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General review

Current Zika virus epidemiology and recent epidemics

Infections par le virus Zika et épidémies récentes

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Abstract

The Zika virus (ZIKV) is a mosquito-borne flavivirus (*Aedes*), similar to other arboviruses, first identified in Uganda in 1947. Few human cases were reported until 2007, when a Zika outbreak occurred in Yap, Micronesia, even though ZIKV activity had been reported in Africa and in Asia through virological surveillance and entomological studies. French Polynesia has recorded a large outbreak since October 2013. A great number of cases and some with neurological and autoimmune complications have been reported in a context of concurrent circulation of dengue viruses. The clinical presentation is a "dengue-like syndrome". Until the epidemic in French Polynesia, no severe ZIKV disease had been described so far. The diagnosis is confirmed by viral genome detection by genomic amplification (RT- PCR) and viral isolation. These two large outbreaks occurred in a previously unaffected area in less than a decade. They should raise awareness as to the potential for ZIKV to spread especially since this emergent disease is not well known and that some questions remain on potential reservoirs and transmission modes as well as on clinical presentations and complications. ZIKV has the potential to spread to new areas where the *Aedes* mosquito vector is present and could be a risk for Southern Europe. Strategies for the prevention and control of ZIKV disease should include the use of insect repellent and mosquito vector eradication.

Keywords: Zika virus; *Aedes*; Arbovirus; Yap; French Polynesia

Résumé

Le virus Zika (ZIKV) est un flavivirus transmis par les moustiques (*Aedes*), proche d'autres arboviroses ; il a été isolé pour la première fois en Ouganda en 1947. Bien que des études de surveillance virologiques et entomologiques aient rapporté une activité ZIKV en Afrique et en Asie, peu de cas humains avaient été décrits jusqu'en 2007, année où une épidémie de Zika a sévi à Yap, en Micronésie. Depuis octobre 2013, la Polynésie française connaît une importante épidémie liée au ZIKV avec un grand nombre de cas et certains avec des complications neurologiques et auto-immunes, rapportés dans un contexte de circulation concomitante de virus de la dengue. Cette infection se caractérise cliniquement par un syndrome de type *dengue-like*. Aucune formes sévères n'avaient été décrites jusqu'à l'épidémie actuelle en Polynésie française. Le diagnostic de référence repose sur l'isolement viral et la RT–PCR. En moins d'une décennie, deux épidémies d'importance sont survenues dans des territoires naïfs et appellent à la plus haute vigilance, ce d'autant que cette pathologie émergente est peu connue et que certaines questions demeurent, tant sur l'existence du/ou des réservoirs et des modes de transmission, que sur le tableau clinique et ses possibles complications. Il existe un risque potentiel de diffusion en Europe du Sud, dans des zones où le vecteur *Aedes* est présent. Les stratégies de prévention et de contrôle des maladies ZIKV doivent inclure l'utilisation de répulsif et la lutte antivectorielle.

Mots clés : Virus Zika ; Arbovirus ; *Aedes* ; Yap ; Polynésie française

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1. Zika virus global data

The Zika virus (ZIKV) is an arbovirus that carries the name of a forest close to Kampala (Uganda). It was first identified in rhesus monkeys in 1947, through a selvatic yellow fever surveillance network in Uganda [1]. It was first isolated in humans in 1952, in Uganda and in Tanzania [2]. In 2007, ZIKV caused an epidemic on the island of Yap, in Micronesia, and another in Gabon [3]. ZIKV has been considered as emergent since 2007: few cases have been described or reported since then. ZIKV has caused a major epidemic in French Polynesia (FP) [4] since October 2013, and the first autochthonous cases in New Caledonia were reported in January 2014 [5].

1.1. The virus

ZIKV is an arbovirus (virus transmitted by arthropods) of the *Flaviviridae* family. This single stranded RNA virus is close to the Spondweni virus, identified in South Africa. Genomic comparisons have revealed various sub-clades indicating two major lineages, Asian and African. The diagnosis of ZIKV infection relies mostly on the detection of viral RNA in blood samples: RT-PCR and viral isolation in blood samples collected less than five days after the onset of symptoms are the reference techniques. The "pan flavivirus" amplification technique combined with sequencing may be used as an alternative [6–9]. The viremic period in humans could be short, from the third to the fifth day after onset of symptoms. Viruria could last longer than viremia and the RT-PCR detection of viral RNA in urine could be an alternative method if genetic material is no longer present in the serum [7,8,10,11].

