



ISSN: 2230-9926

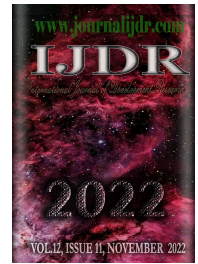
Available online at <http://www.journalijdr.com>

IJDR

International Journal of Development Research

Vol. 12, Issue, 11, pp. 60299-60303, November, 2022

<https://doi.org/10.37118/ijdr.25788.11.2022>



RESEARCH ARTICLE

OPEN ACCESS

CATEGORIZATION OF YELLOW FEVER RISK IN PARAGUAY AFTER THE INTRODUCTION OF THE YELLOW FEVER VACCINE TO THE REGULAR VACCINATION SCHEDULE

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ARTICLE INFO

Article History:

Received 19th August, 2022

Received in revised form

24th September, 2022

Accepted 29th October, 2022

Published online 30th November, 2022

KeyWords:

Yellow fever, Vaccination coverage, Risk, Outbreak.

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ABSTRACT

Introduction: Yellow Fever is a disease with a wide spectrum of symptoms. **Objective:** To identify the Sanitary Regions of Paraguay with high, medium and low risk of yellow fever. **Materials and Methods:** Observational descriptive, cross-sectional study conducted from 2006-2021. Demographic variables: age, Sanitary Region, population, vaccination coverage against yellow fever and epidemiological density (presence of the reservoir and *A. aegypti* (vector), proximity and migration to epizootic areas. A risk matrix was developed and applied to each region: score ≥ 8 considered high, 5-7: medium, ≤ 4 low risk. **Results:** In the last 5 years, the vaccination coverage was 52-80% ($p=0.000047$). Coverage: pre-pandemic 76%, post-pandemic 59% ($p=0.015$). 1-16 y. vaccinated: 79.9%, 17 to 59 y: 85.1% ($p=0.45$). In 2021, almost all health regions had a reservoir of the virus, the vector spread in all Regions, vaccination coverage was $<80\%$ in 8 regions, 84-94% in 10, 95 to 100% in 1. Risk of yellow fever by 2021: high: 17 (89%) regions, medium: 2 (11%), low: none, (high vs low $p=0.00000001$). **Conclusion:** Large gaps in vaccination, expansion of the vector and presence of the reservoir in almost all regions were found. Regions with high, medium and low risk of yellow fever in humans were identified.

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Citation: Araya S, Castro H, Lopez-Benitez J, Von Horoch M, Lugo E, Cousirat L, Britos R, Avalos C, Araya J, Nissen J, Troche A, Chamorro G. "Categorization of yellow fever risk in Paraguay after the introduction of the yellow fever vaccine to the regular vaccination schedule.", *International Journal of Development Research*, 12, (11), 60299-60303.

INTRODUCTION

Yellow fever (YF) is a viral infection transmitted by mosquitoes of the genera *Haemagogus* spp. and *Sabethes* spp., *Aedes aegypti* and/or *Aedes albopictus* species. The infection is more frequent in Africa and South America and it has a wide spectrum of clinical disease, from asymptomatic manifestations to mild or severe disease, in some cases with organ damage (heart, liver, kidney) with or without bleeding. As for severity, about 55% of infected people suffer from the asymptomatic form, 33% from the mild form and 12% from the severe form; in severe forms, between 50 to 67% of them die. (1-2). Three cycles of yellow fever transmission are known: 1) Jungle, 2) Intermediate, 3) Urban (3). The epidemiological situation in Latin America in recent years was as follows: during 2016-2018, two waves of yellow fever transmission were registered, during the first wave between 2016-2017, seven countries registered cases (Bolivia, Brazil, Colombia, Ecuador, French Guiana, Peru and Suriname) while in the second wave, between 2017 and 2018, there were 6 countries that reported confirmed cases (Bolivia, Brazil, Colombia, Ecuador, French Guiana and Peru); in both waves the highest number of cases of epizootics and infection in humans were recorded.

