RAPID RISK ASSESSMENT

Microcephaly in Brazil potentially linked to the Zika virus epidemic

24 November 2015

Main conclusions

The increase in congenital microcephaly observed in Brazil is of concern. Its emergence a few months after the introduction of Zika virus (ZIKV) infection into the country raises questions about the possible role of the infection in congenital microcephaly. There is currently only ecological evidence of an association between the two events. A possible causative nature of the association cannot be ruled out with the evidence available. Further investigations and studies will contribute to a better characterisation of the association, and provide a better understanding of the possible role of other prenatal infections, genetic risk factors, environmental exposures to chemicals or consumption of teratogenic drugs. Studies of the ZIKV genome will provide information on possible changes that might influence ZIKV disease characteristics and vector competence.

As a precautionary measure, pending the results of the ongoing investigations, the Ministry of Health of Brazil emphasises the importance of recommendations that pregnant women should avoid the consumption of alcohol, drugs, medications without prescription and contact with people presenting with fever or infection. In addition, specific recommendations were issued about protection from mosquito bites, such as keeping doors and windows closed or screened, wearing trousers and long-sleeved shirts and using repellents authorised during pregnancy [1].

In the light of the current speculation regarding a yet to be established link between ZIKV and microcephaly, options for public health authorities in EU/EEA Member States to consider for mitigation of risks for travellers to and from Brazil include:

- To enhance vigilance towards the detection of imported cases of ZIKV infection in EU Member States, EU Overseas Countries and Territories, and EU Outermost Regions, in particular where vectors or potential vectors are present in order to reduce the risk of autochthonous transmission.
- To increase awareness of clinicians and travel health clinics about the evolution of the ZIKV outbreak and the endemic areas, especially in Brazil, Colombia, Suriname, Samoa and Cape Verde, in order for them to include ZIKV infection in their differential diagnosis for travellers from those areas. Fever and/or macular or papular rash not attributable to dengue or chikungunya infection among travellers returning from areas currently experiencing ZIKV outbreak should be considered indications for further investigation for ZIKV infection.
- To ensure that advice on specific prevention measures, including information and education about mosquito bite prevention, is directed to pregnant women living in or travelling to areas where ZIKV outbreaks are ongoing.
- Increase awareness among health professionals providing prenatal care of this possible association, and adapt prenatal monitoring according to the exposure of the pregnant women.

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- Advise travellers visiting affected areas, particularly pregnant women, to take individual protective measures to prevent mosquito bites all day round as ZIKV is transmitted by a daytime mosquito and consequently protective measures must be applied during the day (unlike malaria).
- Strengthen the laboratory capacity to confirm suspected ZIKV infections in the European region in order to differentiate ZIKV infections from other arboviral dengue-like infections.
- For blood safety authorities to consider deferral of donors with relevant travel history to areas with active ZIKV transmission, in line with measures defined for West Nile virus.

Source and date of request

ECDC internal decision, 18 November 2015.

Public health issue

This document assesses the possible link between the increased incidence in newborns with microcephaly in Brazil and Zika virus (ZIKV) infection, and assesses the potential risks associated with ZIKV infection for travellers, the EU, the EU Overseas Countries and Territories and Outermost Regions.

The first ECDC rapid risk assessment on Zika virus infections outbreak, entitled 'Zika virus infection outbreak, French Polynesia', is dated 14 February 2014 [2]. The second focusing on the situation in Brazil is dated 25 May 2015 [3].

Detailed information on the epidemiology of the Zika can be found in an ECDC factsheet for health professionals [4].

Consulted experts

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Disease background information

Microcephaly

Congenital microcephaly is a descriptive diagnosis, meaning that the occipital frontal circumference of the head of the newborn child falls below the normal circumference for gestational age, sex and race. The small head is the result of a neurodevelopmental disorder. When the foetal brain does not increase normally in size, the skull will not grow either and the sutures between the bones that make up the skull may close prematurely. The diagnosis is often made prenatally because head circumference is a standard measurement when foetal growth is monitored with ultrasonography. According to WHO, microcephaly is defined as a head circumference equal to or lower than two standard deviations below the mean (≤ -2SD) for age and sex or about less than the second percentile [5]. Head circumference that falls below the -3 SD is sometimes referred to as severe microcephaly. There is an association between the severity of microcephaly and the severity of neurological impairment. The disease is reported in the International Statistical Classification of Diseases and Related Health Problems 10th Revision (code Q02) [6].

