Vaccines licensed by the US Food and Drug Administration (FDA) have been protecting children in the United States for more than 50 years and represent one of the most important health advances of the 20th century. Vaccines are credited with saving more lives and preventing more illnesses than any other medical treatment.
The risks of devastating childhood diseases, such as diphtheria, poliomyelitis, and tetanus, from failure to vaccinate far outweigh the risks associated with adverse reactions from vaccines.1

More than 1 billion doses of vaccines are administered to infants, children, and adults each year in the United States.2 The FDA mandates that vaccines be tested in both animal studies and human clinical trials prior to licensure. Included in this testing process is a review of all active ingredients, as well as additives, in the vaccines in an effort to ensure both safety and effectiveness. After a vaccine is approved, its effectiveness and safety are subsequently monitored by both the FDA and the Centers for Disease Control and Prevention (CDC).2

Vaccines have become a frequent topic of conversation between primary care physicians and their patients—especially parents who express concerns regarding the possibility of their children experiencing hypersensitivity reactions to vaccines. Patients’ safety concerns should be thoroughly addressed before administration of any medication, including vaccines. In the present article, we review the published evidence about hypersensitivity reactions associated with gelatin, antibiotics, and latex in vaccines.

**Gelatin**

In the early 1990s, several case reports implicating gelatin in live vaccines to hypersensitivity reactions surfaced, particularly in medical literature in Japan. Published in 1993, a single case report in the United States of a documented hypersensitivity reaction to the measles, mumps, and rubella (MMR) vaccine that took place in 1991—with confirmed immunoglobulin E (IgE) antibodies to gelatin—led to further investigation into gelatin-mediated vaccine reactions.3 Before that report, egg protein or antibiotics were the suspected culprits in these vaccine reactions and, often in an effort to avoid hypersensitivity events, egg-allergic individuals were appropriately not offered vaccination.4

Gelatin is a partially hydrolyzed protein derived from animal sources (eg, bovine and porcine hide and bones) that is added to vaccines as a heat stabilizer. It is most commonly added to live vaccines, including the MMR vaccine and—until recently—the tetanus, diphtheria, and acellular pertussis (Tdap) vaccines.3 (Most Tdap vaccine formulations are now manufactured without gelatin.) It is also a frequent ingredient in capsules for oral administration, as evidenced by the list of 360 gelatin-containing products in the 1998 Physician’s Desk Reference (published by Thomson Corporation).

The greatest risk for anaphylaxis from gelatin-containing products would be from injection or intravenous administration to a sensitized individual.3 Although there has been speculation that vaccine schedules with administration of an initial gelatin-containing vaccine may sensitize individuals for subsequent gelatin-containing vaccines, it is not entirely clear how susceptible individuals become sensitized or which individuals may be predisposed to serious IgE-mediated reactions.3 Case reports suggest that individuals who show sensitivity to eating gelatin-containing food products may also develop serious anaphylactic reactions to gelatin-containing vaccines.4,5

In addition to being aware of gelatin in the MMR vaccine and the few remaining gelatin-containing formulations of Tdap vaccine, clinicians should also be cautious regarding varicella and influenza vaccines. There have been confirmed cases of urticaria, with positive results to intradermal testing for gelatin, associated with varicella vaccine.6,7 There have also been cases of anaphylaxis, with positive results to IgE immunoblotting, associated with gelatin-containing influenza vaccine.8

In cases for which gelatin-free vaccines are not available and a gelatin allergy is suspected, it is appropriate to refer patients to an allergy-immunology specialist for further evaluation before initiating immunization.9-12 Keep in mind that patients who eat gelatin products are not
likely to have a gelatin allergy. In addition, the CDC provides an online publication titled Guide to Vaccine Contraindications and Precautions for clinician use (www.cdc.gov/vaccines/recs/vac-admin/downloads/contraindications-guide-505.pdf). Included in this guide is an outline of the Vaccine Adverse Event Reporting System (VAERS), a national vaccine safety program administered by the FDA and CDC. Health care professionals, as well as vaccine manufacturers, are required by the National Childhood Vaccine Injury Act of 1986 to report specific adverse events, including hypersensitivity reactions, occurring after the administration of routinely recommended vaccines. The CDC guide also includes Vaccine Information Statements (VISs) for commonly used vaccines. These statements should be given to patients and their caregivers. Vaccine Information Statements in Spanish and other languages can be found on the Immunization Action Coalition website at www.immunize.org/vis/.

