RAPID RISK ASSESSMENT

Zika virus disease epidemic: potential association with microcephaly and Guillain–Barré syndrome

Third update, 23 February 2016

Main conclusions and options for response

Considering the continued rapid spread of Zika virus in the Americas and Caribbean, the growing evidence of an association between Zika virus infection during pregnancy and congenital central nervous system malformations, the association between Zika virus infection and Guillain–Barré syndrome (GBS), and the risk of establishment of local vector-borne transmission in Europe during the 2016 summer season, EU/EEA Member States are recommended to consider the following mitigation measures:

- Travellers visiting countries where there is active transmission of Zika virus should be made aware of the ongoing outbreak of Zika virus infection. A list of countries and territories with documented autochthonous transmission during the past two months is available on the ECDC website.
- Travellers visiting these countries should take measures to prevent mosquito bites indoors and outdoors, especially from sunrise to sunset when *Aedes* mosquito vectors are the most active.
  - Use mosquito repellent in accordance with the instructions indicated on the product label. DEET-based repellent is not recommended for children under two months of age but pregnant women can use it.
  - Wear long-sleeved shirts and long trousers.
  - Sleep or rest in screened or air-conditioned rooms, or under mosquito nets, even when resting during the day.
- Pregnant women and women who are planning to become pregnant should consider postponing non-essential travel to affected areas until after delivery. If travel to affected areas cannot be avoided, pregnant women should follow strict personal preventive measures and consult their healthcare providers before departure and upon return.
- Travellers with immune disorders or severe chronic illnesses should consult their doctor or seek advice from a travel clinic before travelling, particularly on effective prevention measures.
- There is evidence that Zika virus can be transmitted sexually through semen, and there are indications that the Zika viral RNA can be present in semen for at least two months after a man has recovered from a Zika virus infection. Travellers to Zika-affected areas should be advised that using condoms could reduce the risk of sexual transmission from an infected man to another person.
- Travellers showing symptoms compatible with Zika virus disease within three weeks of return from an affected area are advised to contact their healthcare provider and mention their recent travel.
- Pregnant women who have travelled in areas with Zika virus transmission should mention their travel during antenatal visits in order to be assessed and monitored.

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- In order to protect pregnant women, male travellers returning from affected areas should consider using a condom with a pregnant female partner until the end of pregnancy, or for six months with partners at risk of getting pregnant. This precautionary advice is based on limited evidence and will be revised as more information becomes available.

Information to healthcare providers

- Ensure that Zika virus-infected patients in areas with *Aedes* mosquito vectors of Zika virus avoid getting bitten during the first week of illness (insecticide-treated bed nets, screened doors and windows as recommended by PAHO/WHO).
- Increase awareness among health professionals who provide prenatal care of the possible association between Zika virus and microcephaly and adapt prenatal monitoring in accordance with the exposure to the vector.

In addition, due to the unprecedented size of the Zika virus epidemic, health services and practitioners should be alerted to the possible occurrence of neurological syndromes (GBS and other neurological syndromes such as meningitis, meningoencephalitis and myelitis according to WHO/PAHO) and potential disease complications not yet described in the scientific literature and atypical clinical presentation among specific populations (i.e. children, the elderly, immunocompromised individuals and those with sickle cell disease).

This document also includes more specific options for substances of human origin, surveillance and preparedness, and discusses the risk of importation of the disease to continental Europe.

Source and date of request

ECDC internal decision, 15 February 2016

Public health issue

This document assesses the risks associated with the Zika virus epidemic currently affecting countries in South and Central America and in the Caribbean. It assesses the association between Zika virus infection and congenital central nervous system (CNS) malformations, including microcephaly, as well as the association between Zika virus infection and Guillain–Barré syndrome (GBS).

To date, ECDC has published six risk assessments related to Zika virus epidemics:

- 'Zika virus infection outbreak, French Polynesia', 14 February 2014 [1];
- 'Zika virus infection outbreak, Brazil and the Pacific region', 25 May 2015 [2];
- 'Microcephaly in Brazil potentially linked to the Zika virus epidemic', 24 November 2015 [3];
- 'Zika virus epidemic in the Americas: potential association with microcephaly and Guillain–Barré syndrome', 10 December 2015 [4];
- 'Zika virus disease epidemic: potential association with microcephaly and Guillain–Barré syndrome (first update) ', 21 January 2016 [5].
- 'Zika virus disease epidemic: potential association with microcephaly and Guillain–Barré syndrome (second update) ', 8 February 2016 [6].

Consulted experts

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Disease background information

Zika virus disease is caused by an RNA virus transmitted to humans by *Aedes* mosquitoes, especially by the *Aedes aegypti* species. Up to 80 per cent of infections are asymptomatic [8]. Symptomatic infections are characterised by a self-limiting febrile illness of 4 to 7 days' duration accompanied by rash, arthralgia, conjunctivitis, myalgia and headache. In the past, Zika virus has not been noted to cause death, nor has it been linked to intra-uterine infections and congenital CNS anomalies. Zika virus infection was linked to GBS for the first time in 2014 when a possible association between Zika virus infection and GBS was reported during an outbreak in French Polynesia [8]. There is no vaccine to prevent Zika virus infections nor is any specific anti-viral treatment available.

Zika virus infection can be confirmed by direct detection of Zika virus RNA or specific viral antigens in clinical specimens. Virus-specific antibodies can be detected usually from day 5 or 6 of illness, but serological results should be interpreted with caution due to cross-reactivity with with other flaviviruses and according to the vaccination status against flaviviruses. More information on Zika virus disease can be found in the previous risk assessments [2-5] and in the ECDC factsheet for health professionals [9].

Event background information

This section describes the key events in relation to the current Zika virus epidemic in the Americas (Table 1).

In May 2015, autochthonous transmission of Zika virus was confirmed in the states of Bahia and Rio Grande do Norte in northeast Brazil [10]. However, it is likely that Zika virus had been circulating in Salvador de Bahia City earlier than that, as an outbreak of acute exanthematous illness was reported there between 15 February and 25 June 2015 [11]. The Brazilian Ministry of Health reported 56 318 suspected cases of Zika virus infection between May and 1 December 2015 [12].

