

Hypersensitivity Reactions to Vaccine Components

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Vaccines are responsible for the control of many infectious diseases that were once common in the United States, including polio, measles, diphtheria, pertussis (whooping cough), rubella (German measles), mumps, tetanus, and *Haemophilus influenzae* type b. National efforts to generate collaboration between federal, state, and local governments and public and private health care providers have resulted in record high levels of vaccination coverage in the United States. The high rate of US vaccinations is paralleled by growing concerns about the safety of their delivery. The variety of substances used in vaccines sometimes causes the development of cutaneous reactions in susceptible adults and children. This article will review adverse cutaneous events consistent with hypersensitivity reactions to the following ingredients in vaccines: aluminum, thimerosal, 2-phenoxyethanol, formaldehyde, and neomycin.

VACCINATION is an effective method to reduce the prevalence of infectious diseases worldwide. With the increasing number of recommended available vaccines, there are growing concerns about potential adverse effects from multiple immunizations. Serious side effects from vaccines are rare, which indicates that the benefits inherent in their administration outweigh the possibility of a patient's developing a reaction to them.

A comprehensive table lists all Food and Drug Administration (FDA)-approved vaccines and pays particular attention to quantities of the components aluminum, thimerosal, formaldehyde, 2-phenoxyethanol, and neomycin.^{1,2} Although other constituents of vaccines, such as egg protein and gelatin, can cause immediate immunoglobulin E (IgE)-mediated hypersensitivity reactions, this article will focus primarily on delayed hypersensitivity reactions; as such, egg protein and gelatin will not be further discussed.

Aluminum

Aluminum is a tin-white, malleable, and ductile metal used as a pure metal or in alloys. Contact sensitivity to non-injected aluminum is rare but most commonly occurs

during the continual application of aluminum-containing antiperspirants. Aluminum allergy has been reported to be associated with an axillary rash³ and with hand dermatitis.⁴

The more typical route of sensitization, however, is via the absorption of aluminum through hyposensitization injections and vaccines.⁵ Hyposensitization injections are used as treatment for IgE-mediated allergies, and the most commonly used extracts in these solutions are aluminum-containing antigens. Additionally, aluminum compounds have been widely used as adjuvants in prophylactic and therapeutic vaccines to potentiate the immune response. Aluminum-containing vaccines are prepared by the adsorption of antigens onto aluminum hydroxide or aluminum phosphate gels or by the precipitation of antigens in a solution of potassium aluminum sulfate.⁶

FDA regulations limit the aluminum content of an individual dose of a vaccine to 0.85 mg of elemental aluminum.⁷ The diminutive level of aluminum needed in vaccines to induce serious toxicities is evidenced by the undetectable changes in the normal plasma concentration of aluminum (5 µg/L) after intramuscular administration of an aluminum-containing vaccine.⁸

Although the development of painful and pruritic nodules at the site of aluminum-containing injections is a rare event, it is nevertheless the most frequent clinical manifestation of a hypersensitivity reaction to aluminum hydroxide in vaccines and in aluminum-containing antigen solutions.⁹ Such nodules have also been associated with hyper- and hypopigmentation, hypertrichosis, and lichenification.⁹

Of individuals who undergo immunotherapy with aluminum-containing allergen extracts, 33 to 70% develop a local immediate or transient inflammatory reaction^{10,11}

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whereas 0.5 to 6% develop nodules weeks, months, or even years after the introduction of aluminum.¹² Garcia-Patos and colleagues described 10 patients who had a persistent nodular reaction at the injection site of allergen extract preparations containing aluminum. The results of patch tests with 2% aluminum chloride in water were positive in five patients.⁹ Biopsy specimens from nodules appearing 1 to 9 months after the patients were injected were associated with the histopathologic features of a histiocytic foreign-body reaction. Nodular lesions of greater than 1 year's duration, however, showed a granulomatous reaction.

Some patients with hypersensitivity reactions to aluminum develop dermatitis, either localized or generalized.¹³ Cox and colleagues reported on an 18-month-old female child with dermatitis, characterized by acute weeping vesiculation at the vaccination site, that developed 6 months after she received diphtheria and tetanus toxoids and pertussis (DTP) triple vaccine.¹³ A patch-test result for aluminum was positive despite no known exposures to aluminum-containing products.

