Vaccine 30 (2012) 5038–5058

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Viscerotropic disease: Case definition and guidelines for collection, analysis, and presentation of immunization safety data☆

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ARTICLE INFO

Article history:
Received 13 April 2012
Accepted 19 April 2012
Available online 4 May 2012

Keywords:
Viscerotropic disease

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0264-410X/$ – see front matter. Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.vaccine.2012.04.067

Yellow fever vaccine
Adverse event
Immunization
Guideline
Case definition

1. Preamble

1.1. Need for developing case definitions and guidelines for viscerotropic disease as an adverse event following immunization

Viscerotropic disease (VTD) is defined as acute multiple organ system dysfunction that occurs following vaccination. The severity of VTD ranges from relatively mild multisystem disease to severe multiple organ system failure and death. The term VTD was first used shortly after the initial published reports in 2001 of febrile multiple organ system failure following yellow fever (YF) vaccination [1–7]. To date, VTD has been reported only in association with YF vaccine and has been thus referred to as YF vaccine-associated viscerotropic disease (YEL-AVD).

YF vaccine is manufactured from the live attenuated 17D virus substrain. It is considered relatively safe and effective in preventing YF disease, which results from YF virus transmission through the bite of an infected mosquito [8]. YF virus circulates in sub-Saharan Africa and tropical South America, where it causes endemic and intermittently epidemic disease. Most YF disease in these areas is attributable to jungle (sylvatic) or savanna (intermediate) transmission cycles, which occur predominantly in sparsely populated forested areas and rural villages, respectively [8]. To protect vulnerable populations, endemic countries target YF vaccination efforts towards their residents, who reside in both rural and urban settings with varying resources.

YEL-AVD is believed to result from widespread dissemination and replication of live attenuated 17D YF vaccine virus, similar to the natural YF virus. Virologic studies have documented vaccine virus in a number of postmortem tissues obtained from YEL-AVD case patients [1–3,9–14]. The initial symptoms of YEL-AVD are nonspecific, including fever, headache, malaise, myalgia, arthralgia, nausea, vomiting, and diarrhea, and resemble those of the early phase of YF disease. As YEL-AVD progresses, jaundice can appear, along with thrombocytopenia and elevations of hepatic transaminases, total bilirubin, and creatinine. Severe YEL-AVD is characterized by hypotension, hemorrhage, acute renal failure, and acute respiratory failure. Less frequent manifestations include rhabdomyolysis and disseminated intravascular coagulation (DIC). There is no specific therapy for YEL-AVD; treatment is supportive. YEL-AVD is fatal in more than 60% of reported cases [8], although this rate is probably an overestimate because case confirmation is more likely in fatal cases than nonfatal ones.

As of March 2010, the Brighton Collaboration Viscerotropic Disease Working Group had identified 60 published and unpublished reports of YEL-AVD from Asia, Australia, Europe, and North and South America. A number of suspected YEL-AVD cases have been detected in Africa through enhanced surveillance conducted in conjunction with mass YF vaccination campaigns, but information on these cases is limited. YEL-AVD cases have been reported following vaccination with different attenuated 17D YF vaccine virus substrains that have been produced by several manufacturers [8]. YEL-AVD appears to occur only after a person's first YF vaccination; there are no reports of YEL-AVD following booster doses of YF vaccine. The median time from vaccination until symptom onset is 3 days (range: 1–8 days). The median time from YF vaccination until death is 10 days (range: 7–30 days) [8].

Data from US and European travelers indicate that YEL-AVD occurs at a frequency of 0.3–0.4 per 100,000 YF vaccine doses distributed [15–17]. An analysis of fatal cases in mass vaccination campaigns in Brazil yielded a lower risk estimate of 0.0043–0.2131 per 100,000 doses administered [9]. However, more recent risk estimates reported from Brazil, using data from vaccination campaigns in 2008–2009, are similar to those reported from the United States and Europe [18]. In 2007, an unprecedented cluster of five cases of YEL-AVD, four of which were fatal, occurred following the use of a single lot of YF vaccine administered as part of a vaccination campaign in a nonendemic area of Peru. The overall incidence of YEL-AVD in this campaign was 7.9 per 100,000 doses administered, and the lot-specific incidence was 11.7 per 100,000 doses [12]. A thorough investigation found no clear explanation for the substantially higher incidence of YEL-AVD in this campaign or with this specific vaccine lot.

Advanced age has been identified as a risk factor for YEL-AVD. Two analyses of YEL-AVD reports to the Vaccine Adverse Events Reporting System (VAERS) in the United States yielded a reporting rate of 1.4–1.8 cases of YEL-AVD per 100,000 doses for persons aged ≥60 years [15,16]. This rate is several times higher than the overall reporting rate of 0.3–0.4 per 100,000 doses. In addition, a history of thymus disease or thymectomy is considered a risk factor, based on the observation that four of the first 23 reported cases of YEL-AVD had a history of thymectomy for either benign or malignant thymoma [19].

In 2002, an informal Yellow Fever Vaccine Safety Working Group (YFWG) was convened to discuss cases of YEL-AVD. The YFWG included staff of the US Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), various US academic institutions, the US Food and Drug Administration, the US Department of Defense, and vaccine manufacturers. This working group reviewed reports to VAERS of serious adverse events following YF vaccination and developed a case definition for YEL-AVD. This case definition, published in original [8] and in modified form [20], provided the basis for case definitions subsequently used in the investigation of suspected YEL-AVD cases in Brazil and Peru [12], by a major YF vaccine manufacturer, and by WHO [21,22]. However, this case definition was never subjected to a formal peer review process and was never adopted as an international standard.

The original YFWG case definition has limitations. It combines case-finding criteria, useful to search surveillance systems for reports of potential cases of YEL-AVD, with clinical and laboratory abnormalities used for case confirmation. To be classified as YEL-AVD, a case must meet the case-finding criteria (fever and at least one other symptom from a list of nonspecific symptoms) and

Abbreviations: AEFI, adverse event following immunization; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; CDC, Centers for Disease Control and Prevention (US); CPK, creatine phosphokinase; DIC, disseminated intravascular coagulation; FDP, fibrin degradation products; IHC, immunohistochemistry; INR, international normalized ratio; PCR, polymerase chain reaction; PFU, plaque-forming unit; RBC, red blood cell; RNA, ribonucleic acid; ULN, upper limit of normal; UNICEF, United Nations Children's Fund; VAERS, Vaccine Adverse Events Reporting System (US); VTD, viscerotropic disease; WHO, World Health Organization; YEL-AVD, yellow fever vaccine-associated viscerotropic disease; YF, yellow fever; YFI, Yellow Fever Initiative; YFWG, Yellow Fever Vaccine Safety Working Group.