Over the past two months, and as of 18 February 2016, autochthonous cases of Zika virus (ZIKV) infection have been reported from 35 countries or territories worldwide. In the past nine months, 40 countries or territories have reported autochthonous cases of Zika virus infection.

The latest information on the spread of the ZIKV epidemic and an update on adverse pregnancy outcomes and post-infectious GBS is available through the Communicable Diseases Threats Report (dated 19 February 2016) [13]. Regular updates on the epidemiological situation are available on an ECDC webpage entitled Countries and territories with local Zika transmission [14].

As of 19 February 2016, 26 countries in the EU/EEA advise pregnant women to consider postponing travel to affected countries [15].

Key events

Table 1. Key events – Zika virus infection epidemics 2015/2016

Date	Key event	Ref.
May 2015	Autochthonous transmission is confirmed in the states of Bahia and Rio Grande do Norte in Brazil.	[10]
October 2015	Unusual increase in the incidence of microcephaly in north-eastern Brazil confirmed by the Brazilian Ministry of Health.	[16]
11 November 2015	Public health emergency declared and the Ministry of Health activates the emergency operations centre for public health (COES, Centro de Operações de Emergências em Saúde Pública).	[17]
24 November 2015	Congenital CNS malformations (17 cases) reported with temporo-spatial association to a Zika virus outbreak in French Polynesia. None of the cases were tested for Zika virus, and none of the mothers reported symptoms compatible with Zika disease during pregnancy.	[4-6]
1 December 2015	PAHO/WHO issues an epidemiological update on neurological syndromes, congenital anomalies and the Zika virus epidemic, and recommends that its Member States 'establish and maintain the capacity to detect and confirm Zika virus cases, prepare healthcare facilities to respond to a possible increased demand of specialized care for neurological syndromes, as well as to strengthen antenatal care'.	[1,19]
15–16 January 2016	The US Centers for Disease Control and Prevention (US CDC) and the Public Health Agency of Canada (PHAC) issue a travel advice that pregnant women should consider postponing travel to areas with autochthonous Zika transmission.	[20,21]
15 January 2016	The Hawaii Department of Health announces a laboratory-confirmed case of congenital Zika virus infection in a baby born with microcephaly to a mother who lived in Brazil during the first part of her pregnancy in May 2015.	[22]
21 January 2016	ECDC publishes an updated Rapid Risk Assessment with a detailed overview of reported cases of congenital malformations potentially linked with Zika virus infection in Brazil (as of 18 January 2016).	[5]

Date	Key event	Ref.
1 February 2016	WHO declares a Public Health Emergency of International Concern (PHEIC). The Director-General of WHO states that a causal relationship between Zika infection during pregnancy and microcephaly is strongly suspected, though not yet scientifically proven.	[23,24]
2 February 2016	Sexual transmission of Zika virus is reported from the USA. This is only the second time that evidence of sexual transmission was presented.	[25]
10 February 2016	The first documented case of congenital CNS malformation linked to Zika virus is reported in the EU (Slovenia). The mother experienced a Zika-like disease during the first part of her pregnancy while living in north-eastern Brazil. The pregnancy was terminated in Slovenia after severe CNS malformations were diagnosed. Post-mortem examinations detected Zika virus genome and virus particles in the affected brain.	[26]
10 February 2016	Detection of Zika viral genome and antigen in brain tissue from two infants with microcephaly; Zika viral genome and antigen in placental tissues from two early miscarriages.	[27]
12 February 2016	CDC issues interim *Guidelines for prevention of sexual transmission of Zika virus*.	[28]
12 February 2016	WHO issues an interim case definition for Zika virus disease.	[12]
17 February 2016	A case-control study of congenital microcephaly cases commences in Paraíba state. Results are expected by the end of April 2016.	[29]

Microcephaly and congenital central nervous system malformations

As of 13 February 2016, the Brazilian Ministry of Health has reported 5 280 cases of microcephaly. Of these, 3 174 cases (60%) were reported in 2015 and 2 106 (40%) in 2016 [30]. Across the country, 3 935 suspected cases of microcephaly remain under investigation and need to be categorised in accordance with the case definition issued by the Brazilian Ministry of Health [31].

As of 6 February, 462 cases of microcephaly and/or other central nervous system findings suggestive of congenital infection were confirmed by the Ministry of Health. Of these 462 cases, 41 (8.9%) had a laboratory-confirmed Zika virus infection.

On 10 February 2016, a case report described a case of congenital CNS malformation and microcephaly with evidence of transplacental Zika virus infection [26]. The woman reported an episode of Zika-like disease during the first trimester of pregnancy while living in north-eastern Brazil. The pregnancy was terminated after ultrasonography examinations in Slovenia at 28 weeks of pregnancy had revealed severe CNS malformations. Tissue samples from the aborted foetus showed unequivocal evidence of Zika virus infection in the central nervous system. Phylogenetic analysis of the full viral genome demonstrated high level of identity with Zika viral strains isolated in Sao Paulo, Brazil, in 2015 and in French Polynesia in 2013. Other common causes of intra-uterine CNS infections were investigated without positive findings. This is the first documented case of congenital malformation imported in the EU that has been associated with Zika virus infection.

On 10 February 2016, the US CDC published a report on tested samples from two pregnancies that had ended in miscarriage and from two infants with diagnosed microcephaly who died shortly after birth [27]. The four mothers, who originated from north-eastern Brazil (Rio Grande do Norte), reported fever and rash suggestive of Zika virus infection during their pregnancy but were not serologically tested. Brain tissue from the two newborns and placental tissue from the two miscarriages tested positive by RT-PCR assay. Histological observations of foetal tissues indicated the presence of Zika virus. A phylogenetic analysis of the viral strains in the four cases showed a high level of identity to other Zika viral strains circulating in Brazil in 2015.