There are several aetiologies of the neurodevelopmental disorders that cause congenital microcephaly [7]:

- inherited genetic disorders, syndromes and mutations
- brain injury due to teratogenic drugs, toxins and chemical products, including foetal alcohol syndrome
- metabolic diseases
- malnutrition (maternal malnutrition, maternal folate deficiency, placental insufficiency)
- hypoxic-ischemic lesions
- infections: transplacental infections of the central nervous system most commonly due to syphilis, toxoplasmosis, rubella, cytomegalovirus and herpes simplex virus (STORCH infections).

Zika

Zika virus disease

Zika virus disease is a mosquito-borne viral disease caused by Zika virus (ZIKV), a flavivirus from the Flaviviridae family and Spondweni serocomplex. The virus was first identified in 1947 in the Zika forest in Uganda in the rhesus macaque population [8]. There are two main lineages of ZIKV, the African lineage and the Asian lineage [9-11].

The main symptoms of ZIKV disease include:

- low-grade fever (<38.5°C)
- transient arthritis/arthralgia with possible joint swelling mainly in the smaller joints of the hands and feet
- maculo-papular rash often spreading from the face to the body
- conjunctival hyperaemia or bilateral non-purulent conjunctivitis
- general non-specific symptoms such as myalgia, asthenia and headaches.

The incubation period ranges from 3 to 12 days [12]. The disease symptoms are usually mild and last for 2 to 7 days. Infection may go unrecognised or be misdiagnosed as dengue, chikungunya or other viral infections giving fever and rash. Asymptomatic infections are common –as described with flaviviral infections such as dengue and West Nile fever– and only one in four people infected with ZIKV are believed to develop symptoms [13,14].

Association with neurological complications such as Guillain-Barré syndrome has been suspected during the French Polynesia outbreak and remains under investigation [12,15-17]. Most people recover fully without severe complications, and hospitalisation rates are low. To date, there have been no reported deaths associated with ZIKV infection.

Prenatal or perinatal complications of ZIKV infections have not been described in the literature. There is some evidence that perinatal transmission can occur, most probably transplacental or during the delivery of a viraemic mother [14,18,19]. ZIKV transfusion-derived transmission is theoretically possible as 3% of asymptomatic blood donors (42/1 505) were found positive for ZIKV by PCR during the ZIKV outbreak in French Polynesia, from November 2013 to February 2014 [13]. The presence of a viable virus was detected in semen more than two weeks after recovery from an illness consistent with ZIKV infection [20]. Possible cases of sexual transmission of ZIKV have been reported [20,21]. However, the three modes of transmission described above have been rarely reported to date.

Zika virus vectors

In East Africa, ZIKV is maintained in a sylvatic cycle with cyclic epizooty involving non-human primates and a wide variety of sylvatic and peri-domestic *Aedes* mosquitoes [22-25]. In Asia, *Aedes aegypti* is considered an important vector of ZIKV as the virus has been detected in wild-caught *Aedes aegypti*, and experimental infections show that this species is capable of transmitting ZIKV [26,27]. During the outbreak in Yap in Micronesia*, Aedes hensilii* has been suspected as a vector because of its abundance coinciding with the outbreak. ZIKV was not detected in *Aedes hensilii* captured during this outbreak [14], but it has been shown to be a potential vector of ZIKV based on evidence from experimental infections [28]. In Singapore, *Aedes albopictus* is also a potential vector of ZIKV, based on data from experimental infections [29]. *Aedes albopictus* has been found naturally infected in Gabon [30].

