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ANIMAL SCIENCE

Epidemiologic profile and histopathological findings in Neotropical Primates during and after the yellow fever outbreak in Espírito Santo, Brazil

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Abstract: Yellow fever (YF) is a viral disease whose transmission involves non-human primates (NHP), mosquitoes, and humans. Between 2016 and 2018 occurred the largest YF outbreak in the last 100 years in Brazil. We analyzed epidemiologic profile and geographic distribution of epizootics and described most frequent histopathological findings in NHP that died during YF outbreak in the state of Espírito Santo. We consider 487 epizootics notifications registered at the State Health Department from January 2017 to July 2020. Throughout the state, 51 (65.4%) municipalities reported epizootics, with more cases in central and metropolitan areas. Reverse transcription polymerase chain reaction and immunohistochemistry were laboratory tests performed for diagnosis of yellow fever, with 160 (32.9%) positive results, 314 (64.5%) negative and 13 (2.7%) inconclusive. Histopathological findings were compared statistically between positive and negative animals for YF. The liver was the most affected organ. Hemorrhage, hepatocyte necrosis, steatosis, cholestasis and eosinophilic degeneration were statistically more frequent in positive animals. Tubular necrosis, nephritis, congestion and lymphoid hypoplasia on spleen were statistically correlated to positive animals. Knowledge of pathogenic aspect of YF is necessary to guarantee that samples from Neotropical primates are properly used for YF surveillance purposes, to ensure appropriate diagnoses and subsequent public health responses.

Key words: Epizootics, histopathological findings, New World Primates, outbreak, yellow fever.

INTRODUCTION

In the current scenario, we can see that epidemics generate panic, deaths, economic losses and affect everyday life in general. Closer contact between humans and animals has favored the emergence of several diseases, including zoonotic diseases that play an important epidemiological role as they affect the environment, animals, and people.

Yellow fever (YF) is a viral disease endemic to tropical regions of Africa and the Americas. It mainly affects humans and non-human primates (NHP) and is transmitted via the bite of infected mosquitoes (Gardner & Ryman 2010). In Brazil the sylvatic cycle is maintained by forest canopy mosquitoes (*Sabethes* spp. and *Haemagogus* spp.) and New World primates (Brasil 2014).

Between 2016 and 2018 there was a re-emergency of yellow fever mainly in southeastern Brazil, with fewer cases in other

states (Brasil 2017). The impact was very high, with 2.167 confirmed cases and 750 deaths of people (Brasil 2017, 2018, 2019). The total number of epizootics in NHP, recorded due to yellow fever from December 2016 to June 2019, showed that at least 18.101 animals were affected and that the highest number of confirmed epizootics was in the southeast region (Brasil 2017, 2018, 2019).

In the state of Espírito Santo, 888 epizootics were recorded in 2017 alone (Brasil 2017) and, when feasible, biological samples were collected for laboratory tests. In Espirito Santo there are records of the following primate species: *Callicebus personatus* (titi monkey), *Alouatta guariba* (howler monkey), *Brachyteles hypoxanthus* (northern muriqui), *Callithrix flaviceps* (buffy-headed marmoset), *Sapajus nigritus* and *Sapajus robustus* (capuchin monkeys) and *Callithrix geoffroyi* (white-faced marmoset) (Mittermeier et al. 2008). According to Gontijo (2019), in the mountainous region of Espírito Santo there was an observed reduction of 82.5% of howler monkeys and 49.1% of marmosets, being the species most affected by the yellow fever; the premature death of primates could act as sentinel for YF surveillance, helping to prevent the death of the human population (Brasil 2014).

In order to investigate animal deaths, health surveillance monitors epizootic cases through mandatory notification, necropsy and collection of organ fragments for laboratory diagnosis (Brasil 2014). The results point to actions needed to understand epidemiology and outline strategic measures to prevent further outbreaks, such as immediate vaccination of susceptible human populations.

The liver is the most affected organ by yellow fever in humans and other primates. The pathological findings of the effects of yellow fever in different organs of primate populations in Brazil contribute to the increase in knowledge about this disease in different species of NWP (de Azevedo Fernandes et al. 2021).

The aim of the present study was to analyze the epidemiological profile and geographic distribution of the epizootics and to describe the most frequent histopathological findings in Neotropical primates that died during and after the yellow fever outbreak in the state of Espírito Santo.

