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Dengue, chikungunya, and Zika virus infections imported to Paris between 2009 and 2016: Characteristics and correlation with outbreaks in the French overseas territories of Guadeloupe and Martinique

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ABSTRACT

Background: Dengue virus (DENV), chikungunya virus (CHIKV), and Zika virus (ZIKV) infections are rapidly expanding across countries and are being diagnosed in returned travellers who represent epidemiological sentinels. The French Territories of America (FTA) such as Guadeloupe and Martinique see high levels of tourism and have experienced three consecutive outbreaks by these viruses in the last decade.
Objective: This study was performed to evaluate how ill returned travellers could have represented epidemiological sentinels for these three expanding arboviral diseases over eight consecutive years. The degree of correlation between the cases of ill returned travellers arriving at a French tertiary hospital in Paris and the three outbreaks that occurred in the FTA during the study period was estimated.
Methods: All consecutive ill returned travellers diagnosed at the hospital in Paris with imported DENV, CHIKV, or ZIKV infections from January 2009 to December 2016 were included. Epidemiological and clinical variables were evaluated. Data concerning the incidence of arboviruses in the FTA, as well as the temporal relationship between the occurrence of imported cases and outbreaks in the FTA, were analyzed.
Results: Overall, 320 cases of arboviral infection were reported: 216 DENV, 68 CHIKV, and 36 ZIKV. Most of the patients presented with fever and exanthema. One hundred and fifteen patients were exposed in Guadeloupe or Martinique, which were the at-risk destinations in 25% of patients with DENV, 59% of patients with CHIKV, and 58% of patients with ZIKV. The occurrence of cases diagnosed in returning travellers followed the same time pattern as the outbreaks in these areas.
Conclusions: A temporal correlation was found between newly diagnosed imported cases of arboviruses and the three corresponding outbreaks that occurred in Martinique and Guadeloupe during 8 consecutive years. Thus, ill returned travellers act as epidemiological sentinels from the beginning up to the end of outbreaks occurring in touristic locations.
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Introduction

Dengue virus (DENV), chikungunya virus (CHIKV), and Zika virus (ZIKV) are three arboviruses that have caused many large-scale outbreaks in recent years, even reaching non-tropical countries like the southern USA (Añez and Rios, 2013) and the Mediterranean watershed (Succo et al., 2016). DENV is the most

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prevalent of these, and according to the World Health Organization (WHO), it is the most rapidly spreading arbovirus worldwide (Organization, 2009). Numerous DENV outbreaks have been described in the last 15 years (Brathwaite Dick et al., 2012). One of them took place in the Caribbean region during 2009 and 2010 affecting some of the French Territories of America (FTA) (Anon, 2018a,d). A CHIKV epidemic in South America and the Caribbean followed this, starting at the end of 2013 (PAHO WHO, 2018; Fischer et al., 2014). More recently, ZIKV reached almost all tropical areas in the Western Hemisphere, including the FTA, during an outbreak in 2016 (Fauci and Morens, 2016).

DENV, CHIKV, and ZIKV infections are commonly observed in returning travellers. As has already been shown with dengue fever in Brazil (Wilson et al., 2014) and Madeira (Frank et al., 2013), CHIKV in Canadian tourists returning from affected areas (Boggild et al., 2017), and ZIKV disease on the American continent (Hamer et al., 2017), ill returned travellers may act as epidemiological sentinels. Even more recently, yellow fever cases were described in travellers returning from Brazil where an outbreak has been occurring since December 2016 (Hamer et al., 2018). However, the sustainability of the sentinel phenomenon has not been studied.

Moreover, studying travellers with tropical diseases highlights some particular features of these diseases that may be taken for granted or not properly studied in endemic areas. For instance, CHIKV-related chronic arthralgia was first described in returned travellers from Reunion Island (Marimoutou et al., 2012). Additionally, the sexual transmission of ZIKV has been observed in non-travelling sexual partners of infected travellers (Hills et al., 2016).