Serological tests (Elisa or immunofluorescence) are also widely used. The Centers for Disease Prevention and Control (CDC) in Atlanta had developed an ELISA technique to detect specific anti-Zika IgM during the epidemic in Yap, in 2007 [3]. The frequency of cross-reactions with other flaviviruses (dengue, yellow fever) may make the diagnosis difficult. Furthermore, in the early phase of infection, the rate of IgM and IgG may be very low, making it difficult to confirm the diagnosis [8]. The detection of antibodies should be confirmed by a complementary seroneutralization assay allowing determining the specificity of the detected antibodies (e.g. Plaque Reduction Neutralization Test [PRNT]) and proving a 4-fold increase of the antibody titer initially found [8]. No commercial kit is currently available for the detection of antibodies specifically related to ZIKV.

1.2. Transmission and vector

The transmission is mostly vectorial by mosquitoes of the Culicidae family and of the *Aedes* genus (sylvatic and urban transmission) including *Aedes aegypti* (urban transmission). Other species have been reported such as *Aedes polynesiensis* and *Aedes albopictus*. The vector *Aedes hensilli* was identified during the Zika epidemic on the island of Yap in 2007, in Micronesia. The virus is usually transmitted to hematophagous arthropods during their blood meal. The virus breeds in the host vector without affecting it and remains in the insect all life long, and is transmitted to reservoir animals at the next blood meal. The authors of a 2011 article mention a probable sexual transmission but this remains anecdotic.

1.3. Reservoir

The virus reservoir is not completely identified but some authors suggest there is a primate reservoir. Some authors have reported finding anti-Zika antibodies in various animals such as big mammals (orang-outang, zebras, elephants, etc.), and rodents in Pakistan [12,13].

1.4. Geographic distribution

Virological studies, seroprevalence surveys, diagnosis of sporadic cases, and epidemics have allowed identifying the virus in Africa (Senegal, Uganda, Nigeria, Ivory Coast, Gabon, Tanzania, Egypt, Central African Republic, Sierra Leone, etc.) in Asia (Cambodia, India, Indonesia, Malaysia, Pakistan, Philippines, Singapore, Thailand, and Vietnam,) and in Oceania, in the Pacific (Micronesia/Yap, FP, New Caledonia, and Cook islands) [3,4,8,10–13].

2. Clinical presentation

The symptoms appear after an incubation period of a few days after the bite of an infected mosquito and usually last three to 12 days. Asymptomatic presentations are frequent [3,9] but ZIKV infection can cause a broad range of clinical symptoms, presenting as a "dengue-like" syndrome. The symptoms can include: arthralgia, edema of extremities, mild fever, headaches, retro-orbital pain, conjunctival hyperemia and maculopapular rashes usually spreading downward from the face to the limbs and frequently pruritic, vertigo, myalgia, and digestive disorder. Neither severe presentation, nor death had been reported before the current epidemic in FP (cf. Section 3.2).

The clinical presentation is similar to that of other arboviroses (chikungunya, dengue) and may pose diagnostic difficulties.

Table 1
Comparison of symptoms for dengue fever, chikungunya, and Zika.
Clinique comparée de la dengue, du chikungunya et du Zika.

Symptoms	Dengue	Chikungunya	Zika
Fever	++++	+++	+++
Myalgia/arthralgia	+++	++++	++
Edema of extremities	0	0	++
Maculopapular rash	++	++	+++
Retro-orbital pain	++	+	++
Conjunctivitis	0	+	+++
Lymphadenopathies	++	++	+
Hepatomegaly	0	+++	0
Leukopenia/thrombopenia	+++	+++	0
Hemorrhage	+	0	0

Adapted from Halstead, et al. and from the Yap State Department of Health Services presentation.

Table 2
Seroprevalence surveys, entomological survey, or sporadic case reports for the Zika virus.
Études de séroprévalence, entomologique ou rapports de cas sporadiques humains de Zika.

