



RAPID RISK ASSESSMENT

Zika virus infection outbreak, French Polynesia

14 February 2014

Main conclusions and options for mitigation

- This is the first documented outbreak of Zika virus (ZIKAV) infection in French Polynesia and New Caledonia.
- During the course of the ZIKAV outbreak, neurological and auto-immune complications have been reported in a context of concurrent circulation of two dengue serotypes (dengue 1 and 3) since February 2013.
- Vigilance must be enhanced towards imported cases of ZIKAV infection in the EU Member States and EU overseas countries and territories and outermost regions, in particular where effective vectors are present; early detection of cases is essential to reduce the risk of autochthonous transmission.
- Clinicians and travel medicine clinics should be aware of the situation in the Pacific islands and include ZIKAV infection in their differential diagnosis. An isolated positive result for dengue IgM antibodies among travellers returning from areas affected by Zika should prompt a possible investigation for another flavivirus aetiology.
- The potential neurological and auto-immune complications might require specific healthcare capabilities and treatment (ICU) which need to be taken into account in an insular context facing a large-scale Zika outbreak.
- As an emerging pathogen, the laboratory capacity to confirm suspected Zika cases should be strengthened in the region as well as in Europe to differentiate ZIKAV infections from other arboviral dengue-like illnesses. Regional reference laboratories could provide support to confirm suspect cases.
- As many unanswered questions remain, further epidemiological and laboratory investigations could be conducted to establish:
 - evidence about eco-epidemiology of ZIKAV (viral strain genetic characteristics, transmission cycle(s), vectors and reservoir hosts) to assess its implications for public health;
 - the relationship between neurological and auto-immune complications and ZIKAV infection, notably with other aetiologies, previous infection with other infectious agents and human risk factors;
 - the performance of Zika serology and its cross-reactivity with other flaviviral infections;
 - the possibility of using urine samples for detection of the ZIKAV genome as well as other flaviviral infections.
- Blood safety authorities need to be vigilant regarding the epidemiological situation and should consider deferral of donors with travel history in line with measures defined for West Nile virus. Blood safety procedures are already in place in the Pacific region in the context of the ongoing outbreak of dengue and chikungunya and have included ZIKAV nucleic acid testing since early January 2014 in French Polynesia.

Suggested citation: European Centre for Disease Prevention and Control. Rapid risk assessment: Zika virus infection outbreak, French Polynesia. 14 February 2014. Stockholm: ECDC; 2014.

Stockholm, February 2014

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- As exposure to infected mosquitoes is likely to be the principal risk for infection, prevention of ZIKAV infection is based on protection against mosquito bites and vector control; these have to be customised according to the potential vector species actually present in the area.
- Onward transmission in the EU from imported cases during the winter season is not to be expected, but vigilance during the mosquito season is required in areas where a potential vector is present. Indeed the possibility of autochthonous transmission of tropical mosquito-transmitted viruses in continental Europe does exist.

Source and date of request

ECDC internal decision, 24 January 2014.

Public health issue

This document assesses the risk associated with the outbreak of Zika virus infections, considered as an emerging disease, to public health in the EU/EEA and the risk to EU/EEA citizens in order to anticipate future developments. The aim of this risk assessment is to summarise all available evidence on Zika virus epidemiology and disease presentation, and to assess the current outbreak of Zika in French Polynesia in view of this information, including the possible association with neurological and autoimmune complications.

Consulted experts

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

Disease background information

Zika is a mosquito-borne viral disease caused by Zika virus (ZIKAV), a flavivirus from the *Flaviviridae* family [1].

Clinical presentation

The clinical signs of Zika disease include acute onset of fever, non-purulent conjunctivitis, headache, arthralgia, myalgia, asthenia, rash (in general maculo-papular) and, less frequently, retro-orbital pain, anorexia, vomiting, diarrhoea and abdominal pain. In the literature, Zika is described as a mild, self-limiting febrile illness lasting 4–7 days without severe complications, no fatalities and a low hospitalisation rate [2-4].

It should be noted that the description of the clinical presentation is based on a limited number of case reports and outbreak investigations: Uganda (1962, one case), laboratory-acquired infection (1973, one case), Indonesia (1977 and 1978, seven cases), Yap, Federated States of Micronesia (2007, 31 cases), Senegal (2009, two cases), Cambodia (2010, one case), Thailand (2013, two cases) and Indonesia (2013, one case) and recently travellers returning from French Polynesia to Japan and New Caledonia [3,5-12]. Current treatment guidance is based on a limited body of evidence. There is no vaccine. During the outbreak on Yap, the local State Department of Health Services recommended symptomatic treatment based on acetaminophen (paracetamol) for fever and pain and antihistamines for pruritic rash. Treatment with acetylsalicylic acid and no-steroid anti-inflammatory drugs was discouraged because of the increased risk of haemorrhagic syndrome reported with other flaviviruses [13].

The 2007 Zika outbreak on Yap Island in the Federated States of Micronesia is so far the only well documented and investigated large outbreak. Based on the case definition 'acute onset of generalized macular or papular rash, arthritis or arthralgia, or non-purulent conjunctivitis', 185 cases of suspected Zika disease were identified. Of the suspected cases, 49 (26%) were classified as laboratory-confirmed and 59 as probable cases. These cases had onset between early April and mid-July 2007 (13 consecutive weeks), the median age was 36 years and 61% were female. Clinical characteristics were documented for 31 confirmed cases and included: macular or papular rash (frequency 90%, median duration of 6 days ranging from 2 to 14 days), fever either subjective or measured (frequency 65%), arthritis or arthralgia (frequency 65%, median of duration of 3.5 days ranging 1 to 14 days), non-purulent conjunctivitis (frequency 55%), myalgia and headache (both around 45% frequency) and retro-orbital pain (frequency 39%).

