Main conclusions and options for response

Since the beginning of 2018 and as of 24 June, 5,747 autochthonous cases of dengue have been reported in Réunion, with no fatal case directly attributable to dengue reported. Dengue virus (DENV) transmission in Réunion is not unexpected, but the current DENV-2 outbreak is larger compared with previous dengue outbreaks reported on the island over the last 15 years. Aedes albopictus mosquito is considered to be the principal vector. With the arrival of the southern-hemisphere winter in July, and based on the observed pattern of previous outbreaks on the island, this outbreak is expected to weaken in intensity as the climatic conditions will become less favourable for mosquito activity. However, no marked decline has been observed yet.

The probability of onward transmission of dengue fever in the European Union (EU) and the European Economic Area (EEA) Member States is associated with the importation of the virus by viraemic travellers into receptive areas, defined as a location with established and active competent vectors. Aedes albopictus is established in the southern part of the EU (more information about vector distribution is available from: https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps), and environmental conditions are currently favourable for vector activity. In addition, vector abundance is currently considered sufficient to permit autochthonous transmission of dengue virus and potentially generate local outbreaks.

When visiting areas where DENV is circulating, it is advised to take personal protective measures against mosquito bites to limit exposure to DENV; this applies equally to other Aedes-transmitted arboviruses. These measures can reduce the probability of importation of the virus into receptive areas of the EU/EEA.

During the season of high vector activity, early detection of imported dengue cases is essential to prevent the establishment of local transmission. The detection of an autochthonous case in receptive areas in the EU/EEA should trigger epidemiological and entomological investigations to assess the potential for onward transmission and guide vector control measures aimed at lowering the mosquito population density. Increased awareness among clinicians and travellers returning from areas with active dengue virus transmission, combined with adequate laboratory diagnostic capability, are instrumental for the early detection of travel-associated cases.

Travellers returning from areas where dengue virus transmission occurs should be advised to seek medical attention if presenting with symptoms compatible with dengue fever in the first two weeks after return. In order to contribute to reducing the probability of further local transmission, timely detection of cases is particularly relevant for those returning to areas where competent vectors are established. By the same token, symptomatic patients should be advised on how to apply personal protective measures against mosquito bites.
As no vaccines or prophylactic drugs are available, dengue fever prevention is based on protection against mosquito bites. *Aedes* mosquitoes have a diurnal biting pattern, both indoors and outdoors. Personal protection measures should be applied all day long, and especially during the hours of highest mosquito activity (mid-morning, late afternoon to sunset). Personal protective measures to reduce the risk of mosquito bites include the use of mosquito repellent in accordance with the instructions indicated on the product label, wearing long-sleeved shirts and long trousers, and using insecticide-treated mosquito bed nets. Those measures are essential in providing protection from mosquito bites in rooms that are not adequately screened or air-conditioned.

EU/EEA Member States should also consider applying safety measures to prevent the transmission of dengue virus through donations of substances of human origin (SoHO) from travellers returning from Réunion.

Source and date of request
ECDC internal decision, 28 June 2018.

Public health issue
This update of the risk assessment published on 16 April 2018 was triggered by the unusual size and duration of the current dengue fever outbreak driven by *Ae. albopictus*, a mosquito vector present in Réunion and widely distributed in the southern part of EU [1]. The current assessment addresses the public health significance of the event, particularly the likelihood of the introduction of DENV from Réunion, and potential subsequent transmission in EU Member States during the mosquito season in those countries.

Consulted experts
ECDC contributors (alphabetical order): Chiara de Bellegarde de Saint Lary, Olivier Briet, Dragošlav Domanovic, Céline Gossner and Bertrand Sudre.

External experts (alphabetical order): Remi Charrel (EVD-LabNet, Aix-Marseille University, France), François Chieze (Agence de Santé Océan Indien, Réunion), Harold Noel (Santé Publique France, France), Anna Papa (EVD-Labnet, Aristotle University Thessaloniki, Greece) Marie-Claire Paty (Santé Publique France, France), Chantal Reusken (EVD-LabNet, Erasmus MC, Netherlands), Jonas Schmidt-Chanasit (EVD-Labnet, Bernhard Nocht Institute for Tropical Medicine, Germany) and Luce Yemadje Menudier (Santé Publique France, Cire Océan Indien, Réunion).

