RAPID RISK ASSESSMENT

Local transmission of dengue fever in France and Spain – 2018

22 October 2018

Main conclusions and options for response

Main conclusions

In early October, nine cases of autochthonous dengue were confirmed in the EU, three in Spain and six in France, in three separate outbreaks. These are the first autochthonous dengue cases in continental EU/EEA Member States that were reported this year [1]. Prior to these cases, no autochthonous dengue cases had been reported in continental EU/EEA Member States since 2017. Epidemiological investigations are ongoing.

There is no epidemiological link between the two outbreaks in France (five cases in Saint Laurent du Var, one case in Montpellier), and it is uncertain whether the cases in Spain were infected in the region of Murcia or in the Province of Cádiz. The virus was likely to have been introduced into these areas through viraemic travellers returning from endemic areas.

Sporadic autochthonous cases, or small clusters, of dengue fever occasionally occur in Europe after the introduction of Dengue virus (DENV) by viraemic travellers into areas where *Aedes albopictus* mosquitoes have become established and during the season when *Ae. albopictus* are active and temperatures are favourable. Locally acquired dengue cases were documented in southern France in 2010, 2013, 2014 and 2015. In Spain, this is the first recorded cluster of locally acquired dengue cases, which was not unexpected since *Ae. albopictus* has been present in the country since 2004.

Detection of further cases in the affected regions and elsewhere is possible. *Ae. albopictus* is normally active in the area of Saint Laurent du Var until the beginning of November, while in Montpellier the active period for *Ae. albopictus* can even last until early December, as reported for December 2014. The prolonged active period was possibly related to flooding in the area.

Ae. albopictus is active in several provinces in Spain. In previous seasons, *Ae. albopictus* was found to be active until the beginning of December [2-5]. It may, to a limited extent, also be active during winter, but this activity is unlikely to be sufficient to sustain transmission.

The risk that visitors to the affected areas may become infected and introduce the virus to their country of residence cannot be excluded [6]. However, historically, dengue outbreaks in Europe have had a maximum of seven reported autochthonous cases and always occurred during the season of high vector activity. Therefore, the likelihood of onward local transmission and of introduction of the virus from France and Spain into other receptive areas in the EU/EEA with subsequent sustained local transmission is very low.

Suggested citation: European Centre for Disease Prevention and Control. Local transmission of dengue fever in France and Spain – 2018 — 22 October 2018. Stockholm: ECDC; 2018.

Options for response

Early detection of imported cases is key to prevent onward transmission through the introduction of dengue virus by a viraemic traveller into an area where *Ae. albopictus* is established. Awareness among clinicians and information for travellers returning from areas with dengue transmission, combined with appropriate laboratory detection capacity, are essential during high mosquito activity season in areas where *Ae. albopictus* is established. Enhanced surveillance and active case finding should also be considered.

The detection of an autochthonous case should trigger epidemiological and entomological investigations to assess the size of the transmission area and the potential of onward transmission; it should also guide vector control measures.

In addition, personal protective measures against mosquito bites are recommended in affected areas to further reduce mosquito-borne transmission of dengue virus. Indoor and outdoor personal protective measures to reduce 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, especially during the daytime when *Ae. albopictus* mosquitoes are most active; and sleeping and resting in screened or air-conditioned rooms and using mosquito bed nets at night and during the day.

Travellers returning from areas where dengue fever transmission occurs should be advised to seek medical care if they develop symptoms consistent with dengue fever, in particular if they return to areas where *Ae. albopictus* is established, in order to reduce the risk of the virus being introduced into the local mosquito population and prevent further local transmission.

Preparedness regarding dengue fever in the EU requires the capacity to detect cases early in areas with the presence of the competent vectors. This can be achieved by:

- strengthened surveillance systems (including clinician awareness, laboratory capacity and capability for accurate confirmation, and rapid notification of cases);
- regular reviews of contingency plans for mosquito-borne outbreaks;
- education and collaboration of the general public on how to control mosquito breeding sites; and
- strengthened vector surveillance systems and rapid implementation of vector control measures following each case.

Source and date of request

ECDC internal decision 5 October 2018 and revision 10 October 2018.

Public health issue

In the context of locally acquired cases of dengue fever in southern France and Spain, what is the risk of onward vector-borne transmission locally and in other areas of EU/EEA?

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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 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 *Aedes aegypti* but other mosquitoes, including *Aedes albopictus*, have been implicated in virus transmission. The virus is not transmitted directly from human to human, except in the case of mother to unborn child, 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 [7].

