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Zika emergence in the French Territories of America and description of first confirmed cases of Zika virus infection on Martinique, November 2015 to February 2016

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Following of the emergence of Zika virus in Brazil in 2015, an epidemiological surveillance system was quickly implemented in the French overseas Territories of America (FTA) according to previous experience with dengue and chikungunya and has detected first cases of Zika. General practitioners and medical microbiologists were invited to report all clinically suspected cases of Zika, laboratory investigations were systematically conducted (RT-PCR). On 18 December, the first autochthonous case of Zika virus infection was confirmed by RT-PCR on French Guiana and Martinique, indicating introduction of Zika virus in FTA. The viral circulation of Zika virus was then also confirmed on Guadeloupe and Saint-Martin. We report here early findings on 203 confirmed cases of Zika virus infection identified by RT-PCR or seroneutralisation on Martinique Island between 24 November 2015 and 20 January 2016. All cases were investigated. Common clinical signs were observed (maculopapular rash, arthralgia, fever, myalgia and conjunctival hyperaemia) among these patients, but the rash, the

foundation of our case definition, may be absent in a significant proportion of patients (16%). These results are important for the implementation of a suspected case definition, the main tool for epidemiological surveillance, in territories that may be affected by ZIKV emergence, including Europe.

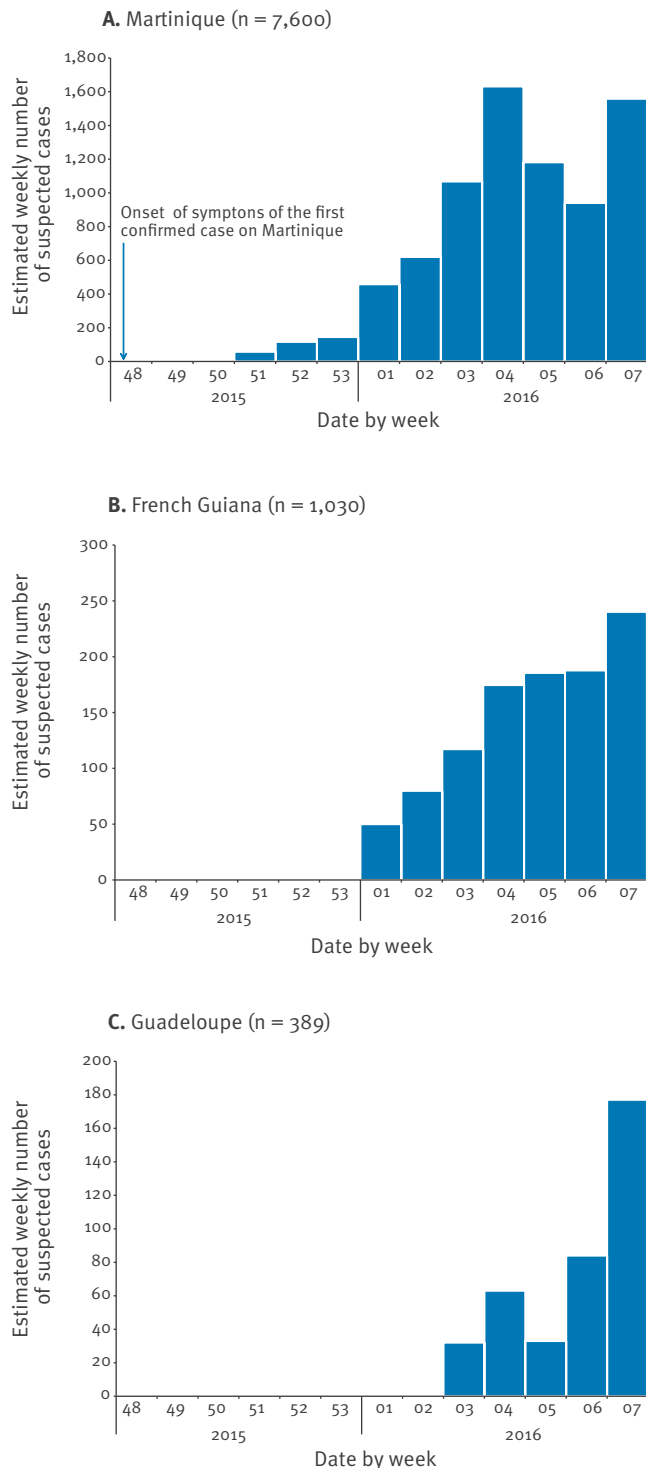
Introduction

Zika virus (ZIKV) is a Flavivirus related to dengue, yellow fever and West Nile viruses, mainly transmitted by *Aedes* mosquitoes [1,2].

In May 2015, the World Health Organization (WHO) reported the first local transmission of ZIKV in the north east of Brazil [3]. On 1 December 2015, Brazil confirmed ZIKV autochthonous circulation. By February 2016, the Brazilian Ministry of Health estimated that 500,000 to 1,500,000 suspected cases of ZIKV disease have occurred, and 20 countries or territories in the Americas have reported autochthonous ZIKV circulation [4,5].

FIGURE 1

