RAPID RISK ASSESSMENT

Dengue outbreak in Réunion, France, and associated risk of autochthonous outbreak in the EU/EEA

18 June 2019

Main conclusions and options for response

Since 2018, Réunion has been facing a major outbreak of dengue, with a first wave observed in 2018 and a second higher wave observed in 2019. In 2018, the peak in cases was during April–May and over 6 700 cases were reported that year. Since the beginning of 2019 and as of 11 June, over 15 000 autochthonous confirmed cases of dengue have been reported. Nine deaths were reported among the cases in 2019, with dengue being identified as the direct cause of death for five. Dengue virus (DENV) transmission in Réunion is not unexpected, but the ongoing outbreak is very large compared to the outbreaks of dengue recorded over the past 15 years. The mosquito *Aedes albopictus* (*Ae. albopictus*) is considered to be the principal vector in Réunion. With the arrival of the southern-hemisphere winter in July, and based on the pattern of previous outbreaks observed on the island, this outbreak is expected to reduce in intensity as the climatic conditions lead to a decrease in the mosquito population and become less favourable for virus replication in the vector.

The likelihood of onward transmission of DENV in the European Union (EU) and the European Economic Area (EEA) is associated with the probability of importation of the virus by viraemic travellers into receptive areas, defined as locations with established and active competent vectors. *Aedes albopictus* is established in parts of southern and central EU (more information about vector distribution is available from the mosquito maps on ECDC's website[1]). Currently and throughout the summer season, environmental conditions are favourable for the activity of the vector, and its abundance should be sufficient to support local outbreaks, as illustrated by sporadic cases associated with autochthonous transmission events that have occurred in recent years in continental EU, notably in France.

Travellers to Réunion, and to other regions with ongoing DENV circulation, should take personal protective measures against mosquito bites to limit exposure to DENV; this applies equally to other mosquito-transmitted arboviruses. These measures can also reduce the probability of the virus being imported into receptive areas of the EU/EEA.

During the period of high vector activity in the EU/EEA, early detection of imported dengue cases is essential to prevent local transmission. The detection of an autochthonous case in receptive areas of continental EU/EEA represents an important trigger for epidemiological and entomological investigations to assess the potential for onward transmission and to guide vector control measures to lower 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.

[1] https://ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps

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Travellers returning from areas where DENV circulation occurs should be advised to seek medical attention if presenting with symptoms compatible with dengue in the first two weeks after return, particularly if returning to areas where the *Ae. albopictus* mosquito is established and during the high vector activity period. Symptomatic patients should be advised on how to apply personal protective measures against mosquito bites in order to prevent transmission of the virus to local mosquitoes in the continental EU/EEA.

As no vaccine or prophylactic drugs are available in the EU/EEA, dengue 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 (morning and 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. These measures are essential for 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 and other countries with ongoing dengue outbreaks.

Source and date of request

ECDC Internal Decision, 11 June 2019.

Public health issue

Following the first update of the risk assessment 'Dengue outbreak in Réunion, France' published on 5 July 2018, this second update has been triggered by the significant size of the outbreak and its expected duration, which is anticipated to overlap with high vector activity in the southern EU [1]. In addition, the vector of the current epidemic is *Ae. albopictus*, a mosquito vector present in Réunion and also widely distributed in the central and southern parts of the EU. The current assessment addresses the public health significance of the event, particularly the potential introduction of DENV from Réunion and the possibility of subsequent transmission in EU/EEA Member States.

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Experts from WHO have reviewed the risk assessment, but the views expressed in this document do not necessarily represent the views of WHO.

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

Disease background information

Dengue virus

Dengue is a mosquito-borne disease caused by viruses of the *Flaviviridae* family. There are four antigenically distinct serotypes of dengue viruses (DENV1–4). The main mosquito vector is *Ae. aegypti* but other mosquitoes, including *Ae. albopictus*, have been implicated in disease transmission. The infection is not transmitted directly from human to human, except in the case of blood transfusion, or organ and tissue transplantation.