Zika virus epidemiology

Since its first isolation in 1947 in Uganda, serological, epidemiological and entomological studies reported the circulation of the ZIKV in tropical areas of western Africa (Nigeria, Sierra Leone, Ivory Coast, Cameroon and Senegal) and of central Africa (Gabon, Uganda and Central African Republic), in Asia (Pakistan, Indonesia, Philippines, Malaysia, Cambodia and Thailand) and in several islands of the pacific region since 2007 (Micronesia, Cook Islands, French Polynesia, New Caledonia, Guam, Samoa, Vanuatu and Solomon Islands).

Outbreaks of ZIKV infection on Yap Island (2007) and in French Polynesia (2013–2014), with further spread to New Caledonia, the Cook Islands and Easter Island, have shown the propensity of this arbovirus to spread outside its usual geographical range and to cause large outbreaks [31].

Between 7 October 2013 and 6 April 2014, 8 750 suspected cases of ZIKV infection were reported by the syndromic surveillance sentinel network of French Polynesia, with 383 confirmed cases and an estimated 32 000 cases having consulted a healthcare facility for the condition [32,33]. During the outbreak, 74 individuals presented with neurological symptoms or auto-immune syndrome following a disease episode with symptoms consistent with ZIKV infection in previous days [17,34-36]. Of these, 42 were confirmed as Guillain-Barré syndrome, with 37 cases having presented with a previous viral syndrome. The causal link between ZIKV infection and Guillain-Barré syndrome is still not established.

Since 2014, indigenous circulation of ZIKV has been detected in the Americas. In February 2014, the public health authorities of Chile confirmed the first case of autochthonous transmission of ZIKV infection on Easter Island and cases were reported until June 2014. Since February 2015, cases of rash illness were reported in north-eastern Brazil in the states of Bahia, Maranhao, Pernambuco, Rio Grande do Norte, Paraíba and Sergipe [37]. A total of 14 835 cases of acute exanthematous illness have been reported in 12 health districts of Salvador – the third city of Brazil – between 15 February 2015 and 25 June 2015 (overall attack rate 5.5 cases/10 000 inhabitants) [38]. Twenty-four case of Guillain-Barré syndrome were hospitalised during this period. The outbreak peaked in May at the time of ZIKV confirmation in patients leaving nearby Salvador city. During the same period the number of dengue cases did not vary substantially and 58 suspected chikungunya were identified by the Salvador Epidemiologic Surveillance Office. The authors suggest ZIKV as an etiological factor of this exanthematous illness outbreak because of the low frequency of arthralgia usually seen in chikungunya disease and concomitant confirmed ZIKV infections in the area [38].

In May 2015, the public health authorities of Brazil confirmed autochthonous transmission of ZIKV in the states of Bahia and Rio Grande do Norte [39]. As of November 2015, 15 states had confirmed autochthonous virus transmission [40]. In Brazil, between January and July 2015, 121 cases of neurological manifestations and Guillain-Barré syndrome have been notified in several north-eastern states with history of previous rash illness [41]. Investigations were launched and are on-going regarding possible association with ZIKV infection [42]. Phylogenetic analysis on serum samples from patients hospitalised in March at Santa Helena Hospital in Camaçari, Bahia, Brazil showed that ZIKV sequences identified belonged to the Asian lineage and showed 99% identity with a sequence from a ZIKV isolate from French Polynesia [43].

In September 2015, Colombian health authorities reported the detection of the first autochthonous cases of ZIKV infection in the state of Bolívar. As of week 45, 488 confirmed cases of ZIKV infections and 1 583 suspected cases have been reported, distributed in 26 of the 36 departments [44].

On 3 November 2015, the Cape Verde Ministry of Health reported that 17 out of 64 blood samples sent for confirmation at Pasteur Institute in Dakar were positive for ZIKV and there were approximately 1 000 suspected cases with symptoms consistent with ZIKV infection as of 1 November 2015 [45].

On 12 November 2015, health authorities in Suriname reported five confirmed cases of ZIKV [46].

