RAPID RISK ASSESSMENT

Zika virus disease epidemic: potential association with microcephaly and Guillain-Barré syndrome (first update)

21 January 2016

Main conclusions

The spread of the Zika virus epidemic in the Americas is likely to continue as the competent vectors *Aedes aegypti* and *Aedes albopictus* mosquitoes are widely distributed there. There is also a significant increase in the number of babies born with microcephaly in the north-eastern states of Brazil, however, the magnitude and geographical spread of the increase have not yet been well characterised. Despite growing evidence of a link between intra-uterine Zika virus infection and adverse pregnancy outcomes, a causal link between these events has not yet been confirmed.

As neither treatment nor vaccines are available, prevention is based on personal protection measures similar to the measures that are applied against dengue and chikungunya infections.

In the light of the current disease trend – and the possible association with severe complications – public health authorities in EU/EEA Member States should consider the following mitigation options.

Surveillance of imported cases

- Increase awareness of clinicians and travel health clinics about the evolution of the Zika virus epidemic and the affected areas so that they can include Zika virus infection in their differential diagnosis for travellers from those areas. Fever and/or maculo-papular rash not attributable to dengue or chikungunya infections among travellers returning from areas currently experiencing a Zika virus outbreak should be indications for further investigation of Zika virus infection.
- Enhance vigilance towards the early detection of imported cases of Zika virus 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.
- Strengthen laboratory capacity to confirm suspected Zika virus infections in the EU/EEA in order to differentiate Zika virus infections from other arboviral infections (e.g. dengue, chikungunya).
- Increase awareness among obstetricians, paediatricians and neurologists in the EU/EEA that Zika virus infections should be investigated for patients presenting with congenital central nervous system malformations, microcephaly and Guillain–Barré syndrome (GBS).

Suggested citation: European Centre for Disease Prevention and Control. Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome (first update) 21 January 2016. Stockholm: ECDC; 2016.

Erratum. On 27 January 2016, the following changes were made: in the section titled 'Risk of Zika virus importation and transmission for EU Overseas Countries and Territories, and Outermost Regions,' the Azores and the Canary Islands were removed as places where mosquito vectors are present.

Safety of substances of human origin

- Blood safety authorities should consider the deferral of donors with a relevant travel history to areas with active Zika virus transmission, in line with measures defined for dengue virus. In unaffected areas with competent vectors for Zika virus, a preparedness plan for prevention and control of outbreaks of Zika virus infection should cover the continuity of blood supply.
- Tissue establishments for assisted reproduction may foresee a need to defer potential semen donors for 28 days after returning from affected areas as a viable virus was detected in semen more than two weeks after recovery from an illness consistent with Zika virus infection.
- As a transfusion-transmitted Zika virus infection may have serious consequences for the health of the recipient and the existing blood safety interventions have limited preventive capacities, the screening of all donated blood for the presence of Zika virus RNA by nucleic-acid amplification test (NAT) may be considered necessary in affected areas. Due to the potential association of Zika virus infection and microcephaly in newborns, health authorities in affected areas may anticipate taking the precautionary measures of using Zika virus negative blood for the transfusion of pregnant women and screening of semen donors/donations for the presence of Zika virus.

Information to travellers and EU residents in affected areas

From media reports, information releases and epidemiological bulletins published by the Ministries of Health of the different countries, as of 19 January 2016, the recent trends can be outlined as follows:

- El Salvador, Venezuela, Colombia and Brazil Suriname, French Guiana, Honduras, Mexico, Panama and Martinique are currently experiencing a rapidly evolving Zika virus epidemic with an increasing or widespread transmission;
- Bolivia, Guyana, Ecuador, Guadeloupe, Guatemala, Paraguay, Puerto Rico, Barbados, Saint Martin and Haiti have only reported sporadic transmission following recent introduction.

The following options should be considered:

- Advise all travellers to affected areas to take individual protective measures to prevent mosquito bites.
- Advise travellers that have immune disorders or severe chronic illnesses to consult their doctor or seek advice from a travel clinic before travelling.
- Advise pregnant women and women who are trying to become pregnant, and who plan to travel to the areas experiencing transmission of Zika virus, to discuss their travel plans with their healthcare providers and to consider postponing their travel to affected areas, especially to areas with increasing or widespread transmission.
- Advise EU citizens who live in areas with Zika virus transmission to take individual protective measures to prevent mosquito bites. This applies particularly for pregnant women and women who are trying to become pregnant living in areas with increasing or widespread transmission.
- Individual protective measures to prevent mosquito bites should be applied all day long, especially during mid-morning and late afternoon to dusk, which are the periods of highest mosquito activity.
- Personal protection measures to avoid mosquito bites should include:
  - Using mosquito repellents in accordance with the instructions indicated on the product label. DEET*-based repellent use is not recommended in children under three months of age.
  - Wearing long-sleeved shirts and long pants, especially during the hours of highest mosquito activity.
  - Using mosquito nets, whether they are impregnated or not, is essential if accommodation is not adequately screened or air-conditioned.
- Travellers showing symptoms compatible with dengue, chikungunya or Zika virus disease within three weeks after returning from an affected area should contact their healthcare provider.
- Pregnant women who have travelled to areas with Zika virus transmission should mention their travel during antenatal visits in order to be assessed and monitored appropriately.

Information to healthcare providers

- Ensure that Zika virus-infected patients in areas with *Aedes* mosquitoes avoid getting bitten during the first week of illness (by using insecticide treated bed nets, screened doors and windows as recommended by the Pan-American Health Organization/World Health Organization.
- Increase awareness among health professionals who provide prenatal care of the possible association of Zika virus and microcephaly and adapt prenatal monitoring in accordance with the exposure to the vector.

* DEET: N,N-Diethyl-meta-toluamide or diethyltoluamide, a common active ingredient in insect repellents.

Source and date of request

ECDC internal decision on 13 January 2016.

Public health issue

This document assesses the risks associated with the evolving Zika virus epidemic currently affecting some countries in the Americas, including the risk for travellers to the affected areas and populations in the affected EU outermost regions. It also assesses the association between intra-uterine Zika virus infection and congenital central nervous system (CNS) malformations, including microcephaly, as well as the association between Zika virus infection and the Guillain–Barré syndrome (GBS).

In the past, ECDC has published four risk assessments related to the expanding Zika virus pandemic:

- 'Zika virus infection outbreak, French Polynesia', 14 February 2014 [1];
- 'Zika virus infection outbreak, Brazil and the Pacific region', 25 May 2015 [2];
- 'Microcephaly in Brazil potentially linked to the Zika virus epidemic', 24 November 2015 [3];
- 'Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome', 10 December 2015 [4].

Consulted experts

ECDC internal response team in alphabetical order: Helena de Carvalho Gomes, Denis Coulombier, Niklas Danielsson, Tarik Derrough, Dragoslav Domanovic, Thomas Mollet, Bertrand Sudre, Wim Van Bortel and Hervé Zeller.

The following experts contributed to this risk assessment:

- WHO Regional Office for Europe, WHO Regional Office for America/Pan American Health Organization, WHO headquarters
- Dr Marie-Claire Paty (Département des Maladies Infectieuses, Institut de veille sanitaire, Paris, France)
- Dr Ingeborg Barisic, president European surveillance of congenital anomalies (EUROCAT)
- Dr Helen Dolk, former project leader European surveillance of congenital anomalies (EUROCAT)

ECDC acknowledges the valuable contributions of all experts. The experts have submitted declarations of interests that were reviewed by ECDC and found not to be in conflict with the comments and suggestions made. The opinions expressed by individual experts do not necessarily represent the opinions of their institutions.

Disease background information

Zika virus disease

Zika virus disease is caused by an RNA virus transmitted to humans by *Aedes* mosquitoes, especially by the *Aedes aegypti* species. Up to eighty per cent of infections are asymptomatic [5]. Symptomatic infections are characterised by a self-limiting febrile illness of 4–7 days duration accompanied by maculopapular rash, arthralgia, conjunctivitis, myalgia and headache. Zika virus has not been noted to cause death in the past, nor has it been linked to intra-uterine infections and congenital CNS anomalies. Nor has Zika virus infection been linked to GBS before 2014 when a possible association between Zika virus infection and GBS was reported during an outbreak in French Polynesia [6]. There is no vaccine to prevent Zika virus infections nor is specific anti-viral treatment available.

Zika virus infection can be confirmed by direct detection of Zika virus RNA or specific viral antigens in clinical specimens. There are no validated assays for serology. More information on Zika virus disease can be found in the previous risk assessments [1-4] and in the ECDC factsheet for health professionals [7].

