



RAPID RISK ASSESSMENT

Zika virus infection outbreak, Brazil and the Pacific region

25 May 2015

Main conclusions

- This is the first documented outbreak of Zika virus (ZIKV) infection in Brazil and the Americas.
- Vigilance should be enhanced 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 potential vectors are present. Early detection of cases is essential to reduce the risk of autochthonous transmission in regions where potential vectors are established.
- Clinicians and travel medicine clinics should be aware of the evolution of ZIKV-affected areas in Brazil and the Pacific region and should 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 prompt further investigation for ZIKV infection.
- Imported ZIKV cases are possible in EU Overseas Countries and Territories and EU Outermost Regions, with onwards autochthonous transmission where potential vectors are present.
- Autochthonous transmission in EU Members States in continental Europe, arising from imported cases during the summer season in areas where *Aedes albopictus* are established, cannot be excluded. Vigilance during the mosquito season is required in areas where potential vectors are present.
- The laboratory capacity to confirm suspected ZIKV infections should be strengthened in the European region in order to differentiate ZIKV infections from other arboviral dengue-like infections.
- Blood safety authorities need to be vigilant regarding the epidemiological situation and might wish to consider deferral of donors with relevant travel history, in line with measures defined for West Nile virus.
- As exposure to infected mosquitoes is the principal risk for infection, prevention of ZIKV infection is based on protection against mosquito bites and vector control, particularly for travellers visiting affected areas.

Source and date of request

ECDC internal decision, 18 May 2015.

Public health issue

This document assesses the risk to public health in the EU/EEA, and the risk to EU/EEA citizens, associated with the outbreak of Zika virus infections in Brazil and the Pacific region.

The first ECDC rapid risk assessment on Zika virus infections outbreak, entitled 'Zika virus infection outbreak, French Polynesia', is dated 14 February 2014 [1]. Detailed information on the epidemiology of the Zika virus can be found in an ECDC factsheet for health professionals [2].

Consulted experts

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Disease background information

Zika is a mosquito-borne viral disease caused by Zika virus (ZIKV), a flavivirus from the Flaviviridae family, initially identified in 1947 in the Zika forest in Uganda in the Rhesus macaque population [3]. Comprehensive genomic comparison showed different sub-clades reflecting the existence of two main lineages, one African and one Asia lineage [4,5] [6].

The main clinical symptoms in patients are low-grade fever ($< 38.5^{\circ}\text{C}$), transient arthritis/arthralgia with possible joint swelling (mainly in the smaller joints of the hands and feet) and maculo-papular rash (that often starts on the face and then spreads throughout the body), conjunctival hyperaemia or bilateral non-purulent conjunctivitis with general non-specific symptoms such as myalgia, asthenia and headaches. Clinical symptoms of Zika disease appear after an incubation period ranging between 3 and 12 days [7]. The disease symptoms are usually mild and short lasting (2–7 days), and infection may go unrecognised or be misdiagnosed as dengue. Association with neurological complications such as *Guillain-Barré* syndrome remains under investigations [7-9].

A high rate of asymptomatic infection with ZIKV is expected, similar to other flaviviral infections, such as dengue and West Nile fever. Approximately one in four people infected with ZIKV are believed to develop symptoms [10,11]. Most people fully recover without severe complications, and hospitalisation rates are low. To date, there have been no reported deaths associated with ZIKV infection.

There is some evidence that perinatal transmission can occur, most probably by transplacental transmission or during delivery when the mother is viraemic [11-13]. ZIKV transfusion-derived transmission is theoretically possible because three per cent of blood donors (42/1505) who were asymptomatic at the time of donation were found positive for ZIKV by PCR during the ZIKV outbreak in French Polynesia (November 2013 to February 2014) [10]. A publication in 2011 reported a possible case of sexual transmission of ZIKV [14]. In another case, presence of viable virus was detected in semen more than two weeks after recovery from an illness consistent with ZIKV infection [15]. However, the three modes of transmission described above are very rare.

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 [16-19]. In Asia, *Aedes aegypti* is considered an important vector of ZIKV: the virus has been detected in wild-caught *Aedes aegypti*, and experimental infections show that this species is capable of transmitting ZIKV [20,21]. During the outbreak in Yap in Micronesia, *Aedes hensilli* has

been suspected as vector because of its abundance coinciding with the outbreak. No ZIKV infection was detected in the mosquitoes captured during this outbreak [11], but it has been shown to be a potential vector of ZIKV based on evidence from experimental infections [22]. In Singapore, *Aedes albopictus* is also a potential vector of ZIKV, based on data from experimental infections [23]. *Aedes albopictus* has been found naturally infected in Gabon [24].

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 its capacity to cause large-scale outbreaks [25].

