Original article

Factors associated with severity of adverse events following yellow fever vaccination during the biggest outbreak of the disease recorded in Brazil, 2016-2017

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Abstract

Objective: to analyze characteristics, incidence and factors associated with serious adverse events (SAEs) following yellow fever vaccination during an outbreak of the disease in Brazil (2016-2017). **Methods**: this was a case-control study using data from the National Immunization Program Information System (SI-PNI); SAE were considered to be cases, and non-serious adverse events (NSAE) were considered to be controls. **Results**: we analyzed 135 SAE cases and 1,058 controls; of the 135 SAE, 79 (58.5%) were males and median age was 28 years [09-49]; incidence in January 2017 reached 1.3 case per 100,000 vaccine doses administered; there was statistical association with males (Odds Ratio [OR] = 1.73 – 95%CI 1.20;2.48), primary vaccination (OR = 1.65 – 95%CI 1.01;2.71), and being 60 years of age or older taking as reference those aged under 5 (OR = 4.4; p-value < 0.02). **Conclusion**: SAE owing to yellow fever vaccine showed a greater chance of occurring in men, the elderly and primary vaccination.

Keywords: Vaccines; Yellow Fever; Drug-Related Side Effects and Adverse Reactions; Immunization; Case-Control Studies.

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Introduction

Yellow fever is an acute vaccine-preventable febrile illness caused by an arbovirus of the *Flavivirus* genus and is transmitted to humans through *Culicidae* family hematophagous insect bites, especially those of the *Haemagogus*, *Sabethes* and *Aedes* genera.[1] Infection can occur either through the urban or the sylvatic transmission cycle, although in both contexts the disease retains the same clinical, etiological, immunological and physiopathological aspects and only differs in terms of the mosquitoes transmitting it and the main vertebrate hosts.[2,3]

With regard to the urban yellow fever transmission cycle, cases were recorded for the last time in 1942 in Brazil in what was then the territory and is now the state of Acre.[3] However, given the occurrence of sylvatic cases, the presence of the urban vector and low vaccination coverage, risk of yellow fever re-urbanization in Brazil does exist, and demands the adoption of prevention and control measures that involve epizootic surveillance and vaccination of the population.[4]

Sylvatic yellow fever case occurrence is endemic in Brazil's Amazon Region. In the Region Outside the Amazon, however, irregular outbreaks of the disease can be found, unleashed by favorable conditions for its transmission, including the high number of individuals susceptible to the disease owing to low vaccination coverage.[5]

> *Adverse events following immunization has been a compulsorily notifiable condition since 2005 in Brazil and must be notified immediately in cases of serious or unusual events.*

The yellow fever vaccine used and distributed in Brazil is derived from the 17D strain (BioManguinhos/Fiocruz 17DD substrains), comprised of attenuated yellow fever virus. It is highly immunogenic and around 90% of vaccinated individuals develop neutralizing antibodies within ten days after vaccination, reaching 99% within 30 days.[6]

Four hundred and five yellow fever cases occurred in Brazil between 1999 and 2013, 44.9% of which were lethal.[7] Between July 2014 and December 2016, when the virus reemerged in the Region Outside the Amazon, 15 human cases were confirmed, the probable places of infection of which were located in the states of Goiás, Pará, Mato Grosso do Sul, São Paulo and Amazonas.[8] At the end of 2016, an outbreak began in Minas Gerais state, where vaccination had been recommended since 2008, and extended to four neighboring states (Espírito Santo, São Paulo, Rio de Janeiro and Bahia), totaling 777 confirmed cases and 261 deaths by July 2017. At that time, 35,033,385 doses of yellow fever vaccine were distributed.[9]

Prior to this Brazil's vaccination schedule recommended two vaccine doses. With effect from April 2017, however, in keeping with the parameters adopted by the World Health Organization (WHO), the Ministry of Health has recommended a single dose.[10]

Yellow fever vaccine is considered to be efficacious and safe. However, it can cause slight adverse events and even serious adverse events. As a natural consequence of mass vaccination strategies, there may be greater occurrence of adverse events following immunization (AEFIs), with increased serious adverse events in adults who do not have prior immunity, given that risk is higher the first time a person is immunized.[11,12]

