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Review

Risk of yellow fever vaccine-associated viscerotropic disease among the elderly: Systematic review☆

Ellen Rafferty[a,*], Philippe Duclos[b], Sergio Yactayo[b], Melanie Schuster[b]

[a] University of Saskatchewan, Saskatoon, Saskatchewan S7 N 5A2, Canada
[b] World Health Organization, 20 Ave Appia, CH-1211 Geneva 27, Switzerland

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ABSTRACT

Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) is a rare and serious adverse event of the yellow fever (YF) vaccine that mimics wild-type YF. Research shows there may be an increased risk of YEL-AVD among the elderly population (≥60–65 years old), however this research has yet to be accumulated and reviewed in order to make policy recommendations to countries currently administering the YF vaccine. This paper systematically reviewed all information available on YEL-AVD to determine if there is an increased risk among the elderly, for both travelers and endemic populations. Age-specific reporting rates (RRs) were re-calculated from the literature using the Brighton Collaboration case definition for YEL-AVD and were then analyzed to determine if there was a significant difference between the RRs of younger and older age groups. Two out of the five studies found a significantly higher rate of YEL-AVD among the elderly population. Our findings suggest unexposed elders may be at an increased risk of developing YEF-AVD, however the evidence remains limited. Therefore, our findings for YF vaccination of elderly populations support the recommendations made by the Strategic Advisory Group of Experts (SAGE) in their April 2013 meeting, mainly vaccination of the elderly should be based on a careful risk–benefit analysis.

Contents

Abbreviations: YF, yellow fever; YEL-AVD, yellow fever vaccine-associated viscerotropic disease; RR, reporting rates; RRR, reporting rate ratios; AVD, viscerotropic disease; AEFI, adverse events following immunization; serious AEFI, serious adverse events following immunization; YFWG, yellow fever vaccine safety working group.

☆ Three of the authors are World Health Organization staff members. The opinions expressed in this article are those of the authors and do not necessarily represent the decisions, official policy or opinions of the World Health Organization.

* Corresponding author. Present address: 247 Edgemont Pl NW, Calgary, AB T3A 2K1, Canada. Tel.: +1 4032390981; mobile: +1 3062032745.
E-mail addresses: err593@mail.usask.ca, ersraffe@gmail.com (E. Rafferty).

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1. Introduction

Yellow fever (YF) is a mosquito-borne disease that is endemic in South American, sub-Saharan Africa and parts of Central America and the Carribean [1]. Fatality rates of YF vary considerably, although research from West African patients with jaundice suggest it is approximately 20% [1]. Current YF vaccines are manufactured using live attenuated YF virus sub-strains, 17DD and 17D-204 [1]. Generally, two distinct groups receive the YF vaccine, individuals traveling to countries where YF is endemic (travelers) and those who live in countries where YF is endemic or is intermittently epidemic (endemic populations).

Serious adverse events following immunization (serious AEFI) associated with the YF vaccine include viscerotropic disease (specifically known as yellow fever vaccine-associated viscerotropic disease – YEL-AVD), neurologic (e.g. encephalitis or acute disseminated encephalomyelitis), and severe hypersensitivity reactions (e.g. anaphylaxis). YEL-AVD is characterized by acute multiple organ system dysfunction due to vaccine virus proliferation [2]. In 2001, the first series of cases of YEL-AVD were reported [2]. Since then, retrospective testing has identified a case of YEL-AVD as early as 1975 [3]. YEL-AVD has a high case fatality rate, with more than 60% of reported cases being fatal [4]. To date, YEL-AVD has only been recognized in primary vaccine recipients [4].

Laboratory tests can identify YEL-AVD by detecting vaccine YF virus strain 17D in the blood and/or the tissue of those infected, through virus cultures and viral RNA amplification [2]. In endemic settings, however, it can be difficult to differentiate between YEL-AVD and wild-type YF, primarily due to suboptimal samples and the limited availability of lab tests [1].

Until May 2012 the "main case definition" used for YEL-AVD was developed by an informal yellow fever vaccine safety working group (YFWG). The YFWG was convened by the Centers for Disease Control and Prevention (CDC) in the US and consisted of a wide range of YF experts. The YFWG case definition was originally created in 2002 and updated in 2008. However, it was never subjected to formal peer review process and was never accepted as the global standard [1,2]. In 2012, the Brighton Collaboration Viscerotropic Disease WG (Brighton WG) published a standardized case definition for viscerotropic disease, as well as guidelines for classifying, analysing and presenting information related to these cases [1].

