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Yellow fever vaccine: An updated assessment of advanced age as a risk factor for serious adverse events

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Abstract

Since 1996, the scientific community has become aware of 14 reports of yellow fever vaccine (YEL)-associated viscerotropic disease (YEL-AVD) cases and four reports of YEL-associated neurotropic disease (YEL-AND) worldwide, changing our understanding of the risks of the vaccine. Based on 722 adverse event reports after YEL submitted to the U.S. Vaccine Adverse Event Reporting System in 1990–2002, we updated the estimates of the age-adjusted reporting rates of serious adverse events, YEL-AVD and YEL-AND. We found that the reporting rates of serious adverse events were significantly higher among vaccinees aged ≥60 years than among those 19–29 years of age (reporting rate ratio = 5.9, 95% CI 1.6–22.2). Yellow fever is a serious and potentially fatal disease. For elderly travelers, the risk for severe illness and death due to yellow fever infection should be balanced against the risk of a serious adverse event due to YEL.

Keywords: Yellow fever vaccine; Vaccination/adverse effects; Adverse drug reaction reporting systems; Age groups

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1. Introduction

Yellow fever vaccine (YEL) has been used for more than 60 years. All yellow fever (YF) virus strains used for vaccine production are derived from the 17D strain [1]. The only YEL licensed for use in the United States is YF-VAX®, manufactured and distributed by Aventis Pasteur, Inc. Annually in the U.S., an average of 600,000 YEL doses is distributed to the U.S. military; another ∼300,000 doses are distributed to travel clinics in the civilian sector (Aventis Pasteur Inc, personal communication, 2003). In the U.S., YEL is recommended for persons aged 9 months or older traveling to areas where YF is endemic [2] and is required for military personnel depending on their duty or likelihood of deployment to an endemic area [4]. Several countries require a certificate of vaccination from all travelers or those arriving from YF-endemic areas [3].

Previously, YEL was believed to be one of the safest vaccines [1]. Since 1996, this belief has changed, when in the U.S., the first four cases of YEL-associated viscerotropic disease (YEL-AVD) and another four cases of YEL-associated neurotropic disease (YEL-AND) were reported [5–7]. In mid-2001, the U.S. Centers for Disease Control and Prevention (CDC) initiated enhanced surveillance [2,6]. Since then, two additional unpublished cases of YEL-AVD and one report of YEL-AND have been identified and reported to the Vaccine Adverse Event Reporting System (VAERS). Similar serious adverse events in persons vaccinated with YEL were described in three additional YEL-AVD case reports from Europe [8–10]. Deaths from YEL-AVD have been reported in Brazil [11] and Australia [12].

Advanced age (65 years and older) was previously identified as a risk factor for systemic adverse events temporally associated with YEL [13–14]. There is some evidence that YEL-AVD and YEL-AND also appear more frequently in persons of advanced age [7]. The objectives of this study were to update our understanding of these age-specific risks by: (1) estimating reporting rates of adverse events after YEL over time, stratified by the civilian and military populations; (2) determining potential risk factors for serious adverse events after YEL; (3) assessing age-adjusted reporting rates of general YEL adverse events, YEL-AVD and YEL-AND; and (4) comparing age-adjusted rates of adverse events after YEL to rates for other travel-related vaccines (Hepatitis A and Typhoid).

2. Methods

VAERS is a passive surveillance system for adverse events following immunization (AEFI) operated jointly by CDC and the U.S. Food and Drug Administration (FDA) [15]. It monitors vaccine safety in the U.S. and occasionally receives reports from other countries on events following administration of U.S.-licensed vaccines. Reports of serious adverse events [16] (see definition in Box 1) are followed up by telephone to obtain additional information about the event and the patient's medical history. For serious YEL AEFI reports, the follow-up is further enhanced, including presentation of case reports to the Yellow Fever Vaccine Safety Working Group for discussion about a possible causal relationship to vaccination. Also for any events similar to YEL-AVD or YEL-AND, samples of serum and/or cerebrospinal fluid are requested for YF IgM or IgG testing at CDC.