Another study published on 17 February reported the identification of Zika virus genome and Zika IgM antibodies in amniotic fluid samples from two pregnant women from north-eastern Brazil (Paraíba) who developed a disease compatible with Zika virus infection on week 10 and 18 of pregnancy, respectively. In both cases, ultrasound identified foetal microcephaly and amniocentesis was done at gestational week 28. Viral genome detection and IgM serology in serum and urine from the pregnant women were negative at that time [32]. The full viral genome demonstrated a high level of identity with Zika virus from French Polynesia in 2013.

The Ministry of Health of Brazil and the US CDC have initiated a microcephaly case-control study in Paraíba state related to Zika virus [29]. The study aims at estimating the proportion of babies born with microcephaly associated with Zika and the risks caused by the infection.

Guillain–Barré syndrome and other post-infectious neurological syndromes

Brazil, Colombia, El Salvador, Venezuela and Suriname have reported unusual increases of Guillain-Barré Syndrome (GBS) concomitant with Zika virus circulation. Since the last update of the RRA on 8 February 2016, the following developments are of note:

- On 29 January 2016, **Suriname** reported an increase in the incidence of GBS during 2015. On average, Suriname registers four cases of GBS per year. In 2015, however, ten cases of GBS were detected. In the first three weeks of 2016, three cases of GBS were detected [18]. So far, two of the GBS cases have tested positive for Zika virus infection.
- On 2 February 2016, **Venezuela** reported an increase in GBS cases since the second week of January 2016, with 252 GBS cases by the end of January; all were associated in time and space with Zika. Zika virus infection was confirmed by RT-PCR in three cases [33] .
- On 17 February 2016, **Colombia** reported 86 GBS cases that showed symptoms compatible with Zika virus infection over a five-week period between mid-December 2015 and the end of January 2016. The number of cases for the period was reported to be at least three times higher than the expected number, based on an average of 242 cases per year over the last seven years [18].

ECDC threat assessment for the EU

Evolution of Zika virus epidemic

The Zika epidemic in the Americas continues to evolve and expand geographically. Since the Rapid Risk Assessment issued on 8 February 2016, four additional countries or territories have reported laboratory confirmed autochthonous transmission: Aruba, Bonaire and Trinidad and Tobago in the Caribbean, and the Marshall Islands in the Pacific region [15].

Severe outcomes

Uncertainties persist about the frequency and clinical spectrum of intra-uterine Zika virus infections and the association between Zika virus and GBS and Zika virus and other neurological complications. The consistency of the concomitant occurrence of Zika virus and severe outcomes as described below indicate an increased likelihood of an association with Zika virus infection.

Microcephaly and congenital central nervous system malformations

There is a significant increase in the number of babies born with microcephaly in the north-eastern states of Brazil [30]. However, the magnitude and geographical spread of the increase has not yet been well characterised. Several case reports describe a sequence of clinical Zika virus infections during pregnancy, followed by adverse pregnancy outcomes and laboratory confirmations of Zika virus [26,27,34,35]. The virus has been detected in amniotic fluid from foetuses that were diagnosed with microcephaly prenatally. It has also been detected in placenta and CNS tissue in children with congenital CNS malformations who died before or soon after birth, and whose mothers had a history of Zika-like infection during pregnancy. The thoroughly investigated and well-documented case of severe CNS malformations recently reported from Slovenia has added to the evidence in favour of a causal link between Zika virus infection during pregnancy and congenital CNS malformations.

The potential of Zika virus to cause transplacental infection has been demonstrated by the case reports [27]. The evidence in favour of a causal link between transplacental infection and congenital CNS malformations is substantial. Although the currently available data are insufficient to quantify the risk of transplacental transmission during pregnancy (or the risk of congenital CNS malformations as a consequence of transplacental infection), there is sufficient evidence to warrant public health action. It is likely that the risk of transplacental infection as well as the risk of developing congenital CNS malformations depends on the gestational age at the time of infection. It is also plausible that other risk factors, such as the mother's age and the nutritional status, also influence the risk of transplacental transmission, but there are currently no data available to explore such risk factors. It is possible that Zika virus infection is a necessary factor in the aetiology of congenital CNS malformations but that there are, as of yet unidentified, co-factors that influence the risk.

It remains to be seen how many of the pregnant women who become infected will transmit the virus to the foetus, and how many foetuses will develop brain damage. In order to estimate the risk of congenital CNS malformation associated with Zika virus infection in pregnancy requires case-control and cohort studies in areas with widespread transmission. Because the populations of the Americas and Caribbean were naïve to Zika infection, the current epidemic offers a unique opportunity to estimate these risks. There are currently no results reported from well-designed studies that could answer these urgent questions. A case-control study announced to start in Paraíba

state in Brazil will hopefully provide evidence on the strength of the association between microcephaly and Zika virus infection during pregnancy [29].

Guillain–Barré syndrome and other post-infectious neurological syndromes

Cases of GBS continue to be reported from the affected countries. No new scientific evidence regarding the association between Zika virus and GBS has been published since the 8 February 2016 Rapid Risk Assessment.

French Polynesia, Venezuela, Colombia, El Salvador and Suriname have reported an unusual increase in GBS incidence above the baseline, together with a temporo-spatial association between the Zika virus epidemic and GBS. In some of these GBS cases, recent Zika virus infections were laboratory confirmed.

These observations support the role of Zika virus infection as a presumptive infection event preceding GBS. The consistency of the concomitant occurrence of Zika infections and GBS over place and time indicate a significant likelihood of an association between Zika virus infection and GBS. However, GBS is also known to be associated with other infectious diseases that are prevalent in the Americas and the Caribbean. Therefore well-designed prospective studies are required to establish the strength and frequency of this association.

Risk of Zika virus transmission via substances of human origin

People with asymptomatic infections and those who are in the incubation period of Zika disease could potentially donate contaminated substances of human origin (SoHO) without their infections being recognised at the time of donation [9]. Zika virus RNA has been detected in blood, urine and saliva during the acute phase of the disease, and seminal fluid after the acute illness [36-39]. Zika virus RNA has also been detected in breast milk of two mothers in French Polynesia but no replicative viral particles were detected in cell culture [40]. Musso et al. reported the presence of Zika virus genome by RT-PCR and replicative Zika viral particles in semen of a 44-year-old man in Tahiti three weeks after onset of symptoms [39]. Hearn et al. detected Zika virus RNA by RT-PCR in a semen sample 28 days after onset of clinical symptoms of Zika virus infection [40,41]. Presence of viral RNA in semen up to 62 days has been recently reported [42]. Data on the survival of Zika virus in processed and stored SoHO are lacking.

