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Original Article

Epidemiological characteristics of yellow fever in Brazil, 2000-2012*

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Abstract

Objective: this study aims to describe the epidemiological characteristics of yellow fever in Brazil in the period 2000-2012. **Methods**: this is a descriptive ecological epidemiological study, using information from Ministry of Health databases. **Results**: 326 cases of yellow fever were confirmed in Brazil during this period, with 156 deaths and an average case fatality rate of 47.8%; the young male adult age group was the most affected; in epizootic terms, 2,856 suspected cases of yellow fever in non-human primates were reported and 31.1% of these were confirmed by laboratory tests; during the study period the area in which sylvatic transmission of the disease occurs was found to have expanded to densely population regions, such as South, Southeast and Midwest Brazil. **Conclusion**: the risk of urban yellow fever transmission persists, as sylvatic incidence of the disease has expanded to regions with high *Aedes aegypti* infestation, this being the mosquito responsible for urban transmission of the disease.

Key words: Yellow Fever; Descriptive Epidemiology; Disease Vectors; Brazil.

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Introduction

The yellow fever (YF) is a short-term (maximum 12 days), acute, febrile and infectious disease, which is non-communicable. Its severity may vary. Clinical manifestations may represent evolutionary stages of disease.[1] The severe form can lead to death, clinically characterized by liver and kidney failure. There is no specific etiologic treatment yet. The disease is caused by an arbovirus of the genus *Flavivirus*, family *Flaviviridae*, and it still is endemic and enzootic in many tropical regions of America and Africa and is responsible for periodic outbreaks of variable magnitude.[2] In the Americas, the potential spread risk to urban areas is to be taken into account.

> *People who are at risk of getting yellow fever are those not vaccinated and exposed to the bites of vectors in forest areas.*

The YF is transmitted to people through the bite of an infected female mosquito and has a seasonal characteristic, being more frequent between the months of January and April, when environmental factors favor the increase of the vector density. Currently, there are two recognized basic cycles of circulation of YF virus: an urban, simple, human-mosquito-human type, in which *Aedes aegypti* is the main vector; and a sylvatic type that is complex, involving different species of mosquitoes, in America and Africa, with the inclusion of non-human primates (NHP) in viral spreadness. In the American continent, the YF is a zoonotic disease transmitted by mosquitoes of two genera, *Haemagogus* (*H. janthinomys* and *H. albomaculatus*) and *Sabethes*. NHP are the main source of infection in the sylvatic cycle, especially among monkeys of the following genus: *Allouata*, *Cebus Atelles* and *Callithrix*. In Africa, the sylvatic cycle involves mosquitoes of the genus *Aedes* (*Ae. Africanus*, *Ae. Simpsoni*, *Ae. Furcifer*, *Ae. Luteocephalus* and *Ae. Taylori*).[3]

The vectors of YF demonstrate predominantly daytime biting activity. After a period that usually ranges from nine to twelve days of infection in a viremic case, mosquitoes are capable of transmitting the disease. The incubation period in humans ranges, on average, from three to six days after the bite of the infected mosquito, and it can also reach up to 10 days.[4]

In 1947, the former National Service of Yellow Fever started the use of dichlorodiphenyl trichloroethane (DDT) in the attempt to fight mosquitoes. In 1950, the activities of this service reached its peak, putting 3,349 active employees in charge of 112,950 locations. In 1958, the National Department of Rural Endemic Diseases, which had already absorbed the National Yellow Fever Service, announced the eradication of *Ae. aegypti* in the country.[5]

Nevertheless, in 1967, the *Ae. aegypti* was again identified in Brazil in the city of Belém, capital of the state of Pará, and two years later, in 1969, in the state of Maranhão. In 1973, a final focus was eliminated and the vector was considered again eradicated from the Brazilian territory.[6,7] In 1976, *Ae. aegypti* reappeared for the second time and reinfested the country, beginning in the city of Salvador, Bahia, due to a failure in entomological surveillance. Social and environmental changes that were considered a result of the rapid urbanization favored the settlement and spread of this mosquito in Brasil.[8] Reinfestations were confirmed in the states of Rio Grande do Norte and Rio de Janeiro, and since then, the Ministry of Health has implemented programs to combat this vector and to reduce the risk of urban transmission of YF and, subsequently, to decrease the incidence of dengue, given that *Ae. aegypti* is also the main vector of this virus.

