



Dengue Fever, Chikungunya and the Zika Virus

Arboviruses are a group of virus that can be transmitted between animals and humans, and they are common to humans and many vertebrates (mammals, birds, reptiles, amphibians). There are over 500 species of arbovirus, sub-divided into approximately 10 different families, including Togaviridae, Flaviviridae, Reoviridae, Rhabdoviridae, and Bunyaviridae. These viruses have RNA with a very heterogeneous structure and are transmitted via bites from hematophagous arthropods such as mosquitoes, sandflies, ticks and mites (arbovirus is short for arthropod-borne virus).

Chikungunya

This disease was first described in Tanzania in 1952. It is caused by an arbovirus of the genus Alphavirus from the Togaviridae family. It was then also described in Africa, Southeast Asia, the Indian subcontinent and the Indian Ocean. Finally, it was first described in Europe in 2007, in Italy.

Chikungunya means "to become contorted" in the Kimakonde language (spoken by a tribe in south east Tanzania) and reflects the severity of the pain that can be associated with this infection.

Globally, the virus is transmitted by female mosquitoes of the species *Aedes albopictus* (tiger mosquito) and *Aedes aegypti*, but in

southern regions of mainland France and on the island of Réunion, *Aedes albopictus* provides the sole vector for transmission.

Transmission

Dengue Fever, Chikungunya and the Zika virus are all transmitted in the same way.

Human to human transmission takes place by mosquito vector in urban areas during epidemics: the mosquito picks up the virus when it bites a carrier, and then transmits it to a healthy person with another bite. The mosquito bites people outside their homes throughout the day, with peak activity at dawn and dusk. The mosquitoes live in urban areas and lay their eggs in pools of stagnant water (250 eggs every 2 days), where they develop into larvae. The eggs are resistant to the cold in winter and hatch when weather conditions improve.

Aedes albopictus is spreading globally; it has adapted to both tropical and temperate climates.

Clinical presentation

There is a short incubation period, which lasts an average of 47 days (1-12 days), after which patients develop sudden high fever of $> 38.5^{\circ}\text{C}$, headache, myalgia or intense, debilitating joint pain, potentially associated with conjunctivitis, maculopapular rash, itching, nausea, mild bleeding (gingivitis,

epistaxis). It should be noted that cases can be asymptomatic (13% of cases on Réunion during the 2007 epidemic). The acute phase (viremic phase during which the disease can be transmitted by a bite) lasts 5-10 days. It is followed by fatigue, weight loss, anorexia with dysgeusia, hair loss, skin disorders (patches of dyschromia, xerosis and itching), and memory impairment. Course of the disease can be rapidly favourable, or recovery may be slow and marked by significant asthenia. Relapses affecting the joints, with or without fever, can occur (but the patient is not contagious). In 30-60% of cases, the disease progresses to a chronic phase characterised by persistent arthralgia and partial disability; this phase can last from a few weeks to several months. Some complications have been observed, such as high fever, extensive vesiculobullous lesions, and involvement of the brain (meningoencephalitis), liver (hepatitis), kidneys (acute renal failure), or the heart (myocarditis). One possible case of mother-to-child transmission has been described on Réunion.

The mortality rate is 3.6 per thousand. Patients have lasting immunity once recovered. There is no treatment or vaccine available.

Biological diagnosis

The test to be performed depends on when the sample is taken in relation to the date on which symptoms first appeared (see Fig. 1):

- **< D5:** RT-PCR
- **D5-D7:** RT-PCR and serology
- **D7:** serology only

Chikungunya: major outbreaks

The first significant outbreak of the disease was reported in the Congo in 1999/2000. Since 2005, there has been an epidemic in the Indian Ocean (with cases imported to Europe); in 2007 there was an outbreak in the north east of Italy, and in late 2013-2014 there was a major epidemic in the West Indies and Guyana and, in 2014 there were cases in the south east of France and in Corsica.

