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Epidemiological, entomological and evolutionary aspects of confirmed yellow fever cases from 2021 to 2022 in CAR

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Ten countries in the African region, including the Central African Republic (CAR), were in epidemics. The objective of this study was to describe the epidemiological, entomological and evolutionary aspects of the yellow fever epidemic in CAR. This is a retrospective study for descriptive purposes. The survey population consists of confirmed yellow fever cases from 2021 to 2022 in CAR. The data came from the basics of epidemiological surveillance, epidemiological and entomological investigations. The data was entered by word 2013 and analyzed by Excel 2013 and Epi Info 7. During the reporting period, 533 suspected cases of yellow fever were reported. Ten confirmed patients and 18 asymptomatic contacts (64%) were included in this study. The case fatality rate was 30%. The symptoms observed in the patients were jaundice (80%) and haemorrhages (10%). Farmers were affected in 61% of cases. The species Aedes aegypti and Aedes vittatus, known in yellow fever transmission, have been found among mosquitoes caught in epidemic districts. Yellow fever is still a public health problem in CAR. Its variable clinical form (symptomatic and asymptomatic) must attract the attention of epidemiological surveillance actors to double their vigilance.

Key works: Yellow fever, investigation, confirmed case, outbreak, CAR.

INTRODUCTION

Yellow fever is a vector-borne viral haemorrhagic disease that occurs in tropical regions of Africa and America (Yao et al., 2014). It mainly affects humans and monkeys (Institut Pasteur, 2021). The virus responsible for the disease is a flavivirus that is transmitted by the bite of *Aedes* mosquitoes and sometimes causes devastating

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outbreaks, which can be prevented and controlled through mass vaccination campaigns (Institut Pasteur, 2021).

By 2023, yellow fever is endemic throughout the country or in parts of 34 countries in Africa and 13 countries in Central and South America (WHO, 2023).

According to the World Health Organization (WHO), the disease affects about 200,000 people worldwide each year and causes 30,000 deaths (Yao et al., 2014; Barnett, 2007; Gubler, 2004). Africa is the most affected with 95% of cases detected worldwide (Institut Pasteur, 2021; Kraemer, 2017). Ten countries in the WHO African Region, including CAR, were in epidemic situations with a risk analysis considered very high for the region and moderate for the global level. This health emergency has been classified grade 2 by the WHO (Kraemer, 2017).

From 1 January 2021 to 7 December 2022, a total of 203 confirmed and 252 probable cases, including 40 deaths (CFR) have been reported to WHO from 13 countries in the WHO African Region (OMS, 2022).

In CAR, the last yellow fever epidemic dates back to September 2018 in the health districts of Bocaranga and Bangui II. After a two-year lull, the confirmed case of yellow fever was detected in August 2021 in Mala, Kemo Health district. A total of seven out of 35 health districts have been affected. The Minister of Health and Population declared the yellow fever epidemic in CAR on 31 December 2021.

The objective of this study was to describe the epidemiological, entomological and evolutionary aspects of the yellow fever epidemic in CAR.

METHODOLOGY

This is a retrospective study for descriptive purposes. The survey population consists of confirmed yellow fever cases from 2021 to 2022 in CAR.

Blood samples taken from people suspected of yellow fever are first tested at the Pasteur Institute in Bangui. The positive samples are then sent to the Pasteur Institute in Dakar for confirmation of yellow fever. This is the WHO reference laboratory for yellow fever. Our study takes into account cases of yellow fever that have undergone these procedures.

Our data came from national yellow fever databases maintained by the Directorate of Public Health Epidemiological Surveillance and Emergency Management and Epidemiological and Entomological Field Investigations.

The sample for our survey is exhaustive. It takes into account all confirmed cases of yellow fever during the period.

The case definition used was that of the WHO Integrated Surveillance and Response Guide 3rd version. The confirmed yellow fever case is defined as:

(1) Probable case and one of the following:
(a) detection of specific yellow fever IgM*;
(b) detection of IgM or IgG titres against yellow fever four times higher between acute phase serum and convalescent phase serum;
(c) detection of neutralizing antibodies specific* of the yellow fever virus.

(2) or any of the following:
(a) detection of genomic sequences of yellow fever virus in blood or organisms by PCR;
(b) immunohistochemical detection of yellow fever virus antigens in blood, liver or other organs.

