

# Hypersensitivity Reactions to Vaccine Constituents: A Case Series and Review of the Literature

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**Vaccines are composed of immunogens, preservatives, adjuvants, antibiotics, and manufacturing by-products. Components of vaccines may rarely elicit adverse reactions in susceptible individuals, thus raising concerns regarding vaccine safety. In this report, we add to the medical literature 3 cases of cutaneous delayed-type hypersensitivity to the vaccine preservative aluminum. We provide a review of major constituents in vaccines that have elicited immediate-type or delayed-type hypersensitivity reactions and describe their clinical manifestations. We include a table of the Food and Drug Administration–approved vaccines, which lists the quantities of major components including ovalbumin (egg protein), gelatin, aluminum, neomycin, 2-phenoxyethanol, thimerosal, and formaldehyde. Our goals were to inform physicians on the variety of hypersensitivity reactions to common vaccines and to provide information on the choice of vaccines in patients with suspected hypersensitivity.**

SINCE THE invention of vaccines more than 200 years ago, once-fatal infectious diseases have become preventable on a global level. Vaccines consist of immunogens (bacterial or viral antigens) in addition to preservatives, adjuvants, antibiotics, and by-products or residuals from the manufacturing process.<sup>1</sup> The additional constituents of vaccines are important in their development, immunogenicity, and safety. Rare case reports document adverse reactions to specific components of vaccines. As such, with the increasing number of available and recommended vaccines, there are concerns about the potential toxicity associated with vaccines.<sup>2,3</sup>

Adverse reactions to vaccines include immediate-type (ie, immunoglobulin E mediated) and delayed-type (ie, type 4) hypersensitivity reactions. Fortunately, the rate of vaccine-induced adverse effects is low, ranging from 4.8 to 83 per 100,000 doses of the most frequently used vaccines.<sup>4</sup> Furthermore, life-threatening anaphylaxis remains extremely rare, averaging 1 per 1,500,000 doses.<sup>4</sup>

We report 3 cases of delayed-type hypersensitivity reactions to vaccine components and review constituents that may elicit adverse reactions. Whereas adverse reactions to vaccines are not limited to hypersensitivity reactions, this review will focus on this aspect of vaccine adverse effects. We discuss some constituents

that can cause immediate-type hypersensitivity, but mainly review delayed-type hypersensitivity reactions. This is an updated report that reevaluates our previous review to: illustrate the problem through the 3 included cases; explore constituents that cause immediate-type hypersensitivity, delayed-type hypersensitivity, or both; and include a comprehensive table of the Food and Drug Administration (FDA)–approved vaccines, including the quantities of various vaccine components (ie, ovalbumin, gelatin, aluminum, neomycin, 2-phenoxyethanol [2-PE], thimerosal, and formaldehyde).<sup>2</sup>

## CASE SERIES

### Case 1

An 11-year-old girl presented 6 months after influenza vaccination and 14 months after a combined diphtheria, tetanus, and acellular pertussis (DTaP) vaccination for evaluation of pruritic eruptions after vaccine administration, partially relieved by oral antihistamines. See Table 1 for description of these reactions and patch test reactions. Past medical history was notable for von Willebrand disease, with no known allergy to eggs.

### Case 2

A 5-year-old boy presented 2 months after DTaP vaccination for evaluation of subsequent exuberant cutaneous reaction that occurred 24 to 36 hours after immunization, relieved by oral prednisone. There was no known allergy to eggs. See Table 1 for description of these reactions and patch test reactions. Our institution's standard series of allergens for pediatric patients were not interpretable and obscured by a robust eczematous reaction.