Disease background information

Dengue virus
Dengue is a mosquito-borne disease caused by dengue virus, a member of the *Flaviviridae* family. There are four antigenically distinct serotypes of dengue virus (DENV 1 to 4). The main mosquito vector is *Ae. aegypti* but other mosquitoes, including *Ae. albopictus*, have also been implicated in virus transmission. The virus is not transmitted directly from human to human, except in the case of blood transfusion, or organ and tissue transplantation from viraemic donors.

The majority of infections are either asymptomatic or result in a mild febrile illness. Symptoms include a sudden onset of febrile illness lasting an average of 2–7 days, usually characterised by severe headache, retro-orbital pain, arthralgia and a maculo-papular rash. The more severe and potentially deadly forms, classified as severe dengue, develop in less than 5% of patients [2].

A DENV infection can be identified through detection of the viral antigen NS1, the viral genome, or DENV-specific antibodies. In primary DENV infections, the NS1 antigen can be detected typically up to day 14 post onset of symptoms while in secondary infections it can be detected up to day five. Viral RNA usually can be detected up to day seven. Confirmation of infection based on routine serology only, is complicated by extensive cross-reactivity between the four serotypes and other flaviviruses (including Zika virus, yellow fever, West Nile virus, tick-borne encephalitis virus and Usutu virus, the latter three being endemic in parts of the EU/EEA) and related vaccines. In addition, an acute flavivirus infection might boost cross-reactive antibodies due to a previous infection with, or vaccination against, another flavivirus thereby interfering with a proper interpretation of serological tests. Serological diagnosis can be performed by detection of DENV-specific IgM antibodies five to six days after onset of symptoms or detection of a fourfold rise in DENV-specific IgG antibody titres on paired serum samples taken 14 days apart. In secondary dengue, IgM antibodies usually appear from day two post symptom onset [3,4]. Diagnostics for DENV are available in reference laboratories in 28 EU/EEA countries, with 25 countries offering molecular detection, 24 countries offering routine serology, and 10 countries offering virus neutralisation tests.
The epidemic curve of autochthonous cases of dengue fever in Réunion since January 2017 is presented in [22]. Between the end of July (week 31) and the end of the year, only sporadic autochthonous cases were reported, mainly in the commune of Saint-Paul, supporting a possible residual low transmission level during the southern-hemisphere winter (June to September) [23].

The epidemic curve of autochthonous cases of dengue fever in Réunion since January 2017 is presented in Figure 1 [24].
Since the beginning of 2018 and as of 24 June, 5,747 autochthonous cases of dengue have been reported in Réunion [24]. One fatal case was reported as indirectly related to dengue. Of these cases, 259 were reported between 18 and 24 June 2018 [24]. The circulating serotype is DENV-2. The main vector of infection implicated in this outbreak is considered to be *Ae. albopictus*.

As of 24 June 2018, the municipality of Saint-Paul, one of the most populated areas in the island, reported 52% of the total number of cases (n=2,989) [24]. Additional cases in the western part of the island were reported in the communes of Le Port (n=629, 11% of total), La Possession (n=480, 8% of total) and Saint-Leu (n=382, 7% of total). In the southern part of the island, the majority of the cases were reported from Saint-Pierre commune (n=543, 10% of total). Four communes, namely Saint Paul, Le Port, La Possession and Saint Leu, reported an overall incidence rate over 100 dengue cases per 10,000 inhabitants (January 2018 to 24 June 2018).
Figure 2. Geographical distribution of autochthonous cases of dengue in Réunion, data from January 2018 to 24 June 2018

Source: Adapted from: Surveillance de la dengue à la Réunion. Point épidémiologique au 3 juillet 2018; Cire océan Indien. Santé publique France (2018) [24].

On 27 March 2018, local authorities decided to activate level 3 of the ORSEC (Organisation de la Réponse de Sécurité Civile) plan to enhance response activities. Alert level 3 corresponds to a ‘low intensity epidemic’. The current response activities include the following measures: intensification of vector control (integrated and multi-sectoral vector control measures), reinforcement of communication to the public and healthcare workers and mobilisation of additional resources. More information is available in a local bulletin entitled ‘Point de situation: zones concernées & chiffres-clé’ [25].