MATERIALS AND METHODS

Authors state that the experiments were performed in accordance to the national guidelines and regulations for the care and use of animals. Samples were provided for research and surveillance purposes under the terms of Resolution 510/2016 of CONEP (National Ethical Committee for Research, Ministry of Health, Brazil). One of the authors is responsible for managing secondary data from the yellow fever monitoring and control actions carried out by the State Health Department.

We analyzed the results of laboratory tests associated with epizootics recorded in the state of Espírito Santo during and after an outbreak of yellow fever. Data were acquired from the platform of the State Health Department of Espírito Santo (SESA), linked to the Central Laboratory of Espírito Santo (LACEN-ES). From 2017 to 2020, SESA received 527 notifications of epizootic diseases, of which 40 had their laboratory tests canceled or not performed. Therefore, we considered 487 epizootics for this study. The samples came from necropsies performed by local investigative officers, including trained veterinarians and other personnel, as instructed by the YF National Surveillance Program. Sample processing, histopathological analysis and diagnostic tests were performed by partner laboratories linked

to LACEN-ES. Reverse transcription quantitative real-time polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC) were the definitive diagnostic tests employed by the official YF diagnostic laboratory. Two groups were defined: one composed of YF-positive neotropical primates and another group of YF-negative or inconclusive animals.

Each laboratory test was individually assessed. The variables tested were the histopathological findings in each organ, by comparing animals positive and negative/inconclusive for yellow fever. Data were registered in a table and the frequency of each variable was calculated. The odds ratio test (contingency testing for two independent samples) was used to compare the incidence of events in yellow fever positive animals versus negative or inconclusive animals. Statistical analysis was performed using the Biostat program (version 5.0). We decided to present all the histopathological findings observed, whether specific for yellow fever in non-human primates, or incidental in animals both positive or negative for the disease. Epidemiological data such as sex, age, primate species and municipality of origin were recorded for the epidemiological characterization of yellow fever in the state of Espírito Santo.

RESULTS

We analyzed all epizootics submitted to laboratory diagnosis, registered at the State Health Department of Espírito Santo from January 2017 to July 2020. The year 2017 had the highest number of records, with 385 (79.1%), followed by 2018 with 78 (16%), 2019 with 21 (4.3%) and 2020 with 3 (0.6%) (Figure 1). Throughout the state, 51 (65.4%) of the municipalities reported cases of epizootic disease (Figure 2), most recorded in central and metropolitan regions, with fewer cases in the northern and southern regions.

Of the 487 epizootics submitted to laboratory tests for yellow fever, 160 (32.9%) were positive, 314 (64.5%) were negative and 13 (2.7%) were inconclusive (Figure 2). The necropsy records did not indicate which species of non-human