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. Data show that Zika virus viraemia could be up to 8.1x10e6 copies/ml and may last up to (and possibly beyond) 14 days, with varying reports of viraemia from 2 days before to 11 days after the onset of symptoms [37,40,45-47]. 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, supporting a potential risk of transfusion-derived transmission [36,47]. The Brazilian media reported probable cases of transfusion-transmitted Zika virus in March 2015 and February 2016 [43,44,48].

The limited set of data indicates that a risk of getting donor-derived Zika virus disease through SoHO is low. However, the growing evidence of association between Zika virus infection and congenital malformations and GBS justifies preventive measures to reduce the risk of transmission via SoHO supply [23].

Risk of sexual transmission

Two studies have demonstrated Zika genome sequences in semen up to 62 days after clinical disease, and one study found replicable Zika virus particles in semen more than three weeks after onset of Zika symptoms [39,42]. There are no data on viral load in semen and only two case reports of actual sexual transmission. In both cases, the men had symptomatic infections and the transmission is likely to have taken place during the period when they were likely to have been viraemic [25,49]. The very limited available data suggest that sexual transmission of Zika virus through semen is possible but that these events are rare. The risk of sexual transmission will be re-assessed as more information becomes available.

The Zika virus genome has also been detected in saliva during the acute phase of the disease but there is no information about the presence of viable virus in saliva, its viral load or kinetics. The risk of transmission via saliva cannot be further assessed at this time.

Zika virus has been found in breast milk during the acute phase of disease [40] but there are no documented transmissions via breastfeeding.

Travel-related risk for EU citizens

The spread of Zika virus infections in the Americas and in the Caribbean constitutes a significant development in the epidemiology of this emerging vector-borne disease. Travellers to countries where competent vectors are

present and Zika virus circulation is documented are at risk of becoming infected through mosquito bites. Due to the growing evidence of a link between Zika infection and severe congenital anomalies, pregnant women and women who are trying to become pregnant constitute a high-risk group with regard to Zika virus infection.

Residents in EU Overseas Countries and Territories, and Outermost Regions with competent and active vectors are at increased risk of exposure to Zika virus.

Risk related to mass gatherings

The Rio 2016 Olympics (5–21 August 2016) and the Paralympic Games (7–18 September 2016) are the two most prominent mass gathering events that will take place in the Americas in the coming months. A large number of visitors are expected for these events. The Olympic Games will take place during Brazil's winter when the cooler, drier weather will reduce mosquito populations and significantly lower the risk of infection for visitors. ECDC is preparing a comprehensive risk assessment for communicable diseases ahead of the Games.

An analysis of the 2014 World Cup in Brazil indicated the following:

- An analysis carried out for the 2014 World Cup in Brazil indicated that the density of dengue cases in Brazil is very low in the southern hemisphere (mid-June to mid-September). Therefore, the risk of vector-borne transmission of Zika virus infection during the Olympic Games is expected to be low – in analogy with the transmission of dengue which involves the same vectors [50].
- Only three exported cases of dengue fever were reported among returning travellers who attended the event [51]. The estimated expected number of dengue cases among the 600 000 foreigner tourists during the World Cup was 33 (range 3 to 59) according to a modelling exercise conducted before the event [52].

Although the probability of being bitten by an infected mosquito is expected to be very low during the events, it cannot be excluded that Zika-infected travellers will return to regions of the EU where competent vectors are active. This may create an opportunity for local vector-borne transmission.

Risk of importation and further transmission in EU Overseas Countries and Territories and Outermost Regions

The epidemic is currently spreading in the Americas and Caribbean. *Aedes aegypti* mosquitoes are present in the EU Overseas Countries and Territories (OCT) and Outermost Regions (OMR) in the Americas and the Caribbean, and several of them have reported autochthonous transmission. The risk of spread to yet unaffected OCTs and OMRs in the area is significant because of the immunologically naïve populations, presence of competent vectors, permissive climate, and the intense movement of people in and between countries and territories.

Other EU OMRs and OCTs outside of the Caribbean where mosquito vectors are present such as La Réunion and Madeira are at risk of establishment of local transmission should the virus be introduced. Madeira is of particular concern because of the close relationship with Brazil and Venezuela where Zika virus is currently circulating. The 2012 dengue epidemic demonstrated the favourable conditions for vector-borne outbreaks in Madeira.

Risk of importation and transmission in the continental EU

The continued rise in cases of Zika virus infection in the Americas and the Caribbean increases the risk of infection among travellers. ECDC is collecting reports of imported cases in the EU/EEA through the media and official government communication lines [15]. Cases of Zika virus infection coming from countries with autochthonous transmission continue to be reported in the EU.

There is no evidence to date that 'airport transmission' of mosquito-borne viral disease occurs, similar to airport malaria [53]. The risk of importation of Zika-infected mosquitoes inside aircraft cabins is low and there is no evidence that this plays a role in the transmission of arbovirus infections. WHO has issued specific guidance and recommendations for aircraft disinsection [24,54].

The risk of transmission of Zika virus infection is variable in the EU and depends on several co-factors, for example:

- The **presence of a potential mosquito vector**: *Aedes albopictus* is established in most places around the Mediterranean coast [55].
- The **competence** of *Aedes albopictus* to transmit Zika virus, which depends on characteristics of the pathogen (strain-specific vector competence) and of the mosquito species. Onward transmission from imported cases within the continental EU is possible because *Aedes albopictus* is considered a competent vector for the transmission of Zika virus, even though this has not yet been confirmed for European mosquito populations; experiments with European *Aedes albopictus* populations are ongoing [56,57].
- The **capacity of the vector** to transmit the infection is determined by a number of factors such as vector competence, the mosquito population density, feeding host preferences, biting rates and survival of the mosquito population. Spatial variation in vector capacity is expected in areas where *Aedes albopictus* is

present, and further depends on environmental conditions and locations. In practice, the presence of a competent vector in a location is necessary, but is not sufficient to allow further transmission when an arbovirus is introduced in a mosquito's population.

