SCIENTIFIC ADVICE

Zika virus and safety of substances of human origin

A guide for preparedness activities in Europe

www.ecdc.europa.eu

ECDC SCIENTIFIC ADVICE

Zika virus and safety of substances of human origin

A guide for preparedness activities in Europe

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

Kari Aranko (European Blood Alliance), Alina Mirella Dobrota (Regional Blood Transfusion Center, Romania), Dragoslav Domanovic (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), Hélène Le Borgne (Directorate-General for Health and Food Safety – European Commission), Giancarlo Liumbruno (National Blood Centre, Italy), Sophie Lucas-Samuel (Agence Biomedicine, France) , 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)

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. Stockholm: ECDC; 2016.

Stockholm, July 2016

ISBN 978-92-9193-898-8

doi 10.2900/518807

Catalogue number TQ-04-16-615-EN-N

Contents

Abbreviations

BE	Blood establishments
BM	Bone marrow
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
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
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)
WHO	World Health Organization

Introduction

The objective of this ECDC document is to support the operational preparation and implementation of national preparedness plans for the safety of substances of human origin (SoHO)[1] during outbreaks of Zika virus infection, in both affected and non-affected areas.

This document includes key elements for consideration 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 guidance is to offer Member States and 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. The possibility of autochthonous transmission of Zika virus in Europe may pose a threat to the safety of the SoHO supply because asymptomatic infected residents of areas with local transmission, as well as travellers returning from affected areas, may donate SoHO infected with Zika virus. 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 this guide for preparedness activities for Zika virus outbreaks in the EU. Additional input on the draft guide from SoHO NCAs was also considered[2].

This document is based on previous preparedness plans for Europe, such as for West Nile Virus and blood safety [1]. This guide elaborates the currently available knowledge on Zika virus infection in humans and will be reviewed and updated as new relevant information becomes available.

[1] 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.

[2] A draft of this guide was presented to the competent authorities on substances of human origin expert group, at the meeting for competent authorities on blood and blood components on 26–27 May 2016, and at the meeting of competent authorities for tissues and cells on 6 and 7 June 2016. The competent authorities for organs were consulted on 17 June 2016.

Background

Disease background information

Zika virus disease is caused by an RNA virus (*Flavivirus* genus, Flaviviridae family) transmitted to humans by *Aedes* mosquitoes, in particular by the *Aedes aegypti* species. The virus can also be transmitted by sexual contact with an infected male and potentially via transfusion or transplantation of SoHO donated by infected donors. To date, no case of Zika virus that has clearly been attributed to transmission via SoHO has been reported.

Foy et al. reported the first case of sexually transmitted Zika virus, from a male infected with the virus in Senegal in 2008 to his wife [2]. During the current Zika outbreak in Americas, several cases of confirmed Zika virus transmission by sexual contact with an infected male have been reported. This also includes cases outside the Americas.

Zika virus infection is asymptomatic in 80% of cases [3]. 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 dengue and chikungunya, although there are several clinical features typical for Zika infection only [4-6].

Zika virus infection was linked to Guillain–Barré syndrome (GBS) for the first time in 2014 during an outbreak in French Polynesia [7]. Although most people with GBS indicate a bacterial or viral infection before they have GBS symptoms, a case-control study in French Polynesia and recent observations support the role of Zika virus infection as a presumptive disease preceding Guillain–Barré syndrome [8].

During the outbreak in Brazil, the higher frequency of congenital malformations after Zika virus infection in pregnant women was recognised and an association was postulated [9,10]. Congenital microcephaly, central nervous system malformations and other foetal malformations potentially associated with Zika virus infection during pregnancy have been reported in several countries or territories [11]. It is probable that the risk of transplacental infection and developing congenital central nervous system malformations depends on the gestational age at the time of infection and other factors. Results from ongoing and further case–control and cohort studies are still required to estimate more accurately the risk of microcephaly and other congenital CNS malformations linked with Zika virus infection. Based on a growing body of research, there is a scientific consensus that Zika virus is a cause of microcephaly and GBS. Several recent publications based on animal models support an in vivo deleterious effect of Zika virus on neural progenitor cells, leading to the reduction of their proliferation and differentiation, and increased apoptosis [12].

To date, there is no vaccine to prevent Zika virus infections nor is any specific antiviral treatment available.

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 [11,13-19] and the ECDC factsheet for health professionals [3]. Up to now, no latency of Zika virus has been observed.

Epidemiological situation

Zika virus was discovered in 1947 in Uganda. 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, as the virus moved from south-east Asia across the Pacific.

During an outbreak in French Polynesia in 2013–14, Zika infection was linked to the neurological disorder GBS. In May 2015, the first reports of locally transmitted infection in South America came from Brazil. In July 2015, Brazil reported an association between Zika virus infection and GBS. In October 2015, Brazil reported an association between Zika virus infection and microcephaly. 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. In the same month, WHO declared that the recent 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 [20].

On 15 June 2016, WHO reported 60 countries and territories with continuing mosquito-borne transmission. Of these, 52 countries and territories have reported autochthonous cases of Zika virus infection during the past nine months. Ten countries have reported evidence of person-to-person transmission of Zika virus, probably via a sexual route. Several countries in the Americas, the Caribbean and the Pacific continue to report autochthonous cases of Zika virus infection.

ECDC collects data regarding imported cases through official government communication lines and media reports. As of 17 June 2016, ECDC has recorded 838 imported cases in 20 EU/EEA countries. The number of imported cases is not based on a systematic reporting surveillance system and cannot be considered comprehensive.

As of 16 June 2016, several of the EU's Outermost Regions and Territories continue to report autochthonous transmission:

- As of 15 June 2016, microcephaly and other central nervous system (CNS) malformations associated with Zika virus infection or suggestive of congenital infection have been reported by twelve countries or territories worldwide. In the EU, Spain (2) and Slovenia (1) reported congenital malformations associated with Zika virus infection after travel in the affected area.
- Thirteen countries and territories worldwide reported an increased incidence of GBS and/or laboratory confirmation of a Zika virus infection among GBS cases.
- Brazil reported 7 936 suspected cases of microcephaly and other nervous system disorders suggestive of congenital infection between October 2015 and 11 June 2016; 1 581 were microcephaly-confirmed cases, 226 of which were laboratory confirmed for Zika virus infection.

For up-to-date information on the epidemiological situation, please refer to: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/epidemiological-situation.aspx#sthash.vVgs8Bbi.dpuf

Several factors might facilitate the spread of Zika virus infection from affected countries to the continental EU: an immunologically naïve population, an infection that is asymptomatic in 80% of cases, the presence of a competent vector, increasingly permissive climate conditions in some Member States, and highly mobile populations.

The importation of the virus is most likely via infected travellers returning from affected countries. Cases of Zika virus infection coming from countries with autochthonous transmission continue to be reported in the EU. However, there is no evidence of airplane transportation of Zika-infected mosquitoes similar to airport malaria to date [21]. The risk of importation of Zika-infected mosquitoes or the transmission of arbovirus infections inside aircraft cabins is low. WHO has issued specific guidance and recommendations for aircraft disinfection [20,22].