Countries and territories	Population countries (Number)	Sporadic cases/epidemics		Seroprevalence survey		Comments
		Number of cases (*n*)	Year	Percentage	Year	
Australia	21,527,000	1	2013	–	–	Imported cases (ex–Thailand)
Cambodia	14,701,717	1	2010	–	–	Sporadic human cases
Ivory Coast	23,202,000	1	1999	–	–	Sporadic human cases Isolation in mosquitoes
Indonesia	244,968,342	1	2013	–	–	Exported cases in Australia in 2013
		17	1977–1978 [9]	–	1977–1978	Serologic study – Java +
		–		13%	1963	Serologic study – Lombok
Malaysia	28,250,000	1	–	–	1969	Serologic study Isolation in mosquitoes [24]
Micronesia, Yap [20]	7391	185 including 108 confirmed and probable	2007	73% (in population)	2007	Epidemic Study seroprevalence in population
Nigeria	170,123,740	2	1975	31%	1968	Study serologic Isolation in mosquitoes sporadic human cases
New-Caledonia	254,000	114	2014	–	–	Autochthonous cases (Dumbea)
		32	2013–2014			Imported cases (e.g. FP)
Uganda	34,131,400	–	–	6.1%	1952	Serologic study [25]
French Polynesia (FP)	268,270	8510 clinical cases 29,000 estimated cases (preliminary figures)	2013–2014	–	–	Epidemic [26]

Table 1 is a list of the most frequently reported clinical symptoms for these three differential diagnoses.

There is no specific treatment or vaccine. The treatment is symptomatic, combining acetaminophen and antihistaminic drugs. Prevention against the infection, since there is no vaccine, relies on individual protection against bites and eradication of mosquitoes (anti-vectorial prevention). Prevention at the community level consists in decreasing the number of mosquitoes by decreasing the number of egg-laying sites (potted plant saucers, moats, water reservoirs, used tires, etc.) by drying them, isolating them, or treating them with insecticides. Deltamethrin could currently be the only insecticide warranting a satisfactory result as aerosol treatment [11]. Individual protection includes, wearing longs and light-colored clothes, using skin repellents and mosquito bed nets (protection of babies and bedridden patients), so as to avoid mosquito bites.

3. Epidemiology

ZIKV was reported in mosquitoes, primates, and humans in 14 countries over three continents (Africa, Asia, Oceania) (Table 2).

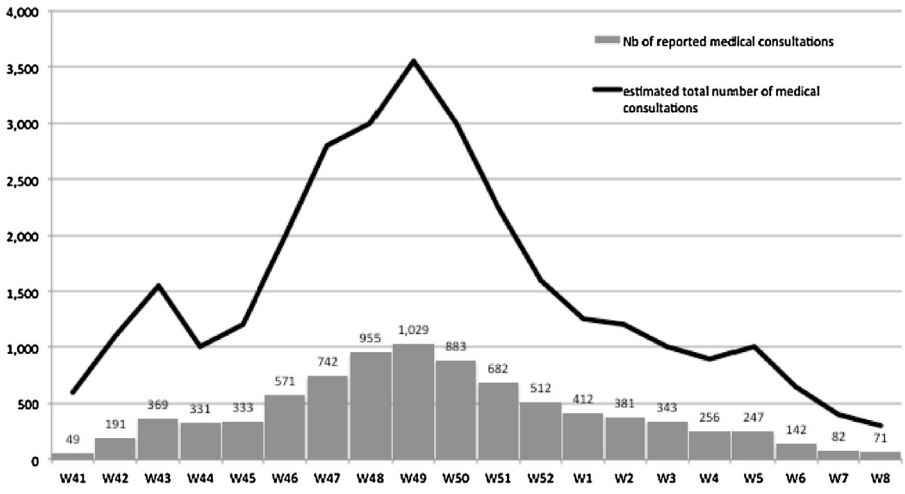
The virus had been the object of few published studies because of the frequency of pauci/asymptomatic presentations before 2013 and because there were no documented severe presentations. Some data is available from prevalence surveys. The prevalence was 6.1% in a standard population of 99 individuals in Uganda, in 1952. The virus was isolated twice in Nigeria, from samples collected in 10,778 febrile patients, between 1971 and 1975. The authors of a serological study of 130 Nigerian symptomatic patients, performed in 1979, reported that 52 (%) had neutralizing antibodies [13]. The authors of a study conducted in Java (Indonesia), between 1977 and 1978, reported that out of 219 patients admitted to the Java island hospital emergency unit for fever, ZIKV prevalence was 7.1% [14]. Sporadic cases were reported in travellers between 2007 and 2013 (Thailand, Cambodia, Indonesia) [15,16].

