



## RAPID RISK ASSESSMENT

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

Fourth update, 9 March 2016

### Main conclusions and options for response

Considering the continued spread of Zika virus in the Americas and Caribbean, the strong 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 a range of mitigation measures.

The following uncertainties have been taken into consideration in developing the proposed options for response:

- At present, there is a lack of evidence at which stage of the pregnancy the foetus is most vulnerable to Zika virus infection. Therefore the entire duration of pregnancy should be considered at risk.
- The presence of infectious Zika virus in semen has been detected up to three weeks after onset of disease; the longest interval reported between the onset of symptoms in a male and the subsequent onset of the disease thought to be due to sexual transmission in a female partner is 19 days.
- The role of asymptomatic males in the sexual transmission to women is unknown.
- The roles of different mosquito species as potential vectors of Zika virus should be clarified. If current assumptions prove inaccurate or incorrect, vector control strategies have to be adapted and revised.

### Information to travellers and EU residents in affected areas

Over the past two months, and as of 7 March 2016, autochthonous cases of Zika virus infection were reported from 39 countries or territories worldwide. In the past nine months, 42 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 and EU citizens residing in areas with active local transmission

- 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 and EU citizens residing in these countries should take measures to prevent mosquito bites indoors and outdoors, especially from sunrise to sunset when *Aedes* mosquito vectors are most active in biting. These measure include:
  - The use of mosquito repellent in accordance with the instructions indicated on the product label.
  - Wearing long-sleeved shirts and long trousers, especially during the hours when the type of mosquito that is known to transmit the Zika virus (*Aedes*) is most active.
  - Sleeping or resting in screened or air-conditioned rooms, otherwise use mosquito nets, even 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.
- Pregnant women who plan to travel to affected areas and pregnant women residing in affected areas should consult their healthcare providers for advice and follow strict measures to prevent mosquito bites.
- 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.
- Travellers to Zika-affected areas and EU citizens residing in affected areas should be advised that using condoms could reduce the risk of sexual transmission through semen.

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

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

### Information to healthcare providers in EU Member States

Ensure that Zika virus-infected patients in areas with *Aedes* mosquito vectors avoid getting bitten during the first week of illness (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 (Guillain-Barré syndrome 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, 29 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 seven 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].
- 'Zika virus disease epidemic: potential association with microcephaly and Guillain–Barré syndrome (third update)', 23 February 2016 [7]

## Consulted experts

ECDC internal response team in alphabetical order: Ninnie Abrahamsson, Denis Coulombier, Niklas Danielsson, Dragoslav Domanovic, Laura Espinosa, Kaja Kaasik-Aaslav, Teija Korhonen, Thomas Mollet, Edit Szegedi, Wim Van Bortel and Hervé Zeller.

ECDC issues this risk assessment document according to Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control. In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

## 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, myalgia and non-purulent conjunctivitis. 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 [9]. 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 samples. Virus-specific antibodies can be detected usually 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 the previous risk assessments [1-7] and in the ECDC factsheet for health professionals [10].

## Event background information

### Zika virus outbreak

#### Situation worldwide

Towards the end of 2014, Brazil detected a cluster of cases of febrile rash in the northeast region of the country. The diagnosis of Zika virus infection was confirmed in May 2015 by polymerase chain reaction (PCR) assay. The Brazilian Ministry of Health estimated that in 2015 between 0.4 and 1.3 million cases of Zika virus infection occurred in the country, significantly exceeding the number of reported or confirmed cases [11]. As of 18 February 2016, Zika virus infection is a notifiable disease in Brazil [12]. Colombia is the second most affected country in the Americas. The epidemic in Colombia seems to have reached its peak, indicated by a decline in the number of reported cases per week over the past four weeks [13].