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 due to extensive cross-reactivity between the four serotypes and other flaviviruses (including Zika virus, yellow fever virus, 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 from 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 [8,9]. 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 (gold standard serologic method). All countries with *Ae. albopictus* presence have DENV diagnostic capacity. A complete overview of DENV diagnostic capacity in the EU/EEA can be found in the EVD-LabNet directory [10].

Patients with severe dengue can recover without sequelae if diagnosed early and treated appropriately. There is currently no recommended vaccine available against dengue fever in Europe, and treatment of the disease is symptomatic and supportive. More information on dengue fever is available in the ECDC dengue fever factsheet [7].

Mosquito vectors

Aedes aegypti is the main primary vector for dengue virus transmission. *Aedes aegypti* has not established itself in the continental EU, but the species has been introduced to the Netherlands and has become established around the Black Sea and in several EU Overseas Counties and Territories such as Madeira and in the Caribbean region. The species was also introduced to Fuerteventura, Canary Islands in December 2017, but after control measures were implemented no further detections were reported. For more information on *Ae. aegypti*, see the ECDC factsheet for experts [68] and the map on the current distribution of *Ae. aegypti* in the EU/EEA [69].

Aedes albopictus is a competent vector for all four dengue virus serotypes, but a less competent vector for DENV than *Ae. aegypti* [11]. From an historical epidemiological perspective, there are indeed only a limited number of dengue outbreaks described that were sustained by *Ae. albopictus*. [11]. However, *Ae. albopictus* might act as a driver of an epidemic in areas where *Ae. aegypti* is absent or its population is too low to have epidemiological importance [12]. For instance, outbreaks likely to have been driven by *Ae. albopictus* in the past include outbreaks in the main islands of Japan; in Hawaii; in the city of Guangzhou, Guangdong Province, China, in a location where *Ae. aegypti* is reported to be absent [12-16], and in Réunion (2004 to 2018) [17].

Since the 1990s, *Ae. albopictus* has become increasingly present in the EU. It is currently established mainly in the southern part of the EU (see Annex 1, Figure 1 for a detailed map) where the vector is active in the summer and early autumn. It plays a role as vector in sporadic events of local transmission of dengue virus and chikungunya virus in the southern EU (See Annex 2).

Event background information

France

Provence-Alpes-Côte d'Azur

On 4 October 2018, the laboratory of virology of Montpellier University Hospital and the French National Reference Laboratory for arboviruses in Marseille confirmed a case of dengue type 2 in Saint Laurent du Var, Alpes Maritimes

department, Provence-Alpes-Côte d'Azur region, in southern France. The case, who had become symptomatic on 21 September, is a resident of Saint Laurent du Var and had no travel history outside the region in the 15 days prior to symptom onset and was assumed to have become infected locally. This was the first autochthonous case of dengue identified in metropolitan France in 2018. Door-to-door case finding conducted on 8–9 October 2018 lead to the diagnosis of four additional cases residing within a 50m-radius from the home of the index case. Onset of symptoms of the five cases detected in Saint-Laurent du Var ranged from 3 September to 3 October.

Occitanie

On 10 October 2018, the French National Reference Laboratory for arboviruses confirmed a case of dengue type 1 in Montpellier, Hérault department, Occitanie region, in southern France. The case, a resident of Le Clapiers, a suburb of the city of Montpellier, developed symptoms on 27 September 2018. The patient had no travel history outside the region in the 15 days prior to symptom onset.

Montpellier is 270 km west of Saint Laurent du Var, where the cases described above occurred. There is no link between the cases in Montpellier (dengue serotype 2) and the ones in Saint Laurent du Var.

Public health authorities implemented the following actions in accordance with national recommendations:

- Epidemiological and entomological investigations.
- Vector control activities in the neighbourhood of the residence of the cases, including removal of mosquito breeding sites in public areas, and chemical treatments.
- Active case finding, including door-to-door investigations in the areas of Saint Laurent du Var and Le Clapiers.
- Raising awareness of healthcare workers and laboratories in the areas.
- Safety measures on substances of human origin, e.g. blood donations.
- Public communication and social mobilisation on mosquito bite prevention and breeding site removal in private areas.