The risk of transmission of Zika virus infection is extremely low in the EU during winter season as the climatic conditions are not suitable for the activity of the *Aedes albopictus* mosquito. During the summer season, autochthonous transmission in the EU following the introduction of the virus by a viraemic traveller is possible in areas where *Aedes albopictus* is established [55]. For the months March to May, the International Research Institute for Climate and Society predicts above-normal temperatures in Europe coinciding with a normal precipitation pattern, which might result in an early start of the mosquito activity season in southern Europe [58].

Conclusions and options for response

Considering the continued rapid spread of Zika virus in the Americas and Caribbean, the growing evidence of an association between Zika virus infection during pregnancy and congenital central nervous system malformations, the association between Zika virus infection and Guillain–Barré syndrome, and the risk of establishment of local vector-borne transmission in Europe during the 2016 summer season, EU/EEA Member States are recommended to consider the following mitigation measures.

Information to travellers and EU residents in affected areas

Over the past two months, and as of 18 February 2016, autochthonous cases of Zika virus (ZIKV) infection have been reported from 35 countries or territories worldwide. In the past nine months, 40 countries or territories have reported autochthonous cases of Zika virus infection.

A list of countries and territories with documented autochthonous transmission during the past two months is available on the ECDC website.

Information for travellers to areas with local transmission of Zika virus

- Travellers visiting countries where there is active transmission of Zika virus should be made aware of the ongoing outbreak of Zika virus infection. A list of countries and territories with documented autochthonous transmission during the past two months is available on the ECDC website.
- Travellers visiting these countries should take measures to prevent mosquito bites indoors and outdoors, especially from sunrise to sunset when Aedes mosquito vectors are the most active.
  - Use mosquito repellent in accordance with the instructions indicated on the product label. DEET-based repellent is not recommended for children under two months of age but pregnant women can use it.
  - Wear long-sleeved shirts and long trousers.
  - Sleep or rest in screened or air-conditioned rooms, or under mosquito nets, even when resting during the day.
- Pregnant women and women who are planning to become pregnant should consider postponing non-essential travel to affected areas until after delivery. If travel to affected areas cannot be avoided, pregnant women should follow strict personal preventive measures and consult their healthcare providers before departure and upon return.
- Travellers with immune disorders or severe chronic illnesses should consult their doctor or seek advice from a travel clinic before travelling, particularly on effective prevention measures.
- There is evidence that Zika virus can be transmitted sexually through semen, and there are indications that the Zika virus genome can be present in semen for at least two months after a man has recovered from a Zika virus infection. Travellers to Zika-affected areas should be advised that using condoms could reduce the risk of sexual transmission.

Information for travellers returning from areas with local transmission of Zika virus

- Travellers showing symptoms compatible with Zika virus disease within three weeks of return from an affected area are advised to contact their healthcare provider and mention their recent travel.
- Pregnant women who have travelled in areas with Zika virus transmission should mention their travel during antenatal visits in order to be assessed and monitored.
- In order to protect pregnant women, male travellers returning from affected areas should consider using a condom with a pregnant female partner until the end of pregnancy, or for six months with partners at risk of getting pregnant.

Surveillance of imported cases and monitoring of transmission in the continental EU

- Increase awareness among clinicians and travel health clinics about the evolution of the Zika virus outbreak and the affected areas so that they can include Zika virus infection in their differential diagnosis for travellers from those areas.
- Enhance vigilance towards the early detection of imported cases of Zika virus infection in EU Member States, EU Overseas Countries and Territories, and EU Outermost Regions, in particular where vectors are present, in order to reduce the risk of autochthonous transmission. Clusters of unexplained rash illness compatible with Zika virus infection should be considered for enhanced surveillance.
- Strengthen laboratory capacity to confirm suspected Zika virus infections in the European region in order to differentiate Zika virus infections from other arboviral infections (e.g. dengue, chikungunya).
- Increase awareness among obstetricians, paediatricians and neurologists in the EU/EEA that Zika virus infections should be investigated in patients presenting with congenital CNS malformations, microcephaly and GBS.

Preparedness in the EU

Preparedness for the prevention and control of Zika virus infection in the EU/EEA will require capacities and capabilities for early detection, response and communication.

The strengthening of the following components might be considered with regard to Zika virus preparedness [59-64]:

- Early detection mechanisms that ensure:
  - the rapid notification of human cases (imported and/or autochthonous);
  - the surveillance of those *Aedes* mosquito species that are vectors for Zika virus; this should include entomological and environmental indicators.
- Response mechanisms that cover:
  - organisational and planning mechanisms aimed at the prevention and control of mosquito-borne diseases;
  - intersectoral and cross-disciplinary collaboration with all relevant partners;
  - case management;
  - gynaecological, obstetric and neonatal services to follow-up on infected pregnant women and to provide reproductive health guidance;
  - outbreak investigation capacity (including epidemiological, entomological and environmental aspects);
  - rapid vector control measures against imported cases in areas with those *Aedes* mosquito species that are vectors for Zika virus.
- Communication mechanisms:
  - Advice to travellers
  - Training of healthcare professionals on health impacts of Zika virus
  - Involvement of mass media for communication purposes and to promote public awareness and protection
  - Community involvement in the control of mosquito populations.

Safety of substances of human origin

Persons with diagnosis of Zika fever, except sperm donors, may be accepted for SoHO donation 28 days after cessation of symptoms. Sperm donors who have been infected with Zika virus should be deferred from donation for six months unless the semen tests negative for Zika virus RNA by nucleic acid testing (NAT). 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. The identification of cases may improve disease surveillance and contribute to the timely implementation of preventive interventions in response to an outbreak.

WHO is currently working on international reference preparations for Zika virus RNA and for Zika virus antibodies to be used for the comparative evaluation of both diagnostic and screening assays [65].

