Anaphylaxis from yellow fever vaccine

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Background: There are very few reports of anaphylactic reactions to yellow fever (YF) vaccine in the literature, and these date from the 1940s.
Objective: We sought to estimate the rate of YF vaccine–related anaphylaxis.
Methods: All reports of adverse reactions to YF vaccine submitted to the Vaccine Adverse Event Reporting System between 1990 and 1997 were reviewed for those meeting criteria for probable or possible anaphylactic reactions.
Results: Of 243 reports submitted, 40 describe probable or possible anaphylactic reactions. In 22 of these 40, YF vaccine was the only vaccine administered. There were 5,236,820 doses of YF vaccine distributed in the United States during this period. By using all 40 cases, the rate of YF vaccine–related anaphylaxis would be 40 in 5,236,820 or about 1 in 131,000. In 35 of the reports, information was provided on whether previous doses of YF vaccine had been given. In 34 of these 35, the reaction occurred after the first dose of YF vaccine, suggesting that vaccine constituents other than the viral proteins may have been the allergens. The vaccine is grown in chicken embryos and contains gelatin as a stabilizer.
Conclusion: YF vaccine can cause anaphylactic reactions. Persons presenting for YF vaccine should be asked if they have had adverse reactions to previous doses of this or other vaccines and if they are allergic to eggs, chicken, or gelatin. Health care workers administering YF vaccine should be prepared to recognize and treat anaphylactic reactions should they occur. (J Allergy Clin Immunol 1999;103:698-701.)

Key words: *Allergy, anaphylaxis, yellow fever vaccine*

Yellow fever (YF) vaccine is recommended for persons living in or traveling to areas of Africa and South America where the disease is endemic or where viral transmission is suspected.[1] The vaccine is routinely administered to members of the United States Armed Forces who are subject to worldwide deployment. After a single primary immunization, booster doses are required every 10 years.[1]

Abbreviations used
MMR: measles, mumps, and rubella
VAERS: Vaccine Adverse Event Reporting System
YF: Yellow fever

YF vaccine, prepared from the 17D strain of the YF virus, is among the safest and most effective viral vaccines ever developed.[2] Local or mild systemic reactions generally have been reported in less than 5% of vaccinees, although with closer monitoring through daily diaries reactions have been solicited in up to 42% of vaccinees.[3,4] Because the vaccine is made in embryonated eggs, a history of egg allergy is considered a contraindication to vaccination. Anecdotal cases of anaphylaxis after vaccination have been reported.[5-7] The Vaccine Adverse Event Reporting System (VAERS) was established by the US Department of Health and Human Services to collect data on all adverse reactions associated with the administration of any US-licensed vaccine in all age groups.[8] VAERS has been operational since 1990. We reviewed all reports of reactions to YF vaccine in this database to characterize those with anaphylactic reactions.

METHODS

During the years 1990 through 1997, 243 VAERS reports describing adverse events after the administration of YF vaccine were submitted. For some of the reports, YF was the only vaccine given. For others, one or more additional vaccines were administered at the same time. These 243 VAERS reports were reviewed and classified, according to the criteria in Table I, as probable anaphylactic reactions or possible anaphylactic reactions. Dermatologic and respiratory signs and symptoms and their timing in relation to vaccine administration were the main criteria used for classification. Although lightheadedness and syncope were noted, if these symptoms occurred in the absence of dermatologic or respiratory symptoms, the events were not classified as anaphylaxis. For example, some reports described probable vasovagal reactions with pallor, bradycardia, and a brief syncopal episode that occurred within seconds of the vaccination and resolved spontaneously.

RESULTS

Of the 243 VAERS forms reviewed, 40 (16%) describe probable or possible anaphylactic events after the administration of YF vaccine. In 22 of the 40 cases, YF was the only vaccine administered. Among these 22, 12 met the criteria for probable anaphylaxis, and 10 met the criteria for possible anaphylaxis. In 18 of the 40 cases, YF was administered with one or more other vaccines. Among these 18, 8 met the criteria for probable anaphylaxis, and 10 met the criteria for possible anaphylaxis. In 35 of the 40 cases, information was provided on whether previous

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doses of YF vaccine had been given. In all but 1 case, the reaction occurred after the first dose of YF vaccine ever received. The nature and timing of all 40 reactions is detailed in Table II. There were 5 additional cases in which the VAERS report was coded as anaphylaxis without sufficient description of the event for categorization as above (eg, no description of the onset interval or symptoms). There were 5,236,820 doses of YF vaccine distributed in the US between 1990 and 1997 (personal communication, Robert Snyder, Centers for Disease Control and Prevention).