Between 2019 and 2021, three countries in the Region of the Americas reported confirmed cases: Peru, Venezuela, and Brazil with dispersal routes in the direction of Rio Grande do Sul (4). There is little history of circulation of yellow fever virus in Paraguay; in between 1974 and 2018, 37 cases have been reported in 4 departments of our country. In 2008, an urban epidemic of Yellow Fever took place in which 28 cases were confirmed, distributed in the departments of San Pedro (15 cases), Central (9 cases) and Caaguazú (4 cases). From that time until the present, no new cases of yellow fever in humans were reported in Paraguay. (5). Vaccination against yellow fever is an effective method of preventing and controlling cases. The 17 D vaccine is a live attenuated virus vaccine developed in 1930. The American Academy of Pediatrics and the Strategic Advisory Immunization Group recommend vaccination against yellow fever beginning at 9 months of age in epidemic areas; it is important to remember that one dose of the vaccine protects for life, with seroconversion rates being 72% when the vaccine is administered between 9-11 months, 88% between 12 - 23 months and 98% in adults, with a vaccine failure rate reported in scientific articles of 7.5% (7, 8, 9). Vaccination against yellow fever in Paraguay began in 2001, with the target population being travelers to endemic areas

and residentes in border areas. In 2006 vaccination against yellow fever was introduced to the regular vaccination schedule at the age of 1 year (5). The eradication of yellow fever is a great challenge, the yellow fever epidemic elimination strategy (EYE) was established by the World Health Organization as a long-term global strategy (2017-2026) aimed at vulnerable countries, in order to eliminate yellow fever epidemics by 2026. The objectives of the strategy are to protect at-risk populations, prevent international transmission and quickly contain outbreaks, which requires maintaining high vaccination coverage in all districts through routine childhood immunization, prevent the international spread of yellow fever, and assess the risk of outbreaks or epidemics in countries in order to establish preventive, prioritized and timely interventions (10). The analysis of the risk of vector-transmitted disease epidemics is complex, since it is necessary to link the etiological agent, the intermediate or reservoir host and man in an environmental context, by carrying out an ecological and epidemiological investigation (11). In the case of yellow fever, threat is associated with the vector's habitat and virus reservoirs, while vulnerability is related to the distribution of the human population (population density), its immune status, and economic or migratory activities (11, 12). In 2019, the Expanded Immunization Program developed a National Vaccination Plan against yellow fever (2019-2026), in accordance with the EYE strategy. As part of this plan, a risk analysis of an outbreak or epidemic of yellow fever in Paraguay in 2019 performed. Based on those findings, a vaccination update campaign against yellow fever was carried out in the Triple Border Region, to keep the country free of cases of yellow fever in humans. (13, 5). Considering that, in 2020 and 2021, the country faced the COVID-19 Pandemic, which had an impact on the vaccination rates of the standard schedule and that, because of global warming, favorable conditions for the vector have been present, the risk of yellow fever outbreaks in Paraguay increased. After the introduction of the yellow fever vaccine into the Regular Vaccination Schedule in December 2021, a need to assess the threats and vulnerabilities of each Sanitary Region in the country was identified, therefore, this study aimed to identify the Sanitary Regions with low, medium and high risks of Yellow Fever outbreaks, in order to develop public policies and health strategies in accordance with current scientific evidence (14).

MATERIALS AND METHODS

This was a cross-sectional, observational study, carried out in Paraguay, in which we analyzed demographic variables such as age, Health Region, population density and epidemiological variables, such as the presence of the yellow fever reservoir, the presence of the *Aedes aegypti* vector, proximity to epizootic areas, migration to areas at risk of epizootics, vaccination coverage against yellow fever (annual country-wide and annual by Health Region). For our purposes, we collected the information corresponding to the period between the years 2006 to 2021, as the introduction of the yellow fever vaccine to the Regular Vaccination Calendar began in 2006. The data sources were: the Department of the Expanded Immunization Program Subsystem for coverage data, SENEPA for larval infestation index by Health Region; for population density the information published by the General Directorate of Statistics, Surveys and Census was used (Year 2012). Regarding the representativeness of the study, all the Health Regions of the Country were included, we note that, although the country has 18 Health Regions, 19 Regions are considered in the program, since the San Pedro Region has been divided into North San Pedro North and South San Pedro. Statistical analyzes were performed, using EPI Info. The ethical principles and the confidentiality of the data of the vaccinated persons were respected, the authors declared no conflict of interest, the work was not subsidized by any vaccine or drug manufacturer.

