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A B S T R A C T

Mayaro Virus is an emerging arbovirus which can be responsible of important outbreaks in tropical regions. A retrospective study was performed in French Guiana, an ultraperipheral region of Europe in Amazonia. We identified 17 human cases between 2003 and 2019. The clinical and biological picture was close to Chikungunya with fever and arthralgia. One patient had acute meningo-encephalitis, and 4 had persistent arthralgia. Physicians should be aware of this virus, as imported cases in Europe have already occurred.

Author summary: Latin America has experienced several epidemics of arboviruses in recent years, some known for a long time, such as the dengue virus, and others of more recent introduction such as the chikungunya or Zika viruses. There are other arboviruses for the moment more discreet which are rife with low noise in several countries of the continent, such as the Mayaro virus. This alphavirus, with a presentation similar to that of the chikungunya virus, is currently confined to transmission by forest mosquitoes, but its potential to be transmitted by coastal mosquitoes such as *Aedes aegypti*, make it a potential candidate for a continent-wide epidemic. It therefore seems necessary to know this virus as well as possible in order to anticipate the occurrence of a possible new epidemic. We present here a both demographic and clinical study of this endemic arbovirus disease in French Guiana.

1. Introduction

The population of French Guiana regularly experiences epidemics of dengue virus (2009, 2013, 2020) (DENV) and there are endemic arboviruses (e.g. Tonate virus (TONV)) (Mutricy et al., 2020). In 2014 it experienced the epidemic of Chikungunya (CHIKV) and in 2016 that of the Zika virus (ZIKV) (Bonifay et al., 2021; Flamand et al., 2019). On a village scale, the Oropouche virus (OROV) has already been responsible for many cases (Gaillet et al., 2021) These epidemiological data show the need to describe arboviruses that are likely to (re)emerge in the future, in order to prepare preventive and diagnostic capacity, and a surveillance system that can promptly detect emergence. The Mayaro virus (MAYV) –a virus that is still relatively unknown—is such a candidate (Acosta-Ampudia et al., 2018). It is an arbovirus of the Togaviridae family, (*Alphavirus* genus) which was first described in 1954 in Trinidad (Anderson et al., 1957). The main vector is the sylvatic *Haemagogus* spp. mosquitoes but *Aedes aegypti* has also been incriminated in the transmission to human host (Hoch et al., 1981; Lednicky et al., 2016). MAYV has circulated in Latin America causing several epidemics among Amazonian rainforest populations in Venezuela, Peru, Bolivia, and Brazil (Causey and Maroja, 1957; Pinheiro et al., 1981; Auguste et al., 2015; Schaeffer et al., 1959; Tesh et al., 1999). MAYV was first isolated in French Guiana (FG), a European outermost region and a French overseas territory in Amazonian South America, in 1996. The local estimation of seroprevalence was 6.3% to reach 34.7% and MAYV affected remote sylvatic areas (Talarmin et al., 1998). More recently, a large seroprevalence study of arboviruses across French Guiana reached 18% in some areas. (Hozé et al., 2020) The study also showed an

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important sylvatic cycle for MAYV with most infections occurring in rural areas, near natural reservoirs, and in individuals more likely to be in contact with the forest (i.e., often adult males)). Whereas prevalence data is available in French Guiana for MAYV, its incidence is unknown.

The objectives of the present study to describe the clinical and biological features of MAYV infection, a subject for which there are few data.

2. Methods

This study took place from January 1st, 2003 to December 31st, 2019 (Mutricy et al., 2020). We included patients from the regional hospital group (including Cayenne, Saint-Laurent du Maroni and Kourou hospitals and patients from health centers in remote villages. All serum samples were sent for arboviral IgM serological diagnosis to the National Reference Centre for arboviruses (NRCA) at Institut Pasteur in French Guiana. Clinical and biological data were collected through the electronic medical and biological records of the health facilities (Cora®, SisV2®, DMU-net®). All sera were tested for a panel of arboviruses circulating in FG including dengue virus DENV, yellow fever virus (YFV), Saint-Louis encephalitis virus (SLEV), TONV, MAYV, CHIKV since 2014 and ZIKV since 2016.