Estimated weekly number of suspected Zika cases reported by general practitioners, 23 November 2015–25 February 2016



A possible association of ZIKV infection with post-infectious Guillain–Barré Syndrome (GBS) and with adverse pregnancy outcomes was noted in Brazil and French Polynesia and raised awareness for these phenomena in all affected territories [6,7].

On Martinique island, a territory of 390,000 inhabitants in the French West Indies, a family cluster of three cases of eruptive disease (rash and/or fever) was reported to the Health Agency of Martinique on 4 December 2015 by a medical laboratory and a paediatrician. Given the epidemiological situation in South America and the Caribbean, it was decided to test for dengue, chikungunya and Zika virus. On 14 December 2015, the French National Reference Centre for Arboviruses (NRC) in Marseille, France, confirmed ZIKV by serology in one member of the household (positive for anti-Zika IgM and anti-*Flavivirus* IgG). Because of the endemic circulation of dengue virus in Martinique with high transmission in August to February, this result could not confirm recent ZIKV infection but only recent infection to *Flavivirus*, and a seroneutralisation was implemented. On 30 December 2015, the NRC reported that seroneutralisation was positive, confirming a ZIKV infection in the initial cluster. This was the first autochthonous case detected in the French overseas territories of America (FTA) with a date of symptom onset on 24 November 2015. On 18 December, the laboratory of virology of the University Hospital of Martinique confirmed a ZIKV infection by RT-PCR in a person not connected to the family cluster and who had not travelled.

On 18 December, the first autochthonous case was confirmed in Saint Laurent du Maroni in French Guiana by RT-PCR at the National Reference Centre for Arboviruses, Influenza virus and Hantavirus at the Institut Pasteur of French Guiana. On 15 January, a first positive RT-PCR for ZIKV was reported both in Saint Martin and in Guadeloupe.

This article describes the surveillance system in FTA and presents a clinical description of all confirmed ZIKV cases in Martinique from the first identified case to the date when laboratory confirmation of individual cases was stopped on 20 January 2016.

