



RAPID RISK ASSESSMENT

Zika virus disease epidemic

Sixth update, 20 May 2016

Main conclusions and options for response

Given the continued spread of Zika virus in the Americas and Caribbean; the evidence of an association between Zika virus infection during pregnancy and congenital CNS malformations; the association between Zika virus infection and Guillain–Barré syndrome and the risk 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:

- There is growing evidence that Zika virus infection during the first and second trimester is associated with increased risk for central nervous system malformation of the foetus. The risk associated with infection during the third trimester is unknown. Therefore, Zika virus infection should be considered as a risk throughout the entire duration of pregnancy.
- The presence of viable Zika virus in semen has been detected up to 24 days after onset of Zika virus infection symptoms. 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.
- All the currently reported sexual transmission events are linked to symptomatic index cases. There is no evidence of transmission by asymptomatic sexual partners.

Information for travellers to and EU citizens residing in areas with active transmission

- Travellers visiting countries where there is active transmission of Zika virus and EU citizens residing in these countries should:
 - be made aware of the ongoing outbreak of Zika virus infection and the fact that Zika virus is usually transmitted by mosquito vectors but can be also transmitted by sexual intercourse;
 - take measures to prevent mosquito bites indoors and outdoors, especially between sunrise and sunset when *Aedes* mosquito vectors are most active and biting. These measures include:
 - The use of mosquito repellent in accordance with the instructions indicated on the product label.

Erratum. The following correction was made on 22 June 2016:

p. 7, second to last paragraph: 'European Transport Networks' Federation' was changed to read 'European Transport Workers' Federation'

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- 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 or otherwise use mosquito nets, at night and during the day.
- Pregnant women and women who are planning to become pregnant and planning to travel to areas with widespread transmission should postpone non-essential travel.
- Pregnant women and women who are planning to become pregnant and planning to travel to areas with sporadic transmission should consult their physician or a travel clinic and consider postponing non-essential travel.
- Pregnant women residing in countries with active transmission (sporadic and widespread) 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 - particularly with regard to effective prevention measures - before travelling to countries with active transmission.
- Travellers to countries with active Zika transmission and EU citizens residing there should be advised that using condoms could reduce the risk of sexual transmission through semen.

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

- Pregnant women who have travelled or resided in areas with active 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 areas with active transmission should consider using a condom with a pregnant partner until the end of pregnancy.
- Travellers returning from areas with ongoing Zika virus transmission should be advised to use a condom for at least one month after returning, in order to reduce the potential risk of onward sexual transmission.
- Travellers, including those with immune disorders or severe chronic illnesses, showing symptoms compatible with Zika virus disease within two weeks of return from an area with active transmission are advised to contact their healthcare provider and mention their recent travel.

Source and date of request

ECDC internal decision, 10 May 2016.

ECDC issues this risk assessment document according to Article 7(1) of Regulation (EC) No 853/2004 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 for the choice of which option to pursue and which actions to take lies exclusively with the EU/EEA Member States.

Public health issue

This document assesses the risks associated with the Zika virus epidemic in currently affected countries, in EU Overseas Countries and Territories (OCTs) and Outermost Regions (OMRs) and in the EU Member States within mainland Europe.

Since February 2014, ECDC has published seven risk assessments related to Zika virus epidemics [1-9].

Consulted experts

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ECDC acknowledges the valuable contributions of all experts. Although experts from the World Health Organization (WHO) reviewed the risk assessment, the views expressed in this document do not necessarily represent the views of WHO. All experts have submitted declarations of interest and a review of these declarations did not reveal any conflicts of interest.

Disease background information

Zika virus disease is caused by an RNA virus transmitted to humans by *Aedes* mosquitoes, especially by the *Aedes aegypti* species. More information about Zika virus disease can be found in the previous risk assessments [1-9] and in the ECDC [factsheet for health professionals](#). Two literature reviews have been published since the previous ECDC risk assessment [10,11].

Highlights of recent scientific developments

Pathogen

Since the last Rapid Risk Assessment update, several studies have been published on the molecular evolution of the virus and the structure of Zika virus, with possible implications for understanding the pathogenesis and neurotropism [12-16]. A number of changes at the nucleotide and amino acid level were found between the epidemic strains and the pre-epidemic strains isolated before 2007 [14]. It should be noted that the sequence analyses and comparisons are made on a limited number of historical sequences and that the ancestral isolates may have acquired mutations as a result of successive passages in mouse brain, potentially limiting the validity of using these historical viral strains for such comparison. Further investigations are needed to determine to what extent these nucleotide and subsequent amino acid substitutions are associated with changes in viral tropism, transmissibility and fitness.

Zika virus is able to infect neural stem cells *in vitro*, which are progenitor cells of neurons and other brain cells. The results strongly suggest that Zika virus abrogates neurogenesis during human brain development. Investigation by immunohistochemistry, real-time RT-PCR analysis and serological assays involving five women infected with Zika virus at different gestational time points provides additional evidence of placental and brain lesions associated with Zika virus. Several recent publications based on animal models support an *in vivo* deleterious effect of Zika virus on neural progenitor cells, leading to reduction of their proliferation and differentiation and increased apoptosis.

