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Adverse event reports following yellow fever vaccination

Nicole P. Lindsey[a,*], Betsy A. Schroeder[b], Elaine R. Miller[c], M. Miles Braun[d], Alison F. Hinckley[a], Nina Marano[b], Barbara A. Slade[c], Elizabeth D. Barnett[e], Gary W. Brunette[b], Katherine Horan[b], J. Erin Staples[a], Phyllis E. Kozarsky[b,f], Edward B. Hayes[a]

[a] Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, United States
[b] Division of Global Migration and Quarantine, National Center for Preparedness, Detection, and Control of Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States
[c] Immunization Safety Office, Office of the Chief Science Officer, Centers for Disease Control and Prevention, Atlanta, GA, United States
[d] Division of Epidemiology, Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, United States
[e] Clinical Immunization Safety Assessment Center, Maxwell Finland Laboratory for Infectious Diseases, Boston Medical Center, Boston, MA, United States
[f] Department of Medicine, Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA, United States

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ABSTRACT

Yellow fever (YF) vaccine has been used for prevention of YF since 1937 with over 500 million doses administered. However, rare reports of severe adverse events following vaccination have raised concerns about the vaccine's safety. We reviewed reports of adverse events following YF vaccination reported to the U.S. Vaccine Adverse Event Reporting System (VAERS) from 2000 to 2006. We used estimates of age and sex distribution of administered doses obtained from a 2006 survey of authorized vaccine providers to calculate age- and sex-specific reporting rates of all serious adverse events (SAE), anaphylaxis, YF vaccine-associated neurotropic disease, and YF vaccine-associated viscerotropic disease. Reporting rates of SAEs were substantially higher in males and in persons aged ≥60 years. These findings reinforce the generally acceptable safety profile of YF vaccine, but highlight the importance of physician and traveler education regarding the risks and benefits of YF vaccination, particularly for travelers ≥60 years of age. Vaccination should be limited to persons traveling to areas where the risk of YF is expected to exceed the risk of serious adverse events after vaccination, or if not medically contraindicated, where national regulations require proof of vaccination to prevent introduction of YF.

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1. Introduction

Yellow fever (YF) vaccine is a live attenuated vaccine that has been used for over seven decades. The U.S. Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) recommend vaccination for travelers aged 9 months and older who are at risk for yellow fever because of travel to endemic areas of South America or Africa [1]. The only YF vaccine currently licensed for use in the United States is YF-VAX®, manufactured by sanofi pasteur (Swiftwater, Pennsylvania).

Adverse reactions to YF vaccine, which are typically mild, may include headache, myalgia, low-grade fever, and discomfort at the injection site [2]. In clinical trials, mild adverse events were reported by about 25% of vaccinees [1,3–5]. Severe reactions to YF vaccine are rare. Anaphylactic reactions (severe allergic reactions with multisystem organ involvement) have been estimated to occur in 0.8 per 100,000 vaccinations, most often among persons with allergies to eggs or other vaccine constituents, such as gelatin [6]. YF vaccine-associated neurotropic disease (YF-AND), which may include post-vaccinal encephalitis, Guillain–Barré syndrome, and autoimmune disease with central or peripheral nervous system involvement, is estimated to occur in approximately 0.4 per 100,000 vaccinations [7]. YF vaccine-associated viscerotropic disease (YF-AVD), a disease clinically resembling naturally acquired YF, is estimated to occur in approximately 0.3 per 100,000 vaccinations [7]. Advanced age and history of thymus disease have been identified as risk factors for systemic adverse events following YF vaccination [7–10].

* Corresponding author at: Division of Vector-Borne Infectious Diseases, National Center for Zoonotic, Vector-Borne, and Enteric Diseases, Centers for Disease Control and Prevention, 3150 Rampart Road, Fort Collins, CO 80521, United States. Tel.: +1 970 266 3595; fax: +1 970 266 3568.
E-mail address: nplindsey@cdc.gov (N.P. Lindsey).