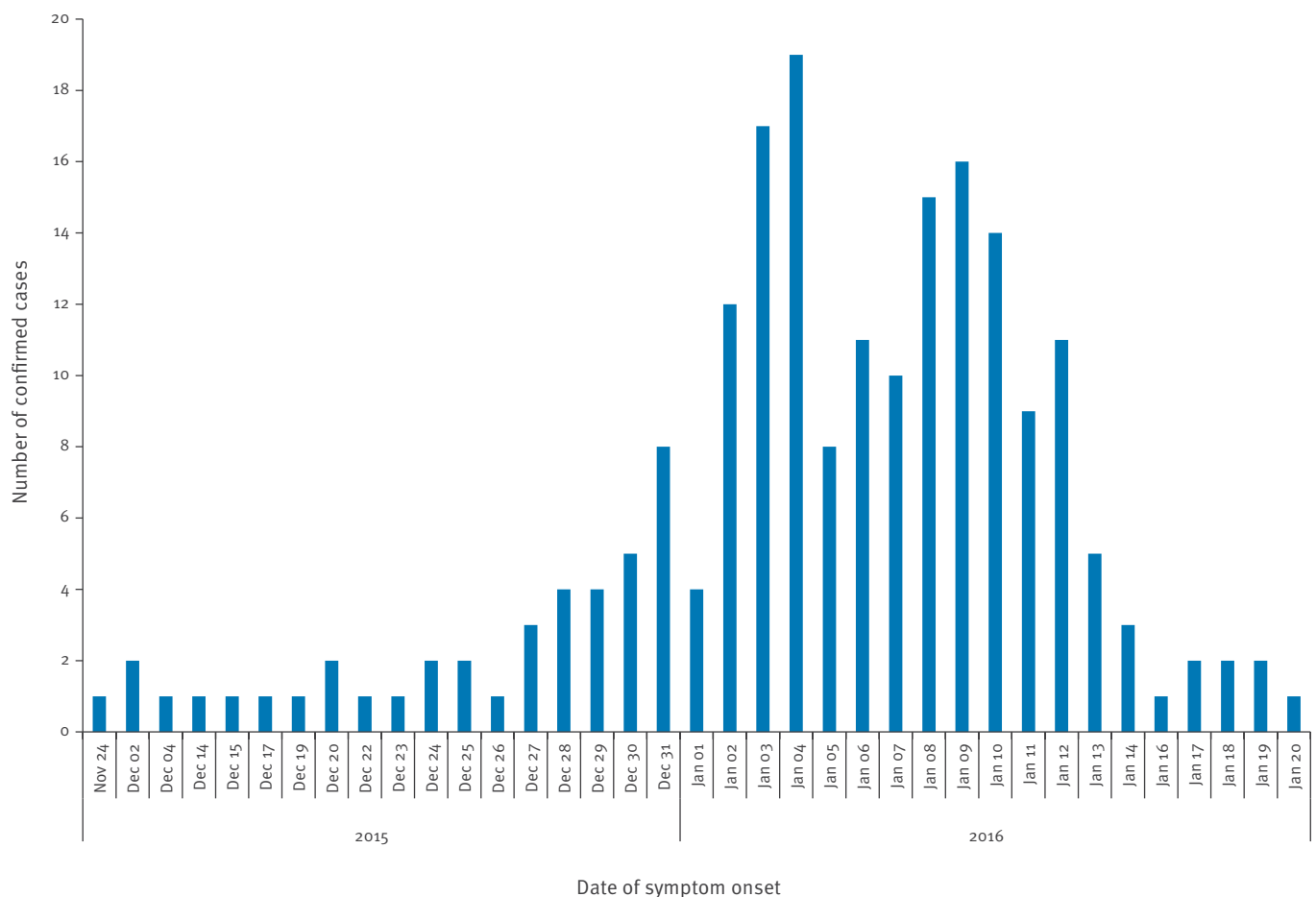
Surveillance system in the French overseas territories of America: French Guiana, Guadeloupe, Martinique, Saint Barthélemy and Saint Martin

In response to dengue outbreaks which are occurring in this area and to the emergence of chikungunya in 2013, each FTA implemented action plans ('Programme de Surveillance, d'Alerte et de Gestion' (Psage)), based on the Integrated Management Strategy recommended by the WHO for dengue [8]. These plans include four phases of increasing epidemic risk. A similar plan was immediately applied to the risk of Zika emergence when the alert for Brazil was launched.