The French Blood Bank (Etablissement Français du Sang) implemented systematic individual nucleic acid testing (NAT) of blood donations on 3 April 2018 to complement its SoHo measures, including reinforced post-donation follow-up, red blood cell quarantine for 72 hours, and pathogen attenuation of the platelets and plasma supply from continental France. Blood collection is interrupted in the affected area (Saint-Paul area). In other French departments, blood donors should be deferred for 28 days after returning from Réunion.

**ECDC risk assessment**

The ongoing dengue epidemic in Réunion has an unusual magnitude compared with previous dengue outbreaks reported since 2004. The high number of cases reported every week indicates that the outbreak is still ongoing. In addition, the fact that cases are reported from almost all communes of the island indicates widespread transmission. The western part of the island is the one most affected, with a moderate level of transmission in several foci.

Based on previous dengue fever outbreaks caused by *Aedes* mosquitoes in Réunion, transmission is expected to persist up to the beginning of the southern-hemisphere winter (July–September); however, a marked decline has not yet been observed. It should be noted that sporadic DENV-2 cases were reported during the inter-epidemic period in 2017, supporting possible transmission even during the austral winter on the island and a potential new outbreak during the austral summer 2018–2019.

While dengue outbreaks occur regularly in many tropical countries, most outbreaks are sustained by *Ae. aegypti* mosquitoes, its primary vector, which is not established in the continental EU. The fact that the implicated vector in the ongoing outbreak in Réunion is *Ae. albopictus* increases the likelihood of sustained local transmission in the continental EU.

To date, there is no evidence of local genetic adaptation of dengue virus to *Ae. albopictus* in Réunion, which could lead to enhanced virus transmission to the *Ae. albopictus* mosquito population in Réunion or the continental EU. While the large outbreak observed in Réunion demonstrates a marked vectorial capacity of the current circulating DENV-2 serotype in the *Ae. albopictus* population, further genetic, molecular and entomological investigations remain of interest to better describe and assess transmission characteristics.

According to data (2011 and 2016) from the International Air Transport Association (IATA), an average of 500 000 people travel from Réunion to the EU/EEA every year. The most popular travel periods are i) December–January and ii) July–August, when between 40 000 to 50 000 people travel to EU/EEA Member States every month, mostly to mainland France. Due to the ongoing outbreak characteristics in Réunion and recent travel-associated dengue...
cases returning from Réunion, travellers visiting areas with current DENV transmission in Réunion should be made aware of the ongoing outbreak and be advised to strictly apply personal protective measures to reduce exposure to mosquitoes bites.

**Introduction and further transmission in the continental EU/EEA**

The likelihood of introduction of the virus to the continental EU/EEA is linked to the number of viraemic travellers returning while the likelihood of sustained transmission is linked to the presence of an established, active and abundant competent vector population.

In 2016, 2 705 imported dengue cases were reported to The European Surveillance System (TESSy), highlighting the noticeable frequency of travel-associated dengue cases reported by EU/EEA countries. Information on suspected country of infection was available for 1 504 of these cases. The most frequently reported suspected countries of infection were Asian countries: Thailand (21%), Indonesia (18%) and India (12%). France reported one imported case from Réunion.

To date in 2018, 57 imported cases have been notified in Aedes-active areas in France, 21% of which were imported from Réunion and 35% from Thailand. The likelihood of introduction of DENV to continental EU/EEA countries is considered to be low. The current outbreak in Réunion would, to some extent, increase the level of likelihood of introduction of DENV to the EU/EEA through viraemic travellers, especially in mainland France.

Environmental conditions in southern EU are currently favourable for vector activity as vector abundance is sufficient to allow the autochthonous transmission of dengue virus, which could potentially lead to a local outbreak. This was exemplified by the chikungunya outbreaks in Italy in 2007 and 2017 and sporadic autochthonous cases of DENV and/or CHIKV reported in France and in Croatia (see Annex 1 of the 2017 ECDC Rapid Risk Assessment: Cluster of autochthonous chikungunya cases in France – 23 August 2017) [21]. With regard to dengue, all reported events of transmission corresponded to sporadic cases or limited clusters of cases and always occurred during the season of high vector activity.

Therefore, the likelihood of local transmission of DENV in these areas is considered to be moderate.

