

Addressing Parents' Concerns: Do Vaccines Contain Harmful Preservatives, Adjuvants, Additives, or Residuals?

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ABSTRACT. Vaccines often contain preservatives, adjuvants, additives, or manufacturing residuals in addition to pathogen-specific immunogens. Some parents, alerted by stories in the news media or information contained on the World Wide Web, are concerned that some of the substances contained in vaccines might harm their children. We reviewed data on thimerosal, aluminum, gelatin, human serum albumin, formaldehyde, antibiotics, egg proteins, and yeast proteins. Both gelatin and egg proteins are contained in vaccines in quantities sufficient to induce rare instances of severe, immediate-type hypersensitivity reactions. However, quantities of mercury, aluminum, formaldehyde, human serum albumin, antibiotics, and yeast proteins in vaccines have not been found to be harmful in humans or experimental animals. *Pediatrics* 2003;112:1394–1401; vaccine safety, thimerosal, aluminum, formaldehyde, gelatin, egg proteins, yeast proteins.

ABBREVIATIONS. FDA, Food and Drug Administration; DTaP, diphtheria-tetanus-acellular pertussis; Hib, *Haemophilus influenzae* type B; EPA, Environmental Protection Agency; ATSDR, Agency for Toxic Substances Disease Registry; MMR, measles-mumps-rubella; IgE, immunoglobulin E; CJD, Creutzfeld-Jacob disease; BSE, bovine spongiform encephalopathy; vCJD, variant Creutzfeld-Jacob disease.

Vaccines contain live viruses, killed viruses, purified viral proteins, inactivated bacterial toxins, or bacterial polysaccharides. In addition to these immunogens, vaccines often contain other substances. For example, vaccines may contain preservatives that prevent bacterial or fungal contamination (eg, thimerosal); adjuvants that enhance antigen-specific immune responses (eg, aluminum salts); or additives that stabilize live, attenuated viruses (eg, gelatin, human serum albumin). Furthermore, vaccines may contain residual quantities of substances used during the manufacturing process (eg, formaldehyde, antibiotics, egg proteins, yeast proteins).

Some parents, alerted by stories in the news media or on the World Wide Web, are concerned that substances such as thimerosal, formaldehyde, alumi-

num, antibiotics, and gelatin are harmful. We review safety data obtained from human exposure and experimental animal studies that address these concerns.

PRESERVATIVES

Preservatives are used in some vaccines to prevent bacterial or fungal contamination. The requirement for preservatives in vaccines arose from many incidents in the early 20th century of children who developed severe and occasionally fatal bacterial infections after administration of vaccines contained in multidose vials.¹ For example, in 1916, 4 children died, 26 developed local abscesses, and 68 developed severe systemic infections after receipt of a typhoid vaccine contaminated with *Staphylococcus aureus*.¹ As a consequence of this and similar incidents, preservatives have been required for vaccines contained in multidose vials (with some exceptions) since the 1930s.²

Three preservatives are used in vaccines licensed in the United States: phenol, 2-phenoxyethanol, and thimerosal (Table 1). Thimerosal, a mercury-containing preservative, has been the focus of intense scrutiny by the US Congress and the news media after its removal from most childhood vaccines in 2001. Attention by the news media has caused some parents to fear that thimerosal contained in vaccines might harm their children.

Removal of thimerosal from vaccines was precipitated by an amendment to the Food and Drug Administration (FDA) Modernization Act, which was signed into law on November 21, 1997.³ The amendment gave the FDA 2 years to "compile a list of drugs and foods that contain intentionally introduced mercury compounds and . . . [to] provide a quantitative and qualitative analysis of the mercury compounds in the list. . . ." The amendment arose from a longstanding interest in lessening human exposure to mercury, a known neurotoxin and nephrotoxin.

At the time the FDA Modernization Act was passed, it was recommended that infants receive 3 different vaccines that contained thimerosal: diphtheria-tetanus-acellular pertussis (DTaP), hepatitis B, and *Haemophilus influenzae* type B (Hib). Infants who received all of these vaccines could have been exposed to a cumulative dose of mercury as high as 187.5 μg by 6 months of age.⁴ This value exceeded guidelines recommended by the Environmental Protection Agency (EPA) but did not exceed those recommended by the Agency for Toxic Substances Disease Registry (ATSDR) or the FDA (Table 2).⁴

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TABLE 1. Preservative Content in Vaccines Licensed in the United States, 2003