Box 1: Code of federal regulations definition of serious adverse events following immunization

Serious adverse event—any adverse experience, occurring after administration of any vaccine dose that results in any of the following outcomes

- Death
- Life-threatening illness
- Inpatient hospitalisation
- Prolongation of existing hospitalisation
- Persistent or significant disability

2.1. Source of cases and case classification

In this study, we included all VAERS reports of events following YEL vaccination during 1990–2002, in U.S. or in U.S. citizens stationed overseas. Data were stratified by military or civilian status. A report was classified as a military report if the vaccine was administered at a military clinic or vaccine was purchased with military funds. In this analysis, we categorized as "serious" all adverse events after YEL that met the regulatory definition [16] of serious (Box 1), with the exception of hospitalized cases of anaphylactic reactions because the risk associated with anaphylaxis has been studied earlier [17]. Cases of anaphylaxis were included in the "non-serious" category. Among serious reports, YEL-AVD and YEL-AND cases were identified according to criteria described in published case reports [5–7,18]. YEL-AVD is a term for multiple organ system failure after yellow fever vaccination that can include renal, hepatic, respiratory failure, myocarditis, disseminated intra-vascular coagulation. YEL-AND includes post-vaccinal encephalitis, Guillain-Barre syndrome and autoimmune disease with central or peripheral nervous system involvement following YEL administration. Data were stratified by age (1–18, 19–29, 30–39, 40–49, 50–59, 60–69, ≥70 years). The investigators that classified the cases were not blinded to their age. We had information on the number of previous YEL doses received in the past only for YEL-AVD and YEL-AND cases.

As comparison groups for our study, we used reports after receipt of two other common travel vaccines: typhoid vaccine (Typh) and hepatitis A vaccine (Hep A). For the civilian population, we selected serious AEFI after Typh reported to VAERS from 1997 to 2002 and after Hep A reported from 1995 to 1998, and calculated age-adjusted reporting rates. For military reports, age-adjusted reporting rates for YEL

were compared with those for Typh for 1998–2002 only. We did not include Hep A data after 1999 because the Advisory Committee for Immunization Practices (ACIP) made recommendations to include Hep A in the childhood immunization schedule [19] in areas with higher incidence of Hepatitis A. Thus, a large proportion of doses sold was used in children, making Hep A an inappropriate comparison to YEL. To avoid double counting, reports that indicated that Typh or Hep A were administered in combination with YEL were analyzed only in the YEL group. There were a total of 360 reports where YEL was co-administered with Typh or Hep A or with both, Typh and Hep A.

For all analyses, we excluded foreign and duplicate reports. Also excluded were three reports of co-incidental deaths caused by pre-existing underlying illness (two deaths were due to coronary failure secondary to coronary artery disease and one due to multiple myeloma) and eight YEL-reports occurring >60 days after vaccination, indicating a lack of temporal association with vaccination.

2.2. YEL AEFI reporting rates over time

To determine reporting rates of adverse events after YEL over time, we divided the number of YEL AEFI cases reported to VAERS by the number of YEL doses distributed by year. The annual number of YEL doses purchased by civilian and military providers in the U.S. from 1990 to 2002, was provided by Aventis Pasteur Inc.

2.3. Age as a risk factor

We used two strategies to examine age as a risk factor for YEL AEFI. First, we used a logistic regression model to identify the factors associated with the YEL AEFI being reported as serious versus non-serious. The model was controlled for age, sex, military status, and YEL administered alone or in combination with other vaccines.

Second, we examined age-specific reporting rates for serious AEFI following YEL and the comparison vaccines. Those rates are a proxy for the true risk. Age-specific reporting rates for serious and non-serious AEFI after YEL, Typh, and Hep A were calculated by dividing the number of AEFI reported to VAERS by the estimated number of people receiving the vaccine in each age group. Age-specific reporting rate ratios (RRR) for serious and non-serious AEFI were calculated with a reference group of 19–29-year-old vaccine recipients. Finally, we compared the YEL AEFI age-adjusted rates with those for Typh and Hep A. Finding higher rates of AEFI among age strata of recipients of YEL than among the same age groups of recipients of the comparison vaccines may suggest that YEL is associated with greater risk for some age groups.

2.3.1. Number of vaccinated civilians, YEL

Telephone surveys with health care providers indicated little or no wastage of YEL [13]; therefore, doses distributed were assumed to be a reasonable estimate of the number of persons vaccinated.