Thimerosal

Thimerosal, or sodium ethylmercurithiosalicylate, is a preservative used in low concentrations mainly in vaccines, cosmetics, ophthalmic and otolaryngologic medications, antitoxins, topical and intramuscular steroid preparations, and intradermal tests.¹⁴ Thimerosal has two distinctive components, an organic mercury compound and thiosalicylate, both of which are involved in thimerosal allergy.

Thimerosal is the fifth most common allergen, according to the North American Contact Dermatitis Group (NACDG).¹⁵ The rate of reactivity is 10.2% with a designated clinical relevance of 7.2%, making it one of the least clinically relevant of the 65 allergens tested by the NACDG.¹⁶ Most patients with a clinically relevant thimerosal allergy are women with a periorbital dermatitis from thimerosal in eye cosmetics or contact lens solutions.¹⁷ Thimerosal has rarely been associated with systemic reactions, including generalized eczema or urticaria¹⁸; one case of airway obstruction was reported as a delayed-type hypersensitivity reaction to thimerosal in throat spray.¹⁹

Despite the low clinical relevance of thimerosal allergy, the rate of thimerosal sensitivity has increased during the last decade, probably because of the increase in vaccines administered during infancy. With the initiation of a mass vaccination campaign in Austria in 1981, the administration of thimerosal-containing vaccines for tick-borne encephalitis (TBE) increased from 6% in 1980 to 86% in 2001. The growing number of people immunized to TBE

has been concomitant with an increase in thimerosal-sensitized individuals in Austria.^{14,20} Bruckner and colleagues investigated the prevalence of positive patch-test results using the TRUE Test system (Mekos Laboratories A/S, Hillerød, Denmark) on children under 5 years of age to determine whether sensitization to contact allergens was common in infancy.²¹ In this study, 24.5% of asymptomatic children from 6 months to 5 years of age were sensitized to one or more contact allergens, and thimerosal was the second most prevalent allergen (after nickel). Vaccines thus appear to sensitize children to thimerosal at a younger age than expected, given the unlikelihood of contact exposure in this age group to other thimerosal-containing products. Osawa and colleagues also demonstrated this phenomenon by associating DTP vaccination with thimerosal sensitivity in a guinea pig model.²²

To determine whether patients with thimerosal allergy could tolerate vaccination, Audicana and colleagues evaluated tolerance to thimerosal-containing vaccines in 125 patients sensitized to mercury derivatives and/or thimerosal.²³ Patch-test results in this patient population revealed that 45% of patients had positive reactions to thimerosal (0.05% in petrolatum), 74% had positive reactions to metallic mercury (0.5% in petrolatum), and 70% had positive reactions to mercury chloride (0.1% in water). In 10 cases, of all mercury derivatives tested, thimerosal yielded the only positive patch-test result. A questionnaire revealed that the likely source of sensitization in the 57 thimerosal patch-test-positive patients was vaccination. Thimerosal-allergic patients were challenged with three intramuscular injections of thimerosal solution (100 µg/mL) into the arm; if no reaction was observed, the dosage was increased (to 0.1 mL, 0.5 mL, and 1.0 mL) every 48 hours, alternating between the right and left arm. Challenge tests resulted in no cutaneous reactions in 91% of thimerosal-allergic patients whereas 9% had a mild reaction characterized by local induration and micropapules that resolved with the third intramuscular dose of thimerosal. Thus, this study demonstrated that vaccination of thimerosal-sensitized individuals may be considered when the benefits outweigh the risks of these local reactions.

In a retrospective case-control study, Cox and Forsyth demonstrated that patients with positive patch-test reactions to thimerosal did not have more vaccination reactions than patch-test negative controls had.²⁴ The conditions of thimerosal delivery in routine vaccines may be sufficient to induce sensitization but insufficient to evoke elicitation.

Much of the controversy around thimerosal in vaccines has centered on the theoretical risk of mercury poisoning. Since 2000, all pediatric hepatitis vaccines in the United

States have been thimerosal free. Some vaccines have trace levels of thimerosal left over from the manufacturing process (less than 1 µg thimerosal per 0.5 mL dose of vaccine),²⁵ an amount that is considered insignificant.