Preservative	Vaccine	Trade Name	Company	Quantity (per Dose)
2-Phenoxyethanol	Inactivated polio	IPOL	Aventis Pasteur	2.5 mg
	DTaP	Daptacel	Aventis Pasteur	3.3 mg
	DTaP	Infanrix	GlaxoSmithKline	2.5 mg
	Hepatitis A	Havrix	GlaxoSmithKline	2.5 mg
	Hepatitis A-hepatitis B	Twinrix	GlaxoSmithKline	5.0 mg
	DTaP-IPV-HBV	Pediarix	GlaxoSmithKline	2.5 mg
Phenol	Pneumococcal polysaccharide	Pneumovax 23	Merck and Co	1.25 mg
	<i>Salmonella typhi</i>	TYPHIM VI	Aventis Pasteur	1.25 mg
Thimerosal	Influenza	FluShield	Wyeth	0.025 mg
	Influenza	Fluzone	Aventis Pasteur	0.025 mg
	Diphtheria-tetanus	DT (pediatric)	Aventis Pasteur	0.025 mg
	Pneumococcal polysaccharide	Pneu-Immune 23	Wyeth	0.05 mg
	Meningococcal	Menomune	Aventis Pasteur	0.025 mg
	Japanese encephalitis virus	JE-Vax	Aventis Pasteur	0.007 mg

TABLE 2. Exposure Limits for Mercury in Infants ≤ 6 Months of Age by Percentile Body Weight Established by the EPA, the ATSDR, and the FDA

Agency	Percentile Body Weight		
	5th	50th	95th
EPA	65 μg	89 μg	106 μg
ATSDR	194 μg	266 μg	319 μg
FDA	259 μg	354 μg	425 μg

Therefore, thimerosal was removed from most childhood vaccines by 2001 as a precautionary measure.⁵

Although no published studies to date have compared the incidence of neurodevelopmental delay in children who received thimerosal-free or thimerosal-containing vaccines, several facts are reassuring that the level of mercury contained in vaccines was not likely to be harmful. Thimerosal contains 49.6% mercury by weight and is metabolized to ethylmercury and thiosalicylate. Ethylmercury is contained in many drugs as well as biologicals. Adults and children who are exposed inadvertently to large quantities of ethylmercury acutely (quantities 1000- to 1 000 000-fold greater than those found in vaccines) can sustain permanent neurologic damage and death.⁶⁻¹¹ However, no data exist on the capacity of low-dose, chronic exposure to ethylmercury to harm the developing nervous system. Guidelines for chronic exposure to ethylmercury were extrapolated from guidelines for methylmercury (the most common form of mercury found in the environment) established by the EPA, ATSDR, and FDA.⁴

Guidelines from the EPA were based in part on data from pregnant women in rural Iraq who were exposed to large quantities of methylmercury.¹² In October 1971, Iraq imported >90 000 metric tons of methylmercury-treated seed grain. The grain, distributed free of charge to farmers throughout the country, was used to make bread. Consumption of this bread caused an extensive outbreak of methylmercury poisoning, resulting in >6000 hospitalizations and 450 deaths. By examining the quantity of methylmercury contained in hair from mothers who ingested methylmercury and comparing calculated exposures to methylmercury with the frequency of neurologic symptoms in their offspring (eg, psychomotor retardation, seizures, impaired vision or hearing), a dose-response curve for fetal exposure to

methylmercury and neurologic damage was established. The EPA determined guidelines by taking the lowest quantity of methylmercury that might have resulted in harm to the fetus, bracketing that dose with 95% confidence intervals and dividing the lower confidence interval by an "uncertainty" factor of 10.⁴

By using data from pregnant women in Iraq who were exposed to methylmercury in the environment to establish guidelines for chronic exposure of infants in the United States to ethylmercury in vaccines, 2 important assumptions were made: 1) that the toxicity and pharmacokinetics of methylmercury are the same as those of ethylmercury and 2) that the central nervous systems of the fetus and newborn are equally susceptible to the harmful effects of mercury. However, the pharmacokinetics of ethylmercury and methylmercury are not the same. Methylmercury has a biological half-life in blood of approximately 50 days compared with that of approximately 7 days for ethylmercury.^{4,13} Because ethylmercury is excreted from the body far more quickly than methylmercury, cumulative dose guidelines would be very different. In support of this important difference, Pichichero et al¹³ found that the level of mercury detected in the blood of 40 full-term infants who were 6 months of age or younger and received thimerosal-containing DTaP, hepatitis B, and Hib vaccines did not exceed recommended guidelines.¹³ Furthermore, the developing central nervous system of the fetus is more susceptible to environmental and toxic insults than that of the newborn.¹⁴⁻¹⁷

