RAPID RISK ASSESSMENT

Zika virus disease in Var department, France

15 October 2019

Summary

On 1 October 2019, a case of locally-acquired Zika virus (ZIKV) disease in France (Hyères city, Var department) was laboratory confirmed. The case had symptoms compatible with ZIKV disease during the first half of August 2019. The cased did not report any history of travel to countries with historical ZIKV transmission. No evidence of sexual transmission was retrieved during the investigation. No imported ZIKV disease cases were reported in the area in 2019. Further epidemiological investigations are ongoing to define the most probable mode of transmission. At this stage, vector-borne ZIKV transmission is the hypothesis which is the basis for this ECDC risk assessment. Vector control measures are being implemented near the residence of the case. To date, investigations did not identify additional cases but further cases may be detected through the ongoing active case finding activities.

Ae. albopictus is widely established in southern Europe (see *Ae. albopictus*, current known distribution, August 2019) and is a competent vector for ZIKV. However, it is considered a less competent vector than the tropical and subtropical vector *Ae. aegypti*. The occurrence of sporadic cases or clusters of locally-acquired vector-borne ZIKV cases is possible notably in the Mediterranean region of Europe when environmental conditions during summer and early autumn can support vector abundance and arbovirus replication at a level that is sufficient for autochthonous transmission of ZIKV. The report of a locally-acquired ZIKV disease case in the southern part of France is thus not unexpected.

To date and based on the ECDC epidemiological assessment, the probability of on-going vector-borne local transmission in Hyères (and surrounding area) is considered very low as current evidence does not indicate that there is a more extensive cluster of ZIKV cases. As the temperature is progressively decreasing during autumn, the environmental conditions are currently not favourable for sustained transmission. The current risk posed to the general population, including pregnant women and their offspring are both very low. If autochthonous, vector-borne transmission were to become documented, for example by the detection of additional locally-acquired cases in the immediate vicinity of the case, pregnant women and their offspring would have been at low risk. It is possible that the ongoing investigation retrospectively identifies locally-acquired cases, because *Ae. albopictus* abundance at the time the case had symptoms would have allowed vector-borne transmission. Currently, however, there is a very low likelihood that travellers to this area would become infected and subsequently introduce the virus and initiate further local transmission in their EU/EEA country of residence.

Substantial uncertainty regarding possible local transmission at the time of publication remains, the level of risk should be re-assessed when significant new facts become available. For options for response, please refer to the "Options for response" section below.

Suggested citation: European Centre for Disease Prevention and Control. Zika virus disease in Var department, France - 15 October 2019. ECDC: Stockholm; 2019. © European Centre for Disease Prevention and Control, Stockholm, 2019

Event background

On 1 October 2019, one locally-acquired Zika virus (ZIKV) disease case was confirmed in Hyères city, Var department, France. The case reported symptoms compatible with ZIKV disease (headache, retro-orbital pain, asthenia and muscle pain) between 29 July and 6 August 2019, followed by arthralgia on 13 August 2019 and a rash around the 15 August 2019. The laboratory confirmation, by the French National Reference Centre for Arbovirus in Marseille, was based on detection of ZIKV RNA in an early sample and detection of IgM and ZIKV-specific neutralizing antibodies in a late sample. Neither the patient nor the partner reported a history of travel to Zika endemic countries. There is no element in the investigation supporting sexual transmission, nor other routes of non-vector borne transmission. As of 14 October, no further cases were reported.

The following actions, in line with national recommendations, were implemented or will soon be initiated by the public health authorities [1]:

- Epidemiological and entomological investigations.
- Ongoing active case finding in the neighbourhood where the case is living.
- Retrospective case finding through a survey with healthcare workers in the private sector, at local health facilities, and clinical laboratories.
- Vector control measures have been implemented according to the ministerial anti-dissemination plan for dengue, chikungunya virus disease and ZIKV disease in metropolitan France since week 41 2019 [2]. The vector control measures are focusing on active search for *Aedes albopictus*, use of insecticides, and placement of mosquito traps.
- Public communication and awareness campaign.

Disease background

Disease characteristics

ZIKV disease

Zika virus disease is a mosquito-borne disease caused by *Zika virus* (ZIKV, family: *Flaviridae*, genus: *Flavivirus*). Most infections are either asymptomatic or cause a mild illness with non-specific symptoms as fever, rash, conjunctivitis, muscle and joint pain, or headache. The duration is usually two to seven days. ZIKV-associated fatalities are rare [3]. However, ZIKV infection during pregnancy has been shown to increase the risk of congenital malformations and birth defects since women can transmit the ZIKV to their unborn babies [4-7]. ZIKV infection during pregnancy is also associated with other complications of pregnancy including preterm birth and miscarriage [8]. In addition, serious neurological conditions were reported among adults and older children associated with ZIKV infection, notably Guillain-Barré syndrome, various neuropathies and myelitis [8]. For more details, a recent review paper by Musso et al. provides a comprehensive overview of evidence, obtained since the pandemic, regarding ZIKV disease [9].