The authors of a retrospective study conducted in 2014, demonstrating a ZIKV epidemic in Gabon in 2007, proved the difficulty of detecting this epidemic in areas of dengue and chikungunya virus circulation [3].

A ZIKV epidemic has been reported in FP since October 2013 [4]. This is the first time such a large epidemic has been described. Cases imported from FP were reported in New Caledonia [5] and, since January 2014, autochthonous cases have been reported there. Cases imported from FP have also been reported in Japan, Norway, Easter Island, and continental France [17,18].

3.1. The yap epidemic (Micronesia)

The island of Yap belongs to the Federated States of Micronesia, in the Pacific Ocean. The population of Micronesia is 11,241 inhabitants including 7391 on the island of Yap according to the 2000 population census [19]. Healthcare authorities reported 185 cases of ZIKV infection from April 2007 to August



Source: Bulletin de Veille Sanitaire, bureau de veille sanitaire de Polynésie française, week 8, 2014

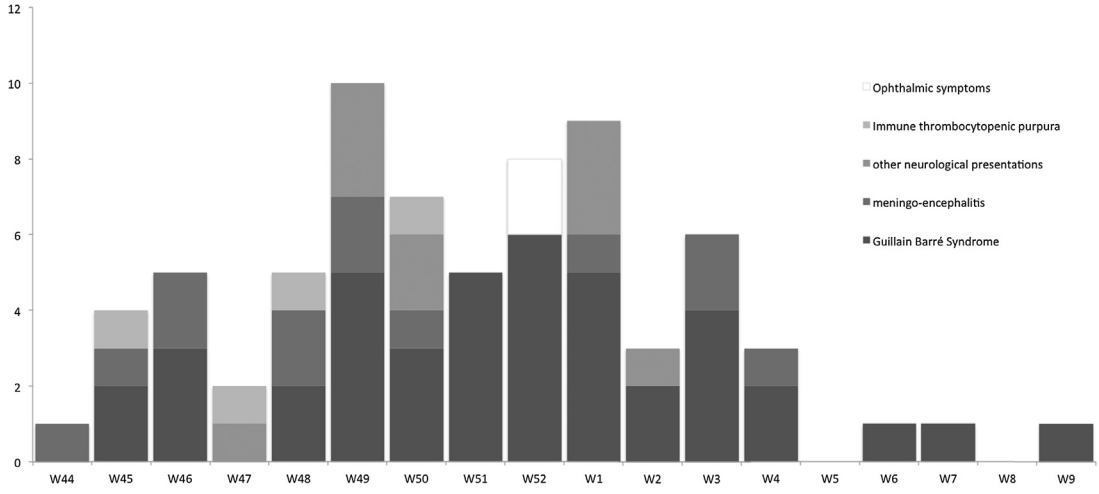
Fig. 1. Evolution of the weekly number of suspected Zika cases in French Polynesia, October 30, 2013 to February 14, 2014 (epidemic still ongoing).
Évolution du nombre hebdomadaire de cas suspects de Zika en Polynésie française, du 30 octobre 2013 au 14 février 2014 (épidémie toujours en cours).

2007, including 108 confirmed cases on the island of Yap. The design of a study conducted between April 1 and July 31, 2007 combined an active screening of cases in the four healthcare centers and in the hospital, with a seroprevalence survey of the global population in a random sample of 200 households. An entomological survey was also performed at the same time [20].

