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

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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 (AEF) 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 AEF were reported from different provinces. Case study analyses were performed using two AEF 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.

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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
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 filing 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 AEFI 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 Vaccination Safety (YPVS) 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 Flav1+, Flav1– (1’ round) and YF2+ and Flav2– (2’ round). The amplicon of the expected size (505 bp) was cut from the agarose gel, purified by using QiAGen 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.
3.3. Inconclusive events

Twelve cases (8 males -66.6%-, range: 7–56 years), were classified as inconclusive since YF viral testing was not performed. Among these, there was a fatal case (#38) of a previously healthy 53-year-old man who developed fever, myalgia, purpuric rash, and abdominal pain 6 days after vaccination. He was prescribed anti-histamines and methylprednisolone with no improvement, requiring hospitalization and intensive care. Blood, urine, and CSF cultures for bacteria, mycobacteria, and fungi, and serologies (HV, HCV, VDRL) were negative. A skin biopsy revealed vasculitis. He died 8 days after admission. Besides, there was one serious adverse event (SAE) classified as inconclusive. It was the case of a 54-year-old woman (case #19) with a history of presumable alcohol-related liver disease and gallbladder lithiasis, and who required admission for ascites, mild transaminase elevation, and marked hyperbilirubinemia 3 days after vaccination. She was treated, and the event was favorably resolved.

3.4. Vaccine-related events

Forty-nine AEFI were classified as YF vaccine-related. The median age was 37 years (range 1–69); 38 patients (77.5%) were male. Twelve events (24.5%) were mild (8 male -66.6%-, age range: 13–59); 13 (26.5%) moderate (10 male -76.9%, age range: 14–69), 23 (47%) serious (20 male -87%, range: 1–67), and one (2%) fatal as determined by the PAHO classification.

Fifty percent of SAEs and all fatal cases occurred in people >50 years old; five (20.8%) cases were in people 51–59 years old, and seven (29.2%) were in people >60 years old. The vaccine-related SAE incidence rate was 12.3/1,000,000 doses. Twelve events were classified as YEL-AVD (Table 1) and 12 as YEL-AND (Table 2). No anaphylactic reactions were reported.

YEL-AND cases consisted of eight definite neurotropic diseases (five meningitis, one meningitis with encephalitis, two encephalitides); one event fulfilled level 1 neurologic disease criteria, two YF vaccine-associated autoimmune disease with central nervous system involvement (YEL-AAD-CNS), and one YF vaccine-associated autoimmune disease with peripheral nervous system involvement (YEL-AAD-PNS). The last three patients and one case of encephalitis had neurologic sequelae (ratio: 33.3%) as of August 2013.

Only one case (#43) met the criteria for definite YEL-AVD. This subject was a 67-year-old male who developed fever, malaise, and watery diarrhea 4 days after YF vaccination. He was admitted to the hospital with mild transaminase elevation, renal failure, and thrombocytopenia. His clinical status rapidly progressed to multiple organ dysfunction syndrome, and he required intensive care. He died 48 h after admission. YEL-AVD was confirmed through RNA sequencing from a liver biopsy. Histopathology examination revealed mid-zonal necrosis, and the presence of Councilman Bodies. Two attempts at viral isolation were unsuccessful. A RT-PCR performed from a serum sample was negative.

The medical conditions were described for cases #47 (end-stage renal disease under hemodialysis), #49 (history of allergy), #59 (hypothyroidism and allergy to penicillin), and #63 (autoimmune interstitial glomerulonephritis and venous thrombosis). Six probable cases met level 1 diagnostic criteria and five cases met level 2 criteria.

The definite YEL-AVD rate was 0.5/1,000,000 doses. When probable cases were included, the rate increased to 6/1,000,000 doses. The case fatality ratio for definite YEL-AVD was 100%. If level 1 and level 2 YEL-AVD events were included, it decreased to 8.3%. The YEL-AND rate was 5.6/1,000,000 doses. If cases that met level 1 criteria were included, the rate increased to 6/1,000,000 doses. There were no fatal cases of YEL-AND.