Rash was not reported for the seven cases in Indonesia in 1977–78 but was present in a Canadian traveller returning from Thailand in January 2013. In addition, three travellers returning from French Polynesia in 2013 confirmed with ZIKAV infection presented with a similar clinical profile mainly including fever, rash and headaches [9-12]. This investigation also provided an estimate that 18% of the infected residents of Yap island had a clinical illness probably attributable to Zika virus, even though the number of infected people is difficult to estimate because of cross-reactivity with other flaviviruses [3,14].

A recent case report about two cases imported to Japan from French Polynesia mentions leucopenia and moderate thrombocytopenia for both cases, and the same findings were reported for the recent confirmed Zika case in a Canadian traveller returning from Thailand [4, 5]. The latter biological feature was not previously reported in the scientific literature.

Because of the overlapping symptoms, clinical diagnosis of Zika remains a challenge in tropical settings, particularly in areas with simultaneous transmission of dengue and chikungunya viruses. The Zika IgM antibody assay might be affected by a high degree of serologic cross-reactivity with other flaviviruses, as observed during the 2007 Yap outbreak in patients previously exposed to dengue virus type 1 in 2004 [15]. Additional estimations of key epidemiological parameters need to be established for Zika on clinical presentation and biological parameter anomalies.

Disease distribution and phylogeny

The first virus isolation was performed in April 1947 from a symptomatic sentinel rhesus monkey in a Yellow fever study in the Zika forest, close to Entebbe [16].

The knowledge of the geographical range of the ZIKAV is coming from the below mentioned case reports, outbreak investigations and serological evidence of infection. Serological and entomological studies reported the circulation of the virus in tropical areas of western Africa such as Nigeria in Oyo state (1971), Sierra Leone (1972), Ivory Coast (1999), Cameroon (2009), Senegal (1993 and 2011) and of central Africa in Gabon (1975, 2007–2010), Uganda (1969–1970), Central African Republic (1979) [17–24].

Zika viruses were isolated in Malaysia (1969), Pakistan (1983), Cambodia (2010), Thailand (2013), Indonesia (in 1981 and more recently one case report documenting a ZIKAV infection among a 52-year-old Australian woman returning from the Jakarta area in 2013) [2,3,7,9,10,12,14,25,26]. Prior to the current outbreak in French Polynesia, the only Zika outbreak that had been identified in the Pacific region was on Yap, Federated States of Micronesia, in 2007, as described above.

The first full-length sequencing of the genome of ZIKAV performed in 2006 reports single-strand positive RNA consisting of 10 794 nucleotides with the Open Reading Frame of 3 419 amino acids encoding structural genes and five non-structural genes [27].

ZIKAV is related to Spondweni virus, a virus identified in South Africa that causes dengue-like illness in humans. Comprehensive genomic comparison showed different sub-clades reflecting the existence of two main virus lineages (African and Asian) [14,28]. Additional phylogenetic analysis confirmed the two geographically distinct lineages of ZIKAV (African and Asian) with a circulation of the virus in South-east Asia for at least the past 50 years [29]. The Yap Island outbreak is assuredly linked with the introduction of a South-east Asian ZIKAV strain(s) and the paediatric cases of ZIKAV infection in Cambodia (2010). A recent study of the molecular evolution of ZIKAV in Africa described the historical diffusion pattern of ZIKAV in Africa with two sub-lineages in West and East Africa. This study highlights several recombination events considered uncommon among flaviviruses, and retrace its probable introduction in Asia (Malaysia) [23].

Eco-epidemiology

In East Africa, ZIKAV is most probably maintained in a sylvatic cycle with cyclic epizooty involving non-human primates and mosquitoes (*Aedes* spp.) in tropical forest [20,30-32].

In West Africa and Asia (South-east Asia), serological surveys indicate a likely silent circulation and antibodies have been detected in various animals including large mammals such as orang-utans, zebra, elephants, water buffalo and rodents [25,29,33]. The virus was isolated in Senegal monkeys (*Cercopithecus aethiops* and *Erythrocebus patas*) [29].

The expansion of outbreaks without monkeys supports the role of humans as an amplifying host as seen with other arboviral diseases. As many unanswered questions remain, each new emergence is of high interest for in-depth assessment of the eco-epidemiology of Zika, its transmission cycle(s) including principal and secondary vectors, mammal and non-mammal reservoir hosts and specific transmission modalities (including non-vector-borne). This information is considered to be key for proper preparedness and response to outbreaks.

Entomological aspect

Historically, the virus was later isolated from *Aedes africanus* mosquitoes and the vector transmission was experimentally established using *Aedes aegypti* mosquitoes between an infected mouse and a monkey in 1956 [16, 17]. Between 1961 and 1963, new investigations in the Zika forest found the virus in *Aedes africanus* collected in the canopy [18].

Two aedine mosquito species of public health importance are present in the Pacific, *Aedes aegypti*, the major vector of dengue in the region and *Aedes polynesiensis*, the major vector of filariasis and vector of dengue. They are spread across all islands of French Polynesia [34].

Aedes aegypti mosquitoes infected with Zika virus have been found in the wild [26,35,36]. The vector competence of the local population is currently tested in the 'Institut Louis Malarde' in Tahiti. Preliminary results support the role of *Ae. aegypti* as a vector of ZIKAV. *Ae. aegypti* present in French Polynesia is the domestic form, spread throughout most of the tropical and subtropical regions of the world through trade. It is a diurnal feeder breeding in artificial containers. Adult mosquitoes are sensitive to temperature and humidity. It is probable that *Ae. aegypti* is the main vector in this outbreak as it is a susceptible vector and capable of transmitting ZIKAV [34].