The FTA, namely Guadeloupe, Martinique, French Guiana, Saint Martin, and Saint Barthélemy, are French overseas departments located in the Caribbean Sea and South America. These destinations are quite popular among French travellers. Due to their location, these territories have also recently been affected by the above-mentioned outbreaks (Anon, 2018c,e,f,g). Of all the FTA, Guadeloupe and Martinique are the two most visited islands, with an estimated 225 000 French tourists in 2007 (Anon, 2007).

The aim of this study was to describe the characteristics of these three imported arboviral diseases, as well as the temporal relationship between the number of returned travellers diagnosed with any of these three viruses at a French tertiary hospital in Paris and the three concurrent outbreaks in Guadeloupe and Martinique, over an 8-year period.

Methods

This retrospective study was conducted at the Hôpital Universitaire La Pitié-Salpêtrière, a tertiary teaching hospital in Paris, France. All patients older than 16 years of age with a confirmed diagnosis of DENV, CHIKV, or ZIKV infection between January 1, 2009 and December 31, 2016 were included.

DENV cases were confirmed either by a positive reverse transcriptase polymerase chain reaction (RT-PCR) in a blood sample, or the presence of non-structural protein 1 (NS1) antigen or specific immunoglobulin M (IgM) antibodies (Anon, 2018b,c). CHIKV cases were confirmed either by a positive RT-PCR in a blood sample, or seroconversion (i.e., a four-fold increase in immunoglobulin G (IgG) levels in two serum samples with a 2-week interval in-between), or specific IgM antibodies (Anon, 2018b,c). ZIKV cases were confirmed by positive RT-PCR in either a blood or a urine sample (Anon, 2016).

The following epidemiological variables were evaluated: age, sex, country of birth, region of exposure (with a focus on the FTA), reason for travelling, time of exposure, time between return and onset of the infection, and whether the patient had received information prior to their departure. Patients attended for either a specialized consultation for ill returned travellers, or were admitted to the infectious diseases ward as inpatients, depending on the severity of their symptoms and comorbidities. Authorization for the study was obtained from the French National Commission for Data Processing and Liberties. No consent form was collected because this study is descriptive and retrospective. Clinical data regarding the most relevant presenting symptoms were also collected.

To determine the incidence of DENV, CHIKV, and ZIKV infection in Martinique and Guadeloupe, a search was performed of the epidemiological data published every week by the former Institut de Vieille Sanitaire (InVS) in the *Bulletin Epidémiologique Hebdomadaire* for the study period. InVS is used to collect all data on transmissible diseases and other diseases in the entire French Republic, including the FTA. Data were collected particularly intensively during these outbreaks as part of the strengthened surveillance framework for DENV (Anon, 2010), CHIKV (Anon, 2013), and ZIKV (Anon, 2016).

A comparison graphic was designed for each disease, encompassing the outbreak periods. Two variables were compared using Microsoft Excel software version 2010. The number of confirmed diagnoses in ill travellers returning from Guadeloupe and Martinique was represented in the form of a histogram. Patients returning from both islands and those who had visited other regions as well were excluded, as the exact region of exposure was not ascertainable. In parallel, curves were drawn to illustrate the total numbers of cases estimated by the InVS for Guadeloupe and Martinique. For didactic reasons, the time periods on each graphic were grouped into either weeks or 3-month periods, depending on the number of cases seen at the study institution and the duration of the outbreaks in Guadeloupe and Martinique.

Results

Demographic and epidemiological characteristics

Overall, 320 patients (151 male and 169 female; median age 41 years) were seen during the study period, including 216 dengue, 68 chikungunya, and 36 Zika cases (Table 1). Most of the patients were tourists, followed by people visiting friends or relatives and business travellers. Overall, 58 (18%) patients were admitted to the hospital.

Table 2 shows the distribution of the diagnoses according to the region of exposure. Guadeloupe and Martinique were the two regions that contributed the highest numbers of sick travellers, with a total of 115 cases (36%), including 60 (19%) from Guadeloupe and 55 (17%) from Martinique. These two islands were followed by Southeast Asia, which contributed 91 (28.44%) of the ill travellers.

