



ORIGINAL ARTICLE

Safety of the Yellow Fever Vaccine: A Retrospective Study

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Background. Yellow fever (YF) vaccine is considered safe; however, severe illness and death following vaccination have been reported.

Methods. Vaccine Safety Datalink (VSD) and US Department of Defense (DoD) data were used to identify adverse reactions following YF vaccination. Within the VSD, YF-vaccine-exposed subjects were compared to age-, site-, and gender-matched unexposed subjects. YF-vaccine-exposed DoD subjects were studied using a risk-interval design. For both cohorts, ICD-9 codes were analyzed for allergic and local reactions, mild systemic reactions, and possible visceral and neurologic adverse events (AEs).

Results. The VSD cohort received 47,159 doses from 1991 through 2006. The DoD cohort received 1.12 million doses from 1999 through 2007. Most subjects received other vaccines simultaneously. In the VSD cohort, rates of allergic, local, and mild systemic reactions were not statistically different between YF-vaccine-exposed and -unexposed subjects. In the DoD, there was an increased risk for outpatient allergic events in the period following vaccination with YF and other vaccines rate ratios [RR 3.85, 95% confidence interval (CI) 3.35–4.41] but with no increased risk for inpatient allergic reactions. In both cohorts, inpatient ICD-9 codes for visceral events were significantly less common following vaccination; inpatient codes for neurologic events were less common in the VSD YF-vaccine-exposed adult cohort, but did not differ between exposed and unexposed periods in the DoD. In the DoD, one fatal case of YF-vaccine-associated viscerotropic disease (YF-vaccine-AVD) was detected. The estimated death rate was 0.89 for 1,000,000 YF vaccine doses (95% CI 0.12–6.31/1,000,000 doses). No YF vaccine-associated deaths occurred in the VSD.

Conclusions. In these closed cohorts we did not detect increased risk for visceral or neurologic events following YF vaccination. The death rate following YF vaccine was consistent with previous reports. These data support current recommendations for use of YF vaccine in young healthy individuals. These data are inadequate to judge safety of YF vaccines in elderly patients.

Yellow fever (YF) is endemic to sub-Saharan Africa and tropical regions of South America. Infections can result in hemorrhagic complications, organ failure, and death. Treatment is limited to supportive care. Thus for populations at risk, including civilian travelers and military personnel, prevention through vaccination is essential.¹ The live attenuated YF vaccine was introduced in 1937 in the United States and was considered safe and effective.

Since 2001, the Centers for Disease Control and Prevention (CDC) have received multiple reports of death and life-threatening disease following vaccination.

Understanding of YF vaccine safety is based on clinical trials, case reports, and passive and active surveillance. No serious adverse events (AEs) or deaths have occurred in recent trials involving several thousand subjects.^{2,3}

The CDC Yellow Fever Vaccine Working Group (YFVSWG) has defined two distinct post-vaccination syndromes. YF-vaccine-associated neurologic disease (YF-vaccine-AND) manifests as several distinct clinical syndromes, including meningoencephalitis, Guillain-Barré syndrome, or acute disseminated encephalomyelitis. Depending on the specific syndrome, YF-vaccine-AND results from either direct viral invasion of the central nervous system or autoimmune mechanisms directed at the central or peripheral nervous systems. YF-vaccine-associated viscerotropic disease (YF-vaccine-AVD) results from widespread

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dissemination of the vaccine virus. It frequently progresses to multiorgan failure. Nearly two thirds of patients with confirmed YF-vaccine-AVD failed to survive.¹ From 1990 to the present there have been 31 cases and 12 deaths from YF-vaccine-AVD reported in international travelers.⁴ More recently, an updated case definition of vaccine-AVD has been published by the Brighton Collaboration.⁵

Considerable questions regarding the use of YF vaccine remain,^{6–14} especially for travelers to destinations with low YF activity, where the risk of disease following vaccination may be comparable to the risk of contracting the disease while traveling.⁴ The goal of this study was to use automated claims data from the Vaccine Safety Datalink (VSD) and the US Department of Defense (DoD) to estimate risks for medical visits following allergic or local reactions and mild systemic reactions and to evaluate the rate of hospitalizations due to medical conditions that have been associated with YF-vaccine-ADV and -AND.