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Previous estimates of the age-specific risks of adverse events following YF vaccination have been based on reports to the U.S. Vaccine Adverse Event Reporting System (VAERS) and the age distribution of vaccine recipients from 13 U.S.-based travel clinics in 1998 [7,8]. There has been speculation that the age distribution of YF vaccine recipients may have changed since that time to include a larger percentage of travelers ≥60 years of age [7]. Additionally, children were under-represented in the travel clinics surveyed in 1998 [8]. Sex-specific risks have not been previously estimated due to lack of data describing the sex distribution of vaccinees. In this paper, we describe adverse events reported to VAERS following YF vaccination from 2000 through 2006 and estimate age and sex-specific reporting rates of serious adverse events using age and sex distributions of administered doses obtained from a survey of authorized YF vaccine providers in 2006.

2. Materials and method

2.1. VAERS

VAERS is a passive surveillance system for adverse events following immunization operated collaboratively by the CDC and the U.S. Food and Drug Administration (FDA) [11,12]. Adverse event reports can be submitted to VAERS from a variety of sources, including vaccine providers and recipients, medical practitioners, and manufacturers. VAERS reports are routinely classified as serious or non-serious, with serious adverse events (SAE) being defined as events in which one of the following outcomes are reported: death, life-threatening illness, hospitalization, prolongation of an existing hospitalization, permanent disability, or other medically important condition. Reports of SAEs are routinely followed up to obtain additional information about the event. Causality of individual adverse events following vaccination usually cannot be determined from the VAERS report alone. It is important to consider the biologic plausibility that reported adverse events could be caused by the vaccine components and whether other contributing factors (such as concurrent illness or medications) might have caused the adverse events. We did not attempt to determine causality for reported adverse events except for evaluation of possible YF-AVD and YF-AND as described below.

2.2. Report selection and case classification

The VAERS database was searched for reports following YF vaccination (given alone or at the same time as other vaccinations). All reports of adverse events following YF vaccinations among civilians in the U.S. reported from 2000 to 2006 with symptom onset during that period were included, except for seven reports in which the adverse event occurred more than 60 days after vaccination. Sixty days was chosen as the longest plausible time that an adverse event associated with a live vaccine is likely to occur. Adverse events reported following administration of vaccine by military organizations were excluded because of potential differences in reporting of adverse events and the different demographics of the military compared with the civilian population. Reports were considered to have originated from military service members if the VAERS report indicated that the vaccine was purchased with military funds or was administered at a military clinic. We reviewed the age and sex of persons with adverse events, the reported signs, symptoms and conditions (using standard coding terms), number of days from vaccination to onset of symptoms, and outcome (as documented on the VAERS report) of the adverse events. Cases of anaphylaxis were identified by reviewing adverse event coding terms for previously described criteria of anaphylaxis as follows: reports were classified as probable anaphylactic reactions if the reaction occurred within 4 h of vaccine administration and included at least one dermatologic symptom coding term (urticaria, flushing, angioedema, pruritis, rash) and at least one respiratory symptom coding term (dyspnea, bronchospasm, pharyngeal edema, wheezing, throat tightness, dysphonia) [6]. In addition, the case definition for anaphylaxis developed by the Brighton Collaboration was also used [13]. However, to allow for comparison with previously published reports of anaphylaxis following YF vaccine administration, the former definition was used in the bulk of this paper, except where otherwise noted. Reports were not classified as anaphylactic reactions in instances where the VAERS report was coded as anaphylaxis without sufficient description of the event to meet the above criteria (i.e. specific symptoms or onset interval were not reported). There were only 2 such reports. In June 2002, CDC

Table 1
Characteristics of persons having an adverse event reported to VAERS following administration of yellow fever (YF) vaccine from 2000 to 2006.