2.3.2. Number of vaccinated civilians, Typh and Hep A

Among civilians, the annual number of Typh doses distributed in the U.S., obtained from the CDC Biologics Surveillance System (personal communication, National Immunization Program, 2003), and the number of Hep A doses distributed, obtained from the manufacturers (Havrix, SmithKline Beecham; and Vaqta, Merck & Co. Inc.), was used to estimate the number of persons vaccinated. The number of doses sold was available for Typh for 1997–2002 and Hep A for 1995–1998. Based on information provided by manufacturers of Typh, it was estimated that 85% of the doses sold were administered [21]. During this period three types of Typh were available in the U.S.: an oral live-attenuated vaccine (Ty21a); a parental heat-inactivated vaccine (Typhoid vaccine), and a parental capsular polysaccharide vaccine (Typhim Vi). For Hep A, it was estimated that 10% of doses were wasted and that 50% of vaccinees received both doses in the series [13]. The total number of Hep A doses sold was reduced accordingly to estimate the total number of persons vaccinated.

2.3.3. Age distribution of civilian vaccinees

Among civilians, the number of persons that received YEL, Hep A or Typh vaccine in each age group was calculated by multiplying the estimated total number of vaccine doses administered by the proportion of persons in each age group according to a survey of the thirteen U.S.-based GeoSentinel travel clinics [13,20].

2.3.4. Number and age distribution of military vaccinees

Information on the number and age distribution of active duty military personnel who received YEL and/or Typh was obtained from the Defense Medical Surveillance System (DMSS) for 1998–2002. DMSS is a large-linked database, which includes military immunization registry data.

2.4. Statistical analysis

Confidence intervals (CI) for RRR were calculated based on standard statistical assumptions for CI for ratios of rates. Cochran-Armitage tests were conducted to examine the significance of the trend in reporting rates over time and age-specific reporting rates. An analysis of all YEL, Typh and Hep A AEFI reports was conducted using SAS version 8.2 (SAS Institute Inc., Cary, NC, USA). We used Epi-Info version 6.04 software (CDC, Stone Mountain, GA) [22] to calculate RRR and 95% CI.

3. Results

In 1990–2002, 144,072 primary adverse event reports for all vaccines used in the U.S. were submitted to VAERS.

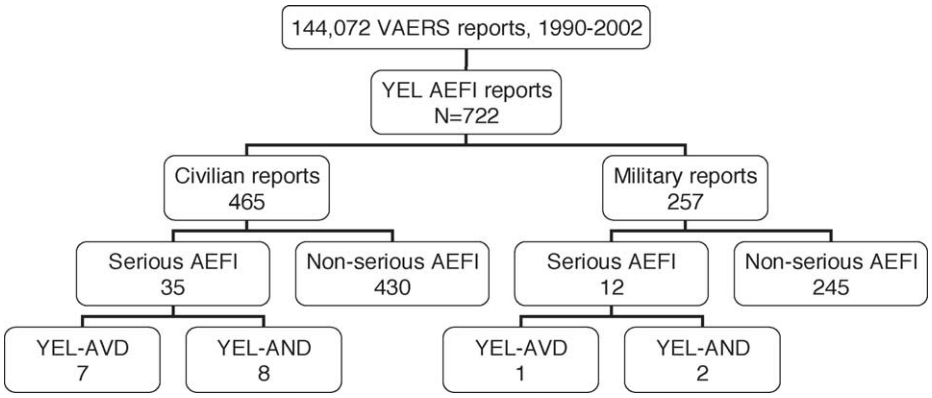

Fig. 1. Diagram of yellow fever vaccine (YEL) adverse events, 1990–2002. *N*, number of reports; VAERS, Vaccine Adverse Event Reporting System; AEFI, adverse events following immunization; YEL-AVD, yellow fever vaccine-associated viscerotropic disease; YEL-AND, yellow fever vaccine-associated neurotropic disease.

Of those, 722 (0.5%) were YEL AEFI reports that met this study's inclusion criteria. Of these, 65 reports were excluded only from the age-specific rate calculation due to missing age data. Of the 722 YEL AEFI reports, 465 (64%) were civilian reports and 257 (36%) were military reports (Fig. 1). Among civilian reports, 35 (8%) were categorized as serious, of which seven were grouped as YEL-AVD cases and eight as YEL-AND cases. Among military reports, 12 (5%) were serious, including one YEL-AVD and two YEL-AND cases. Four deaths occurred among civilian YEL-AVD cases, and one in the military; of the YEL-AND cases, all recovered without sequelae. All YEL-AVD and YEL-AND cases developed in primary yellow fever vaccinees. In 190 (26%) reports, YEL was administered alone, in 360 (50%) reports YEL was co-administered with Typh, HepA or with both of them concurrently along with other vaccines. In the military personnel, anthrax, measles-mumps-rubella, tetanus-diphtheria toxoid, influenza vaccines and many others were co-administered with YEL.