4. Discussion

Between January 2008 and January 2009, Argentina’s Northeast region experienced its first sylvatic YF outbreak in more than 40 years, with nine confirmed cases, two of which were fatal. The last YF human cases had been recorded in 1966 [27]. Until the occurrence of the 2001 epizootic, routine immunization of people living or traveling to Argentina seemed not to be justified, with the exception of certain travelers going to Iguausu Falls. However, the sylvatic episode led to a tremendous demand for vaccination. In fact, a telephone-based survey revealed that more than 80% of people who went to a travel medicine and infectious diseases clinic in Buenos Aires to be vaccinated had no justifiable indication [28]. The fact that YF is a strongly feared illness can explain this phenomenon. In addition, according to Argentina’s immunization policies, YF vaccination can only be denied when medical conditions to contraindicate it are present.

Seventy-seven percent of vaccine-related events cases were male. This percentage was higher (82%) in the subgroup of patients requiring hospitalization. Male sex predominance is consistent with previous reports [12], although the reason remains unclear. In YF sylvatic transmission areas, professional activities are mostly performed by men, what could explain this, but most of our cases were from districts with no YF transmission risk.

It can be argued that DENV could have explained some cases because of the presence of DENV IgM. Cross-reactivity when using ELISA technique is frequent, so DENV, SLEV, WNV, and YFV antigens were employed and compared. PRNT in paired sera was performed when it was possible and seroconversion with higher titers was interpreted as indicating the causative organism in patients showing a primary immune response. Dengue circulation in 2008–2009 did not coincide with the time frame of this study and sign, symptoms and laboratory features coincide with typical mild to moderate adverse events caused by YF vaccine administration, according to the definitions [14]. Thus, cases that fit with mild to moderate illness and had temporal link to YF vaccination where classified as YF vaccine related.

Unfortunately, several cases had to be classified as inconclusive. Many reports were incomplete and difficult to reconstruct, for example case #19: the history of alcohol abuse does not mean that the subject had a diagnosis of liver cirrhosis. Even if this diagnosis was valid, the YF vaccine may also have triggered a compensation. Furthermore, inadequate data for confirming or ruling out a YF vaccine-related event is illustrated by case #38, where clinical picture clearly indicated YEL-AVD, but no viral testing or necropsy were performed. These shortcomings are common with passive surveillance systems [17].