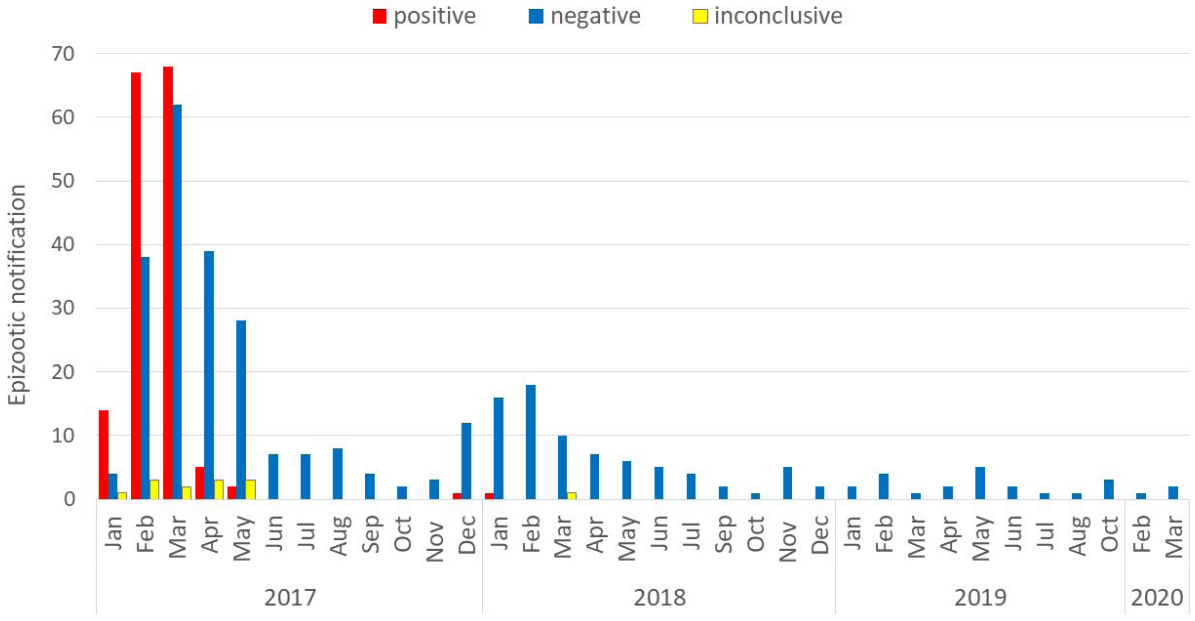

Figure 1. Temporal distribution of epizootics, recorded in the state of Espírito Santo from 2017 to 2020.

primates were found dead, so they were all analyzed together.

The animals were 47 (9.7%) females, 93 (19.1%) males and 347 (71.3%) did not have the sex informed. Unfortunately, data such as age and species of animals were blank or incomplete on the platform where they were recorded, therefore, they were not considered for analysis.

Fragments of organs from each reported epizootic were collected (Table I) and the histopathological findings of each NHP were compared between positive and negative animals for yellow fever (Table II).

The most affected organ was the liver, presenting several histopathological findings. We observed the presence of Councilman's Corpuscles in four animals, all positive for yellow fever. Other histopathological findings in the liver, statistically related to animals positive for yellow fever, were hemorrhage, hepatocyte necrosis, steatosis, cholestasis and eosinophilic degeneration.