Serological diagnosis was performed using an in-house IgM capture enzyme-linked immunobsorbent assays (MAC-ELISA). The detection of serum IgM antibodies to MAYV was performed by the NRCA in FG using an in-house MAC-ELISA test modified from that previously described. (7). Microtitration plates (Nunc Maxisorp; ThermoFisher Scientific, Roskilde, Denmark) were sensitized for 2 h at 37 °C with goat antihuman IgM (Sigma-Aldrich, St. Louis, MO) diluted in phosphate-buffered saline (PBS)–Tween buffer(PBS, 0.1% Tween 20). After three washes with PBS–Tween buffer, sera, positive and negative controls diluted (1/100) inPBS–Tween–milk buffer (PBS, 0.5% Tween 20, and 5% nonfat dry milk) were added to wells and incubated for 1 h at 37 °C. The wells were washed again and incubated overnight at 4 °C in a humidified container with MAYV or normal antigens diluted in PBS–Tween–milk buffer. Antigens were prepared by extracting MAYV-infected or normal brains of suckling mice with sucrose–acetone. Specific antigen binding was demonstrated by using an ascitic fluid from MAYV hyperimmune mice diluted in PBS–Tween–milk buffer incubated for 1 h at 37 °C, followed by incubation of a goat antimouse peroxidase–labeled conjugate (Sigma-Aldrich) diluted inPBS–Tween–milk buffer incubated for 1 h at 37 °C. Antigens and hyperimmune ascitic fluids are produced by the NRCA in FG. Three washes with PBS–Tween buffer were performed between each step. The 3,3,5,59-tetramethylbenzidine liquid substrate system (Sigma-Aldrich) was used as the substrate. The titer of the optical density for MAYV antigen in the patient serum divided by the optical density for negative MAYV antigen in the same serum was measured. The presence of IgM against the studied virus was defined by a ratio higher than 3.

The optical density ratio was calculated by dividing the patient's serum to the considered viral antigen by the optical density of the same serum on a negative antigen. The presence of anti-MAYV IgM was defined by a ratio greater than 3. Molecular RT-PCR diagnosis of MAYV was performed sporadically prior to 2016, and regularly but not consistently from 2017 onward.. (Talarmin et al., 1998).

The exclusion criteria were confirmed alternative diagnosis, detection of IgM against other arboviruses and the absence of medical records. Then, an adjudication committee (two infectious diseases specialists and one virologist) re-evaluated all included patients, and classified them in four categories:

1. Certain probability: positive RT-PCR;
2. High probability: typical arbovirus infection (i.e. with two or more of the following symptoms: fever, chills, headaches, myalgia and arthralgia) and IgM seroconversion (appearance of IgM between 2 consecutive samples collected 5 days apart).
3. Medium probability: typical clinical picture and single positive sample for IgM;
4. Low probability: atypical presentation and single positive sample for IgM;

In order to better describe MAYV infection, only certain, high and medium probabilities groups were retained for analysis.

We calculated the annual incidence rate using census data associated with their 95% confidence interval (95% CI), and we performed a descriptive analysis of clinical and biological features.