AEFI is an unfavorable occurrence which is possible after vaccination and investigation is needed to establish whether or not there is a causal relationship.[13] AEFI has been a compulsorily notifiable condition since 2005 in Brazil and must be notified immediately in cases of serious or unusual events.[12]

AEFIs are classified according to causality: (i) consistent, when it is possible to establish a relationship between the event and the immunobiologic product administered; (ii) indeterminate, when it is not possible to prove a relationship between the event and the immunobiologic product; (iii) inconsistent/coincident, when the event is due to a cause other than the immunobiologic product; and (iv) unclassifiable, when available notification information is not sufficient to enable case classification.[12] AEFIs can appear through locallized or systemic manifestations, and can also be classified according to severity: serious adverse event (SAE) and non-serious adverse event (NSAE). SAE incidence due to yellow fever vaccine in Brazil between 2007 and 2012 was 0.42 case per 100,000 doses administered.[12]

Studies of AEFI occurrence and factors associated with its severity are needed, given the relevance and importance of these events, the need to monitor occurrences and identify patterns and levels of risk (incidence), as well as factors associated with serious cases, above all

during outbreaks of the disease. In view of the scaling up of vaccination strategies in several of Brazil's states, greater occurrence of adverse events has not only been expected but has also been confirmed.

The objective of this study was to describe the main characteristics and incidence of SAEs, as well as to analyze associated factors, following yellow fever vaccination during the outbreak of the disease recorded in Brazil in 2016 and 2017.

Methods

This was a case-control study aimed at identifying factors associated with severity of adverse events following immunization against yellow fever notified in Brazil between July 2016 and June 2017, when the country's biggest ever outbreak occurred.

This study was based on records of AEFI cases notified on AEFI notification/investigation forms held on the Adverse Events Following Immunization Module of the National Immunization Program Information System (SIEAPV/SI-PNI).

The following definitions were used based on the National Immunization Program AEFI manual:[12]

a) Serious adverse event
   A consistent SAE that required hospitalization for more than 24 hours, caused significant patient dysfunction and gave rise to risk of death or resulted in death.
b) Non-serious adverse event
   A consistent NSAE that resulted in the patient having clinical manifestations, but did not meet SAE criteria.

The following variables were analyzed in order to characterize SAEs and NSAEs:

a) age group (in years: under 1 year old, 1-4, 5-9, 10-14, 15-19, 20-29, 30-39, 40-49, 50-59, 60 or over);
b) sex (male; female);
c) race/skin color (yellow, white, brown, black, not informed);
d) Federative Unit (UF) of notification;
e) month vaccine administered;
f) localized manifestations (hotness, pain, edema, erythema/redness, other);
g) systemic manifestations (headache, nausea, vomiting, dyspnea, other);
h) seen by a doctor (yes, no, unknown); and
i) progression (cure, death, unknown).

Absolute and relative frequency, central tendency and dispersion measurements were used, as well as the incidence rate of adverse events per 100,000 doses administered. AEFI incidence was calculated taking the number of serious and non-serious adverse events per 100,000 doses of vaccine administered. The number of dose administered was retrieved from the following Ministry of Health website: 'pni.datasus.gov.br'.

'Cases' were considered to be consistent adverse events classified as serious, while 'controls' were considered to be consistent adverse events defined as non-serious.

In the bivariate analysis of factors associated with severity of AEFI due to yellow fever vaccination, we assessed the following variables sex (male; female), pregnancy (yes; no), vaccine dose (single dose, first dose, revaccination), administration route (subcutaneous; other routes) and age group (in years: under 5 years old, 5-10, 11-19, 20-39, 40-59, 60 or over). If data was missing for a variable, observation of the case or control in question was excluded from the statistical analysis.

Association was measured using the odds ratio (OR), taking a 95% confidence interval (95%CI). When analyzing by age group, we took the group aged under 5 years old as the reference and performed the chi-square test for trend. The categorical variables were analyzed using Fisher's exact test and a 5% significance level ($p \leq 0.05$). Epi Info™ 7, Microsoft Access 2013 and QGIS 2.18 were used to analyze the data.

The study project was approved by the National Health Council (CNS) Research Ethics Committee on March 3rd 2018: CNS Opinion No. 2.522.831.