The capability of *Ae. polynesiensis* to transmit ZIKAV (vector competence) is currently being tested and preliminary results support a probable role for this species as a vector of ZIKAV. Confirmation of these results is in process. *Ae. polynesiensis* has been dispersed rather widely by man in the eastern part of the Pacific region, possibly from Samoa. It is a semi-domestic salt-tolerant species with an extremely wide range of breeding habitats such as tree holes, coconut shells and husks, crab holes, artificial containers of various types, and even small water bodies on the ground. It is frequently found in canoes [37]. *Aedes polynesiensis* females bite humans mainly during the day.

Aedes aegypti is widespread in the South Pacific including New Caledonia [38,39]. *Aedes polynesiensis* is present from French Polynesia up to the Fiji islands but is absent from the western islands such as New Caledonia [37-39].

Aedes albopictus has already been proven to become infectious through experimental infection with ZIKAV [40] and has been found infected in the wild in Gabon [24]. This vector is present in the western part of the South Pacific region (Papua New Guinea, Solomon Islands, Fiji, and Tonga), probably present in Vanuatu, and absent from New Caledonia and French Polynesia. It was not detected during entomological surveys in the Cook Islands or on the Wallis and Futuna Islands in 2007 [41].

Finally, *Aedes hensilli* has a limited spatial distribution (Yap, Palau, Chuuk) [39]. Because of its abundance among the mosquitoes captured on the island, it was suspected to be a vector of ZIKAV during the 2007 outbreak in Yap. However, no ZIKAV infection was detected in the mosquitoes captured during this outbreak [3].

Laboratory diagnosis

Zika diagnosis is primarily based on detection of viral RNA from clinical specimens. The viraemic period has not been established but is believed to be short, allowing for direct virus detection during the first 3–5 days after onset of symptoms [1,14]. Specific assays have been published for Asian and African ZIKAV strains targeting the envelope gene or NS5 region, the latter being highly conserved among flaviviruses compared to envelope genes [1,14,42]. PCR assays for dengue would not detect the Zika viral genome. Pan-flavivirus assays and subsequent sequencing analysis can be used as an alternative screening test for possible ZIKAV infection [43,44]. Virus isolation is carried out for research purposes. The use of urine as a specimen for viral genome detection by RT-PCR might be the laboratory diagnostic method of choice since the disappearance of the genome in serum has been shown for yellow fever, dengue, West Nile virus and Zika [11,45-47].

Dengue NS1 antigen assays (Elisa, Rapid-test) are believed to be specific to dengue virus, and negative dengue NS1 assays should trigger testing for other flaviviruses in a patient with a dengue-like symptomatology.

ZIKAV-specific IgM/IgG antibodies can be detected by Elisa and immunofluorescence assays in serum specimens from day 5–6 of illness. Detection of an increase of antibodies in a pair of sera is recommended. IgM antibody response in primary flavivirus/ZIKAV-infected patients has been reported specific for ZIKAV with minor cross-reactivity with heterologous flaviviruses [14]. Positive results should be confirmed by neutralisation assay (i.e. Plaque Reduction Neutralisation Test (PRNT)) to document at least a fourfold increase of ZIKAV neutralising antibody titres [13]. However, in some patients with a probable previous history of flavivirus infection, a fourfold increase of neutralising antibodies to other flaviviruses has been observed [14]. There are no commercial serological assays available for detection of Zika-specific antibodies to our knowledge.

A recent Zika case reported by Germany in a traveller returning from Thailand exemplified the challenge to diagnose ZIKAV infection. The patient was examined ten days after the onset of dengue-like symptoms with a rash. The dengue serology was positive for IgM antibodies against dengue, both indirect immunofluorescence assay and rapid test (SD BIOLINE Dengue Duo NS1 Ag + Ab Combo), and negative for dengue IgG antibodies and dengue NS1 antigen (tested by ELISA and rapid test). Results of indirect immunofluorescence assay on specimens taken one month after onset gave positive results for IgG and IgM antibodies against ZIKAV, indicating an acute or recent ZIKAV infection but cross reactions with IgM antibodies against dengue, Japanese encephalitis and West Nile viruses could not be excluded [10]. These studies illustrate that cross-reactions between flaviviruses are common and results should be considered carefully.

Event background information

French Polynesia is a French overseas country that covers several groups of Polynesian islands: Marquesas Islands, Society Islands (Leeward Islands and Windward Islands), Tuamotu, Gambier and Austral Islands. The overall population is 268 270 inhabitants (census 2012) living on 67 of the 118 islands spread over an area close to the size of continental Europe, but 75% of the population lives in the two main Islands, Tahiti and Moorea. The climate is tropical with a cool dry season (May to October) and warm rainy season (November to April) but with cooler climate for islands in the southern part. The average annual temperature is 26°C, ranging from a minimum average of 21°C in August and a maximum average of 33°C in March.



Source: Central Intelligence Agency. World Fact Book. <https://www.cia.gov/library/publications/the-world-factbook/geos/fp.html>

Between October 2013 and 7 February 2014, 8 262 suspected cases of ZIKAV infection have been reported by the syndromic surveillance sentinel network of French Polynesia [48]. The effective sentinel network during the epidemic involved between 40 and 50 sentinel sites responding every week; 40% were private physicians and 60% public health centres and hospitals. Coverage is estimated at around 25% for the entire country, with sentinel sites localised on 25 islands from the five archipelagos. A suspected case is defined as 'an individual with maculopapular erythematous rash and/or fever reported measured or $\geq 38.5^{\circ}$ C and at least two of the following symptoms and signs: i) conjunctival hyperemia (red eyes), ii) arthralgia and/or myalgia, and iii) oedema of the hands and/or feet' [48].