In 1990–2002, U.S. civilian providers purchased an estimated 2.2 million doses of YEL, and the military purchased 7.4 million doses. The reporting rates of serious YEL AEFI from the civilian and military sectors significantly increased over time ($p < 0.05$) (Fig. 2). Similar increases were observed for non-serious YEL AEFI. Reporting rates were higher among civilians for both non-serious and serious AEFI. The reporting rate of serious AEFI was 1.6 per 100,000 doses among civilians, and 0.2 per 100,000 doses in the military ($p < 0.05$).

In the logistic regression model decennial age groups ≥40 years were a significant risk factor for serious YEL AEFI (Table 1) (adjusted odds ratios = 3.2–17.2, $p < 0.05$). However, receiving YEL in combination with other vaccines was not a significant risk factor for developing a serious AEFI.

In the civilian population, in the reference age group (19–29 years) the reporting rate for serious YEL AEFI was

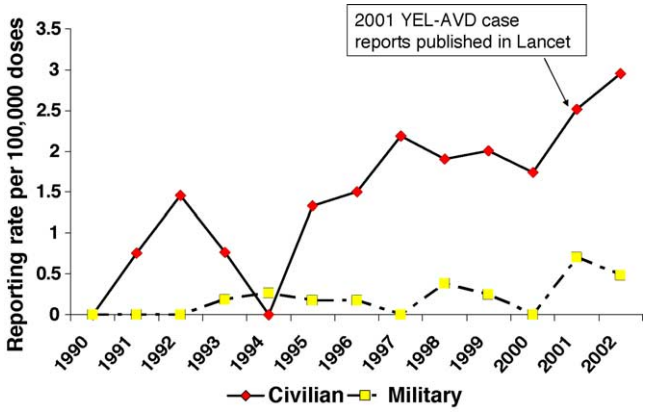

Fig. 2. Reporting rates of serious yellow fever vaccine adverse events from the civilian and military sectors, VAERS, 1990–2002. YEL-AVD, yellow fever vaccine-associated viscerotropic disease.

Table 1
Risk factors for serious adverse events following yellow fever vaccine (YEL) administration, 1990–2002

Risk factor	*N* (%) (serious)	*N* (%) (non-serious)	AOR† (95% CI)
YEL administered			
YEL alone	15 (32%)	175 (26%)	1.4 (0.7–2.7)
YEL with other vaccines	32 (68%)	500 (74%)	Ref
Military status			
Yes	12 (26%)	245 (36%)	1.4 (0.6–3.1)
No	35 (74%)	430 (64%)	Ref
Gender			
Male	25 (54%)	358 (54%)	(0.6–2.0)
Female	21 (46%)	303 (46%)	Ref
Age group (years)			
1–18	4 (8%)	78 (13%)	1.1 (0.3–3.8)
19–29	6 (13%)	205 (34%)	Ref
30–39	7 (15%)	135 (22%)	1.8 (0.6–5.7)
40–49	8 (17%)	92 (15%)	3.2 (1.1–9.8)
50–59	7 (15%)	57 (9%)	4.1 (1.2–14.1)
60–69	8 (17%)	27 (4%)	12.2 (3.6–41.7)
≥70	7 (15%)	16 (3%)	17.2 (4.7–63.0)

CI, confidence intervals; Ref, reference group; AOR†, adjusted odds ratio, logistic regression model.

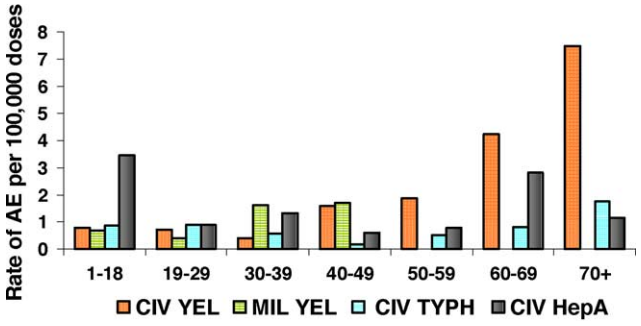

Fig. 3. Reporting rates of serious adverse events (AE) after yellow fever (CIV YEL, 1990–2002), Typhoid (CIV TYPH, 1997–2002) and Hepatitis A (CIV Hep A, 1995–1998) vaccines in U.S. civilians and military (MIL YEL, 1998–2002). CIV, civilian; MIL, military; YEL, yellow fever vaccine; TYPH, typhoid vaccine; Hep A, hepatitis A vaccine.