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**TABLE 1. Three Cases of Delayed-Type Vaccine Hypersensitivity**

| Case | Sex    | Age, y | Vaccine Exposure                                          | Symptoms                                                                                                                                      | Personal or Family History of Atopy                                                                          | Positive Patch Test Reactions*                                                |
|------|--------|--------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| 1    | Female | 11     | Influenza DTaP                                            | Swelling, erythema, and pruritus at the injection site<br>Concurrent pruritic, erythematous eruption of arms and legs                         | Family history of atopic dermatitis and hay fever                                                            | Aluminum chloride hexahydrate (2+)                                            |
| 2    | Male   | 5      | DTaP                                                      | Erythema, edema, and blistering at injection site                                                                                             | Personal history of atopic dermatitis, hay fever, and allergy to nuts, dogs, cats<br>family history of atopy | Aluminum chloride hexahydrate (3+)<br>Glutaraldehyde (1+)                     |
| 3    | Male   | 4      | Nonspecific, multiple (most recent immunization at 18 mo) | Persistent indurated subcutaneous nodules, pruritus at the injection site<br>Recurrence of symptoms during upper respiratory tract infections | Family history of asthma and hay fever                                                                       | Aluminum chloride hexahydrate (strongly positive)<br>Neomycin<br>Formaldehyde |

\*Patients were tested to a standard series of allergens for pediatric patients in addition to vaccine allergens.

### Case 3

A 4-year-old boy with a history of exuberant injection site reactions to vaccines presented for evaluation of reactions occurring 24 to 48 hours after administration of various vaccines. See Table 1 for description of these reactions and patch test reactions. There was no known allergy to eggs. Of note, the patient developed pruritus during patch testing.

### DISCUSSION

Adverse reactions to vaccines range from mild, localized reactions to systemic anaphylaxis. Overall, hypersensitivity reactions to vaccine components are rare. We describe 3 children who developed varied, cutaneous, delayed-type hypersensitivity reactions to components of vaccines. Among the vaccine constituents tested in these patients, patch testing in all 3 patients revealed positive reactions to aluminum. Our patients presented with various cutaneous reactions including erythematous and pruritic eruptions, edema, blistering, and indurated nodules at injection sites. The following discussion addresses individual vaccine constituents, not including immunogens.

### VACCINE COMPONENTS

#### Egg Proteins

Vaccines produced in chick embryo cell lines can contain residual egg proteins, primarily ovalbumin. Measles, mumps, and rubella (MMR), influenza, yellow fever, tick-borne encephalitis (TBE), and rabies vaccines are produced in avian cell lines.<sup>4</sup> Importantly, allergy to ovalbumin is common in the pediatric population, affecting 1.6% to 2.4% of children.<sup>5,6</sup> There may be multiple routes of sensitization with respect to egg protein. Sensitization is thought to occur mainly as a result of oral exposure during infancy.

Reports documenting administration of egg-containing vaccines to patients with egg allergy range from safe administration without any adverse reaction<sup>7-9</sup> to severe and rapidly fatal hypersensitivity to egg proteins.<sup>8,10-12</sup> Regarding safe administration, James et al<sup>7</sup> demonstrated in a multicenter trial that there were no allergic reactions after administering influenza vaccine containing up to 1.2 µg of egg protein/mL to 83 patients with egg allergy, including 27 patients with a history of anaphylaxis to egg protein. Regarding hypersensitivity to egg-containing vaccines, a large study by Patja et al<sup>13</sup> reported that MMR vaccination caused 1 case of anaphylaxis, 1 case of urticaria and 0.3 cases of asthma exacerbation per 100,000 injections.

Vaccines such as MMR, TBE, and rabies contain relatively low quantities of egg proteins. However, influenza and yellow fever virus vaccines can contain higher amounts of ovalbumin and are contraindicated in patients with severe allergic reactions to egg proteins.<sup>4</sup> See Table 2 for ovalbumin-containing vaccines. It is important to ask patients about allergy to egg proteins before administering vaccines. When administering vaccines to patients with egg allergy, it is recommended to choose a vaccine with the lowest quantity of ovalbumin and to closely monitor the patient after administration.<sup>9</sup>

#### Gelatin

Gelatin is an animal protein used as a stabilizer in vaccines such as MMR, Japanese encephalitis virus (JEV), varicella, and DTaP (Table 2).<sup>4</sup> Adverse reactions to gelatin-containing vaccines consist of both immediate-type and delayed-type hypersensitivity reactions.<sup>14</sup>