The majority of infections are either asymptomatic or result in a mild febrile illness. Symptoms include a sudden onset of febrile illness typically lasting 2–7 days, severe headache, retro-orbital pain, arthralgia and maculopapular rash with a duration of up to seven days. The more severe and potentially deadly forms, classified as severe dengue, develop in less than 5% of patients. Patients with severe dengue can recover without sequelae if diagnosed early and managed appropriately. In the EU/EEA, there is currently no recommended vaccine available for dengue. To date, the tetravalent live-attenuated vaccine Dengvaxia® (CYD-TDV) is the only vaccine authorised for use in the EU. The vaccine should only be given to people between 9 and 45 years old, who live in areas where

dengue is endemic and who have been infected with DENV before [2]. However, due to an observed increased risk of hospitalisation and severe dengue in seronegative vaccinees after the first dose compared with unvaccinated seronegative individuals, further safety studies are required [3,4]. Treatment of the disease is symptomatic and supportive. General information on dengue is available in the ECDC dengue fever factsheet[2] and detailed information on laboratory diagnostics is presented in the previous rapid risk assessment 'Local transmission of dengue fever in France and Spain – 2018' [5]. A complete overview of DENV diagnostic capacity in the EU/EEA can be found in the EVD-LabNet directory [6].

Mosquito vectors

Aedes aegypti is considered the main primary vector for dengue virus transmission. *Aedes aegypti* is not present in the continental EU/EEA, but the species is established around the Black Sea and in several EU Overseas Countries and Territories and Outermost Regions, such as Madeira and a number of islands in the Caribbean region (e.g. Martinique and Sint Maarten). It is worth noting that this species was introduced to Fuerteventura, Canary Islands in 2017 and declared eliminated in 2019 [7]. For more information on *Ae. aegypti*, see the ECDC factsheet for experts[3] [8] and the map on the current distribution of *Ae. Aegypti* in the EU/EEA (dated January 2019) [9].

Aedes albopictus is competent for all four dengue virus serotypes, but it is considered less competent for DENV transmission than *Ae. aegypti* [10]. From a historical epidemiological perspective, there are a limited number of dengue outbreaks described that were exclusively sustained by *Ae. albopictus*. Therefore, this mosquito species is considered as a less efficient dengue virus epidemic vector than *Ae. aegypti* [10]. Nonetheless, *Ae. albopictus* can act as the driver of an epidemic in areas where *Ae. aegypti* is absent or its population is too low to be considered as having an epidemiological importance [11]. For instance, outbreaks likely to have been driven by *Ae. albopictus* in the past have occurred on the main islands of Japan, Hawaii, Réunion and in the city of Guangzhou, Guangdong Province, China [11-15]. Since the 1990s, *Ae. albopictus* has become increasingly present in the EU/EEA. It is currently established in the southern and central parts of the EU (Annex 1) where the mosquito is active in the summer and early autumn [43]. The presence of *Ae. albopictus* in continental Europe has led to sporadic events of DENV transmission (Annex 2).

Event background information

Between 2010 and 2017, seasonal limited transmission of DENV was reported on Réunion, with the highest number of cases observed in 2016.

During that period, the reported serotypes were DENV-1, DENV-2 and DENV-3 (Annex 3) [16].

In 2018, Réunion faced a large outbreak of DENV-2, with 6 779 cases reported (data ARS Réunion, [17]). The case numbers peaked in April–May (week 18). Despite strenuous vector control efforts in the aftermath of the 2018 outbreak, sustained low-grade transmission was reported between August and December 2018.