2-Phenoxyethanol

2-Phenoxyethanol (2-PE) is a preservative in some vaccines and is effective against a broad spectrum of microorganisms but particularly against *Pseudomonas aeruginosa*.²⁶ The action of 2-PE on gram-negative bacteria is reported to involve the disruption of cell membranes and the uncoupling of oxidative phosphorylation.²⁷ Since 1970, 2-PE has increasingly been added to cosmetics and pharmaceuticals, including vaccines.²⁸ Sensitivity to 2-PE is detected by patch testing with 2-PE alone or with Euxyl K400, a biocide that consists of 2-phenoxyethanol and methyldibromoglutaronitrile (MDGN) in a ratio of 4:1. 2-Phenoxyethanol rarely causes sensitization, so the majority of allergic contact dermatitis reactions to Euxyl K400 are due to the MDGN component.²⁹

Generalized contact eczema due to 2-phenoxyethanol has been described in a single case report. In the United States, an 18-month-old boy with a strong family history of atopic dermatitis and immediate-type allergy developed generalized eczema twice, both times within 24 hours of routine administration of DTP vaccine.³⁰ Patch testing with the whole vaccine, as well as with its individual components in standardized concentrations and vehicles, was performed on the skin after resolution of the reaction. The patch-test result with 2-PE (2% in petrolatum) was positive. Substitution of 2-PE with thimerosal in a subsequent DTP booster resulted in no cutaneous adverse events.

Formaldehyde

Formaldehyde is nearly ubiquitous, being present in polymerized plastics, metalworking fluids, wood composites, insulation, medicaments, fabrics, cosmetics, detergents, and vaccines. Formaldehyde is the eighth most common allergen and had an 8.4% rate of reactivity in 4,909 patients who were patch-tested. In vaccines, formaldehyde is used as an inactivating agent that can eliminate the harmful effects of bacterial toxins and destroy the capacity of infectious viruses to replicate.⁶ The concerns over formaldehyde in vaccines center on its potential carcinogenicity in vitro.⁶ The quantity of formaldehyde in individual vaccines does not exceed 0.1 mg per dose.

Animals exposed to chronic formaldehyde at doses of 80 to 100 mg per day developed no malignancies over a 2-year period.³¹

Formaldehyde in vaccines has been reported to exacerbate hand eczema, as described in a single case report.³² However, no other cases of formaldehyde-induced cutaneous reactions from vaccine administration have been reported in the literature.

Neomycin

Neomycin is an antibiotic that interferes with bacterial protein synthesis by binding primarily to the 30S subunit of bacterial ribosomes. Many vaccines contain trace amounts of neomycin to prevent bacterial contamination during the manufacturing process. As a topical medicament, neomycin elicits a high sensitization rate. According to the NACDG, neomycin is the third most prevalent allergen that often manifests as a delayed-type contact dermatitis.²⁵

There is little reason to believe that high sensitization rates to neomycin are attributable to vaccines. To date, no cases of local or generalized eczematous reactions to neomycin-containing vaccines have been reported. One case of anaphylaxis has been attributed to neomycin in a vaccine although the causal relationship is uncertain.³³ Measles, mumps, rubella (as well as the MMR vaccine), varicella, and poliovirus vaccines contain ≤ 25 µg of neomycin per dose,³⁴ an amount that typically does not elicit an allergic skin reaction.²⁵ Although contact dermatitis from topical neomycin is common, it is generally not considered to be a contraindication to immunization with neomycin-containing vaccines.³⁵

Conclusion

Adverse reactions to vaccines can be local or systemic and can be immediate or delayed in onset. Contact hypersensitivity reactions to vaccine constituents in susceptible individuals can be identified by patch testing. A positive patch-test reaction to a vaccine component often does not necessarily preclude vaccine administration. Vaccine administration is possible despite patch-test positive results to the aforementioned chemicals because either the component is present in insignificant amounts that are insufficient to provoke elicitation or because the vaccine is given intramuscularly or subcutaneously—routes of administration not commonly associated with allergic contact dermatitis. The risk assessment of vaccination in