As of 7 February 2014, of 746 samples sent for laboratory confirmation, 396 (53.1%) were confirmed by RT-PCR at Institut Louis Malardé. It is estimated that more than 28 000 cases have sought medical care with Zika-like symptoms in French Polynesia since the beginning of the outbreak (around 11.5% of the population of French Polynesia). The clinical presentation of confirmed Zika cases was consistent with the literature: mild fever, rash, non-purulent conjunctivitis, arthralgia, myalgia, headache and distal oedema. None of these mild cases was hospitalised.

According to *Polynesia Epibulletin*, 70 cases presented with neurological or auto-immune complications between November 2013 and 7 February 2014 [48].

Among those, there were 38 cases of Guillain–Barré syndrome (GBS) after the initial ZIKAV infection and 25 had neurological complications (encephalitis, meningo-encephalitis, paraesthesia, facial paralysis and myelitis). Seven cases had other complications: four with immune thrombocytopenic purpura, two were ophthalmologic complications and one had a cardiac complication.

Among the GBS cases, 73% were male, the mean age was 45.9 years (range: 27–70), and almost all cases were ethnic Polynesians. Fifteen cases were admitted to the intensive care unit and nine cases required mechanical ventilation. No deaths have been reported. All GBS cases developed neurological symptoms following a disease episode with symptoms compatible with ZIKAV infection in previous days, one of the cases has been laboratory-confirmed to be Zika by RT-PCR at the initial infection, and other preliminary results show positive IgG against ZIKAV for several cases, after the occurrence of neurological signs [48].

The clustering in time of GBS cases is considered unusual as the annual number of GBS cases in French Polynesia are 5, 10, 3 and 3 in 2009, 2010, 2011 and 2012, respectively.

As of 31 January 2014, five patients remained hospitalised and overall a total of 18 individuals had been admitted to the local rehabilitation centre. The intensive care resources in this insular setting have been under intense stress to cope with patients presenting neurological complications.

Figure 1. Distribution of suspected Zika infection cases notified by sentinel network by week of reporting, as of week 04/2014

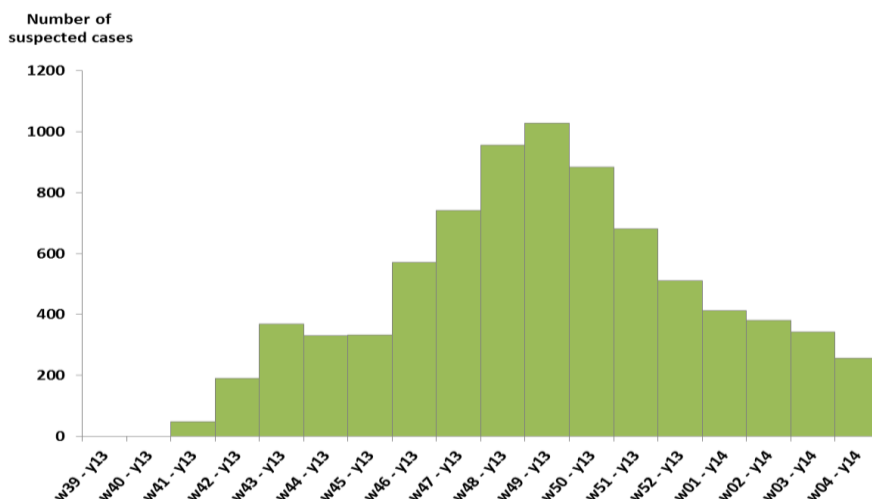
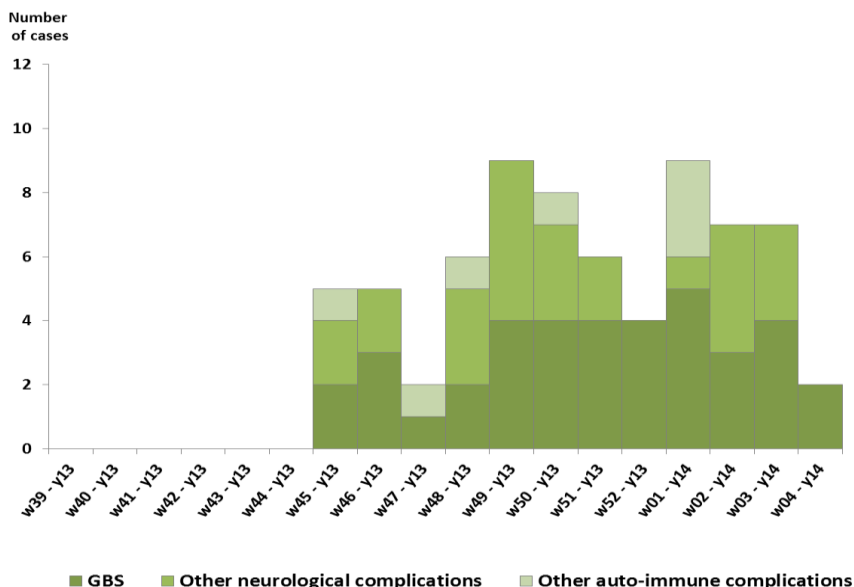


Figure 2. Distribution of suspected Zika infection cases presenting with neurological and auto-immunes complications notified by sentinel network by week of reporting and, as of week 04/2014



Source: Adapted from [48,49]

Figure 1 presents the distribution of suspected cases of Zika infection from the sentinel network of French Polynesia (n=8 039) and cases presenting with neurological or auto-immune complications, by week of reporting, as of week 4 of 2014. It should be considered that winter vacations (week 51 2013 to week 2 2014) might have decreased the number of respondents contributing to the sentinel surveillance system.