With the return of suitable environmental conditions on the island at the beginning of 2019, the transmission rate rapidly increased and the outbreak has spread across the island. Since the beginning of 2019 and as of 12 June 2019, there have been over 15 000 autochthonous confirmed cases and 42 000 suspected cases of dengue in Réunion [18]. Among these cases, 514 were hospitalised and nine died, with five of the deaths directly linked to dengue. Cases reported in 2019 are widespread throughout the island with the following municipalities being the most affected: Saint-Louis, Saint-Pierre, L'Étang-Salé, Saint-Joseph, Le Tampon, L'Entre-Deux and Saint-Philippe in the south. Other municipalities such as Saint-Paul and La Possession in the west or Saint-Denis (north) and Saint-André (east) also reported sustained transmission.

Weekly cases numbers have decreased, especially in the 'historical' foci of the south, for the past five weeks, but dengue circulation remains active in all municipalities of the island.

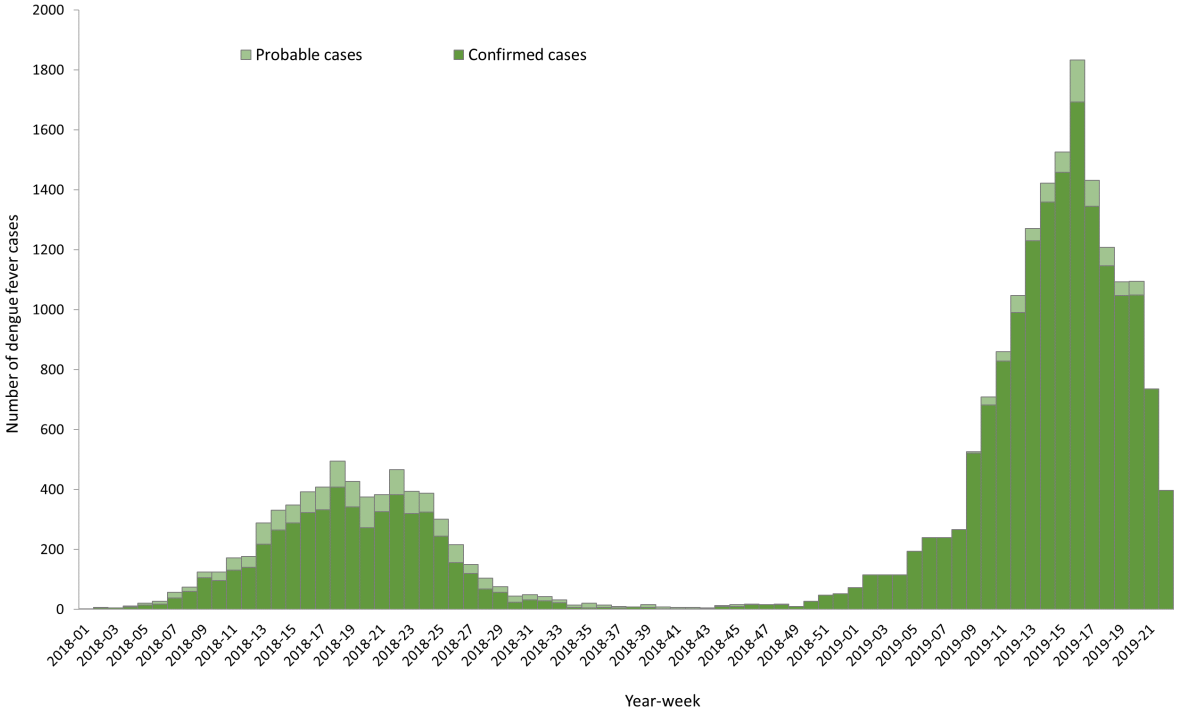
Phylogenetic analyses conducted on two samples from locally-acquired cases in Réunion (one from Saint-Gilles municipality in the west and from Saint-Denis municipality in the north) collected between March and May 2018 highlight a circulation of DENV-2 Cosmopolitan lineage 1 virus. The results indicate epidemic strains clustered with sequences from Seychelles (2017), suggesting a co-circulation in the Indian Ocean islands potentially subsequent to a previous introduction from Asia [19].