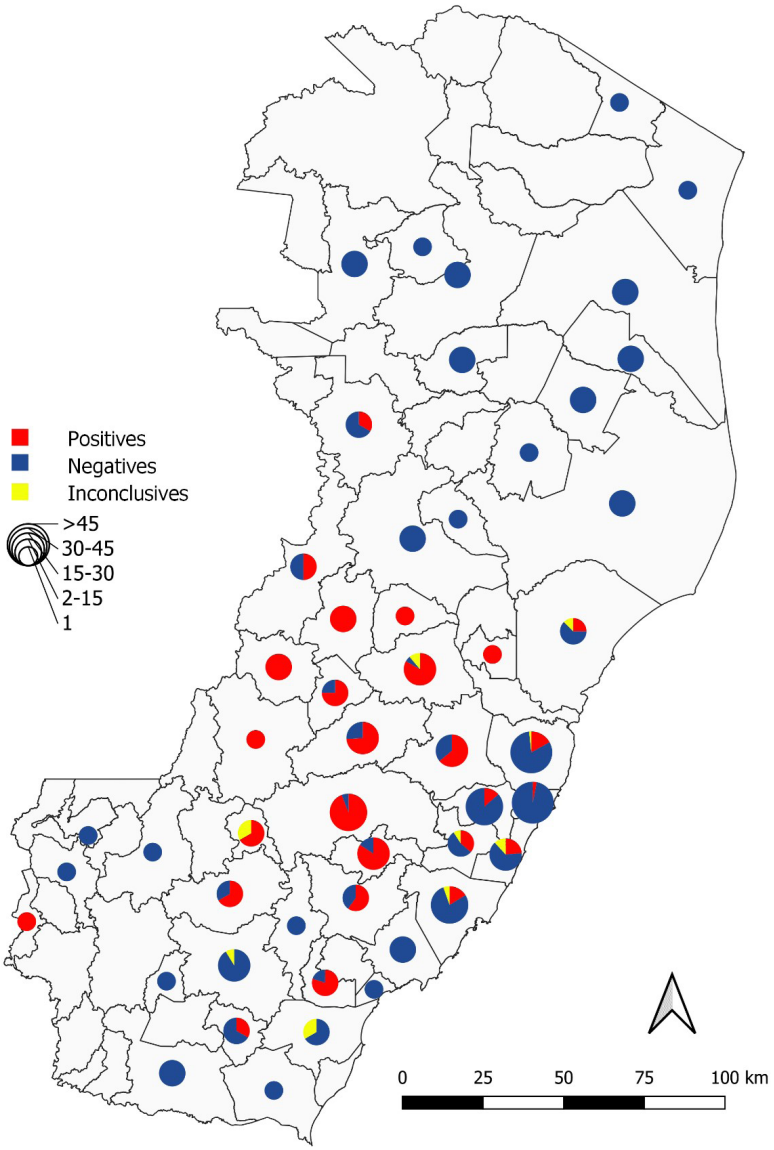

Figure 2. Results of yellow fever RT-PCR and IHC laboratory diagnosis of epizootics, recorded in the state of Espírito Santo from 2017 to 2020. Size of the circle indicates the amount of epizootics.

As for the kidney, the presence of tubular necrosis and inflammation were statistically correlated to positive animals. Splenic white pulp hypoplasia/lymphoid depletion was a significant change in non-human primates positive for yellow fever.

DISCUSSION

Regarding the geographic distribution of cases in Espírito Santo, the metropolitan and central-montane regions were the most affected, as shown in the map. In these regions there are more forest fragments and consequently more species and populations of primates (Espírito Santo 2018). In the rural areas, the proximity of the houses to the forest contributed to the contamination and maintenance of the YF cycle between people who use the forest (to collect wood, hunt etc.) and the primates due to the presence of mosquitoes in this environment.

It is noteworthy that in the state of Espírito Santo few primates with positive results were found north of Rio Doce or only in the surroundings of the river in the municipalities of Pancas and Linhares. It is difficult to explain why this happened, maybe the river has worked as a barrier to the expansion of the YF in some areas or there are less and sparser forest fragments in the region hampering vectors dispersal.

Although NHP species were not indicated in the samples, interviews with people living near the places where carcasses were found indicated that the species affected during the outbreak were the howler monkeys (*Alouatta guariba*), capuchin monkeys (*Sapajus nigritus*), titi monkeys (*Callicebus*), the two species of marmosets that occur in the state, the buffy-headed marmoset (*Callithrix flaviceps*) Geoffroy's marmoset (*C. geoffroyi*) and the northern muriqui (*Brachyteles hypoxanthus*) (Gontijo 2019). During their analysis, Mares-Guia et al. (2020) received samples of these same genera from Espírito Santo, except for the northern muriqui. In the Brazilian surveillance system of the yellow fever in primates, the NHP species most affected across the country were *Alouatta* spp. and *Callithrix* spp., although many records do not have species identification (Brazil 2017). These same genera were positive for yellow fever during the outbreak in 2016-2018 in the states of São Paulo (de Azevedo Fernandes et al. 2021), Bahia and Rio de Janeiro (Mares-Guia et al. 2020). *Alouatta* and *Callithrix* species are more susceptible to the disease than *Sapajus* species (Mares-Guia et al. 2020).

It is very important to identify the NHP individuals examined to understand how differently each species is affected. To intensify surveillance actions, it is necessary to establish

Table I. Frequency of collection of organ fragments from non-human primates tested for yellow fever.

Samples	Positive	%	Negative	%	Inconclusive	%	total
Liver	150	32.4	301	65.0	12	2.6	463
Heart	130	29.7	297	67.8	11	2.5	438
Kidney	125	30.3	280	67.8	8	1.9	413
Spleen	123	34.4	228	63.7	7	2.0	358
Lung	125	29.7	286	67.9	10	2.4	421
Blood	16	57.1	12	42.9	0	0.0	28
Brain	4	36.4	7	63.6	0	0.0	11
Lymph node	5	29.4	12	70.6	0	0.0	17
Other[†]	1	16.7	4	66.7	1	16.7	6

[†]**Other: pancreas (3), stomach (1), adrenal (1), or intestine (1).**

the best form of data and information collection (Mares-Guia et al. 2020). Providing training to health agents who carry out epizootics' surveillance, in relation to the genera and species of primates that occur within the state, allows for a correct identification and an epidemiological characterization more consistent with reality.

Although only 487 epizootics were submitted to laboratory diagnosis, as registered at the State Health Department of Espírito Santo from January 2017 to July 2020, many other primates died and were not collected for examination due to the advanced state of putrefaction, the difficult access to the site, lack of trained personnel for collection and other factors, but they were recorded in the epizootics. From December 2016 to June 2019, 1,044 epizootics in NHP were recorded in Espírito Santo and notified to the Ministry of Health surveillance system (Brasil 2017, 2018, 2019).