Clinical features and sequelae

Besides the known clinical features of Zika virus, meningoencephalitis has been reported in an 81-year-old man [17]. Transient hearing loss for up to four weeks was reported in three adults [18]. Fatal outcome after Zika virus infection remains a rare event. The role of comorbidities as a risk factor of fatal outcome is still to be investigated.

Intracranial calcifications in the periventricular, parenchymal, and thalamic regions were prominent findings in a series of 23 infants from Pernambuco state (Brazil) with severe brain anomalies. The calcifications were similar to those found in other congenital infections. Further studies confirmed the observed pattern, with calcifications in the junction between cortical and subcortical white matter concomitant with congenital malformations during the development of the cortex [19]. Additional findings included delayed myelination, ventriculomegaly, abnormalities of corpus callosum and hypoplasia of the cerebellum and the brainstem.

Microcephaly and congenital central nervous system malformations

Accumulating data from scientific investigations add to the evidence that the emerging Zika virus strain from the Asian lineage can cause transplacental infection and congenital CNS malformations in the developing brain [20,21]. However, the information available is still insufficient to quantify the potential co-factors and the frequency of transplacental transmission. Therefore, the resulting risk of adverse pregnancy complications cannot be assessed.

In late March 2016, WHO reported that there is '*strong scientific consensus that Zika virus is a cause of GBS, microcephaly and other neurological disorders based on observational, cohort and case-control studies currently published*' [22]. Epidemiological observations are now supported by evidence from *in vitro* and *in vivo* laboratory studies of the damaging effect of Zika virus on neuronal tissue, especially neural progenitor cells, therefore possibly impairing the development of the foetus' brain. These laboratory studies are strengthening the coherence of the evidence and its consistency with Hill's criteria for causation.

The likelihood of neurological abnormalities in foetuses and neonates in symptomatic pregnant women is substantial, based on the results of the study in Brazil [23].

Preliminary reports of a prospective case-control study conducted by Microcephaly Epidemic Research Group (MERG) in the city of Recife, Brazil since January 2016 demonstrate a significant and strong association between intra-uterine Zika virus infection during pregnancy and microcephaly in neonates. Final results are expected to be published shortly [24]. These preliminary results support the strength criteria of the Hill's criteria for causation.

It is probable 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 conceivable that other factors, such as the mother's age, genetic co-factors and her nutritional status among others, influence the risk of transplacental transmission. Results from ongoing and further case-control and cohort studies are still required to more accurately estimate the risk of microcephaly and other congenital CNS malformations linked with Zika virus infection.

Severe congenital impairments reported in Brazil might represent the severe phenotype of a broader spectrum of the Zika congenital syndrome. Further epidemiological studies on Zika virus in population will provide a better understanding of the clinical spectrum of the Zika virus disease and the potential cognitive and functional associated sequelae. In addition, further investigations are required into the mode of transmission and viral kinetics in bodily fluids in order to adapt prevention and control measures.

Guillain–Barré syndrome and other post-infectious neurological syndromes

A case-control study in French Polynesia and recent observations support the role of Zika virus infection as a presumptive infection event preceding Guillain-Barré syndrome [25]. Countries reporting an increase of Guillain-Barré syndrome are affected by Zika viral strains from the Asian lineage.

Epidemiology

A retrospective study of acute undifferentiated febrile illness conducted in Haiti identified Zika virus among three children from three different towns in rural Haiti (west of Port-au-Prince) in December 2014 [26]. These findings suggest a circulation of Zika virus near Port-au-Prince already during late autumn 2014.

The first comprehensive study of the Zika virus outbreak in large urban areas (Rio de Janeiro, Brazil) conducted during the first half of 2015 identified 364 suspected cases, 119 of which were laboratory confirmed [27]. The first confirmed cases were retrospectively identified as having occurred in January 2015.

Zika epizootic infections among monkeys were reported in April 2016 for the first time in Brazil and Ecuador [28,29]. The role of these nonhuman primates in the epidemiology of Zika disease, in particular mode of transmission of the infection to monkey and potential sylvatic cycle in the Americas, is unknown.

Transmission

- The first male-to-male sexual transmission of Zika virus was reported in April 2016 [30].
- Zika virus was detected for the first time in *Aedes albopictus*, which was captured in the state of San Luis Potosi, Mexico on 28 March 2016, and the virus was also detected and isolated from *Aedes aegypti* pools of mosquitoes in Rio de Janeiro, Brazil.