Results

During the study period, 2,540 AEFIs due to yellow fever vaccine were notified, 2,092 (82.4%) of which were considered to be consistent, 121 (4.7%) inconsistent, 317 (12.5%) unclassifiable and 10 (0.4%) indeterminate.

Among the consistent AEFIs, 135 (6.5%) were considered to be serious and 1,058 (50.6%) to be non-serious; 899 (42.9%) were immunization errors arising from failure to comply with established norms and techniques, although they did not cause clinical manifestations in those who had been vaccinated.

Higher SAE incidence was found in January 2017, coinciding with the month in which vaccination blockade began to be scaled up, with 1.3 case per 100,000 doses administered. With regard to NSAEs, records oscillated between the months: highest incidence was found in March 2017 (Figure 1).

SAEs were notified in seven UFs and NSAEs in 22 UFs. Highest SAE frequencies occurred in the states of Minas Gerais (36.3%), Rio de Janeiro (23.0%) and Espírito Santo (23.0%). The states of Rio de Janeiro, Minas Gerais and São Paulo had the highest proportions of NSAEs, with 37.7%, 23.0% and 13.3%, respectively; these were also the states with the highest number of doses administered in the period, namely Minas Gerais with 6,176,544, Rio de Janeiro with 4,837,226 and São Paulo with 2,529,915, followed by Espírito Santo with 2,348,252 doses administered (Figure 2).

The highest SAE incidence rates were found in Espírito Santo (1.4 per 100,000 doses administered), São Paulo (0.8 per 100,000 doses administered) and Minas Gerais (0.8 per 100,000 doses administered). The highest non-serious adverse event incident rates were found in the states of Santa Catarina, Paraná and Rio de Janeiro, with 10.4, 8.3 and 8.2 events per 100,000 doses administered, respectively (Figure 2).

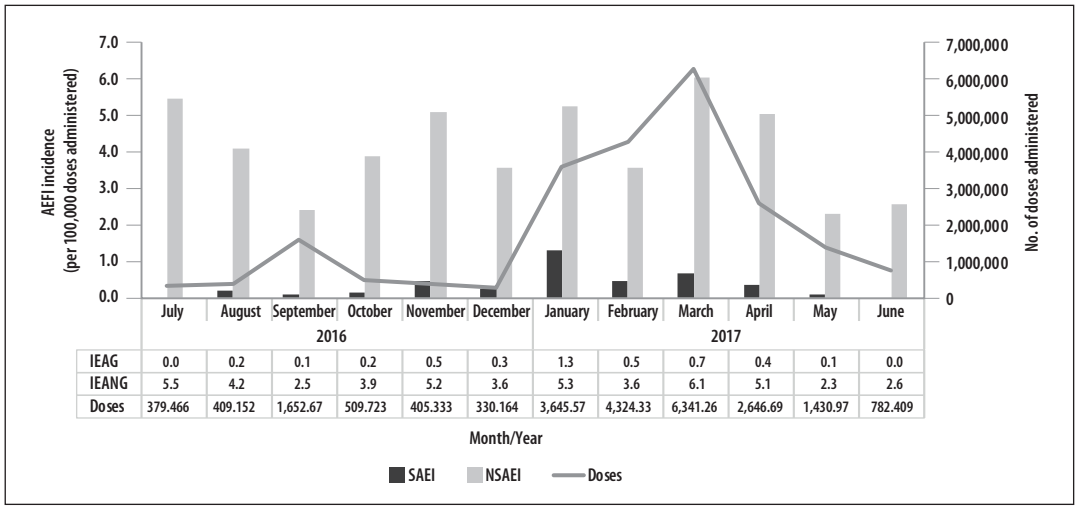
The main AEFI characteristics among SAEs were: predominance of males (58.5%) and the 50-59 year age group (15.6%), as well as median age of 28 years (interquartile range: 9-49 years). Among NSAEs, highest occurrence was found among females (55.1%) and in the 1-4 year age group (19.3%), with median age of 25 years (interquartile range: 7-42 years).