"The specific mention for yellow fever means that the tests for antibodies (IgM or neutralizing antibodies) against other prevalent flaviviruses are negative." This analysis should include IgM tests for at least dengue and West Nile virus and possibly for other flaviviruses depending on local epidemiology (Guide technique pour la surveillance intégrée de la maladie et la riposte dans la région Africaine: Troisième édition (2019). https://www.afro.who.int/fr/publications/guide-technique-pour-la-surveillance-integree-de-la-maladie-et-la-riposte-dans-la).

A contact was any asymptomatic person living in the same household or in the immediate vicinity of a confirmed yellow fever case.

The variables collected for this survey were sociodemographic (age, sex, place of residence, occupation), clinical (symptoms, date of onset), disease outcome (cure and death), entomological (larvae, type of vector), biological (negative or positive results) and related to vaccination status.

The data was entered by word 2013 and analyzed by Excel 2013 and Epi Info 7.

RESULTS

From 2021 to 2022, 533 suspected cases of yellow fever were detected by the epidemiological surveillance service. Blood samples were taken from all patients for laboratory examination. Yellow fever was confirmed in 10 patients (36%) and 18 asymptomatic contacts (64%). Three deaths were recorded among the sick. The case fatality rate was 30% (n=3). The first case was detected in Mala Village in Kemo Health district in the 13th week of 2021. The remaining yellow fever cases were gradually detected in 2022 (Figure 1).

Three clinical cases were detected in Mbaiki (Figure 2). A survey at the Nanga-Boguila DS adjacent to Batangafo district with sampling of target groups had detected confirmed cases of yellow fever in asymptomatic subjects (Figure 2).

The symptoms observed in the patients were jaundice (80%), fever (50%), headache (50%) and digestive disorders (33%) (Table 1). Haemorrhagic forms (10%) with haematemesis type were found in a 5-year-old child (Table 1). The disease had affected people of both genders with 57% for the male sex (Table 2). The average age was 27 years with extremes 1 and 78 years. Children under 5 years of age accounted for 40% of cases. Overall, cases under the age of 30 accounted for 57%. 57% of patients (N=16) came from rural areas (Table 2).

Seven people (25%) were vaccinated against yellow fever, including two clinical cases. The remainder were unvaccinated (50%) or unknown (25%) (Table 2).

The functions of those affected were farmers, pastoralists and health workers with the following proportions, respectively 61, 10, and 4% (Table 2).

In terms of vectors collected during entomological surveys around these different confirmed yellow fever

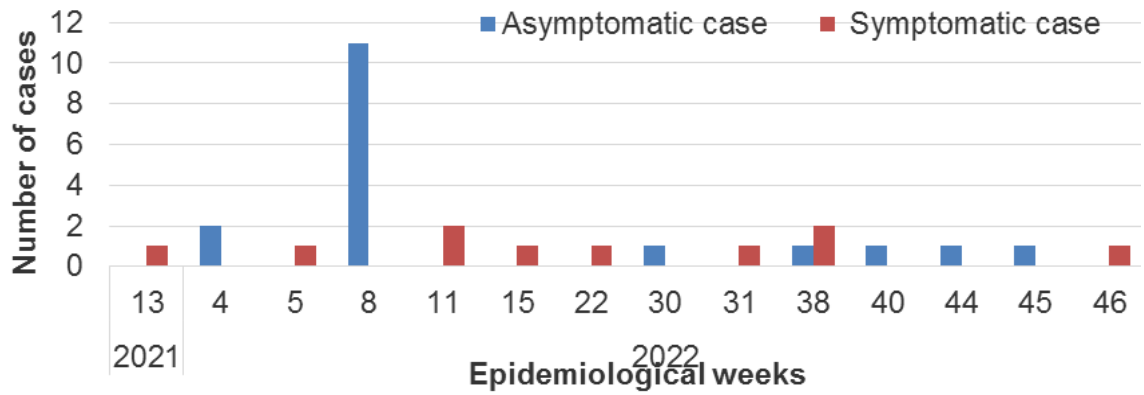

Figure 1. Distribution of yellow fever cases by year and epidemiological week.