Singer et al<sup>15</sup> documented an immediate-type hypersensitivity reaction (ie, severe urticaria) to varicella vaccine. In their report, a positive result in an intradermal test with porcine gelatin confirmed hypersensitivity to the gelatin stabilizer.<sup>15</sup> Kelso et al<sup>16</sup>

**TABLE 2. Food and Drug Administration–Approved Vaccines, Components and Quantities**

| Vaccine (Manufacturer)                                                                                                                                         | Ovalbumin | Gelatin   | Aluminum                                                     | Neomycin | 2-PE   | Thimerosal | Formaldehyde |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------|--------------------------------------------------------------|----------|--------|------------|--------------|
| Adenovirus types 4 and 7, live, oral (Barr Labs)                                                                                                               | —         | —         | —                                                            | —        | —      | —          | —            |
| Biothrax; anthrax adsorbed (Emergent Biodefense Operations Lansing)                                                                                            | —         | —         | Aluminum hydroxide<br>0.83 mg/dose                           | —        | —      | —          | 100 µg       |
| Mycobax; BCG live (Sanofi Pasteur)                                                                                                                             | —         | —         | —                                                            | —        | —      | —          | —            |
| TICE BCG; BCG live (Organon Teknika)                                                                                                                           | —         | —         | —                                                            | —        | —      | —          | —            |
| Diphtheria and tetanus toxoids adsorbed (Sanofi Pasteur)                                                                                                       | —         | —         | Aluminum potassium<br>sulfate ≤0.25 mg/dose                  | —        | —      | 0.01%      | <0.02%       |
| Tripedia; diphtheria and tetanus toxoids and acellular<br>pertussis adsorbed (Sanofi Pasteur)                                                                  | —         | 0.0015 mg | Aluminum potassium<br>sulfate ≤0.17 mg/dose                  | —        | —      | ≤0.00012%  | ≤100 µg      |
| Infanrix; diphtheria and tetanus toxoids and acellular<br>pertussis adsorbed (GlaxoSmithKline)                                                                 | —         | —         | Aluminum hydroxide<br>≤0.625 mg/dose                         | —        | —      | —          | ≤100 µg      |
| DAPTACEL; diphtheria and tetanus toxoids and<br>acellular pertussis adsorbed (Sanofi Pasteur)                                                                  | —         | —         | Aluminum phosphate<br>0.33 mg/dose                           | —        | 3.3 mg | —          | ≤0.1 mg      |
| Pediarix; diphtheria and tetanus toxoids and acellular<br>pertussis adsorbed, hepatitis B recombinant and<br>inactivated poliovirus combined (GlaxoSmithKline) | —         | —         | Aluminum hydroxide<br>0.85 mg/dose                           | ≤0.05 ng | —      | —          | ≤100 µg      |
| KINRIX; diphtheria and tetanus toxoids and acellular pertussis<br>adsorbed and inactivated poliovirus (GlaxoSmithKline)                                        | —         | —         | Aluminum hydroxide<br>≤0.6 mg/dose                           | ≤0.05 ng | —      | —          | ≤100 µg      |
| Pentacel; diphtheria and tetanus toxoids and acellular pertussis<br>adsorbed, inactivated poliovirus and <i>Haemophilus B</i><br>conjugate (Sanofi Pasteur)    | —         | —         | Aluminum phosphate<br>0.33 mg/dose                           | <4 pg    | 3.3 mg | —          | ≤5 µg        |
| PedvaxHB; <i>Haemophilus B</i> conjugate (Merck)                                                                                                               | —         | —         | Aluminum hydroxide<br>0.225 mg/dose                          | —        | —      | —          | —            |
| ActHB; <i>Haemophilus B</i> conjugate vaccine (Sanofi Pasteur)                                                                                                 | —         | —         | —                                                            | —        | —      | —          | <0.5 µg      |
| Hiberix; <i>Haemophilus B</i> conjugate (GlaxoSmithKline)                                                                                                      | —         | —         | —                                                            | —        | —      | —          | ≤0.05 µg     |
| Comvax; <i>Haemophilus B</i> conjugate and hepatitis B<br>recombinant (Merck)                                                                                  | —         | —         | Aluminum hydroxide<br>0.225 mg/dose                          | —        | —      | —          | ≤0.0004%     |
| Havrix; hepatitis A, inactivated (GlaxoSmithKline)                                                                                                             | —         | —         | Aluminum hydroxide<br>0.25 mg/dose                           | <40 ng   | —      | —          | ≤0.1 mg      |
| VAQTA; hepatitis A, inactivated (Merck)                                                                                                                        | —         | —         | Aluminum hydroxide<br>0.225 mg/dose                          | —        | —      | —          | <0.8 µg      |
| Twinrix; hepatitis A inactivated and hepatitis B recombinant<br>(GlaxoSmithKline)                                                                              | —         | —         | Aluminum phosphate<br>and aluminum hydroxide<br>0.45 mg/dose | ≤20 ng   | 5 mg*  | <0.0002%*  | ≤0.1 mg      |
| Recombivax HB; hepatitis B recombinant (Merck)                                                                                                                 | —         | —         | Aluminum hydroxide<br>≤0.5 mg/dose                           | —        | —      | —          | —            |
| Engerix-B; hepatitis B recombinant (GlaxoSmithKline)                                                                                                           | —         | —         | Aluminum hydroxide<br>≤0.5 mg/dose                           | —        | —      | —          | —            |
| Gardasil; human papillomavirus quadrivalent (types 6, 11,<br>16, and 18), recombinant (Merck)                                                                  | —         | —         | Aluminum hydroxyphosphate<br>sulfate 0.225 mg/dose           | —        | —      | —          | —            |