Removal of thimerosal from most vaccines caused several unanticipated consequences. First, before the availability of thimerosal-free DTaP, hepatitis B, and Hib vaccines, hospitals were advised to defer the birth dose of hepatitis B vaccine to 2 to 6 months of age in infants of hepatitis B-seronegative mothers.¹⁸ Some hospitals misinterpreted this guideline and suspended administration of the birth dose of hepatitis B vaccine for all newborns.¹⁹⁻²¹ As a consequence, 1 institution reported that 3 infants of hepatitis B-seropositive mothers did not receive the recommended birth dose of hepatitis B vaccine.²² Another institution reported the death from acute hepatitis B-induced liver failure of a 3-month-old infant who was born to a hepatitis B-seropositive mother; the infant did not receive the hepatitis B

vaccine.¹⁹ Furthermore, although thimerosal-free vaccines are now available, many hospitals continue to defer the birth dose of hepatitis B vaccine inappropriately.^{19–21} Second, the removal of thimerosal from vaccines caused some parents and physicians to believe that vaccines that contain thimerosal were harmful, independent of dose or age of administration. For example, although contrary to recommendations by the Centers for Disease Control and Prevention,²³ some parents and physicians were hesitant to give any thimerosal-containing vaccines to children (eg, influenza vaccine to children at high risk of severe influenza infection). Third, although thimerosal was removed from vaccines in part to “maintain the public’s trust in immunization,” some physicians found that parents were less confident in professional groups that recommended vaccines before than after removal of thimerosal.²⁴

ADJUVANTS

Aluminum salts are the only adjuvants currently licensed for use in the United States (Table 3). Aluminum salts include aluminum hydroxide, aluminum phosphate, and potassium aluminum sulfate (alum). Aluminum-containing vaccines are prepared by adsorption of antigens onto aluminum hydroxide or aluminum phosphate gels or by precipitation of antigens in a solution of alum.²⁵

Aluminum salts were found initially to enhance immune responses after immunization with diphtheria and tetanus toxoids in studies performed in the 1930s, 1940s, and 1950s.^{26–30} Early studies suggested that aluminum salts reduced the rate of elimination of antigens at the site of inoculation (ie, depot effect).³¹ However, subsequent studies questioned the importance of the depot effect and found that aluminum salts enhanced antigen uptake by antigen-presenting cells (eg, dendritic cells),³² activated antigen-presenting cells,³² or induced production of cytokines³³ and complement.³⁴ The importance of each of these mechanisms in enhancing antigen-specific immune responses remains unclear.

The safety of aluminum has been established by experience during the past 70 years, with hundreds of millions of people inoculated with aluminum-containing vaccines. Adverse reactions including er-

ythema, subcutaneous nodules, contact hypersensitivity, and granulomatous inflammation have been observed rarely.³⁵

Aluminum-containing vaccines are not the only source of aluminum exposure for infants. Because aluminum is 1 of the most abundant elements in the earth’s crust and is present in air, food, and water, all infants are exposed to aluminum in the environment. For example, breast milk contains approximately 40 μg of aluminum per liter, and infant formulas contain an average of approximately 225 μg of aluminum per liter.^{36–40} Vaccines contain quantities of aluminum similar to those contained in infant formulas (Table 3). However, because large quantities of aluminum can cause serious neurologic effects in humans,⁴¹ guidelines were established by the ATSDR.

For determining the quantity of aluminum below which safety is likely, data were generated in mice that were inoculated orally with various quantities of aluminum lactate.⁴² No adverse reactions were observed when mice were fed quantities of aluminum as high as 62 mg/kg/day. By applying uncertainty factors of 3 (for extrapolation to humans) and 10 (for human variability), the ATSDR concluded that the minimum risk level for exposure to aluminum was 2 mg/kg/day.⁴³ The half-life of elimination of aluminum from the body is approximately 24 hours.⁴¹ Therefore, the burden of aluminum to which infants are exposed in food^{36–40} and vaccines (Table 3) is clearly less than the guideline established by the ATSDR and far less than that found to be safe in experimental animals.^{41,42}

ADDITIVES

Additives are used to stabilize vaccines from adverse conditions such as freeze-drying or heat. In addition, additives are added to vaccines to prevent immunogens from adhering to the side of the vial. The types of stabilizers used in vaccines include sugars (eg, sucrose, lactose), amino acids (eg, glycine, monosodium salt of glutamic acid), and proteins (eg, gelatin or human serum albumin).