In conclusion, there is limited but increasing knowledge about ZIKV infection in humans [47,48]. Uncertainties remain about disease complications, genetic susceptibility and levels of risk for pregnant women, newborns or patients presenting with specific co-morbidities. The expansion of the ZIKV infections to South America constitutes a significant development in the epidemiology of this emerging vector-borne disease.

Laboratory diagnosis

Laboratory diagnosis is described in the Rapid Risk Assessment 'Zika virus infection outbreak, Brazil and the Pacific region', 25 May 2015 [3].

Event background information

On 11 November 2015, the Brazilian Ministry of Health declared a public health emergency in relation to an unusual increase in the number of children born with microcephaly in 2015 in Pernambuco state [49]. As of 9 November, 141 cases of microcephaly have been notified in newborns in Pernambuco state in 2015 compared with an average of 10 cases per year from 2010–2014. An increase of microcephaly was also reported in the states of Paraíba and Rio Grande do Norte.

In Brazil, 150–200 microcephaly cases have been reported on average every year from 2010 to 2014 (Figure 1).

As of 17 November 2015, 399 cases of microcephaly were being investigated in seven states in the northeast of Brazil. Most of the cases were registered in Pernambuco state (268). Other states that reported microcephaly cases are Sergipe (44), Rio Grande do Norte (39), Paraíba (21), Piauí (10), Ceará (9) and Bahia (8) [1].

Brazilian health authorities have established an emergency operations centre for global health (COES), and deployed rapid response teams to the affected states to support the investigations, to provide guidance on the notification and surveillance processes, to establish prenatal monitoring and to issue recommendations on prevention and control measures. Clinical, laboratory and ultrasound analyses of pregnant women, mothers and newborns are being carried out.

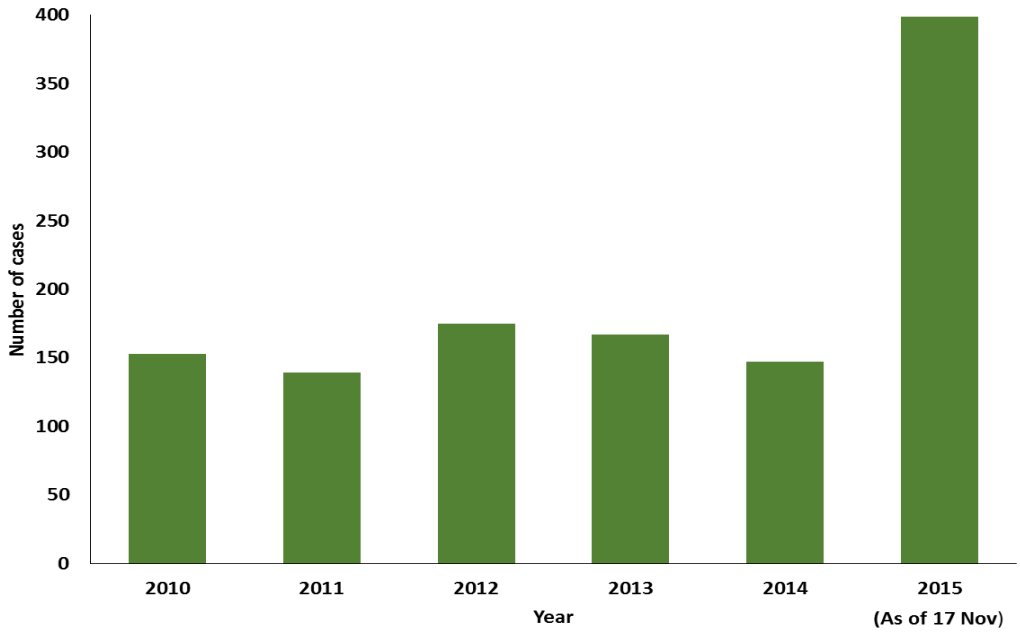
On 17 November, the Ministry of Health of Brazil reported the confirmation by RT-PCR, at the Flavivirus Laboratory at the Oswaldo Cruz Institute, of the presence of ZIKV RNA in amniotic fluid samples collected from two pregnant women with foetal microcephaly from the state of Paraíba [1]. Both pregnant women presented compatible symptoms of ZIKV infection during their pregnancy.