If the PAHO classification had been strictly followed, the hospitalized cases would have been considered serious based on admittance to the hospital alone. The reasons for admission are heterogeneous, so further analysis is necessary to validate the severity criteria. Hospitalization itself as a definition for seriousness could be seen as a limitation of the PAHO classification. One strength of it, however, is that it is highly-sensitive for case capture. On the other hand, case analysis with a classification of high specificity, such as that currently proposed by the YFVS Working Group, may lead to dismissals due to non-compliance with criteria which are difficult to fulfill in certain settings. A YF vaccine AEFI classification that offers the best possible balance between sensibility and specificity is needed, as the current proposal is not sensitive enough to include all possible cases of YEL-AND and YEL-AVD. This is illustrated by case #9 (a 52-year-old male who had fever, malaise, myalgia, headache and abdominal pain 24 h after vaccination; laboratory tests revealed 3800 WBC/µL and 115,000 platelets/µL) which did not meet the criteria for YEL-AVD despite clinical features and bone marrow dysfunction following vaccination. Considering that wild
<table>
<thead>
<tr>
<th>Case#</th>
<th>Age</th>
<th>Gender</th>
<th>Onset from vaccination (days)</th>
<th>Pre-existing conditions</th>
<th>Clinical features</th>
<th>Relevant laboratory/image findings</th>
<th>Outcome</th>
<th>Observations</th>
<th>CDC classification (2010)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>61</td>
<td>M</td>
<td>4</td>
<td>Allergy to bees</td>
<td>Fever (&gt;40 °C), tachycardia, malaise, myalgia, dizziness, loss of appetite, chills</td>
<td>WBC 5500; platelets 140,000</td>
<td>Recovered</td>
<td>Travel to endemic area</td>
<td>Level 2 YEL-AVD criteria</td>
</tr>
<tr>
<td>9</td>
<td>52</td>
<td>M</td>
<td>1</td>
<td>No</td>
<td>Fever, myalgia, headache, rash, conjunctival injection</td>
<td>WBC 3500; platelets 116,000</td>
<td>Recovered</td>
<td>Residence in endemic area</td>
<td>Level 1 YEL-AVD criteria</td>
</tr>
<tr>
<td>27</td>
<td>54</td>
<td>M</td>
<td>5</td>
<td>No</td>
<td>Fever, malaise, myalgia, headache, retroorbital pain</td>
<td>platelets 126,000; YF/DENV MAC ELISA (+) (&gt;optical density for YF virus antigen); RT-PCR YF/DENV (−)</td>
<td>Recovered</td>
<td>Travel to endemic area</td>
<td>Level 1 YEL-AVD criteria</td>
</tr>
<tr>
<td>29</td>
<td>34</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>Fever, malaise, myalgia</td>
<td>No data</td>
<td>Recovered</td>
<td>Residence in endemic area</td>
<td>Level 1 YEL-AVD criteria</td>
</tr>
<tr>
<td>37</td>
<td>30</td>
<td>F</td>
<td>1</td>
<td>No</td>
<td>Myalgia, headache, petechiae and gingival bleeding</td>
<td>Platelets 10,000</td>
<td>Recovered</td>
<td>Residence in endemic area</td>
<td>Level 2 YEL-AVD criteria</td>
</tr>
<tr>
<td>43</td>
<td>67</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>Fever, malaise, diarrhea</td>
<td>MODS. Negative cultures (blood–urine–stool), Liver biopsy YF RT-PCR (+); YF vaccine strain confirmed by RNA sequencing</td>
<td>Recovered</td>
<td>Travel to endemic area</td>
<td>Definite YEL-AVD</td>
</tr>
<tr>
<td>53</td>
<td>60</td>
<td>F</td>
<td>5</td>
<td>No</td>
<td>Myalgia, arthalgia</td>
<td>WBC 1800; platelets 58,000; AST 60; Hct 23; WBC 2,500; platelets 90,000; ESR 60; LDH 469; blood and urine cultures (−); YF MAC ELISA (−)</td>
<td>Recovered</td>
<td>Travel to Venezuela</td>
<td>Level 2 YEL-AVD criteria</td>
</tr>
<tr>
<td>55</td>
<td>66</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>Fever, malaise, myalgia, orchitis</td>
<td></td>
<td>Recovered</td>
<td>Travel to Thailand</td>
<td>Level 2 YEL-AVD criteria</td>
</tr>
<tr>
<td>58</td>
<td>45</td>
<td>M</td>
<td>5</td>
<td>Cardiac valve surgery</td>
<td>Fever</td>
<td>Hct 39; WBC 2800; platelets 155,000; blood and urine cultures (−)</td>
<td>Recovered</td>
<td>Unknown</td>
<td>Level 1 YEL-AVD criteria</td>
</tr>
<tr>
<td>59</td>
<td>26</td>
<td>F</td>
<td>5</td>
<td>Hypo-thyroidism</td>
