Vaccine 32 (2014) 1266–1272

Contents lists available at ScienceDirect

Vaccine

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

Yellow fever vaccine-associated adverse events following extensive immunization in Argentina

Cristián Biscayart[a,*], María Eugenia Pérez Carrega[a], Sandra Sagradini[a], Ángela Gentile[b], Daniel Stecher[c], Tomás Orduna[d], Silvia Bentancourt[e], Salvador García Jiménez[f], Luis Pedro Flynn[g], Gabriel Pirán Arce[h], María Andrea Uboldi[i], Laura Bugna[i], María Alejandra Morales[j], Clara Digilio[j], Cintia Fabbri[j], Delia Enría[j], Máximo Diosque[a], Carla Vizzotti[a]

[a] Programa Nacional de Control de Enfermedades Inmunoprevenibles, Ministerio de Salud de la Nación, Argentina
[b] Sociedad Argentina de Pediatría, Argentina
[c] Sociedad Argentina de Infectología, Argentina
[d] Sociedad Latinoamericana de Medicina del Viajero, Argentina
[e] Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, Argentina
[f] Pan American Health Organization, Argentina
[g] Sanatorio Británico, Rosario, Argentina
[h] Sanatorio Rivadavia, San Luis, Argentina
[i] Dirección Provincial de Promoción y Prevención de la Salud, Provincia de Santa Fe, Argentina
[j] Instituto Nacional de Enfermedades Virales Humanas "Dr. Julio I. Maiztegui", Pergamino, Argentina

ARTICLE INFO

Article history:
Received 1 April 2013
Received in revised form 7 January 2014
Accepted 8 January 2014
Available online 21 January 2014

Keywords:
Yellow fever vaccine
Safety
Argentina
Severe adverse events

ABSTRACT

As a consequence of YF outbreaks that hit Brazil, Argentina, and Paraguay in 2008–2009, a significant demand for YF vaccination was subsequently observed in Argentina, a country where the usual vaccine recommendations are restricted to provinces that border Brazil, Paraguay, and Bolivia. The goal of this paper is to describe the adverse events following immunization (AEFI) against YF in Argentina during the outbreak in the northeastern province of Misiones, which occurred from January 2008 to January 2009. During this time, a total of nine cases were reported, almost two million doses of vaccine were administered, and a total of 165 AEFI were reported from different provinces. Case study analyses were performed using two AEFI classifications. Forty-nine events were classified as related to the YF vaccine (24 serious and 1 fatal case), and 12 events were classified as inconclusive. As the use of the YF 17D vaccine can be a challenge to health systems of countries with different endemicity patterns, a careful clinical and epidemiological evaluation should be performed before its prescription to minimize serious adverse events.

1. Introduction

Argentina's northeastern provinces are considered yellow fever (YF) transitional areas [1]. Wild YF occurs through a cycle sustained by mosquitoes of the genera *Haemagogus* and *Sabethes* [2–4]. Regarding the role of non-human primates of the New World in the infection cycle, it is known that howler monkeys (*Alouatta* spp.) quickly succumb to YF infection; thus they are considered sentinels of sylvatic YF activity [5]. Nonetheless, large epizootics have only recently been reported in this region.

Between December 2007 and April 2009, YF outbreaks affected central and southern states in Brazil [6], Paraguay [7], and Argentina [8]. Increased vaccination demand occurred, particularly from travelers to beach resorts in Brazil for whom vaccination was not recommended by the public health authorities, and especially from people who were not due to travel. Until the occurrence of this outbreak, Argentina had not a large experience using the YF 17D vaccine. In 2007, it was incorporated into the routine vaccination calendar of provinces in the North after epizootics in Rio Grande do Sul [9], a Brazilian state that borders the provinces of Corrientes and Misiones in Argentina, were confirmed.

Since 2001, when the first reports of YF vaccine-associated viscerotropic disease (YEL-AVD) were published [10], safety aspects regarding the use of this live-attenuated vaccine have emerged. YF vaccine-associated neurological disease (YEL-AND) had

* Corresponding author. Tel.: +54 11 4379 9018; fax: +54 11 4379 4806.
E-mail address: cristianbiscayart@hotmail.com (C. Biscayart).

0264-410X/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.vaccine.2014.01.015

previously been reported in infants who were administered the French neurotropic vaccine which was grown in mouse brains [11]. Subsequent surveillance revealed that neurologic events with the 17D vaccine could also occur, especially in infants <6 months of age [12]. The extensive use of YF vaccine during the outbreak of 2008–2009 in Argentina encouraged surveillance for adverse events following immunization (AEFI). The purpose of this paper is to present and describe Argentina's health system experience with YF vaccine AEFI after its exceptional use in a short period of time.

2. Methods

AEFI is defined as any untoward medical occurrence in a person following immunization. Argentina's AEFI surveillance system is passive, and was initiated in 2005 by a formal AEFI study committee. Notification is sent to the National Food, Drug and Medical Technology Regulatory Agency (ANMAT) and/or the National Immunization Program (ProNaCEI) after a health worker detects a case and fills out a case report form (including patient demographic data, date of vaccination, vaccine, batch, date of expiration, site and route of administration, description of the disease, date of onset, clinical manifestations and course, diagnostic tests, management, and follow-up aspects). A case investigation and preliminary analysis is conducted by the local immunization program, and analysis and final case classification is done by a national AEFI committee designed by the ministry of health. Committee members include experts in different fields (e.g., public health, immunization, internal medicine, neurology, and pharmacology).