	Reported events following YF vaccine given in combination (*N* = 470)	Reported events following YF vaccine given alone (*N* = 190)	All reported events following YF vaccine (*N* = 660)
Male[a] (%)	189 (41)	71 (37)	260 (39)
Age[b] (%)			
≤18 years	49 (11)	22 (12)	71 (11)
19–29 years	112 (25)	47 (26)	159 (25)
30–39 years	88 (20)	32 (17)	120 (19)
40–49 years	71 (16)	23 (13)	94 (15)
50–59 years	64 (14)	28 (15)	92 (15)
60–69 years	44 (10)	18 (10)	62 (10)
70 + years	22 (5)	13 (7)	35 (6)
Median age (range)	36 (4–88)	35 (2-85)	36 (2-88)
Median days to onset (range)[c]	1 (0–50)	1 (0-24)	1 (0-50)
Serious adverse events (%)[d]	48 (10)	24 (13)	72 (11)
Death	3 (0.6)	1 (0.5)	4 (0.6)
Life threatening illness	14 (3)	7 (4)	21 (3)
Hospitalization	37 (8)	21 (11)	58 (9)
Prolongation of hospitalization	4 (0.9)	1 (0.5)	5 (0.8)
Permanent disability	7 (1)	0 (0)	7 (1)

[a] Sex unknown for 8 events.
[b] Age unknown for 27 events.
[c] Days to onset unknown for 38 events.
[d] 23 events met more than one 'serious' criteria.

Table 2
Most commonly reported adverse event coding terms following YF vaccination, 2000–2006[a]

All AE (n = 660)	Number (%)	Male (n = 268)	Number (%)	Female (n = 392)	Number (%)
Pyrexia	150 (23)	Pyrexia	72 (27)	Pyrexia	78 (20)
Pain	99 (15)	Headache	50 (19)	Injection site erythema	70 (18)
Pruritus	98 (15)	Pain	38 (14)	Pruritus	68 (17)
Headache	96 (15)	Urticaria	31 (12)	Pain	61 (16)
Injection site erythema	88 (13)	Pruritus	30 (11)	Rash	49 (13)
Urticaria	80 (12)	Dyspnea	25 (9)	Urticaria	49 (13)
Rash	71 (11)	Chills	24 (9)	Headache	46 (12)
Nausea	59 (9)	Asthenia	23 (9)	Nausea	40 (10)
Dizziness	52 (8)	Fatigue	23 (9)	Dizziness	35 (9)
Dyspnea	48 (7)	Myalgia	22 (8)	Injection site swelling	30 (8)

[a] 560 (85%) of reported events included multiple coding terms.

convened a Yellow Fever Vaccine Safety Working Group (YFWG) composed of academicians, clinicians, representatives of vaccine manufacturers, and U.S. government epidemiologists to review surveillance data for serious adverse events after YF vaccination. The YFWG used a consensus process to classify cases as YF-AND and YF-AVD for surveillance purposes [14]. The YFWG has reviewed and classified reports of serious adverse events reported to VAERS since 1996. Current and former members of the YFWG are listed in the acknowledgements. Representatives of vaccine manufacturers did not participate directly in the classification of cases.

2.3. Denominator data

The number of YF-VAX® doses purchased by civilian providers each year from 2000 to 2006 was obtained from the manufacturer, sanofi pasteur. Previously conducted telephone interviews with healthcare providers have indicated little or no wastage of YF vaccine, which is predominately sold in single-dose vials to civilian providers [8]. Therefore, the number of doses sold was assumed to be a reasonable estimate of the number of doses administered.

Approximately 3400 U.S. healthcare providers are authorized to administer yellow fever vaccine. Contact information for these authorized providers was obtained from the U.S. Yellow Fever Vaccination Center Registry, a web-based directory maintained by CDC. All 2941 authorized providers who provided an email address in the registry were surveyed by email to determine the total number of YF vaccine doses administered in 2006 and the date of birth (or age) and sex of each vaccinee. Overall, 1066 clinics responded to the survey, accounting for 95,828 doses (48%) of the approximately 200,000 doses administered to the civilian population in 2006. However, only 77,137 of these had age of vaccinee reported and 76,903 had sex of vaccinee reported, accounting for about 39% of the total number of doses distributed. The number of persons who received YF vaccine by age group and sex per year in the U.S. was estimated by multiplying the estimated total doses distributed each year by the proportion of vaccine recipients in each age and sex group as determined from this survey.