Spain

On 4 October 2018, the Spanish National Reference Laboratory for Arboviruses confirmed two autochthonous dengue cases in Spain [18]. A third case was confirmed on 16 October 2018. All cases belong to the same family and had onset of symptoms in the second half of August (19, 23 and 27 August). During the incubation period, the cases were travelling in a municipality in Murcia Region (4–9 August) and in several municipalities in Cádiz, Andalucía (10–16 August). Considering the incubation period of the disease (3–14 days), the most probable place of infection, which is also compatible with the date of onset of symptoms of the three cases, is the province of Cádiz, although the place of infection cannot be determined with certainty.

All cases fully recovered; they had no recent travel history to dengue-affected areas. This is the first documented episode of autochthonous dengue transmission in Spain.

Public health authorities have implemented, or will start implementing imminently, the following actions (in accordance with national recommendations):

- Epidemiological and entomological investigations.
- Active case finding in the probable places of transmission.
- Raising awareness of healthcare workers and laboratories in the area.
- Safety measures on substances of human origin, e.g. blood donations.
- Public communication, including a press release.

ECDC risk assessment

Introduction of the virus

The virus was probably introduced into France and Spain through viraemic travellers returning from an endemic area. Several countries reported a considerable increase in dengue cases in 2018, especially in South America (Annex 1, Figure 2). Also, Réunion, an outermost region of France in the Indian Ocean, has reported over 6 000 cases of dengue type 2 to date this year. 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

Sporadic autochthonous cases, or small clusters, of dengue in the area are not unexpected, as *Ae. albopictus* mosquitos are known to have become established in Provence-Alpes-Côte d'Azur (2004) and Occitanie (2011) [70]. Locally acquired dengue cases in the region were documented in 2010, 2013, 2014 and 2015 (see Annex 2).

Saint Laurent du Var borders Nice Côte d'Azur Airport. It also has a port and a railway station. The Nice Côte d'Azur airport had 6 587 638 departing passengers in 2017, 30.2% of whom lived on the Côte d'Azur. Nice Airport does not offer direct flights to Réunion and other dengue-affected areas, which reduces the probability that the virus was imported through an infected mosquito.

In 2017, Saint Laurent du Var recorded 25 292 stays from visitors arriving by plane (17% of the total in the zone Metropole Littoral Est), 11 795 of whom were of foreign origin. In September 2017, the zone Metropole Littoral Est recorded a total of 21 709 stays in hotels and residences, 44.3% were of visitors of foreign origin (17.8% from the UK, 11.3% from the USA, 10.8% from Spain, 10.0% from Germany and 8.8% Italy and Malta). In October 2017, the zone recorded 11 023 stays in hotels and residences, 14.8% were from visitors from Italy and Malta, 12.2% from the USA, 12% from Germany, 11.2% from the UK, and 10.9% from Spain [19].

Montpellier is connected to the railway network. Montpellier's Méditerranée Airport, situated 9 km southeast of the city centre recorded 1 849 410 departing passengers in 2017, of whom 661 456 had an international destination [20]. It does not offer direct flights to dengue-affected areas. In September 2018, it recorded 170 982 departing passengers, of whom 67 261 had an international destination [21]. In 2017, the city of Montpellier recorded 1 037 992 overnight stays (approximately 90 000 in September and 85 000 in October) from visitors, of whom 361 585 were of foreign origin. The five countries from which most guests originated were Spain, the UK, USA, Germany and Belgium [22].

Between 1 May and 12 October 2018, 151 imported dengue cases were notified in *Ae. albopictus*-active areas in France (26 in Occitanie and 47 in Provence-Alpes-Côte d'Azur); 24 of the confirmed cases had just returned from a journey to Réunion [23].

Spain

The cases in Spain were the first recorded locally transmitted cases of dengue in Spain. Small clusters like this one are not unexpected in areas where *Ae. albopictus* mosquitoes are established. *Ae. albopictus* mosquitoes were first detected in Spain in 2004 in Catalonia and have since been spreading along the coast. They have been known to be present in the Murcia region since 2011 [2]. The mosquito has been detected in some municipalities of Cádiz since 2015. However, the mosquito has not yet been detected in the municipalities of Cádiz where the cases stayed during their probable time of infection, despite active surveillance in 2017 [3] and active searches in October after the cases were diagnosed. The Spanish authorities are currently conducting further entomological investigations in Murcia and Cádiz.

To date in 2018, a total of 2 273 478 stays from Spanish and non-Spanish residents were reported in Murcia region [24]. Most non-Spanish visitors with an overnight stay in Murcia region are from the UK (27%), followed by France (9%) and Germany (7%) [25]. In the Province of Cádiz, 60 144 overnight stays were recorded in June 2018 [26].