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## Situation in the EU/EEA and EU outermost regions (OMR) and overseas countries and territories (OCT)

As of 7 March 2016, no autochthonous Zika virus transmission has been reported in the continental EU. ECDC is collecting data regarding imported cases through the media and official government communication lines. As of 7 March 2016, ECDC has recorded 224 imported cases in 15 EU/EEA countries: Austria (1), the Czech Republic (3), Denmark (4), Finland (2), France (89), Germany (26), Ireland (3), Italy (9), Malta (1), the Netherlands (30), Portugal (11), Slovakia (1), Spain (32), Sweden (2), and the UK (10). Eleven of the imported cases are pregnant women. In addition, one confirmed case was published following the diagnosis in a Slovenian hospital [14]. (Note: This list may not be exhaustive.)

Several outermost regions (OMR) and overseas countries and territories (OCT) continue to report autochthonous transmission: French Guiana, Guadeloupe, Martinique, Saint Martin and Sint Maarten.

The latest information on the spread of the Zika virus epidemic and an update on adverse pregnancy outcomes and post-infectious GBS is available through [the Zika outbreak webpage](#) [15]. Regular updates on the epidemiological situation are available on an ECDC webpage entitled [Countries and territories with local Zika transmission](#) [16].

As of 7 March 2016, 28 countries in the EU/EEA advise pregnant women to consider postponing travel to affected countries [17].

## Zika mosquito vectors

*Aedes aegypti* and *Aedes albopictus* mosquito populations from South America and the Caribbean appear to have an unexpectedly low competence as vectors for Zika virus [18]. Experimental infections conducted on five *Aedes aegypti* populations from Brazil, French Guiana, Guadeloupe, Martinique and the USA, and two populations of *Aedes albopictus* from Brazil and the USA showed a high infection rate (which refers to the proportion of mosquitoes with infected body), but a lower disseminated infection (which refers to the proportion of mosquitoes with infected head among the previously detected infected mosquitoes). Transmission of Zika virus (strain New Caledonia 2014 from the Asian lineage) was reported 14 days post infection of the mosquito at a low level.

Both species exhibit a similar transmission potential for Zika virus. Virus particles appear in the salivary gland of *Aedes aegypti* and *Aedes albopictus* between 7 to 9 days post-infection for dengue, after 10 days for yellow fever, and from day 2 for chikungunya.

## Microcephaly and congenital central nervous system malformations

Since October 2015 and as of 27 February 2016, Brazil reported 5 909 suspected cases of microcephaly from 1 143 municipalities in 25 states [19]. Of those cases, 641 are confirmed cases of microcephaly, 82 of which are laboratory confirmed for Zika virus. Of the remaining cases, 1 046 were investigated and discarded (no Zika virus infection), while 4 222 cases are still under investigation.

The northeast region of Brazil has reported 81% of all cases. To date, 22 Brazilian states report ongoing transmission of Zika virus.

Among the 5 909 suspected cases of microcephaly, 139 intrauterine or neonatal deaths were reported. Of these, 31 cases were investigated and confirmed (microcephaly and/or central nervous system malformations). Ninety-six cases are still under investigation, and 12 cases were discarded.

On 24 February 2016, Colombia reported a case of microcephaly in a foetus possibly linked to Zika virus infection in Colombia [20]. The mother had a suspected Zika virus infection and had an abortion. However, due to the disposal of the foetal remains, no confirmed diagnosis was possible.

## Guillain–Barré syndrome and other post-infectious neurological syndromes

Since October 2015, five countries or territories have reported increased Guillain–Barré syndrome (GBS) incidence. Three of them, Brazil, Suriname and Venezuela, reported GBS cases with laboratory confirmation of Zika virus infection. El Salvador and Colombia also reported cases of GBS, but without laboratory confirmation of Zika virus infection [21]. In addition, GBS cases with laboratory-confirmed Zika virus infections were reported from Martinique (two cases), Puerto Rico (one case), and Panama – without any increase in GBS incidence [21,22]. In Europe, France reported one case of neurological complications related to Zika virus in a returning traveller [23].

# ECDC threat assessment for the EU

## Evolution of the Zika virus epidemic

The Zika epidemic in the Americas continues to evolve and expand geographically. Since the Rapid Risk Assessment issued on 23 February 2016, three additional countries or territories have reported laboratory-confirmed autochthonous transmission: Saint Vincent and the Grenadines, Sint Maarten and the Philippines [24-26].