Variable definitions: Vaccination Coverage against YF, Regular Schedule: The percentage of the population aged 1 year who had access to vaccination against yellow fever. Calculation of National Vaccination Coverage against YF, Regular Calendar: Number of children who have received the YF vaccine at one year of age

(according to the Paraguay scheme) in relation to the estimated national population for that age range, by 100. Calculation of vaccination coverage against YF (regular calendar) regional level: Number of children who have received the YF vaccine at one year of age (according to Paraguay's scheme) in relation to the estimated total population for that age group in the Health Department or Region, per 100. Cumulative coverage (1 to 59 years): Considering that the YF vaccine can be administered to people from 1 to 59 years of age and that it provides protection for life, the calculation of the vaccinated population of 1 to 59 years of age considered two groups; the group that received the vaccine as part of the regular vaccination calendar from the year 2006 to December 2021, who as of December 2021 are between 1 to 16 years of age and the group that received the YF vaccine because of for travel to countries with active circulation of the virus; this population was between 17 and 59 years of age.

Construction of the Risk Categorization Matrix: For developed of the risk matrix, were taken into account, the variables that affect the appearance of epizootics, the presence of cases of YF and the spread of the disease, which are detailed below:

Scoring system:

- Presence of reservoir: yes (1 Point), no (0 Point)
- Presence of the *Aedes aegypti* vector: yes (1 Point), no (0 Point)
- Proximity to an area with the presence of an epizootic: yes (1 point), no (0 point)
- Settlements in epizootic areas or importation of cases: yes (1 point), no (0 point)
- Migration to areas of risk (with the presence of epizootics or nearby): yes (1 Point), no (0 Point)
- History of yellow fever cases in the last 10 years: yes (1 point), no (0 point)
- Accumulated coverage (1 to 59 years): Coverage less than 80%: 3 points, coverage between 94-80%: 2 points, coverage > 95%: 1 point.
- Population Density: <10 inhabitants per Km²: 0 point, 10 to 20: 1 point, 21 to 40: 2 points, more than 40: 3 points.
- Larval Infestation Risk Scale (SENEPA): less than 0.9% (considered satisfactory) 0 point, from 1-3.9% (alert) 1 point, equal to or greater than 4% (risk) 2 points
- Total Score: 8 point or more: High Risk, 5 to 7 points: Medium Risk, 0 to 4 points: Low Risk

RESULTS

Regarding the regular vaccination schedule against YF, the national vaccination coverage in children at 1 year of age has ranged from 80 to 52% in the last five years, with the difference being statistically significant between the year of highest coverage and lowest coverage ($p=0.000047$) (Table 1). During the COVID-19 pandemic in 2020-2021, the average YF vaccination coverage was 59%, as opposed to the Pre-pandemic period (2017-2019) of 76%, with a significant decrease in coverage during the pandemic ($p=0.015$) (Table 1). When assessing the population aged 1-59 years who were vaccinated at the country level and by Health Regions, the group aged 1 to 16 years achieved a 79.9% of vaccination rate, while in the population aged 17 to 59 years, the vaccination percentage was 85.1% (non-significant difference, $p=0.45$) (Tables 2 and 3). The heterogeneity of coverage between the Health Regions is striking, in both groups (1-16 years) and (17-59 years), as well as in the coverage against YF according to the regular vaccination schedule (Tables 1, 2 and 3). Regarding the categorization of risk of YF by Health Region, at the end of 2021, almost all health regions had a reservoir of the virus (*Cebus* and *Alouatta caraya* primate species) except the Capital and Ñeembucú departments. Although the *Aedes aegypti* vector has spread to all the Sanitary Regions of the country and there have been no cases of YF in humans in the last 10 years, the accumulated vaccination coverage against YF in the population aged 1 to 59 years, since the introduction