2.4. Data analysis

Sex- and age-specific adverse event reporting rates were calculated for SAEs and non-serious adverse events, YF-AND, and YF-AVD

Table 3
Symptoms and time to onset of probable cases of anaphylaxis following YF vaccination

Case number	Dermatologic symptoms	Respiratory symptoms	Time to onset
1	Urticaria	Dyspnea	15 min
2	Rash	Dyspnea, pharyngeal edema	2 h
3	Pruritus	Wheezing, throat tightness	15 min
4	Urticaria, pruritus	Throat tightness	1 h
5	Urticaria, pruritus	Throat tightness	50 min
6	Urticaria	Dyspnea	1 h
7	Flushing	Wheezing	30 min
8	Urticaria	Throat tightness	1 h
9	Urticaria	Dyspnea	45 min
10	Urticaria, rash, pruritus	Dyspnea	30 min
11	Rash	Dyspnea	Same morning
12	Urticaria	Dyspnea, wheezing	45 min
13	Pruritus	Dyspnea	1 h
14	Pruritus	Dyspnea	25 min
15	Urticaria	Dyspnea, throat tightness	30 min
16	Urticaria	Dyspnea	45 min
17	Flushing	Wheezing	15 min
18	Rash	Dyspnea, wheezing	1 h
19	Rash, pruritus	Dyspnea	1 h 30 min
20	Urticaria	Dyspnea, throat tightness	1 h
21	Urticaria, pruritus	Dyspnea	2 h
22	Urticaria	Wheezing	1 h
23	Urticaria	Wheezing, throat tightness	45 min
24	Urticaria, pruritus	Dyspnea	45 min
25	Urticaria	Dysphonia	15 min
26	Urticaria	Dyspnea	15 min
27	Rash	Wheezing	40 min
28	Urticaria	Wheezing	3 h

Table 4
Reporting rates per 100,000 doses administered for adverse events in civilians following YF vaccination, 2000–2006

	Estimated YF doses	All AE ($n=660$)	NSAE[a] ($n=588$)	SAE[b] ($n=72$)	Anaphylaxis ($n=28$)	YF-AND[c] ($n=12$)	YF-AVD[d] ($n=6$)
Sex							
Male	743,305	35	29.1	5.9	2.3	1.2	0.7
Female	790,865	49.6	46	3.5	1.3	0.4	0.1
Age							
≤18	178,454	39.8	35.3	4.6	3.4	1.1	0
19–29	389,018	40.9	36.8	4.1	3.1	0.3	0.5
30–39	210,545	57	53.2	3.8	4.3	0.5	0
40–49	223,233	42.1	37.6	4.5	0.0	0.9	0
50–59	254,719	36.1	33.4	2.7	0.4	0.4	0
60–69	191,025	32.5	26.2	6.3	0.0	1.6	1
70+	87,177	40.1	27.5	12.6	0.0	2.3	2.3
Total	1,534,170	43	38.3	4.7	1.8	0.8	0.4

[a] Non-serious adverse events.
[b] Serious adverse events (one of the following outcomes: death, life-threatening illness, hospitalization, prolongation of an existing hospitalization, permanent disability; includes YF-AND and YF-AVD).
[c] Yellow fever vaccine-associated neurotropic disease.
[d] Yellow fever vaccine-associated viscerotropic disease.

per 100,000 doses distributed. Analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC).

3. Results

From 2000 to 2006, 660 adverse events following YF vaccine administration that met the inclusion criteria for this study were reported to VAERS. Overall, 627 (95%) of these events were reported to have occurred following primary YF vaccination; 33 (5%) occurred in repeat vaccinees. The majority of reported events occurred in females (61%) and in persons aged 19–49 years (Table 1). Adverse events occurred within a median of 1 day after vaccination (range 0–50 days), and 60% occurred within 2 days of vaccination. The most commonly reported adverse event coding terms included fever, pain, pruritus, headache, injection site erythema, urticaria, rash, nausea, dizziness, dyspnea, and fatigue (Table 2). Local inflammatory events accounted for a larger proportion of the adverse events reported by females than by males. Most of the events (71%) occurred after administration of YF vaccine given at the same time as one or more additional vaccines; 29% of events occurred after YF vaccine given alone. Age and sex distributions for events reported after YF vaccination given alone were similar to those reported after YF given in combination with other vaccines (Table 1). Seventy-two reported events (11%) were classified as SAEs, including 12 YF-AND cases, 6 YF-AVD cases, and 4 deaths (2 of the 4 deaths were classified as YF-AVD). All but 3 of the SAEs occurred following primary vaccination; all YF-AVD and YF-AND cases occurred in primary YF vaccinees.