Three issues surround the use of protein additives in vaccines: 1) the observation that immediate-type hypersensitivity reactions are a rare consequence of

TABLE 3. Aluminum Salt (Adjuvant) Content in Vaccines Licensed in the United States, 2003

Adjuvant	Vaccine	Trade Name	Company	Quantity (per Dose)
Aluminum hydroxide	DTaP	Infanrix	GlaxoSmithKline	≤ 0.625 mg
	Hepatitis A	Havrix (pediatric)	GlaxoSmithKline	0.25 mg
		Vaqta (pediatric)	Merck and Co	0.225 mg
		Hepatitis B	Engerix	GlaxoSmithKline
	Hib	PedVax Hib	Merck and Co	0.225 mg
	Hepatitis A-hepatitis B	Twinrix	GlaxoSmithKline	0.45 mg*
Aluminum phosphate	DTaP-IPV-hepatitis B	Pediarix	GlaxoSmithKline	≤ 0.85 mg*
	Pneumococcal conjugate Td (adult)	Prenar	Wyeth	0.125 mg
		None	Massachusetts Department of Public Health	0.45 mg
Aluminum sulfate	DTaP	Daptacel	Aventis Pasteur	0.33 mg
	DTaP	Tripedia	Aventis Pasteur	≤ 0.17 mg
	Td (adult)	None	Aventis Pasteur	0.28 mg
	Hib-hepatitis B	Comvax	Merck and Co	0.225 mg
	Hepatitis B	Recombivax HB	Merck and Co	0.5 mg

* Contains both aluminum hydroxide and aluminum phosphate.

receiving gelatin-containing vaccines, 2) the theoretical concern that human serum albumin might contain infectious agents, and 3) the theoretical concern that bovine-derived materials used in vaccines might contain the agent associated with bovine spongiform encephalopathy ("mad-cow" disease).

Hypersensitivity to Gelatin

In 1993, Kelso et al⁴⁴ reported the case of a 17-year-old girl in California who developed profuse rhinorrhea, hives, laryngotracheal edema, lightheadedness, and a blood pressure of 70/50 within 5 minutes of receiving a measles-mumps-rubella (MMR) vaccine. Her symptoms resolved after treatment with epinephrine and diphenhydramine. When later describing the event, the girl stated that it was "kind of like what happens when I eat Jell-O."⁴⁴ Subsequent testing found that the only component of the vaccine to which the patient was allergic was gelatin.

Before 1993, immediate-type hypersensitivity reactions to the MMR vaccine were attributed to an allergy to egg proteins.⁴⁵ This assumption was based on the fact that both the measles and mumps components of MMR vaccine are grown in chick embryo fibroblast cells. However, most patients with hypersensitivity to MMR vaccine were not allergic to eggs.⁴⁴ The observation by Kelso et al prompted a closer look at the capacity of gelatin-containing vaccines to induce hypersensitivity reactions.

Studies in Japan confirmed the findings of Kelso et al that immediate hypersensitivity to MMR vaccine was associated with the presence of gelatin-specific immunoglobulin E (IgE),⁴⁶ not an allergy to egg proteins. At that time, the rate of immediate hypersensitivity to MMR in Japan was approximately 20-fold higher than that in the United States.^{47,48} The increased incidence of immediate-type hypersensitivity to gelatin in Japan was explained in 2 ways. First, DTaP vaccines made in Japan contained gelatin, whereas DTaP vaccines made in the United States did not.⁴⁸ Second, the type of gelatin used in Japan was not hydrolyzed.⁴⁸ Hydrolysis converts high molecular weight gelatin (>100 000 Da) to low molecular weight gelatin (between 2000 and 5000 Da). Low molecular weight gelatin is less likely to stimulate gelatin-specific IgE than high molecular weight gelatin.⁴⁹ When Japanese vaccine makers eliminated gelatin from DTaP and switched to the use of hydrolyzed gelatin in the MMR vaccine, the incidence of

gelatin-specific immediate-type hypersensitivity reactions decreased dramatically to levels similar to those found in the United States.⁵⁰

Although the incidence of anaphylaxis to gelatin is currently very low (approximately 1 case per 2 million doses), gelatin is the most common identifiable cause of immediate-type hypersensitivity reactions to gelatin-containing vaccines.^{51,52} A list of vaccines that contain gelatin is provided in Table 4 (all gelatin is of porcine origin).