Table 1. Yellow Fever Vaccination Coverage (Regular Schedule) 2017-2021

N°	Health Region	Coverage 2017	Coverage 2018	Coverage 2019	Coverage 2020*	Coverage 2021*
1	Concepción	74	76	70	67	52
2.1	N. San Pedro	85	87	71	59	43
2.2	S. San Pedro	75	67	60	51	39
3	Cordillera	84	81	77	70	60
4	Guairá	65	71	65	65	43
5	Caaguazú	76	76	69	65	56
6	Caazapá	62	63	56	58	48
7	Itapúa	70	67	58	56	45
8	Misiones	76	81	74	68	58
9	Paraguarí	71	68	68	67	44
10	Alto Paraná	87	88	77	73	51
11	Central	79	82	68	62	52
12	Ñeembucú	73	71	72	70	53
13	Amambay	88	94	84	76	60
14	Canindeyú	88	83	71	59	52
15	Pte. Hayes	72	90	64	63	58
16	Boquerón	84	92	90	102	91
17	Alto Py	81	106	97	89	72
18	Capital	90	103	79	72	64
	Country	79	80	70	65	52

*COVID-19 Pandemic

Table 2. Yellow Fever Vaccination Coverage, population aged 1-16, 2006-2021, Paraguay

Health Region	Population aged 1- 16 y, 2021	Vaccinated population aged 1-16y, 2006 al 2021	% de Vaccinated Population to 2021
Concepción	90.617	74.369	82,1
North San Pedro	70.181	56.436	80,4
South San Pedro	79.168	56.099	70,9
Cordillera	90.970	68.965	75,8
Guairá	67.990	49.620	73,0
Caaguazú	184.179	144.072	78,2
Caazapá	66.951	46.952	70,1
Itapúa	199.438	152.779	76,6
Misiones	37.959	28.604	75,4
Paraguarí	73.180	57.824	79,0
Alto Paraná	265.177	230.140	86,8
Central	642.311	501.031	78,0
Ñeembucú	23.406	18.000	76,9
Amambay	56.141	47.156	84,0
Canindeyú	78.731	65.251	82,9
Pte. Hayes	42.910	36.090	84,1
Boquerón	21.653	20.633	95,3
Alto Paraguay	6.121	5.414	88,4
Capital	135.226	123.267	91,2
Total	2.232.308	1.782.703	79,9

Table 3. Yellow Fever Vaccination Coverage, Population aged 17-59, 2006-2021, Paraguay

Health Region	Population aged 17-59, 2021	Vaccinated population aged 17-59, 2006-2021	% Vaccinated Population to 2021
Concepción	139.417	130.507	93,6
North San Pedro	112.871	106.908	94,7
South San Pedro	127.345	111.951	87,9
Cordillera	181.048	118.165	65,3
Guairá	130.560	127.255	97,5
Caaguazú	317.272	210.082	66,2
Caazapá	104.375	96.695	92,6
Itapúa	351.884	314.741	89,4
Misiones	74.723	47.310	63,3
Paraguarí	146.453	132.811	90,7
Alto Paraná	493.170	379.725	77,0
Central	1.342.152	1.142.212	85,1
Ñeembucú	51.901	49.615	95,6
Amambay	99.045	78.383	79,1
Canindeyú	137.500	92.537	67,3
Pte. Hayes	72.654	40.295	55,5
Boquerón	38.774	16.112	41,6
Alto Paraguay	10.239	3.759	36,7
Capital	301.924	405.067	134,2
Total	4.233.306	3.604.130	85,1