The association between auto-immune neurological and haematological complications with primary and/or secondary co-infection with others flaviviruses are under investigation.

Co-infection with dengue virus is a possibility because of an outbreak of dengue virus type 1 and type 3 that has been ongoing since February 2013 in French Polynesia. According to the latest epidemiological bulletin, between 12 400 and 25 700 suspected dengue cases, defined as dengue-like syndrome without laboratory confirmation, arose since February 2013 [48,49]. As of 7 February 2014, 1 656 cases of dengue infection had been laboratory-confirmed. The majority of confirmed cases were notified in Tahiti and Moorea where most of the population resides, and sporadic cases were reported from the Marqueses and Austral islands as of 7 February 2014. Surveillance data indicate that the outbreak is now declining.

In the Pacific region, 'acute fever and rash' is one of the five syndromes (together with 'dengue-like illness', 'influenza-like illness', 'diarrhoea' and 'prolonged fever') under weekly surveillance by the Pacific Public Health Surveillance Network (PPHSN). In addition, the Pacific Syndromic Surveillance System is one of the five service networks of the PPHSN. The 22 Pacific islands Countries and Territories (plus New Zealand) have been

participating in this surveillance system since 2010. Due to the risk of ZIKAV infection spreading in the region, surveillance has been enhanced and passengers arriving from French Polynesia in New Caledonia have been screened since 2 November 2013 [50].

On 10 February 2014, health authorities in New Caledonia reported 64 cases; 30 of which were imported from French Polynesia and 34 were autochthonous infections with ZIKAV in the communities of Dumbea (14 cases), Ouvea (one case) and in Greater Nouméa (19 cases) [51,52]. Two travellers returning from French Polynesia to Japan were recently reported with Zika infection [11].

In-depth molecular analyses are ongoing to determine the lineage and clusters of the Zika viruses in French Polynesia. As the ZIKAV circulation in 2013 is reported in southern Asia and since the connection between the Pacific Islands and South-east Asia is noticeable, it is likely that the current strain belongs to the Asian lineage. Preliminary analysis of the partial ZIKAV E-protein genome sequence (470 bp) from one imported case to Japan shows a 99.1% sequence homology with ZIKAV strain isolated from Cambodia in 2010 and a 97.9% sequence homology with the sequence of a ZIKAV strain isolated on Yap island in 2007 [4, 28]. Additional epidemiological studies, notably a case-control study in French Polynesia and a prospective survey in anticipation of a new outbreak, should investigate the relation between ZIKAV infection and the occurrence of neurological and auto-immune complication. Additional investigations are needed to better describe epidemiological and transmission characteristics and mechanisms (possibility of congenital infection or transmission through blood transfusion or other modes as reported in Foy), establish viral stain genetic characteristics, its pathogenicity and therefore its implications for public health [8].

It is important to note that the Zika outbreak occurred in the context of concurrent circulation of two dengue serotypes, DEN 1 (predominantly) and DEN 3, since February 2013. Prior to 2013, dengue virus serotype 3 (DENV-3) had not been identified in the Pacific island nations for almost 20 years. Meanwhile neurological and auto-immune complications have been reported during outbreaks of different flaviviruses but are not frequent for dengue, and more important for viruses with neurological tropism such as West Nile [53-58]. One case of Guillain-Barré syndrome following DEN 4 infection has been reported in French Polynesia in the literature [59]. Specific studies including genetic investigation would provide additional information to further assess the unusual clinical patterns described during this Zika outbreak.

In conclusion, outbreaks of ZIKAV infection on Yap Island (2007) and in French Polynesia have shown the propensity of this arbovirus to spread outside its usual geographical range and its capacity to cause large-scale outbreaks.

ECDC threat assessment for the EU

French Polynesia is affected by a Zika outbreak representing a risk that the disease will spread further in the Pacific region as the competent vectors are widely present, notably in New Caledonia, where imported cases and recently autochthonous cases have been notified.

The knowledge on the epidemiology of Zika is limited as it is an emerging pathogen, so significant outbreaks need to be carefully investigated to better assess the risk of spread and its consequences for public health.

Risk for the continental EU

Although geographically far from continental Europe, overseas territories of Oceania have close connections with the EU. Therefore, travel-related cases of Zika returning from French Polynesia or from New Caledonia, depending on the evolution of the outbreak, can be expected. Since a possible association with neurological and auto-immune complications has been reported, such as GBS generally occurring at a period after the primary infectious episode, sporadic neurological complications for travel-related cases might be expected. Therefore, vigilance must be enhanced regarding imported cases in the EU Member States, including awareness among clinicians and travel clinics, notably of febrile cases not attributable to dengue and chikungunya infections.

The EU has laboratory capacity to detect ZIKAV. On 7 February 2014, 20 laboratories of the European Network of Viral Imported Diseases (ENIVD) from 13 EU countries have the capacity to detect ZIKAV genome (11 laboratories use a ZIKAV-specific PCR assay and nine laboratories use a generic pan-flavivirus PCR assay and sequencing). Five laboratories already received ZIKA investigation requests. The network provides a standard ZIKAV preparation for PCR diagnostic purpose on request (www.enivd.org).

Viraemic asymptomatic returning travellers could contribute to transmission of the disease if giving blood. Blood safety authorities therefore need to be attentive to the epidemiological situation and should consider deferral of donors with travel history in line with measures defined for West Nile virus, i.e. a deferral period of 28 days after leaving an area with ongoing transmission of ZIKAV to humans [60].