ZIKV diagnostics are based on the detection of viral RNA in clinical specimens and/or the detection of ZIKV-specific antibodies in serum. ZIKV RNA can be detected using nucleic acid amplification tests (NAT) in a variety of body fluids and tissues such as blood (whole blood, plasma and serum), saliva, urine, cerebrospinal fluid, amniotic fluid, semen, and breast milk [8,10]. In comparison to Dengue virus and Chikungunya virus, ZIKV viremia tends to be short and low. Detection of symptoms. Reverse transcription PCR (RT-PCR) is the most reliable method for diagnostic and ZIKV RNA is usually detectable in serum or plasma during the first 3–5 days after the onset of symptoms (sometimes up to 7–8 days) [11]. Whole blood seems to provide a longer detection window for ZIKV RNA in comparison to plasma and serum with detection being reported up to 120 days after onset of symptoms [12-14]ZIKV RNA in plasma and serum by reverse transcription PCR (RT-PCR) is possible from two days before onset of symptoms to usually 3–5 days after the onset of symptoms (sometimes up to 7–8 days) [11]. Whole blood seems to provide a longer detection window for ZIKV RNA in comparison to plasma and serum with detection being reported up to 120 days after onset of symptoms [12-14]. Urine is also known to broaden the detection window: ZIKV RNA has been detected in urine up to 2–3 weeks after onset of symptoms [12].

Counotte et al. performed a systematic review on the sexual transmission of ZIKV and its presence in semen and vaginal fluid after infection [15]. They retrieved evidence from two prospective cohorts that ZIKV RNA is present in human semen with a median duration of 34 days (95% CI: 28–41 days) and 35 days, respectively [15]. Aggregated data about detection of ZIKV RNA from 37 case reports and few case series indicate a median duration of detection of ZIKV RNA of 40 days. The maximum duration of detection of ZIKV RNA reported is 370 days in semen. In human vaginal fluid, median duration was 14 days and maximum duration was 37 days [15].

Serologic methods rely on the detection of IgM, IgG and recently also IgA antibodies by a variety of methods from serum or plasma with the "Gold Standard" serology assay based on the detection of neutralizing antibodies. IgM can typically be detected 5-7 days post onset of illness (range of 2-12 days) and can persist for several months to up to one and a half years [16-18]. Sero-diagnosis of cases relies on detection of ZIKV-specific IgM antibodies and

confirmation by neutralization, seroconversion, or fourfold antibody titre increase of ZIKV-specific antibodies in paired serum samples (acute and convalescent phase). Serological results should be interpreted according to the vaccination status and previous exposure to other arbovirus infections due to extensive cross-reactivity within the genus *Flavivirus* (e.g. dengue virus, West Nile virus, Japanese encephalitis virus and yellow fever virus). It is important to keep in mind that IgM is not always detectable, especially in patients with previous exposure to flavivirus(es) (either vaccination or natural infection). According to US CDC, serum and urine specimens should be collected between symptoms onset up to 10 to 12 weeks after for Zika virus for serology and nucleic acid amplification [19].

ZIKV diagnostics are widely offered in 27 EU/EEA countries. An overview of different types of ZIKV diagnostic is available through EVD-LabNet expert laboratories.

The *Aedes aegypti* mosquito is the main vector but other *Aedes* species can also transmit the virus [20]. The most probable candidate vector for ZIKV in Europe is considered to be *Aedes albopictus* (see below) [20]. An American population of *Ae. vexans* sampled in Colorado has be found competent for ZIKV, but to date no vector competence study is available for mosquitoes population from Europe [21,22]. For *Aedes caspius*, a widely distributed species in the Western Palaearctic, it is considered that vector seems unlikely to support transmission in Europe based on recent study of vector competence for ZIKV using mosquitoes population collected in Catalonia, Spain [23].

ZIKV can also be transmitted from mother to foetus during pregnancy, through sexual contact, through transfusion of blood and blood products. There is no prophylactic or curative treatment, nor a vaccine to protect against ZIKV infection. Therefore, personal preventive measures are recommended to avoid mosquito bites during daytime.

More information about ZIKV disease is available in the ECDC factsheet for health professionals, in previous ECDC risk assessments and in the WHO Zika virus factsheet [8,10,24-29].