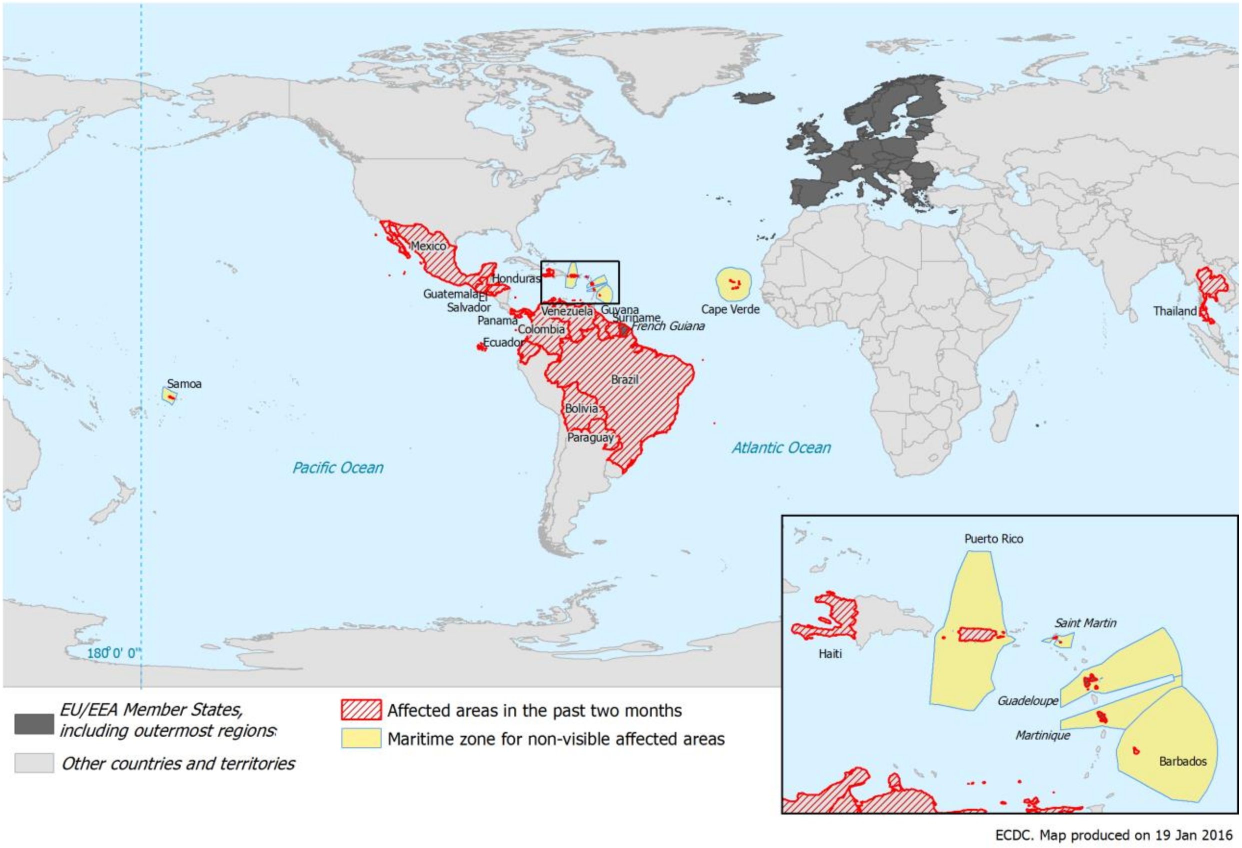
Event background information

In May 2015, autochthonous transmission of Zika virus was confirmed in the states of Bahia and Rio Grande do Norte [8] in Brazil. However, it is likely that Zika virus had been circulating in Salvador de Bahia City prior to that, as an outbreak of exanthematous illness was reported there between 15 February and 25 June 2015 [9]. As of 19 January 2016, autochthonous cases of Zika virus infection were reported from 23 countries or territories worldwide within the past two months (see Figure 1 and Table 1): Barbados, Bolivia, Brazil, Cape Verde, Colombia, Ecuador, El Salvador, French Guiana, Guadeloupe, Guatemala, Guyana, Haiti, Honduras, Martinique, Mexico, Panama, Paraguay, Puerto Rico, Saint Martin, Samoa, Suriname, Thailand and Venezuela. The epidemic is still evolving in the Americas. The map in Figure 1 does not reflect the intensity of Zika virus transmission (see Annex 1 for more information about the recent developments of the Zika virus epidemic). As of 19 January 2016, 27 countries or territories reported autochthonous cases of Zika virus infection within the past nine months (see the list of countries in Table 1 below; ECDC Zika virus worldwide map is available at ECDC webpage).

Table 1. Countries or territories with reported confirmed autochthonous cases of Zika virus infection in the past nine months and past two months, as of 19 January 2016

Country	Autochthonous cases in the past 9 months	Autochthonous cases in the past 2 months
Barbados	Yes	Yes
Bolivia	Yes	Yes
Brazil	Yes	Yes
Cape Verde	Yes	Yes
Colombia	Yes	Yes
Ecuador	Yes	Yes
El Salvador	Yes	Yes
Fiji	Yes	No
French Guiana	Yes	Yes
Guadeloupe	Yes	Yes
Guatemala	Yes	Yes
Guyana	Yes	Yes
Haiti	Yes	Yes
Honduras	Yes	Yes
Maldives	Yes	No
Martinique	Yes	Yes
Mexico	Yes	Yes
New Caledonia	Yes	No
Panama	Yes	Yes
Paraguay	Yes	Yes
Puerto Rico	Yes	Yes
Saint Martin	Yes	Yes
Samoa	Yes	Yes
Solomon Islands	Yes	No
Suriname	Yes	Yes
Thailand	Yes	Yes
Venezuela	Yes	Yes

Figure 1. Countries or territories with reported confirmed autochthonous cases of Zika virus infection in the past two months, as of 19 January 2016



Note: the map does not indicate the extent of the autochthonous transmission in the countries.

In October 2015, following reports of an unusual increase of cases of microcephaly among newborns in the state of Pernambuco, a retrospective analysis of data in the Brazilian live birth information system (SINASC) identified substantial increases in the number of reported cases of microcephaly compared with previous years [10] in several Brazilian states. On 11 November 2015, the Brazilian Ministry of Health declared a public health emergency in response to this public health event, activated the emergency operations centre for public health (COES, Centro de Operações de Emergências em Saúde Pública) and deployed teams to the affected states to support surveillance and response [11].

On 24 November 2015, the health authorities of French Polynesia reported an increase from an average of one reported case annually to 17 cases of CNS malformations in foetuses and infants during 2014–2015. Different CNS malformations were observed among 12 of the cases and were reported by the health authorities of French Polynesia as: microcephaly (head circumference <5th percentile), destruction of cerebral structure, cerebellar hypoplasia, *corpus callosum* agenesis, and severe ventricular dilatation >10 mm at first trimester. The findings led to termination of pregnancy in nine instances. The three remaining cases were born at term with normal body measurements and presented poly-malformations and brains lesions. Cytomegalovirus testing was negative and karyotype was normal. An unusual increase of brainstem dysfunction was observed during the same period (five cases with normal magnetic resonance imaging and standard genetic analyses negative). None of the mothers presented Zika virus infection compatible symptoms. Biological investigations are ongoing. Based on the temporal correlation of these cases with the Zika outbreaks in French Polynesia, the local health authorities hypothesise that Zika virus infection may be associated with these abnormalities if mothers are infected during the first or second trimester of pregnancy [3].

Developments since 10 December 2015

Expansion of the epidemic

The Zika virus epidemic continues to spread in the Americas. Since the Rapid Risk Assessment on 10 December 2015 and as of 19 January 2016, 13 additional countries or territories have reported laboratory confirmed autochthonous transmission including 12 countries in the Americas: Barbados, Bolivia, Ecuador, France (French Guiana, Guadeloupe, Martinique and Saint-Martin), Guyana, Haiti, Honduras, Puerto Rico, and Suriname, as well as one country in Asia: Thailand. In addition, autochthonous transmission was reported retrospectively in the Maldives through a travel-related case returning to Finland in June 2015 [12].

Pan American Health Organization/World Health Organization (PAHO/WHO) issued an epidemiological update on 17 January 2016 on neurological syndrome, congenital anomalies and Zika virus infection. PAHO/WHO recommends to its Member States to '*establish and maintain the capacity to detect and confirm Zika virus cases, prepare healthcare facilities to respond to a possible increase demand of specialized care for neurological syndromes, as well to strengthen antenatal care*' [13].

Travel advice for pregnant women and women trying to become pregnant

Although a causal association between Zika virus infection during pregnancy and adverse pregnancy outcomes has not been confirmed, the concern over a possible causal link has prompted public health authorities to issue travel advice for the affected areas. The European Commission published an Information for travellers to areas with local transmission of Zika virus on 16 December 2015. On 15 January 2016, the US Centers for Disease Control and Prevention (US CDC), 'out of an abundance of caution,' issued an interim Travel Guidance for pregnant women travelling or planning to travel to 14 countries and territories with local transmission [14] in Central and South America and the Caribbean. The US CDC advises pregnant women in any trimester to consider postponing travel to areas where autochthonous transmission is ongoing or, if they must travel, to take necessary precautionary measures to avoid mosquito bites. US CDC also advised women trying to become pregnant to consult their healthcare provider and take steps to prevent mosquito bites. On 16 January, the Public Health Agency of Canada published a Travel Health Notice with regards to pregnant women and those considering becoming pregnant, encouraging them to discuss their travel plans with their healthcare provider to assess their risk and consider postponing travel to areas where the Zika virus is circulating in the Americas [15]. If travel cannot be postponed, then strict mosquito bite prevention measures should be followed.