Twenty-eight reported events were classified as probable anaphylactic reactions (Table 3). These events occurred in individuals aged 6–55 years (median 23 years) and resulted in 22 emergency room visits and 2 hospitalizations. Sixteen (64%) reports stated that anaphylaxis symptoms began less than 1 hour after vaccination. All the probable anaphylactic reactions occurred after primary vaccination, with the exception of three reports that did not list a dose number. Co-administration with at least one other vaccine was described in 20 (71%) of the 28 event reports. Co-administered vaccines included hepatitis A vaccine (12), typhoid vaccine (9), hepatitis B virus vaccine (4), inactivated poliovirus vaccine (4), meningococcal polysaccharide vaccine (3), measles/mumps/rubella virus vaccine (2), and tetanus/diphtheria toxoids vaccine (2). When the Brighton anaphylaxis case definition was applied, 33 reports met the criteria for either Level 1 or Level 2 of diagnostic certainty.

The overall reporting rate of any adverse event following YF vaccination was 43 per 100,000 doses distributed and that of all SAEs was 4.7 per 100,000 (Table 4). The reporting rate of YF-AND was 0.8 per 100,000, and of YF-AVD was 0.4 per 100,000 doses. The reporting rate for anaphylaxis was 1.8 per 100,000 doses distributed (2.2 per 100,000 when the Brighton case definition was applied). Among vaccinees aged ≥60 years, the reporting rates of SAEs, YF-AND and YF-AVD were 8.3 per 100,000, 1.8 per 100,000, and 1.4 per 100,000, respectively. The reporting rates of SAEs, YF-AND and YF-AVD were highest among those ≥70 years. However, the rate of anaphylaxis was higher among younger age groups (Table 4). Although the reporting rate of all adverse events was higher in females than in males, the reporting rate of SAEs, YF-AND, YF-AVD and anaphylaxis were higher among males. The reporting rate of SAEs was consistently higher among males in all age groups.

4. Discussion

Most of the adverse events following YF vaccination reported to VAERS from 2000 to 2006 were mild and self-limited, with fever, pain, pruritus, headache, injection site erythema, urticaria, and rash being among the most commonly reported events. The higher reporting rate of adverse events in females and preponderance of local inflammatory events after YF vaccination are similar to what has been described in VAERS reports after other vaccinations [15], but the reason for this sex difference is unknown. Female sex has also been associated with an increased risk of local adverse reactions with influenza [16–18], pneumococcal [19], and anthrax [20] vaccines. The higher reporting rate of SAEs among males and persons aged ≥70 years is biologically plausible, given that some previous reports and studies have shown that naturally acquired YF is more likely to be severe and fatal among males and elderly persons [2,21,22]. It is notable that several reports of YF-AVD have occurred among females under 30 years of age [23–26]. In fact, of the 27 YF-AVD published cases identified worldwide (with age and sex data), 75% of cases under age 40 were female, compared to 11% of cases ≥40 years [10,23–39]. In the data analyzed in this study, however, the risk of SAEs was higher for males than females in all age groups.