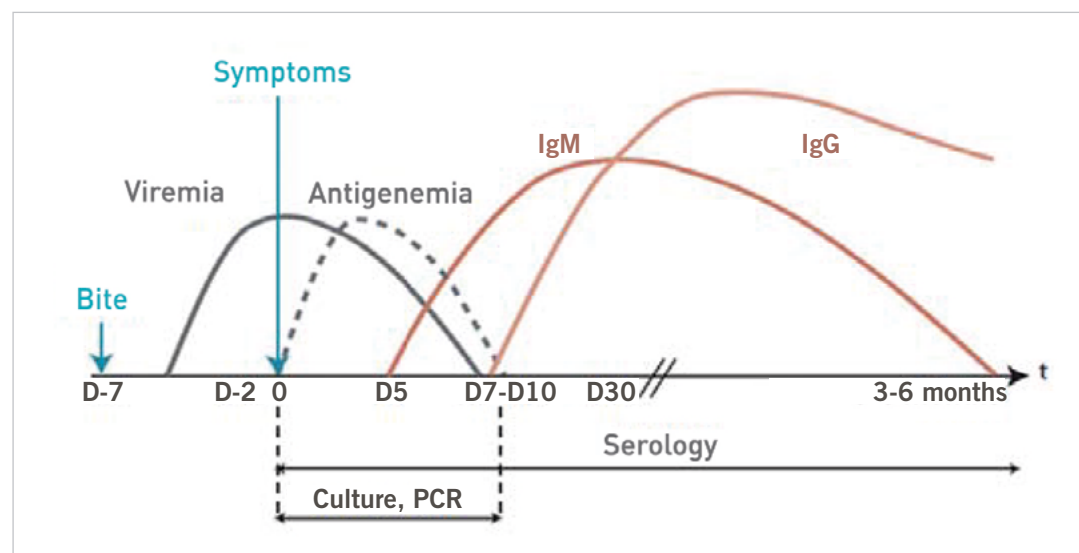
Dengue Fever

This disease is caused by the dengue virus, an arbovirus also transmitted by mosquitoes of the *Aedes* genus. The virus belongs to the *Flavivirus* genus in the family *Flaviviridae*.

Cases of dengue fever appear to be on the rise. There are 4 known serotypes (D1 to D4), and they do not provide crossimmunity (it is possible for one person to have 4 infections in their lifetime).

Serotypes 1, 2, and 3 are more prevalent in Asia and the West Indies/Guyana, and serotypes 1 and 2 are more common in Africa. The 1977-78 epidemic in the Indian Ocean (Réunion) was caused by serotype 2, and the 2004 and 2010 epidemics were caused by serotype 1 and serotype 3 respectively.

Fig. 1: Sequence of the appearance of biological markers



Epidemiology

Dengue fever is hyperendemic in the West Indies and Guyana, as well as in South America and some countries in Africa and Asia. It has also emerged in French territories in the Pacific Ocean and in the south east of mainland France.

- **2010 in the French departments of Alpes-Maritimes and Var:** 2 cases of local transmission of dengue fever (+2 cases of Chikungunya)
- **2013 in the Bouches du Rhône department:** 1 case of local transmission of dengue fever
- **2014:** 4 confirmed cases of local transmission of dengue fever: 2 in the Bouches du Rhône and 2 in the Var
- **2015:** 6 cases of local transmission of dengue fever in Languedoc Roussillon.

Clinical presentation

The infection is asymptomatic in 50 to 85% of cases. When symptoms do occur, they are extremely variable and the course of the disease is unpredictable. There is an incubation period of 4-10 days, after which onset of the disease is sudden and severe, characterised by high fever, widespread pain, rash, fatigue, and gastrointestinal symptoms (loss of appetite, nausea, vomiting). However, in some people the disease can take on a haemorrhagic form or cause dengue shock syndrome. The risk of contracting a more serious form of the disease is higher in cases where there is a higher viral load or where a patient contracts consecutive infections caused by different serotypes (the highest risk of a serious form of the disease comes

from Dengue 1 followed by Dengue 2). The warning signs for complications (or serious forms of dengue fever) are abdominal pain, persistent vomiting, oedema, bleeding mucosa, lethargy or agitation, hepatomegaly, thrombocytopenia and increased haematocrit levels.

