RAPID RISK ASSESSMENT

Zika virus disease epidemic

Ninth update, 28 October 2016

Conclusions and options for response

European Union/European Economic Area (EU/EEA) Member States should consider a range of mitigation measures regarding the Zika virus epidemic due to:

- the current circulation of Zika virus on several continents
- the evidence of an association between Zika virus infection during pregnancy and congenital malformations of the central nervous system (CNS)
- the association between Zika virus infection and Guillain–Barré syndrome (GBS)
- the risk of local vector-borne transmission in Europe in areas where potential vectors are still active (e.g. Madeira) during the 2016 autumn season; in the continental EU, the risk of local vector-borne transmission will decrease in the coming months because the season for Zika virus transmission by vectors will become unfavourable
- the possibility of sexual transmission from returning travellers
- the risk of Zika virus transmission via substances of human origin (SoHO).

The options for risk reduction and the definitions below are based on the current evidence, which take into account current uncertainties. These are subject to change as new evidence emerges.

Options for risk reduction

The predominant mode of transmission of Zika virus is through the bites of infected mosquitoes but the virus can also be transmitted through sexual contact, and by blood and blood components and possibly by other substances of human origin. Pregnant women are the most important risk group and the primary target for preventive measures because Zika virus infection during pregnancy is associated with intrauterine CNS infection, congenital malformations and foetal death.

A map and list of countries and territories with widespread and sporadic transmission during the past three months is available on ECDC website

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Preventive measures

Preventing mosquito transmission

Mosquito-borne transmission occurs when an infective mosquito bites a susceptible person. The risk of mosquito-borne transmission can be reduced by lowering the mosquito population density and by applying personal protective measures against being bitten. The aim is to prevent susceptible people from being bitten by infective mosquitoes, and preventing infected people from being bitten by competent mosquitoes to prevent the continuation of the chain of transmission.

Personal protective measures that reduce the risk of mosquito bites and which should be applied indoors and outdoors are:

- use of mosquito repellent in accordance with the instructions indicated on the product label
- wearing long-sleeved shirts and long trousers, especially during the daytime, when the *Aedes aegypti* and *Aedes albopictus* mosquitoes are most active
- sleeping and resting in screened or air-conditioned rooms, or using mosquito bed nets at night and during the day.

Preventing sexual transmission

Zika virus sexual transmission can be prevented by:

- abstaining from sexual contact with a potentially infectious person; OR
- consistent use of barrier methods* during sexual contact with a potentially infectious person†.

Advice to populations at risk

Residents in affected areas‡

All residents in affected areas are at risk of Zika virus infection unless they have immunity due to a previous infection. Residents should consider taking measures to prevent mosquito-borne and sexual transmission of the virus.

Pregnant women residing in affected areas should consult their healthcare providers for medical advice. They should strictly follow measures to prevent mosquito and sexual transmission for the duration of their pregnancy. Pregnant women should seek medical attention if they develop symptoms compatible with Zika virus infection.

Women of childbearing age should be made aware of the risks of Zika virus infection to the foetus during pregnancy and the possibility of sexual transmission through unprotected sex with a potentially infectious person.

Women and men living in affected areas should discuss pregnancy planning with their healthcare provider.

Travellers to affected areas

All travellers to affected areas are at risk of Zika virus infection unless they have immunity due to a previous infection. Travellers to affected areas should take measures to prevent mosquito-borne and sexual transmission of the virus. This is particularly important for the partners of pregnant women.

Pregnant women should seek medical advice prior to travelling. They should postpone non-essential travel to affected areas with widespread transmission and consider postponing non-essential travel to areas with sporadic transmission for the duration of their pregnancy.

Women of childbearing age who travel to affected areas should be made aware of the risks of Zika virus infection to the foetus during pregnancy and the possibility of sexual transmission. Therefore, they should take measures to prevent mosquito bites and follow recommendations for prevention of sexual transmission while in affected areas.

Travellers with immune disorders or severe chronic illnesses should consult their physician or seek advice from a travel clinic before travelling.

Persons returning from affected areas

All persons returning from affected areas should seek medical attention if they develop symptoms compatible with Zika virus infection within two weeks of arriving from the affected areas, and mention their travel history.

Pregnant women returning from affected areas should:

- inform their antenatal care provider about their travel to an affected area
- take measures to prevent sexual transmission for the duration of the pregnancy in order to minimise the risk of foetal exposure to Zika infection.