Only 32.9% of the 487 epizootics were positive for yellow fever in diagnostic tests. Negative or inconclusive diagnostic test results do not necessarily exclude a case of yellow fever, especially during an outbreak. It is important to highlight those pre-analytical factors, such as adequate material collection, correct sample conditioning, transport time and adequate use of solutions for sample conservation, are essential to ensure a good result in the laboratory test. Additionally, factors such as advanced decomposition, autolysis and freezing artifacts influence the sensitivity of the diagnosis, which can lead to false negative results. Autolysis was a histopathological finding statistically more frequent in organs from animals negative for yellow fever. This contributes to the idea that animals whose necropsy and specimen collection occur long after death, and with an advanced stage of autolysis, are more likely to have negative results in laboratory tests.

The diagnoses of yellow fever in non-human primates were confirmed by Reverse transcription polymerase chain reaction (RT-PCR) and immunohistochemistry (IHC), even for autolyzed cases. In Brazil, the diagnosis of yellow fever within the national surveillance program is achieved by histopathologic, IHC, and PCR results of NHP liver samples, performed by reference laboratories (Fernades et al. 2017). Among the organs with anatomopathological changes, the liver stands out both in humans (Waggoner et al. 2018) and in non-human primates (Sallis et al. 2003, Leal et al. 2016, Santos et al. 2020, Ferreira et al. 2020), showing especially necrosis and fatty degeneration of hepatocytes, as in the cases described in this study. However, the intensity of liver injury is directly related to the susceptibility of the response of different species of non-human primates, which generates injuries of mild to severe intensities (Santos et al. 2020).

Histopathological findings 'vacuolar alterations' and 'microvacuolization of hepatocytes' are generic terms and may be related to fatty degeneration (steatosis) or other intracytoplasmic accumulations, such as glycogen. Histochemical stains for differentiation were not performed. Likewise, bile duct fibrosis and hyperplasia are both associated with parasitism (helminths in the bile duct) and are not correlated with yellow fever.

Hemorrhage results mainly from decreased synthesis of coagulation factors by the injured liver (Gardner & Ryman 2010), a pattern found in other yellow fever outbreaks in non-human primates (Leal et al. 2016, Ferreira et al. 2020). The Councilman-Rocha Lima corpuscle, histologically characterized as a densely eosinophilic apoptotic hepatocyte (Quaresma et al. 2013), was found in 2.7% (4/150) of liver samples; however, even though it is characteristic of the disease, this corpuscle was observed in the minority of yellow fever cases in non-human primates

Table II. Frequency of main histopathological changes in non-human primates during and after the yellow fever virus outbreak in Espírito Santo, Brazil, from 2017 to 2020.

Liver	Positives (150)	%	Others‡ (313)	%	Odds ratio	p value
Normal organ / no pathological changes	1	0.7	12	3.8	5.75	0.05
Autolysis	38	25.3	130	41.5	1.64	0.00
Congestion	36	24.0	124	39.6	1.65	0.00
Bleeding	8	5.3	4	1.3	4.17	0.01
Hepatocyte swelling	2	1.3	76	24.3	18.21	0.00
Vacuolar change	4	2.7	16	5.1	1.92	0.17
Hepatocyte necrosis	102	68.0	7	2.2	30.41	0.00
Fibrosis	2	1.3	24	7.7	5.75	0.01
Steatosis	64	42.7	36	11.5	3.71	0.00
Cholestasis	20	13.3	13	4.2	3.21	0.00
Inflammatory infiltrate	24	16.0	61	19.5	1.21	0.21
Eosinophilic degeneration	62	41.3	12	3.8	10.78	0.00
Helminths in bile ducts	2	1.3	14	4.5	3.35	0.07
Bile duct hyperplasia	1	0.7	7	2.2	3.35	0.20
Hepatocyte microvacuolization	2	1.3	1	0.3	4.17	0.25
Councilman corpuscles	4	2.7	0	0.0		
Heart	Positives (130)	%	Others (308)	%	Odds ratio	p value
Normal organ / no pathological changes	80	61.5	113	36.7	1.68	0.00
Autolysis	12	9.2	95	30.8	3.34	0.00
Congestion	29	22.3	94	30.5	1.37	0.05
Bleeding	1	0.8	5	1.6	2.11	0.40
Pericarditis / myocarditis	4	3.1	4	12.3	2.37	0.19
Kidney	Positives (125)	%	Others (288)	%	Odds ratio	p value
Normal organ / no pathological changes	31	24.8	59	20.5	1.21	0.20
Autolysis	34	27.2	121	42.0	1.54	0.00
Congestion	13	10.4	76	26.4	2.54	0.00
Tubular necrosis	33	26.4	33	11.5	2.30	0.00
Calcification	3	2.4	2	0.7	3.46	0.17
Nephritis	18	14.4	17	5.9	2.44	0.02
Cylindrics	1	0.8	3	1.0	1.30	0.37
Freezing artifacts	2	1.6	2	0.7	2.30	0.37
Spleen	Positives (123)	%	Others (235)	%	Odds ratio	p value
Normal organ / no pathological changes	22	17.9	38	16.2	1.11	0.40
Autolysis	30	24.4	95	40.4	1.66	0.00
Congestion	48	39.0	35	14.9	2.62	0.00
White pulp hypoplasia / lymphoid / follicular / lymphoid depletion	34	27.6	19	8.1	3.42	0.00