Update on the observed increase of congenital microcephaly and other central nervous system malformations in Brazil

From 22 October 2015 until 9 January 2016, Brazilian health authorities have reported 3 530 suspected cases of congenital microcephaly [16] that meet the definition in the epidemiological surveillance protocol issued by the Brazilian Ministry of Health [17]. The surveillance protocol defines suspected cases that should be reported and investigated as:

- Pregnant women with acute exanthema, and excluded other known infectious and non-infectious possible causes
- Foetuses with ultrasonographic head circumference of more than two standard deviations (SD) below the mean for gestational age, with or without further CNS malformations
- Foetuses with ultrasonographic CNS findings suggestive of intrauterine infection
- Spontaneous abortions in women with a report of exanthema during gestation, without other causes identified
- Stillbirths, irrespective of gestational age, in women with a report of exanthema during gestation
- Live newborns of <37 weeks gestational age (preterm delivery) and a head circumference <3rd percentile according to the Fenton growth chart, by sex
- Live newborns of ≥37 weeks gestational age (term delivery) and a head circumference ≤32 cm.

To date, 21 states have reported suspected cases across 724 municipalities. Pernambuco, the first state to identify an increase of microcephaly, has reported the highest number of suspected cases (1 236, 35.0% of the total), followed by Paraíba (569, 16.1%), Bahia (450, 12.7%), Ceará (192, 5.4%), Rio Grande do Norte (181, 5.1%), Sergipe (155, 4.4%), Alagoas (149, 4.2%), Mato Grosso (129, 3.7%) and Rio de Janeiro (122, 3.5%) [16].

On 17 November 2015, PAHO/WHO published an epidemiological alert asking PAHO Member States to report similar events under the International Health Regulations (IHR) [18].

Investigations of a possible causal association between Zika virus infection during pregnancy and the increase of congenital CNS malformations are reported to be in progress in Brazil since October 2015.

At the time of the previous update of the ECDC risk assessment on 10 December 2015, laboratory findings suggesting intra-uterine infection of Zika virus had been reported for three cases with prenatally diagnosed microcephaly and other CNS malformations. In two of these cases, Zika virus RNA was detected in the amniotic fluid by RT-PCR. The third case was a pre-term baby who died shortly after birth, and Zika virus RNA was found in autopsy samples (see Annex 2, Table 1, no. 1 to 3).

On 14 January 2016, findings from investigations of additional four suspected cases were reported; of those, two were miscarriages and two were babies born at term that died shortly after birth (see Annex 2, Table 1, no. 4 to 7).

A recent publication providing further details on the ultrasound findings of the two cases with laboratory confirmation of Zika virus being present in amniotic fluid, also mentions six additional newborns from Paraíba State with confirmed Zika virus infection and congenital malformations of varying severity. However, no further details were reported regarding the laboratory findings and other investigations of the six infants and their mothers [19] (see Annex 2, Table 1, no. 8 to 13).

On 15 January, the Hawaii Department of Health announced a laboratory confirmed case of Zika virus infection in a baby born with microcephaly from a mother who was pregnant when she resided in Brazil in May 2015 [20] (see Annex 2, Table 1, case No. 14).

ECDC currently has no further information on the number of ongoing and concluded investigations, or their results.

Update on Guillain–Barré syndrome

Several countries in south and central Americas have reported unusual increases in cases of Guillain–Barré syndrome (GBS):

- **Brazil**: 121 cases of neurological manifestations and GBS with a history of rash illness have been notified in north-eastern states between January and July 2015 [21,22]. According to the PAHO/WHO alert on 1 December 2015, 76 patients with neurological syndrome had been identified up to 13 July, the majority in the state of Bahia where 42 cases were classified as GBS and five were diagnosed as other neurological conditions. Among the patients with GBS, 62% (26/42) reported symptoms consistent with Zika virus infection preceding the onset of the neurological symptoms [23].
- **Venezuela**: media quoting the president of the Venezuelan Society of Infectious Diseases reported 15 cases of GBS in Sucre state preceded by an Zika-like acute febrile illness [24]. Other cases of GBS possibly associated with Zika virus infection are being investigated in Bolivar, Portuguesa and Capital District [24]. On 12 January 2016, media quoting the 'Red Defendamos la Epidemiología' reported an increase in GBS in several states during the past two weeks among patients who presented in the preceding days with an acute febrile illness of short duration including rash, myalgia and arthralgia compatible with a Zika virus infection. This corresponds to a 1.3 and 2.1 fold increase in cases of GBS compared with the national baseline [25].
- **El Salvador**: from December 2015 to 6 January 2016, 46 cases of GBS were notified to the Ministry of Health [26] of whom 2 died. Most cases were reported from the departments of San Salvador and La Libertad [26]. Of 22 cases investigated in December 2015, twelve (54%) reported a febrile illness with rash from 7 to 15 days before onset of GBS symptoms. The most affected age group was between 20 to 59 years. According to PAHO/WHO, El Salvador is reporting 14 cases of GBS per month on average (169 cases per year), however, there were 46 GBS cases recorded between 1 December 2015 and 6 January 2016, of which 2 died [13]. Media quoting El Salvador Ministry of Health reported 62 GBS cases from 1 December 2015 until 12 January 2016 challenging the intensive care capacity of one of the main hospitals in the country [27]. The Minister of Health quoted by media reported 12 cases of GBS hospitalised in intensive care units (ICU) in the Medico Quirurgico ISSS Hospital (San Salvador) during the past two months, compared with an annual mean of 10 to 14 GBS cases per year [27].
- **Martinique:** On 15 January 2016, public health authorities reported a first case of GBS possibly associated with Zika virus infection. The patient was admitted to an intensive care unit (ICU) [28].

Zika virus genetics

There are two lineages of Zika virus, the African lineage and the Asian lineage [29-31]. Phylogenetic studies indicate that the virus spreading in the Americas is most closely related to the virus from the Asian lineage isolated in French Polynesia in 2013–2014 [32] . Presently, only two full genome sequences of Zika virus from Brazil and Suriname have been published [32]. Molecular analysis of the Zika virus isolated from the travel-related case from the Maldives and diagnosed in Finland in June 2015, showed that it too belonged to the Asian lineage [12].

Recent preliminary findings from molecular investigations of 17 whole genome sequences in the public domain stressed a possible change in the fitness of the Asian lineage through an adaptation of the NS1 codon usage. The researchers suggest that these modifications may have an impact on viral replication rates and viral titres in humans. The authors also reported structural and immunological similarities in the NS1 antigen between Zika and dengue viruses. Both preliminary findings should be further studied and verified on larger whole genome panels [33].

ECDC threat assessment for the EU

Zika virus disease typically produces mild and self-limiting symptoms. The proportion of asymptomatic infections may be as high as 80%. This, paired with limitations in the diagnostic capacity, means that only a small fraction of Zika virus infections are likely to be laboratory confirmed. Monitoring of epidemic expansion and intensity of transmission through laboratory reports is likely to be unreliable. The definition of microcephaly is not standardised and the distribution of occipito-frontal circumferences (OFC) varies with ethnicity, sex, age, and gestational age. OFC alone, particularly its milder forms, is a poor predictor for intellectual deficits. Microcephaly should be evaluated in the context of a child's other body measurements and the OFC of its parents.

It is difficult to assess the significance of the increase in the incidence of microcephaly in Brazil in the absence of the number of births in the affected areas in the affected time periods. Further, the increased awareness about the possible link between intra-uterine Zika virus infections and microcephaly and the changes implemented in the case definition will influence the number of notifications compared to background rates.

Risk of Zika virus importation and transmission in the continental EU

Travel-associated cases of Zika virus infections have been reported in the EU in the past (see Annex 1). However, EU Member States are not required to report Zika virus infections to ECDC and the data do not reflect the true number of cases diagnosed in the EU/EEA. As the Zika virus epidemic continues to spread in the Americas and Caribbean, and the awareness of the risk of infection increases among clinicians and travellers, the number of reported travel-related Zika virus infections is expected to increase in the EU. As an example, the Netherlands recently reported six cases returning from Suriname [34].

The *Aedes albopictus* mosquito species is established in many parts of the EU, primarily around the Mediterranean [35]. Onward transmission from imported cases within the continental EU is possible because *Aedes albopictus* is a competent vector for the transmission of Zika virus, even though this has not yet been confirmed for European mosquito populations [36,37]. The risk of transmission of Zika virus infection is extremely low in the EU during winter season as the climatic conditions are not suitable for the activity of *Aedes albopictus* mosquito. The capacity of European populations of *Aedes albopictus* to transmit Zika virus is not known but is anticipated and should be assessed.

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

The epidemic is currently spreading in the Americas and Caribbean, but widespread transmission is not yet reported in the latter. Because *Aedes aegypti* mosquitoes are present in the EU Overseas Countries and Territories (OCT) and Outermost Regions (OMR) in the Americas and the Caribbean, it is expected that local transmission will occur once the virus is introduced. The risk of spread is significant but will depend of environmental conditions, early detection of cases and subsequent vector control activities.

Other EU OMRs and OCTs on other continents where mosquito vectors are present such as La Réunion and Madeira are at risk of establishment of local transmission should the virus be introduced. Madeira is of concern because of the close relationship with Brazil and Venezuela where Zika virus is currently circulating, the presence of *Aedes aegypti*, and the 2012 dengue epidemic which demonstrated the favourable conditions for vector-borne outbreaks.

Risk of Zika virus infection for travellers to affected regions

The spread of Zika virus infections in the Americas and in the Caribbean constitutes a significant development in the epidemiology of this emerging vector-borne disease. Travellers to countries with competent vectors and circulating Zika virus are at risk of becoming infected through mosquito bites.