Vector competence laboratory studies are providing new insights summarised as follow [31-34]:

- Vector competence studies showed that the transmission rate of two populations of *Aedes aegypti* from Madeira was around 20% at day nine after infection.
- *Aedes albopictus* populations from Europe were shown to be susceptible to Zika virus. A transmission rate ranging from 0 to 50% at day 14 after infection was found for two populations of *Aedes albopictus* from southern France using a Zika virus strain from New Caledonia (2014). These findings are in line with a scientific communication that reported a transmission rate of 10% at day 10 after infection for an *Aedes albopictus* population from Nice, France with Zika virus strain from French Polynesia. Furthermore, a transmission rate of around 29% was found after 11 days post infection using an *Aedes albopictus* vector population from Calabria, Italy with Zika virus strain from French Polynesia.

Diagnostics

Several Zika virus Quantitative PCR (qPCR) protocols assessed in a multicentric study show limited sensitivity and incompatibility with Zika virus 2015-2016 outbreak strains [35].

The US Food and Drug Administration (FDA) has approved a new real-time reverse transcriptase PCR (rRT-PCR) for detection of Zika virus in the blood [36].

CDC recommends that Zika virus RT-PCR detection (CDC Triplex rRT-PCR assay authorised by the Food and Drug Administration) be performed on urine collected <14 days after onset of symptoms in patients with suspected Zika virus disease [37]. The molecular assay should be performed in conjunction with serum testing.

Event background information

Current situation worldwide

Autochthonous transmission of Zika virus was confirmed in Brazil in April 2015. Since January 2016 and as of week 16 of 2016, 120 161 probable cases (incidence rate 58.8 cases/100 000 inhabitants) of Zika virus infection have been reported in 1 605 municipalities across 27 states, of which 39 993 were confirmed cases [38]. The mid-west region has had the highest cumulative incidence rates since 2016 with 130.2 cases/100 000 inhabitants. The most affected states were Mato Grosso (532.6 cases/100 000 inhabitants), Tocantins (238.4 cases/100 000 inhabitants), Bahia (227 cases/100 000 inhabitants) and Rio de Janeiro (195.2 cases/100 000 inhabitants). In the state of Rio de Janeiro between epidemiological week 13 and 16 there was an increase of more than 7 000 cases [39].

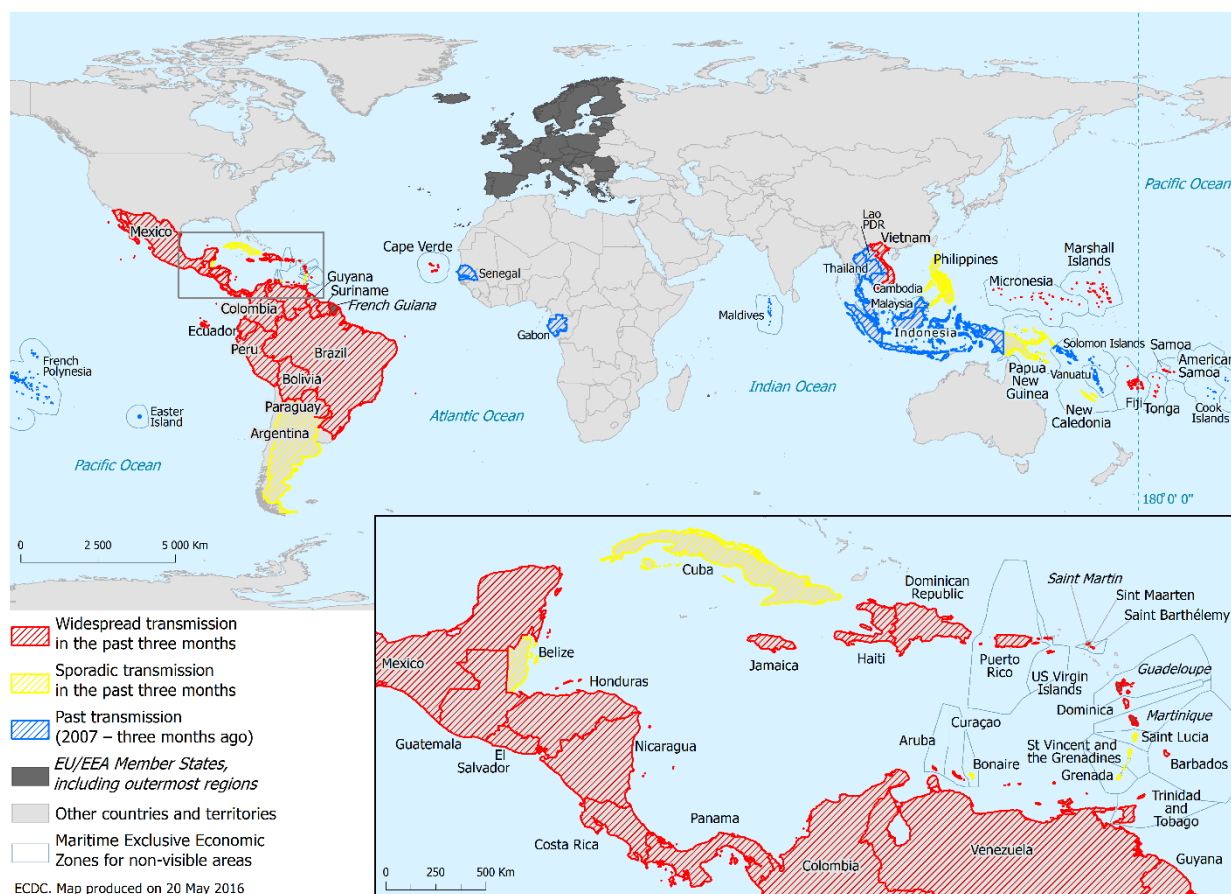
Colombia remains the second most affected country in the Americas. Since October 2015 and as of 7 May 2016, 75 926 suspected and 4 867 confirmed cases have been reported nationally [40]. However, since the epidemic reached its peak in week 5 of 2016, the number of suspected and confirmed cases has been steadily declining.