Methods

Study Population and Design

First, using data from the VSD in a retrospective matched cohort study design, we compared rates of ICD-9 codes for AEs between YF-vaccine-exposed and YF-vaccine-unexposed subjects. The VSD cohort included pediatric (0–17 years) and adult (≥ 18 years) members from eight medical care organizations (MCOs) that collaborate with the CDC on the VSD.¹⁵ The VSD uses linked administrative data on demographics, enrolment, immunizations, mortality, and ICD-9 and CPT codes assigned to inpatient and outpatient encounters for more than 9 million members.¹⁶

The source population included all subjects enrolled in the participating MCOs from January 1, 1991 through December 31, 2006 (dates varied slightly at some sites). YF-vaccine-exposed subjects were compared with randomly selected YF-vaccine-unexposed controls, matched 1:3 on MCO, gender, and birth year. Unexposed subjects were assigned an index date equal to the vaccination date of their match. Unexposed subjects were not required to have a visit during the period of observation. All subjects had to be continuously enrolled in the MCO starting at least 35 days before receiving YF vaccine (or index date) through 45 days after vaccination. Only first YF vaccine doses were studied. Other vaccines administered within 3 days of YF vaccination (or index date) were recorded.

Second, we used data from the DoD to conduct a risk-interval design analysis.¹⁷ The population included all YF-vaccine-exposed military personnel from January 1, 1999 through December 31, 2007. Each person contributed both exposed and unexposed time. YF vaccine is recommended for active-duty personnel deployed to or traveling through YF-endemic regions and is usually administered with multiple other

pre-deployment vaccines.¹⁸ Data on other vaccines administered were not available for this cohort. Only first doses of YF vaccine were studied.

This study was approved by the Institutional Review Boards for all VSD sites and the DoD.

Outcomes

For both the VSD and DoD cohorts, ICD-9 codes for identifying allergic and local AEs were selected as outcomes based on review of prior vaccine safety studies.^{19–22} Additional ICD-9 codes for symptoms and conditions that could be consistent with YF-vaccine-AVD and YF-vaccine-AND were selected in consultation with the CDC YFVSWG.¹ As laboratory and radiology data were not available to confirm whether visceral or neurologic events met formal CDC YFVSWG or Brighton case definitions, outcomes in this study are referred to as “visceral events” and “neurologic events.” In addition, for the VSD cohorts, ICD-9 codes signifying a mild systemic reaction occurring at outpatient visits were evaluated.

For all cohorts, allergic and local reactions included both inpatient and outpatient visits. “Visceral events” and “neurologic events” were limited to inpatient hospitalizations.

A large number of diagnosis codes were used to capture as many events as possible (Table 1). This table also shows the number of diagnoses for each condition in the exposed VSD cohorts. In the VSD cohorts, as the ICD-9 code 995.2 “unspecified adverse event of drug” was non-specific, we further classified these events as allergic, or local or mild systemic reactions based on chart reviews; the numbers in Table 1 reflect these events.

In the VSD cohort, we also audited charts for fatalities among YF-vaccine-exposed subjects with one or more of the ICD-9 codes in Table 1 to determine whether the vaccine may have contributed to the cause of death. Chart audits could not be performed in the DoD cohort. However, a case report of the single death following YF vaccine in this population has been published.¹¹

Risk Windows

For both cohorts, risk windows were based on CDC YFVSWG definitions and the expected time course for vaccine-related AEs. However, these windows were extended to allow lags between onset of symptoms and receipt of medical care. In the VSD, allergic or local reactions occurring during outpatient visits or inpatient hospitalizations were evaluated 0 to 3 days post-vaccination, whereas in the DoD, the risk window for allergic events was 0 to 8 days post-vaccination. For both cohorts, we used a risk window for visceral of 0 to 16 days and for neurologic, 0 to 36 days post-vaccination or matched index date. In addition, in the VSD cohort, we also searched for outpatient codes consistent with mild systemic reactions at 1 to 10 days following YF vaccine or index date.