Biological diagnosis

Diagnosis of the primary infection is based on the detection of the viral genome by RT-PCR (if carried out within the 7 first days) and/or by IgM and IgG serology (from the fifth day of infection)

The serology should be interpreted on two samples, one of which must be drawn ≥ 15 d. This is due to the fact that IgM tests have of lack of specificity (false positive cases).

It is important to pay attention when interpreting secondary dengue infections (patients previously infected with serotype D1 dengue will already have IgG antibodies when infected with serotype D2).

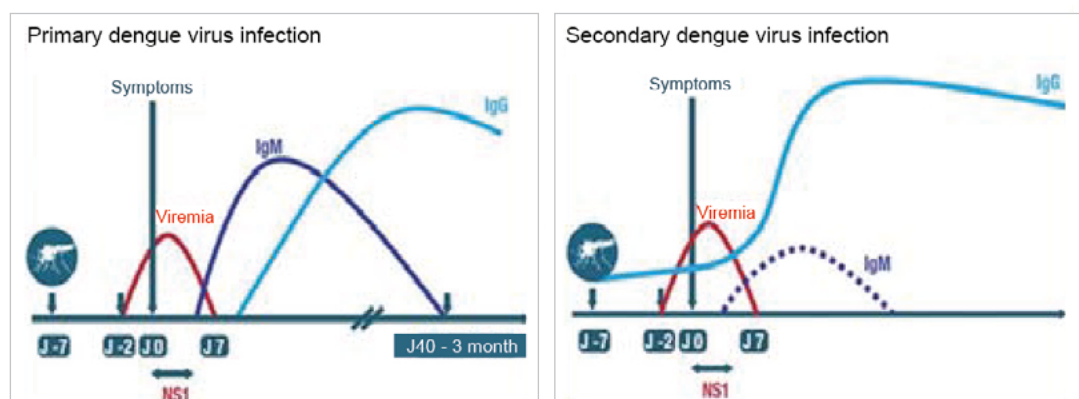
Immunity is present for a given serotype but it does not protect from infections with other serotypes.

Diagnostic strategy

- **from D0 to D5:** PCR only
- **from D5 to D7 inclusive:** PCR and serology
- **after D7:** serology only

Testing for the NS1 antigen is only indicated in regions where there is an outbreak of the disease and from D0 to D5; a negative NS1 antigen test must be confirmed by PCR and/or serology.

Kinetics of the virus and antibodies during infection by the dengue virus



Treatment

There is no specific treatment for dengue fever, but the symptoms can be treated. A vaccine (Dengvaxia®) was granted marketing authorisation in December 2015 in Mexico, the Philippines, and Brazil (and this marketing authorisation is being extended rapidly to other countries). The vaccine is for the prevention of the 4 dengue fever serotypes, for use in endemic areas only, and in people aged 9 to 45 years.

Monitoring plan

The plan for monitoring dengue fever is based on mandatory immediate reporting to the ARS [French regional health authorities] (if 2nd positive serum IgM test). A regional plan for enhanced monitoring has been implemented in the French departments where the mosquito is established.

This plan is active during the mosquito season from 1 May to 30 November.

Finally, the InVs [French Institute for Public Health Surveillance] collects all positive diagnoses from the laboratories performing these analyses.

In 2014: 1,490 suspected cases in 18 departments, including 446 confirmed cases of Chikungunya (all imported cases); 166 confirmed cases of dengue fever (all imported), 6 co-infections and 4 cases of local transmission of dengue fever.