As of 19 May 2016, twenty-three cases of non-vector-borne transmission of Zika virus, most likely through sexual transmission, have been reported in ten countries: Argentina (1), Canada (1), Chile (1), France (5), Italy (1), Germany (1), New Zealand (1), Peru (1), Portugal (in the Autonomous Region of Madeira) (1) and the United States of America (10).

Since the previous Rapid Risk Assessment published on 11 April 2016, five additional countries or territories (Argentina, Peru, Saint-Barthélemy, Grenada and Belize) have reported autochthonous Zika virus transmission. Over the past three months and as of 19 May 2016, autochthonous cases of Zika virus infection have been reported from 50 countries or territories worldwide. In the past nine months, 51 countries or territories have reported autochthonous cases of Zika virus infection. The latest information on the spread of the Zika virus epidemic and an update on adverse pregnancy outcomes and post-infectious Guillain-Barré syndrome is available through the ECDC Zika outbreak [webpage](#) [41]. Regular updates on the epidemiological situation are available on an ECDC webpage [Countries and territories with local Zika transmission](#) [42].

WHO AFRO reported that the strain currently circulating in Cape Verde is genetically related to the strain circulating in the Americas according to Institut Pasteur, Dakar [43]. Between week 41 in 2015 and week 17 in 2016, 7750 suspected Zika case were reported by the Ministry of Health in Cape Verde [44]. WHO and its partners are continuing to support preparedness in the WHO African Region.

Figure 1. Countries and territories with reported confirmed autochthonous vector-borne transmission of Zika virus infection in the past three months*, as of 20 May 2016



* As of week 17 in 2016, ECDC extended the period for classifying whether a country or territory has active local transmission from two to three months. This change is based on the observation that previous Zika virus outbreaks usually lasted more than two months. In addition, ECDC added a 'countries and territories with past vector-borne transmission' category for countries having experienced transmission since 2007 and up to three months ago. More information about country classification is available on the [ECDC website](#).

Situation in the EU/EEA and EU outermost regions and overseas countries and territories

As of 19 May 2016, no autochthonous vector-borne Zika virus transmission has been reported in the EU Member States of mainland Europe. Since January 2016 and as of 19 May, ECDC has recorded 607 imported cases of Zika infection in 18 EU/EEA countries. The number is not based on systematic reporting through surveillance systems and hence cannot be considered exhaustive. Two countries have reported the majority of the imported cases; France reported 317 cases of Zika virus, which corresponds to an average of 20 cases per week since February 2016, and Spain reported 121 cases since late January 2016 [45,46]. Thirty-four of the imported cases were among pregnant women.

Several EU Outermost Regions (OMR) and Overseas Countries and Territories (OCT) continue to report vector-borne autochthonous Zika transmission: French Guiana, Guadeloupe, Martinique, Saint Martin, Saint-Barthélemy. In addition, islands in the Dutch Antilles (Aruba, Bonaire, Curacao and Sint Maarten) continue to report autochthonous transmission. According to the PAHO and WHO, the number of Zika cases is still increasing in the EU Outermost Regions and Overseas Countries and Territories in the Caribbean [47].

Microcephaly and congenital central nervous system malformations

As of 13 May 2016, congenital microcephaly, CNS malformations and other foetal malformations potentially associated with Zika virus infection during pregnancy have been reported in eight countries or territories: Brazil, Cape Verde, Colombia, French Polynesia, Martinique, Marshall Islands, Panama and Puerto Rico. Outside of the epidemic area, two cases exposed during a longer stay in Brazil while pregnant have been diagnosed in Slovenia and USA respectively [48,49], and two cases among travellers returning from the affected areas have been reported, one from USA [49] and one from Catalonia, Spain [50].

Brazil

Since October 2015 and as of 14 May 2016, Brazil has reported 7 534 suspected cases of microcephaly from all states and in the Federal District. Of these cases, 1 384 are reported as confirmed cases of microcephaly, 207 of which had laboratory-confirmed presence of Zika virus infection. Of the remaining cases, 2 818 were investigated and discarded as they did not fit the case definition, while 3 332 cases are still under investigation.

Among the 7 534 suspected cases of microcephaly, 273 intrauterine or neonatal deaths were reported. Of these, 59 cases were investigated and confirmed to have microcephaly or central nervous system malformations [51].