Table II. Continuation.

Follicular / lymphoid hyperplasia	1	0.8	32	13.6	16.75	0.00
Splenitis	2	1.6	2	0.9	1.91	0.90
Lung	Positives (125)	%	Others (296)	%	Odds ratio	p value
Normal organ / no pathological changes	3	2.4	11	3.7	1.55	0.35
Autolysis	17	13.6	81	27.4	2.01	0.00
Congestion	77	61.6	182	61.5	1.00	0.47
Bleeding	45	36.0	118	39.9	1.11	0.26
Edema	48	38.4	106	35.8	1.07	0.35
Pneumonitis / pneumonia	4	3.2	16	5.4	0.59	0.50
Emphysema	4	3.2	3	1.0	3.16	0.12
Atelectasis	4	3.2	2	0.7	4.74	0.06

[‡]Others: negatives and inconclusive.

(Santos et al. 2020), which is in agreement with what we observed in this study.

Renal tubular necrosis was the most common histopathological abnormality observed in the kidneys of non-human primates in this study. These findings are reported in humans as complications of yellow fever infection, probably because of reduced blood perfusion in the organ (Gardner & Ryman 2010, Cavalcante & Tauil 2017). However, renal tubular necrosis in non-human primates is controversial, as in some studies it has not been observed (Sallis et al. 2003, Santos et al. 2020), while others report tubular necrosis in 60% of the samples (Leal et al. 2016), even when studying the same species of non-human primates. Nephritis, despite being statistically correlated with positive animals in this study, does not appear to be an important histopathological finding (Fernandes et al. 2021).

In the spleen, white pulp hypoplasia/ lymphoid depletion prevailed in animals positive for yellow fever, the same already observed in primates (Fernandes et al. 2021), and in humans (Duarte-Neto et al. 2019).

The absence of statistically significant histopathological changes in the heart and lungs reflects the non-relevance of these organs for the diagnosis of yellow fever in non-human primates; the same was observed in a study on histopathological findings of yellow fever in titi monkeys from São Paulo state (Fernandes et al. 2021).

Regarding YF in the state of Espírito Santo, the proper conduct and diagnosis of cases may have helped preventing further human deaths and mitigating the spread of the disease (Fernandes et al. 2017). Epidemiological surveillance is essential for the control and prevention of yellow fever. Understanding the dynamics of yellow fever's natural hosts, diagnosing, reporting pathological findings, evaluating the effects of environmental changes on epizootics and creating alert systems that detect carriers and sick or dead animals in the woods, at the beginning of outbreaks, are essential measures to prevent the spread of diseases and viruses. It is noteworthy that the monitoring of NHP must be constant and associated with environmental studies, where transmission cycles occur, and with case reports in humans, comprising a multidisciplinary approach at One Health.

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Author contributions

A.G. conceived of the presented idea, analyzed the data, and wrote the manuscript in consultation with M.C.O., M.C.M.K. and S.L.M. G.L.A supervised the project and managing secondary data, which came from actions to monitor and control yellow fever by the State Department of Health. O.M.H and M.N.M.B authors contributed to the design of the final version of the manuscript.