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Adverse events following yellow fever immunization: Report and analysis of 67 neurological cases in Brazil

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ABSTRACT

Neurological adverse events following administration of the 17DD substrain of yellow fever vaccine (YEL-AND) in the Brazilian population are described and analyzed. Based on information obtained from the National Immunization Program through passive surveillance or intensified passive surveillance, from 2007 to 2012, descriptive analysis, national and regional rates of YFV associated neurotropic, neurological autoimmune disease, and reporting rate ratios with their respective 95% confidence intervals were calculated for first time vaccines stratified on age and year. Sixty-seven neurological cases were found, with the highest rate of neurological adverse events in the age group from 5 to 9 years (2.66 per 100,000 vaccine doses in Rio Grande do Sul state, and 0.83 per 100,000 doses in national analysis). Two cases had a combination of neurotropic and autoimmune features. This is the largest sample of YEL-AND already analyzed. Rates are similar to other recent studies, but on this study the age group from 5 to 9 years of age had the highest risk. As neurological adverse events have in general a good prognosis, they should not contraindicate the use of yellow fever vaccine in face of risk of infection by yellow fever virus.

1. Background

Yellow fever is an acute infectious disease, transmitted by arthropod vectors of the genus Flavivirus. The prognosis is poor and symptoms include: fever, nausea, vomiting, epigastric pain, hepatitis with jaundice, renal failure, hemorrhage, shock and death in 20–50% of reported cases in Brazil, where the disease is endemic in the North and Mid-West of the country. There is no specific treatment for yellow fever. Within a few years after isolation of the virus by inoculation in monkeys, in 1927, two different live attenuated yellow fever vaccines (YFV) were derived: the French strain, which was later discontinued due to its neurotropism, and the 17D strain [1–4].

Abbreviations: ADEM, acute disseminated encephalomyelitis; AEFI, adverse event following immunization; CDC, Centers for Disease and Control, USA; CSF, cerebrospinal fluid; CIFAVI, Interinstitutional Committee for Evaluation of Adverse Events at the Brazilian Ministry of Health; CT, computed tomography; NIP, National Immunizations Program; YFV, yellow fever vaccine; YFV-17D, yellow fever vaccine, 17D substrain; YFV-17DD, yellow fever vaccine, 17DD substrain; GBS, Guillain-Barré syndrome; MRI, magnetic resonance imaging; RS, Rio Grande do Sul state; YEL-AND, vaccine-associated neurologic disease; 95% CI, 95% confidence interval.

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For development of YFV from the Asibi strain, after intracerebral passages in mice, the virus was passed repeatedly in minced chicken embryos from which the nervous system had been removed, and at this stage, Theiler and Smith observed a decrease in viral neurotropism without increased viscerotropism [5], establishing the 17D strain from which all current vaccines are derived. The 17DD substrain, derived from the 17D strain, was chosen for use in Brazil, due to its excellent immunogenicity and safety profile, and a seed-lot system was established in 1942, assuring the long term maintenance of its properties [6].

Initial reports of meningoencephalitis after YFV 17D/17DD administered worldwide were seen in children less than 7 months of age [1–3]. In the 1960s, recommendations were changed, setting the lower limit of age for immunization at 9 months, or at least 6 months during yellow fever epidemics, and reports of encephalitis/meningoencephalitis after yellow fever vaccine became rarer.

Common adverse events, such as fever, myalgia and pain, and a flu-like syndrome, occur in about 4% of vaccinated people in Brazil [7].

The 17D/17DD live attenuated virus vaccines have been extensively studied, through molecular characterization, pre-clinical studies and clinical studies, and have shown genetic stability through repeated passages [1–4,8–12].

Serious adverse events after 17D/17DD substrains of YFV are rare. Cases of associated neurologic disease are usually self-limiting, neurological sequelae are unusual and deaths are very rare [1].

Yellow fever vaccine is given routinely to children aged 9 months in endemic areas of Brazil, without concomitant vaccines. In campaigns, all age groups are targeted, at or above 6 months of age, also without concomitant vaccines. Surveillance of adverse events following immunization (AEFI) has been conducted in Brazil by the National Immunization Program (NIP) since 1998. The AEFI National Surveillance System processes data generated in a standardized form by vaccination teams and healthcare workers. The sources of information are the more than 35,000 Health Centers all over the country, with evaluation of events at state level and final classification at national level [13].