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 [23]. It has since re-colonised Madeira [24] and parts of southern Russia and Georgia [25] and has been recently imported but not established in the Netherlands [26]. The presence of the potential mosquito vector *Aedes albopictus* is established in most places around the Mediterranean coast [27]. However, the capacity of this species to transmit Zika virus has not yet been determined for European mosquito populations [28,29]. A recent study shows a low vector competence of both *Ae. albopictus* and *Ae. aegypti* for Zika virus [30]. Moreover, *Ae. albopictus* had a lower competence than *Ae. aegypti* when tested in parallel in Italy [31]. This may suggest that other factors such as the large naïve human population for Zika virus infection and the high density of human-biting mosquitoes may contribute to the observed rapid spread of Zika virus infection during the current outbreak in South America.

The risk of autochthonous transmission of Zika virus infection is extremely low in the EU during the winter season as the climatic conditions are not suitable for the activity of the *Ae. albopictus*. Nevertheless, during the summer season, autochthonous transmission in the EU following the introduction of the virus by a viraemic traveller is possible in areas where *Ae. albopictus* is established [27]. For the months July, August and September 2016, the International Research Institute for Climate and Society predicted above-normal temperatures in Europe, coinciding with a normal precipitation pattern, which might have an impact on the mosquito activity in southern Europe [32].

EU legislation

Blood and blood components

EU Directive 2002/98/EC sets the standards of quality and safety for the collection, testing, processing, storage, and distribution of human blood and blood components [33].

EU Member States should adhere to Annex III of EU Directive 2004/33/EC [34], which establishes the eligibility criteria for donors of whole blood and blood components, including deferral criteria. In the case of a Zika outbreak in the EU/EEA, the Member States should apply EU Directive 2004/33/EC. Section 2.2.1 of Annex III foresees a general deferral of at least two weeks after full clinical recovery from an infectious disease. Also, Section 2.3 of Annex III of the Directive stipulates that each Member State should develop deferral criteria after the identification of particular epidemiological situations such as disease outbreaks. Criteria need to be notified by the competent authority to the European Commission with a view to Community action. This provision can be applied to other infectious diseases not specified in the Directive, which may require a deferral period longer than two weeks.

EU Directive 2004/33/EC also specifies that some of the tests and deferrals are not required when donation is used exclusively for plasma for fractionation, providing that producers can document that the applied fractionation process effectively removes or inactivates the pathogen.

Tissues and cells

Selection criteria for donors are based on an analysis of the risks related to the application of the specific cells/tissues. Indicators of these risks must be identified by physical examination, review of the medical, behavioural and travel history, biological testing, post-mortem examination (for deceased donors) and other appropriate investigation methods. Unless donation can be justified by a documented risk assessment approved by the responsible person as defined in Article 17 of EU Directive 2004/23/EC, donors must be excluded from donation if they meet the selection criteria in Directive 2006/17/EC (Annexes I and II) for donors of cells and tissues, and for donors of reproductive cells (Annex III) [35].

Organs

Directive 2010/53/EU lays down standards of quality and safety for human organs intended for transplantation. According to Article 7, Member States shall ensure that all procured organs and donors thereof are characterised before transplantation through the collection of the information as explained in the Annex. In addition, this article highlights the key role of the medical team in the risk–benefit analysis (which also covers life-threatening emergencies) and in the decision process on whether to perform a transplant, even if part of the data on organ and donor characterisation are still missing at the moment of the decision, for example if testing for the presence of pathogen has not been concluded. The Annex of this Directive outlines the dataset which has to be collected for the organ and donor characterisation, which also includes information on the history of communicable diseases for every donor [36,37].

In addition, Commission Implementing Directive 2012/25/EU lays down information procedures for the exchange of human organs intended for transplantation in EU Member States: it sets out exchange procedures for organs, provides details on the information flow for organ and donor characterisation, ensures the traceability of organs, and describes how to report serious adverse events and reactions [29]. A website, established with the support of Eurotransplant, provides a list of authorities appointed as contact points by each Member States for cross-border organ exchange[3].

[3] http://txcontactlist.eu

1 Key elements of a preparedness plan

Member States need to adopt a set of appropriate measures in the national preparedness plans for a rapid response to a Zika virus outbreak. These plans, if considered necessary, should be re-evaluated and updated annually.

In the national preparedness plans, all steps necessary to implement SoHO safety measures should be taken by the relevant entities, i.e. NCA for SoHO, ESoHO (blood or tissue and cell establishments, organ procurement and transplant centres) or by other stakeholders responsible for the safety and quality of SoHO. Moreover, some of the activities could also be performed and supported at the EU level to strengthen cooperation and ensure a coordinated response.

Addressing an epidemic of Zika virus disease requires a broad multidisciplinary approach and should include public health, animal health and entomological expertise and collaboration with NCA for SoHO, ESoHO and the related vigilance services. This multidisciplinary approach allows for continuous risk assessments at national and European levels to facilitate appropriate and timely decision-making in several health fields, including transfusion and transplantation medicine. Please note that this document does not cover possible activities outside the SoHO field.

To develop a national preparedness plan, the following key elements need to be considered:

- Affected areas
- Risk assessment
- Safety measures
- SoHO supply
- Communication among all parties

For each of these elements, activities can be undertaken at the EU, national and local levels. Recommended activities at each level are defined in order to facilitate the response to the threat posed by Zika virus to the safety of SoHO. Proposed activities at the national and local levels are discretionary and include a range of options that 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 Member States (Table 1).

1.1 Activities at the EU level

At the EU level, the European Commission and ECDC support the preparation and implementation of national preparedness plans for Zika virus outbreaks – as demonstrated by this guide. The envisaged activities have the aim of assisting the Member States in their decision-making on how to assess and manage the risks posed by Zika virus to the safety of SoHO. In general, the European Commission facilitates cooperation and communication between NCA in response to a possible Zika outbreak while ECDC provides epidemiological surveillance and scientific advice on the risk and prevention of Zika virus transmission through SoHO.

The foreseen activities for European Commission and ECDC are to:

- perform continuous surveillance and assessment of the epidemiological situation, both for autochthonous Zika virus cases and imported cases;
- ensure updated publicly available maps/lists of the distribution of relevant vectors and of affected areas and countries;
- provide guidance for defining affected areas;
- provide up-to-date rapid risk assessments in respect of the current Zika virus outbreak;
- provide access to, and guidance on, risk assessment tools;
- provide and update options for the mitigation of risks posed by Zika virus to the safety of SoHO;
- provide guidance/tools for assessing the cost-efficiency of possible national measures;
- provide updated information on test kits and protocols that can be considered in national preparedness plans;
- provide contact details for NCA to organise possible cross-border communication;
- share national experiences to ensure the safe supply of SoHO in affected areas, e.g. stopping local collection and the transfer of SoHO collected in non-affected areas;
- identify – with the support of the European Blood Alliance – the Zika screening-capacity and capability of ESoHO in EU Member States in order to provide assistance to affected Member States that lack the capacity to independently screen SoHO donors;
- manage rapid alert platforms (RAB for blood, RATC for tissues and cells, and alerts related to organs);

- ensure communication with other authorities at the EU level, including surveillance authorities (e.g. epidemiological services, and, if relevant, animal health services, entomological services, experts, researchers), authorities responsible for other SoHO, and authorities in charge of pharmaceuticals.