Partners of pregnant women returning from affected areas should:

- follow measures for prevention of sexual transmission for the duration of pregnancy in order to minimise the risk of foetal exposure to Zika virus infection.

Couples who want to conceive should consider the following options to minimise the risk of Zika congenital syndrome if one or both partners have been exposed (i.e. returning from an affected area or having had unprotected sexual contact with a potentially infectious partner):

- Delay pregnancy for at least eight weeks after symptom onset or last possible Zika virus exposure for women, symptomatic or not
- Delay conception for a duration of at least six months after symptoms onset or last possible Zika virus exposure for men, symptomatic or not
- Discuss with their healthcare provider the period for deferring conception/pregnancy in relation to individual exposure characteristics and availability of test results.

All couples who are concerned about sexual transmission of Zika virus infection to their partner may consider the following option:

- Take measures to prevent sexual transmission for at least eight weeks if the returning partner is a woman and six months if a man.

In addition, **all persons who have been in affected areas and travel to areas where the vector is present and active** should:

- take personal protective measures to prevent mosquito bites as described above, for three weeks after having left an affected area to prevent onward vector-borne transmission.

Information to healthcare providers in EU Member States

- Efforts should be made to increase awareness among health professionals providing antenatal care of the risk of neurological congenital syndrome associated with maternal Zika virus infection, especially during the first two trimesters of pregnancy. Pregnant women with exposure to Zika virus (including sexual exposure) since the beginning of their pregnancy should be investigated as part of the routine obstetric monitoring (Algorithm for public health management of cases under investigation for Zika virus infection).
- Antenatal monitoring should be adapted in accordance with the possibility of exposure to the virus through vector or sexual transmission [1,2]. ECDC maps showing Zika transmission in the past nine months are provided to aid medical practitioners assessing returning travellers, especially pregnant women, who have visited countries and territories with recent transmission of Zika virus.
- Health services and practitioners should be aware of the association between Zika virus infections and GBS, the possible associations with other neurological conditions (such as meningitis, meningoencephalitis and myelitis), and with as yet undocumented complications of Zika virus infections, particularly among children, the elderly, immunocompromised individuals and those with sickle cell disease.

Safety of substances of human origin

There is no change in the level of risk of Zika virus transmission through SoHO compared to the previous Rapid Risk Assessment. The measures and main recommendations provided in the ECDC document 'Zika virus and safety of substances of human origin – Guide for preparedness activities in Europe' remain valid [3].

The European Medicines Agency (EMA) and competent authorities in the EU Member States have confirmed that there is no increased risk of Zika virus infection for recipients of plasma-derived or urine-derived medicines [4]. EMA's Committee for Medicinal Products for Human Use Biologics Working Party (CHMP's BWP) assessed that manufacturing processes for these products successfully inactivate or remove virus. Thus,

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* Barrier methods include: male or female condoms for penetrative sex, including sex toys, and male or female condoms or dental dams for oral–genital or oral–anal sexual contact. To increase their effectiveness they should be used consistently and correctly, for the entire duration of sexual contact (United Nations position statement on condoms and the prevention of HIV, other sexually transmitted infections and unintended pregnancy, 7 July 2015).

† A potentially infectious person is defined as: any person who resides in an affected area; OR a woman who has been in an affected area in the past eight weeks; OR a man who has been in an affected area in the past six months; OR a woman who has had unprotected sex in the past eight weeks with a potentially infectious person as defined above; OR a man who has had unprotected sex in the past six months with a potentially infectious person as defined above.

‡ Affected areas are areas where locally vector-borne transmitted cases of Zika virus infection have been reported in the past three months. ECDC classifies Zika-affected areas as having widespread transmission or sporadic transmission based on cases reported in the past three months.

additional safety measures such as the screening of plasma and urine donors or donations or the deferral of donors returning from affected areas are not considered necessary.

Surveillance of imported cases and local transmission in Europe

In order to reduce the risk of local transmission in Europe, EU Member States should:

- Ensure that medical practitioners and travel health clinics are aware of the evolution of the Zika virus outbreak and the areas around the world with active and past transmission (see ECDC website) to allow them to consider Zika virus infection in their differential diagnosis for travellers coming from those areas, or for symptomatic individuals who have not travelled but had sexual activity with a returning traveller from those areas. Medical practitioners should be aware that Zika virus infections can be paucisymptomatic.
- Maintain awareness among obstetricians, paediatricians and neurologists that the possibility of Zika virus infection should be investigated in patients presenting with congenital CNS malformations, microcephaly and GBS.
- Remain vigilant towards the early detection of imported cases of Zika virus infection in EU Member States, EU Overseas Countries and Territories (OCTs) and EU Outermost Regions (OMR), particularly where Zika vectors are present and still active and which have not experienced local vector-borne transmission (e.g. Madeira), in order to reduce the risk of onward autochthonous transmission.
- Ensure timely reporting of autochthonous cases, particularly in the receptive areas of EU Member States in continental Europe.
- Strengthen laboratory capacity and capabilities to confirm Zika virus infections in the EU/EEA and to differentiate Zika virus infections from other arboviral infections (e.g. dengue, chikungunya).