Table 1 ICD-9-CM codes of medically attended signs and symptoms after yellow fever vaccine in the Vaccine Safety Datalink population, and number of events in exposed subjects

Sign or symptom categories	ICD-9 CM codes	Pediatric N (%)	Adult N (%)
<i>Allergic 0–3 days (inpatient/outpatient)</i>		1 (100)	4 (100)
Allergic and local reactions	995.0, 995.1, 995.2,* 999.4, 999.5	1 (100)	4 (100)
<i>Mild systemic reactions 1–10 days (outpatient)</i>		29 (100) [†]	102 (100) [†]
Fever	780.6	10 (33.3)	7 (6.3)
Malaise	780.7		10 (9.0)
Nausea and vomiting	787.0, 787.01–787.03	4 (13.3)	10 (9.0)
Lethargy	780.79	2 (6.7)	6 (5.4)
Headache	307.8, 784.0, 346.2	1 (3.3)	32 (28.8)
Myositis	728	—	
Myalgia	729	6 (20)	28 (25.2)
Other joint issues	719	—	2 (1.8)
Syncope	780.09, 780.2	1 (3.3)	6 (5.4)
Other systemic reaction	995.2*	5 (16.7)	10 (9.0)
<i>Visceral events 0–16 days (inpatient)</i>		1 (100)	3 (100)
Liver disease	070, 570, 572, 573, 782.4, 790	—	—
Coagulopathy	286, 287, 459	1 (100)	—
Cardiac disease	359, 422.9, 427	—	1 (33.3)
Hypotension	458, 785	—	1 (33.3)
Lung disease	518, 786	—	1 (33.3)
Renal disease	581, 583, 584, 586, 588	—	—
Arthritis-arthropathy	711, 714, 716, 791	—	—
<i>Neurologic events 0–36 days (inpatient)</i>		—	6 (100)
Meningitis and encephalitis	047, 049, 063, 136, 232, 321, 323	—	1 (14.3)
CNS demyelinating disease	340, 341, 336	—	1 (14.3)
Hemiplegia and hemiparesis	342	—	—
Seizures and movement disorders	345, 780.3, 781, 780.39	—	1 (14.3)
Peripheral and cranial neuropathy	350–352, 356, 357, 377, 378, 388	—	2 (28.6)
Altered mental status	310, 780.0–780.2	—	2 (28.6)

CNS, central nervous system.

*Chart review performed to assign 995.2 “Unspecified adverse effect of drug medicinal and biological substance not elsewhere classified” to either allergic or mild systemic category.

[†]Some subjects had more than one diagnosis in a category, so the totals are less than the sum of the diagnoses.

In the DoD cohort, rates of AEs following YF vaccine within the windows described above were compared with a post-vaccination control period 48 to 120 days after vaccination. Rates of AEs are expressed as rates per 100,000 doses administered, with time windows in the control period adjusted to match the varying exposed periods.

Analysis

In both cohorts, we calculated the rates for allergic or local reactions, and visceral and neurologic events among YF-vaccine-exposed and YF-vaccine-unexposed subjects. Rates for mild systemic reactions following YF vaccine in the VSD were also calculated. All contrasts were analyzed with a two-sided test with significance defined as $p < 0.05$. For the VSD cohort, we estimated odds ratios (OR) by comparing event rates in YF-vaccine-exposed versus unexposed age-, site-, and gender-matched cohorts using conditional logistic regression via the Cox regression likelihood. The data analysis for this article was generated using SAS/STAT software, Version 9.13, of the SAS System for Windows (SAS Institute Inc.). In the VSD, separate analyses

were conducted for pediatric population (<18 years) and adults (≥ 18 years). For the DoD population, we obtained aggregate data, stratified by age group and by site of care (inpatient vs. outpatient events). Data were analyzed using a Poisson regression model and rate ratios (RR) of exposed windows versus unexposed are reported with 95% confidence interval (CI).