1.2 Activities of the National Competent Authorities

NCAs for SoHO in the fields of blood and blood components, tissues and cells, organ donation and transplantation should cooperate with ESoHO experts to develop and implement SoHO safety measures.

Expected activities for NCAs are to:

- monitor the maps/lists of the distribution of relevant vectors and of Zika-virus-affected areas and countries;
- define the geographical areas where safety measures need to be considered;
- ensure the preparation of a national/regional risk assessment of Zika virus transmission with respect to various SoHO types; if necessary, this should cover affected and non-affected areas (modelling tools such as EUFRAT for blood transfusion may be used for quantitative risk assessments);
- define appropriate SoHO safety measures in the national preparedness plan;
- declare the start and the end date of SoHO safety measures;
- evaluate ESoHO feedback on applied measures;
- analyse the safety impact and cost-effectiveness of measures;
- evaluate the impact of implemented measures on SoHO supply, taking account of the inputs by ESoHO;
- prepare and coordinate with ESoHO measures to ensure a sufficient and sustainable SoHO supply in different areas;
- develop or cooperate in developing information leaflets for donors, clinicians and patients (involvement depends on the situation in the particular Member State);
- communicate changes in existing national/local guidelines to ESoHO;
- regularly inform the ministry of health about the implemented measures and communicate with other authorities at the national level, including public health authorities, veterinary institutions, drug safety authorities, and scientific bodies;
- communicate relevant RAB, RATC and organ alerts to ESoHO, as necessary;
- inform NCAs in other EU Member States through the Rapid Alert Platforms RAB and RATC on the local situation and any implemented measures;
- assess the effectiveness of communication channels and adjust as needed.

1.3 Activities of establishments for SoHO

In collaboration with NCA for SoHO, the respective ESoHO (blood and tissue establishments, organ procurement and transplant centres) should ensure the application of SoHO safety measures.

Foreseen activities of EsoHO are to:

- provide information and cooperate with NCA in monitoring the maps/lists of the distribution of relevant vectors and of Zika-virus-affected areas and countries, and use maps/lists in the donor selection procedure;
- cooperate with NCA in assessing and reassessing the risk;
- apply SoHO safety measures: verify national guidelines on safety measures; implement necessary changes in the protocols for donor information, selection, laboratory screening, processing and vigilance systems in line with national guidelines;
- monitor and manage the use of SoHO in order to maintain the sustainability and sufficiency of SoHO supply in affected and non-affected areas;
- develop or cooperate in developing information leaflets for donors, clinicians and patients, and disseminate the materials (involvement depends on the situation in the particular Member State);
- monitor new information from EU rapid alert platforms RAB and RATC, as submitted by NCA, and share the information as appropriate;
- inform the responsible NCA on the impact of measures taken on the SoHO supply.

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

	Commission/ECDC	NCA for SoHO	Establishments for SoHO
1. Affected areas	• 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 the maps/lists of relevant vector distribution, affected areas and countries in donor selection process
2. Risk assessment	• Rapid risk assessment for Zika virus outbreak, • Risk assessment of Zika virus transmission via SoHO. • Guidance on the use of risk assessment tools	• Ensure that a national/regional risk assessment of Zika virus transmission via particular SoHO** type is prepared	• 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 can 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 • Develop, 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 affected areas • 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	• Manage the 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 the 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

** Involvement of EsoHO and NCAs in the organising and creating of information (leaflets) for donors, clinicians and patients depends on the situation in the particular Member State.*

*** In addition to a general national/regional risk assessment of Zika virus transmission through SoHO, the infectious risk is assessed individually for each transplantation procedure involving tissues, cells, and organs.*

2 EU-level support activities for the safety of SoHO

2.1 Definition of affected areas

2.1.1 Zika virus case definition

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 case definition proposed by ECDC for the surveillance of Zika virus infection is used (Table 2).

Table 2. Case definition for surveillance of Zika virus infection proposed by ECDC

Definition	
Clinical criteria	A person presenting with a rash, with or without fever AND at least one of the following signs and symptoms: • arthralgia or • myalgia or • non-purulent conjunctivitis/hyperaemia
Laboratory criteria	**Laboratory criteria for a probable case** • Detection of Zika-specific IgM antibodies in serum **Laboratory criteria for a confirmed case** At least one of the following: • detection of Zika virus nucleic acid in a clinical specimen • detection of Zika virus antigen in a clinical specimen • isolation of Zika virus from a clinical specimen • detection of Zika virus-specific IgM antibodies in serum sample(s) and confirmation by neutralisation test; • seroconversion or fourfold increase in the titre of Zika-specific antibodies in paired serum samples
Epidemiological criteria	History of exposure in an area with transmission of Zika[4] within two weeks prior to onset of symptoms OR Sexual contact with a male confirmed case of Zika virus infection OR Sexual contact with a male who had been in an area with Zika virus transmission in the past three months
Classification	
Probable case	A person meeting the clinical criteria and the epidemiological criteria. A person meeting the laboratory criteria for a probable case.
Confirmed case	A person meeting the laboratory criteria for a confirmed case.

This case definition is regularly reviewed and updated by ECDC, as new information becomes available. It is available online at: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/patient-case-management/Pages/case-definition.aspx#sthash.rbdGiZ8E.dpuf

2.1.2 Zika-virus-affected areas

Definition of affected area

Current definitions of areas with Zika virus transmission developed by WHO [38], the Centers for Disease Control and Prevention (CDC) [39] and ECDC [40] are oriented to facilitate travel advice. The drafting group for this document agreed that the ECDC definition of 'affected area' is the most pertinent for the purpose of implementing SoHO safety measures.

According to ECDC, countries and territories experiencing Zika virus infection are categorised as follows:

- **Currently affected area:** at least one confirmed local mosquito-borne Zika infection has been reported by health authorities within the last three months
- **Previously affected area:** local mosquito-borne Zika virus transmission has been reported but not in the past three months or in an area experiencing non-conducive environmental conditions.
- **Non-affected area:** no history of local mosquito-borne Zika virus transmission.

For the purpose of applying SoHO safety measures in the EU, the definition of 'currently affected area' with active Zika virus transmission is divided into:

[4] An updated list of Zika-affected areas is available from the ECDC website.

A. An affected area with widespread transmission

- is a single NUTS 3 territorial unit in which the total number of cases exceeds ten[5] locally-transmitted, vector-borne, confirmed or probable Zika cases within a three-month period

or

- is a single NUTS 3 territorial unit in which sporadic transmission has been ongoing for more than three months.

The first case needs to be confirmed; probable cases can be included in the total number of cases.

B. An affected area with sporadic transmission

- is a single NUTS 3 territorial unit in which the total number of cases does not exceed ten locally-transmitted, vector-borne, confirmed or probable Zika cases within a three-month period.

This guide provides measures for areas with widespread transmission, with sporadic transmission, and non-affected areas.