The reemergence of sylvatic transmission of YF outside the Amazon region, from 2007 on, expanded the viral circulation area in Brazil. The areas more recently attacked are in the Southeast and South regions of the country and are important objects because of the proximity to large urban centers, densely occupied by an unvaccinated population; as a consequence, there is no protection against the disease, not to mention the high infestation of *Ae. aegypti*, including dengue transmission in a myriad of municipalities. This fact raised the discussion about the risk of resumption of urban transmission of YF in Brazil, which was recorded for the last time in Sena Madureira, a municipality in the state of Acre, in 1942.[9,4]

Until 1999, the surveillance of YF was based exclusively in the event of suspected human cases. From that year on, with the observation of monkeys' deaths in several municipalities of the states of Tocantins and Goiás and the subsequent appearance of the disease in the human population, these events were seen as possible indicators of risk (sentinel event) of human cases of sylvatic transmission.

People who are at risk of getting YF in the American continent are those not vaccinated and exposed to the bites of vectors in forest areas, in the virus endemic places, especially where there is virus circulation. Forestry and rural areas most affected correspond to the hydrographic basins of the Amazon, Araguaia-Tocantins, Paraná and Orinoco in South America and the Nile and Congo rivers in África.[10]

To contribute to the improvement in the surveillance and control of yellow fever in Brazil, this study aims to describe the epidemiological characteristics of yellow fever in the country from 2000 to 2012.

Methods

This is a descriptive epidemiological study, using as source the database of the Ministry of Health on the incidence of cases and deaths related to YF in humans and in non-human primates – NHP – from 2000 to 2012. These data were provided by the Program of Surveillance, Prevention and Control of Yellow Fever of the Health Surveillance Secretariat of the Ministry of Health (*SVS/MS*); and the Evandro Chagas Institute, from Belém, Pará state (PA), Adolfo Lutz Institute, São Paulo state (SP) and Oswaldo Cruz Foundation (*Fiocruz*) Rio de Janeiro state (RJ). These are reference laboratories and are accredited by the *SVS/MS* to diagnose yellow fever. Whenever a suspicious case is detected in an individual, a blood sample or other tissue sample is sent to one of the aforementioned laboratories.

The notification of YF cases – as well as the epidemiological investigation – must take place within 24 hours after the suspicion. The data collection instrument, an epidemiological investigation form, available at the Information System for Notifiable Diseases (*Sinan*), covers the essential elements to be recorded in a routine investigation.[2]

The human cases were distributed by year and Federative Unit (FU) of occurrence, according to the variables 'age', 'sex', 'occupation' and 'outcome' (death, non-death). The age range, median and standard deviation were calculated. The annual fatality rates for Brazil from 2000 to 2012, and for FU were calculated, and the main occupational activities were described. There was a great diversity in the records for occupations. Thus, the item 'rural worker' was grouped according to the following occupations: agriculturist; cattleman; peasant; farmer; cowboy; rural worker; fisherman; and prospector.

The number of human cases was calculated on a monthly basis, in order to verify the existence of seasonality of the disease during the studied period.

NHP deaths data were collected from reports provided by the reference laboratories and by the Program of Surveillance, Prevention and Control of Yellow Fever.

The data on doses of vaccines administered by FU, provided by the National Immunization Program (*PNI/SVS/MS*) have been consulted.

Taking into account that this is secondary data, with no identification of names of the affected people, the study was exempted from evaluation by the Research Ethics Committee, in accordance with the Resolution of the National Health Council (*CNS*) No. 466, dated December 12, 2012.

Results

From 2000 to 2012, 326 confirmed cases of YF were recorded, all caused by the sylvatic transmission cycle, and there were 156 deaths in the country, resulting in an average fatality rate of 47.8%. The year 2000 was the one with the highest number of cases and deaths (Table 1).

The distribution of YF cases by Federative Unit showed that the state of Minas Gerais was the most affected in the aforementioned period, with 101 confirmed cases and a fatality rate of 40.6%, followed by the state of Goiás, with 77 cases and a fatality rate of 50.6% (Table 1). Of all 326 confirmed cases in the country, 268 (86.7%) involved men, with a fatality rate of 49.6%; higher than that recorded among women: 39.7%. There was a proportion of 4.62 sick men for each sick woman. A similar phenomenon happened concerning deaths ratio: for each woman death there were 5.78 men deaths.