Colombia

Between weeks 1 and 18 in 2016, Colombia reported five confirmed cases of microcephaly associated with Zika virus infection, 24 cases were investigated and discarded and 43 cases are still under investigation [40].

Guillain–Barré syndrome and other neurological syndromes

As of 12 May 2016 in the context of Zika virus circulation, 13 countries and territories worldwide have reported an increased incidence of Guillain-Barré syndrome and/or laboratory confirmation of a Zika virus infection among GBS cases.

ECDC threat assessment for the EU

Since the Rapid Risk Assessment issued on 11 April 2016, the Zika epidemic remains of public health importance. The epidemic continues to evolve and expand geographically across countries and territories in the Americas and Caribbean. The outbreak is unprecedented and constitutes a significant development in the epidemiology of this emerging vector-borne disease. The evolution of the Zika epidemic in the Americas demands close monitoring as it has a direct impact on the risk of importation and possible occurrence of local transmission in the European Union.

The transmission season for dengue is starting in the Central American countries and Mexico and it is expected that the transmission of Zika virus will increase there as well, because vector-borne transmission of Zika virus in these countries is expected to mirror the seasonal pattern of dengue and chikungunya, two arboviruses transmitted by the same vectors *Aedes aegypti* and *Aedes albopictus*. The transmission season coincides with the summer holiday period in Europe and it is expected that there will be an increase in the number of travellers returning to EU with Zika virus viraemia during this period. This will increase the probability of onward transmission of Zika virus in receptive areas in Europe.

The occurrence of occasional cases of Zika virus in Asia is expected in view of the historical records of Zika virus circulation, case reports of travel-related cases and previous sero-surveys.

On 18 April 2016, WHO's Regional Office for Europe published an interim risk assessment on Zika for the WHO European Region and concluded that on the island of Madeira (Portugal), and in the Black Sea coastal areas of Georgia and the Russian Federation where *Aedes aegypti* is established, there is a high likelihood of local Zika virus transmission [52].

Travel-related risk for EU citizens

Travellers to countries where competent vectors are present and Zika virus circulation is ongoing are at risk of becoming infected through mosquito bites. Due to the link between Zika virus 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.

Risk related to mass gatherings

The Rio de Janeiro 2016 Olympic Games (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. ECDC has published a specific risk assessment on these events, including an assessment for Zika virus infection [53]. On 12 May, WHO published a statement on Zika virus and the Olympic and Paralympic Games Rio 2016, providing specific advice for those participating and visiting Brazil for the Games [54]. ECDC is continuing to follow the evolution of the Zika virus epidemic in order to assess and monitor the trends in Brazil [39].

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

Residents in EU Outermost Regions (OMR) and Overseas Countries and Territories (OCT) with competent and active vectors are at increased risk of exposure to Zika virus. *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 (see [Countries and territories with local Zika transmission](#)) [42].

The risk associated with spread to as yet unaffected OCTs and OMRs in the area is significant because of the immunologically naïve populations, the presence of competent vectors, the occurrence of prior outbreaks of arboviruses transmitted by *Aedes* mosquitoes, the permissive climate and the 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 *Aedes aegypti* in Madeira and Mayotte or *Aedes albopictus* in La Réunion, are at risk of local transmission should the virus be introduced.

Madeira is of particular concern because of the presence of *Aedes aegypti* and the probability of transmission of vector-borne pathogens is considered high during the summer months. The 2012 dengue epidemic demonstrated the favourable conditions for mosquito-borne outbreaks during the summer season and the close relationship with countries (such as Brazil and Venezuela) where Zika virus is currently circulating increases the risk of the virus being imported [55].

According to the Interim Risk Assessment issued by WHO's European Region, the capacity to contain Zika virus transmission at an early stage is good for the countries of the WHO European Region overall [52].

Risk of importation and transmission in the continental EU

Zika virus circulation in the Americas and the Caribbean increases the risk of infection among travellers. Cases of Zika virus infection arriving from countries with autochthonous transmission continue to be reported in the EU.

Based on modelling, the number of infections imported into Europe in 2016 from Brazil has been projected to range between 508 and 1 778 in 2016, of which between 116 and 355 are expected to be symptomatic Zika infections. The reported number of imported cases worldwide into the EU/EEA in 2016 already exceeds the lower level of the modelling estimates [56].

There is no evidence to date of 'airport transmission' of mosquito-borne viral disease, similar to airport malaria [57]. 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 [58,59]. On 21–22 April 2016, WHO organised an ad-hoc advisory group to review the evidence on effectiveness of aircraft disinsection to prevent the international spread of mosquito-borne disease, including Zika [60].

On 13 April the SHIPSAN Act Interim guidance on maritime transport and Zika virus disease [61] was updated. The European Transport Workers' Federation (EFT) and European Community Shipowners' Association (ECSA) acknowledged in a common statement the need to draw shipping companies' and seafarer's attention to the risks of the Zika virus and to provide crew members on board ships calling at ports in affected countries with relevant guidance to protect themselves [62].