Over the 2015–2017 period, Spain has reported 557 imported cases of dengue: 168 in 2015, 261 in 2016, and 128 in 2017; 9% of these cases were imported from Thailand and 8% from Paraguay. In 2018, only 18 cases have been reported so far, although the number of cases may be underestimated due to delays in notification.

Further transmission locally and in other areas of EU/EEA

Transmission of dengue virus depends, among other factors, on the presence of active vectors and temperature. Laboratory experiments with *Ae. albopictus* from Shanghai and with dengue 2 virus suggest that transmission is unlikely below 18 °C [27]. Throughout Europe, in areas where *Ae. albopictus* mosquitoes have established themselves and during the season when they are active and temperatures are favourable, autochthonous cases of dengue may occur after the introduction of DENV by viraemic travellers.

France

Detection of further autochthonous cases in the region is possible, as *Ae. albopictus* is normally active in the area of Saint Laurent du Var until the beginning of November [28,29][*]. Further autochthonous cases are also possible in Montpellier based on observations from Italy at this latitude (42–46 °N) [30,31]. However, in 2014, probably due to unusually heavy rainfall (an 'épisode cévenol'), the *Ae. albopictus*-active period in Montpellier lasted until early December [32], although the last associated chikungunya case reported onset of symptoms on 22 October 2014 [33]. Of note, southern France is currently experiencing heavy rainfall events and warm temperatures.

There is thus some risk that visitors from areas where *Ae. albopictus* populations are present may become infected and introduce the virus to their country of residence. However, historically, dengue outbreaks in France were always limited, with a maximum of seven reported cases; cases always occurred during the season of high vector activity (see Annex 2). Therefore, the likelihood of local onward transmission and introduction of the virus from France to other receptive areas in the EU/EEA with subsequent local transmission is considered to be very low.

[*] Based on *Ae. albopictus* eggs laid in ovitraps in the area during 2008–2011 [28,29]. Even though the number of eggs laid is low during October, data from Rome suggests that biting densities may be relatively high at the end of the season [30].

Spain

Detection of further autochthonous cases in the region is possible because *Ae. albopictus* has been found to be active until the beginning of December [2-5] in the region of Murcia and elsewhere. There is also evidence from Murcia that *Ae. albopictus* may, to a limited extent, be active during winter, but unlikely at sufficient levels to sustain transmission [34]. The potential seasonality of mosquito activity could be similar in the Province of Cádiz.

Similar to the risk in affected regions in France, there is some risk in Spain that visitors from areas where *Ae. albopictus* populations are present may become infected and introduce the virus in their country of residence. However, as dengue epidemics in Europe were always limited, with a maximum of seven reported cases and duration restricted to the season of high vector activity (see Annex 2), the likelihood of onward local transmission and of introduction of the virus from Spain to other receptive areas in the EU/EEA with subsequent local transmission is considered to be very low.

Dengue and safety of substances of human origin

DENV can be transmitted through substances of human origin (SoHO) donated by asymptomatic, viraemic donors. Transmission of DENV through transfusion of erythrocytes, platelets and plasma [35-40] as well as through kidney [41,42], liver [42-44], heart [42] and bone marrow [45,46] 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 factors include the hypothetical enhancement of DENV replication and DENV virulence in the salivary gland cells of the mosquito, the presence of protective antibodies among transfusion recipients or in co-transfused antibody-positive blood components [36]. 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 [47]. In affected areas, donors with flu-like symptoms should be deferred for 28 days after the resolution of symptoms [47]; 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 [47].

Donors of organs, cells and tissues living or coming from dengue-affected areas should be tested for the presence of viral RNA using NAT [48,49]. Organs from viraemic donors should not be used without consulting a transplant infectious disease expert [48].

On 8 October 2018, the French National Agency for Medicines and Health Products – Agence Nationale de Securité du Médicament (ANSM) – posted recommendations for dengue-affected areas on the RATC and RAB platforms (Rapid Alert for Tissues and Cells, Rapid Alert for Blood and Blood Components). ANSM recommends two measures: 1) reinforcing post-donation information in the department of Alpes-Maritimes; 2) discontinuation of blood collection by mobile units in cities affected by cases. ANSM also informed teams in charge of the removal of cells, tissues and organs that a human autochthonous dengue case has been detected in the department of Alpes-Maritimes.

In Spain, the measures taken by blood establishments include provisional deferral of blood collections and the recovery of red blood cells that have been obtained in the areas identified as being at risk.