Non-affected areas

Health authorities should implement a precautionary deferral of asymptomatic blood, cells and tissues donors, except sperm donors, for 28 days after return from an affected area. Asymptomatic sperm donors should be deferred for six months after return unless the semen tests negative for Zika virus by NAT [41,42]. NAT testing could also be used to reinstate blood, cells and tissues donors.

Donors who had sexual contact with a person who has been diagnosed with Zika virus infection or with a person who travelled or lived in a Zika-affected area during the three months prior to the sexual contact may only donate blood, cells and tissues after at least 28 days after the last sexual contact [43].

The risk of Zika virus infection in an organ donor should not lead to exclusion from the donation, except when the organ recipient is a pregnant woman [66]. The risk of Zika virus transmission through a living donor should be assessed during a pre-donation evaluation and balanced against the benefits of the transplantation for each potential recipient. The screening of deceased organ donors at risk for the presence of Zika virus is currently under discussion.

SoHO donors should be encouraged to inform SoHO facilities if they develop symptoms compatible with Zika virus infection within 14 days after donation.

A regularly updated list and maps of areas/countries affected with Zika virus are available from the ECDC website.

In unaffected areas with competent vectors for Zika virus, a preparedness plan for the prevention and control of outbreaks of Zika virus infection should be developed to ensure the safety and continuity of SoHO supplies. This plan should also specify the conditions which necessitate the implementation of SoHO safety measures.

National competent authorities may authorise the importation of SoHO from affected areas, but only if the cells and tissues tested negative for Zika virus by NAT or if they were inactivated/sterilised by a validated method.

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 enveloped viruses. Data from model viruses were confirmed with the inactivation of West Nile virus and chikungunya virus [67,68]. For this reason, and in line with the regulations for West Nile virus deferral in EU Directive 2004/33/EC [69], 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 donated in areas affected by Zika fever.

All measures related to urine donation (deferring urine donors from affected areas, screening of urine donors and urine donations) should be based on a risk assessment aimed at ensuring the viral safety of urine-derived medicinal products.

Affected areas

As 80% of humans infected with Zika virus are asymptomatic, donor deferral measures based on fever will be of limited value in detecting viraemic donors. Experience from previous flavivirus outbreaks shows that blood establishments may consider the following:

- Temporarily interrupt donations in affected areas and import blood components from unaffected parts of the country.
- Quarantine collected blood components for five days and release them if donor reports the absence of acute illness. WHO recommends a quarantine period of 7–14 days [65]. (Studies on the effectiveness of temporary quarantine of blood components in the prevention of transfusion-transmitted mosquito-borne infections are lacking.)
- Consider the use of pathogen inactivation for plasma, platelets and some tissues in affected areas. Such methods are effective for other flaviviruses (e.g. West Nile virus and dengue virus) and model viruses for flaviviruses (e.g. bovine viral diarrhoea virus) [70-73]. The amotosalen UV method has been demonstrated to inactivate Zika virus in plasma [74].

As Zika virus infection may have serious consequences for the health of the recipient and because the current SoHO safety interventions have limited preventive capacities, the screening of all donated blood and all donors of cells and tissues for the presence of Zika virus RNA by NAT may be considered necessary in affected areas. Organ donors should be assessed individually, carefully weighing the benefits against the risks.

Due to the potential association between Zika virus infection and congenital CNS malformations, health authorities in affected areas may preemptively screen all blood transfusions for pregnant women so that only Zika virus-negative blood is used. They should also consider screening semen donors/donations for the presence of Zika virus.

SoHO establishments should update the donor information material and health questionnaire to comply with the safety measures.

Information to healthcare providers

- Ensure that Zika virus-infected patients in areas with *Aedes* mosquito vectors avoid getting bitten during the first week of illness (insecticide-treated bed nets, screened doors and windows as recommended by PAHO/WHO).
- Increase awareness among health professionals who provide prenatal care of the possible association between Zika virus and microcephaly and adapt prenatal monitoring in accordance with the exposure to the vector.

In addition, due to the unprecedented size of the Zika virus epidemic, health services and practitioners should be alerted to the possible occurrence of neurological syndromes (GBS and other neurological syndromes such as meningitis, meningoencephalitis and myelitis according to WHO/PAHO [18]) and potential disease complications not yet described in the scientific literature, and atypical clinical presentation among specific populations (i.e. children, the elderly, immunocompromised individuals and those with sickle cell disease).

References

1. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, French Polynesia. 14 February 2014 [Internet]. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/Zika-virus-French-Polynesia-rapid-risk-assessment.pdf.
2. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, Brazil and the Pacific region. 25 May 2015 [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-Zika%20virus-south-america-Brazil-2015.pdf.
3. European Centre for Disease Prevention and Control. Rapid risk assessment - Microcephaly in Brazil potentially linked to the Zika virus epidemic. 24 November 2015 [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf.
4. European Centre for Disease Prevention and Control. Rapid risk assessment - Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome. 10 December 2015 [Internet]. Stockholm: ECDC; 2015. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf.
5. 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 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-zika-virus-first-update-jan-2016.pdf.
6. European Centre for Disease Prevention and Control. Rapid risk assesment - Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome. Second update, 8 February 2016 [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-rapid-risk-assessment-8-february-2016.pdf.
7. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun 11;360(24):2536-43.
8. 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.
9. European Centre for Disease Prevention and Control. Factsheet for health professionals: Zika virus infection [Internet]. Stockholm: ECDC; 2015 [updated 2015 Nov 27]. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx.
10. Ministério da Saúde (Brasil). Confirmação do Zika vírus no Brasil [Internet]. Brasília: Portal da Saúde (Brasil); 2015 [updated 2015 May 14]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/17701-confirmacao-do-zika-virus-no-brasil.
11. Cardoso CW, Paploski IA, Kikuti M, Rodrigues MS, Silva MM, Campos GS, et al. Outbreak of Exanthematous Illness Associated with Zika, Chikungunya, and Dengue Viruses, Salvador, Brazil. Emerg Infect Dis. 2015 Dec;21(12):2274-6.
12. Garcia E, Yactayo S, Nishino K, Millot V, Perea W, Briand S. Zika virus infection: Global update on epidemiology and potentially associated clinical manifestations. Wkly Epidemiol Rec [Internet]. 2016; 91(7):[73-88 pp.]. Available from: http://www.who.int/wer/2016/wer9107.pdf?ua=1.
13. European Centre for Disease Prevention and Control. Communicable Disease Threats Report (CDTR) [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/publications/surveillance_reports/Communicable-Disease-Threats-Report/Pages/cdtr.aspx.
14. European Centre for Disease Prevention and Control. Countries and territories with local Zika transmission [Internet]. Stockholm: ECDC; 2016. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/Zika-countries-with-transmission.aspx.
15. European Centre for Disease Prevention and Control. Weekly epidemiological situation - Zika outbreak in the Americas and the Pacific [Internet]. Stockholm: ECDC; 2016 [updated 2016 Feb 19]. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/zika-outbreak/Pages/epidemiological-situation.aspx.
16. Ministério da Saúde - Secretaria de Vigilância em Saúde (Brasil). Nota informativa N^0 01/2015 – COES Microcefalias. 17 novembro 2015 [Internet]. Brasília: Ministério da Saúde (Brasil); 2015 [cited 2016 Feb 5]. Available from:

http://www.saude.rs.gov.br/upload/1448404998_microcefalia_nota_informativa_17nov2015_MINISTERIO%20DA%20SAUDE.pdf.

17. Ministério da Saúde (Brasil). Ministério da Saúde investiga aumento de casos de microcefalia em Pernambuco. 11 November 2015 [Internet]. Portal da Saúde (Brasil); 2015 [updated 2015 Nov 11]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20629-ministerio-da-saude-investiga-aumento-de-casos-de-microcefalia-em-pernambuco.
18. Pan American Health Organization / World Health Organization, Regional Office for the Americas. Epidemiological Update: Neurological syndrome, congenital malformations, and Zika virus infection. 17 January 2016 [Internet]. Washington, D.C.: PAHO/WHO; 2016. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32879&lang=en.
19. Pan American Health Organization / World Health Organization, Regional Office for the Americas. Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas. 1 December 2015. Epidemiological alert [Internet]. 2015. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32405&lang=en.
20. Centers for Disease Control and Prevention. Media statement: CDC issues interim travel guidance related to Zika virus for 14 countries and territories in Central and South America and the Caribbean. 15 January 2016 [Internet]. Atlanta: CDC; 2016. Available from: http://www.cdc.gov/media/releases/2016/s0315-zika-virus-travel.html
21. Government of Canada. Zika virus infection in the Americas: Travel health notice [Internet]. Government of Canada; 2016 [updated 2016 Feb 19]. Available from: http://travel.gc.ca/travelling/health-safety/travel-health-notices/143.
22. Hawaii Department of Health. News release: Hawaii Department of health receives confirmation of Zika infection in baby born with microcephaly. 15 January 2016 [Internet]. Honolulu: Hawaii Department of Health. Available from: http://health.hawaii.gov/news/files/2013/05/HAWAII-DEPARTMENT-OF-HEALTH-RECEIVES-CONFIRMATION-OF-ZIKA-INFECTION-IN-BABY-BORN-WITH-MICROCEPHALY.pdf.
23. World Health Organization. WHO Director-General summarizes the outcome of the Emergency Committee on Zika. 1 February 2016 [Internet]. Geneva: WHO; 2016. Available from: http://www.who.int/mediacentre/news/statements/2016/emergency-committee-zika-microcephaly/en/.
24. 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/.
25. Dallas County Health and Human Services. DCHHS reports first Zika virus case in Dallas county acquired through sexual transmission. 2 February 2016 [Internet]. Dallas, TX: DCHHS; 2016.
26. Mlakar J, Korva M, Tul N, Popović M, Poljšak-Prijatelj M, Mraz J, et al. Zika virus associated with microcephaly. N Engl J Med. 2016.
27. Martines RB, Bhatnagar J, Keating MK, Silva-Flannery L, Muehlenbachs A, Gary J, et al. Notes from the field: Evidence of Zika virus infection in brain and placental tissues from two congenitally infected newborns and two fetal losses — Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(6):1-2.
28. Oster AM, Brooks JT, Stryker JE, Kachur RE, Mead P, Pesik NT, et al. Interim guidelines for prevention of sexual transmission of Zika virus — United States, 2016. MMWR Morb Mortal Wkly Report. 2016;65(5):120-1.
29. Ministério da Saúde (Brasil). Brasil e EUA iniciam estudo na Paraíba sobre microcefalia associada ao vírus Zika. [Internet]. Brasilia: Portal da Saúde (Brasil); 2016 [updated 2016 Feb 16]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/22199-brasil-e-eua-iniciam-estudo-na-paraiba-sobre-microcefalia-associada-ao-virus-zika.
30. Centro de operações de emergências em saúde pública sobre microcefalias (Brasil). Monitoramento dos casos de microcefalia no Brasil. Semana epidemiológica 06 (07 a 13/02/2016). Informe Epidemiológico [Internet]. 2016; 13. Available from: http://portalsaude.saude.gov.br/images/pdf/2016/fevereiro/17/coes-microcefalia-inf-epi-13-se06-2016.pdf.
31. Centro de operações de emergências em saúde pública sobre microcefalias (Brasil). Monitoramento dos casos de microcefalia no Brasil. Semana epidemiológica 05 (31/01 a 06/02/2016). Informe Epidemiológico [Internet]. 2016; 12. Available from: http://portalsaude.saude.gov.br/images/pdf/2016/fevereiro/12/COES-Microcefalias-Informe-Epidemiologico-12-SE-05-2016-12fev2016-13h30.pdf.
32. Calvet G, Aguiar RS, Melo ASO, Sampaio SA, de Filippis I, Fabri A, et al. Detection and sequencing of Zika virus from amniotic fluid of fetuses with microcephaly in Brazil: a case study. Lancet Infect Dis [Internet]. 2016. Available from: http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(16)00095-5/fulltext.