On 17 November, the Pan American Health Organization/World Health Organization (PAHO/WHO) issued an epidemiological alert regarding the increase of microcephaly in the northeast of Brazil and requested WHO Member States to remain alert to the occurrence of similar events in their territories and to notify its occurrence through the channels established under the International Health Regulations (IHR) [5].

The Ministry of Health of Brazil emphasises the importance of recommendations for pregnant women to avoid the consumption of alcohol, drugs, medications without prescription and contact with people presenting with fever or infection. In addition, specific recommendations were issued relating to protection from mosquito bites, such as keeping doors and windows closed or screened, wearing trousers and long-sleeved shirts and using repellents authorised during pregnancy.

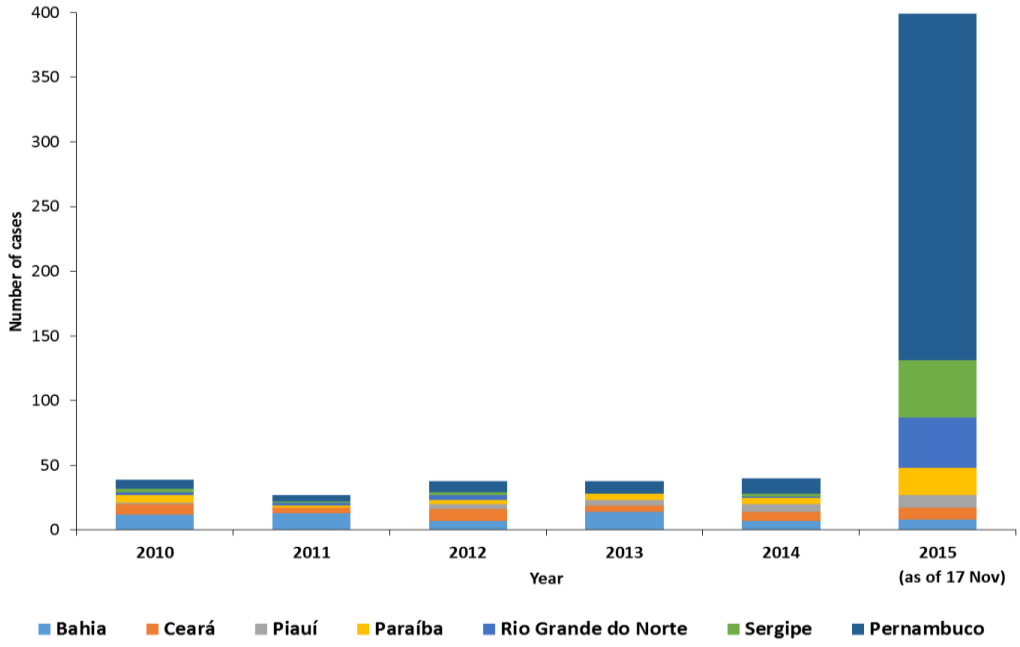
On 24 November 2015, the health authorities of French Polynesia reported an unusual increase of at least 17 cases of central nervous system malformations in foetuses and infants during 2014–2015, coinciding with the Zika outbreaks on the French Polynesian islands. These malformations consisted of 12 foetal cerebral malformations or polymalformative syndromes, including brain lesions, and five infants reported with brainstem dysfunction and absence of swallowing. None of the pregnant women described clinical signs of ZIKV infection, but the four tested were found positive by IgG serology assays for flavivirus, suggesting a possible asymptomatic ZIKV infection. Further serological investigations are ongoing. Based on the temporal correlation of these cases with the Zika epidemic, the health authorities of French Polynesia hypothesise that ZIKV infection may be associated with these abnormalities if mothers are infected during the first or second trimester of pregnancy.

