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Yellow Fever Reemergence Risk in the Guiana Shield: a Comprehensive Review of Cases Between 1990 and 2022

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Abstract

Purpose of Review The aim of this study was to compile all cases of yellow fever (YF) recorded in the Guiana Shield (GS), a region located on the northeastern shore of South America.

Recent Findings Yellow fever causes several deaths in French Guiana during the last years. In this context, we wanted to know if it was due to a lack of vaccination or a reemergence of YF as in Brazil and if it was the same trouble in the neighborhood countries.

Summary People living in or returning from the GS with YF-compatible symptoms confirmed by reverse transcriptase polymerase chain reaction between 1990 and 2022 were included. In French Guiana (FG), patients were identified through results from the National Reference Center for Arboviruses at the Pasteur Institute in FG and hospital medical charts. For the other countries, medical literature and the WHO database were reviewed. Public health and infectious diseases specialists were solicited to identify unknown and unpublished cases. Nine patients were identified in the study period: five in FG, two in Venezuela, one in Suriname, one in Brazil, including six autochthonous people, Guiana Shield native, and three tourists. The case fatality rate was 7/9 (78%) within 8 days (range: 7–11 days). The M/F sex ratio was 6/3 (2). They had severe liver involvement progressing to multivisceral failure in 89% of cases. Only the two native Amerindian patients in FG had previously benefited from a YF vaccination in childhood and/or for more than 10 years. In conclusion, the sylvatic cycle of the YF virus is likely to persist in this region. Absence of vaccination or unknown immunization status was documented in most patients (78%). The mortality rate of this case series was high thus highlighting the need to strengthen vaccination coverage for the population and travelers to the GS.

Keywords Yellow fever · Guiana Shield · French Guyana · Zoonosis · Arbovirus

Abbreviations

ALT	alanine aminotransferase
AST	aspartate aminotransferase
COVID-19	coronavirus disease 2019
FG	French Guiana
GS	Guiana Shield
LMICs	low- and middle-income countries
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
RT-PCR	reverse transcription polymerase chain reaction

SD	standard deviation
YF	yellow fever

Introduction

Yellow fever (YF) is the most severe arbovirus circulating in Latin America [1]. The World Health Organization (WHO) reports about 200,000 annual cases and 30,000 YF-related deaths worldwide, with 95% of these cases occurring in Africa [2]. YF is an RNA flavivirus that occurs in the intertropical regions of South America and Africa, and is transmitted to humans by the bite of infected vectors: *Haemagogus* sp. and *Sabethes* sp. participate in the sylvatic cycle, while *Aedes aegypti* is part of the peri-urban cycle [3,

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4]. YF infection may cause severe acute disease with hemorrhagic hepatorenal syndrome. The enzootic YF scenario in Latin America is very complex, and many of its ecological and biological aspects are not yet fully understood. Inadequate entomological and animal surveillance, especially in ecotones near urban areas, constitutes a risk to non-human primates (NHP) and people [5].

An outbreak of YF occurred in Brazil (São Paulo, Minas Gerais, Espírito Santo, and Rio de Janeiro states), from December 2016 to May 2018 causing 2154 confirmed cases and 745 deaths, being the largest YF outbreak recorded in Latin America [3, 6–8]. Afterwards, from 2018 to 2019, 12 confirmed human cases of YF including six deaths were reported in the same region, and from July 2020 and June 2021, 9 cases were reported [9]. These epidemics occurred in areas previously unaffected by YF, outside the Amazon basin. At that time, those areas were not considered at risk and no YF vaccine was required. YF has been the subject of numerous WHO alerts on the web since 2008, each time requiring the deployment of a massive vaccination campaign to prevent the spread of the disease [7, 9, 10]. This disease remains a public health problem. YF outbreak was recently reported affecting 11 people in Monagas state, Venezuela in September 2021, where the vaccination rate was only 11% [5, 9, 11].

Guiana Shield (GS) region, a geographical area located in the extreme northeastern of South America that included French Guiana (FG), may also be facing a resurgence of YF cases. Between 1902 and 1998, no human case had been reported in the GS; however, the outbreaks in Brazil and repeated cases of YF in FG suggest a risk of YF to the people that living in or traveling to GS. Therefore, the main objective of this study was to identify and describe all YF cases reported in the GS in the last three decades and to assess the risks of YF spread in this region.