<td>Fever, myalgia, headache</td>
<td>WBC 3,600; AST 621; ALT 406; YF MAC ELISA (+)</td>
<td>Recovered</td>
<td>Unknown</td>
<td>Suspect YEL-AVD</td>
</tr>
<tr>
<td>61</td>
<td>1</td>
<td>M</td>
<td>12</td>
<td>No</td>
<td>Fever and vomiting</td>
<td>Hb 10; WBC 16,800; platelets 480,000; AST 683; ALT 822; HAV-HBV-HCV(−); CMV (−)</td>
<td>Recovered</td>
<td>Unknown</td>
<td>Suspect YEL-AVD</td>
</tr>
<tr>
<td>63</td>
<td>52</td>
<td>M</td>
<td>21</td>
<td>Membrane-proliferative nephropathy; hypertension; cardiac failure; pulmonary hypertension; superficial venous thrombosis of left upper limb</td>
<td>Loss of appetite, myalgia, arthralgia, jaundice, dyspnea, confusion</td>
<td>Platelets 28,000; LDH 625; creatinine 1.98; thorax CT: diffuse ground-glass opacity; TTE: pulmonary hypertension</td>
<td>Recovered</td>
<td>Unknown</td>
<td>Level 2 YEL-AVD criteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Case #</th>
<th>Age</th>
<th>Gender</th>
<th>Onset from vaccination (days)</th>
<th>Pre-existing conditions</th>
<th>Clinical features</th>
<th>Laboratory findings</th>
<th>Images</th>
<th>Outcome</th>
<th>Reason for vaccination</th>
<th>CDC Classification</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>M</td>
<td>13</td>
<td>No</td>
<td>Fever, headache, unstable gait, nistagmus, tremor</td>
<td>S1: +</td>
<td>640</td>
<td>ND</td>
<td>NA</td>
<td>Nistagmus, memory impairment</td>
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<tr>
<td>24</td>
<td>63</td>
<td>M</td>
<td>10</td>
<td>Hypertension</td>
<td>Vomiting, headache, confusion</td>
<td>CSF: S1: +</td>
<td>ND</td>
<td>ND</td>
<td>MRI: demyelinating encephalomyelitis</td>
<td>Memory impairment</td>
</tr>
<tr>
<td>25</td>
<td>29</td>
<td>M</td>
<td>13</td>
<td>No</td>
<td>Fever, nausea, vomiting, myalgia, chills, headache, arthralgia, diarrhea</td>
<td>CSF: S1: +</td>
<td>ND</td>
<td>ND</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>63</td>
<td>M</td>
<td>4</td>
<td>No</td>
<td>Encephalitis</td>
<td>CSF: S1: +</td>
<td>ND</td>
<td>ND</td>
<td>MRI: diffuse periventricular hyper-intensity</td>
<td>Recovered</td>
</tr>
<tr>
<td>42</td>
<td>22</td>
<td>M</td>
<td>15</td>
<td>No</td>
<td>Headache, dizziness. Cognitive impairment, hemiparesis, dysarthria</td>
<td>CSF: S1: +</td>
<td>ND</td>
<td>ND</td>
<td>MRI: T2 white matter bilateral hyperintense images; EEG: diffuse low voltage, slow-wave activity</td>
<td>Right hemiparesis</td>
</tr>
<tr>
<td>46</td>
<td>65</td>
<td>M</td>
<td>19</td>
<td>No</td>
<td>Encephalitis</td>
<td>No samples available</td>
<td>No vaccine indication</td>
<td>Level1 YEL-AND</td>
<td>Recovered</td>
<td>Travel to endemic area</td>
</tr>
<tr>
<td>47</td>
<td>28</td>
<td>M</td>
<td>26</td>
<td>End-stage renal disease (hemodialysis)</td>
<td>Fever, headache, obtundation</td>
<td>S1: +</td>
<td>160</td>
<td>&lt;20</td>
<td>Recovered</td>
<td>Travel to endemic area</td>
</tr>
<tr>
<td>48</td>
<td>5</td>
<td>M</td>
<td>9</td>
<td>No</td>
<td>Encephalitis</td>
<td>CSF: S1: +</td>
<td>1280</td>
<td>ND</td>
<td>Recovered</td>
<td>Unknown</td>
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<td>49</td>
<td>11</td>
<td>M</td>
<td>17</td>
<td>Allergy</td>
<td>Fever, malaise, vomiting, myalgia, headache</td>
<td>S2: +</td>
<td>ND</td>
<td>ND</td>
<td>Recovered</td>
<td>Resident in endemic area</td>
</tr>
<tr>
<td>50</td>
<td>53</td>
<td>M</td>
<td>50</td>
<td>No</td>
<td>Fever, malaise, headache; acute demyelinating polyradiculo-neuropathy</td>
<td>CSF: S1: +</td>
<td>1280</td>
<td>ND</td>
<td>Spinal cord MRI: thoracic hyperintense T2 gray matter signa</td>
<td>Sphincter disfunction</td>
</tr>
<tr>
<td>52</td>
<td>58</td>
<td>M</td>
<td>21</td>
<td>No</td>
<td>Fever, malaise, headache, somnolence</td>
<td>CSF: S1: +</td>
<td>ND</td>
<td>ND</td>
<td>Recovered</td>
<td>Resident in endemic area</td>
</tr>
<tr>
<td>62</td>
<td>28</td>
<td>F</td>
<td>19</td>
<td>No</td>
<td>Fever, nausea, vomiting, myalgia, retroocular pain. Meningeal signs</td>
<td>CSF: S1: +</td>
<td>ND</td>
<td>ND</td>
<td>Recovered</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