The likelihood of mosquito-borne transmission of Zika virus infection in the EU is considered plausible only for those areas where mosquitoes capable of carrying and transmitting the virus are present. The transmission depends on several factors related to the mosquito, the virus and the environment [31,63]:

- The introduction of the virus by a viraemic traveller during the summer season where *Aedes albopictus* is established can be expected (see Situation in the EU/EEA and EU Outermost Regions and Overseas Countries and Territories). *Aedes albopictus* is established around the Mediterranean basin. As part of the VectorNet project, ECDC shows the current known distribution of invasive mosquito species in Europe at regional administrative level (NUTS 3) [64].
- The suitable conditions for *Aedes albopictus* activity will increase progressively during the spring (April to June) especially in southern Europe. By analogy with other mosquito-borne disease transmission, the conditions for autochthonous Zika virus transmission will remain favourable in mainland Europe during summer and autumn.
- Factors such as survival, density, and biting behaviour of the vector species will determine the final transmission potential of the vector species. Local vector-borne transmission in the EU is therefore not excluded.

Given the low vector competence of the studied European populations of *Aedes albopictus*, the likelihood of local vector-borne transmission in the EU is considered to be low to moderate.

Risk of Zika virus transmission via substances of human origin

Zika virus RNA has been detected in blood, urine, saliva, seminal fluid and breast milk [65-69] (see Annex 1, Table 1).

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. The virus can also be transmitted by SoHO from donors after clinical recovery from Zika virus disease due to possible prolonged viraemia or a persistence of the virus in semen after viraemia has cleared. There are no data available on the survival of Zika virus in processed and stored SoHO.

Assessing the risk of Zika virus transmission through contaminated SoHO is currently difficult because of the paucity of data on the prevalence of Zika virus in the donor population and the limited number of case reports of transmission via SoHO. According to Musso, et al, during the last Zika virus outbreak in French Polynesia, 42 of 1 505 (3%) blood donors, although asymptomatic at the time of donation, were found to be positive for the Zika virus genome by RT-PCR, supporting a potential risk of transfusion-derived transmission [65,70]. The Brazilian media reported possible cases of transfusion-transmitted Zika virus in March 2015 and February 2016 [71-73].

Several cases of sexual transmission from males to their partners have been reported (see 'Risk of sexual transmission' below).

There are no documented transmissions of the virus via saliva, urine or breastfeeding. 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.

A recent case report of Zika congenital infection showed a prolonged detection of low viral level by quantitative RT-PCR of Zika virus RNA in serum from the mother in weeks 16 and 20 of pregnancy; after termination of the pregnancy, RT-PCR returned to negative. The kinetics of Zika virus RNA in the sera of infected pregnant women are not yet well understood and would require assessment in larger studies [74].

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 Guillain-Barré syndrome justifies preventive measures to reduce the risk of transmission via SoHO supply [75].

Risk of sexual transmission

Replicative Zika virus particles have been detected on two occasions in semen at 21 and 24 days after onset of Zika symptoms [68,76]. Zika viral RNA has been reported in semen at 14 days [77], 21 days [68], 24 days [76] and up to 62 days after clinical onset of disease [78].

Zika virus genome has also been detected in saliva during and after the acute phase of the disease and reported from the symptom onset up to 29 days (see Annex 1, Table 1). A viral isolation from saliva was reported at day 6, a second isolation is reported but the date on sampling is not available [79].

Reports of sexual transmission of Zika virus through contaminated male semen to a female partner or male partner indicate the possible virus transmission through donated sperm [30,80-84].

In all published cases, males presented with a clinical illness compatible with Zika virus infection. The interval between onset of symptoms in the man and in his female partner varies from four to 19 days. So far, no sexual transmission of Zika virus from infected women to their partners has been reported.

Comprehensive data about the presence of viable virus, viral load or kinetics is not available, and at this point in time the risk of transmission via saliva cannot be further assessed. Further comprehensive information about the kinetics of the Zika virus in bodily fluids and the consequent clinical implication is required in order to adapt prevention and control measures accordingly.

Conclusions and options for response

Given the continued spread of Zika virus in the Americas and Caribbean; the evidence of an association between Zika virus infection during pregnancy and congenital CNS malformations; the association between Zika virus infection and Guillain–Barré syndrome and the risk 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:

- There is growing evidence that Zika virus infection during the first and second trimester is associated with increased risk for central nervous system malformation of the foetus. The risk associated with infection during the third trimester is unknown. Therefore, Zika virus infection should be considered as a risk throughout the entire duration of pregnancy.
- The presence of viable Zika virus in semen has been detected up to 24 days after onset of Zika virus infection symptoms. 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.
- All the currently reported sexual transmission events are linked to symptomatic index cases. There is no evidence of transmission by asymptomatic sexual partners.

Information to travellers to and EU residents in areas with active transmission

A list of countries and territories with active transmission (sporadic and widespread transmission) during the past three months is available on the [ECDC website](#).