Methods

Study Design and Population

A descriptive, retrospective, multicentric study was conducted. The study population was people living in or traveling to the GS with YF-compatible symptoms (<https://www.cdc.gov/yellowfever/>) and had YF-molecular confirmation by reverse transcription polymerase chain reaction (RT-PCR) in blood or liver samples between January 1, 1990 and December 31, 2022. The RT-PCR method was used according to Weidmann et al. [12] published in 2010. It is specific of YF and no other flavivirus, and it has been elaborated from a common sequence between the African virus and the South American one.

Study Sites

The GS is a region located on the extreme northeastern of South America, covered by the Amazon rainforest and including, from west to east, the Bolivar and Amazonas states of eastern Venezuela, Guyana, Suriname, FG, and the Brazilian states of Amapá and Pará (Fig. 1). In total, this includes 10,567,000 inhabitants, for a total area of 840,000 km². The climate is described as tropical, with a long rainy season from May to August, then a long sunny season from August to November, a little rainy season from December to January, and a little sunny season from February to March [13].

Inclusion Criteria, Case Definition, and Case Search

For FG, results from the National Arbovirus Reference Center at the Pasteur Institute of FG were examined. Positive YF medical records concerned only Cayenne hospital. Medical records of patients were studied, and demographic, clinical, biological, and outcome variables were collected. For FG and the other countries, a literature review was performed in the web databases ProMED®, PubMed®, Google Scholar®, and ScienceDirect® using the keywords South America, yellow fever, outbreak, and animal reservoir in English, French, Spanish, and Portuguese during the study period. Several public health and infectious diseases specialists from countries in the study sites were solicited for information on possible unpublished cases. The WHO list of YF alerts published on the official WHO website was also screened to be certain no cases were overlooked [14].

Data Collection and Analysis

Several variables such as age, sex, country of birth, country of current residence, concomitant infection with another pathogen agent, presumed site of infection, duration before admission, time to death, and YF vaccination status were collected and analyzed. Continuous variables were summarized by median, interquartile range, and range. Categorical variables were summarized by frequency and percentage. Statistical analysis was performed using Microsoft® Excel® version 2019 (Microsoft, Redmond, WA, USA). All figure and tables are original.

Results

During the study period, nine cases were identified in the GS: five reported in FG (one in 1998, one in 2017, one in 2018, and two in 2020); two linked to Venezuela, one

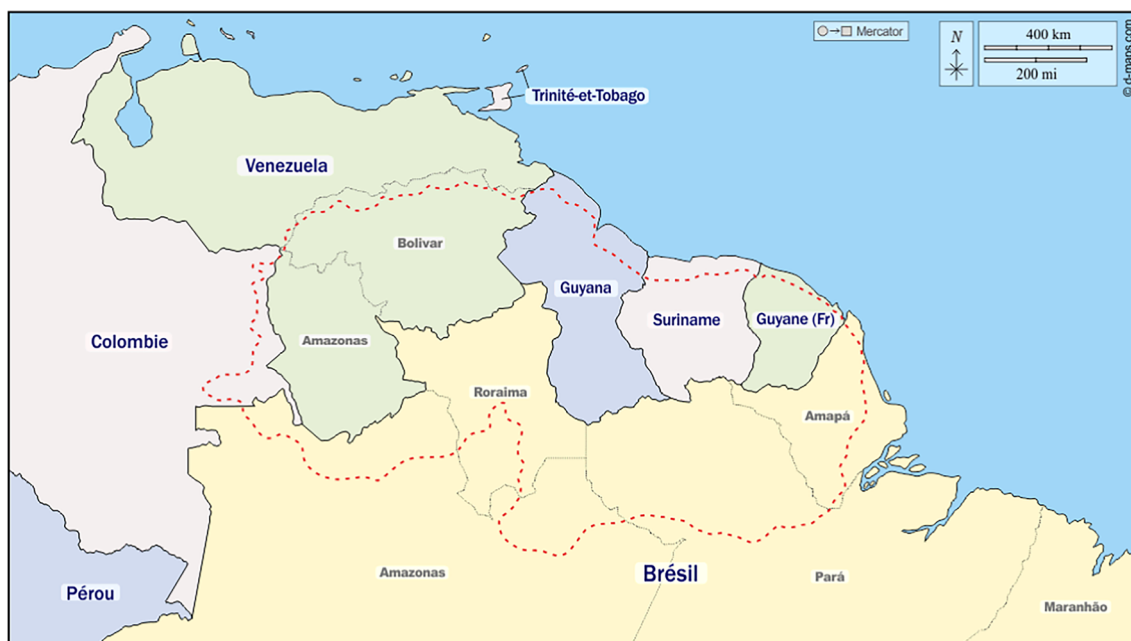


Fig. 1 Map of the Guiana Shield, limited by the spotted dots

reported in a US traveler returning from Venezuela (1999) and one autochthonous case in Bolívar state of Venezuela (2019); one case reported in a Dutch traveler returning from Suriname (2017); and one autochthonous case in Amapá (2021). All cases are summarized in Table 1 and detailed in Supplementary Data 1.