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 consulting cases [26,27]. 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 [27,28]. Of these, 42 were confirmed as *Guillain-Barré* syndrome, with 37 cases having presented with a previous ZIKV-consistent infection [29]. Further investigations with regard to identifying an underlying physiopathological mechanism and/or individual genetic risk factors, and investigations into the potential role of previous/concomitant infections known to be associated or potentially associated with *Guillain-Barré* syndrome are needed to provide a better understanding of the potential causal association between ZIKV disease and neurological complications.

Laboratory diagnosis

ZIKV diagnosis is primarily based on detection of viral RNA from clinical specimens. The viraemic period is considered to be short, allowing for direct virus detection only during the first three to five days after onset of symptoms [3,30]. Specific assays have been published for Asian and African ZIKV strains targeting the envelope gene or NS5 region [3,30,31]. Pan-flavivirus assays and subsequent sequencing analysis can be used as an alternative screening test for possible ZIKV infection [32,33]. The use of saliva samples has been shown to increase the rate of molecular detection in the acute phase, but did not extend the period of detection [34]. The use of urine as a specimen for viral genome detection by RT-PCR might be a diagnostic method to consider in order to extend the period of detection because the disappearance of the genome from serum at an early stage of symptomatic disease has been shown for several other flaviviruses [35–38]. In several patients in French Polynesia, ZIKV RNA has been detected in the urine more than 10 days after onset of disease [39].

ZIKV-specific IgM/IgG antibodies can be detected by ELISA and immunofluorescence assays in serum specimens, usually from day five or six of symptomatic illness. Interpretation of serological results should be considered very carefully as false positive dengue IgM cross reactivity both by indirect immunofluorescence assay and rapid test has been reported in both primary ZIKV-infected patients and also those with a probable history of other prior flaviviral infection [30,40]. Detection of an increase of antibodies in paired sera is recommended. A positive result for dengue IgM antibodies without detection of dengue IgG in paired sera among travellers returning from areas affected by ZIKV should prompt a possible investigation for another flavivirus aetiology. Positive results should be confirmed by neutralisation. However, in some patients with a probable previous history of flavivirus infection, a fourfold increase of neutralising antibodies to other flaviviruses has been observed [30]. To our knowledge, there are no commercially available serological assays for the detection of ZIKV-specific antibodies.

Event background information

Brazil

Since February 2015, the Ministry of Health of Brazil has been investigating an outbreak of exanthematic disease affecting six different states (Bahia, Maranhão, Pernambuco, Rio Grande do Norte, Sergipe and Paraíba) of the north-eastern region. Between February and April 2015, 6 807 cases of mild rash illness have been reported. Samples were tested for dengue, chikungunya, measles, rubella, parvovirus B19, enterovirus and other arboviruses. Of 425 samples tested, 55 resulted positive for dengue while tests conducted for the other pathogens were negative. Samples were sent to the National Reference Laboratory 'Evandro Chagas Institute' for further laboratory investigation and confirmation [41].

On 7 May 2015, the Pan American Health Organization (PAHO)/World Health Organization (WHO) issued a recommendation to member states in the Region of Americas to establish and maintain the capacity for ZIKV infection detection, clinical management, and an effective public communication strategy, as well as to reduce the presence of ZIKV vector(s) [42].

On 15 May 2015, the Ministry of Health of Brazil confirmed the circulation of ZIKV in the country following the identification of ZIKV in 16 samples (eight from Bahia and eight from Rio Grande do Norte) by the National Reference Laboratory. The Ministry of Health is investigating other suspected cases of rash and has strengthened surveillance, prevention and control measures in the country. This is the first report of autochthonous ZIKV infection in Brazil [43].

On 20 May 2015, the state of Sao Paulo notified the detection (at Adolfo Lutz Institute) of a confirmed case without travel history in the municipality of Sumaré, Sao Paulo [44].

Pacific region

In 2015, the Department of Health in Vanuatu reported an unspecified number of confirmed cases of ZIKV [45,46]. This is the first time that Vanuatu has reported the disease.

In the Solomon Islands, an outbreak has been ongoing since February 2015, probably linked to recent outbreaks in other Pacific Island countries. The first laboratory confirmation of ZIKV was reported by the Ministry of Health and Medical Services on 12 March 2015 [47]. Since February 2015, and as of 3 May 2015, 302 cases have been reported, with a decreasing trend in the number of cases [46].

As of 20 May 2015, the Direction des Affaires Sanitaires et Sociales de Nouvelle-Calédonie has reported 82 confirmed cases of ZIKV disease in New Caledonia since 1 January 2015, with more than six cases per week since week 12/2015. Ten imported cases were notified between week 7 and 13/2015 [48].