With regard to race/skin color, both for SAEs and NSAEs, for the most part the option selected in the field for this variable was 'not informed': 51 (37.8%) and 433 (40.9%) records, respectively. Among the records that did provide this information, occurrence was mainly among people of White race/skin color, with 41 SAEs (30.4%) and 322 NSAEs (30.4%) (Table 1).

Regarding localized manifestations found for SAEs, pain was recorded in 6 (4.4%) events and localized edema in 4 (3.0%) events. In relation to NSAEs, the most frequent localized manifestations were pain, with 162 (15.3%) events and erythema/redness, with 151 (14.3%) events.

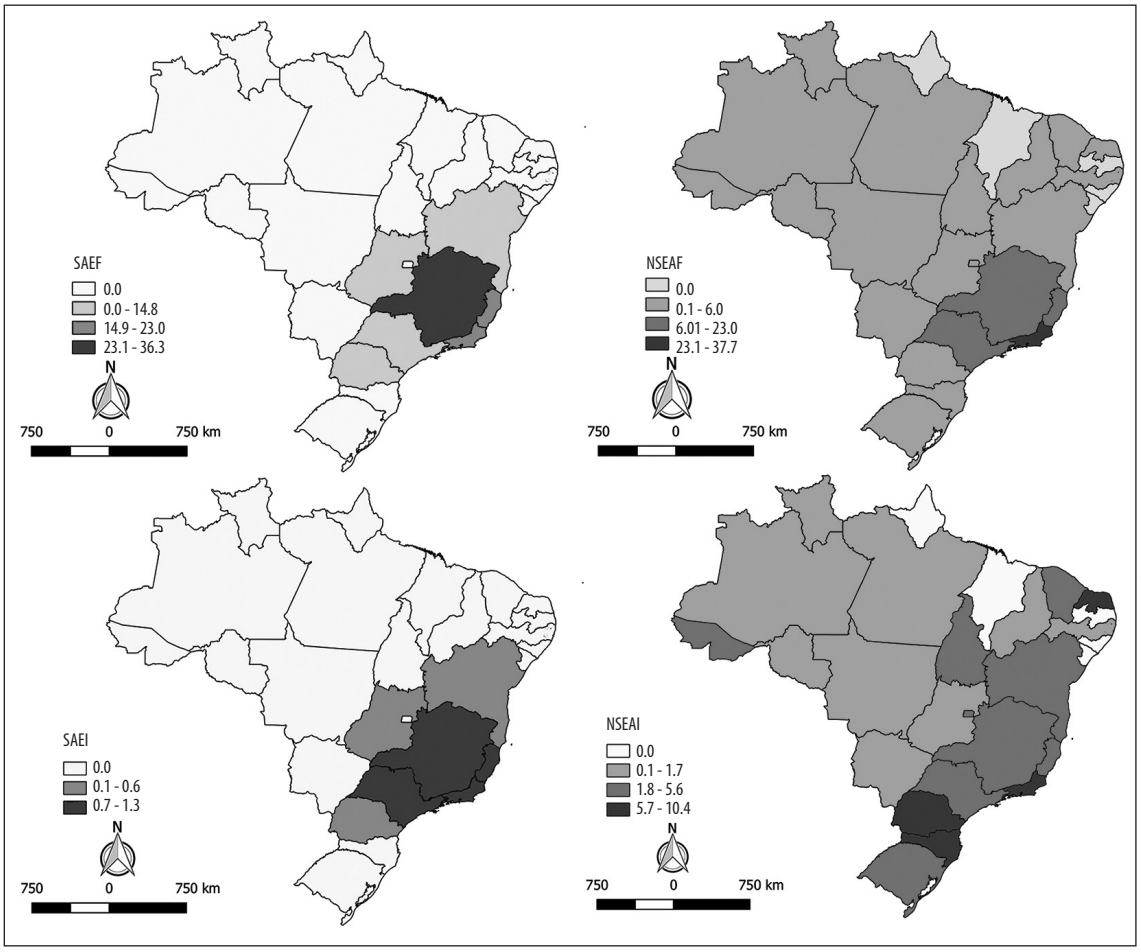
As for systemic manifestations found for SAEs, the most frequent were headache and vomiting, with 44 (32.6%) and 41 (30.4%) events, respectively. In relation to NSAEs, the most frequent systemic manifestations were headache (17.1%) and nausea (11.2%). With regard to being seen by a doctor, this form of care was recorded for 135 (100%) SAEs and 799 (75.5%) NSAEs. In terms of disease progression, 87 (64.4%) SAEs were cured and 6 (4.5%) died, while progression was unknown for 42 (31.1%); among NSAEs, 857 (81.0%) were cured and progression was unknown for 201 (19.0%) according to the records consulted.