Onward transmission from imported cases to the continental EU is not expected during the winter season because of the low activity of the vector but could occur during the summer months in areas where *Aedes aegypti* is established. *Aedes albopictus* is well established in many parts of the EU, primarily around the Mediterranean. The risk of onward autochthonous transmission of ZIKAV during the mosquito season cannot be excluded given the fact

that *Aedes albopictus* is identified as a potential competent vector [24,40]. The capacity of European populations of *Aedes albopictus* to transmit ZIKAV would need to be assessed.

Risk for EU overseas countries and territories and outermost regions

An outbreak of ZIKAV infection has been ongoing in French Polynesia since the beginning of October 2013. The risk of the disease spreading from French Polynesia to other islands in the Pacific region is high. The spread would most likely result from viraemic individuals travelling to areas with competent vectors, as illustrated recently in New Caledonia. The risk for onward transmission is likely because of the widespread distribution of the vectors.

Likewise, outside the Pacific region, the spread to EU overseas countries and territories and outermost regions is conceivable with a risk of onward transmission due to the presence of the competent vectors. Therefore, high vigilance must be ensured regarding imported cases in EU overseas countries and territories and outermost regions including awareness among clinicians and travel clinics, notably to febrile cases not attributable to dengue and chikungunya infections.

Conclusions and options for mitigation

- This is the first documented outbreak of ZIKAV infection in French Polynesia and New Caledonia.
- During the course of the ZIKAV outbreak, neurological and auto-immune complications have been reported in a context of concurrent circulation of two dengue serotypes (dengue 1 and 3) since February 2013.
- Vigilance must be enhanced towards imported cases of ZIKAV infection in the EU Member States and EU overseas countries and territories and outermost regions, in particular where effective vectors are present; early detection of cases is essential to reduce the risk of autochthonous transmission.
- Clinicians and travel medicine clinics should be aware of the situation in the Pacific islands and include ZIKAV infection in their differential diagnosis. An isolated positive result for dengue IgM antibodies among travellers returning from areas affected by Zika should prompt a possible investigation for another flavivirus aetiology.
- The potential neurological and auto-immune complications might require specific healthcare capabilities and treatment (ICU) which need to be taken into account in an insular context facing a large-scale Zika outbreak.
- As an emerging pathogen, the laboratory capacity to confirm suspected Zika cases should be strengthened in the region as well as in Europe to differentiate ZIKAV infections from other arboviral dengue-like illnesses. Regional reference laboratories could provide support to confirm suspect cases.
- As many unanswered questions remain, further epidemiological and laboratory investigations could be conducted to establish:
 - evidence about eco-epidemiology of ZIKAV (viral strain genetic characteristics, transmission cycle(s), vectors and reservoir hosts) to assess its implications for public health;
 - the relationship between neurological and auto-immune complications and ZIKAV infection, notably with other aetiologies, previous infection with other infectious agents and human risk factors;
 - the performance of Zika serology and its cross-reactivity with other flaviviral infections;
 - the possibility of using urine samples for detection of ZIKAV genome as well as other flaviviral infections.
- Blood safety authorities need to be vigilant regarding the epidemiological situation and should consider deferral of donors with travel history in line with measures defined for West Nile virus. Blood safety procedures are already in place in the Pacific region in the context of the ongoing outbreak of dengue and chikungunya and have included ZIKAV nucleic acid testing since early January 2014 in French Polynesia.
- As exposure to infected mosquitoes is likely to be the principal risk for infection, prevention of ZIKAV infection is based on protection against mosquito bites and vector control; these have to be customised according to the potential vector species actually present in the area.
- Onward transmission in the EU from imported cases during the winter season is not to be expected, but vigilance during the mosquito season is required in areas where a potential vector is present. Indeed the possibility of autochthonous transmission of tropical mosquito-transmitted viruses in continental Europe does exist.

