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Review

Risk groups for yellow fever vaccine-associated viscerotropic disease (YEL-AVD)

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ABSTRACT

Although previously considered as the safest of the live virus vaccines, reports published since 2001 indicate that live yellow fever virus vaccine can cause a severe, often fatal, multisystemic illness, yellow fever vaccine-associated viscerotropic disease (YEL-AVD), that resembles the disease it was designed to prevent. This review was prompted by the availability of a listing of the cumulative cases of YEL-AVD, insights from a statistical method for analyzing risk factors and re-evaluation of previously published data. The purpose of this review is to identify and analyze risk groups based on gender, age, outcome and predisposing illnesses. Using a passive surveillance system in the US, the incidence was reported as 0.3 to 0.4 cases per 100,000. However, other estimates range from 0 to 12 per 100,000. Identified and potential risk groups for YEL-AVD include elderly males, women between the ages of 19 and 34, people with a variety of autoimmune diseases, individuals who have been thymectomized because of thymoma, and infants and children ≤11 years old. All but the last group are supported by statistical analysis. The confirmed risk groups account for 77% (49/64) of known cases and 76% (32/42) of the deaths. The overall case fatality rate is 66% (42/64) with a rate of 80% (12/15) in young women, in contrast to 50% (13/26) in men ≥56 years old. Recognition of YEL-AVD raises the possibility that similar reactions to live chimeric flavivirus vaccines that contain a yellow fever virus vaccine backbone could occur in susceptible individuals. Delineation of risk groups focuses the search for genetic mutations resulting in immune defects associated with a given risk group. Lastly, identification of risk groups encourages concentration on measures to decrease both the incidence and the severity of YEL-AVD.

1. Introduction

Yellow fever (YF) is characterized by fever, jaundice, and black vomitus associated with hepatic, renal and cardiac injury and is accompanied by a mortality rate of 20 to 50% [1]. At present YF control is accomplished principally by a highly-effective live virus vaccine (YFVV). Currently available vaccines are derivatives of the 17D strain: 17DD produced in Brazil and used throughout South America and 17D-204 produced and distributed worldwide.

YFVV had been considered the safest of the live virus vaccines. Although retrospective analysis revealed that a case had occurred as long ago as 1973 [2], it was not until 2001 that the vaccine was recognized as rarely causing a serious, frequently fatal, multisystemic illness: yellow fever vaccine-associated viscerotropic disease (YEL-AVD) [3–5]. A comprehensive review of severe adverse reactions to the yellow fever vaccine has been published [6]. However, using data in a CDC listing of YEL-AVD cases, the current review aims to evaluate the significance of YEL-AVD risk groups. The listing makes possible the construction of a figure that suggests groups of cases with particular risk factors. The statistical significance of a group with a given risk factor can then be evaluated using a new method for calculating odds ratios and related statistics [7].

Recognition of YEL-AVD has resulted in changing the judgment of YFVV from being the safest of the live virus vaccines to being one of the least safe [8]. The live YFVV continues to be the lynch pin in the control of yellow fever. It is highly effective as judged by its ability to abort epidemics and the rarity of the disease in previously vaccinated individuals [1]. However, as discussed elsewhere, the decision to vaccinate has become more complex particularly if the risk of exposure to wild-type virus is judged to be less than the chance of acquiring YEL-AVD [9].

Untoward reactions to YFVV also include allergic reactions (principally to egg immunogens) and a predominantly neurological disease termed yellow fever vaccine-associated neurotropic disease (YEL-AND), a symptom complex that is rarely fatal or results in permanent sequelae. The incidence of YEL-AND is substantially

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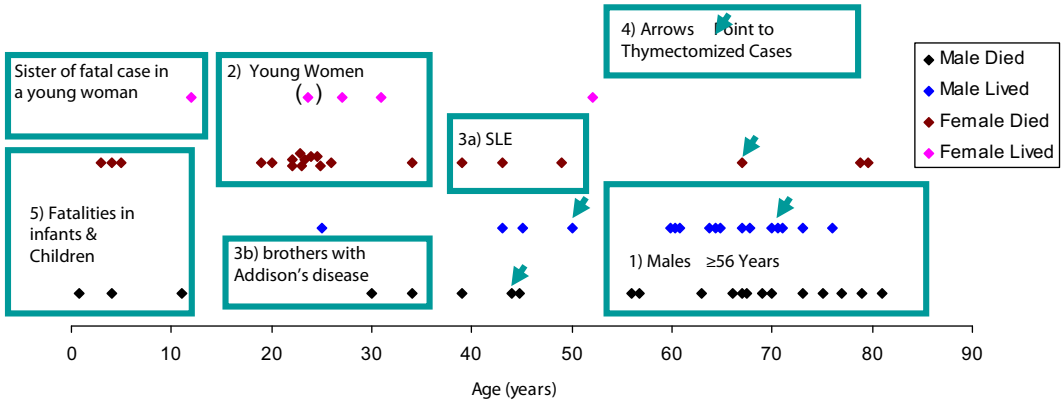

Fig. 1. Risk groups for YEL-AVD with stratification of cases by age, gender, and outcome. Putative risk groups are outlined in rectangles. In one instance a case in a family member is also enclosed in a rectangle. With the thymectomized group, individual cases are pointed to by arrows. YEL-AVD, yellow fever vaccine-associated viscerotropic disease; SLE, systemic lupus erythematosis. YEL-AVD patients with autoimmune diseases include three with SLE, two with Addison's disease, and five individuals ≥67 years old. The latter are not separately indicated in the figure, but are delineated (Table 3). The parentheses on the side of the symbol for one young woman who survived mark an atypical case that had features of yellow fever vaccine-associated-neurotropic disease (YEL-AND). The symbols are offset to make the cases individually visible.

reduced if the vaccine is administered to individuals older than six months [10].