Clinical characteristics

Table 3 shows the frequencies of the main clinical symptoms for each arboviral disease. Almost all patients with DENV presented with fever (and/or sweats and chills), and a skin rash was present in more than half of the patients. There was only one case of complicated dengue, which occurred in a 53-year-old male returning from Martinique. In the CHIKV group, fever was present in most cases, while arthralgia was even more common (93%). Eight patients with CHIKV (12%) went on to develop chronic arthralgia or arthritis, which at the time of data collection for this study had lasted for a median of 75.5 days (range 2–20 months). The most common symptoms in patients with ZIKV were exanthema and musculoskeletal pain, whereas fever was present in 19 patients (53%). At the time of writing, none of them had developed Guillain–Barré syndrome. Other neurological

Table 1
Demographic characteristics of 320 travellers diagnosed with dengue, chikungunya, and Zika virus infections, 2009–2016.

	Dengue (n = 216, n (%))	Chikungunya (n = 68, n (%))	Zika[a] (n = 36, n (%))	Total (n = 320, n (%))
Male	115 (53.24)	22 (32.35)	14 (30.43)	151 (47.19)
Age (years), median (range)	38.01 (17–77)	50.35 (21–77)	40.72 (16–74)	40.93 (16–77)
Inpatients	52 (24)	4 (6)	2 (6)	58 (18)
Time from return to consultation (days), median (range)	5.83 (0–39)	22.03 (0–139)	9.69 (1–39)	9.71 (0–139)
Reason for travelling				
Tourism	169 (78)	30 (44)	22 (61)	221 (69)
Business	28 (13)	9 (13)	1 (3)	38 (12)
Visiting friends or relatives	12 (6)	23 (34)	12 (33)	47 (15)
Other[b]	7 (3)	6 (9)	1 (3)	14 (4)
Pre-travel information received	43 (20)	6 (9)	1 (3)	50 (16)

[a] Including one pregnant woman.
[b] Other reasons for travelling included university exchanges and programmed medical care.

Table 2
Regions of infection by dengue, chikungunya, and Zika virus infections in 320 travellers, 2009–2016.

Region of travel	Dengue (n = 216, n (%))	Chikungunya (n = 68, n (%))	Zika (n = 36, n (%))	Total (n = 320, n (%))
Guadeloupe	29 (13)	20 (29)	11 (31)	60 (19)
Martinique	25 (12)	20 (29)	10 (28)	55 (17)
Martinique AND Guadeloupe	1 (0.50)	–	–	1 (0.30)
Other Caribbean islands	14 (6)	3 (4)	9 (19.57)	26 (8)
Mexico	4 (2)	–	2 (4.35)	6 (2)
Central America	4 (2)	–	1 (2.17)	5 (2)
South America	10 (5)	3 (4)	3 (8.33)	16 (5)
Madeira Island (Portugal)	2 (1)	–	–	2 (0.61)
Africa	9 (4)	3 (4)	–	12 (4)
India and Bangladesh	20 (9)	10 (15)	–	30 (9)
Maldives	2 (1)	–	–	2 (0.6)
Southeast Asia	85 (40)	5 (7)	–	90 (28)
China and Hong Kong	2 (1)	–	–	2 (0.6)
More than one region in Asia	1 (0.5)	–	–	1 (0.30)
French Polynesia and New Caledonia	7 (3)	3 (4)	–	10 (3)

Table 3
Clinical characteristics of dengue, chikungunya, and Zika virus infections in 320 travellers, 2009–2016.

