, February 2016. Euro Surveill [Internet]. 2016; 21(32). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22554.

108. Arsuaga M, Bujalance SG, Diaz-Menendez M, Vazquez A, Arribas JR. Probable sexual transmission of Zika virus from a vasectomised man. Lancet Infect Dis. 2016 Oct;16(10):1107.

109. Mansuy JM, Suberbielle E, Chapuy-Regaud S, Mengelle C, Bujan L, Marchou B, et al. Zika virus in semen and spermatozoa. Lancet Infect Dis. 2016 Oct;16(10):1106-7.

110. Prisant N, Breurec S, Moriniere C, Bujan L, Joguet G. Zika virus genital tract shedding in infected women of child-bearing age. Clin Infect Dis. Epub 2016 Sep 28.

111. Nicastri E, Castilletti C, Balestra P, Galgani S, Ippolito G. Zika Virus Infection in the Central Nervous System and Female Genital Tract. Emerg Infect Dis. 2016;22(12).

112. Penot P, Brichler S, Guilleminot J, Lascoux-Combe C, Taulera O, Gordien E, et al. Infectious Zika virus in vaginal secretions from an HIV-infected woman, France, August 2016. Euro Surveill. 2017;22(3):pii=30444.

113. Paz-Bailey G, Rosenberg ES, Doyle K, Munoz-Jordan J, Santiago GA, Klein L, et al. Persistence of Zika Virus in Body Fluids - Preliminary Report. N Engl J Med. 2017 Feb 14.

114. World Health Organization. Prevention of sexual transmission of Zika virus - Interim guidance update, 6 September 2016 [Internet]. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204421/1/WHO_ZIKV_MOC_16.1_eng.pdf?ua=1.

115. Petersen E, Staples J, Meaney-Delman D, Fischer M, Ellington S, Callaghan W, et al. Interim guidelines for pregnant women during a Zika virus outbreak — United States, 2016. MMWR Morb Mortal Wkly Rep. 2016;65(2):30-3.

116. Australian Red Cross Blood Services. Rapid Risk Assessment:Zika virus risk assessment of donors who have sexual contact with someone who has recently returned from an area with active on-going transmission of Zika virus 2016.

117. Janssen MP. The risk of sexually transmitted Zika infection among Dutch blood donors [Internet]. Sanquin; 2016. Available from: http://www.sanquin.nl/repository/documenten/nl/413511/Mart_P._Janssen_-_The_risk_of_sexually_acquired_Zika_infection_among_Dutch_blood_donors.pdf.

118. Pillonel J, Paty MC, Septfons A, De Valk H. Assessing the risk of blood donations in metropolitan France being infected with the Zika virus after sexual contamination, linked to travelers returning from an area affected by this virus (South America, Central America and the Caribbean). 2016 [cited 2016]. Available from: http://www.invs.sante.fr/Dossiers-thematiques/Maladies-infectieuses/Maladies-a-transmission-vectorielle/Zika/Publications.

119. Barzon L, Pacenti M, Berto A, Sinigaglia A, Franchin E, Lavezzo E, et al. Isolation of infectious Zika virus from saliva and prolonged viral RNA shedding in a traveller returning from the Dominican Republic to Italy, January 2016. Euro Surveill [Internet]. 2016; 21(10). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21409.

120. Bonaldo MC, Ribeiro IP, Lima NS, Santos AAC, Menezes LSR, Cruz SOD, et al. Isolation of infective Zika virus from urine and saliva of patients in Brazil. bioRxiv [Internet]. 2016. Available from: http://biorxiv.org/content/early/2016/03/24/045443.

121. Bierlaire D, Mauguin S, Broult J, Musso D. Zika virus and blood transfusion: the experience of French Polynesia. Transfusion. 2017 Feb 10.

122. Liumbruno GM, Calteri D, Petropulacos K, Mattivi A, Po C, Macini P, et al. The Chikungunya epidemic in Italy and its repercussion on the blood system. Blood Transfus. 2008 Oct;6(4):199-210.