ECDC's Surveillance Atlas of Infectious Diseases publishes weekly lists and maps of affected areas, including affected areas in the EU (at the NUTS 3 region level): http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx

Designation of affected countries outside EU

If an area in a tropical zone outside the EU reports local transmission of Zika virus, the entire country is designated an affected area. Affected areas in non-EU countries and not in a tropical zone, are designated as affected at the state or regional level in order to simplify the application of SoHO safety measures. ECDC publishes lists and maps of affected countries on its website: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx

Designation of affected areas within the EU

If an area with local transmission of Zika virus is within the EU, the status of 'affected area' should be assigned at the NUTS 3 level (Nomenclature of Territorial Units for Statistics level 3). Flight range studies suggest that most female *Aedes aegypti* spend their lifetime in or around the houses where they emerge as adults; they usually only cover a total distance of 400 metres. *Aedes albopictus* is well adapted to rural, suburban and urban human environments, which implies that people, rather than mosquitoes, move the virus within and between communities and places. Experiences with West Nile virus outbreaks show that NUTS 3 areas may effectively define the areas of risk for cases of transmission resulting from the movement of people and mosquitoes at the beginning of the outbreak. Transmission of the virus in big cities may be a problem because of a high population density. Using the NUTS 3 level to designate areas as affected ensures the concise communication of geographical information in an international setting and avoids difficulties in recognising localities below the NUTS 3 level. Areas affected by autochthonous Zika virus transmission in the EU will be recorded at the NUTS 3 level and displayed in an online map available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx

For monitoring purposes an 'area of surveillance' (epidemiological and entomological) might be broader than the 'affected area', taking into account the local topographical characteristics of an area.

[5] The arbitrary cut-off of 10 cases for applying SoHO safety measures in affected areas at the NUTS 3 level (approximately 300 000 inhabitants per NUTS 3) is based on the assumption of high reporting accuracy in EU Member States and a quantified risk estimated with the EUFRAT tool. Assuming that, on average, the proportion of blood donors in the general population of EU Member States is 1%, the relative risk of an infection in a donor is 100%, the proportion of undetected cases is 80%, and the duration of infectivity for acute infection is seven days; a calculation with EUFRAT shows that 10 confirmed or probable cases reported in NUTS 3 within the first week of an outbreak will result in an estimated prevalence of infectious donors of 0.000167. This prevalence gives a probability of having 0.5 infected donors in the assumed donor population of 1% of the general population. Hence, more than 10 cases of Zika virus infection reported per NUTS 3 territorial unit will significantly increase the likelihood of an infected blood donor and subsequent infectious donation.

2.1.3 Initiation and discontinuation of SoHO safety measures

Initiation of SoHO safety measures

SoHO safety measures are initiated by NCAs for SoHO based on an assessment of the risk and information about areas which are designated as affected.

- In affected areas in the EU with widespread active mosquito-borne Zika virus transmission, SoHO safety measures should be applied to donors residing in the area or returning from another affected area.
- In non-affected areas in the EU and affected areas in the EU with sporadic transmission, travel-related SoHO safety measures (deferral based on donor travel history) should be applied to areas and countries that were designated as affected (areas characterised by widespread active mosquito-borne Zika virus transmission). Reference documents on countries affected by Zika virus can be found on the ECDC websites: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx

Discontinuation of SoHO safety measures

- In affected areas with widespread transmission, SoHO safety measures applied locally may be stopped if no evidence of new Zika virus transmission has been provided over the last two months.
- In non-affected areas and affected areas with sporadic transmission, SoHO safety measures should be discontinued in all areas or countries which are declared to be no longer affected by Zika transmission.

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

2.2 Risk assessment

2.2.1 Risk of Zika virus transmission via SoHO

Assessing the risk of Zika virus transmission through contaminated SoHO is currently difficult because of the paucity of data on the prevalence of Zika virus in the donor population and the limited number of case reports of transmission via SoHO. According to Musso et al., during the last Zika virus outbreak in French Polynesia, 42 of 1 505 (3%) blood donors, although asymptomatic at the time of donation, were found to be positive for the Zika virus genome by RT-PCR. These findings suggest that there is a potential risk for transfusion-derived transmission [41,42]. Between 3 April and 11 June 2016, a total of 68 (0.5%) presumptive viraemic donors were identified from 12 777 donations tested in Puerto Rico. The highest weekly incidence was 1.1% for the last week of reporting (5 June to 11 June). The incidence has been increasing over time [43]. The Brazilian media reported possible cases of transfusion-transmitted Zika virus in March 2015 and February 2016 [44,45]. A probable case of transfusion-transmitted Zika virus infection in Brazil has been recently published [46]. Reports of sexual transmission of Zika virus through contaminated male semen to a partner indicate a possible virus transmission route through donated sperm [2,47-50]. There are no documented transmissions of the virus via saliva, urine or breastfeeding. No cases of Zika virus transmission through donated cells, tissues and organs have been reported, but this possibility cannot be excluded due to the confirmed presence of the virus in human blood and bodily fluids.

Following symptom onset, Zika virus RNA was detected up to five days in serum [51], and up to 10–20 days in urine [52]. Recent findings show that Zika virus RNA can be detected in whole blood up to 58 days post-symptom onset although the virus has not been isolated [53].

Data, though limited, indicate that there is a potential risk of Zika virus transmission through SoHO that may have consequences to the health of recipients. The risk of developing GBS or acute Zika virus disease after therapy with SoHO has not yet been assessed, and the scarcity of reported cases of donor-derived Zika virus infection precludes a more accurate risk assessment. However, the association between Zika virus infection and congenital malformations and GBS justifies preventive measures to reduce the risk of transmission via SoHO supply [54].

Competent authorities, establishments, and clinicians dealing with SoHO need to be vigilant and aware of the risk of donor-derived Zika virus transmission through transfusion and transplantation.

2.2.2 Risk of sexual transmission and the donation of SoHO

Zika virus particles have been isolated in semen more than three weeks after the onset of Zika symptoms. Zika viral RNA has been reported to be detectable in semen up to 62 days after clinical disease [55,56]. Zika virus genome has also been detected in saliva during and after the acute phase of the disease. Viral isolation was reported on day 6 after symptom onset [57]. A second viral isolation from saliva was recently reported but the date of sampling is not available [58]. Comprehensive data about the presence of viable virus, viral load or kinetics are lacking, and at this point in time the risk of transmission via saliva cannot be further assessed. In several cases of sexual transmission from males to their partners, except one case where information is currently unavailable, males presented with a clinical illness compatible with Zika virus infection. A case of Zika virus sexual transmission from an asymptomatic male has recently been described [59].

The interval between onset of symptoms in a man and the infection of his female partner varies at between 4 and 41 days [60].

So far, no sexual transmission of Zika virus from infected women to their partners has been documented. On 11 April, WHO published an update of its travel health advice on Zika virus and advised travellers returning from areas with ongoing Zika virus transmission to practice safer sex for at least one month after returning in order to reduce the potential risk of onward sexual transmission [61]. Based on new evidence, WHO recommends that men and women returning from areas where transmission of Zika virus is known to occur should adopt safer sex practices or consider abstinence for at least eight weeks upon return from areas with ongoing Zika virus transmission [62].

Several assessments from Australia [63], Netherlands [64] and France [65] show that the risk of blood donations by persons infected after sexual contact with traveller returning from affected areas is extremely low or even negligible.