Results

Description of Study Populations

The VSD pediatric cohort had a mean age of 10.2 ± 5.5 years and received 9,604 YF vaccine doses (Table 2). The VSD adult cohort had a mean age of 46.1 ± 16.3 years and received 37,555 YF vaccine doses. Sixteen percent of adult VSD vaccinations were in subjects aged 60 to 69, and 8% were given to subjects aged 70 or older. Seventy percent of YF-vaccine-exposed pediatric subjects and 85% of YF-vaccine-exposed adult subjects received another vaccine at the same visit as YF. In the VSD pediatric cohort this most commonly included typhoid vaccine,

Table 2 Demographic characteristics of subjects exposed to yellow fever vaccine in the Vaccine Safety Datalink (1991–2006) and DoD (1999–2007) cohorts

	VSD—pediatric	VSD—adult	Military
Number of subjects	9,604	37,555	1,124,730
Mean age $\pm$ SD	10.2 $\pm$ 5.5	46.1 $\pm$ 16.3	n/a*
<i>Pediatric</i>	<i>Number (%)</i>		
0–4	2,084 (21.7)		
5–9	2,144 (22.3)		
10–14	2,382 (24.8)		
15–17	2,994 (31.2)		
<i>Adult</i>		<i>Number (%)</i>	<i>Number (%)</i>
18		555 (1.5)	211,791 (18.8)
19–29		7,229 (19.3)	687,477 (61.1)
30–39		6,061 (16.1)	179,361 (15.9)
40–49		6,904 (18.4)	43,317 (3.9)
50–59		7,938 (21.1)	2,717 (0.2)
60–69		5,955 (15.9)	67 (0.0)
70+		2,913 (7.8)	0 (0.0)
Female	4,985 (52.0)	20,230 (53.9)	n/a*

DoD, US Department of Defense; VSD, Vaccine Safety Datalink.

*Data not provided by the DoD.

meningococcal polysaccharide vaccine (MPSV4), and hepatitis A vaccine. The mean number of vaccines administered simultaneously (including YF-vaccine) was 3.19. In the VSD adult cohort, this also included tetanus diphtheria toxoids and inactivated polio vaccine, and the mean number of vaccines was 3.35. In contrast, only 1% of unexposed pediatric or adult subjects were vaccinated within 3 days of the index date.

More than 1.12 million YF vaccines were given to military personnel during the study (Table 2). Over 95% of the military cohort was between 18 and 39 years.

Allergic and Local Reactions

In VSD pediatric and adult cohorts, there were no inpatient allergic or local reactions, and no subjects had presumed anaphylaxis (ICD-9 code 995.0 or 999.4). In the adult cohort, outpatient allergic or local reactions occurred at a higher rate in vaccinated subjects, but did not reach statistical significance, RR = 4.0 (0.90–17.87) (Table 3).

In the DoD, there was an excess of outpatient allergic events, RR = 3.85 (3.35–4.41). However, there was no increased risk for inpatient allergic events. There were only four inpatient allergic events in the exposed period in the entire cohort (0.37/100,000 doses). Further details were not available to determine whether any of these represented true cases of anaphylaxis (Table 4).

Mild Systemic Reactions

For VSD pediatric and adult cohorts, there was no significant increase in medically attended mild systemic reactions within 10 days of vaccination (Table 3).

Table 3 Outcomes in VSD cohorts exposed and unexposed subjects

Signs and symptoms	Events (rate per 100,000 doses)		OR (95% CI), <i>p</i>
	Unexposed	Exposed	
<i>Pediatric cohort</i>			
Allergic and local reactions*	0	1 (10.4)	—
Mild systemic reactions†	60 (209.4)	29 (302.0)	1.44 (0.93–2.25), 0.10
Visceral‡	1 (3.5)	1 (10.4)	3.0 (0.19–48.0), 0.44
Neurologic§	2 (7.0)	0	—
<i>Adult cohort</i>			
Allergic and local reactions*	3 (2.7)	4 (10.7)	4.0 (0.90–17.87), 0.07
Mild systemic reactions†	348 (310.3)	102 (271.6)	0.87 (0.70–1.09), 0.22
Visceral	35 (31.2)	3 (8.0)	0.26 (0.17–0.95), 0.02
Neurologic§	44 (39.2)	6 (16.0)	0.41 (0.17–0.95), 0.04
Death	16 (14.3)	5 (13.3)	0.94 (0.34–2.56), 0.90

VSD, Vaccine Safety Datalink; OR, odds ratios.