Recent developments ZIKV disease epidemiology

The ECDC Rapid Risk Assessment on ZIKV transmission worldwide, published on 11 April 2019, provides an extensive overview of the epidemiological situation by world region [30]. In 2019 and as of week 41 the WHO region of PAHO reported a total of 4 299 cases, an increase compared to the same period in 2018 were the reported cases were 2 818. Between the 25th epidemiological week and the 39th, Brazil reported 540 cases, Peru 386, Mexico 18, Puerto Rico 16, Colombia 9, and Bolivia 5. Despite limited data available based on comprehensive epidemiological surveillance, several countries of Southeast Asia, Western Africa and Central Africa, ZIKV is considered as endemic [31,32].

***Aedes albopictus* in Europe**

Ae. albopictus is widely established in southern Europe (see *Ae. albopictus*, current known distribution, August 2019 [33]) and is a competent vector for ZIKV. However, it is considered a less competent vector than the primary tropical and subtropical vector *Ae. aegypti* [34], which is not established in the continental EU (see ECDC factsheet for experts) [10,35,36]. The degree of vector competence in laboratory studies varies with the origin of the ZIKV and the origin of the *Ae. albopictus* colony [34]. The vector is not generally known to act as a driver of ZIKV epidemics in areas where *Ae. aegypti* is absent or where its population is too small to have epidemiological importance (with the possible exception of one study in Gabon [37]), but infection studies of *Ae. albopictus* suggest a possible contribution to ZIKV outbreaks [38-40].

Population dynamics of *Ae. albopictus* are mainly driven by temperature (survival of adults and development of larvae) and rainfall favouring the presence of breeding sites, either of natural origin (small natural water bodies) or man-made (containers of any kind) [41]. *Ae. albopictus* was first detected in France in 2004 in Menton, 130 km northeast of Hyères, and has since been spreading westward and northward [42], establishing itself in Hyères in 2009 [43,44]. The mosquito is now abundant in the region and was incriminated in the transmission of dengue cases in nearby Toulon [45,46]. *Ae. albopictus* is normally active in southeast France from May until the beginning of November [47,48].

Disease surveillance for ZIKV disease in the EU

ZIKV disease is a notifiable disease in the EU (case definition) [49].

Between 2015 and week 40 of 2019, 22 EU/EEA Member States reported case-based data on 2 414 travel-associated ZIKV disease cases through the European Surveillance System (TESSy). Since 2016, when 2 059 travel-associated cases were reported, the number of new travel-associated cases has fallen substantially from 264 to 48 and only 18 travel-associated cases reported in 2017, 2018 and 2019, respectively.

As of week 40, no vector-borne locally-acquired ZIKV disease cases have been reported among EU/EEA countries (continental Europe). However, 25 locally-acquired ZIKV disease – not vector-borne – cases have been reported since 2016. Of these, 22 have been reported as sexual transmission events from returning travellers to their partners in the EU/EEA (20 in 2016, one in 2017 and one in 2019). Of the three remaining locally-acquired ZIKV disease cases, one was reported as a mother to child transmission event and for two, the transmission status was unknown but the reported case resided in a place with absence of *Ae. albopictus*.

In 2019, as of week 40, 19 ZIKV disease cases were reported, of which 18 were travel-associated and one locally-acquired through sexual transmission. Among the travel-associated cases, Thailand was the most frequent probable country of infection (n=9, 50% of the total). The locally-acquired case contracted the infection from a partner who was infected in Thailand.

Between 2015 and week 40 of 2019, France has reported 1 163 travel-associated ZIKV disease cases, of which 1 119 in 2016, 27 in 2017, 10 in 2018 and 7 in 2019. France reported a total of 13 sexually transmitted locally-acquired cases, 12 in 2016 and one in 2017.

Further information can be found in ECDC's Annual epidemiological report [50], the online Surveillance atlas of infectious diseases [51] and the online four-monthly updated table presenting travel-associated Zika virus disease cases in the EU/EEA [52].

Risk assessment questions

This risk assessment addresses the public health significance of the report of a locally-acquired ZIKV disease case in an area with established populations of *Ae. albopictus*.

ECDC risk assessment for the EU/EEA

Although investigations are ongoing, to date the mode of transmission has not been unambiguously established and no primary case identified. No evidence for sexual transmission was found nor for other routes of non-vector borne transmission. Hence, a vector-borne ZIKV transmission event is hypothesized for the assessment below.

The overall number of travel-associated ZIKV disease cases reported among EU/EEA countries has decreased drastically since 2016, mainly due to the general reduction of ZIKV circulation after the epidemic in the Americas in 2015 and 2016. ZIKV disease cases are still reported in various countries of the Americas but also in Africa and Asia and a very low number of travel-associated cases in the EU/EEA has been reported in the past months (see section above). Thus, despite being rare events, the importation of ZIKV by viraemic travellers returning from areas with active ZIKV transmission is possible among EU/EEA countries, especially from or to large touristic destinations. The region where the case resides, Provence-Alpes-Côte d'Azur, France, is a popular tourist destination, with 55 million nights spent in tourist accommodations in 2017 [53].