Source and date of request

ECDC internal decision, 10 October 2016.

ECDC issues this risk assessment document according to Article 7(1) of Regulation (EC) No 851/2004 establishing a European Centre for Disease Prevention and Control. In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility for the choice of which option to pursue and which actions to take lies exclusively with 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 EU Member States within continental Europe. Since February 2014, ECDC has published ten risk assessments related to Zika virus epidemics [5-16].

Consulted experts

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Experts from the following institutions contributed to this risk assessment: WHO Regional Office for Europe, WHO Regional Office for Western Pacific Region and WHO Regional Office for Americas/Pan American Health Organization (PAHO).

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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 [5-16] and in the ECDC factsheet for health professionals (last update 23 June 2016).

Epidemiological developments

Since the eighth Zika virus disease epidemic risk assessment published on 30 August 2016, the outbreak has continued to evolve in Central America and the Caribbean countries and territories. In addition to the Americas, cases have been reported in some Asian countries. Autochthonous transmission is ongoing in the state of Florida (USA) where competent vectors are present and still active.

Between 17 August and 24 October 2016:

- Seven new countries and territories reported locally acquired cases: two in the Caribbean (British Virgin Islands and Saint Kitts and Nevis), four countries in Asia (Malaysia, the Philippines, Singapore and Thailand) and one in the South Pacific (Solomon Islands) [17].
- The Netherlands reported non-vector-borne Zika virus transmission [18].
- Costa Rica, Dominican Republic, Grenada, Guatemala, Haiti and Thailand reported their first cases of microcephaly or CNS malformation associated with Zika virus infection [19].
- Mexico notified cases of GBS associated with Zika virus infection [17].
- On 17 October 2016, the health authorities in Vietnam reported the first case of microcephaly associated with Zika in a four-month-old child living in Krong Buk district, Dak Lak province. Confirmatory tests are being carried out at Nagasaki University in Japan and results are pending [20].

South America

- In 2016, Brazil has reported 200 465 suspected and 109 596 confirmed Zika virus infections as of week 41/2016 [21].
- On 25 July, the Ministry of Health of Colombia declared the end of the Zika epidemic phase [22]. The country remains the second most affected in the Americas with 95 898 suspected and 8 826 confirmed cases (including 5 881 pregnant women) reported up to week 41 in 2016 [23]. The incidence was 376/100 000 population during the epidemic phase in urban areas and is currently around 14/100 000 during the post-epidemic phase. As of week 41, 19 104 notifications of pregnant women with confirmed and suspected Zika virus disease have been reported. Forty-seven cases of microcephaly were associated with Zika virus infection, 213 cases were excluded and 342 cases are under investigation [23]. An increase in the incidence of congenital malformations was observed in September and it is expected to increase further in October 2016.