Outside the continental EU, the EU Overseas Countries and Territories (OCTs) and Outermost Regions (ORs), with established populations of *Ae. aegypti*, remain vulnerable to dengue epidemics, as demonstrated by recurrent dengue fever outbreaks in the Caribbean region and the outbreak in Madeira in 2012 [26,27].

**Dengue and safety of substances of human origin**

DENV can be transmitted through infectious substances of human origin (SoHO) donated by asymptomatic, viraemic donors. Transmission of DENV through transfusion of erythrocytes, platelets and plasma [28-33] as well as through kidney [34,35], liver [35-37], heart [35] and bone marrow [38,39] transplantation have been reported in the past. The precise level of risk of DENV transmission through SoHO cannot be adequately assessed due to the small number of cases reported. The rarity of reported SoHO-transmitted dengue cases could be partly explained by under-recognition and under-diagnosis of this disease in many endemic countries around the world.

Other transmission factors include the hypothetical enhancement of DENV replication and DENV virulence in the saliva of the mosquito, the presence of protective antibodies among transfusion recipients or in co-transfused antibody-positive blood components [29]. Further data are needed to assess the risk of DENV transmission thorough SoHO more precisely.

To prevent transfusion-transmitted DENV infection, blood donors should be deferred for 120 days after full recovery from clinical dengue [40]. In affected areas, donors with flu-like symptoms should be deferred for 28 days after the resolution of symptoms [40]; alternatively, donations should be quarantined for 72 hours and released upon the information of absence of symptoms in the donor.

Donation screening using nucleic acid testing (NAT) is the main tool to reduce the risk of transmission in affected areas when deferrals may potentially affect supply. For plasma and platelets donations, pathogen-reduction technology may also be considered. Post-donation information should be reinforced. Potential asymptomatic donors whose travel histories place them at risk of dengue infection should be deferred for 28 days upon return to non-endemic areas [40].

Donors of organs, cells and tissues living or coming from dengue-affected areas should be tested for the presence of viral RNA using NAT [41,42]. Organs from viraemic donors should not be used without consulting a transplant infectious disease expert [41].
Figure 3. Distribution of *Aedes albopictus* in the EU/EEA and neighbouring countries, June 2018

Source: Ae. albopictus, current known distribution: June 2018 [7]
Annex 2

Table 1. Dengue transmission events with more than 10 cases in Réunion between 2004 and 2017

<table>
<thead>
<tr>
<th>Years</th>
<th>Start month</th>
<th>End month</th>
<th>Number of cases*</th>
<th>Prevalent dengue serotype</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>April</td>
<td>June</td>
<td>228</td>
<td>1</td>
<td>[43]</td>
</tr>
<tr>
<td>2008</td>
<td>January</td>
<td>July</td>
<td>33</td>
<td>1</td>
<td>[44]</td>
</tr>
<tr>
<td>2010</td>
<td>March</td>
<td>May</td>
<td>18</td>
<td>3</td>
<td>[45]</td>
</tr>
<tr>
<td>2012</td>
<td>February</td>
<td>July</td>
<td>31</td>
<td>1 and 3</td>
<td>[46]</td>
</tr>
<tr>
<td>2013</td>
<td>February</td>
<td>July</td>
<td>21</td>
<td>1 and 3</td>
<td>[47,48]</td>
</tr>
<tr>
<td>2014</td>
<td>March</td>
<td>August</td>
<td>29</td>
<td>1</td>
<td>[49]</td>
</tr>
<tr>
<td>2015–2016</td>
<td>October</td>
<td>July</td>
<td>231</td>
<td>1,2 and 3</td>
<td>[50]</td>
</tr>
<tr>
<td>2017–2018</td>
<td>February</td>
<td>Underway†</td>
<td>5 747</td>
<td>2</td>
<td>[24]</td>
</tr>
</tbody>
</table>

Note: * = confirmed and probable dengue cases; † = as of 17 June 2018.
In 2011, only two confirmed sporadic cases were reported: one in May and one in September [51].

Disclaimer

ECDC issued this risk assessment document on the basis of an internal decision 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. In the framework of ECDC’s mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter with their respective advantages and disadvantages. 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 under the coordination of an Internal Response Team at ECDC. All data published in this risk assessment are correct to the best of our knowledge on 26 June 2018. 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.
References