|                                                                                                                            |                      |                                   |   |   |          |      |          |          |   |
|----------------------------------------------------------------------------------------------------------------------------|----------------------|-----------------------------------|---|---|----------|------|----------|----------|---|
| Cervarix; human papillomavirus bivalent (types 16 and 18), recombinant (GlaxoSmithKline)                                   | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| Afluria; influenza virus, and influenza A (H1N1) 2009 monovalent (CSL Limited)                                             | ≤1 µg                | —                                 | — | — | ≤0.2 pg  | —    | 0.01%†   | —        | — |
| FluLaval; influenza virus, trivalent, types A and B, and influenza A (H1N1) 2009 monovalent (ID Biomedical Corp Quebec)    | 0.063 µg             | —                                 | — | — | —        | —    | 0.01%    | ≤25 µg   | — |
| FluMist; influenza, live, intranasal, and influenza A (H1N1) 2009 monovalent (MedImmune)                                   | 0.00076 µg           | 2.00 mg                           | — | — | —        | —    | —        | —        | — |
| Fluarix; influenza virus, trivalent, types A and B (GlaxoSmithKline)                                                       | 0.004 µg             | —                                 | — | — | —        | —    | <0.0004% | ≤5 µg    | — |
| Fluvirin; influenza virus, trivalent, types A and B, and influenza A (H1N1) 2009 Monovalent (Novartis)                     | 0.0551 µg            | —                                 | — | — | ≤2.5 µg  | —    | 0.01%    | —        | — |
| Agriflu; influenza virus, trivalent, types A and B (Novartis)                                                              | Egg proteins <0.4 µg | —                                 | — | — | ≤0.02 µg | —    | —        | ≤10 µg   | — |
| Fluzone; influenza virus, trivalent, types A and B, and influenza A (H1N1) 2009 monovalent (Sanofi Pasteur)                | 0.196 µg             | 0.05% (None in prefilled syringe) | — | — | —        | —    | 0.01%†   | ≤100 µg  | — |
| Ixiaro; Japanese encephalitis virus, inactivated, adsorbed (Intercell)                                                     | —                    | —                                 | — | — | —        | —    | —        | ≤200 ppm | — |
| JE-Vax; Japanese encephalitis virus inactivated (Research Foundation Microbial Diseases Osaka University)                  | —                    | 0.5 mg                            | — | — | —        | —    | 0.007%   | <100 µg  | — |
| Attenuvax; measles virus, live (Merck)                                                                                     | Residual             | 14.5 mg                           | — | — | 25 µg    | —    | —        | —        | — |
| MMR II; measles, mumps, and rubella virus, live (Merck)                                                                    | Residual             | 14.5 mg                           | — | — | 25 µg    | —    | —        | —        | — |
| ProQuad; measles, mumps, rubella and varicella virus, live (Merck)                                                         | Residual             | ≤11 mg                            | — | — | 5 µg     | —    | —        | —        | — |
| Menveo; meningococcal (groups A, C, Y, and W-135) oligosaccharide diphtheria CRM197 conjugate (Novartis)                   | —                    | —                                 | — | — | —        | —    | —        | <0.30 µg | — |
| Menactra; meningococcal polysaccharide (serogroups A, C, Y and W-135) diphtheria toxoid conjugate vaccine (Sanofi Pasteur) | —                    | —                                 | — | — | —        | —    | —        | <2.66 µg | — |
| Menomune-A/C/Y/W-135; meningococcal polysaccharide, groups A, C, Y and W-135 combined (Sanofi Pasteur)                     | —                    | —                                 | — | — | —        | —    | 0.01%†   | —        | — |
| Mumpsavax; mumps virus live (Merck)                                                                                        | —                    | 14.5 mg                           | — | — | 25 µg    | —    | —        | —        | — |
| Pneumovax 23; pneumococcal, polyvalent (Merck)                                                                             | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| Prevnar; pneumococcal 7-valent conjugate (Wyeth)                                                                           | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| Prevnar 13; pneumococcal 13-valent conjugate (Wyeth)                                                                       | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| Poliovax; poliovirus, inactivated (human diploid cell)                                                                     | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| IPOL; poliovirus, inactivated (monkey kidney cell) (Sanofi Pasteur)                                                        | —                    | —                                 | — | — | <5 ng    | 0.5% | —        | ≤0.02%   | — |
| Imovax; rabies (Sanofi Pasteur)                                                                                            | —                    | —                                 | — | — | <150 µg  | —    | —        | —        | — |
| RabAvert; rabies (Novartis)                                                                                                | <3 ng                | <12 mg                            | — | — | <1 µg    | —    | —        | —        | — |
| ROTARIX; rotavirus vaccine, live, oral (GlaxoSmithKline)                                                                   | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| RotaTaq; rotavirus, live, oral, pentavalent (Merck)                                                                        | —                    | —                                 | — | — | —        | —    | —        | —        | — |
| Meruvax II; rubella virus, live (Merck)                                                                                    | —                    | 14.5 mg                           | — | — | 25 µg    | —    | —        | —        | — |
| ACAM2000; smallpox (Vaccinia), live (Sanofi Pasteur)                                                                       | —                    | —                                 | — | — | Residual | —    | —        | —        | — |