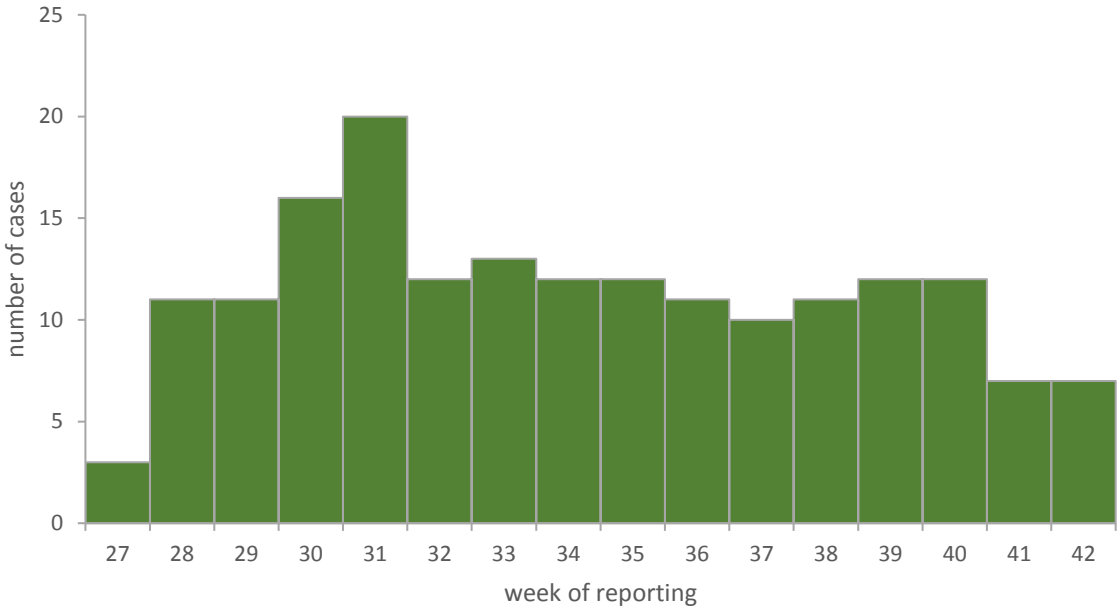
The Caribbean

- Several EU OMRs and OCTs still report vector-borne autochthonous Zika transmission.
- On 14 October 2016, Martinique declared the outbreak phase to be over since only 90 new patients were identified on the island between 26 September and 2 October, compared with 1 140 weekly cases reported during the epidemic peak between 30 May and 5 June 2016 [24].
- The epidemic has been significantly decreasing in Guadeloupe, Saint Martin and French Guiana since July 2016 [25].
- As of week 40, Puerto Rico reported a decrease in the number of new Zika cases during the past six weeks [26].
- The islands of Aruba, Bonaire, Curaçao, Saba and Sint Maarten in the Dutch Antilles have all reported autochthonous transmission.

North America

- As of week 40/2016, more than 200 new confirmed cases have been reported weekly for the past eight weeks in Mexico, with the highest incidence reported from the south-western part of the country [27].
- As of 21 October 2016, Florida authorities reported more than 160 locally transmitted Zika virus cases [28]. Among those, about 150 cases have been reported in Miami-Dade County and a few cases have been reported in the counties of Palm Beach, Broward and Pinellas as of 21 October [29] (Figure 1).

Figure 1. Distribution of locally acquired Zika cases among resident of Florida, by reporting week, Florida, USA, 16 July to 21 October 2016



Source: adapted from the Florida health department website (http://www.floridahealth.gov/newsroom/all-articles.html).

Africa

- In Guinea-Bissau, the gene sequencing results of the four confirmed Zika cases sent in July have preliminarily confirmed that the cases are of the African lineage, i.e. not the predominant global outbreak Asian lineage. The investigation of five reported cases of microcephaly is ongoing [30].

Asia

- On 27 August 2016, Singapore reported its first locally acquired case of Zika virus infection. Since then and as of 22 October 2016, 431 locally acquired Zika virus infections have been recorded in Singapore; 379 of them (88%) having been reported in the three weeks following the initial case [31].
- Thailand reported over 300 confirmed Zika cases in 2016. Malaysia, Vietnam and the Philippines have been reporting locally acquired cases in recent months.
- The Maldives has initiated testing for Zika following several reports of cases who had returned from the Maldives in the past months.

South Pacific

- On 12 October 2016, Australia reported a case of Zika virus infection in a returning traveller from the Solomon Islands [32].

Europe

- As of 24 October 2016, no locally acquired case by vector-borne transmission has been reported by EU/EEA countries in continental Europe.
- Since week 26/2015, 19 countries have reported 1 935 travel-associated Zika virus infections through the European Surveillance System (TESSy). France reported 56% of the cases, Spain 15% and the UK 8%. Over the same period, eight countries reported 91 Zika cases among pregnant women.

A weekly update gathering the latest information of the Zika virus epidemic is available through the ECDC Zika outbreak webpage [33] and a weekly update on the situation is available in an epidemiological update [34] or in the ECDC Communicable Disease Threats Report [35].

Zika-affected areas

ECDC classifies Zika-affected areas as having widespread transmission or sporadic transmission based on cases reported in the past three months:

- Widespread transmission: more than 10 locally transmitted cases of Zika virus in one area, OR local transmission of Zika virus in two or more areas, OR Zika virus transmission ongoing for more than three months.

- Sporadic transmission: no more than 10 locally transmitted cases reported in a single area in the past three months. For more information about the classification of Zika affected areas, please visit the ECDC website.