Risk of microcephaly and other congenital central nervous system malformations

To date, health authorities have reported eight adverse pregnancy outcomes and/or other congenital CNS malformations with laboratory confirmation of Zika virus in amniotic fluid, placenta or foetal tissues. In addition, information on six cases of Zika virus detection in newborns from the Paraíba State with partly severe congenital malformations has been recently published. All fourteen reported cases have history of exposure in Brazil.

After performing a retrospective analysis following the alert from Brazil, the health authorities of French Polynesia reported an increase from an average of one case annually to 17 cases of CNS malformations in foetuses and infants during 2014–2015, following a Zika virus outbreak in 2013–2014.

No cases of microcephaly or other CNS malformations potentially related to Zika virus have been reported from other countries of Americas and Caribbean affected by Zika virus outbreaks. However, autochthonous transmission of Zika virus did presumably not start before the last trimester of 2015 in most of these countries, and the prospective monitoring of congenital malformations will support the evaluation of the association with Zika virus infections.

In summary, the evidence regarding a causal link between Zika virus infections during pregnancy and congenital CNS malformations is growing, although the available information is not yet sufficient to confirm it. The definitions of suspected cases applied in the epidemiological surveillance protocol for Brazil are broad and will capture many healthy children who are within the normal variation as well as children with medical conditions that are unrelated to Zika virus infections. The cases identified with the surveillance protocol will need to be further investigated and assessed, and many will have to be followed over time. It is expected that many of the suspected cases will be reclassified and discarded. So far, no results have been made public from the epidemiological studies that reportedly are ongoing and may substantiate or disprove the association between intra-uterine Zika virus infections and congenital lesions in CNS.

Risk of Guillain–Barré syndrome

No new scientific evidence about the association of GBS and Zika virus infection has been published since the ECDC RRA published on 10 December 2015. Two new countries, El Salvador and Venezuela (according to media), have reported an unusual increase above the baseline, concomitant with the development of Zika outbreaks in the country. This observation supports a temporal and spatial association as that seen in French Polynesia.

Risk of Zika virus infection associated substances of human origin

According to Musso et al., during the last Zika virus outbreak in French Polynesia, 42 of 1 505 (3%) blood donors, although asymptomatic at the time of blood donation, were found positive for Zika virus genome by PCR, supporting a potential risk of transfusion-derived transmission [38]. Transfusion-transmitted Zika virus infection has not been reported in the literature. Media in Brazil reported a case of transfusion-transmitted Zika virus infection in March 2015 from an asymptomatic 52-year-old donor in of Campinas (Unicamp) [39]. Available data suggest that the transmission of Zika virus is possible through blood donated by viraemic, asymptomatic residents or travellers returning from affected areas [38,40,41]. Furthermore, a viable virus was detected in semen more than two weeks after recovery from an illness consistent with Zika virus infection [42]. Possible cases of sexual transmission of Zika virus have also been reported [42,43]. These data imply a possible risk of Zika virus transmission through semen donated by an asymptomatic donor during or after Zika virus infection. The transmission of Zika virus through organ transplantation has not been reported.

Conclusions and options for mitigation

The spread of the Zika virus epidemic in the Americas is likely to continue as the competent vectors *Aedes aegypti* and *Aedes albopictus* mosquitoes are widely distributed there. There is also a significant increase in the number of babies born with microcephaly in the north-eastern states of Brazil, however, the magnitude and geographical spread of the increase has not yet been well characterised. Despite growing evidence of a link between intra-uterine Zika virus infection and adverse pregnancy outcomes, a causal link between these events has not yet been confirmed.

The US CDC and the Public Health Agency of Canada have acted on the signal that Zika virus infections during pregnancy may increase the risk of adverse pregnancy outcomes, and issued travel warnings on 15 and 16 January 2016, respectively. They advise that pregnant women consider postponing travel to the currently affected areas. US CDC also advised women trying to become pregnant to consult their healthcare provider about the risk of Zika virus infection and take steps to prevent mosquito bites during their travel; whereas the Travel Health Notice from

Canada recommends to assess their risk with their healthcare provider and consider postponing travel to areas where the Zika virus is circulating in the Americas. If travel is unavoidable, they are advised to practise strict preventive measures to avoid mosquito bites [14,15]. In addition, US CDC published on 19 January interim guidelines for pregnant women during a Zika virus outbreak [44].

On 15 January 2015, the French Ministry of Health indicated that it will soon communicate on specific measures for patients and pregnant women in particular those who reside in and travel to affected areas. More specific advice will be issued for gynaecologists and obstetricians as well as midwives [28].

Due to the potential link between Zika infection and neurological and autoimmune complications such as GBS, PAHO recommended establishing or strengthening surveillance of neurological syndromes for all age groups on 1 December and reinforced it on 17 January 2016 [13,23]. Further epidemiological studies are required to assess the strength of the association between Guillain–Barré syndrome and Zika virus infection taking account that dengue fever and Chikungunya have been associated with such neurological complications, the frequency of occurrence of this possible neurological impairment and population at risk [44-47].

As neither treatment nor vaccines are available, prevention is based on personal protection measures similar to the measures that are applied against dengue and chikungunya infections.

In the light of the current disease trend – and the possible association with severe complications – public health authorities in EU/EEA Member States should consider the following mitigation options.

Surveillance of imported cases

- Increase awareness of clinicians and travel health clinics about the evolution of the Zika virus outbreak and the affected areas so that they can include Zika virus infection in their differential diagnosis for travellers from those areas. Fever and/or maculo-papular rash not attributable to dengue or chikungunya infection among travellers returning from areas currently experiencing a Zika virus outbreak should be indications for further investigation of Zika virus infection.
- Enhance vigilance towards the early detection of imported cases of Zika virus 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.
- Strengthen laboratory capacity to confirm suspected Zika virus infections in the European region in order to differentiate Zika virus infections from other arboviral infections (e.g. dengue, chikungunya).
- Increase awareness among obstetricians, paediatricians and neurologists in the EU/EEA that Zika virus infections should be investigated for patients presenting with congenital CNS malformations, microcephaly and GBS.

Safety of substances of human origin

- Blood safety authorities should consider the deferral of donors with a relevant travel history to areas with active Zika virus transmission, in line with measures defined for dengue virus. In unaffected areas with competent vectors for Zika virus, a preparedness plan for prevention and control of outbreaks of Zika virus infection should cover the continuity of blood supply.
- Tissue establishments for assisted reproduction may foresee a need to defer potential semen donors for 28 days after returning from an affected area, as a viable virus was detected in semen more than two weeks after recovery from an illness consistent with Zika virus infection.
- As a transfusion-transmitted Zika virus infection may have serious consequences for the health of the recipient and the existing blood safety interventions have limited preventive capacities, the screening of all donated blood for the presence of Zika virus RNA by nucleic-acid amplification test (NAT) may be considered necessary in affected areas. Due to the potential association between Zika virus infection and microcephaly in newborns, health authorities in affected areas may anticipate taking the precautionary measures of using Zika virus negative blood for the transfusion of pregnant women and screening of semen donors/donations for the presence of Zika virus.

Information to travellers and EU residents in affected areas

From media reports, information releases and epidemiological bulletins published by the Ministries of Health of the different countries, as of 19 January 2016, the recent trends can be outlined as follows:

- El Salvador, Venezuela, Colombia, Brazil, Suriname, French Guiana, Honduras, Mexico, Panama and Martinique are currently experiencing an increasing or widespread transmission;
- Bolivia, Guyana, Ecuador, Guadeloupe, Guatemala, Paraguay, Puerto Rico, Barbados, Saint Martin and Haiti have only reported sporadic transmission following recent introduction.

The following options should be considered:

- Advise all travellers to affected areas to take individual protective measures to prevent mosquito bites.
- Advise travellers that have immune disorders or severe chronic illnesses to consult their doctor or seek advice from a travel clinic before travelling.
- Advise pregnant women and women who are trying to become pregnant, and who plan to travel to the areas experiencing transmission of Zika virus, to discuss their travel plans with their healthcare providers and to consider postponing their travel to affected areas, especially to areas with increasing or widespread transmission.
- Advise EU citizens who live in areas with Zika virus transmission to take individual protective measures to prevent mosquito bites. This applies particularly for pregnant women and women who are trying to become pregnant living in areas with increasing or widespread transmission.
- Individual protective measures to prevent mosquito bites should be applied all day long, especially during mid-morning and late afternoon to dusk, which are periods of highest mosquito activity.
- Personal protection measures to avoid mosquito bites should include:
  - Using mosquito repellents in accordance with the instructions indicated on the product label. DEET*-based repellent use is not recommended in children under three months of age.
  - Wearing long-sleeved shirts and long pants, especially during the hours of highest mosquito activity.
  - Using mosquito nets, whether they are impregnated or not, is essential if accommodation is not adequately screened or air-conditioned.
- Travellers showing symptoms compatible with dengue, chikungunya or Zika virus disease within three weeks after returning from an affected area should contact their healthcare provider and mention their travel.
- Pregnant women who have travelled to areas with Zika virus transmission should mention their travel during antenatal visits in order to be assessed and monitored appropriately.

Information to healthcare providers

- Ensure that Zika virus-infected patients in areas with *Aedes* mosquitoes avoid getting bitten during the first week of illness (insecticide treated bed nets, screened doors and windows as recommended by PAHO/WHO).
- Increase awareness among health professionals who provide prenatal care of the possible association of Zika virus and microcephaly and adapt prenatal monitoring in accordance with the exposure to the vector.

* DEET: N,N-Diethyl-meta-toluamide or diethyltoluamide, a common active ingredient in insect repellents.