Clinical symptom	Dengue (n = 216, n (%))	Chikungunya (n = 68, n (%))	Zika (n = 36, n (%))	Total (n = 320, n (%))
Fever/sweat/chills	214 (99.07)	59 (86.76)	19 (52.78)	292 (91.25)
Skin rash	132 (61.11)	33 (48.53)	35 (97.22)	200 (62.50)
Fatigue	64 (29.63)	11 (16.18)	ND	75 (23.44)
Arthralgia/myalgia	33 (15.28)	63 (92.65)	28 (77.78)	124 (38.75)
Gastrointestinal symptoms	21 (9.72)	2 (2.94)	1 (2.78)	24 (7.50)
Headache	9 (4.17)	2 (2.94)	6 (16.67)	17 (5.31)
Haemorrhage	1 (0.46)	–	–	1 (0.31)
Long-term sequelae[a]	–	8 (11.76)	–	8 (2.50)
Conjunctivitis	–	–	3 (8.33)	3 (0.94)

ND,.
[a] Long-term sequelae included arthralgia and arthritis persisting from 2 up to 20 months.

symptoms, like headaches, appeared in 17% of Zika patients. There was one pregnant woman who underwent a pregnancy termination.

Arbovirus outbreaks in Guadeloupe and Martinique

Dengue virus outbreak

The outbreak of DENV started in Guadeloupe during epidemiological week 49 of 2009 (in a given year, epidemiological week 1 ends on the first Saturday in January, as long as it falls at least 4 days into the month), peaked by the end of July (week 30 of 2010), and was considered finished in week 42 of 2010, with a total of 43 990 declared cases of dengue fever (Anon, 2018g). In Martinique, the outbreak started in week 8 of 2010, peaked during week 32, and ended in week 45, with a total of 41 970 declared cases (Anon, 2018f).

Figure 1 compares the number of DENV cases diagnosed at the study institution after travel in Guadeloupe or Martinique with the incidence of declared cases during the outbreak in these FTA. The time periods are grouped into epidemiological weeks starting at week 49 of 2009 and ending with data from epidemiological week 45 of 2010 when the outbreak was declared over in Martinique. Cases increased regularly in travellers returning from Guadeloupe

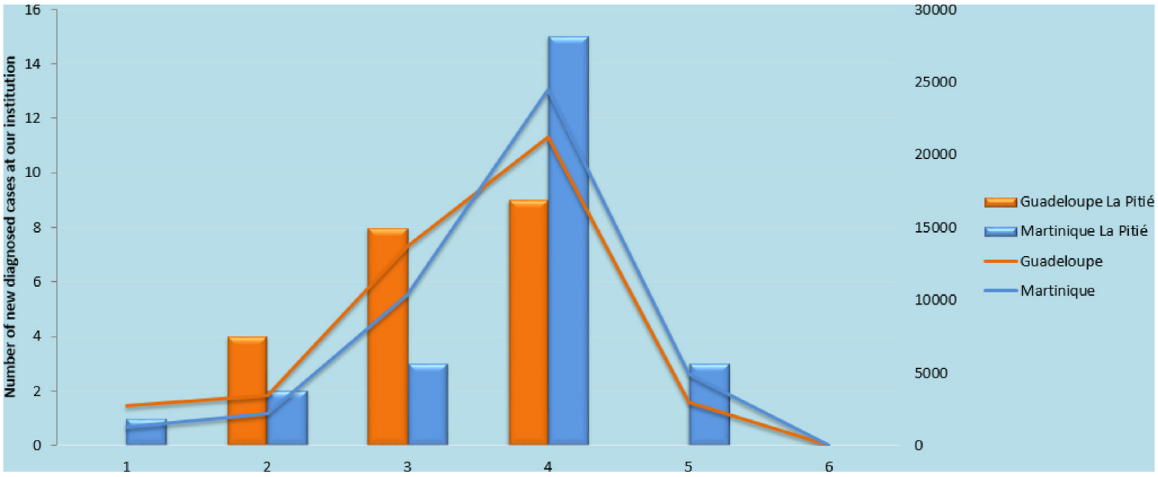


Figure 1. The numbers of travellers returning from Guadeloupe and Martinique diagnosed with dengue virus infections seen at the study institution (bars) and the numbers of cases officially reported in Guadeloupe and Martinique (lines) during the outbreak (week 49, 2009 to week 45, 2010).
The numbers on the *x*-axis represent periods of weeks, as follows: 1 = week 49, 2009 to week 8, 2010; 2 = week 8, 2010 to week 18, 2010; 3 = week 18, 2010 to week 28, 2010; 4 = week 28, 2010 to week 36, 2010; 5 = week 36, 2010 to week 45, 2010; 6 = week 45, 2010 to the end of 2010.