123. Rasongles P, Angelini-Tibert MF, Simon P, Currie C, Isola H, Kientz D, et al. Transfusion of platelet components prepared with photochemical pathogen inactivation treatment during a Chikungunya virus epidemic in Ile de La Reunion. Transfusion. 2009 Jun;49(6):1083-91.

124. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. Emerg Infect Dis. 2008 Aug;14(8):1232-9.

125. Gourinat AC, O'Connor O, Calvez E, Goarant C, Dupont-Rouzeyrol M. Detection of Zika virus in urine. Emerg Infect Dis. 2015 Jan;21(1):84-6.

126. World Health Organization. Guide to cost-effectiveness analysis 2002. Available from: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf.

127. Custer B, Janssen MP. Health economics and outcomes methods in risk-based decision-making for blood safety. Transfusion. 2015 Aug;55(8):2039-47.

128. Bellini R, Calzolari M, Mattivi A, Tamba M, Angelini P, Bonilauri P, et al. The experience of West Nile virus integrated surveillance system in the Emilia-Romagna region: five years of implementation, Italy, 2009 to 2013. Euro Surveill. 2014;19(44).

129. Babo Martins S, Rushton J, Stark KD. Economic Assessment of Zoonoses Surveillance in a 'One Health' Context: A Conceptual Framework. Zoonoses and public health. 2015 Nov 26.

130. Directive 2000/54/EC of the European Parliament and of the Council of 18 September 2000 on the protection of workers from risks related to exposure to biological agents at work (seventh individual directive within the meaning of Article 16(1) of Directive 89/391/EEC). OJ [Internet]. 2000; L262/21. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000L0054&from=EN.

131. Wittek R, Link J. Classification of organisms - Viruses. Environment in practice [Internet]. Berne: Swiss Agency for the Environment, Forests and Landscape; 2005. Available from: http://www2.unil.ch/facs/downloads/Viruses(engl.).pdf.

132. Advisory Committee on Dangerous Pathogens. The approved list of biological agents. 3rd edition [Internet]. Merseyside: Health and Safety Executive (United Kingdom); 2013. Available from: http://www.hse.gov.uk/pubns/misc208.pdf.

133. Altona diagnostics. RealStar® Zika Virus RT-PCR Kit [Internet]. 2016. Available from: http://www.altona-diagnostics.com/realstar-zika-virus-rt-pcr-kit-354.html.

134. U.S. Department of Health and Human Services - Food and Drug Administration. Zika Virus EUA Information. 2017.

135. U.S. Food and Drug Administration. Emergency use authorizations: Zika virus emergency use authorization [Internet]. Silver Spring, MD: U.S. FDA; 2016. Available from: http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika.

136. World Health Organization. Emergency use assessment and listing (EUAL) procedure for Zika virus disease IVDs [Internet]. Geneva: WHO; 2016. Available from: http://www.who.int/diagnostics_laboratory/eual-zika-virus/zika/en/.

137. European Virus Archive. Zika virus diagnostic. [Internet]. 2016. Available from: http://www.european-virus-archive.com/evag-news/zika-virus-diagnostics.

138. Gallian P, de Lamballerie X, Salez N, Piorkowski G, Richard P, Paturel L, et al. Prospective detection of chikungunya virus in blood donors, Caribbean 2014. Blood. 2014 Jun 5;123(23):3679-81.

139. U.S. Food and Drug Administration. News release: FDA allows use of investigational test to screen blood donations for Zika virus, 30 March 2016 [Internet]. Silver Spring, MD: U.S. FDA; 2016. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm493081.htm.

140. Stone M, Lanteri MC, Bakkour S, Deng X, Galel SA, Linnen JM, et al. Relative analytical sensitivity of donor nucleic acid amplification technology screening and diagnostic real-time polymerase chain reaction assays for detection of Zika virus RNA. Transfusion. 2017 Feb 14.

141. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Revised recommendations for reducing the risk of Zika virus transmission by blood and blood components [Internet]. Silver Spring, MD: U.S. FDA; 2016. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM518213.pdf.

142. Jupille H, Seixas G, Mousson L, Sousa CA, Failloux AB. Zika virus, a new threat for Europe? PLoS Negl Trop Dis [Internet]. Epub 2016 Aug 9. Available from: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004901.

143. Ryckebusch F, Matondo M, Misse D, Choumet V. Infection of Aedes albopictus and Aedes aegypti with Zika virus: perspectives for an emergence in Europe. 2016. In: International Zika Summit 2016; 25-26 April 2016 [Internet]. Paris: Institute Pasteur. Available from: http://www.zikasummit2016.org/images/Public/Zika-Abstracts.pdf.

144. World Health Organization. Zika virus technical report: interim risk assessment WHO European Region. May 2016 [Internet]. Geneva: WHO; 2016. Available from: http://www.euro.who.int/__data/assets/pdf_file/0003/309981/Zika-Virus-Technical-report.pdf?ua=1.

145. Biesert L, Suhartono H. Solvent/detergent treatment of human plasma - a very robust method for virus inactivation. Validated virus safety of OCTAPLAS. Vox Sang. 1998;74 Suppl 1:207-12.

146. Seghatchian J, Struff WG, Reichenberg S. Main Properties of the THERAFLEX MB-Plasma System for Pathogen Reduction. Transfus Med Hemother. 2011;38(1):55-64.

147. Irsch J, Seghatchian J. Update on pathogen inactivation treatment of plasma, with the INTERCEPT Blood System: Current position on methodological, clinical and regulatory aspects. Transfus Apher Sci. 2015 Apr;52(2):240-4.

148. Marschner S, Goodrich R. Pathogen Reduction Technology Treatment of Platelets, Plasma and Whole Blood Using Riboflavin and UV Light. Transfus Med Hemother. 2011;38(1):8-18.

149. Faddy HM, Fryk JJ, Prow NA, Watterson D, Young PR, Hall RA, et al. Inactivation of dengue, chikungunya, and Ross River viruses in platelet concentrates after treatment with ultraviolet C light. Transfusion. 2016 Mar 1.

150. Mohr H, Knuver-Hopf J, Gravemann U, Redecker-Klein A, Muller TH. West Nile virus in plasma is highly sensitive to methylene blue-light treatment. Transfusion. 2004 Jun;44(6):886-90.

151. Aubry M, Richard V, Green J, Broult J, Musso D. Inactivation of Zika virus in plasma with amotosalen and ultraviolet A illumination. Transfusion. 2016;56(1):33-40.

152. Santa Maria F, Laughhunn A, Lanteri MC, Aubry M, Musso D, Stassinopoulos A. Inactivation of Zika virus in platelet components using amotosalen and ultraviolet A illumination. Transfusion. 2017 Jul 03.

153. Laughhunn A, Santa Maria F, Broult J, Lanteri MC, Stassinopoulos A, Musso D, et al. Amustaline (S-303) treatment inactivates high levels of Zika virus in red blood cell components. Transfusion. 2017 Feb 05.

154. Lambert BJ, Mendelson TA, Craven MD. Radiation and ethylene oxide terminal sterilization experiences with drug eluting stent products. AAPS PharmSciTech. 2011 Dec;12(4):1116-26.

155. Grieb TA, Forng RY, Stafford RE, Lin J, Almeida J, Bogdansky S, et al. Effective use of optimized, high-dose (50 kGy) gamma irradiation for pathogen inactivation of human bone allografts. Biomaterials. 2005 May;26(14):2033-42.

156. Germain M, Strong DM, Dowling G, Mohr J, Duong A, Garibaldi A, et al. Disinfection of human cardiac valve allografts in tissue banking: systematic review report. Cell and tissue banking. 2016 Dec;17(4):593-601.