In the pre-emergence phase (phase 1), the surveillance aims to detect early and to laboratory-confirm the introduction of the virus. Therefore, general practitioners (GPs) and medical microbiologists are invited to report all clinically suspected cases of Zika. A suspected case is defined as any individual with sudden onset of maculopapular rash with or without fever associated with

FIGURE 2

Confirmed cases of Zika virus infection by date of onset, Martinique, 24 November 2015–20 January 2016 (n = 203)



at least two of the three signs conjunctival hyperaemia, arthralgia and myalgia, lasting for a week or less and without any other aetiology. When reported cases meet the case definition, laboratory investigations are systematically conducted, including identification of dengue, chikungunya and Zika viruses.

Only for Martinique, from the emergence of the current Zika outbreak until late December 2015, samples were sent to the French NRC (IRBA Marseille) for laboratory confirmation. Starting from 4 January 2016, samples were also sent for biological analysis to the Laboratory of Virology at the University Hospital of Martinique. All laboratory results were collected by the Regional Office of the French Institute for Public Health Surveillance and entered into the infectious disease surveillance system. An extension of this system for Zika was developed in agreement with the French Data Protection Authority.

After confirmation of the first autochthonous case in a territory, the phase of active ZIKV circulation (phase 2) is declared and the enhanced surveillance continued, allowing vector control action around each identified case in order to contain the viral circulation.

Once the outbreak is declared (phase 3), i.e. once the weekly number of cases does not allow biological confirmation or vector control around each case, the aim of the surveillance is to monitor the epidemic course and document its severity to help the health authorities in their prevention and healthcare response. In phase 3, laboratory confirmation of all suspected cases is stopped. Instead, the surveillance of Zika syndrome is performed through weekly notification of clinical suspected cases by a voluntary sentinel network of GPs. This sentinel network represents more than 20% of GPs' total activity on each island, with a weekly response rate > 80%. The number of reported GP visits for Zika syndrome is extrapolated to total number of cases on the island using the ratio of all GPs to the participating sentinel GPs. Further, hospitals have to declare all admission for GBS and for other neurological disorders potentially related to ZIKV. An ad hoc surveillance system is in place to monitor and describe confirmed Zika cases in pregnant women as well as brain defects detected or suspected in fetuses or in newborns possibly linked to ZIKV infection.

Phase 4 is the ending of the outbreak and the time to determine the health burden and prepare feedback on the outbreak.

TABLE 1

Epidemiological situation and estimated number of Zika syndromes, confirmed cases of Guillain–Barré syndrome and Zika-positive pregnant women, by territory, as on 25 February 2016 (n = 9,077)

Territory	Week of identification of first confirmed case	Epidemiological phase	Suspected cases	Confirmed Zika cases with Guillain–Barré syndrome	Pregnant women confirmed Zika-positive
Guadeloupe	2016–02	2 - Viral circulation beginning	389	0	2
French Guiana	2015–51	3 - Outbreak	1,030	2 (0)	13
Martinique	2015–51	3 - Outbreak	7,600	4 (2)	31
Saint-Barthélemy	NA	1 - Pre emergence	0	0	0
Saint-Martin	2016–02	2 - Viral circulation beginning	58	0	1

NA: not applicable.

Furthermore, a scientific committee for surveillance of infectious and emerging diseases (Cemie) met regularly in order to assess the epidemiological situation and to raise recommendations regarding control measures.

Results

Epidemiological situation on 25 February 2016

Since the first report of ZIKV in the FTA, the number of confirmed or suspected cases has increased in a way that indicates continuous transmission of the virus in four affected territories. The epidemic phase, phase 3, has been declared on Martinique (20 January 2016) and French Guiana (22 January 2016), while Guadeloupe and Saint-Martin have remained in the phase 2 (active ZIKV circulation) (Table 1). By 25 February 2016, no ZIKV circulation had been detected on Saint Barthélemy.

On Martinique, the shape of the epidemic curve showed an important increase in the number of cases during the first five weeks of the outbreak (Figure 1A). All districts were affected by viral circulation and the estimated number of clinically suspected cases of Zika reported by GPs on Martinique was 7,600.

On French Guiana, the number of suspected cases increased more slowly (Figure 1B) and the outbreak spread in littoral areas (from St Laurent du Maroni to Cayenne). The cumulative estimated number of clinical suspected cases of Zika reported by GPs was 1,030.