Information for travellers to and EU citizens residing in areas with active transmission

- Travellers visiting countries where there is active transmission of Zika virus and EU citizens residing in these countries should:
 - be made aware of the ongoing outbreak of Zika virus infection and the fact that Zika virus is usually transmitted by mosquito vectors but can be also transmitted by sexual intercourse.
 - take measures to prevent mosquito bites indoors and outdoors, especially between sunrise and sunset when *Aedes* mosquito vectors are most active and biting. These measures 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, at night and during the day.
- Pregnant women and women who are planning to become pregnant and planning to travel to areas with widespread transmission should postpone non-essential travel.
- Pregnant women and women who are planning to become pregnant and planning to travel to areas with sporadic transmission should consult their physician or a travel clinic and consider postponing non-essential travel.
- Pregnant women residing in countries with active transmission (sporadic and widespread) 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 - particularly on effective prevention measures - before travelling to countries with active transmission.
- Travellers to countries with active Zika transmission and EU citizens residing there should be advised that using condoms could reduce the risk of sexual transmission through semen.

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

- Pregnant women who have travelled or resided in areas with active 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 areas with active transmission should consider using a condom with a pregnant partner until the end of pregnancy.
- Travellers returning from areas with ongoing Zika virus transmission should be advised to use a condom for at least one month after returning, in order to reduce the potential risk of onward sexual transmission.
- Travellers, including those with immune disorders or severe chronic illnesses, showing symptoms compatible with Zika virus disease within two weeks of return from an area with active transmission are advised to contact their healthcare provider and mention their recent travel.

Surveillance of imported cases and monitoring of transmission in the EU Member States of mainland Europe

- Increase awareness among clinicians and travel health clinics of the evolution of the Zika virus outbreak and the areas with active and past transmission ([ECDC website](#)) to allow them to consider Zika virus infection in their differential diagnosis for travellers from those areas. Clinicians should be aware that Zika virus infection can be pauci-symptomatic.
- Enhance vigilance towards the early detection of imported cases of Zika virus infection into EU Member States, EU OCTs and OMRs, in particular where Zika vectors are present, in order to reduce the risk of onward autochthonous transmission.
- Clusters of unexplained illness with a rash detected in receptive areas of mainland Europe between 1 May and 31 October should be investigated, and Zika virus infection should be considered as a possible cause.
- Ensure timely reporting of autochthonous cases, in particular in receptive areas of EU Member States in mainland Europe.
- Strengthen laboratory capacity to confirm suspected Zika virus infections in the EU/EEA in order to differentiate Zika virus infections from other arboviral infections (e.g. dengue, chikungunya).
- Increase awareness among obstetricians, paediatricians and neurologists that Zika virus infections should be investigated in patients presenting with congenital CNS malformations, microcephaly and Guillain-Barré syndrome.

Information to healthcare providers in EU Member States

It is important to 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).

Efforts should be made to increase awareness among health professionals who provide prenatal care of risk of neurological congenital syndrome associated with Zika virus infection, especially during the two first trimesters, and adapt prenatal monitoring in accordance with exposure to the vector [85,86]. ECDC maps showing [Zika transmission in the past nine months](#) are provided to aid diagnosis of returning travellers, especially pregnant women with travel history during pregnancy - returning from countries and territories that have recently- or are currently experiencing local active Zika virus transmission.

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); potential disease complications as 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).

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 both affected and non-affected areas. Implementation of SoHO safety measures should be defined by the risk assessment performed at the national level. The European Commission's Directorate General for health and food safety established a working group for the preparation of a preparedness plan in Europe related to safety of substances of human origin in the event of a Zika virus outbreak. ECDC will synchronise detailed SoHO safety measures, already described in Annex 1 of the risk assessment dated 9 March 2016 [8], with those defined in the SoHO safety preparedness plan at EU level.

Non-affected areas and areas with sporadic transmission

The primary measure to prevent Zika virus transmission in non-affected areas and areas with sporadic transmission is the temporary deferral of donations from blood donors and living donors of cells and tissues who are at risk of having been infected. When defining donors at risk criteria for consideration are:

- A medical diagnosis of Zika virus disease;
- Returning from areas with widespread transmission;
- Reporting sexual intercourse with males diagnosed with Zika virus disease or who have returned from areas with widespread transmission.

Based on the frequency of travel to currently affected areas, the Netherlands have assessed a risk of Zika virus transmission by blood donors who have had sexual contact with a male returning from affected area as too small to warrant their deferral [87]. Similarly, based on a risk assessment, Australia does not apply deferral to blood donors who have had sexual contact with asymptomatic males returning from affected areas [88]. Thus, current practice, as reported to date, is that the implementation of safety measures for this category of risk donors is being considered and re-assessed as required, as part of the risk assessment for national preparedness plans.

Cells and tissues from deceased donors with a recent medical diagnosis of Zika virus infection should not be accepted for donation. Periods defined for living SoHO donor deferral/acceptance should be set to provide a sufficient safety margin for 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.