The unexpectedly low vector competence of *Aedes aegypti* and *Aedes albopictus* observed during a recent study may suggest that other factors such as the high density of human-biting mosquitoes and a naive population for Zika virus might contribute to the rapid spread of the disease in the Americas. Furthermore, media reports that other mosquito species may be able to carry the Zika virus, e.g. *Culex quinquefasciatus* in Brazil and New Zealand which raises the question of whether these species might also be able to transmit the virus [27,28]. However, before incriminating a new mosquito species as a vector for Zika virus, firm evidence is needed on its vector competence and capacity.

## Severe outcomes

Uncertainties persist about the frequency and clinical spectrum of intra-uterine Zika virus infections. The evidence of the role of Zika virus infection as a presumptive infection event preceding GBS is accumulating. 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

An increase in microcephaly cases and other neonatal malformations is only reported in Brazil and French Polynesia in 2013–2014. In addition, two cases linked to exposure in Brazil were detected in two other countries (once case in Hawaii, USA, and one case published following the diagnosis in a Slovenian hospital [14]). The magnitude and geographical spread of the increase has not yet been well characterised.

The evidence in favour of a causal link between transplacental infection and congenital CNS malformations is substantial and accumulating. A recent study by Tang et al. shows that Zika virus (original strain M766 from the African lineage) targets human brain cells, reducing their viability and growth as neurospheres and cerebral organoids [29]. The Zika virus was able to replicate in infected progenitor cells. The fact that cells infected with Zika virus were growing slowly and cell division cycles stopped could contribute to microcephaly. Another study in Brazil, using the same viral strain, claimed similar findings [30].

Several case reports demonstrate the potential of Zika virus to cause transplacental infections [14,31-34]. The virus has been detected in amniotic fluid from fetuses 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 added to the evidence in favour of a causal link between Zika virus infection during pregnancy and congenital CNS malformations [14]. One case report suggests that in addition to microcephaly there might be a link between Zika virus infection and hydrops fetalis and foetal demise [35].

A recent study provides further evidence of the role of Zika virus infection – despite mild clinical symptoms – in congenital abnormalities at different stages of pregnancy [34]. A group of 88 women who presented with mild illness with or without rash or fever that had developed within five days were followed from September 2015 to February 2016 in Brazil. Forty-two Zika virus-positive women (positive test by PCR in blood and/or urine) and 16 Zika virus-negative women were included in the study. Foetal abnormalities were detected by ultrasonography in 12 of the 42 Zika-positive women (29%) but in none of the 16 women who tested negative. Foetal abnormalities included in utero growth restrictions with or without microcephaly, ventricular calcifications or other CNS lesions, abnormal amniotic fluid volume or cerebral or umbilical artery flow. There were two foetal deaths at 36 and 38 weeks of gestation. Cerebral calcifications were seen in fetuses of women infected as late as 27 weeks, and intrauterine growth restriction was present in fetuses of women infected within a wide range of infant gestational age.

The currently available data are insufficient to quantify the risk of transplacental transmission during pregnancy and the resulting risk of adverse pregnancy outcomes. It is still uncertain how many of the pregnant women who become infected will transmit the virus to the foetus, and how many of the fetuses will develop brain damage or other malformations. 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.

The estimation the risk of congenital CNS malformation associated with Zika virus infection in pregnancy requires additional 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. 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 [36]. For surveillance purposes, the US CDC has developed a voluntary registry to collect information on pregnant women in the US with confirmed Zika virus infection and their infants [37].

## Guillain–Barré syndrome and other post-infectious neurological syndromes

Cases of GBS continue to be reported from the affected countries. Observations support the role of Zika virus infection as a presumptive infection event preceding GBS. Countries reporting an increase of Guillain-Barré syndrome are affected by Zika viral strains from the Asian lineage. However, GBS is also known to be associated with other infectious diseases that are prevalent in the Americas and the Caribbean.