The frequency of serious adverse events following YFV-17DD has been increasingly reported in the last 10 years in Brazil, especially in campaigns Exhaustive studies have not demonstrated mutations in the vaccine virus that could explain these serious adverse events. Accordingly, it is surmised that host intrinsic factors are the most plausible explanation for them [14,15].

The objective of this study is to describe and analyze the neurological cases following administration of YFV-17DD in the Brazilian population, from 2007 to 2012, with estimation of rates of adverse events.

2. Methods

This study is based on YFV-17DD neurological adverse events reported in public health units in Brazil from 2007 to 2012. These cases were obtained from the NIP database in January 31st, 2013, and updated until March 31st. All serious neurological adverse events related to YFV were discussed and classified by the national AEFI committee at the Ministry of Health. Reported cases were classified according to a modified CDC criteria for YEL-AND [4].

We modified CDC criteria for neurotropic disease because cases of neurologic disease (level 1) without neuroimaging or EEG but with positive IgM for yellow fever on CSF were considered confirmed cases of meningoencephalitis. We also confirmed 2 cases of meningoencephalitis which occurred 39 and 36 days after vaccination. For yellow fever vaccine-associated autoimmune disease we followed CDC guidelines without modifications. The initial diagnosis was established at local level, and final classification was done at central level, by a multidisciplinary group, including a neurologist, at the Ministry of Health.

Cases of neurotropic disease were all classified as meningoencephalitis, as a clear distinction between encephalitis and meningitis is frequently impossible, as clinical symptoms may be atypical in young children and in the absence of neuroimaging or cerebral histopathology [16,17]. Cases of neurological autoimmune disease included GBS and ADEM. Other neurological autoimmune diseases included: transverse myelitis, and bilateral optic neuritis. There were two cases characterized by a clinical and laboratorial combination of both neurotropic and neurological autoimmune features, and they are analyzed apart, although they are counted in the total number of neurological events. They were classified as “combined neurological disease”.

For analysis purposes, only the confirmed cases of neurotropic disease were included. Regarding the neurological autoimmune disease, all probable, and suspect reported cases were included in analysis. Cases that did not comply with definitions were not included, but we added some information on them.

The rates of adverse events per 100,000 doses and reporting rate ratios (RRR) were calculated, as described previously [18]. The Brazilian Ministry of Health, through the Health Information System, provided the number of YFV doses administered by age, state and year [19]. The two cases of combined disease were not included on estimation of rates related to neurotropic or autoimmune disease, but were included on estimation of total rate of neurologic events.

Descriptive analysis of variables: age, gender, time of disease onset, hospital discharge, dose, diagnosis, and cerebrospinal fluid (CSF) features were developed for each category of adverse events. The rates of neurotropic disease, neurological autoimmune disease, and combined disease were calculated according to two scenarios: first, the rates were calculated for the whole country, according to year of vaccination and to age groups; and second the rates were calculated for the state of Rio Grande do Sul (RS, Southern region of Brazil) in 2009. The second presentation was chosen due to an intensification of the passive surveillance system and training for detection of neurological events during the year 2009 in RS. Reporting rate ratios and their confidence intervals were calculated for age groups. Rates were also calculated for the country, excluding RS. Data were analyzed using Stata/IC software version 12 (Stata Corporation, College Station, USA).

3. Results

From 2007 to 2012, a total of 129 neurological cases following the YFV-17DD were reported by the NIP in Brazil. Of these, 62 were excluded as shown in Fig. 1. Cases were excluded for the following reasons: 13 discarded, 37 inconclusive or inconsistent, 8 possible or suspect, and 1 probable. The most common reasons of exclusion were negativity of IgM for yellow fever in CSF, cases with clinical or laboratorial evidences against causality to YFV, and cases with insufficient information for classification. There were 3 confirmed cases that were not included, for the following reasons: vaccine from another producer (1 case), and vaccine administered to the mother and YFV transmitted to the infant via breastfeeding (2 cases). A final sample of 67 confirmed neurological cases was analyzed in the present study (Fig. 1). The general features of the neurotropic and autoimmune groups are listed (Table 1). Among the 67 adverse events, 55 were neurotropic (82.1%), and 10 were neurological autoimmune diseases (14.9%), and 2 were combined disease (3%). The group of neurological autoimmune diseases was composed of 5 Guillain-Barré Syndrome cases and 3 Acute