ECDC regularly updates its Zika risk assessment. This risk assessment includes a risk assessment on the safety of SoHO and can be found online: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/Pages/index.aspx

2.2.3 Use of the EUFRAT tool

The European Up-Front Risk Assessment Tool (EUFRAT) aims to assess and quantify the risk of transmission of an emerging infectious disease by blood transfusion during an ongoing outbreak. The tool lets users assess the risks associated with blood transfusion for recipients in an affected region, or, alternatively, assess the risk posed by a donor returning from an affected region. The tool follows several steps that describe the blood transfusion chain from start to finish: from the risk of blood donors in the exposed population of becoming infected to the risk of recipients to become infected from contaminated end products. The tool is available from: http://eufrattool.ecdc.europa.eu/

The tool cannot also be used to assess the risk associated with transmission through other SoHO, such as tissues, cells and organs.

2.3 Safety measures

2.3.1 Possible measures

Measures to mitigate the risk of donor-derived infection in the SoHO sector are based on the exclusion of donors with increased risk of being infected, and laboratory screening of all donations/donors. It is also possible to inactivate/reduce pathogens in some SoHO products. ECDC Zika risk assessments include guidance on possible preventive/corrective measures for SoHO:
http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/Pages/index.aspx

2.3.2 Cost-effectiveness analysis

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 measures for the prevention of Zika virus transmission should therefore be performed within the national context, taking into account the nature of the proposed measures and their country-specific costs.

The recommended methodologies are WHO's guide to cost-effectiveness analysis [66] and the Alliance of Blood Operators' risk-based decision-making framework for blood safety [67] . All approaches, including those that infer cost-effectiveness from the other mosquito-borne disease outbreaks in Europe, are complex and require a sufficient amount of data and a high level of expertise [68] [69] [70].

2.3.3 Availability of laboratory tests

Zika virus is a risk-group-2 pathogen which requires biocontainment precautions at biosafety level 2 (BSL-2) in Europe [71], USA and Canada [72,73]. Laboratory evidence of Zika virus infection is generally established by the detection of viral RNA (molecular testing) and/or specific anti-viral antibodies (serological testing) 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, only one RT-PCR kit for diagnosis (RealStar Zika virus RT-PCR kit 1.0, Altona Diagnostics) acquired a CE mark [74]. 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. Quality control material for validation is available from the global European virus archive [75]. The US FDA has authorised the emergency use of several tests [76] in order to ensure timely access to diagnostic tools: CDC's Zika immunoglobulin M (IgM) antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) and Trioplex rRT-PCR [77], Zika virus RNA qualitative real-time RT-PCR (Focus Diagnostics) [76], and RealStar Zika virus RT-PCR kit US (Altona Diagnostics) [74].

A number of commercial laboratory tests for the in vitro diagnostics of Zika virus infection have also been submitted to WHO for an emergency use assessment and listing (EUAL) [78]. WHO will make a decision on the product's suitability for WHO procurement based on a review of the documentation submitted through the EUAL procedure. Review criteria include quality, safety, performance, and an independent laboratory evaluation. Products that are reviewed favourably are then listed as eligible for WHO procurement and can be used for an emergency application until the final registration/approval for commercial use is available.

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. So far, however, commercial Zika tests for screening are still under development. SoHO establishments and laboratories may develop in-house tests or adapt commercial diagnostic tests for screening purposes. The use of such screening tests in the situation of Zika virus outbreak should be validated and approved by the responsible national authority. Some establishments are gaining experience with in-house testing or using adapted commercial tests. Semi-automated platform for NAT screening using CE marked kits for diagnostic have been implemented for NAT screening in French West Indies during the 2014 outbreak of chikungunya [79] and is currently implemented for NAT screening of Zika virus in French Antilles using the RealStar RT-PRC Zika kit 1.0, Altona. 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 [80].

Once screening tests become widely available, the guidance on safety measures might change significantly. It is, therefore, important to monitor these developments. Regularly updated information is available online from WHO, CDC, and ECDC.

2.3.4 Donor selection and deferral

NCAs, SoHO establishments and clinicians need to be aware of the risk of donor-derived Zika virus transmission through transfusion and transplantation. Measures to prevent Zika virus transmission through transfusion and transplantation in affected and non-affected areas should focus on the following donors:

- People with a recent medical diagnosis of Zika virus disease
- Residents of affected areas
- Travellers returning from affected areas
- People who had sexual contacts with men who have been diagnosed with Zika virus infection or who travelled or lived in a Zika-affected area during the three months prior to the sexual contact.

In accordance with the national preparedness plan, NCAs are encouraged to reassess and quantify the level of risk posed by these donor categories. Laboratory evidence of Zika virus infection is generally established by the detection of viral RNA (molecular testing) and/or specific anti-viral antibodies (serological testing) in biological samples.

For further SoHO-specific information on preventive/corrective measures, please see below. Additional information is available at: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1466

2.4 Supply management

The SoHO supply is vulnerable to incidents affecting the health of donors. A large Zika virus outbreak may temporarily reduce the availability of SoHO donors and staff in SoHO establishments, creating difficulties in the adequate and timely treatment of patients. In order to maintain the SoHO inventory and supply chain, SoHO establishments should evaluate their current supply management policy and strengthen their contingency planning [70].

For instance, blood and blood components from the continental United States are being shipped to Puerto Rico to stem the possibility of the Zika virus spreading through blood transfusions. Simultaneously, the US FDA approved the use of a new investigational test for emergency use application.

NCAs meet regularly and, thanks to their good contacts, would be able to help with cross-border shipments of SoHO supplies to areas where local collection is limited or impossible, for example in affected areas with widespread transmission or in areas that just reported their first autochthonous cases.

In order to facilitate the possible use of NAT screening in countries that do not have adequate laboratory capacities, it is considered to contract out NAT laboratory services to providers in other EU countries. In this respect, the European Blood Alliance will support the European Commission and ECDC in gathering information on NAT Zika testing capacities of blood donors.

Blood, and tissues and cells should not be imported from areas with widespread transmission of Zika virus. In special circumstances or for life-saving procedures, blood, tissues and cells may be imported from affected areas if tested negative for the presence of Zika virus. The importation of organs from areas with widespread 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.

2.5 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 unforeseen events and help to keep negative economic consequences to a minimum while maximizing the desired outcome of all public health measures [81].

National preparedness plans for SoHO safety should outline a communication strategy which addresses all levels. This includes the exchange of information with international organisations and keeping the public health sector, the healthcare sector and the wider population informed, both of the latest developments and the impact of the measures that were implemented 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 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 establishments for SoHO, which collect and manage alerts on product donated and used in Member States.

Alerts should be communicated to relevant SoHO establishments, 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 Medicine 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 Health and Food Safety – Unit B4-SoHO) can assure the consistency of information across Europe.

3 Safety measures by type of SoHO

NCAs, SoHO establishments 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 both affected and non-affected areas. Implementation of SoHO safety measures should be defined by a risk assessment performed at the national level.