TABLE I. Classification of reports

Probable anaphylactic reaction
Reaction occurring within 4 hours of vaccine administration to include the following:
Dermatologic signs and/or symptoms; ie, pruritus, urticaria, angioedema, flushing
AND
Respiratory signs and/or symptoms; ie, dyspnea, bronchospasm, glossal/pharyngeal edema, hoarseness, and nose/eye symptoms (ie, nasal congestion, rhinorrhea, sneezing, red, itchy, watery eyes)
Possible anaphylactic reaction
Dermatologic or respiratory symptoms (but not both)
Dermatologic and/or respiratory symptoms happening more than 4 hours after vaccination

DISCUSSION

A review of 243 VAERS reports submitted over an 8-year period disclosed 40 cases of probable or possible anaphylactic reactions to YF vaccine. In the 22 in which YF was the only vaccine given, the reactions were almost certainly caused by the YF vaccine. In those cases in which other vaccines were administered together with YF, the etiology of the reactions was less clear. These reports indicate that, despite the paucity of previous reports,[5-7] reactions meeting a rigorous clinical definition of anaphylaxis do occur after YF vaccination. Because reporting to VAERS is passive and depends on the compliance of practitioners, the rate of these hypersensitivity events can only be estimated. By using only the 22 probable and possible anaphylactic reactions reported here in which YF was the only vaccine given, the rate of YF vaccine–related anaphylaxis would be 22 in 5,236,820 or about 1 in 238,000. By using all 40 reactions, including those in which YF was given with other vaccines, the rate would be 40 in 5,236,820 or about 1 in 131,000. This compares to a rate of about 1 in 587,000 for probable and possible anaphylactic reactions reported to VAERS for measles, mumps, and rubella (MMR) vaccine (personal communication, Vitali Pool, Centers for Disease Control and Prevention). Previous studies suggest that the reporting sensitivity of VAERS varies from less than 1% to approximately 70%; serious adverse events and events with an acute onset, like anaphylaxis, had higher reporting rates.[9] Thus the true rate of these reactions could be higher.

Vaccines are complex mixtures, containing not only immunizing agents, but also other potentially allergenic substances. By far the greatest number of reported cases of vaccine allergy are to MMR vaccine.[10] Although these reactions were initially thought to be caused by egg protein,[11] subsequent reports have indicated that the vaccine, which is grown in chick embryo fibroblasts (not eggs), contains negligible amounts of egg protein, and these reports have confirmed that the vaccine can be safely administered to children allergic to eggs.[10] In the 1997 edition of the *Red Book* from the American Academy of Pediatrics, egg allergy is no longer listed as a contraindication to MMR vaccination.[12] However, 2 other vaccines, for influenza and YF, do contain egg protein, and patients allergic to eggs may have allergic reactions to them. In 1993, a report implicated gelatin, which is added to several vaccines as a stabilizer, as the allergen responsible for anaphylaxis to MMR vaccine.[13] Since then, other reports have confirmed that most allergic reactions to MMR and varicella vaccines are caused by sensitivity to the gelatin component of the vaccine.[14,15]

The particular constituent of YF vaccine that may cause allergic reactions is unknown. Most antigens, and therefore most allergens, are proteins, and these molecules are the most likely suspects. The protein constituents of YF vaccine include the live-attenuated YF 17D virus, which potentially could be allergenic.[16] Allergy, however, requires prior exposure, and with only 1 exception, the reactions reported here occurred after the first dose of YF vaccine. Thus YF viral proteins themselves seem unlikely to be the cause of these reactions, although it is possible that cross-reactivity may exist between YF viral proteins and other allergens to which the subjects may have been previously exposed.

The YF 17D vaccine is prepared from infected chicken embryos and may contain residual egg or chicken proteins.[16] For this reason, it should not be administered to persons with a history of egg or chicken allergy until allergy testing with the vaccine is performed. Patients given the vaccine are routinely asked if they are allergic to eggs or chicken, and those who answer in the affirmative are typically not given the vaccine or are referred for allergy testing.[17] It is possible, however, that some of the allergic reactions to YF vaccine reported through the VAERS were caused by egg or chicken allergy.