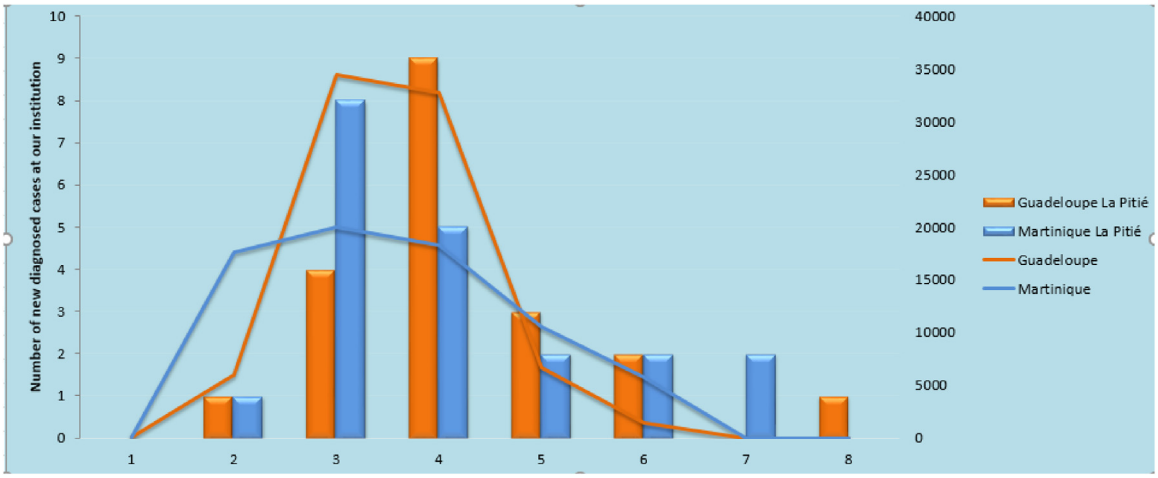


Figure 2. Comparison of the numbers of confirmed cases of chikungunya virus infection coming from Guadeloupe and Martinique seen at the study institution (bars) and the cases reported in Guadeloupe and Martinique in the *Bulletin Epidémiologique Hebdomadaire* (Weekly Epidemiological Bulletin) during the outbreak (week 49, 2013 to week 2, 2015).
The numbers on the *x*-axis represent weeks, as follows: 1 = week 49, 2013; 2 = week 16, 2014; 3 = week 24, 2014; 4 = week 32, 2014; 5 = week 40, 2014; 6 = week 50, 2014; 7 = week 2, 2015; 8 = week 9, 2015.

or Martinique, with a peak paralleling that of the outbreak on each island, followed by a constant decrease in both the imported cases seen at the study institution and in those regions.

Chikungunya virus outbreak

The CHIKV outbreak in the FTA started in epidemiological week 49 of the year 2013. Martinique was involved first, and saw a progressive decrease after week 28 of 2014; the outbreak was declared over in the second week of 2015, with a total of 72 664 declared cases. In Guadeloupe, the outbreak started later (week 52 of 2013), peaked between weeks 20 and 28 of 2014, and was declared over during week 47 of 2014. The total number of declared cases in Guadeloupe was 81 200 (Anon, 2018e).

Figure 2 compares the numbers of CHIKV in ill travellers returning from Guadeloupe and Martinique, and the incidence rates of declared cases on these islands. This time, the numbers were grouped into epidemiological weeks starting from week 49 of 2013 and ending at week 9 of 2015. In 2014, there were more imported cases coming from Martinique within the first weeks (nine cases up until week 24), following which this number tended to decrease constantly. This correlated with the curve of declared cases in Martinique, which peaked around weeks 20 and 28, with a constant decrease thereafter. For Guadeloupe in 2014, the number of imported cases correlated with the incidence on the island as well. The highest number of cases at the study institution was seen between weeks 24 and 32 (nine patients in these 8 weeks), with a constant decrease thereafter. This correlated with the peak of in situ cases during the outbreak between weeks 20 and 28.