Regarding factors associated with severity, the ratio between cases and controls was 1:8. In the bivariate analysis statistical association was found for (i) the male sex and (ii) having had a single/first vaccine dose. SAEs (cases) were 73% more likely to be male and 65%



AEFI: Adverse events following immunization.
SAEI: Serious adverse event incidence.
NSAEI: Non-serious adverse event incidence.

Figure 1 – Incidence of serious adverse events (N=135), non-serious adverse events (N=1058) and administered doses of (attenuated) yellow fever vaccine (N=22,857,762) by month administered, Brazil, July 2016 - June 2017



SAEF: Serious adverse event frequency.
NSAEF: Non-serious adverse event frequency
SAEI: Serious adverse event incidence
NSAEI: Non-serious adverse event incidence

Figure 2 – Distribution of frequency and incidence of serious adverse events (SAEs) and non-serious adverse events (NSAEs) following (attenuated) yellow fever vaccine administration, by Federative Unit (UF), Brazil, July 2016 - June 2017

more likely to have had a single/first vaccine dose, when compared to NSAEs (controls). Administration route and being pregnant showed no statistical significance between cases and controls (Table 2).

When comparing events by age, taking under five-year-olds as a reference, the older the age group, the greater the likelihood of having SAE, with cases having 4.4 times more likelihood of being 60 years old or over in comparison with the control group (p-value <0.02) (Figure 3).

Discussion

The study revealed greater SAE frequency among males, adults aged 50-59 years and unvaccinated individuals having their first dose of yellow fever vaccine. SAE records were predominant between January and March 2017, the period in which vaccination was intensified – selectively – to contain the outbreak of the disease.[14] The states with the highest SAE frequency were Minas Gerais, Rio de Janeiro and Espírito Santo, whilst incidence was highest in Espírito Santo, São Paulo and Minas Gerais. Particularly noteworthy is Espírito Santo, a state which had not been categorized as an area where vaccination was recommended but which intensified vaccination during the outbreak among people who had never been vaccinated.

With regard to the study, it is important to take into consideration differences in sensitivity among surveillance services and health professionals in relation to notifying events attended to by them, which can lead

Table 1 – Characterization of consistent adverse events following (attenuated) yellow fever vaccine administration, by sex, pregnancy, race/skin color, age group and median age, among cases and controls, Brazil, July 2016 – June 2017

Characteristics	SAE[a] (n=135)		NSAE[b] (n=1058)	
	n	%	n	%
Sex				
Male	79	58.5	475	44.9
Female	56	41.5	583	55.1
Pregnant	n=25		n=329	
Yes	2	8.0	19	5.8
No	23	92.0	310	94.2
Race/skin color				
Yellow	17	12.6	110	10.4
White	41	30.4	322	30.4
Not informed	51	37.8	433	40.9
Black	7	5.2	30	2.8
Brown	19	14.1	163	15.4
Age group (in years)				
<1[c]	–	–	1	0.1
1-4	18	13.3	204	19.3
5-9	18	13.3	130	12.3
10-14	11	8.1	83	7.8
15-19	7	5.2	61	5.8
20-29	15	11.1	108	10.2
30-39	15	11.1	167	15.8
40- 49	18	13.3	133	12.6
50-59	21	15.6	140	13.2
≥60	12	8.9	31	2.9
	Median		**Interquartile range**	
Age of vaccinee with SAE (in years)	28		9 - 49	
Age of vaccinee with NSAE (in years)	25		7 - 42	

a) SAE: serious adverse event.
b) NSAE: non-serious adverse event.
c) Lowest vaccinee age was 11 months.'

to underreporting or imprecision in estimations and comparison between states, so that this analysis should be interpreted with caution.