(Continued on next page)

**TABLE 2. (Continued)**

| Vaccine (Manufacturer)                                                                                  | Ovalbumin | Gelatin  | Aluminum                                    | Neomycin | 2-PE   | Thimerosal | Formaldehyde |
|---------------------------------------------------------------------------------------------------------|-----------|----------|---------------------------------------------|----------|--------|------------|--------------|
| Tetanus and diphtheria toxoids adsorbed (MassBiologics)                                                 | —         | —        | Aluminum phosphate<br><0.53 mg/dose         | —        | —      | ≤0.00012%  | <0.02%       |
| DECAVAC; tetanus and diphtheria toxoids adsorbed for adult use (Sanofi Pasteur)                         | —         | —        | Aluminum potassium sulfate<br>≤0.28 mg/dose | —        | —      | ≤0.00012%  | ≤100 µg      |
| Tetanus toxoid (Sanofi Pasteur)                                                                         | —         | —        | —                                           | —        | —      | 0.01%      | <0.02%       |
| Tetanus toxoid adsorbed (Sanofi Pasteur)                                                                | —         | —        | Aluminum potassium sulfate<br><0.25 mg/dose | —        | —      | 0.01%      | <0.02%       |
| Adacel; tetanus toxoid, reduced diphtheria toxoid and acellular pertussis, adsorbed (Sanofi Pasteur)    | —         | —        | Aluminum phosphate<br>0.33 mg/dose          | —        | 3.3 mg | —          | ≤5 µg        |
| Boostrix; tetanus toxoid, reduced diphtheria toxoid and acellular pertussis, adsorbed (GlaxoSmithKline) | —         | —        | Aluminum hydroxide<br>≤0.39 mg/dose         | —        | —      | —          | ≤100 µg      |
| Vivotif; typhoid live oral Ty21a (Berna Biotech)                                                        | —         | —        | —                                           | —        | —      | —          | —            |
| TYPHIM Vi; typhoid Vi polysaccharide (Sanofi Pasteur)                                                   | —         | —        | —                                           | —        | —      | —          | —            |
| Varivax; varicella virus, live (Merck)                                                                  | —         | 12.5 mg  | —                                           | Residual | —      | —          | —            |
| YF-Vax; yellow fever (Sanofi Pasteur)                                                                   | Residual  | 0.025 mL | —                                           | —        | —      | —          | —            |
| Zostavax; zoster, live (Merck)                                                                          | —         | 15.58 mg | —                                           | Residual | —      | —          | —            |