Figure 1. Notified cases of microcephaly in Brazil, 2010–2015



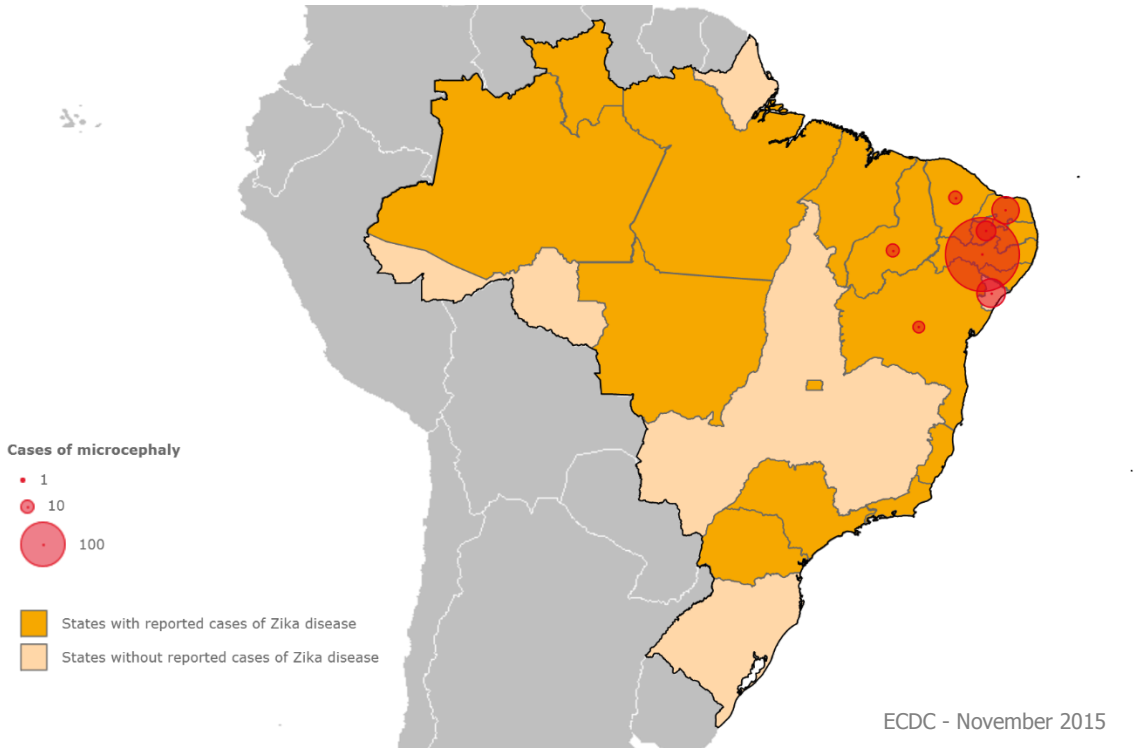
Adapted from [1]

Figure 2. Number of cases of microcephaly reported annually in the seven Brazilian states reporting an unusual increase of microcephaly, 2010–2015



Adapted from [1]

Figure 3. States of Brazil with reported confirmed autochthonous cases of ZIKV virus infection 2014–2015, and reported cases of microcephaly in 2015, as of 17 November 2015.



Adapted from [1] and [40]

Potential association between Zika virus infection and congenital brain malformation

The epidemiological data available as of November 2015 indicate a ten-fold increase in the incidence of microcephaly among newborns in the north-eastern Brazilian states of Pernambuco, Rio Grande do Norte and Sergipe. The magnitude of the increase cannot be explained by random clustering of cases alone (Poisson cumulative probability $<1^{-12}$). The presence of microcephaly is easy to establish and likely to be detected at birth, during late pregnancy, or very early during childhood. Therefore, a change in detection or reporting of microcephaly is unlikely to account alone for the increase.

The Ministry of Health of Brazil has suggested a possible relationship between the increase in notifications of microcephaly and the outbreak of ZIKV infections as the increase is within nine months of the emergence of ZIKV disease in the north-eastern regions of Brazil. The ongoing investigation, led by the public health authorities in Brazil, is also examining additional hypotheses among known aetiologies of microcephaly [1,49].