157. Pfaender S, Vielle NJ, Ebert N, Steinmann E, Alves MP, Thiel V. Inactivation of Zika virus in human breast milk by prolonged storage or pasteurization. Virus Res. 2017 Jan 15;228:58-60.

158. Kuehnert MJ, Epstein JS. Assuring blood safety and availability: Zika virus, the latest emerging infectious disease battlefront. Transfusion. 2016 Jul;56(7):1669-72.

159. European Blood Alliance [Internal report]. Report on blood safety measures and donor testing capacity for Zika virus. 2016 Dec 29.

160. Musso D, Baud D, Freedman DO. Should testing of donors be restricted to active Zika virus areas? Lancet Infect Dis.16(10):1108-9.

161. World Health Organization. Maintaining a Safe and Adequate Blood Supply during Pandemic Influenza. Guidelines for Blood Transfusion Services. [Internet]. 2011. Available from: http://www.who.int/bloodsafety/publications/WHO_Guidelines_on_Pandemic_Influenza_and_Blood_Supply.pdf.

162. European Medicines Agency. Zika virus infection: plasma- and urine-derived medicines safe to use [Press release]. 2016 Sep 21. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/09/news_detail_002606.jsp&mid=WC0b01ac058004d5c1.

163. European Medicines Agency. BWP Report on viral safety of plasma-derived and urine-derived medicinal products with respect to Zika virus. 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/09/WC500213035.pdf.

164. Kuhnel D, Muller S, Pichotta A, Radomski KU, Volk A, Schmidt T. Inactivation of Zika virus by solvent/detergent treatment of human plasma and other plasma-derived products and pasteurization of human serum albumin. Transfusion. Epub 2016 Dec 26.

165. Farcet MR, Kreil TR. Zika virus is not thermostable: very effective virus inactivation during heat treatment (pasteurization) of human serum albumin. Transfusion. Epub 2016 Dec 17.

166. Blumel J, Musso D, Teitz S, Miyabayashi T, Boller K, Schnierle BS, et al. Inactivation and removal of Zika virus during manufacture of plasma-derived medicinal products. Transfusion. 2016 Oct 12.

European Centre for Disease Prevention and Control (ECDC)

Postal address:
Granits väg 8, SE-171 65 Solna, Sweden

Visiting address:
Tomtebodavägen 11A, SE-171 65 Solna, Sweden

Tel. +46 858601000
Fax +46 858601001
www.ecdc.europa.eu

An agency of the European Union
www.europa.eu

Subscribe to our monthly email
www.ecdc.europa.eu/en/publications

Contact us
publications@ecdc.europa.eu

Follow us on Twitter
@ECDC_EU

Like our Facebook page
www.facebook.com/ECDC.EU

ECDC is committed to ensuring the transparency and independence of its work

In accordance with the Staff Regulations for Officials and Conditions of Employment of Other Servants of the European Union and the ECDC Independence Policy, ECDC staff members shall not, in the performance of their duties, deal with a matter in which, directly or indirectly, they have any personal interest such as to impair their independence. Declarations of interest must be received from any prospective contractor(s) before any contract can be awarded.
www.ecdc.europa.eu/en/aboutus/transparency

HOW TO OBTAIN EU PUBLICATIONS

Free publications:

- one copy:
  via EU Bookshop (http://bookshop.europa.eu);
- more than one copy or posters/maps:
  from the European Union's representations (http://ec.europa.eu/represent_en.htm);
  from the delegations in non-EU countries (http://eeas.europa.eu/delegations/index_en.htm);
  by contacting the Europe Direct service (http://europa.eu/europedirect/index_en.htm) or
  calling 00 800 6 7 8 9 10 11 (freephone number from anywhere in the EU) (*).

  (*) The information given is free, as are most calls (though some operators, phone boxes or hotels may charge you).

Priced publications:

- via EU Bookshop (http://bookshop.europa.eu).

Publications Office