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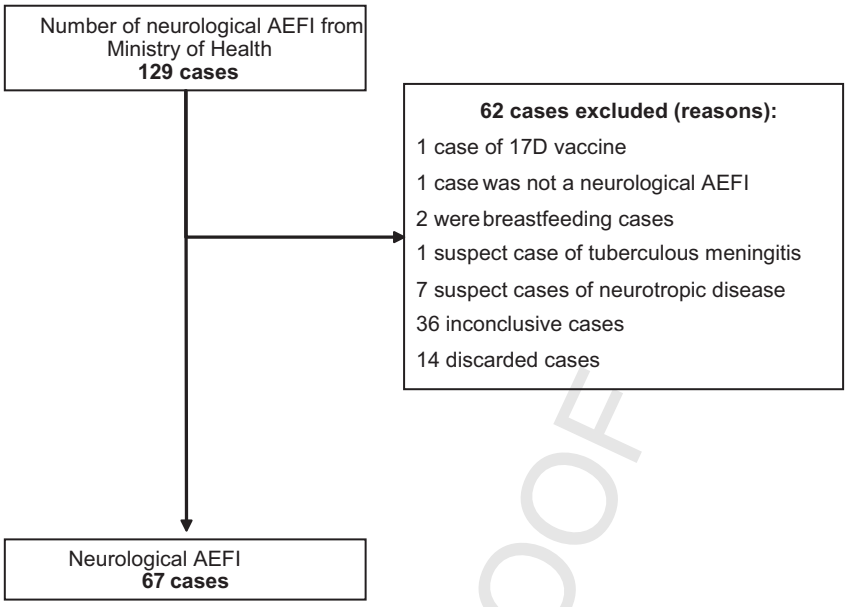

Fig. 1. Flowchart of the study sample size.

Disseminated Encephalomyelitis cases. The 2 remaining cases were composed of other neurological autoimmune diseases, namely transverse myelitis and bilateral optic neuritis (1 case for each diagnosis). The two combined neurological disease patients had the following diagnosis: meningoencephalitis with polyradiculoneuritis and Kinsbourne syndrome, a distinct disorder characterized by opsoclonus, myoclonus, and ataxia, along with marked irritability and behavioral changes [20]. The first patient, a 28 years of age male, presented high an persistent fever 15 days after YFV, and 6 days later was hospitalized. CSF had hypercellularity, moderately elevated protein, positive IgM for yellow fever and negative for dengue and Rocio. There were clinical and electromiographical evidences of demyelinization, and he received the diagnosis of meningoencephalitis with polyradiculoneuritis. He left hospital

Table 1
General features of 129 neurological adverse events (neurotropic disease, neurological autoimmune disease, and excluded cases) following YFV, all doses, Brazil, 2007–2012.

	Neurotropic disease ($n=55$)	Neurological autoimmune disease ($n=10$)	Excluded ($n=62$)
Female (%)	40.0	70.0	41.0
Median age in years (range)	28 (0.75–66)	38.5 (4–63)	14 (0.08–85)
First dose (%)	100.0	80.0	88.7
Hospital discharge (%)			
Without sequelae	98.2	66.7	85.0
With sequelae	1.8	33.3	11.7
Death	–	–	3.3
Diagnosis (%)			
Meningoencephalitis	98.2	NA[a]	77.4
GBS	NA	50.0	3.2
ADEM	NA	30.0	1.6
Transverse myelitis	NA	10.0	1.6
Bilateral optic neuritis	NA	10.0	–
Meningoencephalitis with polyradiculoneuritis	NA	NA	–
Kinsbourne syndrome	NA	NA	–
Peripheral facial paralysis	1.8	NA	1.6
Other	NA	NA	14.5
Median time of disease onset in days (range)	15 (2–39)	12.5 (2–28)	16 (<1–30)
CSF[b]			
Cellularity (median, range)	98 (21; 651)[c]	1 (0; 90)[g]	NA
Protein (median, range)	62 (20; 205)[d]	105 (38; 301)[g]	NA
Glucose (median, range)	54.5 (40; 98)[e]	58.5 (42; 94)[h]	NA
Positive YF IgM (%)[g]	100.0[f]	NA	NA