Definition of potentially infectious person

A potentially infectious person is defined as:

- any person who resides in an affected area; OR
- a woman who has been in an affected area in the past eight weeks; OR
- a man who has been in an affected area in the past six months; OR
- a woman who has had unprotected sex* in the past eight weeks with a potentially infectious person as defined above; OR
- a man who has had unprotected sex* in the past six months with a potentially infectious person as defined above.

Scientific developments

The main findings with regards to Zika virus research are:

- Mosquito vectors:
  - Guo, et al [36] testing a *Culex quinquefasciatus* population from China and Guedes, et al (preprint [37]) studying a population of the same species from Brazil concluded that this species is a competent vector of Zika virus based on experimental infections. Yet four studies using colonies or recently collected populations of *Culex quinquefasciatus* (California, USA; Florida, USA; Rio de Janeiro, Brazil; Brisbane, Australia) reported that this species is not a competent vector of Zika virus [38-41]. The conflicting results might be due to different experimental setups, the use of different Zika virus strains for infection or the fact that different mosquito populations were tested. Before incriminating a new mosquito species as a vector for Zika virus, further evidence is needed on its vector competence and vector capacity.
  - Experimental infections showed that *Culex pipiens* mosquitoes from Italy [42] and from the USA (California and New Jersey) [40] do not transmit Zika virus.
- Persistence of Zika virus in semen and the genital tract:
  - The longest reported duration of Zika virus RNA persistence in the semen of symptomatic men is 181 and 188 days [43,44] but recent findings indicate that it has been described for as long as eight month in one case [Luisa Barzon, personal communication]. Infectious virus particles were detected through semen culture at 69 days after onset [45]. For asymptomatic men, Zika RNA was documented in semen 39 days after returning from an affected area [46]. Zika virus antigens were identified inside the spermatozoa of a symptomatic man 56 days after onset (with 3.5% of the cells infected) [47].
  - Sexual transmission was documented from a vasectomised man with Zika virus RNA identified in semen [45] and from a man with azoospermia with Zika RNA present in semen plasma [46].
  - A follow-up study of five Zika infected women showed the virus RNA disappearing from genital tract three weeks after symptom onset [48]. Zika virus RNA was detected in a vaginal swab up to days 13 and 14 after onset, respectively [49,50].
- Vaccine development:
  - Recent studies showing protective efficacy of multiple vaccine platforms against Zika virus challenge in rhesus monkeys are supporting the rapid clinical development of Zika virus vaccine for humans [51]. The first Phase I trials of two Zika virus DNA vaccine candidates to evaluate safety, tolerability and immunogenicity on healthy adult volunteers are starting in the US and Canada [52].

A detailed report about the relevant scientific literature published since the last rapid risk assessment (8th Update – 30 August 2016) is available on the ECDC webiste Zika epidemic scientific advance.

*Protected sex is defined as sexual contact during which appropriate barrier methods are correctly and consistently used in order to reduce the risk of sexually transmitted infections and sexually transmissible infections such as Zika virus. Barrier methods include: male or female condoms for penetrative sex, including sex toys, and male or female condoms or dental dams for oral–genital or oral–anal sexual contact. To increase their effectiveness they should be used consistently and correctly, for the entire duration of sexual contact (United Nations position statement on condoms and the prevention of HIV, other sexually transmitted infections and unintended pregnancy, 7 July 2015).

International guidance, response and preparedness plans update

Since the last ECDC rapid risk assessment, WHO and the US Centers for Disease Control and Prevention updated the following documents:

- WHO: Prevention of sexual transmission of Zika virus Interim guidance update, 6 September 2016 [53]
- CDC guidance: Interim guidance for preconception counselling and prevention of sexual transmission of Zika virus for persons with possible Zika virus exposure - United States, September 2016 [54]
- Zika CDC interim response plan, September 2016 [55].

ECDC threat assessment for the EU

The Zika epidemic remains a significant concern for public health. The third meeting of the International Health Regulations Emergency Committee on 14 June 2016, 'concurred with the international scientific consensus … that Zika virus is a cause of microcephaly and GBS, and, consequently, that Zika virus infection and its associated congenital and other neurological disorders is a Public Health Emergency of International Concern (PHEIC)' [56].

