Main conclusions

- This is the first documented outbreak of Zika virus (ZIKV) infection in Brazil and in the Americas.
- Vigilance must be enhanced towards detection of imported cases of ZIKV infection in EU Member States and EU overseas countries and territories and the 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 a possible investigation for ZIKV infection.
- Imported ZIKV cases in the EU overseas countries and territories and the EU outermost regions with onwards autochthonous transmission is possible 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 a potential vector is present.
- The laboratory capacity to confirm suspected ZIKV infections should be strengthen in the European region 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’ was dated 14 February 2014 [1]. Detailed information about the Zika virus epidemiology can be found in the ECDC factsheet for health professional [2].

Consulted experts

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External experts consulted and acknowledgements

The following experts contributed to this risk assessment:

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- WHO Regional Office for Europe, WHO Regional Office for America/Pan America Health Organization.

ECDC acknowledges the valuable contributions of all experts. All experts have submitted declarations of interest. ECDC has reviewed these and finds that none of them presents a conflict of interest with the comments and suggestions the experts have made. It should be noted that opinions expressed by individual experts do not necessarily represent the opinion of their institutions.

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°C), transient arthritis/arthritis 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 none specific symptoms such as myalgia, asthenia and headaches. Clinical symptoms of Zika disease appear after an incubation period ranging between three to 12 days [7]. The disease symptoms are usually mild and short lasting (2-7 days) and infection may go unrecognized 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 hospitalization 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 may occur as reported during the ZIKV outbreak in French Polynesia during which, from November 2013 to February 2014, three per cent of blood donors (42/1 505), who were asymptomatic at the time of donation, were found positive for ZIKV by PCR [10]. A publication in 2011 reported a possible ZIKV sexual transmission [14]. In another case, presence of viable virus was detected in semen more than two weeks after recovery from an illness compatible with a ZIKV infection [15]. However, the three above described modes of transmission 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 as 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 (the Pacific region), *Aedes hensilii* 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]. *Aedes albopictus* in Singapore is also a potential vector of ZIKV, based on data from experimental infections, [23] and 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, 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 have been reported by the syndromic surveillance sentinel network of French Polynesia with 383 confirmed cases and an estimated number of consulting cases of 32 000[26,27]. During this outbreak, 74 individuals presented with neurological symptoms or auto-immune syndrome following a disease episode with symptoms compatible 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 compatible infection [29]. Further investigations with regards 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 3–5 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 sample has been shown to increase the rate of molecular detection in the acute phase, but did not extend the window of detection [34]. The use of urine as a specimen for viral genome detection by RT-PCR might be a diagnostic method to consider to extend the window of detection since 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 more than 10 days after onset of disease in the urine [39].

ZIKV-specific IgM/IgG antibodies can be detected by Elisa and immunofluorescence assays in serum specimens usually from day 5–6 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]. There are no commercial serological assays available for detection of ZIKV specific antibodies to our knowledge.

**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 Paraiba) 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 (8 from Bahia and 8 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 May 20, 2015, the state of Sao Paulo notified the detection of a confirmed case without travel history in the municipality of Sumaré, Sao Paolo by the Adolfo Lutz Institute [44].

**Pacific region**

In 2015, the Department of Health on the South Pacific island nation of Vanuatu reported an unspecified number of confirmed cases of the mosquito borne virus, ZIKV [45,46]. This is the first time that Vanuatu has experienced this disease.

In the Solomon Islands, an outbreak has been on-going since February 2015, probably linked with 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]. As of 3 May 2015, 302 cases have been reported since February 2015 with a decreasing trend in number of cases [46].

In New Caledonia, as of 20 May 2015, the Direction des Affaires Sanitaires et Sociales de Nouvelle-Calédonie has reported 82 confirmed cases of ZIKV disease since 01 January 2015, with more than 6 cases per week since week 12 of 2015. Ten imported cases were notified between week 7 and 13 in 2015 [48].

**ECDC threat assessment for the EU**

An outbreak of ZIKV infection has been confirmed as occurring in two eastern states of Brazil, Bahia and Rio Grande do Norte, which are highly populated and where the two potential vector species *Aedes aegypti* and *Aedes albopictus* are widely distributed [49-51]. In addition, the report for one autochthonous case in the state of Sao Paulo on May 20 2015 needs to be further monitored [44]. These factors favour 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 in the EU Member States. This is particularly relevant for the on-going mass gathering event related to the Milano Worlds’ Fair in Italy from May to October expecting over 20 million visitors [52].

The EU has laboratory capacity to detect ZIKV. At least 20 laboratories of the European Network of Viral Imported Diseases (ENIVD) in 13 EU countries 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 were *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.

By 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 on-going outbreaks of ZIKV infection. As neither treatment nor vaccine is available, prevention is based on personal protection measures similar to the once to protect 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.

**Risk for blood donation**

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

**Conclusions and options for mitigation**

- This is the first documented outbreak of ZIKV infection in Brazil and in the Americas.
- Vigilance must be enhanced towards detection of imported cases of ZIKV infection in EU Member States and EU overseas countries and territories and the 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 a possible investigation for ZIKV infection.
- Imported ZIKV cases in the EU overseas countries and territories and the EU outermost regions with onwards autochthonous transmission is possible 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 a potential vector is present.
- The laboratory capacity to confirm suspected ZIKV infections should be strengthen in the European region 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 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.

**References**