Table 4. Yellow Fever Risk Categorization by Health Region, Paraguay, 2021

Health Region	Presence of risk/epizootic expansion				Risk of the presence of cases				Disease dissemination				Risk	Total Score	Risk
	Reservoir presence *Cebus sp. &Alouattacara ya	Vector present	Proximity to an epizootic area	Risk	Settlements in areas with epizootic risk and/or case importation	Migration to risk areas (epizootic presence or nearness)	History of cases in last 10 years	Risk	Accumulated coverage (ages 1-59) 2006-2021		Population Density	<i>Aedes aegypti</i> infestation index Intervention, 2021			
	Yes= 1, No=0	Yes = 1, No=0	Yes = 1, No=0		Yes= 1, No=0	Yes= 1, No=0	Yes= 1, No=0		%	Value		Value			
Alto Paraná	1	1	1	3	1	1	0	2	84	2	3	2	7	12	HIGH
Caaguazú	1	1	0	2	1	1	0	2	71	3	3	0	6	10	HIGH
Central	1	1	0	2	1	1	0	2	83	2	3	2	7	11	HIGH
Canindeyú	1	1	1	3	1	1	0	2	73	3	2	1	6	11	HIGH
North San Pedro	1	1	0	2	1	1	0	2	89	2	2	1	5	9	HIGH
South San Pedro	1	1	0	2	1	1	0	2	81	2	2	1	5	9	HIGH
Amambay	1	1	1	3	1	1	0	2	81	2	1	1	4	9	HIGH
Cordillera	1	1	0	2	0	0	0	0	69	3	3	1	7	9	HIGH
Guairá	1	1	0	2	0	0	0	0	89	2	3	2	7	9	HIGH
Itapúa	1	1	0	2	0	0	0	0	85	2	3	1	6	8	HIGH
Capital	0	1	0	1	1	0	0	1	120	1	3	2	6	8	HIGH
Concepción	1	1	1	3	1	1	0	2	89	2	1	1	5	10	HIGH
Caazapá	1	1	0	2	0	0	0	0	84	2	2	2	6	8	HIGH
Misiones	1	1	0	2	0	0	0	0	67	3	2	1	6	8	HIGH
Paraguari	1	1	0	2	0	0	0	0	33	3	2	1	6	8	HIGH
Pdte. Hayes	1	1	0	2	0	0	0	0	66	3	1	2	6	8	HIGH
Ñeembucú	0	1	0	1	0	0	0	0	88	2	1	1	4	5	MEDIUM
Alto Paraguay	1	1	1	3	0	0	0	0	56	3	0	2	5	8	HIGH
Boquerón	1	1	0	2	0	0	0	0	61	3	0	1	4	6	MEDIUM

of the vaccine, has been heterogeneous, with coverage below 80% in eight Regions, between 80 and 94% in ten Regions and from 95 to 100% in one Sanitary Region. (Table 4) When assessing the variable related to the spread of the disease (larval infestation index according to the last intervention carried out by SENEPA during the year 2021), it was satisfactory only in one health region (Caaguazú), with the rest of the Health Regions having unsatisfactory values above 0.9% (Table 4). Finally, when categorizing the risk of yellow fever outbreak at the end of the year 2021, 17 (89%) Health Regions were found to be in a High Risk situation, 2 (11%) in a Medium Risk situation, and none of them in low risk (High risk vs Low risk $p=0.00000001$) (Table 4).