Although continuing, vector-borne transmission seems to be slowing down in Central American countries and the Caribbean. The outbreak continues to evolve in Mexico and the southern part of the US, as weather conditions still favour seasonal vector activity. The report of locally acquired cases in Florida is not unexpected as small outbreaks of local transmission of dengue and chikungunya have been reported in Florida in the past and the area is receptive for *Aedes* transmitted diseases [57,58]. Additionally, four of the seven countries and territories that for the first time reported locally acquired cases between 17 August and 24 October 2016 are from Southeast Asia and the first cases of microcephaly are reported from Southeast Asia (Thailand).

There is a consensus that Zika virus infection during the first and second trimester of pregnancy is associated with an increased risk for CNS malformations and microcephaly. The risk of CNS malformations when the infection occurs during the third trimester of pregnancy is unknown, hence Zika virus infection should be considered as a risk throughout the duration of pregnancy. To date, there is insufficient data to provide a robust estimate of the risks of adverse pregnancy outcomes by gestational age and the role of potential co-factors. Further, prospective epidemiological studies of Zika-virus-affected populations should provide a clearer picture of the clinical spectrum of diseases caused by Zika virus.

It is conceivable that co-factors, such as the mother's age, nutritional status, genetic predisposition, socio-economic status, environmental exposures, immune status, and concomitant infections, influence the probability of Zika transplacental transmission and congenital malformations. New investigations are ongoing to clarify the likely determinants of the reported incidence of Zika congenital syndrome in the northeast region of Brazil [59].

Vector-borne transmission remains the primary route of transmission. Sexual transmission does occur, and while it increases the risk of infection and epidemic size and duration, it may not initiate or sustain an outbreak by itself [60]. Comprehensive data on the presence and duration of Zika virus in bodily fluids, especially in semen, is required to assess the risk of sexual transmission at the population level.

The outbreak is unprecedented in terms of size and public health impact, and constitutes a significant development in the epidemiology of this emerging vector-borne disease. The evolution of the Zika epidemic in the Americas, Southeast Asia and other world regions demands close monitoring as it has a direct impact on the risk of importation to Europe. It is expected that Zika-viraemic travellers will continue to return to the EU. It is not expected that this will lead to local vector-borne transmission in the coming months because the seasonal conditions for Zika virus transmission by vectors will become unfavourable (except in Madeira). Options for prevention and response are presented above (see 'Conclusions and options for response'). ECDC continues to monitor new scientific evidence and will update the assessment of the risk of transmission and options for prevention and control accordingly.

Travel-related risk for EU citizens

Travellers to affected areas are at risk of becoming infected through mosquito bites and sexual transmission. Due to the link between Zika virus infection and severe congenital anomalies, pregnant women and women who may become pregnant constitute a high-risk group for serious adverse outcomes of Zika virus infection.

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

Residents in EU OMRs and OCTs with competent and active vectors are at 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).

EU OMRs and OCTs outside of the Caribbean where mosquito vectors are present, such as Madeira and Mayotte with *Aedes aegypti* or La Réunion with *Aedes albopictus*, are at risk of local transmission should the virus be introduced [61].

Madeira is of particular concern because of the presence of *Aedes aegypti*. The probability of vector-borne pathogen transmission is still considered high during autumn as the previous dengue outbreak lasted until January 2012. There is frequent travel between Madeira and the Americas, thus the risk of the virus being imported remains [62].

According to the Interim Risk Assessment issued by the WHO Regional Office for Europe, the capacity to contain Zika virus transmission at an early stage is good for the countries of the WHO European Region overall [63].

Risk of importation and transmission within the continental EU

The outbreak in the Americas has considerably increased Zika virus importation into the EU through infected returning travellers and visitors from the affected areas. Cases of Zika virus infection arriving from countries with autochthonous transmission continue to be reported in the EU and it is expected that this will continue.

Given the low vector competence of the studied European populations of *Aedes albopictus* [64-66], the likelihood of local vector-borne transmission in the EU is considered to be low to moderate during the summer period. Further, the likelihood of mosquito-borne transmission of Zika virus infection in the EU will decrease in the coming autumn and winter seasons when *Aedes albopictus* activity will reduce [67].

As of 24 October 2016, no cases of locally acquired mosquito-borne Zika transmission have been reported to ECDC in continental Europe.

Risk of sexual transmission

While Zika virus is considered to be a mild disease for the general population, the severity of foetal impairment in pregnant women infected by Zika virus implies the need to reduce the risk of infection in pregnant women and women of childbearing age through vector-borne and/or sexual transmission, and to adapt gamete donation and pre-conception counselling recommendations.