The occurrence of sporadic cases or clusters of locally-acquired vector-borne ZIKV cases is possible in the Mediterranean region and southern parts of EU/EEA countries during the summer and autumn seasons due to the presence of established and active populations of *Ae. albopictus,* a competent vector for ZIKV. In the southern part of Europe in areas with established populations of *Ae. albopictus*, environmental conditions during summer and early autumn can support vector abundance and arbovirus replication at a level that is sufficient for autochthonous transmission of ZIKV, which could then lead to sporadic cases or localised cluster/outbreaks after importation of the virus. Environmental conditions may remain suitable for significant vector activity until the middle of October [41,47] but are expected to become progressively less suitable during October and November [41,47]. There is no evidence of sufficient ZIKV replication in *Ae. albopictus* to support transmission at or below 18 °C [54]. One study in *Ae. aegypti* suggests a thermal range for vector competence of 22.9–38.4°C [55], while another did find evidence of ZIKV in saliva of *Ae. aegypti* kept at 20°C [56].

The report of a locally-acquired ZIKV disease case in the southern part of France is not unexpected and was anticipated in previous ECDC risk assessments [30]. This is supported by the recurrent events of other arbovirus transmission in the south of Europe throughout the past decade, for example locally-acquired dengue cases, a closely related arbovirus in the genus *Flavivirus*, and chikungunya virus disease cases [57,58]. Nonetheless, at this time of the year, the likelihood of local onward vector-borne transmission of ZIKV disease in the Provence-Alpes-Côte d'Azur region in France is considered very low with the temperature progressively decreasing during autumn and a reduction of vector population.

To date and based on ECDC epidemiological assessment and information available, the probability of current vector-borne transmission in Hyères is very low as no cluster of cases has been identified and the environmental conditions are currently not favourable for sustained transmission. The likelihood that travellers to this area (Hyères city) become infected and subsequently introduce the virus and initiate further local transmission in their EU/EEA country of residence remains very low. Given the current very low likelihood of local vector-borne transmission, the current risk posed to the general population, including pregnant women and their offspring is very low. If local vector transmission were to become documented, for example by detection of additional locally-acquired cases in the immediate vicinity of the case, pregnant women and their offspring would have been at low risk. In case epidemiologic investigations fail to identify the primary (imported) case and thus evidence for local

vector-borne transmission, this case – without recent travel history – would be classified as a 'cryptic' ZIKV disease case[1].

Data, though limited, indicate that there is a risk that ZIKV transmission can occur through substances of human origin (SoHO), especially through blood transfusion [59,60]. The high proportion of asymptomatic cases [61-64], the documented occurrence of Zika RNA-positive blood donations during epidemics [65-67], and the reports of probable transfusion-transmitted cases during outbreaks [68,69] indicate that Zika-positive blood, donated by an asymptomatic infectious donor, may enter the blood supply and could be transfused to a patient. However, the low number of transfusion-transmitted cases, all without clinical consequences in recipients, preclude a more accurate risk assessment. The likelihood of maternal and foetal exposure to blood products and presumably to other SoHO is very low [70]. No cases of Zika virus transmission through donated cells, tissues, and organs have been reported, but transmission cannot be excluded due to the confirmed presence of the virus in human blood and body fluids. Considering the current assessment of the risk of vector-borne transmission in the Hyères city area being very low, the risk of ZIKV transmission through SoHO in this area, as well as the risk of ZIKV infection in donors visiting this area, would also be very low.

With the information available currently, there is substantial uncertainty regarding the possibility of local transmission. At the time of publication, the extent of such focal transmission based on a single case is expected to be very limited and local. However, it is possible that the currently ongoing investigation identifies retrospectively locally-acquired cases, because *Ae. albopictus* abundance around the time the case had symptoms would probably have been permissive for vector-borne transmission. Nonetheless, based on the currently available information, the overall public health risk associated to the event is very low.

The level of risk should be re-assessed if significant new facts become available through the epidemiological, laboratory and entomological investigations.

Options for response

In the case of confirmed vector-borne transmission, Member States may consider applying risk control measures that are outlined in the previous ECDC Rapid Risk Assessment Zika virus transmission worldwide [30].

Limitations

This risk assessment is based on information available at the time of publication. While the epidemiological investigation is ongoing, there is a substantial uncertainty regarding the extent of potential circulation of the virus; further cases might be detected through active case finding.

Source and date of request

ECDC internal decision, 10 October 2019.

Consulted experts

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All experts have submitted declarations of interest, and a review of these declarations did not reveal any conflict of interest.

Disclaimer

[1] 'cryptic' in this context indicates 'of unknown origin', in analogy with the term used in malariology (see US CDC glossary)

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency, and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

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