A study conducted in eight African countries between 2007 and 2010, when a large-scale vaccination campaign involving more than 38 million people was carried out, recorded SAE incidence of 0.43 case per 100,000 people vaccinated,[15] this being below incidence found in some UFs in our study.

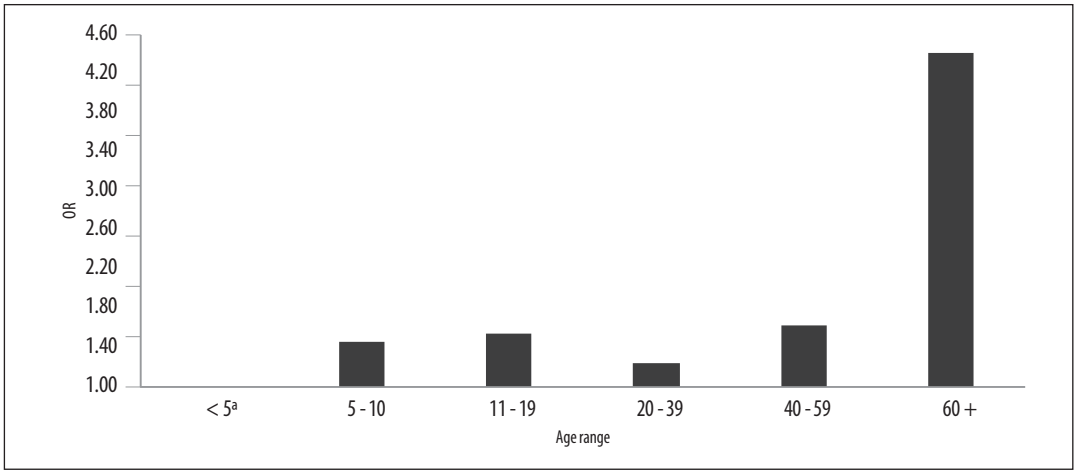
Regarding SAEs, the most common localized manifestations were pain and localized edema, while the most common systemic manifestations were headache and vomiting. A study conducted in Japan found that in terms of localized manifestations erythema (redness) was most frequent in 20.0%, followed by swelling in 19.2%; while the most frequent systemic manifestations were malaise in 27.5% and fever in 12.3%.[16]

Case progression description showed that the majority were cured. However, the high amount of unknown data stands out and this prevented us from analyzing progression of all the adverse events. When analyzing factors associated with the severity of the events, association was found with being male, having had a first/single vaccine dose and being 60 years old or over. A study that evaluated older age as a risk factor for serious adverse events following yellow fever vaccination found SAE notification rates significantly higher among vaccinated people ≥60 years old when compared to those in the 19-29 years age range (SAE incidence =5.9); that study also analyzed other vaccines but did not find statistical significance for the 'age' factor among them, suggesting that there really is a higher SAE rate due to yellow fever vaccine among the elderly and that this higher rate could be

Table 2 – Bivariate analysis for factors associated with severity of adverse events following (attenuated) yellow fever vaccine administration (N=1193), Brazil, July 2016 - June 2017

Associated factors	SAE[a]		NSAE[b]		OR[c] (95%CI[d])	P[e]
	n	%	n	%		
Sex						
Male	79	58.5	475	44.9	1.73 (1.20;2.48)	<0.01
Female	56	41.5	583	55.1		
Dose						
Single/first dose	115	85.2	822	77.7	1.65 (1.01;2.71)	<0.05
Revaccination	20	14.8	236	22.3		
Pregnant	N=25		N=329			
Yes	2	8.0	19	5.8	1.42 (0.31;6.46)	0.65
No	23	92.0	310	94.2		
Administration route						
Other routes[f]	9	7.1	50	4.9	1.47 (0.71;3.07)	0.30
Subcutaneous	118	92.9	965	95.1		

a) SAE: serious adverse event.
b) NSAE: non-serious adverse event.
c) OR: odds ratio.
d) 95%CI: 95% confidence interval.
e) Fisher's exact test.
f) Intramuscular, intradermal and endovenous routes, considering that the correct administration route is the subcutaneous route.



a) Reference age = 11 months to <5 years.