Since 2017, the most commonly reported serotype was DENV-2, with DENV-1 and DENV-4 being occasionally identified among imported cases (Annex 2). However, as of 19 May 2019, 19 locally acquired cases of DENV-1 have been reported [20].

[2] Available at: http://ecdc.europa.eu/en/dengue-fever/facts/factsheet

[3] Available at: http://ecdc.europa.eu/en/disease-vectors/facts/mosquito-factsheets/aedes-aegypti

Figure 1. Number of dengue autochthonous cases by week of onset between week 1–2018 and week 21–2019 in Réunion



Source: Adapted from 'Dengue à la Réunion: baisse épidémique. Point épidémiologique au 2 juin 2019', Cire océan Indien. Santé publique France (2019) [18].

In July 2018, local authorities raised the level of emergency risk of the civil security plan to level 4, corresponding to a medium-level epidemic [21]. This risk level is still valid to date. Local authorities have implemented a number of actions on Réunion, including strengthened vector control measures, enhanced surveillance of cases, strengthening of SoHO safety measures and hospital capacity, social mobilisation, targeted risk communication, including awareness campaigns at schools and door-to-door information on removing mosquito breeding sites [16].

On Réunion, according to the French National Agency for Medicines and Health Products Safety (ANSM), all blood donations are tested with nucleic acid testing (NAT). Cells, tissues and organs are not collected if the donor is a suspected or confirmed dengue case unless dengue NAT is performed on a living donor. For organ donation, the decision is based on an individual benefit/risk assessment for the recipient. In other French departments, blood, cell, tissue and organ donation is deferred for a period of 28 days in travellers returning from Réunion. Preventive measures remain in place in 2019.

ECDC threat assessment for the EU

The ongoing dengue epidemic in Réunion has an unusual magnitude compared with previous dengue outbreaks reported since 2004. The high number of cases reported in recent weeks indicates that the outbreak is ongoing, with widespread transmission throughout the island. This second wave follows the report of sporadic DENV-2 cases during the inter-epidemic period 2018–2019, supporting low-level transmission during the last austral winter. As expected, after a peak during week 16–2019, with the start of the southern-hemisphere winter, a decline in the weekly number of cases is now being seen.

Introduction and further transmission in continental EU/EEA

The likelihood of DENV being introduced to the continental EU/EEA is linked to the number of viraemic travellers returning from areas with active DENV circulation, while the likelihood of ongoing transmission is linked to the presence of an active and abundant competent vector population in the areas to which an infected traveller returns.

According to the International Air Transport Association (IATA) data, between 2011 and 2017, there were, on average, 500 000 travellers returning from Réunion to the EU/EEA every year. In 2017, the number reached 580 000, 98% of whom arrived in mainland France. The most popular travel months are December–January and July–August, when about 50 000 people are travelling monthly.

In 2017, 2 026 imported dengue travel-associated cases returning from areas with DENV circulation were reported through the European Surveillance System (TESSy). The probable place of infection was known for 1 132 cases [22]. Germany and the United Kingdom reported the highest number of cases among returning travellers with 635 and 465 cases, respectively. France, Italy and Spain, three EU countries where *Ae. albopictus* is established in several areas, reported 264, 95 and 128 imported cases, respectively. The most frequently reported probable countries of infection were Asian countries: India (22%), Thailand (19.7%) and Sri Lanka (11.3%).

It is expected that the virus will be introduced into receptive areas of the EU through travel-associated cases returning both from Réunion and other areas where there is ongoing circulation of the virus (Annex 4). In 2019, as of 7 June 2019, 109 imported dengue cases had been reported from areas in continental France where *Ae. albopictus* is established. Forty percent of these cases were imported from Réunion [23]. In comparison, France reported 33 imported dengue cases from Réunion in 2018 through TESSy; these cases were reported between April and September 2018, with a peak in June mirroring the observed epidemic pattern on the island. In 2017, France reported only four imported dengue cases from Réunion. Due to the higher number of dengue cases in Réunion in 2019 compared to 2018 and the peak in travel volume during July and August every year, a higher number of cases is expected to be imported into continental EU, principally in France.