To analyze AEFIs linked to YF vaccine in this context, causality was reviewed by an ad hoc committee led by authorities from ProNaCEI and ANMAT, with the participation of experts from Pan American Health Organization (PAHO), National Institute for Human Viral Infections (INEVH), and scientific societies such as the Latin American Society for Travel Medicine (SLAMVI), Infectious Diseases Society of Argentina (SADI), and Pediatrics Society of Argentina (Sociedad Argentina de Pediatría – SAP).

Each event was analyzed according to the PAHO classification [13]: (1) coincidental event (i.e., illness caused by another etiology); (2) vaccine-related event, including errors related to vaccine handling (program error) or to vaccine components; (3) inconclusive event, in which the available evidence prevents unequivocal conclusions from being made about the etiology. Events were subclassified into four categories: mild (no interference with everyday activities), moderate (some interference with routine activities; need of medical assistance and/or medication prescription), serious (hospitalization, sequelae), and fatal.

Because the PAHO classification does not include specific events related to the YF vaccine, cases were further classified as follows: (1) mild to moderate: presence of a flu-like syndrome defined as myalgia, in addition to headache or fever, according to the definitions by Bastos Camacho [14]; and (2) serious and fatal: YEL-AVD, YEL-AND, and anaphylactic reactions. For YEL-AVD and YEL-AND, the Yellow Fever Vaccine Safety (YFVS) Working Group case definitions [11] were used. Anaphylaxis was defined according to Kelso [15]. First analysis was made in 2008–2009; for the purpose of this publication a revision was done in 2010, after the YFVS Working Group released new case definitions [16].

When feasible, serum, cerebrospinal fluid (CSF), and tissue samples were sent to the INEVH. Laboratory diagnosis of YEL-AVD was performed through genome amplification of YF virus (17D vaccine strain) RNA using Nested reverse transcription (nRT)–PCR assay. The (nRT)–PCR assay was performed as described by Sanchez-Seco et al. [17], employing the primers Flavi1+, Flavi1− (1° round) and YF2+ and Flavi2− (2° round). The amplicon of the expected size (505 bp) was cut from the agarose gel, purified by using QIAquick kit (Qiagen) according to the manufacturer's protocol, and sequenced directly from both strands of each reverse transcription-PCR product for verification. The analysis of the nucleotide sequence of 407 bp fragment of a genomic region of the NS5 protein was performed to classify the virus as wild-type or vaccine-derived, comparing the amplified product with other YFV strain sequences deposited in GenBank. Sequences were edited and aligned with BioEdit program by ClustalW method (available from http://www.mbio.ncsu.edu/BioEdit/bioedit.html). The phylogeny of the sequences was constructed using Neighbor Joining Method by MEGA 5 Software [18].

Viral isolation was attempted as described in [19]. Briefly, 20% homogenate of liver tissue was prepared and cultured in Vero cells for 14 days. Cultures were examined daily for evidence of viral cytopathic effect and evaluated by immunofluorescent assay (IFA) [20] for flavivirus antigen, by using fluorescein isothiocyanate-labeled flavivirus polyclonal antisera (Centers for Disease Control and Prevention, Puerto Rico), and for YFV antigen by using the specific monoclonal antibody Mab FA 2D12). Cultures were blindly passaged one more time onto fresh Vero monolayers.

YEL- AND laboratory diagnosis was made when positive CSF YF virus IgM results were obtained by MAC-ELISA. IgM detection was made also in the acute sera sample by MAC ELISA employing Dengue (DENV), Saint-Louis Encephalitis Virus (SLEV), West Nile Virus (WNV) and YF virus antigens [21]. Serological cross reaction was evaluated by PRNT [22] performed in paired serum samples for YF virus, DEN-1, DEN-2, DEN-3, DEN-4, SLEV, and WNV, the most prevalent flaviviruses in Argentina in the last years [23–26]. Serum was considered positive to a virus species when it reduced at least 90% of the formation of plaques of this virus at ≥1:20 dilutions and its neutralizing antibody titer was ≥four-fold greater than what was observed for the other tested flaviviruses.

Epi Info ™ software version 7.0.8.0 was employed for descriptive analysis.

3. Results

Between January 1, 2008, and January 31, 2009, 1,943,000 doses of 17DD YF vaccine (Bio-Manguinhos/FIOCRUZ, Brazil) were administered, and 165 AEFI were reported (i.e. 84.9/1,000,000 doses). The median age of cases was 38 years old (range 1–92), and 55% were male. AEFI were not associated with a particular vaccine batch.

There were 35 serious events (i.e.18/1,000,000 doses), of which 28 (80%) were male. Two of these were coincidental, nine were inconclusive, and twenty-four were vaccine-related.

3.1. Coincidental cases

Four events were coincidental, including the two aforementioned serious cases; namely, one septic shock caused by *Escherichia coli* (case #3), and one status epilepticus in a patient who was diagnosed with a brain tumor. In addition, there was one case of pharyngitis, and one case of headache and malaise with clinical onset a week before vaccination.

3.2. Program errors

One hundred program errors were registered from a cluster of 100 consecutive subjects vaccinated with multi-dose vials. All received 10 times the usual dose. Of note, 35 were people >60 years of age. There were no reports of adverse events.