According to the Guide to Vaccine Contraindications and Precautions, the following vaccines should not be administered to individuals with a known hypersensitivity to gelatin: MMR, varicella, and yellow fever. These contraindications are specifically stated on the VISs for those vaccines. In addition to being given the appropriate VISs, patients or their caregivers should be questioned about previous reactions to any vaccines or vaccine components, as well as about any food hypersensitivities. Such questions will allow clinicians to proactively identify those individuals who may be predisposed to hypersensitivity reactions.

Given the large number of routinely administered vaccines, concerns about possible hypersensitivity reactions to vaccines are commonly raised by many patients and by many parents of young patients. These concerns may be partly related to living in a society with heightened awareness and easy accessibility to information regarding other life-threatening hypersensitivity reactions, such as those associated with food or stinging insects. However, the actual prevalence of hypersensitivity to gelatin-containing vaccines appears to be small, and the benefit of vaccination against common devastating childhood diseases is great. Thus, vaccination with gelatin-containing vaccines should be encouraged, except in cases in which patients have a history of hypersensitivity to such vaccines or to foods containing gelatin products.

**Aminoglycoside antibiotics**

Aminoglycoside antibiotics are used to treat patients who have infections caused by aerobic, gram-negative bacteria. However, because of toxicities effects known to be associated with aminoglycoside antibiotics, their systemic use has been limited to empiric treatment of patients with severe infections. These antibiotics are often discontinued once culture results establish a narrower spectrum, better-tolerated treatment option. The everyday use of aminoglycosides in clinical practice has shifted primarily to topical preparations, such as neomycin sulfate ointment, gentamicin otic drops, and gentamicin ophthalmic solution. Neomycin is also used as a preservative in vaccines.

In the early 20th century, the history of vaccine administration in children was tarnished by reports of severe and sometimes fatal bacterial infections resulting from contaminated vaccines. As a result, vaccines are commonly raised by many patients and by many parents of young patients. These concerns may be partly related to living in a society with heightened awareness and easy accessibility to information regarding other life-threatening hypersensitivity reactions, such as those associated with food or stinging insects. However, the actual prevalence of hypersensitivity to gelatin-containing vaccines appears to be small, and the benefit of vaccination against common devastating childhood diseases is great. Thus, vaccination with gelatin-containing vaccines should be encouraged, except in cases in which patients have a history of hypersensitivity to such vaccines or to foods containing gelatin products.

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preservatives began to be added to vaccines. Neomycin is one of several antibiotics used in vaccine manufacturing to prevent bacterial contamination for the duration of the vaccine’s shelf life. Other antibiotics used as preservatives in vaccines include amphotericin B (an antifungal), chlortetracycline, polymixin B, and streptomycin. However, neomycin is the only antimicrobial used in detectable quantities in vaccines.

Neomycin preserves vaccine sterility by binding to the 30S ribosomal subunit of gram-negative bacteria, thereby interrupting protein synthesis. The blocked protein synthesis, in turn, increases permeability of the bacterial cell membrane, resulting in a potent bactericidal effect. As shown in the Figure, vaccines containing neomycin include those for the following illnesses: hepatitis A, influenza, MMR, pertussis and poliomyelitis, rabies, and varicella. Patients with a known history of hypersensitivity reactions to aminoglycosides may also have adverse reactions to vaccines containing neomycin. This association has raised parental concern about the safe use of neomycin-containing vaccines in children.

A review of the literature evaluating the risk of hypersensitivity reactions to aminoglycosides revealed a propensity toward mild type IV (ie, delayed or cell-mediated) reactions, with life-threatening type I anaphylactic reactions being rare. Furthermore, cross-reactivity among members of this drug class have been noted.14,15 The following text discusses reported hypersensitivity reactions to aminoglycoside antibiotics in topical, intravenous, and intramuscular preparations, as well as vaccines.