During the outbreak of Zika virus in French Polynesia between October 2013 and April 2014, an increase of Guillain-Barré syndrome was reported. A recently published case-control study examined the linkages between Zika infection and Guillain-Barré syndrome [38]. Of the 42 patients diagnosed with Guillain-Barré syndrome during the outbreak, 98% had anti-Zika IgM or IgG antibodies. All 42 had neutralising antibodies against Zika, compared with 56% in the control group (patients treated at the hospital for other illnesses). In addition, 37 of the 42 patients with Guillain-Barré syndrome (88%) reported symptomatic Zika virus infection that preceded the occurrence of neurological symptoms by a median of six days. Most patients (95%) with Guillain-Barré syndrome had pre-existing dengue immunity, but this did not differ significantly from the control groups. The incidence of Guillain-Barré cases during the Zika epidemic in French Polynesia was 24 per 100 000 population over the seven months of the epidemic, a rate significantly higher than the baseline incidence rate of 1 to 4 per 100 000 per year prior to the epidemic.

## Risk of Zika virus transmission via substances of human origin

People with asymptomatic infections and those who are viraemic 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 [10]. The virus can also be transmitted by SoHO from donors after clinical recovery of Zika virus disease due to possible prolonged viraemia or a persistence of the virus in semen after viraemia has cleared. Zika virus RNA has been detected in blood, urine, saliva seminal fluid and breast milk [39-43] (Table 1). 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. 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 [39,44]. The Brazilian media reported possible cases of transfusion-transmitted Zika virus in March 2015 and February 2016 [45-47]. Reports of sexual transmission of Zika virus through contaminated male semen to a partner indicate the possible virus transmission through donated sperm [28,48-51]. 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 not been reported, but this possibility cannot be excluded due to the confirmed presence of the virus in human blood and bodily fluids.

**Table 1. Time of detection and Zika virus RNA load in samples of infected individuals**

Sample origin	Time of detection (days)		Viral RNA load	Isolation of replicative particles	References
	Before the onset of symptoms	After the onset of symptoms			
Blood	2-3	11	up to $8.1 \times 10^6$ copies/mL	+	[39]
Urine	-	10 to 20	$0.7-220 \times 10^6$ copies/mL	+	[22,40]
Saliva	-	2 to 8	NA	NA	[41,52]
Seminal fluid	-	21 to 62	$1.1 - 2.9 \times 10^7$ copies/mL	+	[42,53,54]
Breast milk	-	3 to 8 after delivery	up to $2.1 \times 10^6$ copies/mL	+	[43,55]

The limited set of data indicates that there is a potential risk of Zika virus transmission through SoHO that may cause serious consequences to the health of recipients. However, a scarcity of reported cases of donor-derived Zika virus infection precludes a more accurate risk assessment. The evidence of association between Zika virus

infection and congenital malformations and GBS justifies preventive measures to reduce the risk of transmission via SoHO supply [56].

## Risk of sexual transmission

Live Zika virus particles have been detected on one occasion in semen more than three weeks after onset of Zika symptoms. Zika viral RNA has been reported in semen up to 62 days after clinical disease [42,54].

Zika virus genome has also been detected in saliva during the acute phase of the disease [52]. 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.

Several cases of sexual transmission from males to their partners have been reported or are under investigation in recent weeks (USA, Italy, Argentina, France and New Zealand) [28,37,48-50]. In all cases, males presented with a clinical illness compatible with Zika virus infection. Five male-to-female sexual transmission cases for which detailed information is available are shown in Table 2. The interval between onset of symptoms in the man and in the woman partner varies between 4 and 19 days. The shortest period reported corresponded to a male who might have had sexual contact several days before onset of disease.

So far, no sexual transmission of Zika virus from infected women to their partners and from persons who are asymptotically infected has been reported.

**Table 2. Sexual transmission of Zika virus from returning male travellers to female sexual partners**

Date of reporting	Country (travel origin, year)	No. of cases (detection)	Interval between onset of symptoms in man and woman sexual partners	Reference
2011	USA (Senegal, 2008)	1 (serology)	4	[51]
25 Feb 2016	Italy (Thailand, 2014)	1 (serology)	19	[48]
26 Feb 2016	USA (Central America, 2016)	1 (PCR)	10	[57]
26 Feb 2016	USA (Caribbean, 2016)	1 (PCR)	13	[57]
26 Feb 2016	USA (Central America, 2016)	1 (serology)	13	[57]

## 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 serious adverse outcomes of Zika virus infection.

Residents in EU OCTs and OMRs with competent and active vectors are at increased risk of exposure to Zika virus.