Annex 1. Zika virus epidemiology (as of 19 January 2016 12:00 CET)

Countries and territories with autochthonous transmission cases of Zika virus 2013-2014

In 2013 and 2014, Zika virus outbreaks were notified in several islands of the Pacific region:

- **French Polynesia** reported an outbreak with 8 750 suspected cases of Zika virus infection, identified by the syndromic surveillance sentinel network of French Polynesia. There were 383 confirmed cases, and Zika virus may have been the cause of disease in an estimated 32 000 patients presenting to healthcare facilities between October 2013 and April 2014 [6].
- Further spread to **New Caledonia**, the **Cook Islands** and later to **Easter Island** (Chile) has shown the propensity of this arbovirus to spread in the Pacific region, outside its usual geographical range in Africa and south-east Asia [49]. The virus found on Easter Island was closely related to the virus identified during the French-Polynesian outbreak, and cases were reported until June 2014 [22,50].

Countries and territories with autochthonous transmission of Zika virus in 2015 and 2016

Since January 2015, countries or territories reported autochthonous transmission of Zika virus as follows.

South America

Brazil: In May 2015, autochthonous transmission of Zika virus was confirmed in the states of Bahia and Rio Grande do Norte [8]. In a study conducted by the Salvador Health Authorities, twelve health districts in Salvador City reported 14 835 cases of exanthematous illness between 15 February and 25 June 2015 [9]. The authors suggest that the outbreak was caused by Zika virus because the number of confirmed dengue cases did not vary substantially during the period; only 58 cases were diagnosed as chikungunya, and confirmed Zika virus infections occurred at the same time in other cities within metropolitan Salvador [9,51,52]. A phylogenetic analysis of serum samples from patients hospitalised in March at Santa Helena Hospital in Camaçari, Bahia, showed that the identified Zika virus sequences belonged to the Asian lineage and were 99% identical with one partial Zika virus envelope gene region from a Zika virus isolate from French Polynesia [52]. Zika virus infections have been laboratory confirmed in 20 stat es in Brazil since February 2015 (Roraima, Amazonas, Rondônia, Pará, Mato Grosso, Mato Grosso do Sul, Paraná, São Paulo, Rio de Janeiro, Espírito Santo, Federal District, Bahia, Tocantins, Maranhão, Piauí, Ceará, Rio Grande do Norte, Paraíba, Pernambuco and Alagoas) [16].

According to preliminary estimates from the Brazilian Ministry of Health, between 440 000 to 1 300 000 cases of Zika virus infections may have occurred in 2015 in the Brazilian states that have reported laboratory-confirmed autochthonous cases of Zika virus [17]. As of week 48 2015, the Brazilian Ministry of Health reported 15 650 cases of chikungunya (suspected and confirmed) and approximately half a million probable cases of dengue to PAHO with the circulation of the four serotypes [53,54].

Colombia: In September, the state of Bolívar reported nine confirmed autochthonous cases of Zika virus disease. From the epidemiological week 40 of 2015 up to epidemiological week 01 2016, 13 531 cases were reported, including 776 laboratory-confirmed cases in 28 of the 36 local authorities, 10 837 clinically confirmed cases from 26 of the 36 local authorities and 1 918 suspected cases from 32 of the 36 local authorities. There is an increasing trend from the start of the outbreak with a plateau in the last 5 weeks (around 1 440 cases reported per week). The majority of the cases are reported from the Caribbean Costal areas. Most of the cases are reported among women (60.9%) and the largest proportion of cases (45.9%) occurs among the 20–39 years of age group. The Ministry of Health has enrolled 560 pregnant women (30 laboratory confirmed, 429 clinically confirmed and 101 suspect cases) in a cohort study [55].

Paraguay: On 27 November, Paraguay reported six confirmed Zika virus infections in the city of Pedro Juan Caballero, which borders Brazil, after an increase in the number of notified fever cases [56]. On 11 January 2016, health authorities declared a national epidemiological alert for dengue fever, chikungunya and Zika virus infections [57].

Venezuela: On 27 November, the Venezuelan IHR Focal Point notified seven Zika virus cases, four of which were confirmed by RT-PCR [58]. On 13 January 2015, media quoting the Ministry of Health reported 23 cases in at least six parishes of Maracaibo and San Francisco [59].

Suriname: On 2 November 2015, the IHR Focal Point for Suriname notified PAHO/WHO of 2 autochthonous cases of Zika virus infection. Zika strain isolated from a patient in early October 2015 belongs to the Asian genotype and is closely related to the strain that was circulating in French Polynesia in 2013 [32]. On 8 January 2016, media quoting the public health laboratory reported 108 confirmed cases between week 43 and 51 of 2015 [60].

French Guiana: The first imported case was confirmed on 15 December 2015. On 15 January 2016, 15 confirmed autochthonous Zika virus infections were reported [28].

Ecuador: the Ministry of Health reported two confirmed cases of Zika in Quito, believed to have been imported from Colombia in the period up to 9 January 2016 [61]. On 15 January 2016, 5 confirmed autochthonous Zika virus infections was reported by the authorities [62].

Guyana: media quoting the Ministry of Health reported the first locally acquired case of Zika virus infection on 12 January 2016 [63].

Bolivia: On 19 January 2016, according to a media report, the first local case of Zika virus infection was detected [64]. The local health authorities in Bolivia posted a Facebook message regarding the measures taken [65].

Central America

El Salvador: On 24 November, the IHR Focal Point for El Salvador notified three confirmed autochthonous cases of Zika virus infection. On 3 December, the media reported 240 cases across the country [66]. On 10 January 2016, media quoting the Ministry of Health reported 3 836 cases across the country, among those 63 pregnant women are being followed-up due to the foetuses being diagnosed with microcephaly [67].

Guatemala: On 1 December, the media quoting authorities, reported 17 suspected cases of Zika virus infection, 14 of which were among hospital employees. Blood samples were collected and sent to the US CDC for analysis [68]. So far, one of the samples has been reported as positive.

Mexico: On 26 November, the Mexican Ministry of Health acknowledged three Zika virus cases, including two autochthonous cases reported from Nuevo León and Chiapas. The imported case had a recent travel history in Colombia [69].The Ministry of Health of Mexico reported 13 additional Zika virus cases during the week 52 2015 (9 in Chiapas, 3 in Nuevo León and one in Jalisco) [70].

Panama: On 3 December 2015, the local health authorities reported three autochthonous cases among residents of the district of Ailigandi, in the north-eastern province of Guna Yala [71]. On 22 December, the Ministry of Health notified WHO about 95 cases of suspected Zika virus disease in Guna Yala province (Ustupu and Ogobsugun islands) [72]. On 30 December, media reported 24 confirmed cases of Zika virus in Panama, and 60 cases under investigation [73].

Honduras: On 16 December 2015, the Ministry of Health of Honduras reported two (2) autochthonous cases of Zika virus infection [74]. The Secretary of Health has declared an epidemiological alert over the increase of Zika cases in Honduras, at the same time calling on doctors to be aware of complications the virus can cause. Media quoting the Ministry of Health of Honduras, reported 116 Zika virus cases, with the most affected departments being reported to be Paraíso, Choluteca and Valle [75].

Caribbean countries and territories

Martinique: On 21 December 2015, authorities reported the first case of Zika. On 15 January 2015, 47 autochthonous confirmed Zika virus cases were reported and 610 suspected cases are being investigated [28].

Saint Martin: on 15 January 2016, one locally-acquired Zika virus case was confirmed by the authorities [28].

Puerto Rico (USA): On 31 December 2015, the Puerto Rico Department of Health reported the first locally acquired case of Zika virus in a resident of Puerto Rico without recent travel history prior to symptoms [76].

Haiti: According to the Ministry of Health, there is autochthonous circulation of Zika virus in Haiti with 5 confirmed cases as of 14 January 2016 [77].

Barbados: On 15 January 2016, the government press agency, quoting the Ministry of Health reported three cases of Zika virus infection [13,78].

Guadeloupe: On 18 January 2016 France reported through the Facebook account of the Ministry of Social Affairs, Health and Women's Rights one confirmed autochthonous Zika virus case in Guadeloupe [79].

Other countries

Cape Verde: Between the end of September and 6 December 2015, Cape Verde reported 4 744 suspected cases of Zika virus infection from several municipalities on Santiago Island (Praia, Santa Catarina, Santa Cruz, São Domingos and Tarrafal) as well as others islands, including Maio, Fogo and Boa Vista to WHO. The municipality of Praia reported 81% of the cases (3 845). So far, no neurological complications have been reported [80].

In the Pacific region, autochthonous cases of Zika virus infection have been reported in 2015 from **Samoa and Solomon Islands** (310 cases from February to May), **New Caledonia** (January to early August), **Fiji** (August) and at least one confirmed case in **Vanuatu** [81-83].

Maldives: One confirmed case was reported in a patient with fever and rash returning from the Maldives to Finland [12].

Thailand: On 19 January 2016, the Taiwan CDC and media reported a confirmed case of Zika virus in a 24-year old Thai male, who is a foreign worker. He arrived from Thailand to Taiwan on 10 January 2016. The case has no recent travel history outside of the two countries [84].

Countries with imported confirmed cases (travel-related)

In the past weeks, several countries without autochthonous transmission reported travel-related cases of Zika virus:

USA: On 11 January 2016, CDC confirmed one case of Zika virus infection in a resident from Texas who had returned from Latin America [85].