33. World Health Organization. Zika virus: News and updates [Internet]. Geneva: WHO; 2016 [updated 2016 Feb]. Available from: http://who.int/emergencies/zika-virus/timeline-update/en/#.

34. Schuler-Faccini L, Ribeiro E, Feitosa I, Horovitz D, Cavalcanti D, Pessoa A, et al. Possible association between Zika virus infection and microcephaly — Brazil, 2015. MMWR Morb Mortal Wkly Rep. 2016;65(3):59-62.

35. Melo OAS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol. 2016 Jan;47(1):6-7.

36. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill [Internet]. 2014; 19(14):[pii=20761 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20761.

37. 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.

38. Musso D, Roche C, Tu-Xuan N, Robin E, Teissier A, Cao-Lormeau VM. Detection of Zika virus in saliva. J Clin Virol. 2015;68:53-5.

39. 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.

40. Besnard M, Lastere S, Teissier A, Cao-Lormeau V, Musso D. Evidence of perinatal transmission of Zika virus, French Polynesia, December 2013 and February 2014. Euro Surveill [Internet]. 2014; 19(13):[pii=20751 p.]. Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20751.

41. Hearn PT, Atkinson B, Hewson R, Brooks T. Identification of the first case of imported Zika Fever to the UK: A novel sample type for diagnostic purposes and support for a potential non-vectorborne route of transmission. Am J Trop Med Hyg. 2014;91(5):62-3.

42. Atkinson B, Hearn P, Afrough B, Lumley S, Carter D, Aarons. Emma J, et al. Detection of Zika virus in semen. Emerg Infect Dis. 2016;22(5).

43. U.S. Food and Drug Administration. Recommendations for donor screening, deferral, and product management to reduce the risk of transfusion - transmission of Zika virus. Guidance for industry [Internet]. Silver Spring, MD: FDA; 2016. Available from: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM486360.pdf.

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

45. 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.

46. Herriman R. Transfusion-associated Zika virus reported in Brazil. 18 December 2015 [Internet]. Outbreak News Today; 2015 [cited 2016 Feb 3]. Available from: http://outbreaknewstoday.com/transfusion-associated-zika-virus-reported-in-brazil-76935/.

47. Secretaria de Saúde de Campinas (Brasil), Hemocentro da Unicamp. Notícias: Campinas tem o primeiro caso de Zika vírus confirmado. 2 February 2016 [Internet]. Campinas: Prefeitura de Campinas (Brasil); 2016. Available from: http://www.campinas.sp.gov.br/noticias-integra.php?id=29241.

48. 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

49. 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.

50. Aguiar M, Rocha F, Pessanha JE, Mateus L, Stollenwerk N. Carnival or football, is there a real risk for acquiring dengue fever in Brazil during holidays seasons? Sci Rep. 2015;5:8462.

51. Aguiar M, Coelho GE, Rocha F, Mateus L, Pessanha JE, Stollenwerk N. Dengue transmission during the 2014 FIFA World Cup in Brazil. Lancet Infect Dis. 2015 Jul;15(7):765-6.

52. Massad E, Burattini MN, Ximenes R, Amaku M, Wilder-Smith A. Dengue outlook for the World Cup in Brazil. The Lancet Infectious Diseases.14(7):552-3.

53. Gratz NG, Steffen R, Cocksedge W. Why aircraft disinsection? Bull World Health Organ. 2000;78(8):995-1004.

54. International Programme on Chemical Safety (IPCS). Chemicals for aircraft disinsection [Internet]. Geneva WHO; 2013. Available from: http://www.who.int/ipcs/assessment/aircraft_disinsection_review/en/.

55. 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.

56. Grard G, Caron M, Mombo I, 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.

57. 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.

58. International Research Institute for Climate and Society (IRI). Seasonal climate forecasts [Internet]. Palisades, NY: Columbia University; 2016 [cited 2016 Feb 3]. Available from: http://iri.columbia.edu/our-expertise/climate/forecasts/seasonal-climate-forecasts/.

59. Special edition: Chikungunya and Zika virus, October 2014. Euro Surveill [Internet]. 2014. Available from: http://www.eurosurveillance.org/images/dynamic/ET/V19N02/V19N02.pdf.

60. European Centre for Disease Prevention and Control. Dengue outbreak in Madeira, Portugal, October–November 2012 [Internet]. Stockholm: ECDC; 2013. Available from: http://ecdc.europa.eu/en/publications/publications/dengue-outbreak-madeira-mission-report-nov-2012.pdf.

61. European Centre for Disease Prevention and Control. Dengue outbreak in Madeira, Portugal, March 2013. [Internet]. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/dengue-madeira-ECDC-mission-2013.pdf.

62. European Centre for Disease Prevention and Control. Guidelines for the surveillance of invasive mosquitos in Europe [Internet]. Stockholm: ECDC; 2012. Available from: http://ecdc.europa.eu/en/publications/Publications/TER-Mosquito-surveillance-guidelines.pdf.

63. European Centre for Disease Prevention and Control. Guidelines for the surveillance of native mosquitoes in Europe [Internet]. Stockholm: ECDC; 2014. Available from: http://ecdc.europa.eu/en/publications/Publications/surveillance-of%20native-mosquitoes%20-guidelines.pdf.

64. European Centre for Disease Prevention and Control. The climatic suitability for dengue transmission in continental Europe [Internet]. Stockholm: ECDC; 2012. Available from: http://ecdc.europa.eu/en/publications/publications/ter-climatic-suitablility-dengue.pdf.

65. World Health Organization. Maintaining a safe and adequate blood supply during Zika virus outbreaks. Interim guidance, February 2016 [Internet]. Geneva: WHO; 2016. Available from: http://apps.who.int/iris/bitstream/10665/204436/1/WHO_ZIKV_HS_16.1_eng.pdf?ua=1.

66. Organ Procurement & Transplantation Network. Guidance for organ donation and transplantation professionals regarding the Zika virus [Internet]. U.S. 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/.

67. 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 Oct;52(10):2122-30.

68. 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.

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

70. 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.

71. 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.

72. 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.

73. 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.

74. 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.