0.7 per 100,000 doses (Table 2), and it increased significantly for persons ≥60 years of age ($p < 0.0001$). Overall, among civilian vaccinees aged ≥60 years, the estimated reporting rate of serious AEFI was 5.3 per 100,000 vaccinations, risk of YEL-AVD was 1.8 per 100,000 and of YEL-AND 1.4 per 100,000 vaccinations. Compared with the reference group, the reporting rate ratio (RRR) for serious AEFI for those 60–69 years of age was 5.9 (95% CI 1.6–22.2); for those ≥70 years of age, it was 10.4 (95% CI 2.7–40.2). The results remained significant when only reports of AEFI after YEL administered alone were analyzed. When the analysis was restricted to vaccinees that developed YEL-AVD or YEL-AND, the pattern was similar to the RRR for serious YEL AEFI (Table 2). Compared with the reference group, the RRR for YEL-AVD for those 60–69 years of age was 4.4 (95% CI 0.4–48.7); for those ≥70 years of age, it was 13.4 (95% CI 1.4–128.5). There was an increase in RRR for YEL-AND in age groups 60–69 years and ≥70 years of age but it was not significant ($p > 0.05$) (Table 2).

In the military population, the age-specific reporting rates for serious YEL AEFI were similar to those in civilians (Table 3). There were no serious YEL AEFI reports for persons ≥50 years of age. There was no trend of serious AEFI reporting rates with increasing age ($p > 0.1$) (Fig. 3).

From 1995 to 1998, it was estimated that 3.2 million doses of Hep A were administered in the civilian population, and 44 serious AEFI reports were submitted to VAERS. The reporting rate for serious AEFI in vaccinees 60–69 years of age was 2.8 per 100,000 persons vaccinated. However, there was no significant consistent increase in the reporting rate of serious AEFI for older age groups ($p > 0.05$) as found for YEL (Fig. 3).

From 1997 to 2002, an estimated 3.2 million Typh doses were administered among civilians. Of all the Typh AEFI reports, 63% were after Typhim Vi, 16% after Ty21a, 7% after whole cell Typhoid vaccine and 14% with unknown manufacturer. During that period, 21 serious Typh AEFI reports were submitted to VAERS. The reporting rate for serious AEFI in those 60–69 years of age was 0.8 per 100,000. As with Hep

Table 2
Reporting rates and reporting rate ratios for yellow fever vaccine adverse events, yellow fever vaccine-associated viscerotropic and neurotropic disease by age in the civilian sector, 1990–2002

Age (years)	Number of YEL[a] doses	Number of Ser. AEFI[b]	Ser AEFI[b] reports/100,000 doses	RRR[c] (95% CI)	Number of YEL-AVD[d]	YEL-AVD[d] reports/100,000 doses	RRR[c] (95% CI)	Number of YEL-AND[e]	YEL-AND[e] reports/100,000 doses	RRR[c] (95% CI)
1–18	262852	2	0.8	1.1 (0.2–6.3)	0	0	Undef	1	0.4	0.9 (0.1–9.3)
19–29	416908	3	0.7	Ref	1	0.2	Ref	0	0	Undef
30–39	505685	2	0.4	0.6 (0.1–3.3)	0	0	Undef	0	0	Undef
40–49	444324	7	1.6	2.2 (0.6–8.5)	0	0	Undef	2	0.5	Ref
50–59	318556	6	1.9	2.6 (0.7–10.5)	1	0.3	1.3 (0.1–20.9)	1	0.3	0.7 (0.1–7.7)
60–69	188870	8	4.2	5.9 (1.6–22.2)	2	1.1	4.4 (0.4–48.7)	3	1.6	3.5 (0.6–21.1)
≥70	93565	7	7.5	10.4 (2.7–40.2)	3	3.2	13.4 (1.4–128.5)	1	1.1	2.4 (0.2–26.2)
Total	2230760	35	1.6		7	0.3		8	0.4	

CI, confidence intervals; Undef, undefined; Ref, reference.
[a] YEL, yellow fever vaccine.
[b] Ser AEFI, serious adverse events following immunization.
[c] RRR, reporting rate ratio.
[d] YEL-AVD, yellow fever vaccine-associated viscerotropic disease.
[e] YEL-AND, yellow fever vaccine-associated neurotropic disease.