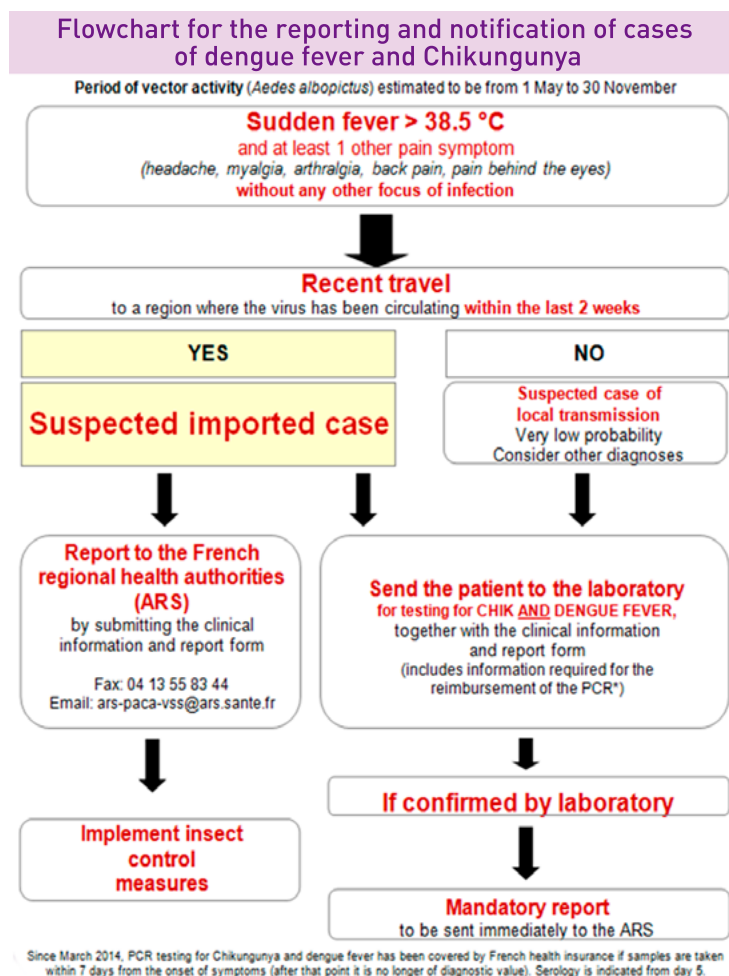
From 1 May to 27 November 2015: 127 confirmed cases of imported dengue fever; 30 confirmed cases of imported Chikungunya; 6 confirmed cases of local transmission of dengue fever.

The Zika virus

The Zika virus is an enveloped Flavivirus with a singlestranded RNA genome. There are two strains of the virus: one African strain (with two substrains) and an Asian strain. It was first isolated in 1947 in a monkey in Uganda (in the Zika forest from which it takes its name), and then in humans in 1952 (Uganda, Tanzania). It has been circulating in Africa and Asia for a long time. There have been epidemics in Micronesia (2007), French Polynesia (2013) and New Caledonia (2014). Like dengue fever and Chikungunya, the vector is a mosquito of the genus *Aedes*. In addition to transmission by mosquito vector, there is evidence that sexual and perinatal transmission of the Zika virus is also possible, as well as transmission via blood transfusion.

Current and recent epidemics

There was an epidemic of the Zika virus in Brazil in May 2015. Enhanced surveillance was put in place in the West Indies and Guyana. In early December 2015, cases of what was presumed to be the Zika virus were described in Martinique. On 15 December 2015, the first case of Zika was confirmed in Guyana, followed by confirmation of another 10 cases, all of which were imported. On 22 December 2015, two cases of local transmission



Data from enhanced monitoring in mainland France in 2014 and 2015

were confirmed in Martinique, followed by five more in Guyana. In early 2016, the epidemic had reached Guadeloupe and the northern Caribbean islands.