DISCUSSION

Although Paraguay introduced vaccination against yellow fever to the Regular Vaccination Schedule 16 years ago, the vaccination schedule has been similar to that of other non-epidemic countries, with the target population being children of 1 year of age. Surprisingly, the national vaccination coverages against yellow fever during the last five years have not been ideal, reaching figures of 70-80% (average 76%) during 2017-2019, corresponding to the COVID-19 pre-pandemic period, and 65-52% (average 58.5%) during 2020-2021, which corresponded to the COVID-19 Pandemic; the same phenomenon of decrease in coverage during the COVID-19 Pandemic has been verified in other countries such as Brazil, Bolivia, Peru, having as a consequence the appearance of cases of yellow fever in humans in these countries (4,15). Even so, the regular vaccination coverage achieved by

Paraguay was higher than the global yellow fever vaccination coverage during the same time interval, with the global yellow fever vaccination coverage being 44-48% during the pre-pandemic period (2017- 2019) and 47% during the pandemic period (2020-2021). The Americas Region has been characterized by achieving higher vaccination coverage than the other World Regions, however, the regular vaccination coverage against yellow fever in the Americas during the years 2017 to 2021 reached figures of 57 to 61%, according to official data published by nations through the JRF (15). Regarding the vaccination coverage necessary to eliminate the risk of YF epidemics in endemic countries, the World Health Organization has recommended that countries achieve homogeneous vaccination coverage of at least 80%. A recent scientific article published in the Journal Infectious Diseases in June 2020 has concluded that when vaccination coverage is heterogeneous between regions or between districts and the difference is equal to or greater than 10%, it is necessary to achieve coverage of 90% or more to eliminate the risk of YF in humans (15,2). In this regard, if we analyze the population vaccinated against YF aged 1-59 years in Paraguay and divide it into two groups (1-16 years) who received the routine vaccine at one year of age during the years 2006 to 2021 and (17- 59 years) who received the vaccine for reasons of travel or catch-up campaigns, the accumulated vaccination coverage in the first group is 79.9% and in the second group 85.1%, which is far from the 90% required, requiring emphasis on complying with regular YF vaccination at one year of age. When comparing the current risk of appearance of YF cases in humans with the current risk situation during 2019 and categorizing by risk levels, it was found that in the year 2019: 12/19 (63%) Sanitary Regions were at High Risk, 5/19 (26%) were at Medium Risk and 2/19 (11%) were at Low Risk, with the level of risk at the end of 2021: 17/19 (89%) Regions in a High Risk situation

and 2/19 (11%) Sanitary Regions in a Medium Risk situation, with none in a low risk situation (Table 4). After that, we observed that during the COVID-19 Pandemic there was an increase of 42% of Health Regions with High Risk of Outbreak of Human Yellow Fever (17/19 Health Regions), with almost the entire country in a situation of high risk (Table 4) (13). Other countries, such as Brazil, Peru, Argentina and some African countries, have analyzed the risk of an epidemic and focused their attention on vaccination coverage (2,3). However, in the epidemiological surveillance of this disease there are other relevant factors that must be addressed in addition to vaccination coverage, such as the presence of the competent vector, presence of the reservoir, proximity to areas with a reservoir, population density, which is why in this study, all the variables mentioned in each of the country's Health Regions have been taken into account, with limited international publications taking all of these factors into consideration (12). Finally, humans are not the only reservoir of yellow fever, thus, vaccination against yellow fever as the only strategy will not be sufficient to prevent sporadic cases, outbreaks or epidemics of the disease. It would be unlikely to achieve and maintain coverage vaccination rates between 90% and 100%, even with vaccination coverage close to the threshold required for the prevention of epidemics, there would still be the possibility of sporadic introduction of yellow fever cases through infected non-human reservoirs. To eliminate the risk of YF Outbreaks or Epidemics, the coordinated work of vaccination programs, vector control programs and active surveillance of epizootics is required. Maintaining high vaccination coverage, carrying out an effective fight against the vector, identifying epizootics in a timely manner and assertive coordination between the programs involved and the citizenry is paramount.

CONCLUSION

These results demonstrate the existence of large gaps in vaccination, vector expansion throughout the national territory, and reservoir presence in almost all the country's Sanitary Regions. Regarding the risk categorization, it was possible to identify the regions with high, medium and low risk of yellow fever in humans, with 89% of the Sanitary Regions in high risk situations. These findings are extremely useful for the planning of future vaccination campaign strategies and effective vector control actions that would allow the achievement of the EYE Strategy objectives.

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