On Guadeloupe, there were cases in most districts and the number of suspected cases reported by GPs increased steadily every week (Figure 1C). The cumulative estimated number of clinical suspected cases of Zika reported by GPs was 389 and the number of confirmed cases was 35.

On Saint Martin, the cumulative estimated number of clinical suspected cases of Zika reported by GPs was 58 and the number of confirmed cases was 11. No Zika

case was laboratory-confirmed and no clinical suspected cases were reported on Saint-Barthélemy. Four cases of GBS related to ZIKV infection were reported on Martinique and two on French Guiana. Two of the four cases on Martinique occurred in ZIKV-infected patients [9] and biological investigations are ongoing for the other cases. One hospital admission for neurological disorders potentially related to Zika was reported on Guadeloupe (Table 1). Thirty-one cases of ZIKV infection in pregnant women were reported on Martinique, 13 on French Guiana, two on Guadeloupe and one on Saint-Martin. No central nervous system malformations related to ZIKV infection were reported, no malformations in fetuses or infants and no deaths were identified as potentially linked to Zika.

Description of confirmed cases of Zika virus infection on Martinique from 24 November 2015 to 20 January 2016

Between 24 and November 2015, the day of symptom onset in the first case on Martinique, and 20 January 2016, 203 suspected cases of Zika infection were laboratory-confirmed by RT-PCR and/or seroneutralisation. Figure 2 shows their distribution by date of onset.

The male:female sex ratio was 0.43, with 61 men and 142 women. Among the 203 confirmed cases, ZIKV infection was confirmed for 11 pregnant women and for a hospitalised patient presenting GBS [9]. No death due to Zika infection was identified during the analysed period. The mean age of confirmed cases was 43 years with a standard deviation of ± 18 years (range: 4–89 years). Half of the confirmed cases were younger than 42 years.

Data from Martinique were compared with those from French Polynesia. The suspected case definition applied in French Polynesia was: maculopapular rash and/or fever and at least two of the following signs: conjunctival hyperaemia, arthralgia and/or myalgia or oedema of the hands/feet. The distribution of symptoms matching the case definition on Martinique vs French Polynesia is shown in Table 2.

TABLE 2

Frequency of case definition symptoms in confirmed Zika cases, Martinique (n = 203) and French Polynesia (n = 297), 24 November 2015–20 January 2016

Signs	Martinique (n = 203) n (%)	French Polynesia (n = 297) n (%)	Chi-squared test
Maculopapular rash	170 (84)	276 (93)	p = 0.001
Arthralgia	135 (67)	193 (65)	No difference
Fever	121 (60)	214 (72)	p < 0.05
Myalgia	121 (60)	131 (44)	p < 0.001
Conjunctival hyperaemia	68 (33)	187 (63)	p < 0.001

The most frequently reported symptoms were maculopapular rash (84%) and arthralgia (67%). Sixty percent of confirmed cases had fever and myalgia. Among the symptoms listed in the Zika case definition, the least frequently reported symptom was conjunctival hyperaemia (33%). Among the 33 confirmed cases without rash (16%), the reported clinical signs were arthralgia (n = 21), fever (n = 20) myalgia (n = 12) and conjunctival hyperaemia (n = 9).

Other clinical symptoms reported by cases but not included in the case definition are shown in Table 3 and included for example headaches (14%), pruritus (8%), gastrointestinal symptoms (8%), asthenia (5%), lymphadenopathy (5%), oedema (4%), retro-orbital pain (4%), ear, nose and throat symptoms (3%) and dizziness (1%).

Discussion

An epidemiological surveillance system for ZIKV infections was quickly implemented based on the previous experiences with dengue and chikungunya and has detected ZIKV circulation in the FTA. Monitoring data allowed us to follow the dynamics at the beginning of outbreak in the different territories. Nevertheless, owing to the large proportion of asymptomatic cases [10], the number of the estimated suspected cases (symptomatic cases) is likely to represent only the tip of the iceberg.