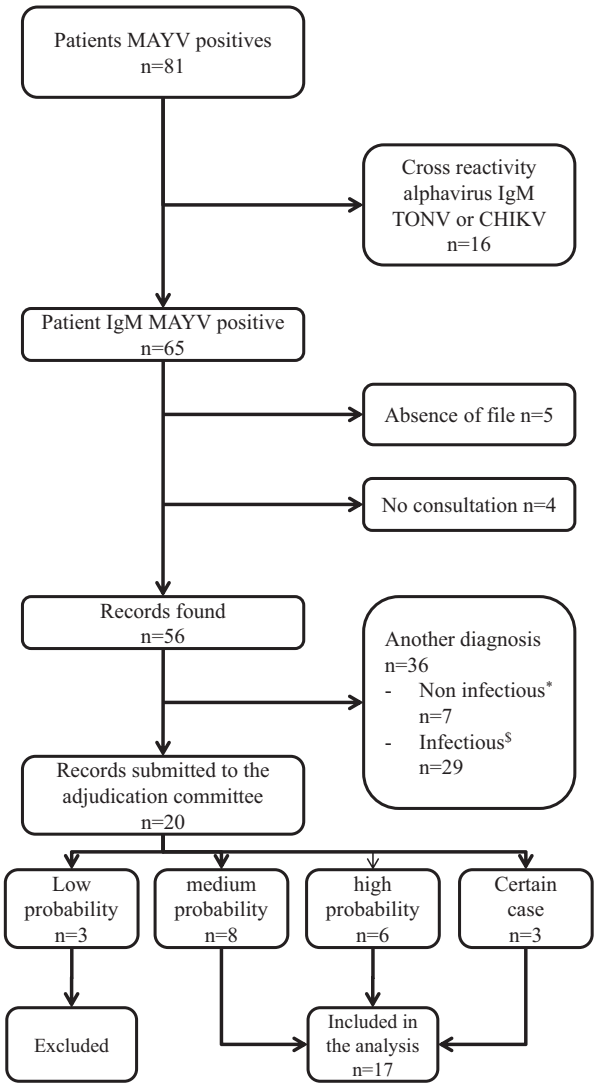

Fig. 1. Flowchart of the study on Mayaro virus (MAYV) in French Guiana 2003–2019.
TONV: Tonate virus; CHIKV: chikungunya virus.
Certain probability: positive RT-PCR; High probability: typical arbovirus infection (i.e. with two or more of the following symptoms: fever, chills, headaches, myalgia and arthralgia) and IgM seroconversion (appearance of IgM between 2 consecutive samples collected 5 days apart); Medium probability: typical clinical picture and single positive sample for IgM; Low probability: atypical presentation and single positive sample for IgM.
* 1 childbirth, 1 breakthrough bleeding, 1 malaise, 1 depression, 1 wall hematoma during pregnancy, 1 chronic hepatitis B complicated with hepatocellular carcinoma, 1 acute hepatobiliary disease.
$. 9 chikungunya, 1 dengue, 3 Amazon toxoplasmosis, 3 pyelonephritis, 2 Q fever, 2 *Plasmodium vivax* malaria attacks, 1 angina, 1 community acquired pneumonia, 3 leptospirosis, 1 IRIS on HIV, 3 unknown diagnosis.