References

1. Balm MN, Lee CK, Lee HK, Chiu L, Koay ES, Tang JW. A diagnostic polymerase chain reaction assay for Zika virus. *Journal of medical virology*. 2012 Sep;84(9):1501-5.
2. Heang V, Yasuda CY, Sovann L, Haddow AD, Travassos da Rosa AP, Tesh RB, et al. Zika virus infection, Cambodia, 2010. *Emerging infectious diseases*. 2012 Feb;18(2):349-51.
3. Duffy MR, Chen TH, Hancock WT, Powers AM, Kool JL, Lanciotti RS, et al. Zika virus outbreak on Yap Island, Federated States of Micronesia. *The New England journal of medicine*. 2009 Jun 11;360(24):2536-43.
4. sanitaire. Idv. Point épidémiologique - Virus Zika. In: Régions. DCdAed, editor. Saint-Maurice. France.: Institut de veille sanitaire.; 2014. p. 1-6.
5. Simpson DI. Zika Virus Infection in Man. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1964 Jul;58:335-8.
6. Filipe AR, Martins CM, Rocha H. Laboratory infection with Zika virus after vaccination against yellow fever. *Archiv fur die gesamte Virusforschung*. 1973;43(4):315-9.
7. Olson JG, Ksiazek TG, Suhandiman, Triwibowo. Zika virus, a cause of fever in Central Java, Indonesia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1981;75(3):389-93.
8. Foy BD, Kobylinski KC, Chilson Foy JL, Blitvich BJ, Travassos da Rosa A, Haddow AD, et al. Probable non-vector-borne transmission of Zika virus, Colorado, USA. *Emerging infectious diseases*. 2011 May;17(5):880-2.
9. Kwong JC, Druce JD, Leder K. Zika virus infection acquired during brief travel to Indonesia. *The American journal of tropical medicine and hygiene*. 2013 Sep;89(3):516-7.
10. Tappe D RJ, Gabriel M, Emmerich P, Günther S, Held G, Smola S, Schmidt-Chanasit J. First case of laboratory-confirmed Zika virus infection imported into Europe, November 2013. *Eurosurveillance*. 2014 30 January 2014;19(4)::pii=20685.
11. Kutsuna S KY, Takasaki T, Moi ML, Kotaki A, Uemura H, Matono T, Fujiya Y, Mawatari M, Takeshita N, Hayakawa K, Kanagawa S, Ohmagari N. . Two cases of Zika fever imported from French Polynesia to Japan, December to January 2013. *Eurosurveillance*. 2014;19(4)::pii=20683.
12. ProMED-mail. ZIKA VIRUS - CANADA ex THAILAND. 2013 [cited 2013 29 March 2013]. Archive Number: 20130529.1744108.]. Available from: <http://www.promedmail.org/direct.php?id=1744108>.
13. Services YSDoH. Zika virus. Information for clinicians and other health professionals. Federated States of Micronesia: Yap State Department Of Health; 2007. p. 2.
14. Lanciotti RS, Kosoy OL, Laven JJ, Velez JO, Lambert AJ, Johnson AJ, et al. Genetic and serologic properties of Zika virus associated with an epidemic, Yap State, Micronesia, 2007. *Emerging infectious diseases*. 2008 Aug;14(8):1232-9.
15. Durand MA, Bel M, Ruwey I, Marfel M, Yug L, Ngaden V. An outbreak of dengue fever in Yap State. *Pac Health Dialog*. 2005 Sep;12(2):99-102.
16. Dick GW, Kitchen SF, Haddow AJ. Zika virus. I. Isolations and serological specificity. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1952 Sep;46(5):509-20.
17. International catalogue of arboviruses, including certain other viruses of vertebrates. In: Karabatsos N, editor. 3rd ed. ed. San Antonio, Texas :: American Society of Tropical Medicine and Hygiene for The Subcommittee on Information Exchange of the American Committee on Arthropod-borne Viruses; 1985.
18. Fagbami AH. Zika virus infections in Nigeria: virological and seroepidemiological investigations in Oyo State. *The Journal of hygiene*. 1979 Oct;83(2):213-9.
19. Jan C, Languillat G, Renaudet J, Robin Y. [A serological survey of arboviruses in Gabon]. *Bulletin de la Societe de pathologie exotique et de ses filiales*. 1978 Mar-Apr;71(2):140-6.
20. McCrae AW, Kirya BG. Yellow fever and Zika virus epizootics and enzootics in Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1982;76(4):552-62.
21. Saluzzo JF, Gonzalez JP, Herve JP, Georges AJ. [Serological survey for the prevalence of certain arboviruses in the human population of the south-east area of Central African Republic (author's transl)]. *Bulletin de la Societe de pathologie exotique et de ses filiales*. 1981 Sep-Oct;74(5):490-9.
22. Monlun E, Zeller H, Le Guenno B, Traore-Lamizana M, Hervy JP, Adam F, et al. [Surveillance of the circulation of arbovirus of medical interest in the region of eastern Senegal]. *Bulletin de la Societe de pathologie exotique*. 1993;86(1):21-8.
23. 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 neglected tropical diseases*. 2014;8(1):e2636.
24. 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 neglected tropical diseases*. 2014.
25. Darwish MA, Hoogstraal H, Roberts TJ, Ahmed IP, Omar F. A sero-epidemiological survey for certain arboviruses (Togaviridae) in Pakistan. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1983;77(4):442-5.