Figure 3 – Odds ratio distribution for severity of adverse events following (attenuated) yellow fever vaccine administration (N=1193), by age group, Brazil, July 2016 - June 2017

biologically plausible: there is indeed increased risk of elderly people becoming seriously ill following infection by wild-type yellow fever virus.[17]

Another study of adverse events worthy of mention was conducted in the United States between 2007 and 2013 and identified greater SAE occurrence during the first vaccine dose in 64.3% of cases,[18] thus confirming the findings of our study, in particular SAE incidence in Espírito Santo state where vaccination had not been recommended and incidence reached 1.4 case per 100,000 doses administered.

In our study, event severity was not related to pregnancy. This finding also appeared in a systematic review regarding vaccination of pregnant women, which showed that they did not have SAEs, despite the author highlighting that due to the number of events originating from passive surveillance being small, it would not be possible to reach any conclusion.[19]

A literature review conducted in 2012 cited a study about risks and benefits of yellow fever vaccine. Its author concluded that (i) there is minimum risk of congenital infection following vaccination with 17D,

and that (ii) pregnant women at high risk of exposure to yellow fever should be vaccinated, while vaccination should be avoided or postponed in other cases.[20] Further studies are needed about vaccinating pregnant women against yellow fever in order to evaluate risks associated with severity related to pregnancy, even when there are outbreaks of the disease.[12] However, regardless of the possibility of adverse events occurring, it is important to highlight the fact that vaccination against yellow fever is the best way of avoiding the disease.[21]

This study has limitations that must be taken into consideration regarding characterization of AEFIs, evaluation of their severity and associated factors. The high frequency of 'unknown' variables, for instance, may have influenced the results obtained for some event characteristics. Moreover, the possibility of classification bias, in view of the severity of the notified event being based not only on the symptoms presented, but also on information on being hospitalized for more than 24 hours, makes it impossible to conclude as to what were serious manifestations in patients for all records. Consequently, it is possible that SAEs have been overestimated in this study. It was also not possible to make a comprehensive analysis of vaccinated pregnant women, including exposure in areas with occurrence of outbreaks where vaccination was recommended. Another limitation of the study is related to lack of information about the number of doses administered (vaccination for the first time or revaccination) and sex, since higher occurrence of SAE in males may be related to the greater number of doses administrated (in relation to females), as well as occurrence of first-time vaccination among males, although it was impossible to confirm this hypothesis owing to missing data. Lack of information about associated diseases or conditions capable of causing immunodepression in an individual, together with other factors having the potential for association with occurrence of event severity, are further limitations of the analysis of SAE association with other variables. A final limitation to be mentioned is the percentage of events considered to be unclassifiable or indeterminate owing to lack of data to enable their adequate classification.

In view of these situations, the study was limited to performing crude analysis using data available on the system, and it was not possible to perform more robust analysis of the diverse patient-related factors capable of influencing occurrence of SAE. This fact draws attention to the importance of better investigation of AEFIs, the notification and investigation record quality of which on national information systems contributes to performing adequate evaluations, especially in outbreak situations, when timely analyses should be made.

Ensuring active surveillance and systematic and timely monitoring of AEFIs is essential for guaranteeing yellow fever vaccine quality and safety, principally in areas with outbreaks where vaccination intensification and scaling up strategies are needed.

It is important to implement actions to provide guidance for health professionals on intensifying surveillance of adverse events. During yellow fever epidemics vaccination strategies are expanded and, consequently, occurrence of AEFIs expands as well. At such times, it is essential to raise health professional awareness about the importance of filling in fields on AEFI notification and investigation forms with completeness and quality, as well as recording them on the information system. It is equally important to establish a nominal information system in vaccination rooms in order to enable better demographic characterization of the population immunized.

Finally, we recommend that health professionals make a careful assessment before indicating yellow fever vaccination for more sensitive situations, as is the case of pregnant women and the elderly (first-time vaccination), bearing in mind its benefits and risks.

Authors' contributions

Lucena ARFP took part in the conception and design of the study, data tabulation, analysis and interpretation, and was responsible for all aspects of the work. Souza LRO, Percio J, Carvalho SMD, Domingues CMAS and Romano APM took part in the conception and design of the study, data analysis and interpretation. All the authors took part in critically reviewing the intellectual content of the manuscript, approved its final version and declare themselves to be responsible for its accuracy and integrity.

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