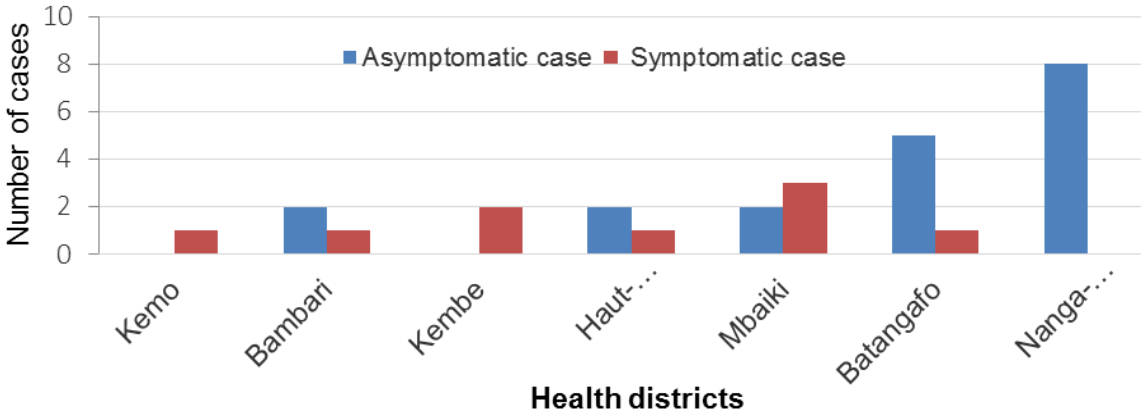

Figure 2. Distribution of yellow fever cases by district from 2021 to 2022.

Table 1. Distribution of yellow fever patients according to clinical signs observed (n=10).

Clinical signs	Number of cases	Percentage
Fever	5	50
Headache	5	50
Vomiting	3	33
Jaundice	8	80
haemorrhage	1	10

cases, we have, for example, *Aedes aegypti*, generally involved in the urban cycle of yellow fever, which was collected in Bambari (n = 179) followed by Kembé (Table 3). Then there was *Aedes vittatus* sampled at Kemo (n = 313) and then at Bambari (n = 88). Finally, *Aedes albopictus*, *Aedes africanus* and *Aedes opok*, which are also vectors of the yellow fever virus were very poorly represented. In the shreds of mosquito pools analyzed by the arbovirus laboratory of the Institut Pasteur in Bangui, none had tested positive for the yellow fever virus, including the other targeted arboviruses: dengue, chikungunya, zika, etc.

DISCUSSION

For each confirmed yellow fever case, a multidisciplinary investigation was conducted to collect additional information on the index case and the search for other suspected cases to determine the extent of the disease. Yellow fever is a surveillance and immediately notifiable disease. Only one case confirmed by the WHO reference

Table 2. Distribution of yellow fever cases by age, sex, vaccination status, place of residence and function.

Age range	Symptomatic	Asymptomatic	Total	Percentage
0 - 9	4	4	8	28.6
10 - 29	3	5	8	28.6
30 - 59	2	8	10	35.7
60 et plus	1	1	2	7.1
Total	10	18	28	100.0
Sex				
Male	4	12	16	57.1
Female	6	6	12	42.9
Total	10	18	28	100.0
Vaccination status				
Vaccinated	2	5	7	25
Unvaccinated	5	10	14	50
Unknown	3	3	7	25
Total	10	28	28	100
Place of residence				
Urban	4	8	12	42.9
Rural	6	10	16	57.1
Total	10	18	28	100.0
Function				
Children	4	4	8	28.6
Farmer	6	11	17	60.7
Pastor	0	2	2	7.1
Nurse	0	1	1	3.6
Total	10	18	28	100.0

Table 3. Number and species of mosquitoes captured by district following detection of a confirmed yellow fever case.

Genera and species	Haut-Mbomou	Kembé	Bambari	Sangha-Mbaéré	Mbaïki	Kémo	Batangafo	Total
A. aegypti	-	33	179	3	-	18	16	249
A. albopictus	1	-	-	-	-	-	-	1
A. vittatus	4	-	88	-	-	313	-	405
A. africanus	-	1	-	-	-	-	-	1
A. Opok	-	7	-	-	-	-	-	7
C. duttoni	-	-	38	17	448	-	-	503
C. quinquefasciatus	-	-	88	-	1	1	-	90
C. tigripes	-	-	-	2	-	-	-	2
Culex spp.	72	227	35	117	1	-	194	646
A. gambiae s.l.	1	-	-	-	2	-	-	3
A. funestus	1	-	4	-	-	-	1	6
A. coustani	-	-	-	-	5	-	2	7
M. africana	2	-	-	-	272	-	-	274
M. uniformis	-		-	-	27	-	-	27
Ereptmapodite spp.	-	7	-	1	-	-	-	8
Phlébotomes	-	-	-	-	-	-	1	1
Total	81	275	432	140	756	332	214	2230

laboratory is an outbreak. Several districts were declared epidemics in 2022. In addition, the Republic of Chad, neighbouring CAR, also declared the yellow fever epidemic during the same period.