Transmission of dengue virus depends, among other factors, on the presence of active vectors and suitable temperatures. Laboratory experiments with *Ae. albopictus* from Shanghai with DENV-2 suggest that transmission is unlikely below 18°C [24]. In the southern part of continental EU in areas with established populations of *Ae. albopictus*, during summer and early autumn, environmental conditions can support a vector abundance sufficient for autochthonous transmission of dengue virus, which could potentially lead to a local outbreak. This was exemplified by the autochthonous cases of dengue reported in Croatia, France and Spain between 2010 and 2018 (Annex 2). All reported events of dengue transmission corresponded to sporadic cases or limited clusters of cases and always occurred during the summer season.

While dengue outbreaks occur regularly in many tropical countries, most outbreaks are sustained by the *Ae. aegypti* mosquito, its primary vector, which is not established in the continental EU. To date, there is no evidence of local genetic adaptation of dengue virus to *Ae. albopictus* in Réunion that could lead to enhanced virus transmission to or by the *Ae. albopictus* mosquito population in Réunion and/or continental EU. However, the large outbreak observed in Réunion demonstrates a marked vectorial capacity of the current circulating DENV-2 in the *Ae. albopictus* population, which could indicate an increased likelihood of local transmission in areas with established *Ae. albopictus*.

Despite the overall number of imported dengue travel-associated cases every year, the probability of local transmission within continental EU remains low, as illustrated by the limited number of autochthonous transmission events reported until now. The risk of further spread would be mitigated by early case detection of travel-associated cases, notably from Réunion, in areas with an established population of *Ae. albopictus* and by timely implementation of response measures.

While the outbreak of dengue on Réunion is unprecedented and it is likely that there will be associated imported cases to continental EU, this outbreak should be put in a global context and the risk for the EU/EEA should be assessed at the global level. In this context, there are currently large outbreaks observed in other parts of the world and, in particular, in several Asian and American countries (Annex 4). It is therefore likely that DENV travel-associated cases will be reported throughout the summer coming from these locations.

Outside the continental EU, the EU Overseas Countries and Territories and Outermost Regions, with established populations of *Ae. aegypti* and *Ae. albopictus,* remain vulnerable to dengue epidemics, as demonstrated by recurrent dengue outbreaks in the Caribbean region, the outbreak in Madeira in 2012 and the ongoing DENV circulation in Mayotte [25, 26].

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 [27–32] as well as through kidney [33,34], liver [34–36], heart [34] and bone marrow [37,38] 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 the disease in many endemic countries around the world [28]. Further data are needed to assess the risk of DENV transmission through SoHO more precisely.

To prevent transfusion-transmitted DENV infection, current EU guidance is that blood donors should be deferred for 120 days after full recovery from clinical dengue [39]. In affected areas, the guidance is that donors with flu-like symptoms should be deferred for 28 days after the resolution of symptoms [39]. Alternatively, donations should be quarantined for 72 hours and released once information becomes available on the absence of symptoms in the donor.

Donation screening using NAT is the main tool to reduce the risk of transmission in affected areas when deferrals may potentially affect supply. For plasma and platelet 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 [39].

Donors of organs, cells and tissues living in or coming from dengue-affected areas should be tested for the presence of viral RNA using NAT [40,41]. Organs from viraemic donors should not be used without consulting a transplant infectious disease expert [40].