Patient characteristics are presented in Tables 2 and 3. The median age was 40 years (range = 14–48; IQR 27–46). The M/F sex ratio was 2. 7/9 (78%) went to ICU. The median duration between the symptoms onset and admission was 5 days (range = 2–12). The median duration of intensive care unit (ICU) care was 5.5 days (range = 4–7) and time to death was 8 days (range = 7–13). The median diagnosis delay was 16 days (range = 6–60). There were one Swiss citizen, one Venezuelan, one American, and one Dutch. Three patients were Brazilian and worked in the region as gold miners and two were French Amerindians of the Wayana ethnic group. One of them received a liver transplant. Finally, 2/9 patients were vaccinated against YF (22%) and 7/9 (78%) were considered unvaccinated (4/9 really unvaccinated and 3/9 unknown). The median mortality rate was 7/9 (78%).

Almost half of the patients had proven co-infection with another infectious agent: *Plasmodium falciparum*, SARS-CoV-2, *Escherichia coli*, and *Aspergillus* sp. (Table 1). All presented particularly severe forms, and all died. A summary of the serological status of each of the patients (Table 4) shows that the two vaccinated patients, case 1 and case 7, did not have anti-YF IgG. Only case 8 had IgG. 5/7 patients had positive IgM.

Discussion

This study describes a case series of nine cases with YF in the GS from 1990 to 2022. Most of the cases were described in FG: one from Suriname (traveler), two from Venezuela, and one from Amapá (Brazil). No cases have been reported in Guyana, and no autochthonous case in Suriname.

Case-Fatality Rate

With a 78% case-fatality rate, the results of the present study differ significantly from other results in the literature in South America [14, 15]. Indeed, pre-existing studies mentioned a case-fatality rate of 20% in Africa and 33% during the Brazilian epidemic [4, 16]. However, the small number of patients included in this study and the severity of their clinical state on arrival may affect the relevance of the result obtained. Moreover, there is no systematic biological research of YF against any undocumented infectious disease case, so the real incidence may be underestimated, mainly in FG wedged between countries that have recently experienced epidemics.

Co-infections

In this case series, almost half of the patients had a co-infection with another pathogen. This differs sensibly from what is described in the literature [17]. Co-infection with yellow fever is rare, but has been described in the literature. Dengue serotype 2 an YF co-infection was reported during the YF

Table 1 Characteristics of the nine cases of yellow fever on the Guiana Shield

Case	Time	Sex	Age	Place of contamination	Place/territory of birth	Death	Diagnosis	Coinfections		Vaccination		Transplantation
								Yes: <i>P. falciparum</i>	Yes: disseminated aspergillosis	Yes: 1985	No	
Case 1	March 1998	F	30	Haut Maroni	French Guiana	Yes	RT-PCR on hepatic biopsy post mortem	Yes: <i>P. falciparum</i>	No	Yes: 1985	No	No
Case 2	October 1999	M	48	Canaima (Bolivar)	USA	Yes	PCR on hepatic biopsy post mortem	Yes: disseminated aspergillosis	No	No	No	No
Case 3	2017	F	27	Brokopondo	The Netherlands	No	PCR on total blood	Doubt about leptospirosis	No	No	No	No
Case 4	August 2017	F	45	Amapá or Petit Saut	Brazil	Yes	RT-PCR on total blood	No	No	No	No	No
Case 5	August 2018	M	47	Roura	Switzerland	Yes	RT-PCR on total blood	No	No	No	No	Yes
Case 6	September 2019	M	46	Ulliman (Venezuela)	Venezuela	No	PCR on total blood	Doubt about HAV and leptospirosis	No	No	No	No
Case 7	June 2020	M	14	Kayodé	French Guiana	Yes	RT-PCR on total blood	Yes: SARS-CoV-2	Yes	Yes	No	No
Case 8	October 2020	M	40	Maripasoula	Brazil	Yes	RT-PCR on total blood	Blood cultures positive: <i>E. coli</i>	No	No	No	No
Case 9	July 2021	M	21	Afia (Para) or Macapá (Amapá)	Brazil	Yes	RT-PCR on total blood	No	No	No	No	No

outbreak in Brazil [6]. In Angola, a study reported a co-infection between Japanese encephalitis and YF [18]. In the Kedougou region, Senegal, seven cases of *P. falciparum* and YF co-infection were reported [19]. Arbovirus and malaria co-infections have already been described, but more often with dengue [20]. A case of West Nile virus co-infection has also been described in evidence of arbovirus co-infection in patients with malaria and typhoid fever in Nigeria [21]. All these pathologies are transmitted by mosquitoes and the same mosquito carries different viruses/parasites. Thus, the Brazilian *Aedes aegypti* is a competent vector for multiple complex arboviral co-infections [22]. Moreover, it is also possible that in these regions where mosquitoes are numerous, co-infection is the result of the bite of several mosquitoes, each being vector of one disease.