[a] Non applicable.
[b] Cerebrospinal fluid.
[c] Number of patients with results (n) = 53.
[d] $n=49$.
[e] $n=48$.
[f] $n=55$.
[g] $n=9$.
[h] $n=8$.
[i] Number of excluded patients with results: $n=61$, for Female; 61 for median age; 62 for first dose (including 2 vaccines given to mothers, with meningoencephalitis in infants).

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with a sequel, difficulty in walking. The second, a 13 years of age male, presented low fever, opsoclonus (horizontal and vertical clonic eye movements), myoclonic movements, ataxia, diagnosed as Kinsbourne syndrome, an autoimmune disease. CSF had slight increase in cellularity, elevated protein, dengue and toxoplasma tests were negative, and IgM for yellow fever in CSF was positive. Computed tomography in thorax and abdomen in search of neuroblastoma was negative. He was cured without sequel. So, both patients had a mixed pattern of invasive and autoimmune disease.

According to data obtained from Brazilian passive surveillance system, among neurotropic cases 1 case had sequela after hospital discharge (1.8%); among neurological autoimmune disease 3 cases had sequelae after hospital discharge (33.3%) (Table 1) Among all neurological cases, 5/67 (7.5%) had sequelae after discharge Details of sequelae were not available.

Time of disease onset after vaccination was similar among groups. Cases that were excluded from analysis had about the same profile, but lower ages. As they are a mix of neurotropic, autoimmune cases, other diagnosis, and have many missing data, we did not present their CSF findings.

All neurotropic cases (meningoencephalitis) were reported only after the first dose. The global rate of adverse events following YFV 1st doses in Brazil from 2007 to 2012 was 0.20 neurological adverse events per 100,000 doses. The total rate for neurotropic cases was 0.17 per 100,000 doses. Among the neurological autoimmune cases ($n = 10$), 8 of them occurred after a first dose of YFV and 2 after a booster dose.

Considering Brazil during the whole period, without RS, the total rate (first doses) of neurotropic disease was 0.05/100,000 doses, and of neurological autoimmune disease 0.02/100,000 doses.

There were two cases of autoimmune disease after a booster dose of YFV. One of them occurred in a 62-year old woman that received a booster of YFV on May 27, 2011 and an unknown period of time after vaccination presented flaccid tetraparesis. The CSF had 1 cell/mm^3 (99% mononuclear cells), glucose = 60 mg/dL; protein = 205 mg/dL, and absence of bacteria; electroneuromyography of the limbs showed polyradiculoneuropathy compatible with GBS. There is also the information that this patient received a dose of influenza vaccine on April 26, 2011. This case was evaluated at CIFAVI and was classified as probable. The second case was a 20-year old man who received a booster dose of YFV and fourteen days later presented drowsiness, blurred vision, diplopia, aphasia, hemiparesis of lower limbs. He evolved with respiratory failure requiring mechanical ventilation. Electroencephalogram and skull CT were normal. The MRI showed lesions of inflammatory leukoencephalopathy, so the case was diagnosed as ADEM. This man evolved to death due to a sepsis complication. The authors have no additional information or the date of death. CIFAVI classified this case also as probable.

Thus, the rates for neurological autoimmune disease after the first dose and after the booster dose were 0.03 per 100,000 doses, and 0.01 per 100,000 doses, respectively. There was an increase in rates in 2009, especially for neurotropic disease reports, due to an intensification of the passive surveillance system and training for detection of neurological events during a campaign in state of Rio Grande do Sul, in that year (Table 2).

Table 3 shows the rates for first vaccine doses of neurotropic disease and neurological autoimmune disease according to age groups. The lowest rates of neurotropic disease occurred in the age groups less than 1 year, and from 1 to 4 years. The highest rate occurred in the age group from 5 to 9 years. Compared to the age group from 15 to 59 years (reference), these individuals had a risk more than 3 times higher of having a neurotropic adverse event (RRR = 3.40; 95% CI: 1.57–7.34). For neurological autoimmune and combined diseases the number of cases is small and evaluation of risks by age groups is difficult.