S1: sample (acute phase); S2: sample (convalescent phase); ND: not done; NA: not available; EEG: electroencephalography; S2: sample (convalescent phase); CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

* Reciprocal of serum dilutions.
YF infection encompasses a clinical range from asymptomatic to malignant with up to 60% fatality, the same should be true for YEL-AVD. That is, viscerotropism could be more common than it currently appears, as all diagnostic criteria to date target only the most serious forms of YEL-AVD.

Regarding YEL-AND, case #39 illustrates how diagnostic criteria must be periodically revised based on new available evidence. In 2008–2009, our committee analyzed the case when the patient first consulted with encephalitis after vaccination. However, as CSF biochemical parameters were normal and a CSF YF IgM was negative, the case was dismissed as YEL-AND since it did not meet the YFVS Working Group definitions at the time [17]. Several weeks later, since the patient did not have a clear diagnosis or show clinical improvement, he was transferred from his original province to Buenos Aires for further study. Another CSF sample was obtained, revealing a lymphocytic pleocytosis and a positive YF ELISA IgM [29]. Interestingly, we found this and another YEL-AND case (a longitudinal myelitis with onset 45 days after vaccination [30]) as published reports. None of these were reported to the health authority. Finally, as another YEL-AND case with a late-onset presentation was reported [31], a new revision of the time frame for YEL-AND case definition should be considered.

As for risk factors, it is worth noting that case #63 had an autoimmune disorder and a history of renal and thrombotic manifestations, and two cases had hypothyroidism. Autoimmune diseases are increasingly considered to be predisposing factors toward the development of YF vaccine-related SAE [12]. Pathology of the thyroid constitutes the most frequent autoimmune disease, and is much more common in young women [32,33]. At least two cases of YEL-AVD were found to have disorders of this gland [16,34]. More evidence is needed to determine if thyroid disease could have an association with adverse events after YF vaccination and even to underlie the higher fatality ratio reported in young women [35].

YEL-AND and AVD rates in this study were slightly higher than those previously reported if we included cases that met level 1 and 2 criteria. Reported rates for YEL-AVD and YEL-AND vary depending on the source. For VAERS, the rate for YEL-AVD and YEL-AND was estimated in 0.4/100,000 and 0.8/100,000 doses [36]. A higher rate (7.9/100,000) for YEL–AVD in a non-endemic population was documented from Peru [34].

The case of the patient with definite YEL-AVD is worth expanding upon. This patient was due to fly to Sudan to work in areas depicted as endemic for YF transmission [37]. Moreover, before flying the higher risk of SAE due to his age was explained; however he decided to be immunized. New YF risk maps were subsequently released in which those areas were excluded for vaccine recommendations. It is clear that accurate information is needed to better define actual risk areas.

An inactivated, whole virus vaccine was proven to be safe and reasonably efficacious in a phase I clinical study [38]. If it is available in the future, it will help to safely immunize individuals with medical conditions that put them at risk of developing SAEs after administration of YF 17D vaccine. In the meantime, a judicious use of this vaccine in countries like Argentina is mandatory, given that the risk of SAEs could outweigh the potential benefits of vaccination, especially under the exceptional circumstances registered in the 2008–2009 regional outbreak.

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References