The first confirmed cases of ZIKV infection in Brazil were reported in May 2015. Transmission of the virus in Brazil is likely to have started several months before because the disease is new and mild, and could have been unrecognised or misdiagnosed, as dengue and chikungunya epidemics were ongoing. Microcephaly when due to an infection, is usually caused by transplacental infections occurring early in pregnancy and tends to be detected only during the second half of pregnancy or after birth. The observed six months delay between the recognition of the transmission of ZIKV in May 2015, and the detection of an increase in microcephaly in November 2015, is therefore compatible with a temporal association between the two events.

Initial investigations suggest an increase of microcephaly in some states where ZIKV circulation has been detected, suggesting a spatial association between the two events (Figure 3).

Materno-foetal transmission has been demonstrated for several Flaviviruses (dengue, West Nile fever) and other Flavivirus infections are known to have the potential to cause premature birth, congenital defects and microcephaly. For instance, the risk of vertical transmission with dengue virus exists, but whether maternal dengue infection is a significant risk for adverse pregnancy outcome remains inconclusive [50]. Among 72 births following West Nile virus (WNV) infection in pregnant women in the US in 2003–2004, O'Leary described two microcephaly cases in infants born at term of which one died at day three and the second reported to have a normal development. Serum and cerebrospinal fluid (CSF) of the two infants were negative for WNV IgM antibodies. Likewise, cord blood, cord tissue and the placenta were negative for WNV RNA by RT-PCR. WNV infection in the mother probably occurred during the second semester [51].

It is therefore plausible that ZIKV infections can cause such infections even though the involvement of ZIKV in microcephaly and prenatal neurological impairments is not documented in the scientific literature. RNA of ZIKV was reported in amniotic fluid samples collected from two pregnant women with foetal microcephaly from the state of Paraíba in 2015 [1]. This demonstrates transplacental capabilities of ZIKV and the possibility of the infection of the foetus.

The occurrence of microcephaly in association with ZIKV has not been documented in recent outbreaks in Micronesia and New Caledonia. However, an increase of central nervous system malformations in foetuses and newborns has been reported in French Polynesia following an epidemic of ZIKV infection. The size of the affected populations (French Polynesia, 270 000 inhabitants; Yap island 11 241 and Pernambuco State, 8.8 million inhabitants) and the number of births are much smaller in these places than in Brazil [52-54] and could make it difficult to recognise an uncommon and previously unknown phenomenon, even if the outcome event is highly identifiable.

Other causes of microcephaly and possible predisposing factors should be systematically investigated such as previous or concomitant infections, individual genetic risk factors, or other aetiologies such as environmental exposures to chemicals or consumption of teratogenic drugs. In addition, other infections, including these caused by the STORCH group of diseases, have been associated with such congenital defects as well and cannot therefore be ruled-out.

In conclusion, a causative association between microcephaly in newborns and ZIKV infection during pregnancy is plausible, but not enough evidence is available yet to confirm or refute it.

ECDC threat assessment for the EU

Risk of Zika virus importation and transmission in continental EU

Few travel-associated cases of ZIKV infections have been reported in the EU, following exposure in Asia or in French Polynesia [55-58]. With the extension of the ZIKV epidemic in the Americas, the likelihood of travel-related cases of ZIKV infection in the EU is increasing. However, the majority of infections may not be recognised, as the disease is generally mild. *Aedes albopictus* mosquito species is established in many parts of the EU, primarily around the Mediterranean [59]. Onward transmission from imported cases within continental EU is possible as *Aedes albopictus* has been recognised as a competent vector for the transmission of ZIKV even though it has not been confirmed yet among European mosquito populations [29,30].

The EU has the capacity to detect ZIKV genome in at least 20 laboratories in 13 EU countries.

The risk for transmission of ZIKV infections is currently extremely low in the EU as the climatic conditions are not suitable for the activity of potential vectors. Consequently, the risk in the EU to be exposed to ZIKV is similarly extremely low during the winter season.