With regard to occupation, 45% of the people affected by YF were rural workers. According to age group, it was observed that the group of young adults was the most affected. The average age was 32 years old, with a range from zero to 93 years old. The state with the highest average age was Mato Grosso do Sul: 43 years old. (Table 2).

With regard to seasonality of the YF, 95% of the cases were registered from January to June (Figure 1).

In epizootic terms, there were a total of 2,856 non-human primates notified with suspected YF, of which 889 cases (31.1%) were confirmed by laboratory tests. Among all the Federative Units, Rio Grande do Sul recorded the

Table 1 - Distribution of confirmed cases and deaths caused by sylvatic yellow fever transmission and fatality rates, according to the year of occurrence and Federative Unit. Brazil, 2000-2012

Year	Confirmed cases (N)	Deaths (N)	Fatality rate (%)
2000	85	40	47.0
2001	41	22	53.6
2002	17	8	47.0
2003	62	21	33.8
2004	6	3	50.0
2005	3	3	100.0
2006	2	2	100.0
2007	13	10	76.9
2008	46	27	58.6
2009	47	17	36.1
2010	2	2	100.0
2011	2	1	50.0
2012	–	–	–
2012	–	–	–
Federative Unit	**Confirmed cases (N)**	**Deaths (N)**	**Fatality rate (%)**
Minas Gerais	101	41	40.6
Goiás	77	39	50.6
São Paulo	32	15	46.9
Rio Grande do Sul	21	9	42.9
Mato Grosso	20	11	55.0
Amazonas	18	11	61.1
Pará	14	8	57.1
Bahia	10	3	30.0
Mato Grosso do Sul	10	3	30.0
Distrito Federal	8	6	75.0
Tocantins	6	4	66.7
Roraima	5	4	80.0
Paraná	2	1	50.0
Acre	1	–	–
Rondônia	1	1	100.0
Total	326	156	47.8

highest number of NHP with positive laboratory test: 77.5% of NHP reported in the whole country and with results that confirmed yellow fever (Table 3).

According to the Ministry of Health, 110,081,513 doses of vaccines against YF were administered in Brazil, from 2000 to 2012, immunizing the population in all Federative Units

Table 2 - Distribution of confirmed cases of yellow fever caused by sylvatic transmission according to age, by Federative Unit. Brazil, 2000-2012

Federal Unit	Confirmed cases (N)	Age (years)		
		Average (standard deviation)	Range	Median
Minas Gerais	101	39 (14.3)	16-82	38.0
Goiás	77	36 (14.0)	11-74	35.0
São Paulo	32	32 (11.6)	0-51	35.0
Rio Grande do Sul	21	34 (15.4)	10-73	33.0
Mato Grosso	20	32 (16.0)	7-65	30.0
Amazonas	18	30 (13.5)	9-61	29.0
Pará	14	36 (15.2)	4-93	24.0
Bahia	10	29 (12.9)	13-52	27.5
Mato Grosso do Sul	10	43 (14.8)	22-69	40.5
Distrito Federal	8	41 (15.3)	21-59	40.5
Tocantins	6	27 (6.7)	18-35	28.0
Roraima	5	20 (6.4)	15-28	16.0
Paraná	2	31 (5.6)	27-35	–
Acre	1	21 (0.0)	–	–
Rondônia	1	35 (0.0)	–	–
Total	326	32.4 (5.5)	0-93	27.5