Another hypothesis is YF may work by altering immune defense systems and facilitating co-infections. This has already been described with measles: measles pneumonitis is frequently a source of bacterial and viral co-infection [23, 24]. A third hypothesis may also be that serological diagnostic methods lack specificity. It has been described in March 2019 a 20-year-old Peruvian young man positive by RT-PCR for YF in Condorcanqui, Department of Amazonas. He also had a positive microscopic agglutination test for leptospirosis. Discussion does not allow to decide between false positive and real co-infection [25].

YF Spread Risk in the GS

There are three types of YF transmission cycles. The first is a wild and sylvatic cycle where NHP are the primary reservoir with occasional transmission to humans. The second cycle is semi-domestic, at the forest edge, where mosquitoes infect both monkeys and people [26]. The last cycle is urban, when infected people introduce the virus into densely populated areas with high mosquito density and where people have little immunity. In these conditions, infected mosquitoes transmit the virus from person to person and may be responsible for epidemics such as recently occurred in Brazil.

Currently, only the wild cycle exists in FG and is vectored by *Haemagogus* and *Sabethes* mosquitoes [27, 28]. The high vaccination coverage rate and the low population density in these areas undoubtedly contribute to epidemic risk control. However, semi-domestic and urban areas harbor *A. aegypti*, which may be an effective vector of YF. The latter is already responsible for dengue epidemics, the emergence of chikungunya virus in 2013 and Zika virus in 2016, in the GS. Moreover, *A. aegypti* represents a potential vector of YF which could thus spread in cities [29]. The animal reservoir of YF also plays an important role in the risk of spread: it relies mainly on NHP, but it is important to note that the virus has been documented in many tropical species [28, 29]. Thus, although there are no recent studies

Table 2 Continuous variables analysis for patient with confirmed yellow fever on the Guiana Shield between 1990 and 2022

Variable	Median	Quartile 25–75	Minimum–maximum
Age (years)	40	27–46	14–48
Delay before hospitalization (days)	5	3–7	2–12
Delay before admission in ICU (days)	5.5	4.5–7	4–7
Delay until death (days)	8	7–11	7–13
Delay until diagnosis (days)	16	13.25–18	6–60

Table 3 Analysis of categorical variables of patients with confirmed diagnosis of YF on the Guiana Shield between 1998 and 2021

	N	Percentage
Nationality		
France	2	22%
Switzerland	1	11%
Brazil	3	33%
The Netherlands	1	11%
Venezuela	1	11%
American	1	11%
Gender		
Female	3	33%
Male	6	66%
Medical history: survival	2/9	22%
Confirmed concomitant infection	4/9	44%
Confirmed alternative diagnosis	4/9	44%
Liver transplantation	1/9	11%
Vaccination	2/9	22%
Death	7/9	78%

Table 4 Summary of positive PCRs and serologic statuses of different patients

	Sample type	PCR	IgM YF	IgG
Case 1	Liver	+	+	–
Case 2	Liver	+	–	–
Case 3	Blood	+	+	–
Case 4	Blood	+	+	–
Case 5	Blood	+	+	–
Case 6	Blood	+	Unknown	Unknown
Case 7	Blood	+	–	–
Case 8	Blood	+	+	+
Case 9	Blood	+	Unknown	Unknown

performed on YF virus circulation in primates in the GS, it has previously been strongly associated with infection of red howler monkeys (*Alouatta seniculus*) [28]. Monkeys are particularly susceptible to the disease and act as a reservoir [3]. Nevertheless, even though the virus is currently circulating in forest habitats, anthropogenic activities increase

the risk of transmission. Deforestation, especially for agriculture and cattle grazing, is associated with the emergence of YF outbreaks [27]. Host density is also a crucial factor of transmission rates. These environmental changes, such as immigration and economic development responsible for increased population density, may create new foci of transmission or new sources of zoonotic infections [27]. Finally, during the global COVID-19 pandemic, many preventive programs, such as YF vaccination, have been delayed for several months. This disruption may participate in increasing the risk of YF emergence [30, 31].