Table 3
Reporting rates and reporting rate ratios for yellow fever and typhoid vaccine adverse events by age in the U.S. military, 1998–2002

Age (years)	Number of doses	Number of Ser AEFI[a]	Ser AEFI[a] reports/100,000 doses	RRR[b] (95% CI)
Yellow fever vaccine				
17–18	148776	1	0.7	1.8 (0.2–19.3)
19–29	519908	2	0.4	Ref
30–39	185765	3	1.6	4.2 (0.7–25.1)
40–49	58984	1	1.7	4.4 (0.4–48.6)
≥50	13552	0	0	0
Total	926985	7	0.8	
Typhoid vaccine				
17–18	78916	1	1.3	4.3 (0.4–40.9)
19–29	1007770	3	0.3	Ref
30–39	498458	4	0.8	2.7 (0.6–12.0)
40–49	164567	1	0.6	2.0 (0.2–19.6)
≥50	38154	1	2.6	8.8 (0.9–84.6)
Total	1787865	10	0.6	

CI, confidence intervals; Ref, reference.
[a] Ser AEFI, serious adverse events following immunization.
[b] RRR, reporting rate ratio.

A, there was no significant increase for serious Typh AEFI for each older age group ($p > 0.1$), and although recipients ≥70 years of age had a higher reporting rate, it was not significantly different from those aged 19–29 years (RRR = 2.0, 95% CI 0.4–10.3) (Fig. 3). There was no significant increase in reporting rates of serious AEFI after Typh by age in the military ($p > 0.1$) (Table 3).

4. Discussion

Next to smallpox vaccine, YEL has been in use the longest among the live viral vaccines. While YEL had the reputation of being extremely safe [1], its safety profile now needs to be updated. Two serious and frequently fatal AEFIs mimicking wild YF disease, YEL-AVD and YEL-AND, have been newly recognized as clinical entities [5–7,11,18]. In this extended U.S. study based on 12 years of VAERS data, we confirmed that the relative risks of serious YEL AEFI are higher in persons of advanced age. We used YEL AEFI data from civilians and, for the first time, military service members' reports. In addition, we were able to estimate the minimal risk of YEL-AVD and YEL-AND based on passive surveillance.

We determined that advanced age is a risk factor for serious YEL AEFI from multiple lines of evidence. Using logistic regression, we found an increase in the reporting rate of serious YEL AEFI in all age groups ≥40 years, with a significant increase in reporting rates in persons ≥60 years of age. In the civilian population, using age-adjusted reporting rate calculations, we also identified a significant increase in the rate of serious YEL AEFI in persons aged ≥60 years and of YEL-AVD in those ≥70 years of age. The reporting rates of YEL-AND also increased for persons aged ≥60 years, although not significantly. In the military, we were not able to see the effect of advanced age on serious YEL AEFI because the age of its population is typically 17–50 years.

In contrast, no significant increases in reporting rates of serious AEFI in older age groups were found for two other travel vaccines, Hep A and Typh. This suggests that the higher reporting rate of serious YEL AEFI in persons of advanced age is real and not an artifact associated with passive surveillance. The increased rate of serious YEL AEFI is biologically plausible, as there is an increased risk of developing serious illness in persons of older age after the wild YF virus infection [23].

During 1990–2002, overall YEL AEFI reporting rates to VAERS increased both in the civilian and military populations. The reporting patterns of AEFI from the military are different from those in the civilian sector. Until 1999, YEL AEFI reports submitted from the military tended to include primarily serious reports, because the regulations [4] that mandated reporting of AEFI [16] did not emphasize reporting of non-serious events. The increase in reporting rates in the military corresponds to the changes in policy of reporting AEFI related to the use of anthrax vaccine, when all AEFI were encouraged to be reported to VAERS [24].

The military reporting rates over time are underestimates due to the large difference between doses purchased and administered. For calculation of these rates, we used denominator provided by the vaccine manufacturer. However, for the last 4 years, we saw the difference between these data and immunizations received that were captured in DMSS. The reporting rates of serious AEFI in the military for the age 17–49 years are comparable with those in civilian population in the same age deciles. The data presented in Tables 2 and 3 and Fig. 3, support the presence of age confounding in the military. More than 98% of military vaccinations occur among persons aged <50 years, the point at which the reporting rates for serious YEL AEFI in the civilian population begin to increase significantly. The military purchases more YEL doses, but the total number of AEFI reports and overall reporting rates for YEL are lower than in the civilian sector. However, it is still a substantial contribution to YEL AEFI reporting.