Table 4 shows the rates for first vaccine doses of neurotropic and neurological autoimmune adverse events in RS according to year of occurrence. Combined disease cases did not occur in this state (1 case belonged to Santa Catarina's state, in the Southern region of Brazil, and 1 case came from São Paulo, a state in the Brazilian Southeastern region). There is a higher number of doses of YFV administered in 2009 and also, an impressive increase in the rate of reported cases in 2009 and 2010, and to a lesser extent in 2011, compared to other years, probably due to a continued intensification in the passive surveillance system during these years.

In order to evaluate age variation regarding neurological adverse event risk, for first vaccine doses, a specific analysis in RS state in 2009 was conducted (Table 5). The highest rate of neurotropic disease (2.66 per 100,000 vaccine doses) was reported in the age group from 5 to 9 years. The risk of having neurotropic disease, in this age group, was 2.7 times the risk in the reference group (15–59 years old). There were only 2 cases of neurological autoimmune diseases in RS state from 2007 to 2012. One case belonged to the age group of 1–4 years and the other to the age group of 15–59 years (Table 5).

Two cases of neurotropic disease acquired through breastfeeding were not included in the analysis because the doses were not administered to the children, and our denominators refer to vaccines applied directly on individuals. These cases were confirmed vaccine encephalitis transmitted through breast-feeding that occurred in 2009 at RS [21,22]. One of these cases was in a 23-day-old female infant and the second case in a 38-day-old male infant. One had a serious sequela and the other recovered.

4. Discussion

The present study evaluated the features and rates of 67 neurological cases (neurotropic, neurological autoimmune and combined disease) following the administration of YFV-17DD in Brazil. Two scenarios were analyzed: the whole country and the state of Rio Grande do Sul. For most analyses we used first doses as the denominator, as all neurotropic (meningoencephalitis) cases were after the first dose. For the whole country and for the RS state, in 2009, children from 5 to 9 years old had the highest rate of neurotropic disease. The overall rate of neurotropic disease was higher in RS than the national rate, probably due to intensification and training in the passive surveillance system in the former. The overall rate of autoimmune disease was also higher for the state analysis than for the whole country.

Few studies worldwide have estimated the rate of neurological adverse events after the administration of YFV-17D or YFV-17DD. McMahon et al. studied 15 cases of neurological adverse events following YFV in the United States and found risk rates of 2.3 cases for encephalitis, 1.9 cases for GBS and 0.4 cases for ADEM per 100,000 doses [23]. This study alerted and guided us regarding diagnostic and classification criteria. Breugelmans et al. studied the implementation of large-scale YF preventive vaccination campaigns and pharmacovigilance systems in eight African countries from 2007 to 2010 (Benin, Cameroon, Guinea, Liberia, Mali, Senegal, Sierra Leone and Togo). During this period, 3116 adverse events were reported, of which 5% were serious. Concerning neurological events, the authors found a risk rate of 0.016 per 100,000 doses [24]. Guimard et al. reviewed all cases of serious neurologic adverse events that occurred between 2000 and 2008, in a French Health Institution. They studied 4 cases and found a risk rate of 9.9 neurologic events per 100,000 doses, which is 10 times higher than previous estimates [25].

In Brazil, efforts to prevent reintroduction of yellow fever in urban areas were intensified through massive routine vaccination in endemic areas, and vaccination campaigns in circulating wild virus areas, with epizootics and/or human cases. During the same

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Table 2
Rates (per 100,000 vaccine first doses administered) of neurotropic disease and neurological autoimmune disease, Brazil, 2007–2012.

Year	Number of doses (first dose)	Neurotropic disease		Neurological autoimmune disease[a]		Total	
		Number of cases	Rate (per 100,000)	Number of cases	Rate (per 100,000)	Number of cases	Rate (per 100,000)
2007	3,738,402	0	0.00	1	0.03	1	0.03
2008	9,950,486	4	0.04	1	0.01	5	0.05
2009	8,178,009	43	0.53	2	0.02	45	0.55
2010	3,358,152	4	0.12	2	0.06	6	0.18
2011	3,218,023	2	0.06	1	0.03	3	0.09
2012	2,991,559	2	0.07	1	0.03*	3	0.10
Total	31,434,631	55	0.17	8	0.03	63	0.20

[a] 2 cases were not included because they occurred after a booster dose.

