

Vaccination of persons allergic to latex: a review of safety data in the Vaccine Adverse Event Reporting System (VAERS)

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Abstract

Vaccine products currently licensed in the US and other countries are marketed in vials and syringes that may contain natural latex allergens. Little scientific information exists regarding the safety of vaccination of latex-allergic individuals. A review of data within the Vaccine Adverse Event Reporting System (VAERS), a large registry of reported possible vaccine adverse reactions was conducted. A search of the database, which contains >160,000 vaccine adverse event reports, revealed only 28 cases of possible immediate-type hypersensitivity reactions in vaccine recipients with a history of allergy to latex. Given the large number of immunizations administered every year in the US, the reported risk of allergic reactions possibly due to latex contamination of vaccines appears to be very small.

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1. Introduction

Natural latex is a milky fluid obtained from the *H. brasiliensis* (rubber tree). It contains *cis*-1,4-polyisoprene in a colloidal suspension, as well as some proteins. Latex is used to manufacture a large number of consumer and medical products. Latex can be processed in two different ways. One process yields dipped products such as medical gloves. These products are referred to as natural rubber latex (NRL). The other process yields molded products such as medication vial stoppers and syringe plungers (including the ones used for vaccines). These products are referred to as dry natural rubber (DNR). It is more difficult to extract latex protein allergens from DNR products than from NRL products [1]. Nonetheless, it is theoretically possible that latex allergen contamination of vaccine solutions that contact DNR vial stoppers or syringe plungers could occur and cause allergic

reactions when the vaccines are administered to latex-allergic individuals. It should also be noted that many vial stoppers and syringe plungers are made from synthetic rubber. Such products contain no natural latex and pose no risk to latex-allergic individuals. The National Immunization Program of the United States Centers for Disease Control and Prevention occasionally receives requests for guidance on immunization of persons allergic to latex. Package inserts for many vaccines used in the US indicate that the vaccine packaging contains DNR and include cautionary statements regarding possible risks for latex-allergic vaccine recipients. To respond to such inquiries the Advisory Committee on Immunization Practices (ACIP) in the US developed the following recommendations: "If a person reports a severe (anaphylactic) allergy to latex, vaccines supplied in vials or syringes that contain natural rubber should not be administered, unless the benefit of vaccination outweighs the risk of an allergic reaction to the vaccine. For latex allergies other than anaphylactic allergies (e.g. a history of contact allergy to latex gloves), vaccines supplied in vials or syringes that contain dry natural rubber or natural rubber latex can be administered" [2]. These recommendations

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were partially based on an unpublished review of safety data in the Vaccine Adverse Event Reporting System (VAERS). In this letter, we present details of that review.

2. Methods

VAERS is a large national spontaneous reporting system for adverse events following immunization. Since November 1990, it has received >160,000 reports. Among persons who

submit notifications to VAERS are vaccine providers, other health care workers, vaccine recipients and their parents. Detailed descriptions of the system are presented elsewhere [3]. VAERS reports submitted from 1 January 1991 to 15 October 2003 were queried using a text string search on “latex” and “rubber”. The reports were manually reviewed to select cases that mentioned a history of allergy to latex. Of these, a subset of reports describing a possible immediate-type hypersensitivity reaction was selected based on the following criteria: (1) onset of symptoms within 4 h of vaccination or immediately

Table 1

Reported cases of possible immediate-type hypersensitivity reactions in vaccine recipients with a history of latex allergy, VAERS 1991–15 October 2003