The reporting rates for SAEs and anaphylaxis calculated in this study are higher than those previously reported. Khromava et al. (2005) estimated the risk of any SAE following YF vaccination as 1.6 per 100,000 doses (4.2 per 100,000 doses for those aged 60–69

years, and 7.5 per 100,000 doses for those ≥70 years), compared with the 4.7 per 100,000 doses calculated in our study (6.3 per 100,000 doses for those aged 60–69 years, and 12.6 per 100,000 doses for those ≥70 years) [7]. The risk of SAE for two other travel vaccines, hepatitis A and typhoid, has been estimated at 1.4 and 0.7 per 100,000 doses respectively [7]. Khromava et al. used the regulatory definition for SAE (as was done in this analysis) with an additional exclusion criterion; hospitalized cases of anaphylactic reactions were not considered serious. Applying this additional exclusion criterion to our analysis decreased the risk of SAE to 4.4 per 100,000 doses. Kelso et al. [6] estimated 0.8 anaphylactic reactions per 100,000 doses distributed, with probable cases accounting for only 0.4 anaphylactic reactions per 100,000 doses, compared with the 1.8 per 100,000 estimated in our analysis [6]. In order to compare the rates of anaphylaxis following yellow fever vaccine over time, we focused on the definition of anaphylaxis previously described by Kelso et al. [6]. However, when we applied the Brighton case definition for anaphylaxis to these data the estimated reporting rate was further increased. The higher risk found in this study for SAEs and anaphylactic reactions might be at least partially due to increased adverse event reporting following CDC's initiation of enhanced surveillance for adverse events following YF vaccination in 2001. Reporting rates of YF-AND and YF-AVD reported here are comparable with those previously reported [7,40].

The risk of acquiring YF for any given traveler is unknown and depends on a number of factors including destination, season, local YF virus activity, and occupational and recreational activities while traveling [40]. The risk of YF in an unvaccinated traveler to endemic areas in West Africa during the highest risk season has been estimated to be 50 per 100,000 for a 2-week stay, 10 times the risk for travelers to South America (5 per 100,000 travelers) [41]. The overall risk of YF in all U.S. travelers has been estimated to be 0.05–0.5 per 100,000 travelers to endemic areas [40]. For any traveler, the risk of SAEs should be balanced against the risk of acquiring YF. Vaccination should be limited to travelers with itineraries that present a risk of yellow fever that is reasonably expected to exceed the risk of a severe adverse event after vaccination, or for which vaccination is required to prevent introduction of YF.

This study has several limitations. Because VAERS is a passive surveillance system, adverse events are likely underreported. The reporting sensitivity of VAERS is unknown, but has been shown to increase with the severity of the adverse event [42]. VAERS reports are also subject to coding errors. Because reports can be filed by a number of different sources, including vaccinees and their family members, the accuracy and completeness of the information provided in VAERS reports is variable. Most of the adverse events reported following YF vaccination (71%) occurred following receipt of multiple vaccines. At least some of these adverse events may actually be reactions to other vaccines or some combination thereof. Age and sex distributions of individuals with adverse events following YF vaccine administered in combination with other vaccines and those following YF vaccine administered alone were similar. However, we are unable to calculate the reporting rate of serious adverse events among persons receiving YF vaccine given alone due to lack of availability of denominator data for administration of multiple versus single vaccines.

Although previously conducted surveys of YF vaccine providers have indicated little wastage of vaccine, the number of doses sold might overestimate the number of doses administered, leading to an underestimate of the risk of adverse events. The estimated age distribution of all civilian vaccinees from 2000 to 2006 was determined by data available for approximately 39% of persons vaccinated in 2006. Whether these data are generalizable to all persons vaccinated in 2006 is not known. Despite this limitation, since the data come from more than 1000 clinics, we think that these estimates are more accurate that those used in previous studies, which were based on a 1998 survey of 13 travel clinics [8]. Annual reports published by the International Trade Administration (ITA) indicate that the proportion of travelers' aged ≥ 65 years has increased from 7.8% in 2003 to 10.2% in 2006 (U.S. Department of Commerce, ITA, 2006). This increase in proportion of elderly travelers over the time period of the adverse event reports examined in this study could have caused us to underestimate the reported incidence of adverse events in this age group.