YF vaccine also contains sorbitol and gelatin added as stabilizers.[16] Sorbitol is an alcohol and is very unlikely to be allergenic. Gelatin added to vaccines is composed of bovine or porcine connective tissue protein, which is hydrolyzed to prevent gelling. As noted above, gelatin has been implicated as the allergen in the majority of allergic reactions to other gelatin-containing vaccines.[13-15] Such reactions may occur after the first dose of vaccine because of prior exposure to gelatin in other medications or vaccines or by ingestion of gelatin-containing foods. Clinical allergy to the ingestion of gelatin may or may not be present in patients who have allergic reactions to the systemic injection of gelatin.[18] Thus gelatin allergy could be responsible for some of the YF vaccine allergic reactions reported here.

TABLE II. YF vaccine–induced anaphylaxis

Case no	No of previous YF vaccine doses	Other concurrent vaccine(s)	Dermatologic symptoms	Respiratory symptoms	Other symptoms	Onset time after vaccination
Probable anaphylaxis						
1	0	None	Urticaria	Hoarseness	—	60 min
2	?	None	Angioedema	"Respiratory symptoms"	—	30 min
3	0	None	Pruritus, flushing	Rhinorrhea	—	15 min
4	1	None	Angioedema, pruritus	Pharyngeal edema	—	1 h 15 min
5	0	None	Pruritus	Dyspnea	Lightheaded, hypotension	30 min
6	0	None	Flushing	Dyspnea, wheeze	Lightheaded	1 h
7	0	None	Rash	Dyspnea, laryngeal edema	—	1 h 5 min
8	0	None	Urticaria	Throat tight	—	1 h 10 min
9	0	None	Urticaria	Dyspnea	Hypotension?	Same morning
10	0	None flushing	Pruritus,	Cough	—	30 min
11	0	None	Flushing	Respiratory distress	—	3 h 14 min
12	0	None	Pruritus	Hoarseness	Lightheaded	5 min
13	0	Typhoid #1	Angioedema	Glossal edema, cough	—	35 min
14	?	Tetanus #?, PPD	Urticaria	Dyspnea	—	30 min
15	0	Gamma globulin (IM)	Urticaria	Dyspnea	—	2 h 30 min
16	0	Hepatitis A #1	Urticaria	Dyspnea	—	15 min
17	0	Hepatitis A #1	Urticaria	Dyspnea	—	25 min
18	0	Hepatitis A #1	Flushing	Throat tight	—	15 min
19	0	Hepatitis A #1	Angioedema	Dyspnea, throat itch	—	15 min
20	0	Hepatitis A #1, hepatitis B #1	Angioedema, flushing	Dyspnea	—	30 min
Possible anaphylaxis						
21	0	None	Pruritus, "rash"	—	—	1 h 30 min
22	0	None	Urticaria, angioedema	—	—	1 h
23	0	None	Urticaria	—	—	4 h
24	0	None	—	Dyspnea, wheeze	Lightheaded	15 min
25	0	None	—	Dyspnea	—	30 min
26	0	None	Urticaria	Wheezing, dyspnea	—	4 h 29 min
27	0	None	Urticaria	—	—	45 min
28	0	None	Angioedema, pruritus	—	—	2 h
29	0	None	Pruritus	Dyspnea	—	>24 h?
30	0	None	—	Dyspnea	—	2 h 45 min
31	?	Cholera #?	Angioedema	—	—	50 min
32	?	Typhoid #?	Angioedema	—	—	5 h
33	0	Oral polio #?, cholera #1, hepatitis B #1	—	Dyspnea, wheeze	—	55 min
34	0	Oral typhoid #1, hepatitis B #1	Angioedema	—	"Shock"	4 h 25 min
35	0	Tetanus/diphtheria #?	—	Dyspnea, cough	—	1 h 30 min
36	?	Typhoid #?	—	Dyspnea, glossal edema	—	2 h 30 min
37	0	Tetanus/diphtheria #?	Pruritus, "rash"	—	—	8 min
38	0	Meningitis #1	Urticaria	—	—	1 h
39	0	Typhoid #1, hepatitis A #1	—	—	Lightheaded	20 min
40	0	Hepatitis A #1, tetanus/diphtheria #?	Urticaria	—	—	21 h

In conclusion, YF vaccine can cause anaphylactic reactions. Persons presenting for YF vaccination should be asked if they have had adverse reactions to previous doses of this or other vaccines and asked if they are allergic to eggs, chicken, or gelatin. Those indicating such allergy should be referred to an allergist for testing and

disposition. Such screening may not prevent all allergic reactions to the first or subsequent doses of YF vaccine, and health care workers administering YF vaccine should be prepared to recognize and treat anaphylactic reactions should they occur.

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