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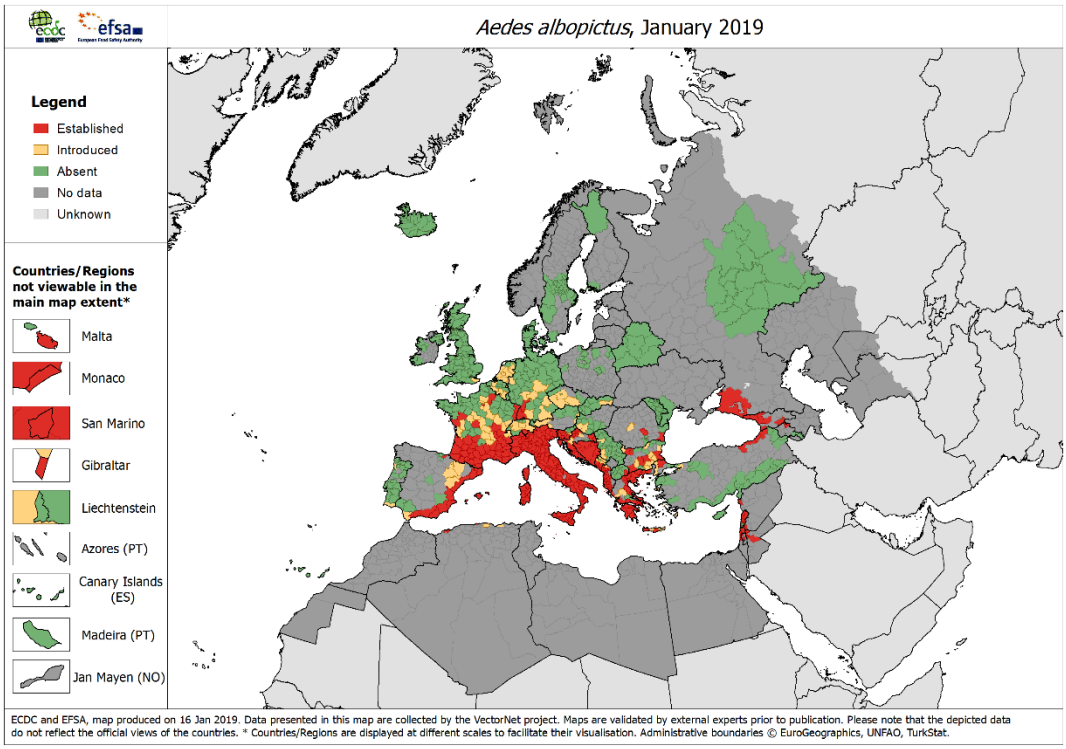
Annex 1. Distribution of *Aedes albopictus* in Europe, January 2019



Source: *Aedes albopictus*, current known distribution: January 2019 [42].

Annex 2. Autochthonous transmission of dengue in continental Europe, 2010–2018

Year	Country, region, municipalities	Number of cases	Period	Origin of primary case	DENV serotype	Reference
2010	Croatia, Korčula Island and the Pelješac peninsula	Three, plus one by serology	August–17 October	Unknown	DENV-1	[43-45]
2010	France, Alpes-Maritimes department, Nice (city)	Two	End August–September	Unknown	DENV-1	[46]
2013	France, Bouches du Rhône department, in the vicinity of Aix-en-Provence.	One	October	Guadeloupe	Most probably DENV-2	[47]
2014	France, Var department, Toulon.	One	Early August	Unknown	DENV-1	[48]
2014	France, Var department, Toulon	One	Early September	Unknown	DENV-2	[48]
2014	France, Bouches du Rhône department, Aubagne.	Two	Late August–September	Unknown	DENV-2	[48]
2015	France, Gard department, Nîmes.	Eight	8 August–11 September	Possibly French Polynesia	DENV-1	[49, 50]
2018	France, Alpes Maritimes department, Saint Laurent du Var	Five	3 September–3 October	Unknown	DENV-2	[5]
2018	France, Hérault department, Montpellier	One	27 September	Unknown	DENV-1	[5]
2018	Spain, Murcia Region and possibly Province of Cádiz	Five	17 August – late September	Unknown	Not available	[5, 51]

DENV-1 and DENV-2: Dengue virus serotype 1 and 2, respectively.