**Topical, intravenous, and intramuscular reactions**

Numerous case reports have shown topical reactions in the forms of rashes associated with use of topical aminoglycosides. All 10 cases reviewed of type I hypersensitivity reactions secondary to use of topical aminoglycosides displayed stereotypical signs and symptoms of such reactions (eg, bronchospasm, dizziness, hypotension).16,17 In 3 cases, the aminoglycoside reportedly breached the dermal layer to cause anaphylaxis. Although skin-prick testing suggested reactions to the aminoglycoside antibiotics, this association could not be confirmed because of a lack of standardized testing to the reagents. Radioallergosorbent testing showed an increase in IgG but no other direct correlation to an IgE hypersensitivity reaction.

Five cases were identified in which the use of intravenous or intramuscular aminoglycosides were associated with type I hypersensitivity reactions.21-25 In 3 of these cases, the use of an aminoglycoside antibiotic resulted in a stereotypical anaphylactic reaction, but no postreaction workup was performed.21-23 In the other 2 cases, individuals who experienced anaphylactic reactions to aminoglycosides had positive results to postreaction skin patch testing.24,25 No further intradermal testing was pursued in those cases.

**Vaccine reactions**

There have been 2 published reports of isolated hypersensitivity reactions to direct administration of aminoglycoside-containing vaccines.26,27 In both of these case reports, children who had been previously exposed to an aminoglycoside were given the MMR vaccine. One child was found to have an anaphylactoid response after receiving an intramuscular injection of the vaccine. The other child, who previously had a dermal reaction to otic drops, showed no signs of anaphylaxis or anaphylactoid reaction after administration of the vaccine. Because of the cross-reactivity described in the literature, if a patient has had an adverse reaction to any aminoglycoside, he or she should be considered as hypersensitive to the neomycin in vaccines. Thus, the patient should be questioned regarding this type of hypersensitivity before the administration of a neomycin-containing vaccine.

There is general agreement that children should not be vaccinated if they have had anaphylactic reactions to topical or systemic administration of neomycin or any other aminoglycoside.28 According to the
American Academy of Pediatrics and the CDC, the following information should be kept in mind:29,30

- Certain vaccines contain trace amounts of neomycin. Persons who have experienced anaphylactic reactions to neomycin should not receive these vaccines.

- Most often, neomycin allergy is a contact dermatitis, a manifestation of a delayed type (cell-mediated) immune response, rather than anaphylaxis.

- A history of delayed-type reactions to neomycin is not a contraindication for administration of these vaccines.31

**Latex**

Natural rubber latex is manufactured from the milky sap of the commercial rubber tree, *Hevea brasiliensis*, which grows naturally in Malaysia, Indonesia, and Thailand.32-34 There are various ways to prepare latex from the sap, including adding ammonia and other preservatives.34 These different preparations yield varying amounts of latex protein in the end product. This protein, which makes up 1% to 2% of the latex in the final product,33 is responsible for type I hypersensitivity reactions.

The packaging and mode of administration of vaccines can present problems for individuals who have severe latex hypersensitivities. Dry natural rubber, which contains latex, can be found in the syringe tip cap, syringe plungers, and vial stoppers of some vaccines. Synthetic rubber and synthetic latex do not cause hypersensitivity reactions, because they do not contain the latex proteins that natural rubber latex and dry natural rubber contain.32

The most common hypersensitivity reaction to latex is contact dermatitis. However, anaphylaxis could also occur as a result of latex hypersensitivity.35 Anaphylaxis is an IgE-mediated response that occurs minutes to hours after exposure to an allergen. An anaphylactic reaction to latex may include symptoms of mouth or throat swelling, urticaria or hives, wheezing or other breathing trouble, hypotension, or shock. Medical intervention is necessary if any of these symptoms occur.35

If the patient does not report an anaphylactic reaction after exposure to latex, it is safe to administer vaccines in vials or syringes that contain latex. It is essential that physicians and their staff be aware of which vaccines pose potential latex-related threats to their patients. Anaphylactic reactions to vaccine administration are rare—and can remain that way with proper screening.35

Certain vaccines are available in preparations without latex in the packaging.35 If the vaccine cannot be made without latex and the latex is in the vial stopper, it may be possible to remove the stopper before proceeding with the vaccination. If there is no alternative to giving the vaccine without exposing the patient to latex, the physician must determine if the risk outweighs the benefit. It is an option to proceed with vaccination in such patients, but they must be observed for at least 30 minutes after administration of the vaccine for signs of adverse reactions.36

The names of vaccines that pose a potential risk to individuals with a history of anaphylaxis from latex are listed below. These lists are based on the location of the latex—in the vial or in the syringe or syringe tip cap. Not all preparations of a particular vaccine are problematic. Physicians preparing to administer a vaccine need to check packaging inserts before administration.