The working group behind the production of this guide agreed that the implementation of safety measures for donors who have had sexual contact with males returning from affected areas 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. Summary of proposed safety measures by type of SoHO and presence of Zika infection in an area

Type of SoHO	Non-affected areas and areas with sporadic transmission	Affected areas with widespread transmission
Whole blood and blood components	Deferral of donors for 28 days (i) after return from an affected area, (ii) after cessation of symptoms in case of confirmed Zika virus infection and (iii) after sexual contact with a male who has been diagnosed with Zika virus infection or with a man who travelled or lived in a Zika-affected area during the three months prior to the sexual contact[6] OR NAT screening if available OR application of plasma and platelet pathogen inactivation techniques	NAT screening or deferral of all donors, suspension of local blood donations with simultaneous importation of supplies OR, if local collection is still needed, mandatory NAT-testing of blood products for pregnant women. OR application of plasma and platelets pathogen inactivation techniques
Plasma for fractionation	It is not essential to exclude blood donors who have returned from affected areas from donating plasma for fractionation. It is also not essential to screen plasma for fractionation that was collected in areas affected by Zika fever.	It is not essential to exclude blood donors who have returned from affected areas from donating plasma for fractionation. It is also not essential to screen plasma for fractionation that was collected in areas affected by Zika fever.
Sperm	Deferral of donors for (i) six months after cessation of symptoms in case of confirmed Zika virus infection, (ii) eight weeks after return from an affected area, (iii) eight weeks after sexual contact with a male who travelled to an affected area within the last three months or was diagnosed with Zika. OR NAT screening if available	NAT screening
Other tissue and cell materials	Deferral of donors during 28 days (i) after returning from an affected area, (ii) after cessation of symptoms in case of confirmed Zika, and (iii) after sexual contact with a person who travelled to an affected area within the last three months or was diagnosed with Zika. OR NAT screening if available	NAT screening OR suspend local donation and import tissue and cell materials from non-affected areas OR if local collection is needed, ensure that pregnant women only get NAT-tested tissue and cell materials donations.
Organs	Individual assessment of organ donors, carefully weighing the benefits against the risks for the potential organ recipient; final decision lies with the transplant team.	Individual assessment of organ donors, carefully weighing the benefits against the risks for the potential organ recipient. NAT testing may be used in symptomatic living donors to identify the pathogen.

3.1 Blood safety measures

3.1.1 Non-affected areas and areas with sporadic transmission

3.1.1.1 Donor information

Blood establishments should update donor information materials and add information on Zika virus infection, including information on clinical signs and the risk of getting infected. The information should also include advice on donor self-deferral for 28 days if one of the following criteria is met:

- A medical diagnosis of Zika virus infection
- After returning from a Zika-virus-affected area
- If the donor develops symptoms of Zika virus infection 14 days after returning from an affected area
- If the donor had sexual contact with man who has been diagnosed with Zika virus infection or with a man who travelled or lived in a Zika-affected area during the three months prior to the sexual contact[6].

[6] The working group agreed that the implementation of safety measures for this category of risk donors may be reassessed and justified by a risk assessment and outlined in the national preparedness plan.

3.1.1.2 Donor questionnaire

Non-affected areas and areas with sporadic transmission

Donor history questionnaires already contain a question about travelling abroad. For donors with a history of travelling to Zika-affected-areas with widespread transmission, physicians should ask questions about the period of stay in the affected area, about Zika symptoms, and about any Zika diagnosis. Questions about sexual contacts with males who have been diagnosed with Zika virus infection or sexual contacts with males who travelled or lived in a Zika-affected areas during the three months prior to the sexual contact should be included in the questionnaire if warranted by a risk assessment conducted within the framework of the national preparedness plan.

Areas with widespread transmission

The donor history questionnaire should contain questions about a history of medical diagnosis of Zika virus within the last 28 days and sexual contact with males who have been diagnosed with Zika virus infection.

3.1.1.3 Donor eligibility

Deferral for 28 days if one of the following criteria are met:

- People diagnosed with Zika virus infection after cessation of symptoms.
- People who just returned from an affected area.
- Donors who had sexual contacts with men who have been diagnosed with Zika virus infection or who travelled or lived in a Zika-affected area during the three months prior to the sexual contact[7].

NAT testing could be used to reinstate blood donors in accordance with donor protocols.

The deferral period for travellers returning form a Zika-affected area already affected by another vector-borne disease (e.g. malaria) should be extended to the longer deferral period previously implemented for the other disease.

3.1.2 Affected areas with widespread transmission

Depending on the risk posed by Zika virus infection to the safety of blood and blood components in affected areas with widespread transmission, the blood establishment can either temporarily suspend or continue blood donations.

In this context, the following criteria need to be observed:

Temporary suspension of blood donation

Blood establishments may temporary suspend blood donation in areas with widespread transmission and source all necessary blood components from non-affected parts of the country. 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 NCA for blood and blood components in order to assure an adequate and timely supply of blood components from non-affected areas to the area with temporary suspended donations. Blood donors must be informed of the measures.

Continuation of blood donation

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

Blood establishments may continue with blood donations partially or completely. Donor information and health questionnaires should be the same as in non-affected areas.

Partial continuation of blood donation:

- Continue with the apheresis collection of platelets and plasma; platelets and plasma should later be pathogen inactivated. Pathogen inactivation treatment of platelets and plasma (amotosalen–UV light, riboflavin–UV light, methylene blue–UV light, and UV–C light) are effective in the inactivation of flaviviruses [82-85]. The amotosalen–UV light method has been demonstrated to inactivate Zika virus in plasma [86]. Other methods have been used successfully against similar flaviviruses like dengue virus and West Nile virus [87,88]
- Import only red blood cells from unaffected parts of the country
- Use fresh frozen plasma collected before outbreak if possible
- 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 multiple pathogen reduction steps used in the manufacturing process of plasma-derived medicinal products have been shown to be robust in the removal of lipid-enveloped viruses. Data from model viruses were confirmed with the inactivation of West Nile virus and chikungunya virus [89-91]. For this reason, and in line with the regulations for West Nile virus deferral in EU Directive 2004/33/EC [34], the International Plasma Fractionation Association [92], the Plasma Protein Therapies Association [93], and the Biologics Working Party of the European Medicines Agency have advised that Zika virus will be inactivated by the fractionation procedures and that no additional measures to prevent Zika virus transmission through plasma-derived medicinal products are required upon collection of plasma specifically destined to the manufacture of plasma products.

It is not essential to exclude blood donors who have returned from affected areas from donating plasma for fractionation. It is also not essential to screen plasma for fractionation which was collected in areas affected by Zika fever.

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 disease in the donor. If the donor is infected with the Zika virus, all blood components from these donors should be destroyed or appropriately labelled for use investigation except pathogen inactivated blood components and plasma for fractionation. 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 within the 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 involved blood components. 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

The risk of Zika virus transmission through human tissues and cells is merely theoretical. As stated previously, Zika virus has been detected in blood, sperm, urine, saliva, and breast milk. Cases of Zika virus transmission through infected tissues and cells including corneas, bone, skin, heart valves, haematopoietic stem cells from bone marrow, peripheral blood or cord blood, and reproductive cells such as 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 majority of tissue and cell recipients are immunosuppressed and are more likely to develop serious disease symptoms after Zika virus infection.

Characteristics of tissues and cells, and possible Zika virus inactivation during processing and storage should be evaluated and considered in the risk assessment. If validation shows that an inactivation of the virus is effective or it can be assumed, based on the results of inactivation of similar model viruses, no other safety measures related to donor selection or screening would be necessary.