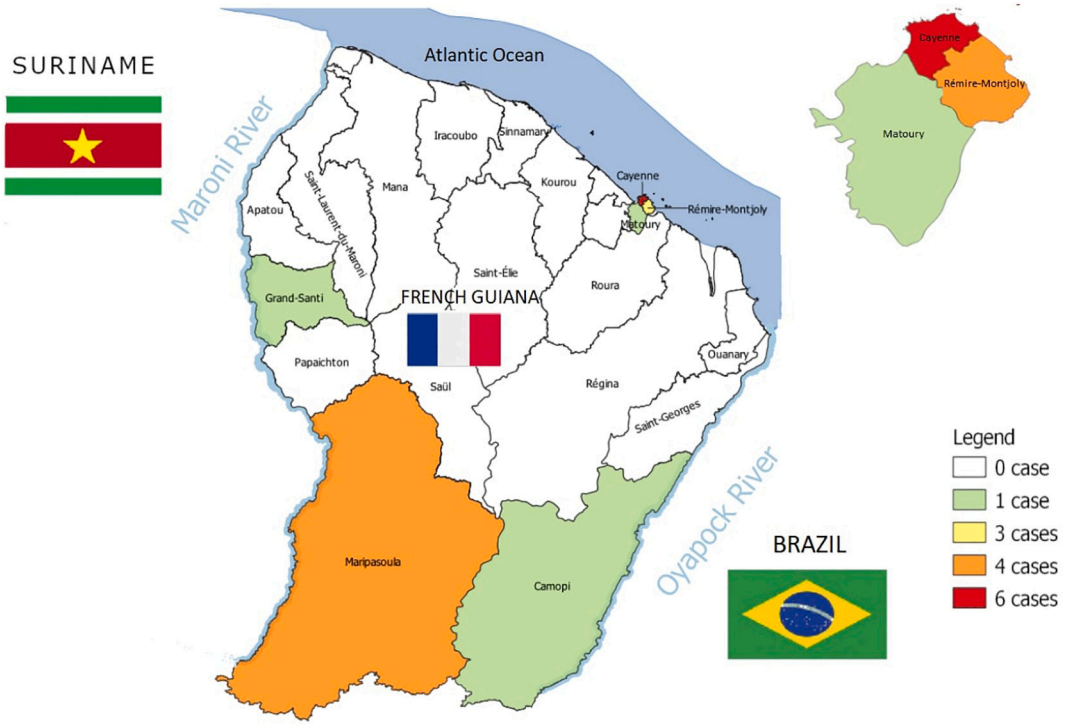

Fig. 2. Distribution by commune of the 17 cases of Mayaro virus infections in French Guiana, 2003-2016.

2.1. Ethical statement

The study followed the Declaration of Helsinki. The ethics committee of Cayenne hospital gave its approval. Records data were anonymized. The database was declared to the *Commission Nationale de l'Informatique et des Libertés* (CNIL): n°2145898.

3. Results

During this study, 65 patients had a positive IgM serology for MAYV only (Fig. 1), but only seventeen were validated by the scientific committee. Among them, 3 had certain, 6 high, and 8 medium probabilities. The Fig. 2 shows the distribution by commune of the 17 cases of Mayaro virus infections in French Guiana, 2003-2016 by commune (Fig. 2). Three patients were finally excluded by the adjudication committee because of a single positive IgM serology (and not a seroconversion) and a clinical picture too aspecific to be taken into account (acute decompensation of a psychiatric pathology, workup of adenopathy in a schoolboy and workup of pain in the hand and inflammatory throat in an 11-year-old child). There were 7 women (41%) and 10 men. Age range was 1–54 years (median = 30; IQR = 22–47). Among the 16 with known country of birth, 5 (31%) were born in Brazil, 4 (25%) in mainland France and 3 (19%) in French Guiana (plus 1 in Dominican Republic and 1 in French Polynesia). At least 11/15 (73%) reported a journey in the forest. Among the 12 for whom the data was available, 5 (42%) were soldiers of the French army, 4 (33%) were illegal goldminers, and 3 (25%) had a job not linked to the forest. One patient had a significant medical history (high blood pressure). Three patients were hospitalized, all recovered. At least 3 of them (18%) presented persistent arthralgia beyond one month. Clinical and biological features are reported in Table 1 and compared with other publications, and the detail of the clinical picture of each patient is reported in Table 2. One patient was a 47-year-old Brazilian man working in an illegal gold mining site in the deep rainforest, presented an unusual acute meningo-encephalitis. He had a five-day history of frontal headaches, photophobia, meningeal stiffness, Kernig and Brudzinski signs, diarrhea, fatigue, aphasia, and confusion. Leukocytes were at 9.40 G/L, neutrophils at 7.5 G/L; CRP was 4.8 mg/L. Cerebrospinal fluid (CSF) showed: white blood cell count 450/mm^3 (20% neutrophils, 73% lymphocytes, 7% monocytes), blood cell count 660/mm3, protein 0.77 g/L, and glucose 2.30 mmol/L (concomitant blood glucose was 6 mmol/L). Etiological investigations were negative for malaria, but showed IgM MAYV seroconversion. The clinical evolution was favorable in two days without any neurological sequelae. CSF abnormalities disappeared six days after the initial screening.

4. Discussion

This is the first study that describes clinical symptoms associated to MAYV infection in French Guiana. Here the incidence was low whereas seroprevalence studies reached 2.8 to 6.3% (Talarmin et al., 1998; Hozé et al., 2020). The absence of systematic screening, lack of knowledge of the physicians and misdiagnosis probably led to major under-estimation. This highlights the importance of improving the bio-clinical description of MAYV in order to improve practitioners diagnostic accuracy. In French Guiana, most physicians are unaware of MAYV, which is easily confused with other better known arboviruses, notably for arthritogenic alphaviruses, CHIKV which was detected in FG 2013–2015 (Bonifay et al., 2018a).Surprisingly, there are few studies describing the clinical presentation of MAYV infection (Pinheiro et al., 1981; Auguste et al., 2015; Tesh et al., 1999; Azevedo et al., 2009; Vieira et al., 2015; Halsey et al., 2013). Fever (99%), arthralgia (83%) and headaches (83%) are often reported whereas cutaneous rashes are not so frequent (50%), similar to chikungunya infection (but without tenosynovitis) (Bonifay et al., 2018b). Classical blood tests are generally normal or show non-specific anomalies. The patient's place of stay or life may also guide diagnosis, as *Haemagogus* spp. (main vector of MAYV) is sylvatic whereas *Aedes Aegypti* (main vector of CHIKV) is urban.