The following vaccines are exposed to latex in the vial:35

- **ActHIB** (*Haemophilus influenzae* type B conjugate vaccine [tetanus toxoid conjugate]; only the diluent vial) (Sanofi Pasteur Inc, Swiftwater, PA)

- **BioThrax** (anthrax vaccine adsorbed) (Emergent BioDefense Operations Lansing Inc, Lansing, MI)

- **Convax** (*Haemophilus influenzae* type B conjugate/hepatitis B vaccine) (Merck & Co Inc, Whitehouse Station, NJ)

- **Diphtheria and tetanus toxoids adsorbed (generic)** (Sanofi Pasteur Ltd, Toronto, Ontario, Canada)

- **Agriflu** (influenza virus vaccine) (Novartis Vaccines and Diagnostics, Marburg, Germany)

- **Boostrix** (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed) (GlaxoSmithKline Biologicals, Rixensart, Belgium)

- **Cervarix** (human papillomavirus bivalent [types 16 and 18] vaccine, recombinant) (GlaxoSmithKline Biologicals, Rixensart, Belgium)

- **Decavac** (tetanus and diphtheria toxoids adsorbed for adult use) (Sanofi Pasteur Inc, Swiftwater, PA)

- **Menactra** (meningococcal [groups A, C, Y, and W-135] polysaccharide diphtheria toxoid conjugate vaccine) (Sanofi Pasteur Inc, Swiftwater, PA)

- **Menomune-A/C/Y/W-135** (meningococcal polysaccharide vaccine, groups A, C, Y, and W-135 combined) (Sanofi Pasteur Inc, Swiftwater, PA)

- **Recombivax HB** (hepatitis B vaccine, recombinant) (MassBiologics, Boston, MA)

- **Diptheria and tetanus toxoids and acellular pertussis vaccine adsorbed** (Sanofi Pasteur Inc, Swiftwater, PA)

- **Vaqta** (hepatitis A vaccine, inactivated) (Merck & Co Inc, Whitehouse Station, NJ)

- **YF-Vax** (yellow fever vaccine) (Sanofi Pasteur Inc, Swiftwater, PA)

The following vaccines are exposed to latex in the syringe or syringe tip cap:35

- **Adacel** (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed) (Sanofi Pasteur Ltd, Toronto, Ontario, Canada)

- **Diptheria and tetanus toxoids adsorbed** (Sanofi Pasteur Inc, Swiftwater, PA)

- **Boostrix** (tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine adsorbed) (GlaxoSmithKline Biologicals, Rixensart, Belgium)

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According to the VAERS, the overall risk of an adverse reaction after vaccination is low for an individual with latex hypersensitivity. Out of a database of more than 160,000 vaccine-related adverse events, Russell et al found only 28 possible hypersensitivity reactions to vaccines among people with a history of latex allergy. Those reactions occurred 5 minutes to 3 1/2 hours after vaccination. Reported reactions included diarrhea; dyspnea; edema of the face, tongue, and throat; generalized urticaria and pruritic rash; lip numbness; nausea; tachycardia; vasodilation; vomiting; and wheezing. There was 1 report of anaphylaxis in a latex-sensitive patient after receiving the hepatitis B vaccine. At the time of vaccine administration to that patient, the latex was in the rubber stopper. Preparations of hepatitis B vaccines now contain latex only in the syringe preparation.

Latex hypersensitivity is not an overwhelmingly common phenomenon. The highest rates of this condition occur among individuals who work in health care fields. Latex hypersensitivity tends to develop in the professional health care population as a result of repeated and excessive exposure to latex, mainly in gloves, which is used to prevent personal infection. Repeated latex exposure is also the reason that patients with spina bifida are considered to be at high-risk of latex hypersensitivity. Those patients typically undergo numerous surgeries and, thus, have repeated, excessive exposures to latex.

Although latex hypersensitivities are not common in the general population, many parents may have concerns regarding latex in vaccines for their children. Therefore, it is beneficial for physicians to be familiar with all aspects of treating their latex-sensitive patients.

References


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