*Allergic and local reactions (inpatient and outpatient) at 0 to 3 days.

†Mild systemic reactions (outpatient only) at 1 to 10 days.

‡Visceral events (inpatient only) at 0 to 16 days.

§Neurologic events (inpatient only) at 0 to 36 days.

Table 4 Adverse events following yellow fever vaccination based on risk interval design, DoD data 1999–2007

	Events (rate per 100,000 doses)		Rate ratio (95% CI), <i>p</i>
	Exposed period	Unexposed period	
<i>Allergic*</i>			
Outpatient	290 (26.6)	695 (6.9)	3.85 (3.35–4.41), <0.0001
Inpatient	4 (0.37)	19 (0.19)	1.94 (0.66–5.7), 0.23
<i>Visceral*</i>			
Inpatient	64 (5.8)	401 (8.0)	0.73 (0.56–0.94), 0.02
<i>Neurologic*</i>			
Inpatient	179 (16.0)	356 (15.9)	1.01 (0.84–1.21), 0.94

DoD, US Department of Defense.

*Allergic reactions at 0 to 8 days, visceral-related events at 0 to 16 days, and neurologic-related events at 0 to 36 days.

Visceral Events

Visceral events were rare following YF vaccination. In the VSD pediatric cohort, there was only a single inpatient visceral ICD-9 code occurring within 16 days of vaccination (10/100,000 doses); while in the VSD adult cohort only three occurred (8/100,000 doses) (Table 3). In both the VSD adult and DoD cohorts, visceral events resulting in a hospitalization were significantly less common in YF-vaccine-exposed adults.

Neurologic Events

Neurologic inpatient events following YF vaccine occurred infrequently. There were no events in the

VSD pediatric cohort and only six inpatient neurologic events occurred within 36 days of vaccination in the VSD adult cohort (16/100,000 doses) (Table 3). There was a decreased risk for neurologic events in the VSD adult cohort. In the DoD cohort, risks for neurologic events did not differ between YF-vaccine exposed and unexposed periods.

Death

No deaths occurred in the VSD pediatric population. In the VSD adult population, no difference in mortality rates was observed between exposed (5 deaths) and unexposed (16 deaths) (OR 0.94, 0.34–2.56). Only one of the five deaths in the VSD YF-vaccine-exposed adults had an inpatient code possibly related to a visceral event. After chart review, the case was judged not to be related to YF vaccine. In the DoD population, one death occurred that was due to confirmed YF-vaccine-AVD.¹¹ The point estimate of the death rate for the DoD population was 0.89 for 1,000,000 YF vaccine doses (95% CI 0.12–6.31/1 million doses).

Discussion

This study examined safety of more than 1 million doses of YF vaccine in two large, closed cohorts. The events studied consisted of ICD-9 codes for signs and symptoms of allergic or local reactions, and minor systemic reactions, and inpatient ICD-9 codes representing neurologic or visceral events. Rates for outpatient allergic events were increased after vaccination in the DoD with an odds ratio approaching 4. In the VSD adult cohort, the point estimate was similar, but not significant due to small numbers. All the other outcome events including those leading to hospitalization were not increased in YF-vaccine-exposed subjects.

In these closed cohorts, only one death was directly attributable to YF vaccine. The point estimate risk for death was 0.89 per million, which is consistent with the rates reported by Struchiner et al.²³ using Brazilian surveillance data.

Compared to the unexposed, the lower rate of hospitalization for visceral and neurologic events among YF-vaccine-exposed VSD adults was likely due to the “healthy traveler” effect. Similarly, compared to unexposed post-vaccination periods, the lower rate for visceral events immediately following vaccination in the DoD cohort was likely due to the “healthy warrior” effect. That is, only healthy persons travel internationally or get deployed in the military. Because of this inherent bias, no attributable risk could be calculated.