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):

- After a medical diagnosis of Zika virus infection
- After returning from a Zika-virus-affected area
- If the donor develops symptoms of Zika virus infection 14 days after returning from an affected area
- If the donor had sexual contacts with men who have been diagnosed with Zika virus infection or men who travelled or lived in a Zika-affected area during the three months prior to 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 affected areas. Questions about sexual contacts with males who returned from affected areas (where they stayed for three months before the sexual contacts) could be included into the questionnaire if warranted by the type of cells and tissues to be transplanted and according to the assessed risk of Zika virus transmission by sexual contact.

Reproductive tissues and cells

Tissues and cells establishments should temporarily postpone assisted reproductive technology procedures for people who could potentially become infected with Zika virus disease. Under specific conditions, procedures can be continued, e.g. for fertility preservation or when postponing an assisted reproductive technology procedure would significantly worsen a couple's chances to conceive, but all donors 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 negative NAT in sperm.

A case of late sexual transmission of Zika virus in a woman was reported. The woman had sexual contact with an infected man 34 to 41 days after he experienced onset of symptoms [60]. Therefore ECDC recommends the use of condoms for eight weeks after onset of Zika virus disease symptoms.

Sperm donation: Non-affected areas and areas with sporadic transmission

Continue with sperm donation, but apply the following selection criteria for donors:

- Deferral of six months of persons diagnosed with Zika virus infection after cessation of symptoms
- Deferral of eight weeks of asymptomatic persons after their return from an affected area
- Deferral of eight weeks of persons who have had a sexual contact with men who have been diagnosed with Zika virus infection or with men who travelled or lived in a Zika-affected area during the three months before disease onset
- 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].

Sperm donation: Affected areas with widespread transmission

Tissue establishments in affected areas need to temporary suspend assisted reproductive technology procedures and reproductive tissues and cell donations, except under specific conditions. Procedures can be continued for fertility preservation or when suspending the assisted reproductive technology procedure would significantly worsen a couple's chances to conceive. NAT testing should be performed on sperm and serological test should be performed on blood samples [94].

Protocols for different scenarios should be produced, both for fertility preservation in men and women, or for assisted reproductive technology procedures for women who are close to a critical age for conception. Additional tests should be performed, taking into account the specific situation.

Other reproductive tissues and cells: oocytes, embryos, ovarian and testicular tissues

One has to distinguish between fertility preservation (ovarian and testicular tissues) and assisted reproductive technology (oocytes and embryos).

- For children, fertility preservation should not be postponed but the use of preserved tissues will depend on NAT test results and the available technology.

For adults the procedure should be postponed if possible. If this is not possible, NAT test results (urine, blood and sperm) should be consulted before making a decision.

- For assisted reproductive technology procedures, the same measures as for the sperm donation should be applied. In non-affected areas:
  - Female donations (fertility preservation and assisted reproductive technology procedure): deferral for 28 days of asymptomatic persons after returning from affected areas
  - Male donations (fertility preservation): all donor sperm from donors who returned from an affected area six or fewer months ago is NAT tested, regardless of Zika infection status.

According to the WHO interim guide on laboratory testing for Zika virus infection, NAT testing on blood or urine samples in affected areas 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 an affected area with widespread 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 affected areas with widespread 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 that had been 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/PBHSCT 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.

Non-affected areas and areas with sporadic transmission

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

- Donors diagnosed with Zika virus infection after cessation of symptoms
- Asymptomatic donors after returning from an affected area
- Donors who had sexual contacts with men who have been diagnosed with Zika virus infection or men who travelled or lived in a Zika-affected area during the last three months

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 widespread transmission

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

3.2.2 Post-mortem donation

Non-affected areas and areas with sporadic 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 Zika-virus-affected areas, should not be used as tissue or cell donors.

Affected areas with widespread transmission

Using only a donor's medical and behavioural history in the selection of deceased donors may be insufficient in affected areas with widespread 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 affected areas with widespread transmission under specific conditions. The type of measures implemented should be coordinated between ESoHOs and NCA at the national level.

If tissue donation was temporarily suspended in an area with widespread transmission, needed tissue products should be supplied from non-affected parts of the country. If tissue donation in such an area continues, all tissue

donors have to be laboratory screened, and, if possible, tissue products should be inactivated using appropriate pathogen inactivation technology.

3.3 Organ safety measures

At the time of preparation of this guide, the risk of Zika virus transmission through solid organ transplantation is unknown. The virus may infect deceased organ donors prior or during their terminal illness. It can also infect 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 unknown, however, 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 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].

In addition, information on the severity of Zika virus infection in immunosuppressed patients is lacking. Therefore, the level of risk for solid organ recipients travelling from/to affected areas or being exposed to infection cannot be assessed.

3.3.1 Affected and non-affected areas

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 Zika-virus-affected and non-affected areas. 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 could 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

The 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 cells

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 two weeks 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 supplied 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 to the national biovigilance system. If 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. 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 2012. Brussels: European Commission; 2012: http://ec.europa.eu/health/blood_tissues_organs/docs/wnv_preparedness_plan_2012.pdf.
2. 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.
3. European Centre for Disease Prevention and Control. Factsheet for health professionals: Zika virus infection [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx.
4. 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.
5. 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.
6. 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.
7. 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.
8. 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).
9. World Health Organization. Zika situation report: Neurological syndrome and congenital anomalies. 5 February 2016. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204348/1/zikasitrep_5Feb2016_eng.pdf.
10. Rasmussen SA, Jamieson DJ, Honein MA, Petersen LR. Zika Virus and Birth Defects--Reviewing the Evidence for Causality. N Engl J Med. 2016 May 19;374(20):1981-7.
11. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus disease epidemic: potential association with microcephaly and Guillain-Barre syndrome. Fifth update, 11th April 2016. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-11-april-2016.docx.pdf.
12. 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.
13. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus infection outbreak, Brazil and the Pacific region. 25 May 2015. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-Zika%20virus-south-america-Brazil-2015.pdf.
14. European Centre for Disease Prevention and Control. Rapid risk assessment - Microcephaly in Brazil potentially linked to the Zika virus epidemic. 24 November 2015. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf.
15. 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. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf.
16. European Centre for Disease Prevention and Control. Rapid risk assesment: Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome. First update, 21 January 2016. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-zika-virus-first-update-jan-2016.pdf.
17. 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. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-8-february-2016.pdf.

18. 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. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-23-february-2016.pdf.
19. 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. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-9-march-2016.pdf.
20. 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/.
21. Gratz NG, Steffen R, Cocksedge W. Why aircraft disinsection? Bull World Health Organ. 2000;78(8):995-1004.
22. 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.
23. Reiter P. Yellow fever and dengue: a threat to Europe? Euro Surveill. 2010 Mar 11;15(10):19509.
24. 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.
25. 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.
26. 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).
27. European Centre for Disease Prevention and Control. Mosquito maps: Current known distribution as of October 2015 [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx.
28. 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.
29. 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.
30. 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 Mar;10(3):e0004543.
31. 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. 2016 May 5; 21(18):[pii=30223 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=22468.
32. International Research Institute for Climate and Society (IRI). Seasonal climate forecasts [Internet]. Palisades, NY: Columbia University; 2016. Available from: http://iri.columbia.edu/our-expertise/climate/forecasts/seasonal-climate-forecasts/.
33. 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.
34. European Commission. 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, 2004 [cited 2016]. Available from: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:091:0025:0039:EN:PDF.
35. 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.
36. 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.
37. 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).