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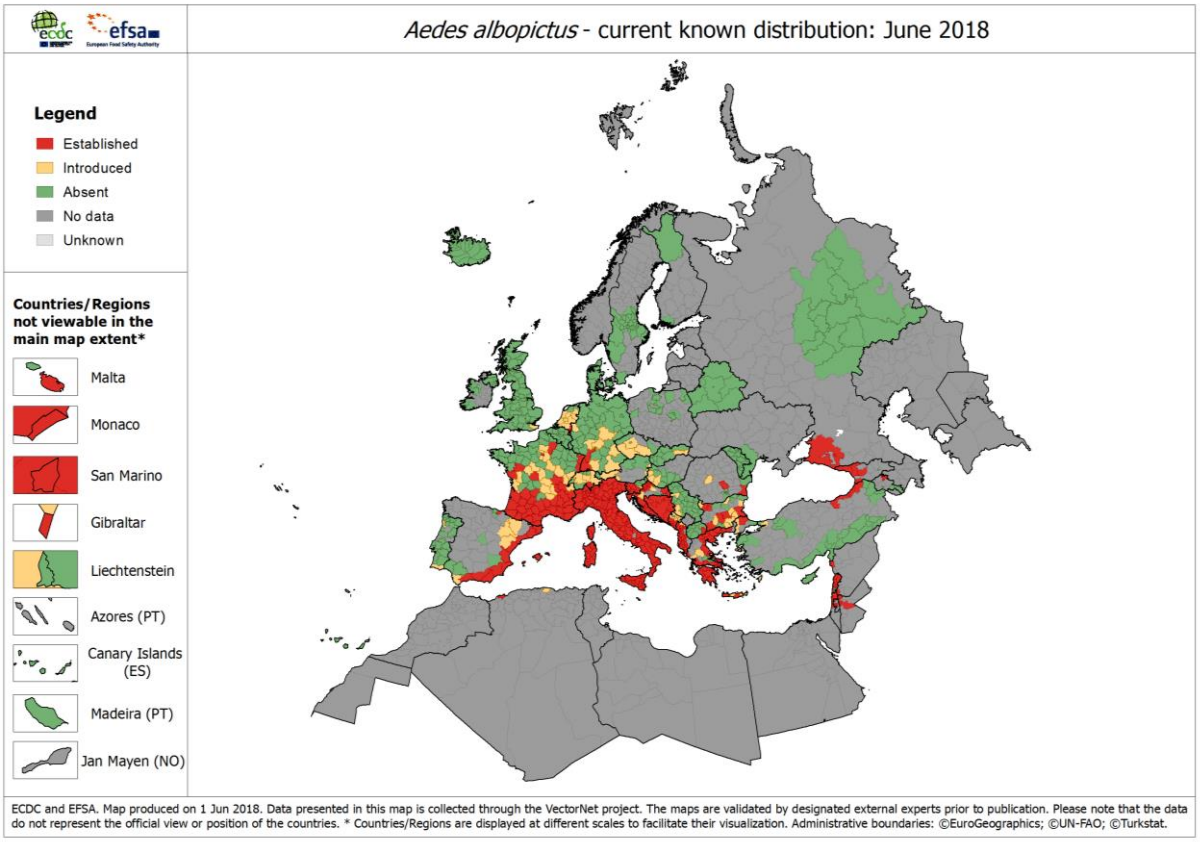
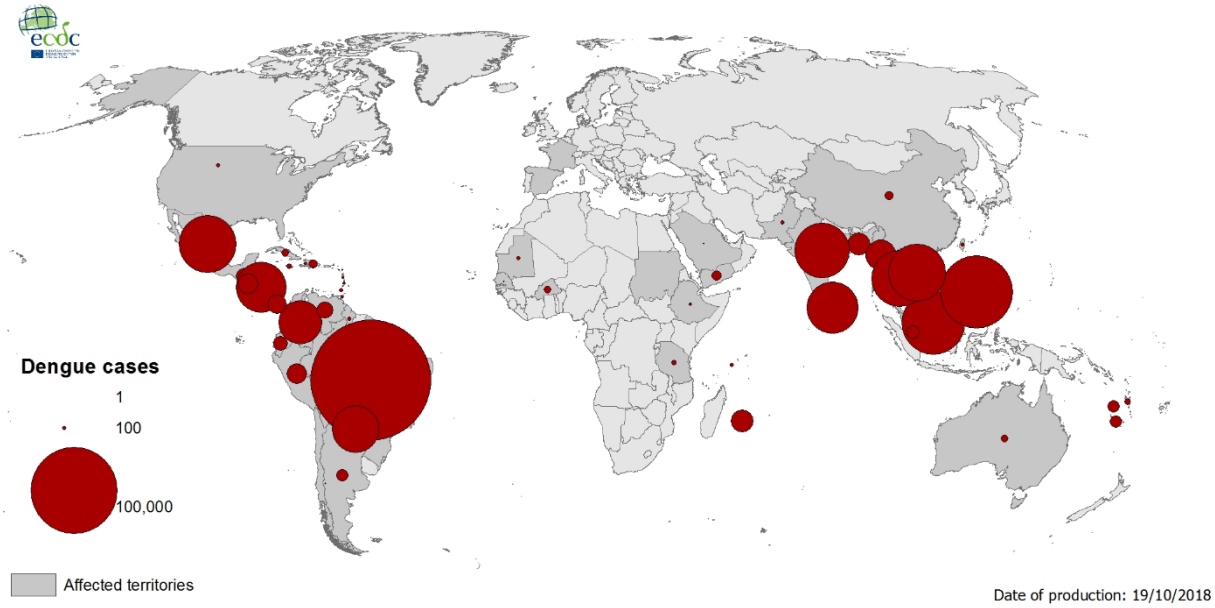
Annex 1