Clinical presentation

The infection is asymptomatic in 70-80% of cases. In cases that do develop symptoms there is an incubation period of 3 to 12 days, after which patients experience flu-like symptoms and a diffuse, itchy, maculopapular rash. The rash covers a large area and spreads downwards from the face to the extremities, remaining for about 6 days, predominantly on the torso. Other symptoms include asthenia, fever (or temporary low-grade fever), arthralgia (lasting 3-5 days), headaches with pain chiefly behind the eyes, myalgia, and conjunctivitis. Although it is not immediately serious, the infection can develop neurological complications: Guillain-Barré syndrome, 2-23 days after the viral infection, encephalitis, meningoencephalitis, optical neuritis or

autoimmune complications (purpura). If the Zika virus is contracted during pregnancy, it can also cause intrauterine brain development abnormalities and microcephaly (observed in Brazil and Polynesia among the newborn babies of mothers who were infected during the first or second trimester of pregnancy).

In patients who have recently returned from an epidemic area, the Zika virus is to be suspected in those presenting with a maculopapular rash with or without fever, even moderate fever, and at least two of the following symptoms: conjunctival hyperaemia, arthralgia, myalgia, in the absence of any other aetiology.

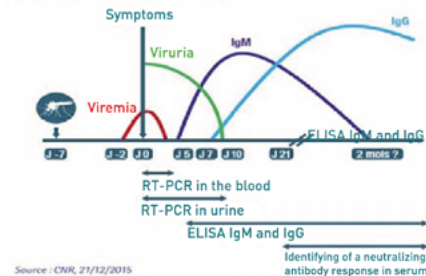
Arboviruses: comparison of clinical symptoms

(from Halstead SB et al, A J Trop Med Hyg and the booklet of the Yap State Department of Health Service)

Symptoms	Dengue fever	Chikungunya	Zika
Fever	++++	+++	+++
Myalgia / arthralgia	+++	++++	++
Maculopapular rash	++	++	+++
Pain behind the eyes	++	+	++
Conjunctivitis	0	+	+++
Enlarged lymph nodes	++	++	+
Hepatomegaly	0	+++	0
Leukopenia, thrombocytopenia	+++	+++	0
Haemorrhagic events	+	0	0

Diagnostic biologique

KINETICS OF INFECTION WITH THE ZIKA VIRUS
(Current state of knowledge)



Diagnosis is based on using RT-PCR to detect the viral genome.

- **In the blood:** viremia is transient and viral load is low and short-lived (0 to 7 days after the onset of clinical symptoms);
- **In saliva:** the virus is present and can be detected for the same period of time as in the blood; the value of the viral load is unknown;
- **In urine:** the virus is present up to 10 days after onset of symptoms, and the viral load is higher.

Anti-Zika IgM and IgG serology can currently be performed at the National Reference Centre [CNR] (Marseille) with whole virus, but there are cross-reactions with other Flaviviruses, and this test does not differentiate between dengue virus and Zika (serology tests positive for Flavivirus; if the neutralisation test is negative for dengue virus, it may be positive for Zika by default). The NRC recommends monitoring serology at 1 month.

Conclusion

There is currently an epidemic of Zika virus in the French West Indies. The conditions for an epidemic in mainland France are present, and there is a real risk from May to November. In the light of the presence of transmission vectors and influx of passengers, the French Public Health Council [Haut Conseil de la Santé] has concluded that "the risk of transmission of Zika virus

- is high in the French departments in the Caribbean (Guyana, Guadeloupe, Martinique) where the vector *Ae. aegypti* is present, and this risk concerns the whole of the population residing or holidaying there;
- is real in Réunion (presence of *Ae. albopictus*) and in Mayotte (presence of *Ae. albopictus* and *Ae. aegypti*), and this risk concerns the whole of the population residing or holidaying there;
- is real in the departments of mainland France where *Ae. albopictus* is established; this risk exists during its period of activity from May to November, particularly in the event of virus circulation in the Caribbean. This risk concerns the whole of the population residing or holidaying there."

Carole Emile, based on a statement by Véronique Jacomo, Biomnis Lyon (February 2016)