These findings reinforce the generally acceptable safety profile of YF vaccine but highlight the importance of physician and traveler education regarding the risks and benefits of YF vaccination, particularly for elderly travelers. Travel itineraries should be carefully considered and vaccination should be limited to persons traveling to areas where the risk of YF is expected to exceed the risk of SAE after vaccination, or where national regulations require proof of vaccination to avoid introduction of YF. Before vaccination is given solely to meet travel regulations, particular care should be taken to assess any underlying risk factors that might predispose to adverse events following vaccination and that could warrant a medical waiver to vaccination. This paper reinforces the recommendation that travelers ≥60 years of age should discuss with their physicians the risks and benefits of vaccination in the context of their destination-specific risk for exposure to YF.

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References

[1] Cetron MS, Marfin AA, Julian KG, Gubler DJ, Sharp DJ, Barwick RS, et al. Yellow fever vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2002. MMWR Recomm Rep 2002;51(RR-17):1–11.
[2] Monath TP. Yellow fever vaccine. In: Plotkin SA, Orenstein WA, editors. Vaccines. 4th ed. Philadelphia, PA: Elsevier; 2004. p. 1095–176.
[3] Lang J, Zuckerman J, Clarke P, Barrett P, Kirkpatrick C, Blondeau C. Comparison of the immunogenicity and safety of two 17D yellow fever vaccines. Am J Trop Med Hyg 1999;60(6):1045–50.
[4] Monath TP, Nichols R, Archambault WT, Moore L, Marchesani R, Tian J, et al. Comparative safety and immunogenicity of two yellow fever 17D vaccines (ARILVAX and YF-VAX) in a phase III multicenter, double-blind clinical trial. Am J Trop Med Hyg 2002;66(5):533–41.
[5] Pfister M, Kursteiner O, Hilfiker H, Favre D, Durrer P, Ennaji A, et al. Immunogenicity and safety of BERNA-YF compared with two other 17D yellow fever vaccines in a phase 3 clinical trial. Am J Trop Med Hyg 2005;72(3):339–46.
[6] Kelso JM, Mootrey GT, Tsai TF. Anaphylaxis from yellow fever vaccine. J Allergy Clin Immunol 1999;103(4):698–701.