One hundred and eighty-five cases of ZIKV infection including 49 (26%) confirmed cases and 59 probable cases (32%) were identified in nine of the ten Yap communities at the end of the active screening. The attack rate was 14.6 per 1000 inhabitants. Sixty-one percent of the cases were female patients and the median age was 36 years (range, 1 to 76). The symptoms of ZIKV infection in patients with biological confirmation ($n = 31$) included arthralgia, mild fever, headaches, a rash, conjunctivitis, retro-orbital pain, myalgia, edema, and digestive disorders. No hospitalization, or death was reported. The prevalence of antibody carriers in the global population three years of age or more was estimated at 73% with a CI of 95 [68–77%]. Most of these patients were asymptomatic. The authors of the entomologic study reported a majority of *A. hensilli* mosquitoes in several site: the ZIKV could not be isolated in the mosquitoes [20].

3.2. FP epidemic

FP is an overseas country of the French Republic, with five archipelagos including 119 islands, 74 of which are inhabited. The total population was 268,270 inhabitants according to the 2012 census [21]. FP had been confronted to a dengue epidemic due to serotypes DEN1 and DEN3 for several weeks, when on October 30, 2013, the healthcare authorities reported a ZIKV epidemic for the first time, on the Society, Marquesas, and Tuamotu islands which later spread to all the islands of



*** Guillain-Barré Syndrome (GBS), immune thrombocytopenic purpura (ITP), meningo-encephalitis (ME)**
Source: Bulletin de Veille Sanitaire, bureau de veille sanitaire, week 8- 2014

Fig. 2. Number of cases with neurological complications by hospital admission day in French Polynesia, 2013–2014 ($n = 73$).
Nombre de cas avec complications neurologiques/auto-immunes par jour d'admission au centre hospitalier de Polynésie française, 2013–2014 (n = 73).

the archipelagos [4,22]. Healthcare professionals were informed and community surveillance was reinforced by the network of sentinel physicians. Eight thousand five hundred and ten suspected cases were reported by the sentinel network from the beginning of the epidemic to February 14, 2014, leading to estimating at 29,000 (10% of the population), the number of patients having consulted for a ZIKV infection (Fig. 1). Samples were collected from 746 patients, and 396 (53%) cases were confirmed biologically. Seventy-two cases of severe presentations with severe neurological symptoms were notified. Among these, 40 Guillain-Barre syndromes were diagnosed in three months (compared to five usually diagnosed during that period) (Fig. 2). Nevertheless, the direct involvement of the ZIKV on the occurrence of these severe presentations still needs to be investigated because of prolonged co-circulation of the dengue and Zika viruses. No infection related death was reported.

The epidemic peaked at the ninth week; then a decreasing trend was observed in the global number of clinically suspect cases since mid-December 2013 (Fig. 1) with variations among the various islands and archipelagos (Fig. 1).

The entomological study pointed at *A. aegypti* and *A. polynesiensis* as vectors of the ZIKV at this stage of the epidemic.

Patients presenting with ZIKV infection from FP were reported in Japan [7], in continental France[1], in Norway [18], on the Easter Island, and in New Caledonia where autochthonous circulation of the virus was observed with 114 cases reported as of March 3, 2014 [22,23].

4. Conclusion

The ZIKV infection has caused two major epidemics in Pacific previously naive territories, in less than a decade. This emergent arbovirosis transmitted by mosquitoes of the *Aedes* genus has a high potential for spreading in countries where the vector is present.

This situation requires the highest vigilance, especially since this disease is not well known and that some questions remain unanswered, concerning the reservoir(s) and modes of transmission, the clinical presentation, and possible complications. Some uncertainties remain on the outcome of co-infections with other arboviroses such as the dengue fever.

The vector *A. albopictus* is present in the south of Europe and more precisely in 18 of continental France departments (administrative subdivisions) and the great number of exchanges between continental France and the territories with an ongoing epidemic may facilitate the emergence of this infection in these departments and requires a reinforced surveillance of this arbovirosis during the summer season.

Disclosure of interest

SI wrote the article; HPM, ILG, VG, TC, MH reviewed and edited the article, HP. Mallet specially focusing on the epidemiology in French Polynesia, and I. Leparc Goffart on the biological and virological section. All authors read and approved the final manuscript. The authors declare that they have no conflicts of interest concerning this article.

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