This study has several limitations. First, VAERS has methodological limitations inherent to passive surveillance systems, such as underreporting, incomplete reporting and lack of consistent diagnostic criteria [25]. Thus, the estimates of events obtained from VAERS may underestimate the true rates of serious YEL AEFI. Second, using other sources to obtain an overall number of persons vaccinated may lower the risk estimates. The number of people receiving vaccine in the military was obtained from DMSS. However, it may under-represent some of the branches (e.g., Navy and Army) due to the differences in reporting to DMSS. For civilians, we used doses sold as an estimate for doses administered, which is likely to be an overestimate. Third, the 1998 GeoSentinel survey [13], used to estimate the number of doses of vaccine administered in each age group, has the following limitations: children might have been underrepresented and the age distri-

bution of travelers receiving YEL could have changed over time. The number of elderly travelers may have increased, since 1998. If this is true, then we might have overestimated the RRR for the elderly.

Our study emphasizes the need for travelers and physicians to be educated on the risks and benefits of YEL vaccinations. The CDC has developed a yellow fever vaccine information sheet. The FDA and the U.S. vaccine manufacturer have revised the package insert to caution yellow fever vaccination of older age groups [26]. The majority of the YEL-AVD and YEL-AND cases have been published in the scientific literature [5–7]. Most challenging, however, is the continual need to better educate physicians to weigh the risks and benefits of YEL vaccination in older travelers. In doing so, there are five basic actions: assessing baseline health, reviewing intended journey itinerary, assessing disease exposure risk, deciding upon and administering vaccines, and educating on disease prevention and health maintenance [27]. Health care providers may wish to consider a medical waiver for those travelers who have contraindications to yellow fever vaccine but require documentation of vaccination for entry purposes.

The true risk of getting YF disease for a traveler is unknown and depends on the country, area in the country, season and YF virus activity. An estimate of the risk of getting YF illness for unvaccinated traveler to YF-endemic areas in Africa is 1/4,200 (23.8 per 100,000 per week) and 1/280 (357 per 100,000 per week) for YF epidemic areas in Africa [28]. These estimates are based on research in indigenous populations and might overestimate the risk of illness in a traveler. Based on data from U.S. travelers, the risk of YF disease in a traveler has been estimated to be 0.4–4.3 cases per million travelers to YF-endemic countries [3]. Unfortunately, in our study, we likely underestimate the true risk of serious YEL AEFI due to underreporting inherent in passive surveillance. Nevertheless, these data suggest this risk is $\geq$1.6 per 100,000 vaccinations, the risk of developing YEL-AVD or YEL-AND are $\geq$0.3 per 100,000. In vaccinees $\geq$60 years of age, the risk of serious AEFI increases to $\geq$5.3 per 100,000 and of YEL-AVD $\geq$1.8 per 100,000 vaccinations. All the cases of YEL-AVD and YEL-AND reported to this date occurred in primary yellow fever vaccinees. Although the true risk for travelers is unknown, YEL is beneficial for prevention of YF disease with a mortality rate of 20–50% [28]. It is critical to emphasize that this risk-benefit analysis is limited to travelers moving from low or no risk areas to YF-endemic or epidemic areas and does not apply to natives living in areas of YF transmission for whom the benefits of YEL clearly outweigh the risks. However, for individuals, especially older persons, it is important to weigh the potential risk of developing systemic illness after YEL and the choice of making a trip to YF-endemic area.

YF is a serious and potentially fatal disease. YEL vaccine is highly efficacious and rarely causes serious AEFI [1–2]. There is a need to continue to vaccinate travelers that are going to YF-endemic areas. The data from this study emphasize the importance of carefully screening travel itineraries, particularly of older travelers, and vaccinating only those traveling to YF-endemic or epidemic areas.

Physicians should work with travelers to ensure that they understand the risk and benefit of YEL vaccination. Travelers who opt against vaccination need to be counseled thoroughly by their physician on alternative precautions (e.g., use of DEET, bed nets, appropriate clothing) to prevent mosquito bites. Further studies are underway in the U.S. to improve the estimate of the true risk of serious and systemic YEL AEFI.

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