Please refer to vaccine package inserts.

\*Preservative-free form available.

†In multidose form only (not present in single-dose form).

Residual indicates quantity not listed in package insert.

reported a case of a 17-year-old girl with severe anaphylaxis to gelatin-containing MMR vaccine resolving with epinephrine and oral antihistamine. Other severe immediate reactions to gelatin in vaccines have been reported after varicella and JEV vaccinations.<sup>17</sup> Although anaphylaxis to measles vaccination is rare (0.18 per 100,000 given doses),<sup>18</sup> 1 study found that 28% of subjects with immediate-type reaction after MMR vaccine demonstrated immunoglobulin E antibodies to gelatin.<sup>13</sup>

Nonanaphylactic reactions to gelatin-containing vaccines have also been reported. These reactions include localized erythema and induration at the injection site, systemic rash or fever 3 to 48 hours after inoculation.<sup>19</sup> In vitro studies in patients with these nonanaphylactic reactions to gelatin-containing vaccines demonstrated positive lymphocytic responses consistent with delayed-type hypersensitivity in 61 (80%) of 76 patients.<sup>19</sup>

## Aluminum

Aluminum is a malleable metal that is the most widely used adjuvant in human vaccines. Aluminum may be found in various forms in vaccines, including aluminum hydroxide, aluminum potassium, or aluminum phosphate. As an adjuvant, aluminum functions to potentiate the immune response to vaccination.<sup>20</sup> Contact dermatitis to aluminum is well documented, with axillary dermatitis resulting from aluminum-containing antiperspirants as an example.<sup>21,22</sup>

Aluminum adjuvants may be found in many widely administered vaccines including tetanus, diphtheria, pertussis, hepatitis A, and hepatitis B.<sup>20</sup> See Table 2 for a comprehensive list of aluminum-containing vaccines. The FDA limits the aluminum content in a vaccine to 0.85 mg of elemental aluminum.<sup>23</sup> Hypersensitivity to aluminum is a rare complication that has been documented after administration of certain vaccines and allergy injections.<sup>24</sup>

As reflected in the patients we present in this article, the clinical manifestations of aluminum vaccine hypersensitivity are variable and multiple. Patients may develop localized or generalized dermatitis.<sup>25</sup> The most common presentation of vaccine hypersensitivity to aluminum are painful, pruritic nodules at the injection site(s) that develop weeks, months, or even years after the introduction of aluminum.<sup>26–28</sup> Changes in pigmentation, hypertrichosis, and lichenification may be associated with such nodules.<sup>27</sup> The pruritic, nodular reactions can persist for years and may be exacerbated during upper respiratory infections and application of aluminum-containing substances onto the skin such as sunscreens.<sup>26,27</sup> Patients with hypersensitivity to aluminum-containing vaccines generally demonstrate positive patch testing to aluminum.<sup>26,27</sup> Histopathologic examination of biopsy specimens reveals granulomatous and foreign body reactions.<sup>27</sup>

