ECDC Threat Assessment

Dengue fever, autochthonous transmission, France

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SOURCE AND DATE OF REQUEST

EWRS message, France

PUBLIC HEALTH ISSUE

First (threat assessment 15 Sep) and second (update 20 Sep) reported autochthonous case of dengue fever in metropolitan France

CONSULTED EXPERTS

Institut de Veille Sanitaire (INVS), France: Marc Gastellu-Etchegorry, Dominique Dejour Salamanca, Guy La Ruche
Institut de Recherche pour le Développement (IRD): Didier Fontenille
Institut Pasteur, France: Philippe Despres
World Health Organisation (WHO)

DISEASE BACKGROUND INFORMATION

Dengue is a mosquito borne disease and is caused by viruses of the Flaviviridae family. The most common mosquito vector is *Aedes aegypti* but *Aedes albopictus* mosquitoes have also been implicated in disease transmission [1].

There are four serotypes of dengue viruses (DEN1-4). The incubation period ranges from 1 to 12 days, with an average of 3–7 days. Up to 40–80% of all dengue infections are mild or asymptomatic. The most commonly reported symptoms of dengue fever include sudden onset of high fever, severe headache and retro-orbital pain, myalgia, arthralgia, a maculo-papular rash and minor haemorrhage. Illness rarely lasts for more than ten days, but convalescence can be prolonged and debilitating. A proportion of dengue-infected individuals (usually under 5%) will go onto develop more severe clinical presentation (more frequently in children and adolescents). This condition can be fatal. Case fatality ratio varies between 0 and 5% of all reported cases. There is currently no vaccine available for dengue fever and treatment of disease is based on symptomatic care [1].

Laboratory diagnosis of dengue infection relies on identification of the virus, viral antigen of dengue and dengue-specific antibodies in the serum of an infected case [1-4]. Viral RNA can be detected using PCR up to day 5 to 7 after fever onset. The detection of non-

structural protein (NS1) of the dengue virus genome using ELISA is very specific for acute dengue infections up to day five after fever onset. Serological diagnosis can be performed by detection of dengue IgM antibodies in serum specimen from day 5 or 6 after fever onset, or detection of a four-fold rise of specific IgG antibody titre on a pair of sera (acute and convalescent specimens). In a secondary dengue infection, dengue IgM antibodies usually appear earlier from day 2–3 post fever onset and with a shorter duration. Serological diagnosis relies on an increase in dengue IgG titre. Serological cross-reactions between dengue viruses and closely related flaviviruses are frequently reported.

In Europe, the last dengue epidemic was reported between 1927 and 1928 in Greece with high mortality with *Aedes aegypti* as the vector. However, more recently, imported cases of dengue fever from travellers returning from dengue epidemic countries in Asia, Africa and Latin America are frequently reported [5-11]. In metropolitan France, the laboratory network surveillance system detected around 350-400 imported cases per year between 2006 and 2009 [12, 13]. Between 1 May and 10 September 2010, a total of 108 imported cases of dengue have been reported in the departments of South-East France where *Aedes albopictus* is established [14].

Since the 1970s, mainly through global trade of tyres, *Aedes albopictus* has become increasingly established in EU countries, and these include Italy, France, Slovenia, Spain, Greece and the Netherlands (though only in greenhouses) [15]. This mosquito species is also established in neighbouring countries such as Albania, Bosnia-Herzegovina, Croatia, Monaco, Montenegro, San Marino, Switzerland and the Vatican City [16, 17]. *Aedes aegypti* has also been recently identified in the Autonomous Region of Madeira, Portugal in 2004-2005 [18].

EVENT BACKGROUND INFORMATION

On 13 September, the Ministry of Health of France reported the first case of dengue fever from autochthonous transmission in metropolitan France. The case was detected through enhanced surveillance for dengue fever, which is implemented from May to November in the South-East of France where *Aedes albopictus* mosquito populations were detected in 2004 and are known to be established since 2005.

A 64-year old man, resident in Nice (department Alpes Maritimes), developed symptoms which included fever, myalgia and asthenia on 23 August 2010. He was hospitalised on 27 August, 2010. Laboratory tests conducted on his serum samples indicate positive serology for IgM and IgG antibodies against dengue virus as well as NS1 antigenic test positive during the potential viraemic period. The serotype of dengue virus is currently unknown.

In terms of exposure, the case had no recent history of international travel or blood transfusion. Friends from the West Indies are staying with him since April 2010. Investigations have also shown that there are 6 confirmed recent dengue cases detected in Nice between 24 July and 23 August 2010. Of these, four cases were confirmed PCR positive for dengue. Further epidemiological and virological investigations around the current case are ongoing.

On 18 September, media reported a second case of dengue in a 18 year-old man in the same area in Nice, which was confirmed the next day by the French Ministry of Health as the second autochthonous case of dengue virus infection. This second case had onset of symptoms on 11 September and was laboratory confirmed by PCR on 17 September.