Zika virus outbreak

The ZIKV outbreak started officially during epidemiological week 3 of 2016 in Martinique and week 17 in Guadeloupe. Martinique experienced a longer outbreak period of 39 weeks compared to the 22 weeks in Guadeloupe. During this period, there

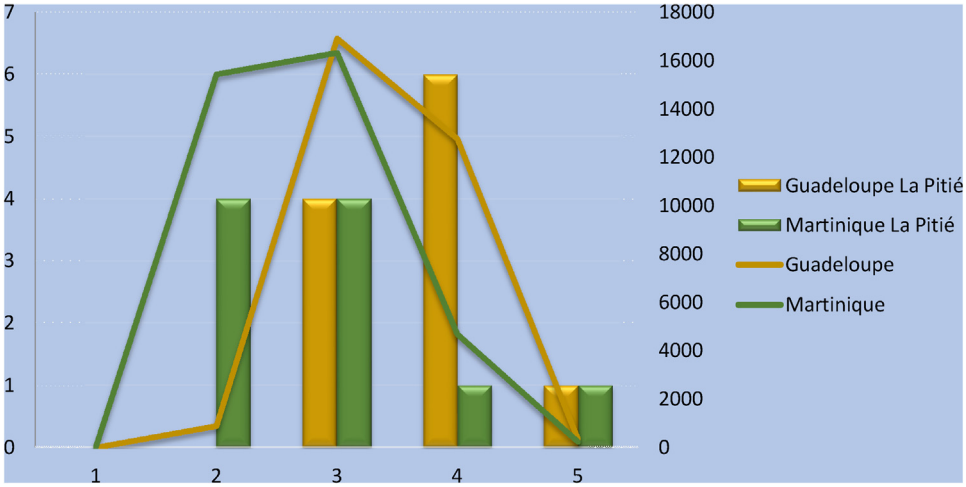


Figure 3. Comparison of the numbers of confirmed cases of Zika virus infection returning from Guadeloupe and Martinique seen at the study institution (bars) and the cases reported in Guadeloupe and Martinique in the *Bulletin Epidémiologique Hebdomadaire* (Weekly Epidemiological Bulletin) during the outbreak (week 3, 2016 to week 41, 2016). The numbers on the *x*-axis represent months, as follows: 1 = December 2015; 2 = January–March 2016; 3 = April–June 2016; 4 = July–September 2016; 5 = October–December 2016.

were 28 345 declared cases of ZIKV infection in Guadeloupe and 35 190 in Martinique. The outbreak peaked at week 23 for Guadeloupe and week 11 for Martinique (Anon, 2018c). Figure 3 shows the correlation of these outbreaks with the numbers of imported ZIKV cases. The first period corresponds to the number of confirmed cases between November 24, 2015 and the first publication on January 7, 2016 (Anon, 2016). Until that time there had been 12 cases of ZIKV in Martinique and none in Guadeloupe. Cases at the study hospital peaked during the first 3-month period, as did the incidence of ZIKV in Martinique. The decrease was then constant until the end of the outbreak. The same correlation was seen for Guadeloupe. The peak of declared cases on the island during the second 3-month period paralleled the peak of cases at the study institution (eight cases in the second 3-month period). Of note, seven new diagnoses were observed during the third 3-month period, corresponding to the persistence of the outbreak after the peak and the main summer holiday season in France (July and August).

Discussion

This study showed how returned ill travellers diagnosed with DENV, CHIKV, and ZIKV acted as epidemiological sentinels over an 8-year period, paralleling three successive outbreaks occurring on two different islands that are highly popular amongst French travellers. Some of the epidemiological and clinical characteristics of these three imported arboviral diseases deserve further comment.