Among the Zika infection cases reported to ECDC, five European countries have reported 16 sexual transmission events, all from males to their female partners: France (11 cases), Italy (2 cases) and one case each from the Netherlands, Portugal and Spain. It is likely that these figures underestimate the dimension of sexual transmissions from returning travellers, at least due to the possibility of asymptomatic infections in both returning travellers and their sexual contacts.

The evidence on sexual transmission can be summarised as follows:

- Several events of sexual transmission from symptomatic cases in the early phase of infection have been described in peer-reviewed literature [68-74], with the longest interval of 44 days reported between the onset of symptoms in a man and in his female partner [73]. These data suggest sexual transmission most likely occurs in the early period after onset in the primary case.
- Two events of asymptomatic transmission from male partners have been described; sexual transmission likely occurred between day 21 and day 36 after return from an area with ongoing vector-borne transmission in one couple and between day 10 and day 14 after return in the other couple [46,75]. This would also support a higher probability of sexual transmission during the early period of infection.
- The longest duration of Zika virus RNA persistence in semen after onset of symptoms has previously been reported to be 181 days in a study by Barzon, et al [43] and 188 days by Nicastri, et al [44]. Through a recent personal communication, Barzon, et al indicated that Zika virus RNA was detected in the semen of the followed-up patient up to eight months after onset. Among persons with asymptomatic Zika infection, only one study reports duration of Zika virus RNA persistence in semen with the latest detection at 39 days following return from an affected area [46].
- Since Zika RNA viral detection in a bodily fluid does not necessarily imply the presence of infectious viral particles, culture of Zika virus is required to provide evidence for replicative and therefore potentially infectious virus. Zika virus has been cultured from semen from symptomatic men in four studies [45,69,76,77] with the longest duration being 69 days after onset of symptoms [45]. The relevance of prolonged Zika RNA detection in semen with regard to the risk of sexual transmission is not yet clear.
- Male-to-male and female-to-male transmission has been reported previously [78,79]. Transmission was documented from both a man with azoospermia [46] and a vasectomised man [45].
- Limited data exist on the virus clearance from the female genital tract. A recent follow-up study of five Zika-infected women showed the virus RNA disappearing from the genital tract three weeks after symptom onset (last detection at 12 days – weekly testing for the first month, then monthly) with no reappearance over a three-month period of genital sampling [80]. A recent case report detected Zika virus RNA in vaginal swabs up to day 13 after onset [49] and day 14 [50]; previously viral RNA was detected in genital secretions only at 11 days after onset [80].

Limited data about the presence of viable virus, viral load or kinetics in saliva and other oral secretions are available through case reports. A study on non-human primates reported extended Zika virus shedding in the saliva in comparison to the blood, suggesting that the oral mucosa can sustain viral replication over extended periods and may facilitate viral transmission beyond the symptomatic period [81]. These data do not provide clear evidence on whether saliva is an effective vehicle for Zika virus transmission, and the risk of transmission via saliva cannot currently be assessed.

On 6 September 2016**,** WHO increased the duration for sexual precautions from eight weeks to six months for males and females exposed to Zika virus infections, whether they were symptomatic or not [53]. Using all available evidence, and in recognition of the broad range of Member State contexts and capacities, WHO has considered the highest level of precaution in issuing its guidance on avoidance of sexual transmission of Zika virus infection in both men and women. It is expected that individual Member States, through context-specific assessment and guidance from technical partners, may adapt these recommendations as suitable to their local contexts.

On 30 September, the US CDC extended the period for sexual precaution for couples planning to conceive to up to six months for exposed males, symptomatic or not, becoming aligned with WHO recommendations only for males, but it kept the eight-week period for sexual precaution for females exposed to Zika virus infections [54]. Given the risk of congenital malformation associated with Zika virus infection, ECDC, as is the US CDC, is asking EU Member States to consider a period for sexual precaution for couples planning to conceive of six months for exposed men regardless of their symptomatic status and eight weeks for exposed women.

Standardised data from longitudinal cohorts on the frequency of presence and duration of Zika virus in bodily fluids are urgently required to establish the risk of transmission at population level. Systematic investigation of the infectiousness of male patients with long-term shedding of Zika virus RNA is warranted in order to build the evidence for formulating recommendations around sexual transmission.