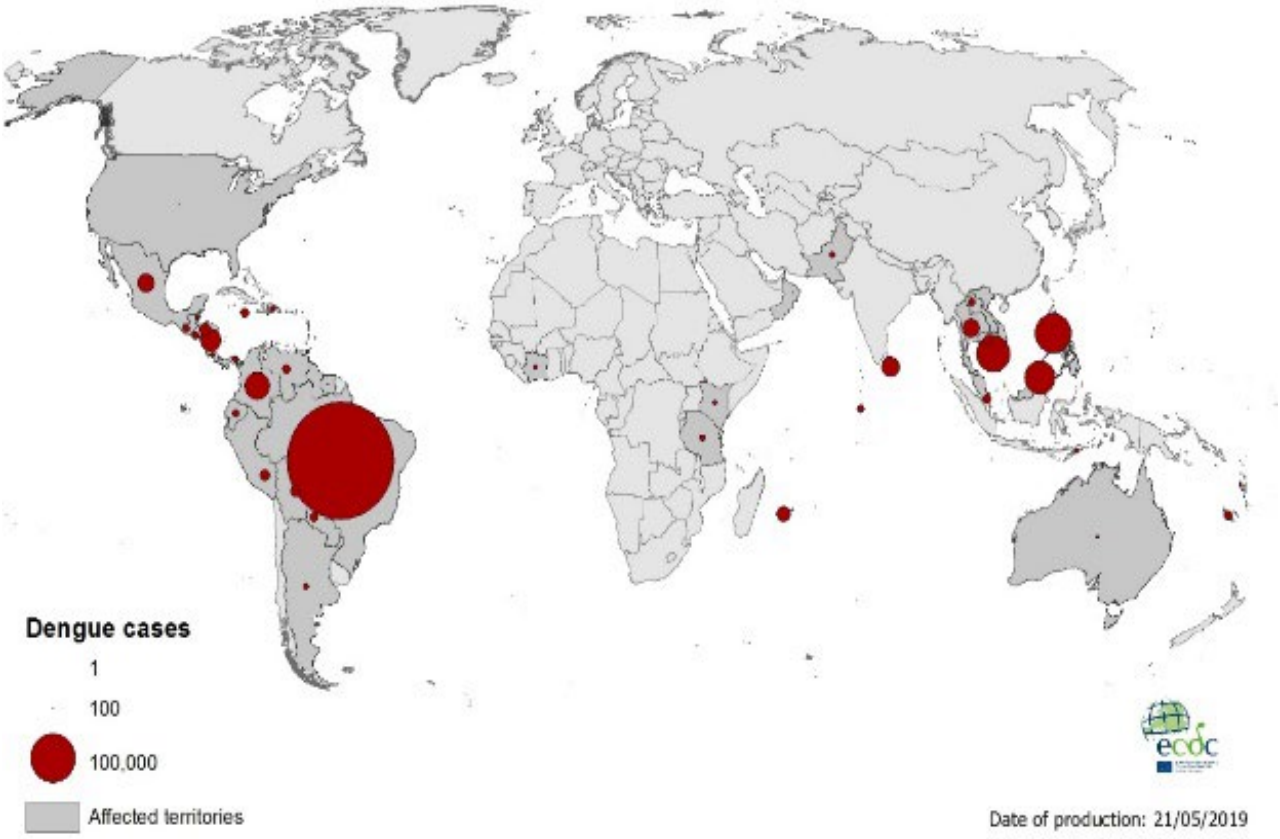
Annex 3. Dengue transmission events with more than 10 cases in Réunion between 2004 and 2019