Case #	Sex	Age (years)	Vaccine	Vaccination year	Onset of symptoms (min)	Symptoms	Comments
1	F	28	ANTad	Unknown	120	Pruritic rash on face	History of multiple allergies
2	F	Unknown	HBV	1991	20	Generalized urticaria	History of multiple allergies
3	F	36	HBV	1991	120	Generalized urticaria	
4	M	11	MMR	1994	15	Edema of face and throat, pruritus, tachycardia	
5	M	8	MMR	1994	— ^a	Vasodilation, urticaria, nausea, vomiting, diarrhea	
6	F	45	HBV	1995	120	Dyspnea, urticaria, pruritus, chest pain	History of multiple allergies
7	F	26	Td	1997	— ^a	Edema at injection site, urticarial rash	
8	F	45	INFi	1998	60	Generalized urticaria, edema of throat, wheezing	History of multiple allergies
9 ^b	F	54	INFi	1998	180	Itchy watery eyes, wheezing, edema of throat, diarrhea	History of multiple allergies
10	F	48	INFi	1998	20	Generalized urticaria, dyspnea	
11	F	35	INFi	1998	30	Edema of tongue and throat	
12	F	32	INFi	1998	60	Wheezing, nausea	
13	F	47	INFi	1999	5	Tachycardia, chest pain, numbness around lips, weakness	History of asthma
14	F	37	Td	1999	60	Cough, chest tightness	Treatment with antihistamines pre- and post-vaccination
15 ^b	F	22	HAV, MMR, Td	2000	15	Urticaria, dyspnea, pallor	History of multiple allergies
16	F	6	HAV, IPV	2000	40	Vomiting, lethargy, pallor, dyspnea	History of multiple allergies
17	F	43	INFi	2000	60	Edema of throat and tongue	History of multiple allergies
18	F	Unknown	MMR	2000	— ^a	Edema at injection site, generalized urticaria, wheezing, tachycardia	
19	F	44	INFi	2001	15	Generalized urticaria, hypertension	
20	F	46	INFi	2001	10	Pruritus, chest tightness, urticaria on neck	
21	F	29	INFi	2001	60	Urticaria on torso, red and sore injection site	History of multiple allergies
22	F	30	Td	2001	— ^a	Dyspnea	
23	M	1	MMR + VAR	2001	10	Urticaria, edema of face	
24	F	16	HBV	2002	120	Urticarial rash from shoulder to elbow	History of drug allergy
25	F	39	INFi	2002	210	Generalized urticaria	History of multiple allergies
26	F	29	RUB	2002	— ^a	“Classic anaphylactic reaction” (per reporter)	
27	F	24	YEL	2003	15	Wheezing, edema of throat	History of asthma and multiple allergies
28	M	2	VAR	2003	60	Generalized urticaria, vomiting	

Vaccine abbreviations: ANTad; anthrax vaccine, adsorbed; INFi; influenza virus inactivated vaccine; HAV; hepatitis A vaccine; HBV; hepatitis B vaccine; IPV; poliovirus inactivated (injectable) vaccine; MMR; measles, mumps, rubella vaccine; Td; tetanus toxoid, and diphtheria toxoid vaccine, for adult use; YEL; yellow fever vaccine; VAR; varicella; RUB; rubella.

^a Reports states that the reaction started immediately.

^b Required hospitalization.

after injection (if no exact interval is mentioned); and (2) presence of at least one of the following groups of symptoms: dermatological, respiratory, gastrointestinal or cardiovascular. Reports describing local injection site reactions (e.g. itching, rash, hypersensitivity and/or pain localized to the site of injection) were excluded.

3. Results

As on 15 October 2003, VAERS received 167,233 notifications. Of these, 147 (0.1%) reports mentioned a history of latex allergy in the vaccine recipient. Of the 147, 28 (19%) developed a possible allergic adverse event (Table 1). Two patients required hospitalization for 1 day, with both reporting a complete recovery. The majority of patients were female ($N = 24$, 86%). Ages ranged from 1 to 54 years. Onset of first symptoms ranged from 5 min to 3.5 h after injection. Eleven cases (39%) received inactivated influenza vaccines; four (21%) received hepatitis B vaccines. The remaining reports mentioned hepatitis A vaccines, tetanus and diphtheria toxoids, measles–mumps–rubella vaccine, rubella vaccine, varicella vaccine, inactivated polio vaccine, anthrax vaccine adsorbed, and yellow fever vaccine. Fourteen (50%) cases reported a history of hypersensitivity to various drugs, foods or aeroallergens, in addition to latex allergy.