Table 3
Rates (per 100,000 vaccine first doses administered) of neurotropic and neurological autoimmune diseases, according to age groups, Brazil, 2007–2012.

Age groups	Number of doses (first dose)	Neurotropic disease			Neurological autoimmune disease			Total		
		No. of cases	Rate (per 100,000)	RRR (95% CI)	No. of cases	Rate (per 100,000)	RRR (95% CI)	No. of cases	Rate (per 100,000)	RRR (95% CI)
Less than 1 year	8,442,107	2	0.02	0.11 (0.03–0.44	0	0.00	Undef	2	0.02	0.09 (0.02–0.38)
From 1 to 4 years	2,222,775	1	0.04	0.20 (0.03–1.46	1	0.04	1.40 (0.16–12.01)	2	0.09	0.351 (0.08–1.45)
From 5 to 9 years	1,079,662	8	0.74	3.30 (1.53–7.12)	1	0.09	2.89 (0.34–24.72)	9	0.83	3.25 (1.58–6.70)
From 10 to 14 years	1,928,089	6	0.31	1.39 (0.58–3.30	0	0.00	Undef	6	0.31	1.21 (0.51–2.86)
From 15 to 59 years	15,592,430	35	0.22	Ref	5	0.03	Ref	40	0.26	Ref
60 years or more	2,169,568	3	0.14	0.62 (0.19–2.00)	1	0.05	1.44 (0.17–12.30)	4	0.18	0.52 (0.26–2.01)
Total	31,434,631	55	0.17		8	0.03		63	0.20	

Ref = Reference; Undef = Undefined.

Table 4
Rates (per 100,000 vaccine first doses) of neurotropic and neurological autoimmune diseases, according to year, in the state of Rio Grande do Sul.

Year	Number of doses (first dose)	Neurotropic disease		Neurological autoimmune disease		Total	
		No. of cases	Rate (per 100,000)	No. of cases	Rate (per 100,000)	No. of cases	Rate (per 100,000)
2007	59,034	0	0.00	0	0.00	0	0.00
2008	556,535	1	0.18	1	0.18	2	0.36
2009	3,697,838	38	1.03	2	0.05	40	1.08
2010	154,541	2	1.29	0	0.00	2	1.29
2011	199,543	1	0.50	1	0.50	2	1.00
2012	227,632	0	0.00	0	0.00	0	0.00
Total	4,895,123	42	0.86	4	0.08	46	0.94

period, surveillance system for adverse events was being improved. Fernandes et al. found 12 cases of aseptic meningitis temporally related to yellow fever vaccine in the city of Juiz de Fora (Southeast of Brazil) during a campaign in 2001, with a risk rate of 3.87 per 100,000 doses [26]. All cases recovered without sequelae.

Khromava et al. analyzed the risk of YEL-AND according to age, and found that reporting rates of neurotropic disease increased for persons aged 60 years or more, compared to lower ages, although they were not statistically significant [189]. Studies have found rates of encephalitis varying from 0.5 to 4.0 per 1000 doses in children younger than 9 months, and 0.4/100,000 doses from 1 to 18 years of age [3,18].

Our data point to a higher risk of neurotropic disease after YFV in children from 5 to 9 years of age according to local and national analysis. For the age groups of less than 1 year, and from 1 to less than 5 years, low rates were found both for the country and for Rio Grande do Sul. One possible explanation for the unexpected low neurotropic disease rate in children less than 5 years of age is that

Table 5
Rates (per 100,000 vaccine first doses) of neurotropic and neurological autoimmune diseases, according to age groups, in the state of Rio Grande do Sul, in 2009.

