Vaccine xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

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

Q1 Reinaldo de Menezes Martins[a,*], Ana Luiza Braz Pavão[b], Patrícia Mouta Nunes de Oliveira[c], Paulo Roberto Gomes dos Santos[d], Sandra Maria D. Carvalho[e], Renate Mohrdieck[f], Alexandre Ribeiro Fernandes[g], Helena Keico Sato[h], Patricia Mandali de Figueiredo[i], Vanessa dos Reis von Doellinger[j], Maria da Luz Fernandes Leal[k], Akira Homma[l], Maria de Lourdes S. Maia[j]

Q2 [a] Bio-Manguinhos, Fiocruz, and CIFAVI (National Interinstitutional Committee for Pharmacovigilance in Vaccines and other Immunobiologicals), Brazil
Q3 [b] Bio-Manguinhos, Fiocruz, and Institute of Scientific and Technological Communication and Information in Health, Fiocruz, Brazil
[c] Pharmacovigilance Unit, Clinical Advisory Unit, Bio-Manguinhos, Fiocruz, Brazil
[d] Qualified Person Responsible for Pharmacovigilance, Pharmacovigilance Unit, Clinical Advisory Unit, Bio-Manguinhos, Fiocruz, Brazil
[e] Adverse Events Following Immunization Group, MoH, and Member of CIFAVI, Brazil
[f] Adverse Events Following Immunization Group, Rio Grande do Sul, and Consultant to CIFAVI, Brazil
[g] Fluminense Federal University, and Consultant to CIFAVI, Brazil
[h] Immunizations Program, São Paulo, and Consultant to CIFAVI, Brazil
[i] Brazilian National Regulatory Agency and Member of CIFAVI, Brazil
[j] Clinical Advisory Unit, Bio-Manguinhos, Fiocruz, Brazil
[k] Bio-Manguinhos, Fiocruz, Brazil
[l] Policy and Strategy Council, Bio-Manguinhos, Fiocruz, Brazil

ARTICLE INFO

Article history:
Received 20 January 2014
Received in revised form 4 April 2014
Accepted 1 May 2014
Available online xxx

Keywords:
Yellow fever vaccine
Adverse event
Neurological disease
Neurotropic disease
Neurological autoimmune disease

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.

Q4 * Corresponding author at: Av. Brasil 4365, Manguinhos, Rio de Janeiro, RJ, CEP 21040-900, Brazil. Tel.: +55 21 38829497; fax: +55 21 38827176.
E-mail addresses: rmenezes@bio.fiocruz.br, reinaldomm@ig.com.br (R.d.M. Martins).

http://dx.doi.org/10.1016/j.vaccine.2014.05.003
0264-410X/

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

Please cite this article in press as: Martins RdM, et al. Adverse events following yellow fever immunization: Report and analysis of 67 neurological cases in Brazil. Vaccine (2014), http://dx.doi.org/10.1016/j.vaccine.2014.05.003