People thymectomized as treatment of thymoma were one of two groups initially recognized as being at increased risk for developing YEL-AVD [11]. The elderly were identified as another [12,13]. Subsequent analysis indicated that the elderly risk group consisted almost entirely of men [7,9]. Another risk group consists of women between the ages of 19 and 34 [14]. Calculations involving patients with a variety of autoimmune diseases substantiate their increased risk [7]. One case of fatal YEL-AND has been reported in an HIV-infected individual [15]. Although HIV viral load rather than CD4 count is predictive of a poor response to vaccination [16], the lack of reports of HIV patients developing YEL-AVD means that there are no data supporting an increased risk, Nevertheless, the occurrence of the one fatal case of YEL-AND and the panoply of immune defects associated with HIV suggests that the vaccine should not be given to individuals with documented AIDS or CD4 counts <200.

The current report reviews data associated with suspected and confirmed risk groups. In many instances, factor-specific vaccination ("denominator") data are not available so that precise estimates of attack rates using traditional methods are not possible. Delineation of a risk group can still be accomplished by the association of cases with potential risk factors combined with calculation of odds ratios using a method that does not require knowledge of such denominator data [7].

2. Methods

A listing of 65 YEL-AVD cases accepted by CDC as of January, 2011 was used as the core of this review (Tables S1A and S1B). As is indicated in bold in the tables, this listing was modified by an analysis of articles cited in a comprehensive review of the literature [6], by direct contact with some of the authors, and by articles published subsequent to the CDC listing, In three of the CDC accepted cases the age and gender are not known. They were not included. Two additional cases have been described, one in case report [17] and one at the American Society of Tropical Medicine and Hygiene national meeting in November, 2012 by Turpo, G. et al., making a total of 64 cases in this review.

Although the definition of viscerotropic disease has been revised by the Brighton Collaboration Viscerotropic Working Group [18], in many instances insufficient data are available to evaluate a given case. Accordingly acceptance by CDC was the primary criterion for inclusion. No virologically-confirmed YEL-AVD cases have been reported from Africa in series totaling more than 40 million vaccinees [19,20]. One suspect case included from Germany did not have evidence by culture or RT-PCR of virus, but had an abnormally high serum plaque reduction neutralization test (PRNT) of 1:10,240 [21]. Such a high titer, at least 16 times the maximum expected after vaccination, has been found in two cases in the United States [3] and in another German [22,23]. A suspected mild case in a 21 year old male U.S. soldier was not included because of atypical symptoms and the absence of virological confirmation [24].

Identification of possible risk groups, the core of the data analysis, was done by a consideration of potential risk groups reported in the literature supplemented by identification of groups of cases depicted by age, gender, and outcome (Fig. 1). A previously reported method was used to estimate the statistical significance of the suspected risk groups [7].

3. Results

3.1. Estimation of frequency of YEL-AVD

Estimates of the frequency of the occurrence of YEL-AVD vary from zero [27] to 12 [16] per 100,000 vaccinees (Table 1). Values from U.S. vaccinees vary from 0.3 to 0.4 per 100,000 [12,25]. These figures are based on a passive reporting system, the Vaccine Adverse Event Reporting System (VAERS). The years covered in the above references are 1990–2002 and 2000–2006, respectively. Numerators for the estimates are small, 7 (with 4 deaths) and 6 (with 2 deaths). The first of the VAERS estimates includes the years 1990–2000, years in which YEL-AVD had not been recognized thereby increasing the possibility of underreporting. Combining the two estimates yields an estimate of the incidence of YEL-AVD of 0.35 per 100,000.

An estimate of the incidence of YEL-AVD 33 fold higher than the US VAERS ones comes from Peru [26]. Following an earthquake in a yellow fever free area, vaccine was administered. With one vaccine lot, the incidence of YEL-AVD was 12 per 100,000 (5/42,742). All four fatal cases belong to risk groups. Viral sequences (including extensive repetitive sequencing of the envelope gene (E) for quasispecies from the fatal cases) did not differ significantly from the vaccine seed lot that had been in use for many years [26,27]. Contributing factors to this increased incidence include that, for the vast majority of vaccinees, this was the first YFVV they had received. With the exception of one suspected case in whom "limited investigations" were performed, YEL-AVD has not been reported in individuals on re-vaccination [21]. The safest age group for vaccine administration in a large Brazilian study was 9 months