Age groups	Number of doses (first dose)	Neurotropic disease			Neurological autoimmune disease			Total		
		No. of cases	Rate (per 100,000)	RRR (95% CI)	No. of cases	Rate (per 100,000)	RRR (95% CI)	No. of cases	Rate (per 100,000)	RRR (95% CI)
Less than 1 year	40,103	0	0.00	Undef	0	0.00	Undef	0	0.00	Undef
From 1 to 4 years	210,950	0	0.00	Undef	1	0.47	11.59 (0.72–185.23)	1	0.47	0.46 (0.06–3.42)
From 5 to 9 years	263,294	7	2.66	2.71 (1.17–6.28)	0	0.00	Undef	7	2.66	2.60 (1.12–6.01)
From 10 to 14 years	344,522	5	1.45	1.48 (0.56–3.87)	0	0.00	Undef	5	1.45	1.42 (0.54–3.71)
From 15 to 59 years	2,444,095	24	0.98	Ref	1	0.04	Ref	25	1.02	Ref
60 years or more	394,874	2	0.51	0.52 (0.12–2.18)	0	0.00	Undef	2	0.51	0.50 (0.12–2.09)
Total	3,697,838	38	1.03		2	0.05		40	1.08	

Ref = Reference; Undef = Undefined.

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meningeal and other signs and symptoms of neurological disease may be less characteristic in young children, making the diagnosis more difficult [16,17]. Age distribution similar to this study, but with much higher rates, have been found in a study conducted in 1942, which evaluated the occurrence of encephalitis in man following vaccination with YFV-17D, substrain 17D NY-104, no longer used [27].

It should be noted that, with the French strain, also no longer in use, meningoencephalitis rates by age groups cannot be surely ascertained retrospectively, due to lack of denominators, but in a large campaign in Dakar, most cases were on the age group from 3 to 11 years (mainly at 4, 5 and 6 years of age) and the risk on this age group was estimated at about 1–2/1000 vaccinations, that is, much higher than with the current vaccine [28].

Regarding neurological autoimmune disease, the small number of cases makes difficult evaluation of risks by age groups.

There is another interesting finding to point out. There were two cases with clinical and laboratorial evidences of a mixed condition, autoimmune neurological and neurotropic disease.

The exact mechanism that determine this combination is not clearly understood, and it may be possible that the autoimmune inflammatory involvement of the central nervous system could increase the permeability of the brain–blood barrier, allowing IgM and cells from blood to pass into the CSF, without a true neurotropic disease. On the other hand, the neurotropic disease could be a trigger to this group of diseases in predisposed individuals and both conditions can really occur in combination.

The greatest limitation of the present study was the use of passive surveillance data [29–31]. However, the analysis in RS, where an intensified surveillance system was in place during a large campaign in 2009, may attenuate this limitation. Another potential limitation to consider in this study is the misclassification of cases due to flavivirus cross-reactivity that could occur, as tests for other flavivirus were not always done, which means that cases could have been incorrectly classified as related to YFV.

This study demonstrates that finding of neurological cases is highly dependent on increased alertness and training, as most cases occur several or many days after vaccination and confirmation of diagnosis relies on cerebrospinal fluid examination.

5. Conclusions

The current study analyzed the largest series of neurological adverse events following a 17D yellow fever vaccine in current use and showed that the number of neurological adverse events temporally associated to the vaccine is substantial. However, these events have in general a good prognosis. Yellow fever is a serious condition, of high lethality, and without the yellow fever vaccine we would have large scale epidemics, as the potential vectors of the disease are widespread in Brazil and many other countries, and due to an ever increasing movement of people around the globe. It is a highly effective vaccine, as demonstrated by the low number of yellow fever cases being reported in Brazil, and prompt containment of outbreaks. As neurological adverse events have in general a good prognosis they should not contraindicate the use of yellow fever vaccine in face of risk of infection by yellow fever virus.

Authors' contributions

All authors contributed to the discussions on diagnosis and classification of cases, and to the study concept, design, acquisition of data, analysis, interpretation, and to the manuscript; all approved the manuscript final version.

Conflicts of interest

Reinaldo de Menezes Martins, Ana Luiza Braz Pavão, Patrícia Mouta Nunes de Oliveira, Paulo Roberto Gomes dos Santos, Vanessa dos Reis von Doellinger, Maria da Luz Fernandes Leal, Akira Homma and Maria de Lourdes S. Maia work for Bio-Manguinhos, a government-owned and not for profit producer of vaccines for the Brazilian Ministry of Health, including the yellow fever vaccine analyzed on this study

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