A parallelism has been found between cases of DENV imported in Western countries by travellers returning from Brazil and the occurrence of DENV outbreaks in Brazil (Wilson et al., 2014). Similarly, in Madeira, an island affected by a DENV outbreak during the autumn of 2012 that caused over 2000 autochthonous cases, imported cases pointed to the influence of the rainy season on the occurrence of DENV (Frank et al., 2013). The same phenomenon has been described for imported CHIKV after the Americas outbreak in 2013 (Boggild et al., 2017; Organization and Asia, 2008) and for imported ZIKV in parallel with the most recent outbreak (Hamer et al., 2017; WHO, 2018; Leder et al., 2017). The role of travellers as epidemiological sentinels was recently focused on dengue genotypes (Jelinek et al., 2002). Looking at the dengue cases imported into some European countries between 2012 and 2014, the DENV genotypes matched those causing outbreaks in other parts of the globe at the same time.

Overall, the clinical characteristics of the study patients were in agreement with those described for each of the arboviral diseases in other settings (Hamer et al., 2017, 2018; Leder et al., 2017; Neumayr et al., 2017). In the DENV group, fever was present in almost every patient and over 60% of them presented exanthema. Only one patient presented with severe haemorrhagic fever. DENV infection was the arboviral disease with the highest percentage of hospitalized ill patients. In concordance with previous reports, most of the imported cases of dengue fever came from Southeast Asia, followed by the Americas (Jelinek et al., 2002).

Unsurprisingly, musculoskeletal and articular pain, as well as fever, was present in more than 85% of patients with CHIKV infection. In more than 10% of these patients, the articular and muscular pain was chronic, lasting for a median of 75.5 days after onset. The longest duration for arthralgia was 20 months in a patient returning from Guadeloupe. It has been shown previously in returning travellers that CHIKV infection can be followed by chronic rheumatic symptoms: these symptoms were seen in up to 44% of 85 patients at >30 months after disease onset (Marimoutou et al., 2012).

All except one of the 36 study patients with ZIKV presented a skin rash, and the next most frequent symptom was musculoskeletal pain, as described in another larger series of imported ZIKV (Hamer et al., 2017). None of the 46 cases with ZIKV had returned from regions other than the Americas. However, it should not be forgotten that ZIKV infection may also affect travellers to endemic areas other than the Americas (Kwong et al., 2013). The only woman diagnosed with ZIKV while pregnant underwent a pregnancy termination due to her anxiety regarding the risk of congenital Zika syndrome, which had already been reported in Brazil (Rasmussen et al., 2016). Of note, 10 asymptomatic pregnant women (data not shown) also consulted the hospital with the same anxiety, as they had also returned from endemic countries; however they were found not to be infected with ZIKV.

Seeking pre-travel medical advice is considered a major way of avoiding any infectious complications while on holiday (Lestelle et al., 2015). In a French random sample telephone survey, 53% of interviewed travellers thought that the risk of acquiring an infectious disease while visiting a tropical country was important, and 75% thought that consulting a physician before travelling abroad was justified (Anon, 2007). However, this is in contrast with the low percentage (15%) of patients in the present study who sought pre-travel advice. This renders the question of how many cases could have been avoided with adequate pre-travel counselling.

Among the limitations of this study, it is important to highlight that cases declared by the InVS in Guadeloupe and Martinique were estimations and not confirmed cases, as in the returning travellers (Anon, 2018c,e,f,g). The time periods were grouped according to the dates on which the numbers of cases were available. In all cases, it was observed graphically how the cases diagnosed at the study institution were concordant with the evolution of the outbreaks in the FTA, regardless of the period of the year when these outbreaks erupted. As a retrospective descriptive study, all of the limitations of this type of study are implied.

In conclusion, ill returned travellers diagnosed with infections caused by three arboviruses (DENV, CHIKV, and ZIKV) were epidemiological sentinels for three successive outbreaks occurring in two popular destinations for French tourists. The description of imported diseases is a continuous source of knowledge for infectious diseases specialists. This highlights the importance of making a firm aetiological diagnosis in returning travellers and maintaining awareness of the existing outbreaks in countries visited by travellers.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Declaration

All authors have seen and approved the manuscript, and all contributed significantly to the work. The manuscript has not been published previously nor is it being considered for publication elsewhere.

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