One track for the future would be the use of mosquitoes infected with *Wolbachia*, as in the article by Utarini et al. By infecting *Ae. aegypti* in Indonesia, they showed a decline significant dengue-related infections and a decrease in hospitalizations [32].

Vaccination Against YF Virus and Recommendations on Vaccine and Therapeutic Strategies

In this case series, two patients were vaccinated, three were not vaccinated, and four had an undetermined status. In FG, where most cases were recorded, YF vaccination coverage was estimated at 95% (95% CI = 93.4–96.2) [33]. This result was heterogeneous, with the lowest levels near the border with Suriname [34, 35]. Moreover, the two vaccinated patients did not have IgG, reflecting a lack of vaccine immunity. The first patient got YF 13 years after vaccination, which was attributed to a poor antibody response, or an inadequate vaccine storage, breaking the thermostability chain, or a deficient immune system. The second patient received the vaccine before her second birthday, but never received the recommended booster.

In 2013, WHO advocated that a single dose of vaccine was sufficient for life, whereas vaccination was reviewed every previous decade [36]. Justification for the absence of booster dose in endemic areas is that immunity may be naturally boosted as a result of exposure to the wild-type virus. Nevertheless, data from the 2016 Brazilian epidemic do not support this theory, where 3.24% (27/832) of YF patients had already received vaccination less than 10 years earlier, and 52% (432/832) had been vaccinated more than 10 years

earlier [37, 38]. Amanna and Slifka's findings argue for a loss of immunization: antiviral immunization might be lost in 1-in-3 to 1-in-5 individuals within 5 to 10 years after a single vaccination. Early vaccination during childhood may be an increased risk for failure [39]. Thus, the booster dose, although outside the recommendations, remains controversial in immunocompromised individuals or immunocompetent subjects traveling 10 years after their first doses in endemic areas [40, 41].

The Brazilian Ministry of Health has chosen to maintain two doses of YF vaccine in the national calendar, whereas the French health authorities adopted, according to the Strategic Advisory Group of Experts on Immunization and the amendments of the International Health Regulations in February 2016, the use of a single dose of vaccine for residents and travelers [27]. This is even more relevant given the shortage of YF vaccines during the 2016 epidemic, where Brazilians were vaccinated with doses corresponding to 1/5 of the dose usually used, to allow sufficient vaccination coverage. More generally, there is no common YF vaccination strategy in the GS.

About the limitations of this study, only one hospital reviewed case histories. We can also add that it relied only on published cases, and even had to look for experts. The nature of the study does not allow estimating mortality or morbidity of the disease in GS, because only the serious cases are published. Finally, we can affirm we have a problem of epidemiological surveillance for yellow fever.

Conclusions

With only 9 cases reported over the past 30 years, this series of cases allows us to conclude that yellow fever remains a rare disease on the GS. However, this raises some questions about the actual incidence of the disease in the region and whether to define a vaccination strategy to adopt: epidemiological surveillance needs to be optimized in at-risk areas such as where these cases occurred. Seroprevalence studies and cross-sectional studies in icterohemorrhagic febrile syndrome are required. Due to the region's economic development and significant population movements and population growth, particularly in FG, the risk remains real. We remember YF outbreaks in Brazil and Venezuela. The fact that 2 of 9 patients had received a single dose of vaccine is a preoccupying finding questioning the current single dose vaccination recommendation. The need for a vaccine booster remains to be debated in further studies.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s40475-023-00289-6>.

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Author Contribution Loïc Epelboin led literature research. FSC-N, DLM-M, ÓDO-Á, SRR, AM-O, ML-P, and DAF-P were responsible for designing. FSC-N, ML-P, JT, and ÓN-G supervised the completion of this case series and substantively revised it. All authors read and approved the final manuscript.

Data Availability All data and materials in this article are included in the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors were performed in accordance with all applicable ethical standards including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines. The medical records of patients whose case was not yet published were retrospectively reviewed. All data collected were anonymized using standardized forms according to the procedures of the Commission Nationale de l'Informatique et des Libertés (the French Information Protection Commission). The study was approved by the local ethics committee, as this research conformed to the French MR004 reference methodology and fell within the framework of so-called internal research; that is, the data were collected as part of individual follow-up of patients, by the staff responsible for such follow-up, and for their exclusive use. In accordance with European regulation on data protection, the study was registered in the hospital's registry of processing activities by the data protection officer and the collective information was made available to patients by means of a poster in the department, allowing them to express their refusal to participate, if necessary.

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