ECDC threat assessment for the EU

An outbreak of ZIKV infection has been confirmed in the populous eastern states of Bahia and Rio Grande do Norte, Brazil, where two potential vector species (*Aedes aegypti*, *Aedes albopictus*) are widely distributed [49-51]. In addition, a report (20 May 2015) about one autochthonous case in the state of Sao Paulo needs to be further monitored [44]. Factors such as the presence of potential vectors and high population density favour the possible further spread of ZIKV in the country and the South American region. As yet, however, the understanding of the epidemiology of Zika is limited and the evolution of the outbreak needs to be carefully investigated to better assess the risk of spread and its consequences for public health. The knowledge of the circulating ZIKV lineages in Brazil is considered essential, as the Asian lineage seems to have a high epidemic potential.

Risk for the continental EU

Depending on the evolution of local outbreaks, travel-related cases of Zika returning from affected areas in Brazil or the Pacific region can occur. Consequently, awareness and vigilance among clinicians and travel clinics must be enhanced regarding possible imported cases not attributable to dengue or chikungunya infections. This is particularly relevant for the Expo 2015 in Milan, Italy, which runs from May to October. The Expo expects to attract over 20 million visitors [52].

The EU has laboratory capacity to detect ZIKV. At least 20 laboratories (in 13 EU countries) of the European Network of Viral Imported Diseases (ENIVD) have the capacity to detect ZIKV genome [1].

The capacity of European populations of *Aedes albopictus* to transmit ZIKV is not known but is anticipated and should be assessed. Onward transmission in the EU from imported cases during the summer in areas where *Aedes aegypti* and *Aedes albopictus* mosquitoes are established cannot be excluded, and vigilance is required in areas where these potential vectors are present [53].

Risk for EU Overseas Countries and Territories and Outermost Regions

The EU Overseas Countries and Territories include Anguilla, Aruba, Bermuda, Bonaire, British Virgin Islands, Cayman Islands, Montserrat, Curacao, Saba, Sint Eustatius, Sint Maarten, and Turks and Caicos Islands in the Caribbean region as well as French Polynesia, New Caledonia, and Wallis and Futuna in the Pacific region. The EU outermost regions include the four French overseas departments Guadeloupe, French Guiana, Martinique and La Réunion, the Canary Islands that are part of Spain, and the Azores and Madeira as parts of Portugal [54,55].

The probability of introduction of the virus from Brazil and from the Pacific region to EU Overseas Countries and Territories and EU Outermost Regions is possible and will depend on the evolution of current outbreaks. Considering the presence of competent vectors in these Overseas Countries, Territories and Outermost Regions, local transmission is possible once the virus is introduced.

Due to its close relationship with Brazil and the presence of competent vectors, the introduction and autochthonous transmission of the disease in Madeira is possible.

Risk for travellers to affected regions

Travellers visiting Brazil, in particular the states of Bahia, Rio Grande do Norte and Sao Paulo, and those visiting the affected islands in the Pacific region, should be aware of the ongoing outbreak of ZIKV infection. As neither treatment nor vaccines are available, prevention is based on personal protection measures similar to the ones against dengue and chikungunya. *Aedes* mosquitoes bite during the day as well as in the late afternoon and early evening. As exposure to infected mosquitoes is the principal route of infection, prevention of ZIKV infection is based on protection against mosquito bites.

Risks associated with blood donations

Unequivocal evidence of transfusion-transmitted Zika virus infection has not been documented. However, viraemic asymptomatic travellers returning from affected areas could potentially transmit the disease through blood donation. Therefore, EU blood safety authorities need to be attentive to the changing epidemiological situation of ZIKV in Brazil and the Pacific region and should consider a temporary deferral from blood donation of persons with a travel history to the affected areas. The deferral could be set to 28 days, which is also the deferral period for West Nile fever. In areas endemic for *Aedes* species, a preparedness plan to respond to future outbreaks of ZIKV infection should consider measures to sustain the supply of blood and blood products.

Conclusions and options for mitigation

- This is the first documented outbreak of Zika virus (ZIKV) infection in Brazil and the Americas.
- Vigilance should be enhanced 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 potential vectors are present. Early detection of cases is essential to reduce the risk of autochthonous transmission in regions where potential vectors are established.
- Clinicians and travel medicine clinics should be aware of the evolution of ZIKV-affected areas in Brazil and the Pacific region and should 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 prompt further investigation for ZIKV infection.
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- The laboratory capacity to confirm suspected ZIKV infections should be strengthened in the European region in order to differentiate ZIKV infections from other arboviral dengue-like infections.
- Blood safety authorities need to be vigilant regarding the epidemiological situation and might wish to consider deferral of donors with relevant travel history, in line with measures defined for West Nile virus.
- As exposure to infected mosquitoes is the principal risk for infection, prevention of ZIKV infection is based on protection against mosquito bites and vector control, particularly for travellers visiting affected areas.

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