Figure 1. Distribution of *Aedes albopictus* in the EU/EEA and neighbouring countries, June 2018



Source: ECDC online maps: Aedes albopictus*, current known distribution: June 2018. Available from: https://ecdc.europa.eu/en/publications-data/aedes-albopictus-current-known-distribution-june-2018*

Figure 2. Geographical distribution of worldwide dengue cases detected in 2018, as of 19 October 2018



Source: ECDC

Annex 2

Table 1. Autochthonous transmission of dengue and chikungunya in Europe, 2007–2017

Year	Country, region, municipalities	Disease	Number of cases	Period	Origin of primary case	CHIKV genotype DENV serotype	Reference
2007	Italy, region of Emilia Romagna, main transmission areas in Castiglione di Cervia and Castiglione di Ravenna villages	CHIKV	≈ 330 suspected and confirmed	July–September (4 July–21 September)	India	ESCA E1-V226 CHIKV strain	[50,51]
2010	Croatia, Korčula Island and the Pelješac peninsula	DENV	Three, plus one by serology	August–17 October	Unknown	DEN-1	[6,52,53]
2010	France, Alpes-Maritimes department, Nice (city)	DENV	Two	End August–September	Unknown	DEN-1	[54]
2010	France, Var department, Fréjus	CHIKV	Two	September	India	ESCA E1-A226 CHIKV	[54,55]
2012	Portugal, Madeira island, Funchal city and surroundings.	DENV	≈ 2 100	September–January	Unknown*	DEN-1	[56,57]
2013	France, Bouches du Rhône department, in the vicinity of Aix-en-Provence.	DENV	One	October	Guadeloupe	Most probably DEN-2	[58]
2014	France, Hérault department, Montpellier	CHIKV	12	18 September–22 October	Cameroon	ESCA E1-V226 CHIKV	[33]
2014	France, Var department, Toulon.	DENV	One	Early August	Unknown	DEN-1	[59]
2014	France, Var department, Toulon	DENV	One	Early September	Unknown	DEN-2	[59]
2014	France, Bouches du Rhône department, Aubagne.	DENV	Two	Late August–September	Unknown	DEN-2	[59]
2015	France, Gard department, Nîmes.	DENV	Seven	8 August–11 September	Possibly French Polynesia	DEN-1	[60] [61]
2017	France, Var department, Le Cannet-les-Maures	CHIKV	17: 11 in Cannet-des-Maures and six in Taradeau	July–8 September (all cases occurred within 60 days from 11 July)	Central Africa	ECSA E1-A226V CHIKV strain (with mutation)	[62,63]
2017	Italy, Lazio region (Anzio, Latina and Rome) and Calabria region (Guardavalle marina)	CHIKV	270 confirmed and 219 probable. The latest date of onset was 5 November 2017 (Anzio, Lazio region)	August–November	In Lazio: Asia (India/Pakistan) In Calabria: Unknown	In Lazio: ECSA E1-A226 CHIKV strain (without mutation) In Calabria: Unknown	[64-66]

DENV: Dengue virus
DEN-1 and DEN-2: Dengue seroptype 1 and 2, respectively.
CHIKV: Chikungunya virus.
ESCA: East-South-Central Africa CHIKV lineage.
** Genetic analysis supports an importation from Venezuela [67]*