Risk of Zika virus transmission via substances of human origin

Since the last update of the Rapid Risk Assessment, there have been no new cases of Zika virus transmission through blood transfusion, while transmission through cells, tissues and organs remains unknown. Four probable cases of transfusion transmission from three symptomatic Zika-infected donors in Brazil did not develop symptoms compatible with Zika virus infection although tested positive for viral RNA [82,83]. This suggests that transfusion-transmitted Zika virus infection might occur unrecognised considering that only four cases of transmission have been reported and 0.5% to 2.8% of donations in blood supply tested positive for Zika virus RNA [84-86]. The consequences for the foetus of a transfusion-transmitted Zika virus infection to pregnant women are not yet ascertained. Nevertheless, congenital malformations associated with vector-borne transmission of the virus call upon the use of Zika-virus-negative blood or other types of SoHO in pregnant patients. There is no change in the level of risk of Zika virus transmission through SoHO compared to the previous RRA.

The first four cases of Zika virus infection in immunosuppressed patients have recently been reported in two kidney and two liver transplant recipients in Brazil [87]. All patients presented with bacterial infection and required hospitalisation. Besides symptoms of acute infection, the patients also had thrombocytopenia and worsening allograft function but not typical Zika symptoms like skin rash, conjunctivitis or neurological signs. The small number of cases is, however, insufficient to draw any inference about the effect of immunosuppression on the clinical course of Zika virus infection in solid organ transplant patients and the impact of Zika virus on allograft function.

Detection of Zika virus RNA in whole blood for a longer period than in serum or plasma [50,88] is consistent with similar findings for both West Nile virus [89,90] and dengue viruses [91]. This longer period of detection of the virus RNA has been attributed to the erythrocyte component of whole blood. Infectivity of such Zika virus RNA-positive whole blood samples has not been proven and requires further investigation [50].

The European Medicines Agency (EMA) and competent authorities in the EU Member States have confirmed that there is no increased risk of Zika virus infection for recipients of plasma-derived or urine-derived medicines [4]. EMA's Committee for Medicinal Products for Human Use Biologics Working Party (CHMP's BWP) assessed the manufacturing processes for these products and concluded that they successfully inactivate or remove virus. Thus, additional safety measures such as the screening of plasma and urine donors or donations or the deferral of donors returning from affected areas are not considered necessary [92].

On 26 August 2016, the US Food and Drug Administration (FDA) issued revised guidance recommending universal screening of donated whole blood and blood components for the presence of Zika virus by nucleic acid testing and to use pathogen reduction technology using an FDA-approved device in the USA and its territories [93]. This recommendation does not apply to the collection of source plasma for production of plasma-derived medicinal products.

The guidance recognises Zika virus infection as a relevant transfusion-transmitted infection and is based on assumptions that in the situation of rapidly expanding epidemics and the evolving significance of sexual transmission, geographic deferral policy in non-affected areas will become ineffective; logistically complex while

also resulting in significant donor deferrals potentially compromising adequacy of the blood supply. The laboratory screening will provide a highly sensitive detection of Zika virus in blood donations independent of a donor's medical or travel history status and safeguard against transfusion risk related to sexual transmissions assuring an adequate blood supply.

- In the light of this FDA guidance, ECDC suggests continued adherence in the EU to the universal screening of blood donations only in Zika-virus-affected areas as proposed in the 'Guide for preparedness activities for prevention of Zika virus transmission through SoHO in the EU' [94] considering that the rapid spread of Zika virus in permissive areas of EU Member States is not expected because the likelihood of local vector-borne transmission in the EU is considered to be low to moderate due to the low vector competence of the studied European populations of *Aedes albopictus* [64-66]. Also, according to the Interim Risk Assessment issued by the WHO Regional Office for Europe, the capacity to contain Zika virus transmission at an early stage is good for the countries of the WHO European Region overall [63].
- Previous outbreaks of chikungunya and dengue in the EU show that Member States are experienced and capable of early detection and reporting of cases. In addition, Member States were efficient in travel-based donor deferral and maintaining the sustainability of the blood supply.
- Vector-borne transmission remains the primary route of transmission. Sexual transmission does occur, but its role in spreading the epidemic remains to be determined.

In addition, ECDC considers that an ongoing validation of screening assay during universal application in the US may facilitate approval of the use of this laboratory test for blood screening purposes. ECDC also supports and recommends the use of pathogen reduction technologies that have been approved and are used in several EU Member States.

Recent media reports have quoted the FDA as stating that donated blood in Florida has tested positive for the Zika virus [95]. Zika-positive blood donations are expected when screening is performed in affected areas because of a high proportion of asymptomatic cases. Such positivity has also been found in French Polynesia [86] and Puerto Rico [85]. As of today, the FDA has not reported Zika RNA-positive donations detected in non-affected areas, despite the fact that screening of blood donations is recommended throughout the US [93].

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