We described a case of acute meningoencephalitis attributed to MAYV. A single neurological presentation associated to MAYV infection has also previously been described in Mexico. This patient presenting hemorrhages, thrombocytopenia, jaundice and encephalopathy, leading to death (Navarrete-Espinosa and Gomez-Dantes, 2006). Alphaviruses are known to be responsible for central nervous system infections,

Table 1
Main clinical and biological characteristics of 17 patients with MAYV infection and comparison with the main studies found in the literature.

Variables	Mutricy et al.	Azevedo et al. (Tesh et al., 1999)	Vieira et al. (Talarmin et al., 1998)	Pinheiro et al. (Anderson et al., 1957)	Halsey et al. (Hozé et al., 2020)	Auguste et al. (Hoch et al., 1981)	Tesh et al. (Causey and Maroja, 1957)
Date	2003–2019	2008	2014	1978	2010–2013	2010	1995–1998
Type of study	Monocentric retrospective	Epidemicinvestigation	Study of serum during a dengue epidemic	Epidemicinvestigation	Cohort study	Epidemic Surveillance Program	Surveillance Program
Sites	Cayenne, French Guiana	Santa Barbara, State of Pará, Brazil	State of MatoGrosso, Brazil	Belterra, State of Para, Brazil	Amazon basin, Peru	The Estacion village, State of Portuguesa, Venezuela	Peru
Number of patients	17	36 of which 3 were asymptomatic	6	43	16	6	22
Diagnostic method	RT-PCR or IgM Serology	IgM serology	RT-PCR	Inoculation with mouse	Cell Culture, RT-PCR, IgM Serology	Cell culture	Viral Culture or IgM Serology
Median age (IQR) (year)	35 (26–47) Range (1–54)	From 4 to 55	22,5 (16,5–55)	From 2 to 62	34 (12–43)	42 (17–60)	From 9 to 65
Sex ratio (m/f)	1.4	1.4	1		0.8	1	0.8
Symptoms/Clinical signs = N(%)							
Fever n(%)	17/17 (100)	33/33 (100)	6/6 (100)	43/43 (100)	16/16 (100)	5/6 (83,3)	22/22 (100)
Arthralgia n(%)	11/17 (65)	29/33 (89)	5/6 (83,3)	43/43 (100)	15/16 (93,8)	6/6 (100)	11/22 (50)
Headache n(%)	12/17 (71)	21/33 (64)	6/6 (100)	40/43 (86)	15/16 (93,8)	3/6 (50)	22/22 (100)
Rash n(%)	5/17 (29)	16/33 (49)	–	29/43 (67)	8/16 (50)	1/6 (16,7)	7/22 (31,9)
Myalgia n(%)	6/17 (35)	25/33 (75)	6/6 (100)	32/43 (74)	14/16 (87,5)	–	17/22 (77,3)
Low back pain n(%)	4/17 (24)	–	–	–	–	–	–
Fatigue n(%)	7/17 (41)	–	–	–	–	–	–
Chills n(%)	5/17 (29)	–	–	35/43 (81)	–	2/6 (33,3)	13/22 (59,1)
Retro-orbital pain n (%)	2/17 (12)	15/33 (44)	4/6 (66,6)	16/43 (38)	12/16 (75)	–	14/22 (63,6)
Confusion n(%)	2/17 (12)	–	–	–	–	–	–
Vomiting n(%)	4/17 (24)	1/33 (3)	6/6 (100)	9/43 (21)	11/16 (68,8)	–	3/22 (13,6)
Pruritusn(%)	0/17 (0)	11/33 (33)	–	–	–	–	–
Nausea n(%)	2/17 (12)	–	–	15/43 (35)	11/16 (68,8)	2/6 (33,3)	4/22 (18,2)
Diarrhea n(%)	2/17 (12)	–	–	2/43 (5)	–	–	2/22 (9)
Abdominal pain n(%)	3/17 (18)	–	3/6 (50)	–	8/16 (50)	–	3/22 (13,6)
Cough n(%)	2/17 (12)	–	–	–	–	2/6 (33,3)	4/22 (18,2)
Pharyngitis n(%)	1/17 (6)	–	–	–	4/16 (25)	2/6 (33,3)	4/22 (18,2)
Conjonctivitis n (%)	1/17 (6)						
Dizziness n(%)	–	8/33 (25)	–	18/43 (42)	10/16 (62,5)	–	–
Anorexia n(%)	5/17 (29)	7/33 (22)	–	–	12/16 (75)	–	–
Gingivorrhagian(%)	–	–	–	–	–	–	1/22 (4,5)
Photophobia n(%)	1/17 (6)	–	–	3/43 (7)	–	–	1/22 (4,5)
Biological features							
Lymphocyte<1500/ mm^3	7/13 (60)	–	–	–	–	–	–
Platelets <150,000/ mm^3	3/13 (23)	–	4/6 (66,6)	–	–	–	–
Leukocytes >10,000/mm^3	1/15 (7)	–	3/6 (50)	–	–	–	–
Neutrophils >7500/ mm^3	1/14 (7)	–	–	–	–	–	–
CRP > 50 mg/L	2/15 (13)	–	–	–	–	–	–