Years	Start month	End month	Number of cases	Prevalent dengue serotype	Source
2004	April	June	228	1	[52]
2006–2007	December	October	1 in 2006, 27 in 2007	1	[53]
2008	January	July	33	1	[53]
2010	March	May	18	3	[54]
2012	February	July	31	1 and 3	[55]
2013	February	July	21	1 and 3	[56, 57]
2014	March	August	29	1	[58]
2015–2016	October	July	231	1,2 and 3	[59]
2017	January	December	97	2	Data ARS Réunion, [60]
2018	January	December	6 779	2	[17]
2019	January	ongoing	15 523	1 and 2	Data ARS Réunion, [18]

In 2011, only two confirmed sporadic cases were reported: one in May and one in September [61] .

Annex 4. World distribution of the cumulative number of dengue cases reported in 2019 (as of 21 May 2019)

The map below presents the cumulative number of cases per country according to epidemic intelligence activities at ECDC, as of 21 May 2019. Dengue circulation is mainly reported in south-east Asia and within the intertropical range in Americas.



Annex 5. Cumulative number of reported dengue cases by WHO region/country, 1 Jan 2019 –18 May 2019

More detailed information on dengue situation in the world is available in the section on monitoring global outbreaks of dengue (Communicable Disease Threats Report Week 20, 12–18 May 2019), as summarised in the table below [62]. The number of cases presented represents cases detected through epidemic intelligence activities.

WHO regions and countries	Cumulative cases	Date of most recent report
AFRO	**2 962**	
Cote d'Ivoire	606	08/05/19
Kenya	946	08/04/19
Mauritius	122	03/05/19
United Republic of Tanzania	1 288	28/04/19
AMRO/PAHO	**691 512**	
Antigua and Barbuda	7	26/01/19
Argentina	1 154	20/04/19
Aruba	59	23/03/19
Barbados	2	23/03/19
Belize	647	20/04/19
Bermuda	1	23/03/19
Bolivia	4 560	20/04/19
Brazil	586 569	20/04/19
British Virgin Islands	7	23/03/19
Cayman Islands	17	26/01/19
Colombia	32 267	27/04/19
Costa Rica	668	27/04/19
Dominica	11	09/02/19
Dominican Republic	1 391	06/04/19
Ecuador	1 910	20/04/19
El Salvador	2 602	27/04/19
Grenada	46	06/04/19
Guadeloupe	192	16/02/19
Guatemala	2 259	20/04/19
Guyana	4	26/01/19
Honduras	6 300	20/04/19
Jamaica	3 229	13/04/19
Martinique	93	09/02/19
Mexico	12 900	27/04/19
Nicaragua	21 593	27/04/19
Panama	1 293	20/04/19
Paraguay	3 058	27/04/19
Peru	4 772	20/04/19
Puerto Rico	1	27/04/19
Saint Lucia	12	13/04/19
Saint Martin	20	16/02/19
Saint Vincent and the Grenadines	5	23/03/19
Suriname	30	04/05/19
Trinidad and Tobago	106	09/02/19
United States of America	91	27/04/19
Venezuela	3 636	27/04/19
EMRO	**1 254**	
Oman	48	12/01/19
Pakistan	1 206	28/04/19
EURO	**14 000**	
Réunion	14 000	01/06/19
SEARO	**32 644**	
Maldives	2 102	14/05/19
Sri Lanka	16 681	13/05/19
Thailand	13 329	13/05/19
Timor Leste	532	10/04/19
WPRO	**186 858**	
Australia	429	30/04/19
Cambodia	5 045	27/04/19
Cook Islands	40	01/05/19
French Polynesia	260	05/05/19
Lao People's Democratic Republic	2 405	27/04/19
Malaysia	47 147	13/05/19
New Caledonia	3 081	06/05/19
Philippines	67 106	20/04/19
Singapore	3 236	11/05/19
Taiwan	13	05/01/19
Vanuatu	216	30/04/19
Vietnam	57 880	04/05/19