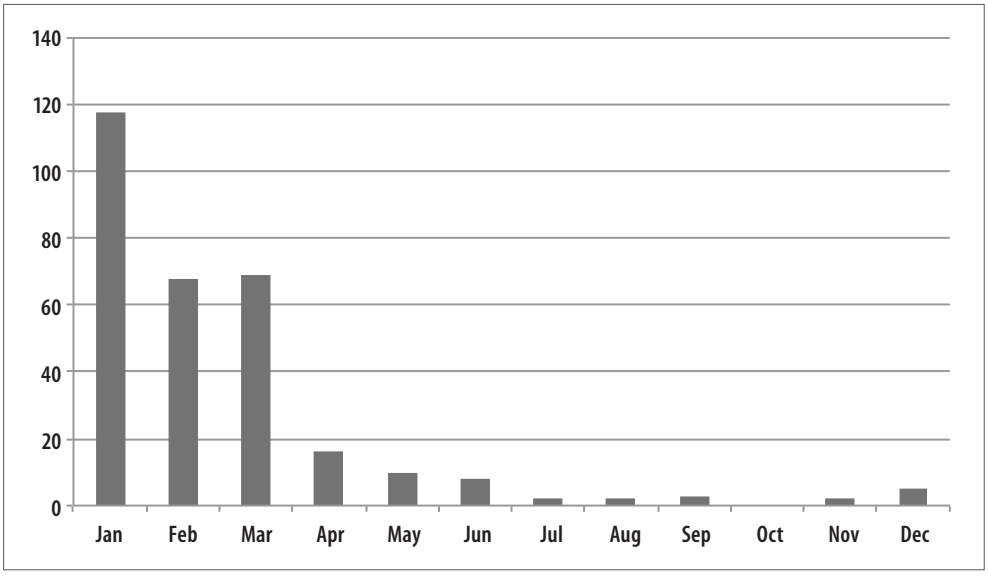

Figure 1 - Monthly distribution of the number of cases of yellow fever caused by sylvatic transmission. Brazil, 2000-2012

(Table 4). The observation of epizootics served as a risk predictor element of occurrence of YF in humans (Ordinance No. 5 issued by SVS/MS, dated, February 21, 2006) and triggered a series of actions, including dynamic revision of the transmission areas and adequacy to vaccination strategies each time the local vaccination coverage was expanded.

Discussion

Ninety-five percent of cases of YF presented in this study were confirmed by laboratory tests. The most affected group was the young adult male rural workers. Rural areas are considered risk for the spreading of this virus.

The year 2000 was the one with the highest number of confirmed cases in the country, during the studied period. A large number of cases in densely populated areas has been identified, such as in the regions South, Southeast and Midwest, areas with high density of infestation of the urban vector, *Aedes aegypti*. This fact is preocupying, given that it indicates the possibility of an increase of risk of re-urbanization of the disease transmission, since the sylvatic transmission seems to be migrating to densely populated areas, where the mosquito vector of urban cycle, the *Ae. Aegypti*, is abundant. The reasons for this geographic expansion, for now, are not fully known.

Table 3 – Distribution of the number of non-human primates notified and confirmed for yellow fever, by Federative Unit. Brazil, 2000-2012

Federal Unit	Notified primates	Confirmed primates	
	N	N	(%)
Rio Grande do Sul	1,151	689	59.8
Goiás	378	63	16.6
Minas Gerais	347	27	7.7
São Paulo	295	24	8.1
Distrito Federal	173	66	38.1
Tocantins	107	1	0.9
Rio de Janeiro	89	–	–
Paraná	56	4	7.1
Santa Catarina	49	–	–
Bahia	48	2	4.1
Mato Grosso	35	2	5.7
Rio Grande do Norte	32	–	–
Roraima	18	5	27.7
Rondônia	15	–	–
Pará	14	2	14.2
Mato Grosso do Sul	13	2	15.3
Maranhão	9	–	–
Espírito Santo	7	–	–
Amapá	5	–	–
Amazonas	4	2	50.0
Acre	4	–	–
Piauí	3	–	–
Ceará	3	–	–
Pernambuco	1	–	–
Total	2,856	889	31.1

Table 4 - Amount of yellow fever vaccine doses administered by Federative Unit. Brazil, 2000-2012