Canada: On 9 January 2016, Columbia confirmed one imported case in a resident who had recently travelled to El Salvador [86].

Germany: In December 2015, German authorities confirmed one case in a German national having travelled to Haiti [87].

The Netherlands: A confirmed case of Zika virus infection was reported in a 60-year-old, who had returned from Suriname on 29 November 2015, following a 3-week holiday [88]. RIVM has reported six imported cases of Zika virus infection from Suriname [34].

Finland: in June 2015, one confirmed case was reported in a patient with fever and rash having travelled to the Maldives [12].

Annex 2. Summary of the reported congenital malformations potentially linked to Zika virus infection in Brazil

Table 1. Characteristics of reported cases of congenital malformation potentially linked with Zika virus infection in Brazil (as of 18 January 2016)

No.	Date of report location	Clinical findings	Laboratory findings	Reference
1	17 November 2015 Paraíba state	Foetus with microcephaly at ultrasound exams (US) 30.1 weeks' gestation Head circumference <2.6 SD Observed lesions (US): - Brain atrophy with coarse calcifications involving the white matter of the frontal lobes, including the caudate, lentostriatal vessels and cerebellum. - Corpus callosal and vermian dysgenesis. - Enlarged cisterna magna Mother: symptoms compatible with Zika virus infection at week 18-19 of gestation*	RT-PCR Zika virus positive in amniotic fluid (Instituto Oswaldo Cruz)	[19,89]
2	17 November 2015 Paraíba state	Foetus with microcephaly at ultrasound exams 29.2 weeks' gestation Head circumference < 3.1 SD Observed lesions (US): - cerebral hemispheres were markedly asymmetric (severe unilateral ventriculomegaly) - almost complete disappearance or failure to develop the thalami - thin pons and brainstem Mother: symptoms compatible with Zika virus infection at week 18-19 of gestation*	RT-PCR Zika virus positive in amniotic fluid (Instituto Oswaldo Cruz)	[19,89]
3	28 November 2015 Ceara state	Newborn Born the 18 November 2015 (residing Tejuçuoca, Ceara State) No measurement of head circumference at birth Weight: 945 grams at birth Died within 5 min after birth Observed lesions (US, 13 Nov 2015): - microcephaly (head circumference 190 mm) - fetal anasarca - polydramnios	Presence of Zika viral genome in blood and tissue samples of the newborn (Evandro Chagas Institute)	[23,90]
4	5 January 2015 Rio Grande do Norte state	Case: miscarriage, foetus with congenital malformations Observed lesions: - Congenital malformation Mother presented with rash and fever during pregnancy	Positive PCR test for Zika virus on foetal sample in samples of the placenta (US CDC laboratory)	[19]
5	5 January 2015 Rio Grande do Norte state	Case: miscarriage, foetus with malformations Mother reported rash and fever during pregnancy	Positive PCR test for Zika virus on foetal sample (US CDC laboratory)	[19]
6	5 January 2015 Rio Grande do Norte state	Case: Full term baby with malformations who died within 24 hrs after birth Mother reported rash and fever during pregnancy	Positive PCR test and immunohistochemistry for Zika virus on foetal sample (US CDC laboratory)	[19]
7	5 January 2015 Rio Grande do Norte state	Case: Full term baby with malformations who died within 24 hrs after birth Mother reported rash and fever during pregnancy	Positive PCR test and immunohistochemistry for Zika virus on foetal sample (US CDC laboratory)	[19]
8–13	5 January 2015 Rio Grande do Norte state	Cases: six children with microcephaly (head circumference below the 10th percentile) of whom: - two with cerebellar involvement on foetal ultrasound examinations, - three with brain calcifications, - one with arthrogryposis. All mothers reported rash and fever during pregnancy	Diagnosed with Zika virus infection (no details provided) (laboratory not reported)	[19]
14	15 January 2016 Hawaii (USA)	Case: baby with congenital microcephaly who was born recently on Oahu island, Hawaii. Mother had a probable exposure to Zika virus when she was residing in Brazil in May 2015 (no further details provided)	Laboratory confirmation of a past Zika virus infection (no details) (US CDC laboratory)	[20]

**: Data on courtesy of F.Bozza (MD, PhD, National Institute of Infectious Disease, Oswaldo Cruz Foundation, Ministry of Health, Rio de Janeiro, Brazil)*

References

1. European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, French Polynesia: ECDC; 2014 [updated 2014 Feb 14]. Available from: http://ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1025.

2. European Centre for Disease Prevention and Control. Zika virus infection outbreak, Brazil and the Pacific region: ECDC; 2014 [updated 2015 May 26]. Available from: http://ecdc.europa.eu/en/publications/Publications/rapid-risk-assessment-Zika%20virus-south-america-Brazil-2015.pdf.

3. European Centre for Disease Prevention and Control. Microcephaly in Brazil potentially linked to the Zika virus epidemic Stockholm: ECDC; 2015 [updated 2015 Nov 25]. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-microcephaly-Brazil-rapid-risk-assessment-Nov-2015.pdf.

4. European Centre for Disease Prevention and Control. Zika virus epidemic in the Americas: potential association with microcephaly and Guillain-Barré syndrome Stockholm: ECDC; 2015 [updated 2015 Dec 10]. Available from: http://ecdc.europa.eu/en/publications/Publications/zika-virus-americas-association-with-microcephaly-rapid-risk-assessment.pdf.

5. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. N Engl J Med. 2009 Jun 11;360(24):2536-43.

6. Mallet HP, Vial AL, Musso D. BISES: Bulletin d'information sanitaires, épidémiologiques et statistiques [Internet]. Papeete: Bureau de veille sanitaire (BVS) Polynésie française; 2015 [cited 13 Mai]. Available from: http://www.hygiene-publique.gov.pf/IMG/pdf/no13_-_mai_2015_-_zika.pdf.

7. European Centre for Disease Prevention and Control. Zika virus infection (factsheet for health professionals) [Internet]. Stockholm: ECDC; 2015 [cited 2015 18 May 2015]. Available from: http://ecdc.europa.eu/en/healthtopics/zika_virus_infection/factsheet-health-professionals/Pages/factsheet_health_professionals.aspx.

8. Ministério da Saúde (Brazil). Confirmação do Zika Vírus no Brasil, [Internet]. Brasília: Ministério da Saúde (Brazil); 2015 [updated 2015 May 14; cited 2015 May 14]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/17701-confirmacao-do-zika-virus-no-brasil.

9. Cardoso CW, Paploski IA, Kikuti M, Rodrigues MS, Silva MM, Campos GS, et al. Outbreak of Exanthematous Illness Associated with Zika, Chikungunya, and Dengue Viruses, Salvador, Brazil. Emerg Infect Dis. 2015 Dec;21(12):2274-6.

10. Secretaria de Vigilância em Saúde - Departamento de Vigilância Epidemiológica. Nota informativa N^{0} 01/2015 – COES Microcefalias. Brasília: Ministério da Saúde , Brazil, 2015 2015 Nov 17. Report No.

11. Ministério da Saúde (Brazil). Ministério da Saúde investiga aumento de casos de microcefalia em Pernambuco [Internet]. 2015 [updated 2015 Nov 11; cited 2015 Nov 11]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20629-ministerio-da-saude-investiga-aumento-de-casos-de-microcefalia-em-pernambuco.

12. Korhonen E, Huhtamo E, Smura T, Kallio-Kokko H, Raassina M, Vapalahti O. Zika virus infection in a traveller returning from the Maldives, June 2015. Eurosurveillance. 2015;21(2).

13. Pan American Health Organization, World Health Organization. Regional Office for the Americas. Neurological syndrome, congenital malformations, and Zika virus infection – Epidemiological Update (17 January 2016) [Internet]. 2016 [cited 2015 Jan 18]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32879&lang=en.

14. US Centers for Disease Control and Prevention. CDC issues interim travel guidance related to Zika virus for 14 Countries and Territories in Central and South America and the Caribbean [Internet]. 2016 [cited 2016 Jan 15]. Available from: http://www.cdc.gov/media/releases/2016/s0315-zika-virus-travel.html

15. Government of Canada. Zika virus infection in the Americas - Travel Health Notice [Internet]. 2016 [cited 2016 Jan 15]. Available from: http://travel.gc.ca/travelling/health-safety/travel-health-notices/143.

16. Centro de operações de emergências em saúde pública sobre microcefalias. Monitoramento dos casos de microcefalias no Brasil informe. Epidemiológico Nº 01/2016 – semana epidemiológica 01 (3/01 a 9/01/2016) [Internet]. 2015 [cited 2016 Jan 14]. Available from: http://portalsaude.saude.gov.br/images/pdf/2016/janeiro/13/COES-Microcefalias---Informe-Epidemiol--gico-08---SE-01-2016---Valida----o-12jan2016---VALIDADO-PELO-CLAUDIO--e-com-os-estados-por-webconfer--n.pdf.

17. Ministério da Saúde. Ministério da Saúde publica Protocolo de Vigilância sobre microcefalia e vírus Zika [Internet]. Brasilia2015 [cited 2015 Dec 9]. Available from: http://portalsaude.saude.gov.br/images/pdf/2015/dezembro/09/Microcefalia---Protocolo-de-vigil--ncia-e-resposta---vers--o-1----09dez2015-8h.pdf.