Some vaccines with documented hypersensitivity reactions to aluminum include DTaP, DTaP/poliomyelitis/*Haemophilus influenzae*, and the quadrivalent human papillomavirus vaccine.<sup>25,26,29</sup> Children with documented contact allergy to aluminum should also avoid other aluminum-containing products

including aluminum-containing antiperspirants and skincare products such as aluminum-containing sunscreens. Patients with hypersensitivity to aluminum-containing vaccines may be at increased risk for having adverse reactions to subsequent injections of aluminum-containing booster vaccines.<sup>26</sup>

## Thimerosal

Thimerosal is a mercury-containing compound that has been used as a preservative in various vaccines such as influenza, DTaP, pneumococcus, meningococcus, hepatitis B, and JEV (Table 2).<sup>30,31</sup> It is also found in items including but not limited to ophthalmic products, cosmetics, and tattoo inks.<sup>30</sup> Thimerosal has been previously documented as the fifth most common allergen by the North American Contact Dermatitis Group.<sup>32</sup> A meta-analysis investigating positive patch tests with the T.R.U.E. Test system in children younger than 5 years found thimerosal to be the second most prevalent allergen. One hypothesis for the prevalence of contact dermatitis to thimerosal is sensitization from exposure in vaccines.<sup>33</sup>

Hypersensitivity to thimerosal most commonly presents as periorbital dermatitis in relation to eye cosmetics and contact lens solutions.<sup>34</sup> Less common reactions to thimerosal from nonvaccine products include generalized eczema, urticaria, and delayed-type hypersensitivity manifesting as airway obstruction in association with a thimerosal-containing throat spray.<sup>22,35</sup> Patients with a history of previous sensitization to topical thimerosal (ie, contact lens solution) may rarely then develop systemic contact dermatitis and positive patch testing after administration of thimerosal-containing vaccines.<sup>36</sup>

Immediate-type and delayed-type hypersensitivity reactions to thimerosal-containing vaccines have been documented. Immediate hypersensitivity to thimerosal has been reported with skin prick testing of the adult influenza vaccine.<sup>37</sup> The reported patient developed wheals and an anaphylactic response with pruritus, throat tightness, cough, and shortness of breath that resolved with intramuscular epinephrine.<sup>37</sup> Of note, the patient also had a history of eyelid pain and erythema after use of thimerosal-containing contact lens solution 15 years prior.<sup>37</sup>

Delayed-type hypersensitivity reactions to thimerosal can have various cutaneous manifestations. For example, a case of delayed-type hypersensitivity to a thimerosal-containing vaccine manifested with oral erosions and targetoid bullae with erythematous borders and hemorrhagic crusting consistent (along with histopathologic examination) with erythema multiforme.<sup>38</sup> A case of delayed-type hypersensitivity to a thimerosal-containing influenza vaccine manifested with a pruritic, erythematous, maculopapular eruption that resolved with oral prednisone and antihistamines. The latter patient was found to have a history of eyelid dermatitis from a thimerosal-containing contact lens solution.<sup>36</sup>

A history of sensitization to thimerosal-containing products is important to elicit before vaccination. Patch testing can confirm clinical suspicion of prior sensitization.<sup>30</sup> It is possible for patients with thimerosal allergy to tolerate thimerosal-containing vaccines.

One study demonstrated that more than 90% of patients with thimerosal allergy tolerated intramuscular injections of thimerosal at concentrations comparable to vaccines. Less than 5% of such patients developed mild localized reactions.<sup>39</sup> The US Public Health Service and the American Academy of Pediatrics recommended the removal of thimerosal from pediatric vaccines for children younger than 6 years secondary to the theoretical risk of mercury toxicity and potential neurologic effects.<sup>30,31</sup>

## 2-Phenoxyethanol

2-Phenoxyethanol is a preservative used in vaccines. It functions to prevent contamination with microorganisms, particularly *Pseudomonas aeruginosa*.<sup>40</sup> Various toiletries, cosmetics, and pharmaceuticals contain 2-PE.<sup>41,42</sup>

There is 1 reported case of hypersensitivity to 2-PE associated with vaccination. The patient was an 18-month-old boy with a family history of atopic dermatitis who developed eczematous dermatitis less than 24 hours after routine administration of DTaP vaccine on 2 separate occasions.<sup>43</sup> The dermatitis was more severe during the second episode, involving the whole body. Patch testing was positive for 2-PE, and substitution of 2-PE for another preservative resulted in no adverse reactions after administration of a vaccine booster shot.<sup>43</sup> See Table 2 for vaccines containing residual quantities of 2-PE.