The Brighton WG case definition of AVD outlines three levels of diagnostic certainty, with Level 1 having the highest specificity [2]. Each case of viscerotropic disease can then be categorized into one of the three levels of diagnostic certainty based on the presence of major and minor criteria. Cases that do not meet the requirements for one of the three levels of diagnostic certainty are classified as having 'insufficient evidence' [2]. The Brighton WG also developed a causality algorithm to assess the association of viscerotropic disease with the YF vaccine; this algorithm was included as an appendix to the case definition. [2]. There are four categories of causality, Definite, Probable, Suspected or Insufficient evidence [2]. The determination of causality into one of these categories is primarily based on the isolation and/or amplification of 17D virus or 17D RNA from the blood or tissue of the infected individual [2].

Studies suggest that there is a higher risk of serious adverse events following YF vaccination (YF-AEFI), in particular for YEL-AVD, among the elderly [5–9]. These studies primarily use age-specific reporting rates (RRs) and reporting rate ratios (RRRs) as proxies for determining risk in the elderly population [5–9]. However, researchers have never systematically reviewed the methodology, populations and generalization of these studies. In fact, depending on the study, elderly (or advanced age) was defined differently, ranging from ≥60 to ≥65. A recently published systematic review on the safety of YF vaccine in high risk groups, including the elderly, simply restated the conclusion of the previous studies without utilizing a uniform case definition or more specifically using the updated Brighton case definition for viscerotropic disease [10]. Therefore, the objective of this review is to re-calculate the current risk of YEL-AVD (using the Brighton Collaboration case definition) among the elderly for both travelers and endemic populations.

2. Methods

2.1. Overview

This review uses 3 steps to determine the risk of YEL-AVD among the elderly:

1. Identify, classify (Brighton Classification – diagnostic certainty and causality), and categorize by age, all published cases of YEL-AVD.
2. Identify and review articles identifying advanced age as a risk factor for YEL-AVD in travelers and critically analyze their methodology. Including, re-calculation of RRs and RRRs using the Brighton Classification.
3. Identify and review articles concerning advanced age as a risk factor for YEL-AVD in endemic populations and identify general RRs of YEL-AVDs in endemic populations to estimate the risk in this group.

2.2. Search method

For the literature search, this systematic review primarily builds on the work of Thomas et al. (2012) [10]. In their review, Thomas et al. (2012) searched nine databases, all languages, no date limits and up until December 2010 [10]. Databases searched included the Cochrane Library (Cochrane CENTRAL Register of Controlled Trials, the Cochrane Database of Systematic Reviews and the NHS Database of Abstracts of Reviews of Effects (DARE)), MEDLINE (OVID 1950 to present), EMBASE (OVID 1910 to present), and BIOSIS [10]. After duplicates were removed, all abstracts were read by two independent reviewers [10]. Articles were included if they had data on the risk factors (e.g. pregnancy, elderly, HIV+) associated with serious AEFI after YF vaccination [10].

We also identified articles through an extended literature search modeled on Thomas et al. (2012). This literature search used corresponding search terms, in all languages, from two databases (Pubmed and MEDLINE (OVID 1950 to present)). We included articles published between December 2010 and May 2012, previously not covered by Thomas et al. (2012). Furthermore, articles were obtained from additional sources, including scanning the reference lists of included articles for relevant studies and receiving articles from YF experts who had access to additional and pre-published sources.

After removing any duplicates, we screened all the articles' titles and abstracts for inclusion and exclusion based on specific criteria. We excluded any literature reviews, non-research letters, articles relating to a specific population other than the elderly (e.g. HIV+ patients) and any article prior to 2001. We excluded any article prior to 2001 as YEL-AVD was first described in 2001 [1]. We included any article that had YEL-AVD case-specific information, RRs of YF-AEFI among the elderly and general RRs of YF-AEFI in endemic populations. Subsequently, we reviewed the full-text of all remaining articles. We included articles in the final systematic review based on the above inclusion/exclusion criteria, as well as their relevance to the three method areas outlined at the beginning of the Methods section (Section 2.1).

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