Control measures implemented include:

1. Dissemination of information about dengue virus for health professionals and the public;
2. Active case finding in the neighbourhood of residence and areas that the case visited, on a weekly basis until 45 days after the onset of disease for the last detected autochthonous case;
3. Vector control activities in and around the neighbourhood of residence of cases, *including around ports and airports.*

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Based on the currently available information, this is the first occurrence of autochthonous transmission of dengue fever in metropolitan France and continental Europe, since the outbreaks in 1927 and 1928 in Greece - apart from one case of dengue nosocomial infection reported from Germany in 2004 [19]. This event is not entirely unexpected; as it is known that France, as well as other countries in Europe, have mosquito species that are competent vectors for flavivirus transmission in other regions of the world. Previous experience, such as the Chikungunya outbreak in Italy in 2007 in which over 300 cases were reported, has shown that other arboviruses can be efficiently transmitted in non-endemic continental Europe when introduced.

Whether the transmission of dengue virus in France followed a bite from infectious mosquitoes imported to the area via airplanes or boats or by local mosquitoes after biting a viraemic person residing or visiting Nice, remains to be determined. *However, with the second confirmed case, the latter scenario is confirmed to be the most likely one. Therefore, taking into consideration the longest possible incubation period for dengue fever, it can be considered that the parameters for successful transmission of dengue virus to humans existed in Nice during August 2010.* To date only two autochthonous case of dengue have been detected in Nice, but the identification of new dengue cases in the near future cannot be excluded. The enhanced surveillance and strong vector control measures are expected to limit the risk for further spread as much as possible.

The risk for further spread to humans in Europe, as well as the possibility for the establishment of dengue transmission in Nice or neighbouring areas in France, appears limited. Recent evidence demonstrates that compared to *Aedes aegypti*, which was the vector in the majority of large dengue outbreaks worldwide, *Aedes albopictus* is a less efficient vector of this virus [17]. It has been implicated in outbreaks of dengue in Japan (1942-1945), Seychelles (1977), Hawai (2001-2002) and La Reunion island (2004). Furthermore, vertical transmission of dengue virus from mosquitoes to their offspring is not efficient either, and therefore overwintering of the virus in continental European *Aedes albopictus* populations is also unlikely [17]. The public health importance of *Aedes albopictus* in this context would appear to be more important for the transmission

of other arboviruses such as Chikungunya; better competence for this virus has been recently demonstrated [20]. It should also be noted, that this area of France as well as other countries in Europe receive a high number of imported annual dengue cases (this year, large outbreaks are reported from the Indian Ocean and West Indies), despite this and established potential mosquito vector populations, we have never observed established transmission of the dengue virus in mainland Europe.

In terms of blood safety, reported dengue infection following blood transfusion in dengue endemic areas is rare [21-23], but is also difficult to detect as a large proportion of the population would already have antibodies against the virus. However, as dengue infection is mild or asymptomatic in 40-80% of infected persons (depending on the area) it does pose a risk to blood safety. The single identified case in Nice is suggestive that there might be other infected persons in the city during the same period of exposure, but who never developed symptoms. Such asymptomatic, viraemic carriers of dengue viral infection could pose a potential risk to blood safety if they donated blood during their viraemic period. It is possible, however, that the duration of viraemia in mild or asymptomatic cases is shorter and the titre is lower than in symptomatic persons. At the present time it is impossible to quantify this risk, and a retro-active survey of blood supplies from Nice between July and September 2010 would allow to further estimate it. The French blood authorities currently exclude all febrile and sick donors from donation, and no additional exclusion measures have been implemented as the risk is considered low.

Further investigations to identify the likely exposure of the current case will hopefully allow for a better understanding of this event. The reactive surveillance in addition to the routine enhanced surveillance (from May to November each year) put in place by the French authorities is likely to identify new symptomatic cases in the area, determining also the potential geographic extension of the risk. Identification of the sero- and genotype of dengue virus that infected the current reported case may also facilitate the identification of the origin of the virus. Finally, better understanding is needed on how the vector abundance, activity and competence of *Aedes albopictus* for dengue transmission influence the risk for further transmission in the region [20, 24].

CONCLUSIONS

The current two cases of dengue fever from autochthonous transmission in Nice, France is a significant public health event, but not unexpected; more cases can be anticipated. Previous events, including a mosquito-borne arbovirus outbreak in Italy, the occurrence of vector-borne diseases around airports and other ports of entry and a previous risk assessment on dengue introduction in the EU [15] all indicate that autochthonous transmission in continental Europe is possible, *as this current event also confirms. With the end of the mosquito season, and Aedes albopictus being a secondary vector, the risk for establishment of dengue transmission in south-eastern France or further spread in Europe currently appears limited.* Further information in the near future will allow to re-assess this likelihood.

CONTACT: support@ecdc.europa.eu

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