4. Discussion

The direct scientific evidence that vaccines which come into contact with DNR products present a problem in clinical settings is limited. There are various views expressed in the literature regarding the potential of latex proteins in vial stoppers and syringe plungers to elicit allergic reactions in latex-allergic individuals [4–8]. Two reports provide strong circumstantial evidence for the association [9,10]. These describe two diabetic patients who developed local reactions after insulin injections that appeared to be caused by latex antigens in the insulin vial stopper and/or syringe. When insulin was administered in latex free syringes from latex-free vials in these patients, no reaction occurred.

Only one report in the literature describes a case of anaphylaxis following vaccination of a latex-sensitive patient [11]. The authors hypothesized that vaccine contamination happened when the needle was passed through the rubber vial stopper as the vaccine was drawn up. Particles of rubber could have thus been transferred into the needle and then into the patient. No reaction occurred in this patient on re-vaccination when the vaccine was drawn up using a glass syringe from a vial with the stopper removed.

Severe hypersensitivity reactions following immunization are extremely rare [12]. In this review, we found only 28 patients with a history of latex allergy who had possible immediate-type hypersensitivity reactions following receipt of vaccines that could theoretically be contaminated with la-

tex proteins from the packaging. Most of these vaccines contain small amounts of other known potential allergens, such as yeast proteins in hepatitis B vaccines, egg proteins in influenza vaccines, and egg proteins and gelatin in yellow fever vaccines. Therefore, it is not possible to implicate latex proteins as the only possible cause of these reactions. Even if it is assumed that all cases in this review reacted to latex allergens in the vaccines, the corresponding vaccine specific risk is probably extremely small considering that hundreds of thousands of latex-sensitive persons get vaccinated every year (approximately 200 million doses of vaccines are administered in the US each year and approximately 1–6% of the population may be sensitized to latex) [13,14].

Eighty-six percent of the vaccinees in this case series were female. One possible explanation for this observation is the fact that both vaccination coverage and prevalence of latex sensitivity is quite high among health care workers [15], the majority of whom are women (in the US, 94% of registered nurses and 47% of medical students are women) [16,17]. As VAERS reports do not include occupational status of cases, our review could not determine the extent of reporting by health care workers.

There are several well-known limitations of using VAERS data, incomplete documentation of adverse events and underreporting being two of the most important [3,18,19]. Similar to other spontaneous reporting systems, the extent of this underreporting bias in VAERS for most adverse events is unknown. However, the degree of underreporting tends to be smaller for serious medical events [20,21], and it is reassuring that there were no such events in this review. As a result of incomplete documentation of adverse events and patient medical histories, VAERS data are also subject to significant variability in the completeness of information provided in each case report. It is possible that the true number of vaccine recipients with histories of latex allergy within VAERS is higher than the 147 cases that were documented in the database, however, the VAERS reporting form has a field specifically designated for pre-existing physician-diagnosed allergies and medical conditions (the form can be viewed at http://www.vaers.org/pdf/vaers_form.pdf).

The current package inserts for 31 different vaccines from seven different US vaccine manufacturers indicate that they contain dry natural latex rubber in the vaccine vial stopper, syringe plunger or needle cover. The US Food and Drug Administration issued a rule in September of 1997 (effective in September of 1998) “requiring labeling statements on medical devices, including device packaging, containing natural rubber that contacts humans” [22]. They specifically cited vial stoppers and syringe plungers as examples of products that may contain dry natural rubber. The VAERS reports that are the subject of this paper cover a period from 1991 to 2003, before and after the FDA rule on latex labeling. We do not know whether or not the vials and syringes used to administer the vaccines to the subjects in this report contained latex. Even if we had package inserts contemporary to the time of vaccine administration, we would not know if packaging that

did not describe latex meant that none was present or that it was simply not a requirement to label the packaging as such. It is unlikely that all 28 of the subjects reported here received vaccines from vials or stoppers that contained latex. Based on the current package inserts, only 19 of the 28 would have done so. Nonetheless, we have included all 28 as a conservative approach to the assessment of the risk.

In conclusion, immunization of latex-sensitive individuals using vaccines that contain DNR in the packaging appears to be associated with minimal risk of immediate-type hypersensitivity allergic reactions.

Substituting DNR with synthetic materials in vaccine packaging whenever possible will further reduce this preventable risk.

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