18. Pan American Health Organization, World Health Organization. Regional Office for the Americas. Epidemiological Alert: Increase of microcephaly in the northeast of Brazil - 17 November 2015 [Internet]. 2015 [cited 2015 Nov 17]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=32285&lang=en.

19. Melo OAS, Malinger G, Ximenes R, Szejnfeld PO, Alves Sampaio S, Bispo de Filippis AM. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? Ultrasound Obstet Gynecol. 2016 Jan;47(1):6-7.

20. Hawaii Department of health. Hawaii Department of health receives confirmation of Zika infection in baby born with microcephaly (News Release). Honolulu, 2016.

21. Ministério da Saúde (Brazil). Evento de saúde pública relacionado aos casos de Febre do Zika [Internet]. 2015 [updated 2015 Aug 13; cited 2015 Aug 13]. Available from: http://portalsaude.saude.gov.br/index.php/o-ministerio/principal/secretarias/svs/noticias-svs/19139-evento-de-saude-publica-relacionado-aos-casos-de-febre-do-zika.

22. Pan American Health Organization -World Health Organization - Regional Office for the Americas. Epidemiological Alert: Zika virus infection: 7 May 2015 [Internet]. Washington: PAHO; 2015. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&Itemid=270&gid=30075&lang=en.

23. Pan American Health Organization, World Health Organization. Regional Office for the Americas. Epidemiological Alert: Neurological syndrome, congenital malformations, and Zika virus infection. Implications for public health in the Americas [Internet]. Washington: World Health Organization; 2015 [updated 2015 Dec 1; cited 2015 Dec 1]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32405&lang=en.

24. Jorge M.l Evalúan si el zika provocó 15 casos de Guillain Barré Caracas: El Nacional; 2016 Jan 12 Available from: http://www.el-nacional.com/sociedad/Evaluan-provoco-casos-Guillain-Barre_0_773922686.html.

25. Contreras C.. Relacionan casos de Guillain-Barré en el país con virus zika: El Universal; 2016 Jan 12 Available from: http://www.eluniversal.com/vida/160112/relacionan-casos-de-guillain-barre-en-el-pais-con-virus-zika.

26. ProMED-mail. Zika - El Salvador: Sindrome de guillain-barre, aumento marcado, alerta sanitaria [Internet]. 2016 [cited 2016 Jan 10]. Available from: http://www.promedmail.org/post/3924202.

27. Casos de Guillain Barré aumentan a 62 en el país: Elslavadordotcom; 2016 Jan 14. Available from: http://www.elsalvador.com/articulo/casos-guillain-barre-aumentan-pais-98677.

28. Ministère des Affaires sociales de la Santé et des Droits des femmes. Début d'épidémie d'infections à virus Zika en Martinique et Guyane [Internet]. Paris2016 [cited 2016 Jan 16]. Available from: http://social-sante.gouv.fr/actualites/presse/communiques-de-presse/article/debut-d-epidemie-d-infections-a-virus-zika-dans-les-departements-francais-d.

29. Kuno G, Chang GJ, Tsuchiya KR, Karabatsos N, Cropp CB. Phylogeny of the genus Flavivirus. J Virol. 1998 Jan;72(1):73-83.

30. Faye O, Freire CC, Iamarino A, Faye O, de Oliveira JV, Diallo M, et al. Molecular Evolution of Zika Virus during Its Emergence in the 20(th) Century. PLoS Negl Trop Dis. 2014;8(1):e2636.

31. Haddow AD, Schuh AJ, Yasuda CY, Kasper MR, Heang V, Huy R, et al. Genetic characterization of Zika virus strains: geographic expansion of the Asian lineage. PLoS Negl Trop Dis. 2012;6(2):e1477.

32. Enfissi A, Codrington J, Roosblad J, Kazanji M, Rousset D. Zika virus genome from the Americas. The Lancet.387(10015):227-8.

33. Freire CC, Iamarino A, Neto D, Sall AA, Zanotto PM. Spread of the pandemic Zika virus lineage is associated with NS1 codon usage adaptation in humans. bioRxiv. 2015 15 Nov 2015.

34. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). LCI-richtlijn Zikavirus [Internet]. 2016 [cited 2016 Jan 14]. Available from: http://www.rivm.nl/dsresource?objectid=rivmp:300032&type=org&disposition=inline&ns_nc=1.

35. European Centre for Disease Prevention and Control. Mosquito maps. [Internet]. Stockholm: European Centre for Disease Prevention and Control; 2015 [cited 2015 Nov 20]. Available from: http://ecdc.europa.eu/en/healthtopics/vectors/vector-maps/Pages/VBORNET_maps.aspx.

36. Grard G, Caron M, Mombo I, Nkoghe D, Mboui Ondo S, Jiolle D, et al. Zika Virus in Gabon (Central Africa) – 2007: A New Threat from *Aedes albopictus*? PLoS Negl Trop Dis. 2014.

37. Wong PS, Li MZ, Chong CS, Ng LC, Tan CH. *Aedes (Stegomyia) albopictus* (Skuse): a potential vector of Zika virus in Singapore. PLoS Negl Trop Dis. 2013 Aug;7(8):e2348.

38. Musso D, Nhan T, Robin E, Roche C, Bierlaire D, Zisou K, et al. Potential for Zika virus transmission through blood transfusion demonstrated during an outbreak in French Polynesia, November 2013 to February 2014. Euro Surveill. 2014;19(14).

39. Outbreak News Today. Transfusion-associated Zika virus reported in Brazil [Internet]. 2015 [cited 2016 Jan 14]. Available from: http://outbreaknewstoday.com/transfusion-associated-zika-virus-reported-in-brazil-76935/.

40. Aubry M, Finke J, Teissier A, Roche C, Broult J, Paulous S, et al. Seroprevalence of arboviruses among blood donors in French Polynesia, 2011-2013. Int J Infect Dis. 2015 Oct 23;41:11-2.

41. Aubry M, Richard V, Green J, Broult J, Musso D. Inactivation of Zika virus in plasma with amotosalen and ultraviolet A illumination. Transfusion (Paris). 2015 Aug 18.

42. Musso D, Roche C, Robin E, Nhan T, Teissier A, Cao-Lormeau VM. Potential sexual transmission of Zika virus. Emerg Infect Dis. 2015 Feb;21(2):359-61.

43. Hearn PT, Atkinson B, Hewson R, Brooks T. Identification of the first case of imported Zika Fever to the UK: A novel sample type for diagnostic purposes and support for a potential non-vectorborne route of transmission. Am J Trop Med Hyg. 2014;91(5):62-3.

44. Petersen E, Staples J, Meaney-Delman D, Fischer M, Ellington S, Callaghan W, et al. Interim Guidelines for Pregnant Women During a Zika Virus Outbreak — United States, 2016. Morb Mortal Wkly Rep. 2016.

45. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. Lancet Neurol. 2013 Sep;12(9):906-19.

46. Tournebize P, Charlin C, Lagrange M. [Neurological manifestations in Chikungunya: about 23 cases collected in Reunion Island]. Rev Neurol (Paris). 2009 Jan;165(1):48-51.

47. Lebrun G, Chadda K, Reboux AH, Martinet O, Gauzere BA. Guillain-Barre syndrome after chikungunya infection. Emerg Infect Dis. 2009 Mar;15(3):495-6.

48. Villamil-Gomez W, Silvera LA, Paez-Castellanos J, Rodriguez-Morales AJ. Guillain-Barre syndrome after Chikungunya infection: A case in Colombia. Enferm Infecc Microbiol Clin. 2015 Jul 8.

49. Roth A, Mercier A, Lepers C, Hoy D, Duituturaga S, Benyon E, et al. Concurrent outbreaks of dengue, chikungunya and Zika virus infections - an unprecedented epidemic wave of mosquito-borne viruses in the Pacific 2012-2014. Euro Surveill. 2014;19(41).

50. Tognarelli J, Ulloa S, Villagra E, Lagos J, Aguayo C, Fasce R, et al. A report on the outbreak of Zika virus on Easter Island, South Pacific, 2014. Arch Virol. 2015 Nov 26.

51. Zammarchi L, Tappe D, Fortuna C, Remoli ME, Gunther S, Venturi G, et al. Zika virus infection in a traveller returning to Europe from Brazil, March 2015. Euro Surveill. 2015;20(23).

52. Campos GS, Bandeira AC, Sardi SI. Zika Virus Outbreak, Bahia, Brazil. Emerg Infect Dis. 2015 Oct;21(10):1885-6.

53. Pan American Health Organization, World Health Organization. Regional Office for the Americas. Number of Reported Cases of Chikungunya Fever in the Americas by Country or Territory, 2015 [Internet]. 2015 [cited 2016 Jan 14]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=270&gid=32664&lang=en.

54. Pan American Health Organization, World Health Organization. Regional Office for the Americas. Number of Reported Cases of Dengue and Severe Dengue (SD) in the Americas by Country or Territory, 2015 [Internet]. 2015 [cited 2016 Jan 14]. Available from: http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&Itemid=&gid=32742&lang=en.

55. Instituto Nacional de Salud. Boletín Epidemiológico Semanal. Semena 1 2016. [Internet]. 2015 [cited 2016 Jan 17]. Available from: http://www.ins.gov.co/boletin-epidemiologico/Paginas/default.aspx.

56. Ministry of Public Health and Social Welfare Paraguay. Introducción de virus Zika (ZIKAV) en el Paraguay [Internet]. 2015 [cited 2015 Nov 30]. Available from: http://www.mspbs.gov.py/v3/wp-content/uploads/2015/12/Alerta-Introduccion-de-virus-Zika.pdf.