	Yellow fever vaccine doses administered (D1 + R1a) by Federative Unit, macroregion and Brazil												
	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Rondônia	211,016	186,696	104,735	115,022	82,304	116,433	103,106	127,215	275,495	116,841	126,951	112,975	106,064
Acre	64,157	53,164	43,132	48,338	35,875	50,872	48,258	64,519	96,375	67,102	59,678	106,311	55,403
Amazonas	415,695	336,329	252,583	237,617	183,438	233,206	282,665	299,490	461,396	246,279	253,981	256,538	266,312
Roraima	62,296	47,140	41,361	61,590	47,606	81,272	58,150	67,252	76,350	42,070	36,529	35,158	30,367
Pará	1,011,092	599,046	419,592	596,873	424,269	430,103	371,547	421,241	764,911	403,433	371,444	408,617	398,256
Amapá	89,652	78,454	48,167	37,051	23,305	30,885	32,643	41,677	107,756	35,394	39,503	35,868	42,164
Tocantins	248,854	93,013	94,856	106,538	128,093	134,711	95,644	119,852	288,825	99,588	124,776	88,868	86,240
North	2,102,762	1,393,842	1,004,426	1,203,029	924,890	1,077,482	992,013	1,141,246	2,071,108	1,010,707	1,012,862	1,044,335	984,806
Maranhão	1,369,280	469,462	343,393	353,607	298,931	411,535	360,002	2,289	612,596	331,002	425,547	391,174	377,515
Piaui	899,816	256,362	96,661	87,036	82,649	106,728	107,203	152,244	260,079	85,042	120,575	118,173	129,967
Ceará	386,570	50,504	10,859	3,874	8,789	17,434	11,981	12,118	46,084	20,799	16,186	19,180	18,677
Rio Grande Do Norte	66,947	15,117	6,828	7,935	5,696	16,388	10,478	6,789	26,075	8,052	8,248	10,821	10,856
Paraíba	5,664	4,857	3,110	1,738	2,554	2,919	3,215	4,201	18,796	8,858	6,524	7,008	7,300
Pernambuco	114,732	91,987	39,542	36,067	34,498	14,232	13,006	13,810	68,301	24,809	19,889	20,641	25,221
Alagoas	23,225	13,811	5,017	3,856	3,075	3,592	2,595	3,768	22,075	8,651	7,363	5,453	7,156
Sergipe	277,265	38,340	2,724	2,334	2,100	2,275	2,594	3,689	23,385	4,925	6,738	6,568	6,367
Bahia	3,029,516	2,230,375	715,468	673,436	554,804	627,939	556,271	232	865,682	449,485	657,400	702,722	564,131
Northeast	6,173,015	3,170,815	1,223,602	1,169,883	993,096	1,203,042	1,067,345	199,140	1,943,073	941,623	1,268,470	1,281,740	1,147,190
Minas Gerais	3,429,168	5,385,206	455,499	837,679	556,529	539,727	534,378	645,699	2,148,668	1,109,589	1,362,924	1,557,063	1,076,331
Espírito Santo	122,166	327,550	9,508	187,772	308,696	88,092	69,897	105,020	136,958	28,528	21,033	22,285	22,989
Rio De Janeiro	651,110	457,662	36,103	34,089	37,990	70,643	48,547	66,685	366,771	82,595	84,376	94,837	92,354
São Paulo	3,266,142	552,836	519,732	578,909	348,563	434,014	421,434	486,578	2,440,560	2,196,497	1,195,040	731,861	720,704
Southeast	7,468,586	6,723,254	1,020,842	1,638,449	1,251,778	1,132,476	1,074,256	1,303,982	5,092,957	3,417,209	2,663,373	2,406,046	1,912,378
Paraná	993,991	963,614	322,304	261,130	475,347	559,662	387,594	344,839	1,505,913	549,125	669,482	610,535	427,472
Santa Catarina	40,937	333,341	69,810	52,010	38,387	45,944	47,100	50,255	202,976	189,701	121,271	321,911	193,378
Rio Grande Do Sul	51,105	398,870	104,896	121,510	44,139	48,359	55,966	63,149	565,418	3,712,245	160,271	291,616	260,932
South	1,086,033	1,695,825	497,010	434,650	557,873	653,965	490,660	458,243	2,274,307	4,451,071	951,024	1,224,062	881,782
Mato Grosso Do Sul	524,577	172,191	211,717	167,807	97,248	114,066	122,400	207,962	807,631	114,144	147,240	153,154	157,241
Mato Grosso	937,049	205,935	195,909	314,780	147,536	180,757	158,354	178,020	712,598	164,586	201,448	160,365	167,690
Goiás	2,795,787	251,646	209,540	227,059	261,678	276,839	271,589	687,801	2,784,332	214,564	316,453	309,557	289,407
Distrito Federal	1,284,060	92,302	72,777	72,205	74,752	74,270	80,950	233,640	1,481,448	103,334	150,151	111,161	124,173
Midwest	5,541,473	722,074	689,943	781,851	581,214	645,932	633,293	1,307,423	5,786,009	596,628	815,292	734,237	738,511
Brazil	22,371,869	13,705,810	4,435,823	5,227,862	4,308,851	4,712,897	4,257,567	4,410,034	17,167,454	10,417,238	6,711,021	6,690,420	5,664,667

a) D1 = first dose.
b) first boost.