38. World Health Organization. Surveillance for Zika virus infection, microcephaly and Guillain-Barré syndrome Interim guidance, 7 April [Internet]. Geneva: WHO; 2016. Available from: http://www.who.int/csr/resources/publications/zika/surveillance/en/.
39. Centers for Disease Control and Prevention. Travel health notices – Zika virus [Internet]. Atlanta: CDC; 2016 [updated 2016 Feb 18]. Available from: http://wwwnc.cdc.gov/travel/notices/alert/zika-virus-caribbean.
40. European Centre for Disease Prevention and Control. Countries and territories with local Zika transmission. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx.
41. 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. 2014; 19(14):[pii=20761 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20761.
42. 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.
43. 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.
44. Herriman R. Transfusion-associated Zika virus reported in Brazil. 18 December 2015. Outbreak News Today; 2015. Available from: http://outbreaknewstoday.com/transfusion-associated-zika-virus-reported-in-brazil-76935/.
45. 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.
46. Barjas-Castro ML, Angerami RN, Cunha MS, Suzuki A, Nogueira JS, Rocco IM, et al. Probable transfusion-transmitted Zika virus in Brazil. Transfusion (Paris). 2016 Jun 21.
47. 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.
48. 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. 2016; 21(8):[pii=30148 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=21395.
49. 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/.
50. 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.
51. 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. Forthcoming.
52. 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.
53. 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. 2016;21:30269.
54. World Health Organization. WHO Director-General summarizes the outcome of the Emergency Committee on Zika. 1 February 2016. Geneva: WHO; 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/.
55. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis. 2015 Feb;21(2):359-61.
56. Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons EJ, et al. Detection of Zika Virus in Semen. Emerging infectious diseases. 2016 May;22(5):940.
57. 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. EuroSurv. 2016;21(10).

58. Bonaldo MC RI, Lima NS, Santos AAC, Menezes LSR, Cruz SOD, et al. Isolation of infective Zika virus from urine and saliva of patients in Brazil. 2016 [cited 2016]. Available from: http://biorxiv.org/content/early/2016/03/24/045443.
59. 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. 2016 Jun 9; 21(23):[30254 p.]. Available from: http://www.eurosurveillance.org/images/dynamic/EE/V21N23/art22500.pdf.
60. 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 Jun 7.
61. World Health Oganization. Travel health advice on Zika virus 2016 [cited 2016]. Available from: http://www.who.int/ith/updates/2016_04_11/en/.
62. World Health Organization. Prevention of potential sexual transmission of Zika virus. Interim guidance, 7 June 2016. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204421/1/WHO_ZIKV_MOC_16.1_eng.pdf.
63. 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 ongoing transmission of Zika virus 2016.
64. Janssen MP. The risk of sexually transmitted Zika infection among Dutch blood donors. 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.
65. 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.
66. World Health Organization. Guide to cost-effectiveness analysis 2002. Available from: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf.
67. Custer B, Janssen MP. Health economics and outcomes methods in risk-based decision-making for blood safety. Transfusion (Paris). 2015 Aug;55(8):2039-47.
68. 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).
69. 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 transfusion = Trasfusione del sangue. 2008 Oct;6(4):199-210.
70. 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.
71. 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.
72. Wittek R, Link J. Classification of organisms – viruses. Environment in practice. Berne: Swiss Agency for the Environment, Forests and Landscape; 2005. Available from: http://www2.unil.ch/facs/downloads/Viruses(engl.).pdf.
73. Advisory Committee on Dangerous Pathogens. The approved list of biological agents. 3rd edition. Merseyside: Health and Safety Executive (United Kingdom); 2013. Available from: http://www.hse.gov.uk/pubns/misc208.pdf.
74. 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.
75. European Virus Archive. Zika virus diagnostic. [Internet]. 2016. Available from: http://www.european-virus-archive.com/evag-news/zika-virus-diagnostics.
76. US Food and Drug Administration. Emergency use authorizations: Zika virus emergency use authorization [Internet]. Silver Spring, MD: FDA; 2016. Available from: http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm#zika.
77. Centers for Disease Control and Prevention. Zika virus. Diagnostic testing [Internet]. 2016. Available from: http://www.cdc.gov/zika/hc-providers/diagnostic.html.

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

79. 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.

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

81. World Health Organization. Maintaining a Safe and Adequate Blood Supply during Pandemic Influenza. Guidelines for Blood Transfusion Services. Geneva: WHO; 2011. Available from: http://www.who.int/bloodsafety/publications/WHO_Guidelines_on_Pandemic_Influenza_and_Blood_Supply.pdf.

82. 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.

83. 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.

84. 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.

85. 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.

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

87. 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 (Paris). 2016 Mar 1.

88. 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 (Paris). 2004 Jun;44(6):886-90.

89. Leydold SM, Farcet MR, Kindermann J, Modrof J, Polsler G, Berting A, et al. Chikungunya virus and the safety of plasma products. Transfusion (Paris). 2012;52(10):2122-30.

90. Kreil TR, Berting A, Kistner O, Kindermann J. West Nile virus and the safety of plasma derivatives: verification of high safety margins, and the validity of predictions based on model virus data. Transfusion (Paris). 2003 Aug;43(8):1023-8.

91. Dichtelmuller HO, Biesert L, Fabbrizzi F, Gajardo R, Groner A, von Hoegen I, et al. Robustness of solvent/detergent treatment of plasma derivatives: a data collection from Plasma Protein Therapeutics Association member companies. Transfusion (Paris). 2009 Sep;49(9):1931-43.

92. International Plasma Fractionation Association. IPFA position paper on Zika virus and the safety of plasma-derived medicinal products. 2016 [cited 2016]. Available from: http://www.ipfa.nl/UserFiles/IP-16-041%20IPFA%20Position%20paper%20Virus%20ZIKA%20FINAL.pdf.

93. Plasma Protein Therapeutic Association. Zika virus and plasma protein therapies, 2016 [cited 2016]. Available from: http://www.pptaglobal.org/media-and-information/ppta-statements/969-zika-virus-and-plasma-protein-therapies.

94. World Health Organization. Laboratory testing for Zika virus infection. 2016 [cited 2016]. Available from: http://www.who.int/csr/resources/publications/zika/laboratory-testing/en.

95. Pan American Health Organization. Epidemiological Alert: Neurological syndrome, congenital malformations, and Zika virus infections. Implications for public health in the Americas, 2015. Available from: http://www.paho.org/hq/index.php?option=com_content&view=article&id=10898&Itemid=41443&lang=en.

96. Organ Procurement & Transplantation Network. Guidance for organ donation and transplantation professionals regarding the Zika virus [Internet]. US Department of Health & Human Services [updated 2016 Feb 4]. Available from: https://optn.transplant.hrsa.gov/news/guidance-for-organ-donation-and-transplantation-professionals-regarding-the-zika-virus/.

97. European Directorate for the Quality of Medicines and Healthcare. Guide to the quality and safety of organs for transplantation. 6th ed. Strasbourg: Council of Europe; 2016. [in press].

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