Table 1. Components of Vaccines Approved by the Food and Drug Administration

Vaccine (Manufacturer)	Component				
	Neomycin	Aluminum	2-Phenoxyethanol	Thimerosal	Formaldehyde
Anthrax vaccine (Biopart Corporation)	—	Aluminum hydroxide 1.2 mg/mL	—	—	100 µg/mL
Cholera (Wyeth-Ayerst)	—	—	—	—	—
Tripedia; DTP (Aventis Pasteur)	—	Aluminum potassium sulfate, 0.170 mg aluminum/dose	—	—	≤ 0.02%
Tetanus and diphtheria toxoids* (Aventis Pasteur)	—	Aluminum potassium sulfate, 0.28 mg aluminum/dose	—	0.01%	≤ 0.02%
Diphtheria and tetanus toxoids† (Lederle)	—	Aluminum phosphate, 0.23–0.30 mg aluminum/dose	—	0.01%	≤ 0.02%
Infanrix; DTP (GlaxoSmithKline)	—	Aluminum hydroxide, 0.625 mg aluminum/dose	2.5 mg/dose	—	≤ 0.02%
Act-HIB; <i>Haemophilus</i> b conjugate vaccine/tetanus toxoid conjugate (Aventis Pasteur)	—	—	—	—	—
HibTITER; <i>Haemophilus</i> b conjugate vaccine/diphtheria CRM ₁₉₇ protein conjugate (Lederle)	—	—	—	50 µg/dose	—
Liquid PedvaxHIB; <i>Haemophilus</i> b conjugate vaccine/meningococcal protein conjugate (Merck)	—	Aluminum hydroxide, 0.225 mg aluminum/ dose	—	—	—
Comvax; <i>Haemophilus</i> b conjugate/ meningococcal protein conjugate and recombinant HBV vaccine (Merck)	—	Aluminum hydroxide, 0.225 mg aluminum/ dose	—	50 µg/dose	—
Energix-B; recombinant HBV vaccine (GlaxoSmithKline)	—	Aluminum hydroxide, 0.5 mg aluminum/mL	—	25 µg/adult dose; ≤ 0.5 µg/pediatric dose	—
Recombivax HB; recombinant HBV vaccine (Merck)	—	Aluminum hydroxide, 0.5 mg aluminum/mL	—	50 µg/mL for adult formulations; pediatric vaccine available without thimerosal	—
Vaqa; hepatitis A vaccine (Merck)	—	Aluminum hydroxide, 0.45 mg aluminum/mL	—	—	< 0.8 µg
Havrix; hepatitis A vaccine, inactivated (GlaxoSmithKline)	—	Aluminum hydroxide, 0.5 mg aluminum/mL	0.5%	—	—
Typhim Vi; typhoid Vi polysaccharide vaccine (Aventis Pasteur)	—	—	—	—	—
Fluzone; influenza vaccine, trivalent, types A and B (Aventis Pasteur)	—	—	—	50 µg/dose	—
FluShield; influenza vaccine, trivalent, types A and B (Wyeth-Ayerst)	—	—	—	50 µg/dose	—
Fluogen; influenza vaccine, trivalent, types A and B (Parkdale)	—	—	—	50 µg/dose	—

(continued)

Table 1. (continued)

Vaccine (Manufacturer)	Component				
	Neomycin	Aluminum	2-Phenoxyethanol	Thimerosal	Formaldehyde
JE-VAX; Japanese encephalitis virus vaccine (Aventis Pasteur)	—	—	—	70 µg/dose	< 100 µg/dose
LYMERix; Lyme disease vaccine (GlaxoSmithKline)	—	Aluminum hydroxide, 0.5 mg aluminum/dose	2.5 mg/dose	—	—
MMR II (Merck); each component also marketed separately as Attenuvax (measles), MumpsVax (mumps), MeruvaxII (rubella), M-R-VaxII (measles and rubella), and BiavaxII (mumps and rubella)	25 µg/dose	—	—	—	—
Prenar; pneumococcal seven-valent conjugate vaccine/diphtheria CRM ₁₉₇ protein conjugate (Lederle)	—	Aluminum phosphate, 0.125 mg aluminum/dose	—	—	—
Pnu-Imune 23; pneumococcal vaccine polyvalent (Lederle)	—	—	—	50 µg/dose	—
IMOVAX rabies virus vaccine (Aventis Pasteur)	< 150 µg/dose	—	—	—	—
RabAvert; rabies virus vaccine (Chiron)	< 1 µg	—	—	—	—
Dryvax, smallpox vaccine (Wyeth Ayerst)	Trace	—	—	Trace	—
Tetanus toxoid, adsorbed (Lederle)	—	Aluminum phosphate, 0.8 mg aluminum/dose	—	0.01%	≤ 0.02%
Vivotif Berna; live oral typhoid vaccine (Berna)	—	—	—	—	—
VARIVAX; varicella virus vaccine (Merck)	Trace	—	—	—	—
YF-VAX; yellow fever vaccine (Aventis Pasteur)	—	—	—	—	—

DTP = diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed; HBV = hepatitis B virus; MMR = measles, mumps, and rubella vaccine, live.

*Adsorbed for adult use.

†Adsorbed for adult and pediatric use.

known allergic individuals should include the information contained herein.

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