57. Ministerio de Salud Pública y Bienestar Social. Declared an epidemiological alert for dengue, Chikungunya and Zika nationwide [Internet]. Asuncion, 2016 [cited 2016 Jan 14]. Available from: http://www.mspbs.gov.py/v3/declaran-alerta-epidemiologica-por-dengue-zika-y-chikungunya-en-todo-el-pais/.

58. World Health Organization. Disease Outbreak News : Zika virus infection – Venezuela 2015 [cited 2015 Dec 3]. Available from: http://www.who.int/csr/don/03-december-2015-zika-venezuela/en/.

59. NN. There have been 23 cases of zika at least six parishes in Maracaibo: El Venezolano; 2016 Jan 13. Available from: http://www.elvenezolano.com/2016/01/13/se-registrado-23-casos-zika-al-menos-6-parroquias-maracaibo/.

60. NN. 108 ZIKA-gevallen positief getest tot oktober-3 januari Paramaribo: StarNieuws; 2016 Jan 8. Available from: http://www.starnieuws.com/index.php/welcome/index/nieuwsitem/33179.

61. Ministerio de Salud Pública del Ecuador. Ecuador confirma dos casos importados de Zika [Internet]. Quito, 2016 [cited 2016 Jan 14]. Available from: http://www.salud.gob.ec/ecuador-confirma-dos-casos-importados-de-zika/.

62. Ministerio de Salud Pública del Ecuador. MSP confirma primeros casos autóctonos de Zika en Ecuador [Internet]. Quito, 2016 [cited 2016 Jan 17]. Available from: http://www.salud.gob.ec/msp-confirma-primeros-casos-autoctonos-de-zika-en-ecuador/.

63. NN. Zika virus detected in Guyana – Minister Norton: Stabroek News; 2016 Jan 14. Available from: http://www.stabroeknews.com/2016/news/stories/01/14/zika-virus-detected-guyana-minister-norton/.

64. La Razon. Salud confirma el primer caso nativo de zika 2016 [cited 2016 19/01/2016]. Available from: http://www.la-razon.com/sociedad/Ministerio-Salud-confirma-primer-nativo-zika_0_2420757912.html.

65. Salud SDd. La limpieza evita las enfermedades trasmitidas por el mosquito 2016 [cited 2016 2016 Jan 19]. Available from: https://www.facebook.com/media/set/?set=a.442512059290125.1073742169.144859202388747&type=3.

66. World Health Organization. Disease Outbreak News : Zika virus infection – El Salvador: WHO; 2105 [cited 2015 Nov 27]. Available from: http://www.who.int/csr/don/27-november-2015-zika-el-salvador/en/.

67. Centro Nacional de Información de Ciencias Médicas. Suman ya tres mil 836 casos de zika en El Salvador 2016 [cited 2016 Jan 17]. Available from: http://boletinaldia.sld.cu/aldia/2016/01/10/suman-ya-tres-mil-836-casos-de-zika-en-el-salvador/.

68. Gómez V. Autoridades sospechan de otros posibles casos del virus del zika. Prensa Libre [Internet]. 2015. Available from: http://www.prensalibre.com/guatemala/zacapa/sospechan-de.

69. World Health Organization. Disease Outbreak News : Zika virus infection – Mexico 2015 [cited 2015 Dec 3]. Available from: http://www.who.int/csr/don/03-december-2015-zika-mexico/en/.

70. Dirección General de Epidemiología. Boletín epidemiológico. N 52 - Vol 32 - Semena 52. [Internet]. Distrito Federal, 2015 [cited 2016 Jan 14]. Available from: http://www.epidemiologia.salud.gob.mx/doctos/boletin/2015/sem52.pdf.

71. Ministerio de Salud de la República de Panamá. Ministerio de Salud comunica a la población panameña sobre el virus zika [Internet]. Ancon, 2015 [cited 2015 Dec]. 3]. Available from: http://www.minsa.gob.pa/noticia/ministerio-de-salud-comunica-la-poblacion-panamena-sobre-el-virus-zika.

72. World Health Organization. Disease Outbreak News : Zika virus infection – Panama: WHO; 2015 [cited 2016 Jan 14]. Available from: http://www.who.int/csr/don/22-december-2015-zika-panama/en/.

73. NN. Zika virus spreading, dengue deaths down Panama: Newsroom - Panama; 2015 Dec 30. Available from: http://www.newsroompanama.com/news/panama/zika-virus-spreading-dengue-deaths-down.

74. World Health Organization. Disease Outbreak News : Zika virus infection – Honduras: WHO; 2015 [cited 2016 Jan 14]. Available from: http://www.who.int/csr/don/21-december-2015-zika-honduras/en/.

75. Redacion. Alerta en Honduras por aumento de casos del virus zika. El Sol de honduras. 2016 Jan 13 2016.

76. Departemento de Salud. Comunicado de prensa: Confirman primer caso de zika en puerto rico enfatizan medidas de prevención contra los mosquitos Aedes aegypti [Internet]. 2015 [cited 2016 Jan 14]. Available from: http://www.salud.gov.pr/Prensa/Comunicados%20de%20Prensa/CP%20ZIKA%2012%2031%202015.pdf.

77. Ministère de la Santé Publique et la Population. Confirmation de la maladie à virus Zika en Haïti - 15 Janvier 2016 [Internet]. 2016 [cited 2016 Jan 16]. Available from: http://www.mspp.gouv.ht/site/downloads/Communique%20de%20presse%20No%202%20Zika.pdf.

78. Government Information Service. Three Zika Virus cases confirmed in Barbados [Internet]. St. Michael2016 [cited 2016 Jan 15]. Available from: http://gisbarbados.gov.bb/index.php?categoryid=9&p2_articleid=15336.

79. ARS Guadeloupe. Deux cas de Zika confirmés 2016 [cited 2016 Jan 19]. Available from: https://www.facebook.com/212063409135139/photos/a.212168805791266.1073741828.212063409135139/214730088868471/?type=3&theater.

80. World Health Organization. Zika virus infection – Cape Verde [Internet]. 2015 [updated Dec 21 2015; cited Jan 14 2016]. Available from: http://www.who.int/csr/don/21-december-2015-zika-cape-verde/en/.

81. WHO WPR, World Health Organization. Regional Office for the Western Pacific Region. Pacific syndromic surveillance report (Week 33, ending 16 August, 2015) [Internet]. Manila, 2015 [cited 2015 Aug 16]. Available from: http://www.wpro.who.int/southpacific/programmes/communicable_diseases/disease_surveillance_response/PSS-16-August-2015/en/.

82. WHO WPR, World Health Organization. Regional Office for the Western Pacific Region. Pacific syndromic surveillance report (Week 17, ending 26 April, 2015) [Internet]. Manila, 2015 [cited 2015 Apr 26]. Available from: http://www.wpro.who.int/southpacific/programmes/communicable_diseases/disease_surveillance_response/PSS-26-April-2015/en/.

83. Auckland Regional Public Health Service. Dengue Fever, Zika and Chikungunya (Situation Update: October 2015) [Internet]. Auckland2015 [updated 2015 Nov 27; cited 2015 Nov 27]. Available from: http://www.arphs.govt.nz/health-information/communicable-disease/dengue-fever-zika-chikungunya#.VlHRNMuFPDc

84. Focus Taiwan. First Zika virus case detected in Taiwan 2016 [cited 2016 19/01/2016]. Available from: http://focustaiwan.tw/news/asoc/201601190009.aspx.

85. Harris County Public Health and Environmental Services. Travel-Related Zika Virus Infection Has Been Identified in the Harris County Area [Internet]. 2016 [cited 2016 Jan 14]. Available from: http://hcphes.org/UserFiles/Servers/Server_72972/File/News%20and%20Media/Media%20Advisory_ZIKA%20virus_1%2011%2016.pdf.

86. Public health Agency of Canada. Public Health Notice - Zika Virus [Internet]. 2016 [cited 2016 Jan 14]. Available from: http://www.phac-aspc.gc.ca/phn-asp/2016/zika-eng.php.

87. Reynoso S. German who visited Haiti and Guadeloupe tested positive for Zika. ElCaribe [Internet]. 2016 Jan 14 2016. Available from: http://www.elcaribe.com.do/2016/01/14/alemana-que-visito-haiti-dio-positivo-zika.

88. ProMED-mail. ZIKA VIRUS - NETHERLANDS ex SURINAME [Internet]. 2015 [cited 2016 Jan 18]. Available from: http://www.promedmail.org/post/3858300.

89. Ministério da Saúde (Brazil). Microcefalia - Ministério da Saúde divulga boletim epidemiológico [Internet]. Brasília: Ministério da Saúde; 2015 [updated 2015 Nov 17; cited 2015 Nov 17]. Available from: http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/20805-ministerio-da-saude-divulga-boletim-epidemiologico.

90. Centro de operações de emergências em saúde pública sobre microcefalias. Monitoramento dos casos de microcefalias no brasil informe epidemiológico Nº 02/2015 – semana epidemiológica 47 (22 a 28/11/2015) [Internet]. 2015 [cited 2015 Nov 30]. Available from: http://portalsaude.saude.gov.br/images/pdf/2015/novembro/30/coes-microcefalias---informe-epidemiol--gico---se-47.pdf.