especially Western, Eastern and Venezuelan Equine Encephalitis, but so-called arthritic viruses, such as chikungunya, may also cause neurological impairment (Oliveira et al., 2016).

Serologic diagnosis is also difficult to interpret due to antibody cross-reactivity between MAYV and other alphaviruses. Immunological reactivation or IgM persistence is also observed in other infections, or even non-infectious conditions: 39 of the 56 excluded patients (69.6%) had positive MAYV IgM associated with other infectious or a non-infectious pathology.

Practitioners should perform MAYV confirmation in front of isolated fever, "chikungunya-like" syndrome, or central nervous system involvement: RT-PCR in early phase then IgM seroconversion. These diagnostic tools should be more widely available.

MAYV is considered to have an important potential for emergence in America, in Amazonia and beyond, as illustrated by the recent MAYV emergence in a rural area of Haiti (Lednicky et al., 2016). Then, its secondary spread is probable because *A. aegypti* (and maybe *A. albopictus*) is a competent vector (Long et al., 2011), possibly mediating urban cycles and outbreaks (Acosta-Ampudia et al., 2018). Furthermore, two recent publications describing MAYV in travelers returning from French Guiana to Europe (where *A. albopictus* is spreading) illustrate this new threat (Friedrich-Janicke et al., 2014; Llagonne-Barets et al., 2016). This scenario is well known and needs anticipation.

5. Conclusion

MAYV infection has a similar presentation as chikungunya. Although

Table 2
Characteristics of the 17 patients with MAYV infection.