Previous studies of YF vaccine safety in US populations have relied on reports to the Vaccine Adverse Event Reporting System (VAERS). These studies estimated the rates of YF-vaccine-AND to be 0.4 to 0.8/100,000 doses and the rates of YF-vaccine-AVD to be 0.3 to 0.4/100,000 doses.^{13,14} Kitchener²⁴ reported a rate of 1.3 per million for both YF-vaccine-AVD

and -AND based on European surveillance data. More recently, using active surveillance from Brazil, Martins et al.²⁵ reported state-specific rates of YF-vaccine-AVD of 0.31/100,000 YF vaccine doses in Sao Paulo state and 0.11/100,000 doses in Rio Grande do Sul state. The intensity of active surveillance varied from state to state. Recently, Thomas^{26,27} has summarized many of these studies.

This study was unable to answer two important public health questions. First, it was underpowered to assess the risk of death following YF vaccine. Second, analyses of data from passive reports to VAERS have suggested that advanced age was a risk factor for severe disease and death in these cases.^{28–31} Other studies have suggested that advanced age is a risk for serious AEs.³² Owing to inadequate numbers of elderly subjects in both cohorts, we were underpowered to determine whether AEs were more common with increased age.

This study has several other limitations. First, in both cohorts, diagnostic codes for symptoms and signs of neurologic and visceral events have unknown sensitivity and specificity for identifying reactions to YF vaccine. Thus, our results represent an estimate of rates of medically attended events for symptoms and signs that appear in the CDC YFVSWG case definitions, not diagnoses of either YF-vaccine-AVD or YF-vaccine-AND.¹ Second, in the DoD population, only aggregate electronic data were available. Codes representing hypersensitivity reactions could not be confirmed by chart review, and data on egg allergy for patients experiencing reactions was not available. Third, most subjects in both cohorts received multiple other vaccines simultaneously with YF vaccine. Thus, we were unable to assess whether any of the outcomes were due to YF vaccine or other vaccines.

This study provides a useful description of events following YF vaccine administration in the context of standard travel and military vaccination protocols in the United States. Our findings may not be generalizable to YF vaccine in other settings. The rates of AEs may be lower in national and regional YF vaccine campaigns when it is administered as a single vaccine.

Conclusion

This was the largest-ever study of the safety of the YF vaccine in the United States. Severe AEs resulting in hospitalization did not differ between the vaccinated and unvaccinated. In this closed population, only one death occurred, consistent with death rates obtained from other studies. These data are inadequate to judge safety in elderly patients, but they support current CDC recommendations for judicious use of YF vaccine in young healthy individuals.¹

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Declaration of Interests

The authors state they have no conflicts of interest.