When comparing the clinical description of confirmed cases on Martinique to the ones on French Polynesia [11], we observed a statistically significant difference between the frequency of rash: 93% on French Polynesia and 84% on Martinique (p < 0.001). This clinical symptom was not mandatory in the case definition on French Polynesia but was more frequently reported than in Martinique. This difference can be due to the difficulty observing a rash on dark skin. The most important difference in reported symptoms was for conjunctival hyperaemia, with 63% of Polynesian confirmed cases vs 33% on Martinique (p < 0.001). Fever was also less frequent among ZIKV cases on Martinique than on French Polynesia, with respectively 60% and 72% (p < 0.05). Conjunctival hyperaemia and myalgia were not dependent on the case definition. This study of laboratory-confirmed cases selected through a case

definition did not allow testing the specificity and sensitivity of our case definition. However, our results show that the rash, foundation of our case definition, may be absent in a considerable proportion of patients.

These results are of importance for the implementation of a suspected case definition, the main tool for epidemiological surveillance systems, in territories where ZIKV infection is currently spreading. The case definition adopted on Martinique is maintained for outbreak surveillance by GPs as it has a suitable positive predictive value. Furthermore, widening of the case definition criteria could be considered so as to be more sensitive in specific situations such as the diagnosis of Zika in pregnant women for a reactive intervention.

The epidemiological situation in the FTA is a concern for European areas where *Aedes albopictus* is established [12]. To adapt prevention messages and improve knowledge, it is essential to continue the global surveillance with particular attention to complications (neurological cases [13]), pregnant women and children born from infected mothers [14].

At this stage of the introduction of ZIKV on the South American mainland, the laboratory of the NRC in French Guiana who first sequenced the ZIKV genome circulating in America [15] do not see a marked spatiotemporal phylogeny (Asian lineage in the Americas), nor a specific cluster. Given the low genetic variability observed (in 10,000 bp), using a Bayesian maximum clade credibility model did not seem suitable.

Current situation

As on 7 July 2016, the epidemic phase (phase 3) has been declared on Guadeloupe (28 April 2016) and Saint-Martin (15 June 2016); ZIKV circulation has been detected on Saint-Barthélemy and 185 clinical suspected cases have been estimated.

The cumulative estimated number of clinical suspected Zika cases reported by GPs since the beginning of outbreak is 32,400 on Martinique, 20,070 on Guadeloupe, 8,715 on French Guiana and 1,260 on Saint-Martin. Twenty-one cases of GBS related to ZIKV infection have been reported on Martinique, four on French Guiana and four on Guadeloupe. In addition, biological

TABLE 3

Other clinical signs in confirmed Zika cases, Martinique, 24 November 2015–20 January 2016 (n = 203)

Signs	Number of cases	Frequency
Headaches	28	14%
Itch	17	8%
Gastrointestinal signs	16	8%
Asthenia	10	5%
Lymphadenopathy	10	5%
Oedema	8	4%
Retro-orbital pain	8	4%
Ear, nose and throat signs	6	3%
Dizziness	3	1%

investigations are ongoing for sixteen further GBS cases. A total of 744 cases of ZIKV infection in pregnant women have been reported on French Guiana, 384 on Martinique, 225 on Guadeloupe and 12 on Saint-Martin. Nine malformations in fetuses or infants related to ZIKV infection have been reported or suspected to be in FTA. Finally, one death has been identified as potentially linked to Zika on Martinique [16].

Zika Surveillance Working Group

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Conflict of interest

None declared.

Authors' contributions

EDV, ML and AC wrote the manuscript. Staff of the Regional Office of French Public Health Agency and the Zika Surveillance Working Group took part in alert and surveillance systems of Zika. FN, RC, ILG, MM, OF, DR, SM, CH and PHA collaborated in molecular biology and serological techniques. All authors participated in the Zika surveillance. All authors read and approved the final manuscript.

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