## Risk related to mass gatherings

The Rio de Janeiro 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 and 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:

- The density of dengue cases in Brazil was 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 [58].
- Only three exported cases of dengue fever were reported among returning travellers who attended the event [59]. 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 [60].

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.

People travelling to Brazil before the Olympic Games should follow the precautions and recommendations issued by their national health authorities. CDC issued specific travel recommendations related to the Olympics and the Paralympic Games [61].

## Risk of importation and transmission in EU OCTs and OMRs

*Aedes aegypti* mosquitoes are present in the EU OCTs and OMRs in the Americas and the Caribbean, and most of them have reported autochthonous transmission. The risk associated with 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 [62].

## 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 [17]. Cases of Zika virus infection coming from countries with autochthonous transmission continue to be reported in the EU.

There is no evidence to date of 'airport transmission' of mosquito-borne viral disease, similar to airport malaria [63]. 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 [64,65].

The risk of transmission of Zika virus infection in the EU is variable 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 [66].
- 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* might be considered a competent vector for the transmission of Zika virus, although a recent study showed an unexpected low vector competence of this species [18]. The vector competence of this species has not yet been confirmed for European mosquito populations; experiments with European *Aedes albopictus* populations are ongoing [67,68].
- 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 the 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 [66]. 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 [69].

## Conclusions and options for response

Considering the continued spread of Zika virus in the Americas and Caribbean, the strong 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 a range of mitigation measures.

The following uncertainties have been taken into consideration in developing the proposed options for response:

- At present, there is a lack of evidence at which stage of the pregnancy the foetus is most vulnerable to Zika virus infection. Therefore the entire duration of pregnancy should be considered at risk.
- The presence of infectious Zika virus in semen has been detected up to three weeks after onset of disease; the longest interval reported between the onset of symptoms in a male and the subsequent onset of the disease thought to be due to sexual transmission in a female partner is 19 days.
- The role of asymptomatic males in the sexual transmission to women is unknown.

- The roles of different mosquito species as potential vectors of Zika virus should be clarified. If current assumptions prove inaccurate or incorrect, vector control strategies have to be adapted and revised.

## Information to travellers and EU residents in affected areas

Over the past two months, and as of 7 March 2016, autochthonous cases of Zika virus infection have been reported from 39 countries or territories worldwide. In the past nine months, 42 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 and EU citizens residing in areas with active local transmission

- 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 and EU citizens residing in these countries should take measures to prevent mosquito bites indoors and outdoors, especially from sunrise to sunset when *Aedes* mosquito vectors are most active in biting. These measure include:
  - The use of mosquito repellent in accordance with the instructions indicated on the product label.
  - Wearing long-sleeved shirts and long trousers, especially during the hours when the type of mosquito that is known to transmit the Zika virus (*Aedes*) is most active.
  - Sleeping or resting in screened or air-conditioned rooms, otherwise use mosquito nets, even 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.
- Pregnant women who plan to travel to affected areas and pregnant women residing in affected areas should consult their healthcare providers for advice and follow strict measures to prevent mosquito bites.
- 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.
- Travellers to Zika-affected areas and EU citizens residing in affected areas should be advised that using condoms could reduce the risk of sexual transmission through semen.

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

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

## 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 OCTs and OMRs, in particular where vectors are present, in order to reduce the risk of autochthonous transmission.
- Clusters of unexplained rash illness detected in receptive areas between 1 May and 31 October should be investigated, and Zika virus infection should be considered as an underlying cause.
- 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.

## Safety of substances of human origin

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. Measures to prevent Zika virus transmission through SoHO should be taken in affected and non-affected areas. Detailed SoHO safety measures are described in Annex 1.