26. Marchette NJ, Garcia R, Rudnick A. Isolation of Zika virus from *Aedes aegypti* mosquitoes in Malaysia. *The American journal of tropical medicine and hygiene*. 1969 May;18(3):411-5.
27. Kuno G, Chang GJ. Full-length sequencing and genomic characterization of Bagaza, Kedougou, and Zika viruses. *Archives of virology*. 2007;152(4):687-96.
28. Kuno G, Chang GJ, Tsuchiya KR, Karabatsos N, Cropp CB. Phylogeny of the genus *Flavivirus*. *Journal of virology*. 1998 Jan;72(1):73-83.
29. 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 neglected tropical diseases*. 2012;6(2):e1477.
30. Haddow AJ, Williams MC, Woodall JP, Simpson DI, Goma LK. Twelve Isolations of Zika Virus from *Aedes (Stegomyia) Africanus (Theobald)* Taken in and above a Uganda Forest. *Bulletin of the World Health Organization*. 1964;31:57-69.
31. Kirya BG. A yellow fever epizootic in Zika forest, Uganda, during 1972: Part 1: Virus isolation and sentinel monkeys. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1977;71(3):254-60.
32. Kirya BG, Okia NO. A yellow fever epizootic in Zika Forest, Uganda, during 1972: Part 2: Monkey serology. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1977;71(4):300-3.
33. Wolfe ND, Kilbourn AM, Karesh WB, Rahman HA, Bosi EJ, Cropp BC, et al. Sylvatic transmission of arboviruses among Bornean orangutans. *The American journal of tropical medicine and hygiene*. 2001 May-Jun;64(5-6):310-6.
34. Institut Louis Mallardé. Infomoustiques. [07 February 2014]. Available from: <http://www.ilm.pf/infomoustiques>.
35. Boorman JP, Porterfield JS. A simple technique for infection of mosquitoes with viruses; transmission of Zika virus. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 1956 May;50(3):238-42.
36. Li MI, Wong PS, Ng LC, Tan CH. Oral susceptibility of Singapore *Aedes (Stegomyia) aegypti* (Linnaeus) to Zika virus. *PLoS neglected tropical diseases*. 2012;6(8):e1792.
37. Belkin JN. *The mosquitoes of the South Pacific (Diptera, Culicidae)*. Berkeley and Los Angeles: 1962.
38. Baudon D. Institut Pasteur de Nouvelle-Calédonie. La Recherche - Rapport d'activités 2012. Nouvelle-Calédonie: 2013.
39. Guillaumot L. Arboviruses and their vectors in the Pacific--status report. *Pacific health dialog*. 2005 Sep;12(2):45-52.
40. Wong PS, Li MZ, Chong CS, Ng LC, Tan CH. *Aedes (Stegomyia) albopictus* (Skuse): a potential vector of Zika virus in Singapore. *PLoS neglected tropical diseases*. 2013 Aug;7(8):e2348.
41. Guillaumot L, Ofanoa R, Swillen L, Singh N, Bossin HC, Schaffner F. Distribution of *Aedes albopictus* (Diptera, Culicidae) in southwestern Pacific countries, with a first report from the Kingdom of Tonga. *Parasites & vectors*. 2012;5:247.
42. Faye O, Faye O, Dupressoir A, Weidmann M, Ndiaye M, Alpha Sall A. One-step RT-PCR for detection of Zika virus. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology*. 2008 Sep;43(1):96-101.
43. Patel P, Landt O, Kaiser M, Faye O, Koppe T, Lass U, et al. Development of one-step quantitative reverse transcription PCR for the rapid detection of flaviviruses. *Virology journal*. 2013;10:58.
44. Johnson N, Wakeley PR, Mansfield KL, McCracken F, Haxton B, Phipps LP, et al. Assessment of a novel real-time pan-flavivirus RT-polymerase chain reaction. *Vector borne and zoonotic diseases*. 2010 Oct;10(7):665-71.
45. Domingo C, Yactayo S, Agbenu E, Demanou M, Schulz AR, Daskalow K, et al. Detection of yellow fever 17D genome in urine. *Journal of clinical microbiology*. 2011 Feb;49(2):760-2.
46. Hirayama T, Mizuno Y, Takeshita N, Kotaki A, Tajima S, Omatsu T, et al. Detection of dengue virus genome in urine by real-time reverse transcriptase PCR: a laboratory diagnostic method useful after disappearance of the genome in serum. *Journal of clinical microbiology*. 2012 Jun;50(6):2047-52.
47. Barzon L, Pacenti M, Franchin E, Pagni S, Martello T, Cattai M, et al. Excretion of West Nile virus in urine during acute infection. *The Journal of infectious diseases*. 2013 Oct 1;208(7):1086-92.
48. Direction de la Santé BdVs, Polynesie Francaise. Surveillance de la dengue et du zika en Polynésie Française 2014 [07 february 2014]. Available from: <http://www.hygiene-publique.gov.pf/spip.php?article120>.
49. Direction de la Santé BdVs, Polynesie Francaise. Surveillance and veille sanitaire en Polynesie francaise 2014 [07 february 2014]. Available from: http://www.spc.int/phs/pphsn/surveillance/Routine_reports.htm.
50. Direction des Affaires Sanitaires et Sociales de Nouvelle Calédonie. Information aux professionnels de santé et au public. Dengue, Chikungunya, Zika-virus 2014 [cited 2014 31 Januray 2014]. Available from: <http://www.dass.gouv.nc/portal/page/portal/dass/librairie/fichiers/24792169.PDF>.
51. Direction des Affaires Sanitaires et Sociales de Nouvelle Calédonie. Veille Sanitaire - Zika: Direction des Affaires Sanitaires et Sociales de Nouvelle-Calédonie (DASS-NC); 2014 [cited 2014 31 January 2014]. Available from: http://www.dass.gouv.nc/portal/page/portal/dass/observatoire_sante/veille_sanitaire/Zika.
52. Direction des Affaires Sanitaires et Sociales de Nouvelle Calédonie. Alertes - Zika virus. Noumea.2014 [cited 2014 31 Januray 2014]. Available from: <http://www.dass.gouv.nc/portal/page/portal/dass/alertes>.

53. Gupta M, Nayak R, Khwaja GA, Chowdhury D. Acute disseminated encephalomyelitis associated with dengue infection: a case report with literature review. *Journal of the neurological sciences*. 2013 Dec 15;335(1-2):216-8.
54. Carod-Artal FJ, Wichmann O, Farrar J, Gascon J. Neurological complications of dengue virus infection. *Lancet neurology*. 2013 Sep;12(9):906-19.
55. Puccioni-Sohler M, Orsini M, Soares CN. Dengue: a new challenge for neurology. *Neurology international*. 2012 Oct 5;4(3):e15.
56. Soares CN, Cabral-Castro MJ, Peralta JM, Freitas MR, Puccioni-Sohler M. Meningitis determined by oligosymptomatic dengue virus type 3 infection: report of a case. *International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases*. 2010 Feb;14(2):e150-2.
57. Lyons J, McArthur J. Emerging infections of the central nervous system. *Current infectious disease reports*. 2013 Dec;15(6):576-82.
58. Sumner N, Jones L. Multifocal neuropathy associated with West Nile virus infection. *Neurology*. 2008 Sep 30;71(14):1123.
59. Oehler E, Le Henaff O, Larre P, Ghawche F. [Guillain-Barre syndrome following type 4 dengue in Polynesia]. *Medecine tropicale : revue du Corps de sante colonial*. 2011 Apr;71(2):203-4.
60. European Commission. Commission Directive 2004/33/EC: Official Journal of the European Union; 2004. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:091:0025:0039:EN:PDF>.