Areas with widespread transmission

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 nucleic acid testing (NAT) may be considered necessary to assure the safety and sustainability of supply in areas with widespread transmission. A systematic review and pooled analysis to estimate the distribution of times from Zika infection to symptom onset, seroconversion and viral clearance showed that symptom-based screening reduces the risk of a positive Zika virus blood donation by 7% (RR 0.93, 95% CI 0.86–0.99), and antibody screening by 29% (RR 0.71, 95% CI: 0.28–0.88) [89]. This estimate confirms that in areas with a high incidence of Zika virus, blood establishments may consider NAT testing to identify lots safe for use in pregnant women.

Test kits, registered/approved for use as screening tests, should be used for determining SoHO donor/donation suitability. Commercial Zika tests for screening are still under development. Based on scientific data, SoHO establishments and laboratories may develop in-house or adapt available commercial diagnostic test for screening purposes. The use of such screening tests in the event of a Zika virus outbreak should be validated and approved by the responsible national authority. Some blood establishments are gaining experience with in-house testing or using adapted commercial tests. Semi-automated platforms for NAT screening using CE marked kits for diagnostics were implemented for NAT screening in the French West Indies during the 2014 outbreak of chikungunya [90] and are currently being implemented for NAT screening of blood donors for Zika virus in the French Antilles using the RealStar RT-PRC Zika kit 1.0, Altona. At the end of March 2016, the US Food and Drug Administration approved the use of an investigational test to screen blood donations for Zika virus under a new drug application being investigated for areas with an active mosquito-borne transmission of Zika virus [91]. Those European Member States that are most likely be impacted by a spread of the Zika virus infection could potentially use this test for screening blood donations.

Irrespective of 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.

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. ECDC has published a [preparedness planning guide for diseases transmitted by *Aedes aegypti* and *Aedes albopictus*](#). The guide focuses on the main components that should be considered when developing preparedness plans. Consistent with the evidence presented in this document, the following components might be considered with regard to Zika virus preparedness [55,92-96].

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. ECDC Guidelines for the surveillance of invasive mosquitoes in Europe provide a useful overview of entomological surveillance at national and subnational levels [97].
- Laboratory diagnosis capacity.

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 *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.
- Community involvement in the control of mosquito populations through both individual and collective preventive measures.
- Involvement of mass media for communication purposes and to promote public awareness and protection.

Annex 1. Time of detection Zika virus in biological samples

Table 1. Time of detection of Zika virus in human samples

Sample origin	Methods	Range of detection in days from onset of symptoms			
		Minimum (days)	Ref.	Maximum (days)	Ref.
Blood	Molecular diagnostic	One day prior to symptoms	[98]	14	[77]
	Virus isolation				
Urine	Molecular diagnostic	One day prior to symptoms	[98]	15 to 29	[66,99-101]
	Virus isolation			4	[102]
Saliva	Molecular diagnostic	1	[67]	29	[100]
	Virus isolation			6	[100]
Seminal fluid	Molecular diagnostic	14	[77]	62	[78]
	Virus isolation			21 to 24	[68,76]
Breast milk	Molecular diagnostic	3 (after delivery)	[69]	8 (after delivery)	[69]
	Virus isolation			4 (after delivery)	[103]

According to communication during the international Zika summit which took place in Paris on 25–26 April 2016, Zika virus RNA was detected in three asymptomatic individuals during a biological, clinical, serological and virological follow-up of a military community exposed to Zika virus in Suriname over a two-week period (two urine samples and one blood sample) [98].

The main features of detection Zika virus in human samples can be summarised as follow:

- In the blood, Zika virus is usually detected between the day of onset of symptoms and five days after (up to 14 days) [77]. Molecular diagnostics were found positive the day prior the onset of symptoms and in one asymptomatic patient [98]. It is estimated that Zika virus clearance in the blood takes on average 9.9 days (95% CI: 6.8–21.4) [89].
- In the urine, molecular diagnostic results were positive up to 29 days [100] and viral isolation at day four after onset [102].
- In the saliva, the Zika virus RNA was detected for up to 29 days [100]. Zika virus isolation from saliva has been reported on day six after onset of a febrile illness in a patient returning from the Dominican Republic to Italy [100]. Further investigation would be needed to evaluate the infectivity of Zika virus in saliva as a non-vector-borne viral transmission mode of Zika disease.
- In breast milk two studies have been published (see table above) along with a recent review [104].

Based on a modelling study, seroconversion occurs on average at 9.0 days (95% CI, 7.0–11.6) after infection but serological results should be interpreted with caution due to cross-reactivity with other flaviviruses and depending on the vaccination status against flaviviruses [89,105]. A recent case report of Zika congenital infection showed a prolonged detection at low level by quantitative RT-PCR of Zika virus RNA in serum from the mother at between weeks 16 and 20 of pregnancy and after termination of the pregnancy, RT-PCR returned to negative. The kinetics of Zika virus RNA in the sera of infected pregnant women are not yet well understood and would require assessment in larger studies [74].

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