The investigation did not formally establish a link between the index case and the others. Given the silent circulation of the virus and the delay of 21 to 30 days for the delivery of the results of samples sent to the Dakar laboratory, it is difficult to establish links between two districts in epidemic. To deal with this epidemic, a vaccination response was organized in five districts with coverage ranging from 67 to 102% (OMS, 2022).

With regard to the space in which the disease occurs, major yellow fever epidemics are observed in urban areas because of the concentration of the population. However, more than half of the confirmed cases in our investigation resided in rural areas and engaged in agriculture as their main activity. The results of yellow fever investigations from Tchetgna et al. (2022) in CAR also confirmed cases in a village in a farmer. The low vaccination activity in remote areas, as well as the large number of unvaccinated cases found during the investigation, could partly explain this situation.

In its clinical manifestation, yellow fever evolves in two symptomatic or asymptomatic forms. According to Oliosi and Caumes (2020), the virus causes febrile hepatitis, which can lead to bleeding complications and death. Severe and fatal forms represent a small proportion of all infected people.

This corroborates the research findings of Nobrega Litvoc et al. (2018) reporting that the most severe forms occur in about 15% of infected people, with high case fatality rates. In our context, the haemorrhagic form has been observed in one in ten yellow fever patients. Adogo and Ogoh (2020) and Marielton et al. (2019) reported a yellow fever case fatality similar to ours of 19 and 35.4%, respectively.

For Issa (2015), the clinical signs observed during the yellow fever epidemic in Mali in 2015 were: hyperthermia, agitation and jaundice. The variation of clinical signs in the different studies should attract the attention of those involved in epidemiological surveillance to be warned of the atypical form of yellow fever.

However, yellow fever is a disease that can be ignored, in its asymptomatic form. In our series, more than half of the confirmed cases had the yellow fever virus without developing the disease. Our data confirm Yuill (2021)'s statement that yellow fever virus infection can range from asymptomatic forms, in 5 to 50% of cases, to hemorrhagic fever with mortality of up to 50%. Targeted screening in at-risk areas can detect virus circulation early and improve yellow fever surveillance.

The patients in our series were young. This can be justified by the fact that the Central African population is predominantly young. Our results confirm the WHO report which reports that globally, 71% of confirmed yellow fever cases are aged 30 years and younger, and children (10 years and younger) are disproportionately affected (OMS, 2022). Conversely, the work of Fernanda et al found 57% of male patients aged 30 to 59 years (Fernanda et al., 2022).

Entomological in terms of mosquitoes, the mosquito species that generally ensure the transmission of the yellow fever virus, namely, *A. aegypti* and *A. vittatus* collected in large numbers were present at the majority of sites where cases were confirmed. They were obtained by laying traps, through larval surveys and by human capture, both inside and outside homes. PCR analysis of the shredded pools of these mosquitoes in the laboratory gave no positive results for yellow fever virus.

Ngoagouni et al. (2012)'s work in CAR had obtained similar results. In contrast, Diallo et al. (2013) in Senegal in 2013 had isolated two strains of the yellow fever virus from *Aedes furcifer* captured in a village where yellow fever cases and deaths have been reported. In our context, the negativity of the PCR results could be justified by the fact that people who contracted the disease must have been infected elsewhere, probably deep in the forest rather than in their immediate environment as Ngoagouni et al. (2012) pointed out in 2012.

In addition, it is consistent with survey data collected in this paper which show that growers were the most represented (61%) and the latter are assumed to be in frequent contact with vectors.

Conclusion

Yellow fever is still a public health problem in Central Africa in general and in CAR in particular. Its variable clinical form should draw the attention of those involved in epidemiological surveillance to be doubly vigilant. For asymptomatic forms, targeted screening in at-risk areas can detect virus circulation early and improve yellow fever surveillance.

A programme to strengthen vaccination to increase immunity in rural areas would limit the outbreak of yellow fever.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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