Case	Sex	Age	Residential commune	Country of birth	Travel in the last 15 days	Profession	Medical history	Clinical	Complications	Biology	PCR	Probability
1	F	19	Trois-sauts	French Guiana	No	NA	Cutaneous leishmaniasis, scorpion sting	Fever, arthralgia	Persistence of arthralgia for 2 months	Not done	NP	Certain Positive viral culture
2	M	47	Matoury	Brazil	No	Gold miner	No	Fever, arthralgia, rash, inflammatory throat	Hyperimmune splenomegaly on frequent malaria	Leukopenia, neutropenia, lymphopenia, thrombocytopenia	NP	High seroconversion
3	M	47	Maripasoula	Brazil	No	Gold miner	High blood pressure	Fever, headache, asthenia, confusion, phonophotophobia, signs of Kernig and Brudzinski positive	Meningoencephalitis	Lymphopenia CRP[1] = 21	NP	High seroconversion
4	F	22	Rémire-Montjoly	French Guiana	No	NA	Left pneumonia, intellectual disability	Fever, back pain, retro-orbital pain	No	Normal	NP	High seroconversion
5	F	26	Rémire-Montjoly	Metropolitan France	Living in the forest	Engineer	No	Fever, headache, chills, arthralgia, low back pain, asthenia, rash	No	Not done	Neg	High seroconversion
6	M	30	Maripasoula	Brazil	NA	Gold miner	No	Fever, headache, arthralgia, myalgia, anorexia	Headache resistant to analgesic treatment	Normal	NP	Medium Compatible clinic and 1 positive serology
7	F	1	Rémire-Montjoly	NA	No	Without	No	Fever, vomiting, conjunctival hyperemia	No	Normal	NP	Medium Compatible clinic and 1 positive serology
8	F	54	Cayenne	NA	Living in the forest	NA	No	Fever, headache, arthralgia	Persistence of arthralgia for 2 months	Anemia, leukopenia, neutropenia, CRP = 11	NP	Medium Compatible clinic and 1 positive serology
9	M	41	Cayenne	NA	Living in the forest	Soldier	No	Fever, headache, arthralgia, myalgia, rash	No	Lymphopenia, CRP = 8.4	Neg	Medium Compatible clinic and 1 positive serology
10	M	31	Grand Santi	French Guiana	Living in the forest	NA	Chronic hepatitis B	Fever, arthralgia	No	Normal	Neg	Medium Compatible clinic and 1 positive serology
11	M	55	Cayenne	Brazil	Journey in forest	Hunter	Malaria, dyslipemia	Fever, chills, headaches, arthralgia, myalgia, asthenia, anorexia, abdominal pain, cough	No	Lymphopenia, thrombocytopenia (129 G/L)	Neg	High seroconversion
12	F	36	Maripasoula	Brazil	NA	NA	NA	Fever, headache, arthralgia, asthenia, rash, intraoral rash, anorexia	No		Neg	Medium Compatible clinic and 1 positive serology
13	F	28	Maripasoula	Dominican Republic	Journey in forest	Goldminer	No	Fever, headache, back pain, asthenia, abdominal pain	No	Anemia (9.4 g/dl), lymphphopena, CRP 205 mg/L	Pos	Certain. Positive PCR.
14	M	35	NA	NA	NA	Soldier	NA	Fever, headache, arthralgia	No	Lymphopenia	Pos	Certain. Positive PCR.
15	M	36	Cayenne	French Polynesia	Journey in forest	Soldier	No	Fever, chills, myalgia, confusion, anorexia, vomiting, diarrhea, cough	No	Lymphopenia, thrombocytopenia (125 G/L), CRP 152 mg/L, SGOT/SGPT twice the normal	Neg	Medium
16	M	26	Cayenne	France	Journey in forest	Soldier	No	Fever, chills, headache, arthralgia, myalgia, back pain, retroorbitalain, asthenia, rash, anorexia, vomiting	Persistence of arthralgia for 1.5 months	CRP 88 mg/L	NP	Compatible clinic and 1 positive serology
17	M	47	Cayenne	French Guiana	No	Soldier	No	Fever, chills, headache, myalgia, asthenia, nauseas, diarrhea, abdominal pain	No	CRP 88 mg/L	NP	High seroconversion

its clinical picture is mainly mild, it could be responsible for meningo-encephalitis and persistent arthralgia as observed for CHIKV. Its low incidence in French Guiana where seroprevalence reaches 6.3% (even more in some remote areas), suggests that the diagnosis is often missed. Nevertheless, lessons from CHIKV and ZIKV outbreaks remind us that this seemingly anecdotal virus mostly confined to forested-areas could cause bigger urban outbreaks, and rare complications such as neurological involvement could then amount to significant public health challenges.

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No competing interests.

Author contributions

RM, DR & LE conceptualized the study.
DR, FD & LE belonged to the adjudication comitee.
DR & SM performed the biological analyses.
RM & LE wrote the manuscript.
EM, EML, FN & PN supported the patients.
SM, EM, EML, FDL, MN, FN, PN, FD & DR reiewed the MS.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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