References

1. Staples JE, Gershman M, Fischer M. Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010; 59:1–27.
2. Monath TP, Nichols R, Archambault WT, 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; 66:533–541.
3. Ripoll C, Ponce A, Wilson MM, et al. Evaluation of two yellow fever vaccines for routine immunization programs in Argentina. *Hum Vaccin* 2008; 4:121–126.
4. Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. *Expert Rev Vaccines* 2012; 11:427–448.
5. Gershman MD, Staples JE, Bentsi-Enchill AD, et al. Viscerotropic disease: case definition and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2012; 30:5038–5058.
6. Hayes EB. Is it time for a new yellow fever vaccine? *Vaccine* 2010; 28:8073–8076.
7. Vasconcelos PF, Luna EJ, Galler R, et al. Serious adverse events associated with yellow fever 17DD vaccine in Brazil: a report of two cases. *Lancet* 2001; 358:91–97.
8. Martin M, Tsai TF, Cropp B, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. *Lancet* 2001; 358:98–104.
9. Chan RC, Penney DJ, Little D, et al. Hepatitis and death following vaccination with 17D-204 yellow fever vaccine. *Lancet* 2001; 358:121–122.
10. Doblas A, Domingo C, Bae HG, et al. Yellow fever vaccine-associated viscerotropic disease and death in Spain. *J Clin Virol* 2006; 36:156–158.
11. Gerasimon G, Lowry K. Rare case of fatal yellow fever vaccine-associated viscerotropic disease. *South Med J* 2005; 98:653–656.
12. Munoz J, Vilella A, Domingo C, et al. Yellow fever-associated viscerotropic disease in Barcelona, Spain. *J Travel Med* 2008; 15:202–205.
13. Belsher JL, Gay P, Brinton M, et al. Fatal multiorgan failure due to yellow fever vaccine-associated viscerotropic disease. *Vaccine* 2007; 25:8480–8485.
14. McMahon AW, Eidex RB, Marfin AA, et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. *Vaccine* 2007; 25:1727–1734.
15. DeStefano F. The Vaccine Safety Datalink project. *Pharmacoepidemiol Drug Saf* 2001; 10:403–406.
16. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics* 2011; 127(Suppl 1):S45–S53.
17. Glanz JM, McClure DL, Xu S, et al. Four different study designs to evaluate vaccine safety were equally validated with contrasting limitations. *J Clin Epidemiol* 2006; 59:808–818.
18. Grabenstein JD, Pittman PR, Greenwood JT, Engler RJ. Immunization to protect the US Armed Forces: heritage, current practice, and prospects. *Epidemiol Rev* 2006; 28:3–26.
19. Jackson LA, Yu O, Belongia EA, et al. Frequency of medically attended adverse events following tetanus and diphtheria toxoid vaccine in adolescents and young adults: a Vaccine Safety Datalink study. *BMC Infect Dis* 2009; 9:165.
20. Jackson LA, Yu O, Nelson J, et al. Risk of medically attended local reactions following diphtheria toxoid containing vaccines in adolescents and young adults: a Vaccine Safety Datalink study. *Vaccine* 2009; 27:4912–4916.
21. Jackson LA, Yu O, Nelson JC, et al. Injection site and risk of medically attended local reactions to acellular pertussis vaccine. *Pediatrics* 2011; 127:e581–e587.
22. Bohlke K, Davis RL, Marcy SM, et al. Risk of anaphylaxis after vaccination of children and adolescents. *Pediatrics* 2003; 112:815–820.
23. Struchiner CJ, Luz PM, Dourado I, et al. Risk of fatal adverse events associated with 17DD yellow fever vaccine. *Epidemiol Infect* 2004; 132:939–946.
24. Kitchener S. Viscerotropic and neurotropic disease following vaccination with the 17D yellow fever vaccine, ARILVAX. *Vaccine* 2004; 22:2103–2105.
25. Martins RMMM, Santos EM, et al. Yellow fever vaccine post-marketing surveillance in Brazil. *Procedia Vaccinol* 2010; 2:178–183.
26. Thomas RE, Lorenzetti DL, Spragins W, Jackson D, Williamson T. Reporting rates of yellow fever vaccine 17D or 17DD-associated serious adverse events in pharmacovigilance data bases: systematic review. *Curr Drug Saf* 2011; 6:145–154.
27. Thomas RE, Lorenzetti DL, Spragins W, Jackson D, Williamson T. Active and passive surveillance of yellow fever vaccine 17D or 17DD-associated serious adverse events: systematic review. *Vaccine* 2011; 29:4544–4555.
28. Khromava AY, Eidex RB, Weld LH, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* 2005; 23:3256–3263.
29. Martin M, Weld LH, Tsai TF, et al. Advanced age a risk factor for illness temporally associated with yellow fever vaccination. *Emerg Infect Dis* 2001; 7:945–951.
30. Lindsey NP, Schroeder BA, Miller ER, et al. Adverse event reports following yellow fever vaccination. *Vaccine* 2008; 26:6077–6082.
31. Lawrence GL, Burgess MA, Kass RB. Age-related risk of adverse events following yellow fever vaccination in Australia. *Commun Dis Intell Q Rep* 2004; 28:244–248.
32. Monath TP, Cetron MS, McCarthy K, et al. Yellow fever 17D vaccine safety and immunogenicity in the elderly. *Hum Vaccin* 2005; 1:207–214.