Risk of Zika virus importation and transmission for EU Overseas Countries and Territories and Outermost Regions

The probability of introduction of the virus from Brazil, Colombia, Cape Verde and Suriname to EU Overseas Countries and Territories and EU Outermost Regions, especially in South America and in the Caribbean region, has increased since the rapid risk assessment published on 25 May 2014 [3], as the epidemic is currently spreading in South America. Considering the presence of competent vectors in these Overseas Countries, Territories and Outermost Regions, the establishment of local transmission is possible once the virus is introduced. The risk of introduction and spread of the ZIKV infections includes Madeira because of its close relationship and intense trade and travel with Brazil and Cape Verde, where ZIKV is currently circulating, and the presence of competent vectors (*Aedes aegypti*).

Risk of Zika virus infection for travellers to affected regions

Travellers to countries where ZIKV is circulating are at risk of developing the disease through mosquito bites.

Risks of Zika virus infection associated with blood donations

According to Musso et al, 42 of 1 505 (3%) blood donors in French Polynesia, although asymptomatic at the time of blood donation, were found positive for ZIKV by PCR supporting a potential risk of transfusion-derived transmission [13]. Viraemic asymptomatic travellers returning from affected areas could potentially transmit the disease through blood donation.

Conclusions and options for mitigation

The increase in congenital microcephaly observed in Brazil is of concern. Its emergence a few months after the introduction of ZIKV infection into the country raises questions about the possible role of the infection in congenital microcephaly. There is currently only ecological evidence of an association between the two events. A possible causative nature of the association cannot be ruled out with the evidence available. Further investigations and studies will contribute to a better characterisation of the association, and provide a better understanding of the possible role of other prenatal infections, genetic risk factors, environmental exposures to chemicals or consumption of teratogenic drugs. Studies of the ZIKV genome will provide information on possible changes that might influence ZIKV disease characteristics and vector competence.

As a precautionary measure, pending the results of on-going investigations, the Ministry of Health of Brazil emphasises the importance of recommendations that pregnant women should avoid the consumption of alcohol, drugs, medications without prescription and contact with people presenting with fever or infection. In addition, specific recommendations were issued about protection from mosquito bites, such as keeping doors and windows closed or screened, wearing trousers and long-sleeved shirts and using repellents authorised during pregnancy [1].

In the light of the current speculation regarding a yet to be established link between ZIKV and microcephaly, options for public health authorities in EU/EEA Member States to consider for mitigation of risks for travellers to and from Brazil include:

- To enhance vigilance towards the detection of imported cases of ZIKV infection in EU Member States, EU Overseas Countries and Territories, and EU Outermost Regions, in particular where vectors or potential vectors are present in order to reduce the risk of autochthonous transmission.
- To increase awareness of clinicians and travel health clinics about the evolution of the ZIKV outbreak and the endemic areas, especially in Brazil, Colombia, Suriname, Samoa and Cape Verde, in order for them to include ZIKV infection in their differential diagnosis for travellers from those areas. Fever and/or macular or papular rash not attributable to dengue or chikungunya infection among travellers returning from areas currently experiencing ZIKV outbreak should be considered indications for further investigation for ZIKV infection.
- To ensure that advice on specific prevention measures, including information and education about mosquito bite prevention, is directed to pregnant women living in or travelling to areas where ZIKV outbreaks are ongoing.
- Increase awareness among health professionals providing prenatal care of this possible association and adapt prenatal monitoring according to the exposure of the pregnant women.
- To advise travellers visiting affected areas, particularly pregnant women, to take individual protective measures to prevent mosquito bites all day round as ZIKV is transmitted by a daytime mosquito and consequently protective measures must be applied during the day (unlike malaria).
- To strengthen the laboratory capacity to confirm suspected ZIKV infections in the European region in order to differentiate ZIKV infections from other arboviral dengue-like infections.
- For blood safety authorities, to consider deferral of donors with relevant travel history to areas with active ZIKV transmission, in line with measures defined for West Nile virus.

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