The incidence of sylvatic YF proved to be seasonal, coinciding with the rainy season in the endemic area, when there is increased density of vectors. In Brazil, this period ranges from January to June. Over the years, the incidence of YF has shown a cyclical trend, with an increase within every five to seven years. This fact is explained by the higher viral circulation, due to the accumulation of susceptible monkeys.[1]

The fatality rate of YF in Brazil is very high, and is indeed, too relevant. Besides, the virulence of the infectious agent, the delay in identifying the disease and the absence of effectively ethiologic treatment contribute to the high fatality rate.[1]

The occurrence of cases and deaths was higher among men, probably due to the work in rural areas and, consequently, a greater exposure to infection. According to the results of the present study, as noted above,[11] the most affected group by YF showed a similar profile, mostly represented by male young adults, with an average age of 32 years old and usually rural workers. It is the population under greater exposure to environments where the viruses are circulating.

The Epizootics Surveillance System in non-human primates was released in 1999, after an intense transmission period in the Midwest region of the country, where the occurrence of animal diseases in NHP preceded and followed the occurrence of human cases of sylvatic transmission. Since then, the Ministry of Health started to encourage regional initiatives to detect virus circulation in its enzootic cycle.[12]

The main prevention measure of YF in humans is vaccination. Since 1998, the Ministry of Health has intensified the implementation of the YF vaccine, including it in the vaccination calendar. The vaccine is produced in Brazil and prepared with live attenuated virus; generally, there are a few reactions, respecting contraindications, and it has been used for more than 60 years, proving to be the most effective method to prevent yellow fever. By the time of the conclusion of the present study, there was no record in the database on the vaccination status of the vast majority of cases occurred during the studied period. The administration of the vaccine aims at protecting the population by fostering the development of protective antibodies[13] and to establish an epidemiological barrier to the spread of the sylvatic virus in urban areas, where the *Ae. aegypti* is present.[14]

In the country, the areas considered at higher risk for YF include the North and Midwest regions, the states of Minas Gerais and Maranhão and part of Bahia, Piauí, São Paulo, Rio Grande do Sul, Santa Catarina and Paraná.[2] Considering the risk of yellow fever virus ciruclation, Brazil is divided into two main areas. The first area, target of vaccine recommendation presents the highest risk for the disease. The second, an area with no vaccine recommendation represents a smaller risk for the disease. [2]

After the occurrence of recent serious events – even lethal – ascribed to the YF vaccine, there is no agreement on the vaccination of the population that lives in areas infested by *Ae. aegypti* and (or) by *Ae. albopictus*. Specialists who are not in favor of the geographical expansion of immunization coverage take into account relevant facts, such as the occurrence of deaths associated with the vaccine in the states of São Paulo, Minas Gerais, Rio Grande do Sul and Goiás. In the literature, there have been reports of death associated with the vaccine in the United States and Australia. The factors that lead some people to present serious adverse events associated with the vaccine are not fully known.[3]

There are also favorable views on expanding the present area of vaccination coverage, depending on the sylvatic YF transmission detection in regions of the states of Bahia and Sao Paulo (2000) and Minas Gerais (2001). Those areas are infested with *Ae. aegypti* and have had no cases of the sylvatic form of the disease for years. In 2001, in the western region of Rio Grande do Sul state, there was viral circulation with the death of monkeys confirmed in by laboratory tests, in a place where there had also been no record of animal diseases by YF for more than 20 years.[3]

A limitation of this study lies in the use of secondary data, which can lead to a possible underreporting of cases. The low number of cases of sylvatic yellow fever reduces the risk of reintroduction of the urban form of the disease. However, when visiting cities with high infestation by *Ae. aegypti*, people from endemic areas in the early stages of the disease and during the period of transmissibility, bring risk to urban transmission of yellow fever in Brazil.

Authors' contributions

Cavalcante KRLJ contributed to the analysis, interpretation of data and writing of the manuscript.

Tauil PL contributed in the conception and design of the study and on the relevant critical review of the intellectual content of the manuscript.

Both authors approved the final version of the manuscript and are responsible for all aspects of the study, ensuring its accuracy and integrity.

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