### Non-affected areas

The primary measure to prevent Zika virus transmission in non-affected areas is the temporary deferral of blood donors from donation. Living donors of cells and tissues who are at risk of being infected should also be deferred. Criteria for deferral are:

- a medical diagnosis of Zika virus disease;
- return from affected areas; and
- sexual intercourse with males diagnosed with Zika virus disease or returned from affected areas.

Deceased donors of cells and tissues with a recent medical diagnosis of Zika virus infection should not be accepted for donation. Periods defined for donor deferral/acceptance should provide a sufficient safety margin for a virus-free donation. This includes taking into account viral persistence in the particular type of SoHO during and after the clinical course of Zika virus disease (see Annex 1 for suggested deferral periods).

### Affected areas

Blood and tissue establishments may temporarily interrupt donations and import blood components or cells and tissues from unaffected parts of the country and consider the use of pathogen inactivation for plasma, platelets and some tissues. 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 to assure the safety and sustainability of supply in affected areas. Irrespective to the presence of ongoing local virus transmission in the area, the risk of Zika virus transmission through organs donated by living or deceased donors should be recognised and assessed during a pre-donation evaluation and balanced against the benefits of the transplantation for each potential recipient.

## Information to healthcare providers in EU Member States

Ensure that Zika virus-infected patients in areas with *Aedes* mosquito vectors avoid getting bitten during the first week of illness (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 (Guillain-Barré syndrome 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).

## 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. Consistent with the evidence presented in this document, the following components might be considered with regard to Zika virus preparedness [62,70-74].

Early detection mechanisms should ensure the following:

- Rapid notification of human cases (imported and/or autochthonous)
- Surveillance of those *Aedes* mosquito species that are vectors for Zika virus; this should include consideration of entomological and environmental indicators.

Response mechanisms should cover the following:

- 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
- Safety of substances of human origin
- 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, with special focus on pregnant women
- 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.

## Annex. Prevention of Zika virus transmission by substances of human origin

In order to prevent Zika virus transmission through substances of human origin (SoHO), a range of measures is possible: informing donors about the infection, temporary deferral of donors based on the recent travel history to affected areas, and medical diagnosis of Zika virus infection. The use of pathogen-inactivated blood components and tissues, or laboratory screening of donors/donations for Zika virus disease are recommended in affected areas. At present, no laboratory screening assays are commercially available.

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 [75]. A regularly updated list and maps of areas/countries affected with Zika virus are available from the [ECDC website](#).

### Non-affected areas

Blood and tissue establishments should update their donor information materials and health questionnaires to comply with the proposed safety measures.

Persons with diagnosed with Zika virus infection, except sperm donors, may be accepted for blood, cell and tissue 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).

Health authorities should implement a precautionary deferral of asymptomatic blood, cell and tissue donor, 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 [53,54]. NAT testing could also be used to reinstate blood, cell and tissue donors.

Donors who had sexual contact with a man who has been diagnosed with Zika virus infection or with a man who travelled or lived in a Zika-affected area during the six months prior to the sexual contact may only donate blood, cells and tissues after at least 28 days after the last sexual contact [76].

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 [77]. 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. If indicated, donations by living donors at risk of Zika virus infection could be postponed for 28 days after possible exposure or cessation of Zika virus disease symptoms. The laboratory testing of deceased organ donors at risk for the presence of Zika virus infection may contribute to transplantation safety and unnecessary organ loss.

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

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 [78,79]. For this reason, and in line with the regulations for West Nile virus deferral in EU Directive 2004/33/EC [80], 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 and tissue establishments may consider the following:

- Temporary interruption of donations in affected areas and importation of blood components from unaffected parts of the country.

- Pathogen inactivation for plasma, platelets [81-84] and some tissues. The amotosalen UV method has been demonstrated to inactivate Zika virus in plasma [85].
- Screening of all donated blood and all donors of cells and tissues for the presence of Zika virus RNA by NAT.
- Individual assessment of organ donors, carefully weighing the benefits against the risks. Laboratory testing of living and deceased organ donors for the presence of Zika virus infection may contribute to transplantation safety and unnecessary organ loss.

SoHO establishments should update their donor information materials and health questionnaires to comply with the safety measures.

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