[7] Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. Vaccine 2005;23(25):3256–63.
[8] Martin M, Weld LH, Tsai TF, Mootrey GT, Chen RT, Niu M, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. Emerg Infect Dis 2001;7(6):945–51.
[9] Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. Commun Dis Intell 2004;28(2):244–8.
[10] Barwick R. History of thymoma and yellow fever vaccination. Lancet 2004;364(9438):936.
[11] Iskander JK, Miller ER, Chen RT. The role of the vaccine adverse event reporting system (VAERS) in monitoring vaccine safety. Pediatr Ann 2004;33(9):599–606.
[12] Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the vaccine adverse event reporting system. Pediatr Infect Dis J 2004;23(4):287–94.
[13] Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine 2007;25(31):5675–84.
[14] McMahon AW, Eidex RB, Marfin AA, Russell M, Sejvar JJ, Markoff L, et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. Vaccine 2007;25(10):1727–34.
[15] Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: vaccine adverse event reporting system (VAERS)—United States, 1991–2001. MMWR Surveill Summ 2003;52(1):1–24.
[16] Cook IF, Barr I, Hartel G, Pond D, Hampson AW. Reactogenicity and immunogenicity of an inactivated influenza vaccine administered by intramuscular or subcutaneous injection in elderly adults. Vaccine 2006;24(13):2395–402.
[17] Beyer WE, Palache AM, Kerstens R, Masurel N. Gender differences in local and systemic reactions to inactivated influenza vaccine, established by a meta-analysis of fourteen independent studies. Eur J Clin Microbiol Infect Dis 1996;15(1):65–70.
[18] Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. BMJ 1993;307(6910):988–90.
[19] Cook IF, Pond D, Hartel G. Comparative reactogenicity and immunogenicity of 23 valent pneumococcal vaccine administered by intramuscular or subcutaneous injection in elderly adults. Vaccine 2007;25(25):4767–74.
[20] Pittman PR, Kim-Ahn G, Pifat DY, Coonan K, Gibbs P, Little S, et al. Anthrax vaccine: immunogenicity and safety of a dose-reduction, route-change comparison study in humans. Vaccine 2002;20(9–10):1412–20.
[21] Tuboi SH, Costa ZG, da Costa Vasconcelos PF, Hatch D. Clinical and epidemiological characteristics of yellow fever in Brazil: analysis of reported cases 1998-2002. Trans R Soc Trop Med Hyg 2007;101(2):169–75.
[22] Hanson H. Observations on the age and sex incidence of deaths and recoveries in the yellow fever epidemic in the department of Lambayeque P, in 1921. Am J Trop Med Hyg 1929;9:233–9.
[23] Gerasimon G, Lowry K. Rare case of fatal yellow fever vaccine-associated viscerotropic disease. South Med J 2005;98(6):653–6.
[24] Belsher JL, Gay P, Brinton M, DellaValla J, Ridenour R, Lanciotti R, et al. Fatal multiorgan failure due to yellow fever vaccine-associated viscerotropic disease. Vaccine 2007;25(50):8480–5.
[25] Doblas A, Domingo C, Bae HG, Bohorquez CL, de Ory F, Niedrig M, et al. Yellow fever vaccine-associated viscerotropic disease and death in Spain. J Clin Virol 2006;36(2):156–8.
[26] Vasconcelos PF, Luna EJ, Galler R, Silva LJ, Coimbra TL, Barros VL, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. Lancet 2001;358(9276):91–7.
[27] Martin M, Tsai TF, Cropp B, Chang GJ, Holmes DA, Tseng J, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. Lancet 2001;358(9276):98–104.
[28] Bae HG, Domingo C, Tenorio A, Ory FD, Munoz J, Weber P, et al. Immune response during adverse events after 17D-derived yellow fever vaccination in Europe. J Infect Dis 2008.
[29] Adhiyaman V, Oke A, Cefai C, Adhiyaman V, Oke A, Cefai C. Effects of yellow fever vaccination. Lancet 2001;358(9296):1907–8.
[30] Werfel U, Popp W. Effects of yellow fever vaccination. Lancet 2001;358(9296):1909.
[31] Troillet N, Laurencet F. Effects of yellow fever vaccination. Lancet 2001;358(9296):1908–9.
[32] Struchiner CJ, Luz PM, Dourado I, Sato HK, Aguiar SG, Ribeiro JG, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. Epidemiol Infect 2004;132(5):939–46.
[33] Zhou Q, Liu DW, Shi Y, Long Y, Li DJ, Liu HZ, et al. Adverse effects of attenuated yellow fever vaccine with multiple organ injury—a case report. Zhonghua Yi Xue Za Zhi 2005;85(13):936.
[34] Vellozzi C, Mitchell T, Miller E, Casey CG, Eidex RB, Hayes EB. Yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and corticosteroid therapy: eleven United States cases, 1996–2004. Am J Trop Med Hyg 2006;75(2):333–6.
[35] Pulendran B, Miller J, Querec TD, Akondy R, Moseley N, Laur O, et al. Case of yellow fever vaccine-associated viscerotropic disease with prolonged viremia, robust adaptive immune responses, and polymorphisms in CCR5 and RANTES genes. J Infect Dis 2008;198(4):500–7.
[36] Chan RC, Penney DJ, Little D, Carter IW, Roberts JA, Rawlinson WD. Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. Lancet 2001;358(9276):121–2.
[37] Engel AR, Vasconcelos PF, McArthur MA, Barrett AD. Characterization of a viscerotropic yellow fever vaccine variant from a patient in Brazil. Vaccine 2006;24(15):2803–9.
[38] Munoz J, Vilella A, Domingo C, Nicolas JM, de Ory F, Corachan M, et al. Yellow fever-associated viscerotropic disease in Barcelona. Spain J Travel Med 2008;15(3):202–5.
[39] CDC. Adverse events associated with 17D-derived yellow fever vaccination—United States, 2001–2002. MMWR 2002;51(44):989–93.
[40] CDC. Health information for international travel 2008. Atlanta: US Department of Health and Human Services PHS; 2007.
[41] Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. Clin Infect Dis 2002;34(10):1369–78.
[42] Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. Am J Public Health 1995;85(12):1706–9.