## Formaldehyde

Formaldehyde is widely used in a variety of commercial products in which it acts to diminish the effects of bacterial toxins and reduce the infectivity of viruses.<sup>31</sup> It is found in residual quantities, less than 0.1 mg, in various vaccines such as influenza, poliomyelitis, and DTaP (Table 2).<sup>31</sup>

There is 1 reported case of formaldehyde-containing hepatitis B vaccine aggravating eczematous dermatitis on the hands.<sup>44</sup> The patient developed an erythematous and vesicular eruption after initial vaccination, with a positive patch test to formaldehyde. The second administration of the vaccine resulted in a milder dermatitis, and a third resulted in mild generalized pruritus for 1 day.<sup>44</sup> No other documented cases of formaldehyde-induced hypersensitivity from vaccine administration have been described in the literature.

Concerns about the safety of formaldehyde have stemmed from in vitro studies demonstrating that, in high concentrations, formaldehyde may induce DNA damage and malignant transformation of cells. Nevertheless, formaldehyde has not been associated with carcinogenesis in humans.<sup>31</sup>

## Neomycin

Antibiotics such as neomycin, streptomycin, polymyxin B, and chlortetracycline have been used to prevent bacterial contamination of vaccines. Of these antibiotics, neomycin is typically contained in detectable quantities and can be found in MMR, DTaP, TBE, hepatitis, varicella, influenza, and rabies vaccines.<sup>31</sup>

See Table 2 for vaccines containing neomycin. Because antibiotics in general may cause immediate-type hypersensitivity reactions in children, there are concerns about the use of antibiotics in vaccines.<sup>31</sup>

There is 1 reported case of anaphylaxis associated with neomycin in an MMR vaccine. This patient had a history of prior sensitization to topical neomycin, which manifested as a maculopapular eruption after use of a cream and lip balm containing neomycin.<sup>45</sup> Of note, there was no skin test performed to attribute the anaphylactic response to neomycin.

Although neomycin elicits a high rate of contact dermatitis and is considered the third most commonly patch test–positive allergen according to North American Contact Dermatitis Group, there are no reported cases of contact dermatitis associated with its use in vaccines.<sup>46</sup> Immunization with neomycin-containing vaccines is not contraindicated in patients with ACD from topical neomycin.<sup>47</sup> Neomycin-containing vaccines typically contain less than 150 µg per dose. Of note, the T.R.U.E. Test epicutaneous patch test contains 0.19 mg (190 µg) of neomycin sulfate per patch.<sup>48</sup>

## CONCLUSIONS

Adverse reactions to vaccine constituents are rare and may manifest locally or systemically with immediate or delayed onset. We review the major components of vaccines, not including the primary immunogens, and describe some of the associated adverse reactions. We highlight the vaccines which contain relevant constituents such as egg protein, gelatin, aluminum, thimerosal, 2-PE, formaldehyde and neomycin. In addition, we illustrate the quantities of these constituents in FDA-approved vaccines. Contact hypersensitivity reactions (ie, delayed-type hypersensitivity reactions) to vaccine components in susceptible individuals may be identified by patch testing. A positive patch test reaction to a vaccine component does not necessarily preclude subsequent administration. Decisions to revaccinate patients with known hypersensitivity should be individualized to the patient's needs, evaluating the importance of the vaccination and the severity of the prior hypersensitivity. Especially in the event of suspicion for an immediate-type hypersensitivity, referral to an allergist is recommended. Because vaccinations are among the most important means of preventing potentially fatal infectious illnesses, it is important to consider the risks and benefits of each vaccination in children with documented hypersensitivities to vaccine components on a case-by-case basis and to seek vaccines free from such allergens in these children whenever possible.

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