Some patients with immediate hypersensitivity reactions to gelatin have a history of allergies to gelatin-containing foods.⁵¹ This is explained, in part, by the extensive cross-reactivity found between bovine gelatin contained in many foods and porcine gelatin contained in vaccines.⁵³ Therefore, it would be of value to ask about food allergies before vaccination with gelatin-containing vaccines.⁵⁴ If children have either a history of food allergy to gelatin or a history of immediate-type hypersensitivity reactions to gelatin-containing vaccines, then gelatin-containing vaccines should not be administered and an immunologic evaluation should be performed.⁵⁴ Evaluation may include either detection of gelatin-specific IgE by solid-phase immunoassay or skin testing with increasing concentrations of gelatin.⁵⁴ Vaccination of people who have immunologic evidence for gelatin hypersensitivity should be performed with the ready availability of equipment and medications required for the treatment of anaphylactic reactions or deferred completely.

Theoretical Risk of Infectious Agents in Human Serum Albumin

Human serum albumin (0.3 mg/dose) is contained in measles vaccine (Attenuvax; Merck and Co, West Point, PA); mumps vaccine (Mumpsvax; Merck and Co); rubella vaccine (Meruvax; Merck and Co); and measles, mumps, and rubella vaccine (MMR_{II}; Merck and Co). Because human serum albumin is derived from human blood, there is a theoretical risk that it might contain infectious agents. However, the FDA requires that human serum albumin be derived from blood of screened donors and be manufactured in a manner that would eliminate the risk of transmission of all known viruses. The result is that no viral diseases have ever been associated with the use of human serum albumin.

TABLE 4. Gelatin Content of Vaccines Licensed in the United States, 2003

Vaccine	Trade Name	Company	Gelatin Quantity (per Dose)
DTaP	Tripedia	Aventis Pasteur	0.0015 mg
Influenza	Fluzone	Aventis Pasteur	0.025 mg
Measles	Attenuvax	Merck and Co	14.5 mg
Mumps	Mumpsvax	Merck and Co	14.5 mg
Rubella	Meruvax II	Merck and Co	14.5 mg
Measles, rubella	MRVAX II	Merck and Co	14.5 mg
Mumps, rubella	Biavax II	Merck and Co	14.5 mg
MMR	MMR II	Merck and Co	14.5 mg
Varicella	Varivax	Merck and Co	12.5 mg
Rabies	Rabavert	Chiron	<12 mg
Japanese encephalitis	JE-Vax	Aventis Pasteur	0.5 mg

Theoretical Risk of “Mad-Cow” Disease From Bovine-Derived Reagents

Creutzfeldt-Jacob disease (CJD) in humans is caused by a unique infectious agent (proteinaceous infectious particles, or prions) that also causes encephalopathies in other mammals such as cows (bovine spongiform encephalopathy [BSE]) and sheep (scrapie).⁵⁵ Between 1995 and 1997, a new “variant” form of CJD (vCJD) in humans was reported from the United Kingdom after an outbreak of BSE in cows.^{56–60} The timing of these events raised the possibility that people who ate products from cows that were infected with BSE developed vCJD. Several epidemiologic, clinical, and pathologic features of vCJD supported a causal link between BSE and vCJD.^{55,61–64}

Vaccines contain several reagents that are derived from cows (eg, gelatin, glycerol, enzymes, serum, amino acids). Because of concerns about vCJD, the FDA recently prohibited the use of bovine-derived materials obtained from countries that are known to have cattle that are infected with BSE.⁶⁵ However, before this ban, some materials used in vaccines might have been obtained from cows that were infected with BSE in England. (It should be noted that US vaccine manufacturers were not allowed to use bovine products imported from outside the United States to protect against the possible importation of foot-and-mouth disease). This raised the question of whether children who were inoculated with vaccines were at risk for vCJD. Newspapers reported this possibility in the late 1990s,⁶⁶ and some parents were concerned about bovine-derived products contained in vaccines. However, several epidemiologic observations and features of the manufacturing process should reassure parents that vaccines could not cause vCJD. First, prions are detected in the brain, spinal cord, and retina of cows with BSE and not in blood or other organs.⁵⁵ Therefore, serum (present in media that support the growth of microorganisms or cells used to make vaccines) is not likely to contain prions. Consistent with these observations, no cases of CJD have been transmitted by blood or blood products, and a history of blood transfusion does not increase the risk for CJD.^{67–69} Second, prions are not detected in connective tissue of cows with BSE.⁵⁵ Therefore, gelatin (made by boiling the hooves and

skin of pigs or cows) is unlikely to contain prions. Third, epidemiologic evidence does not support vaccines as a cause of vCJD in England.⁷⁰ Human exposure to cows that were infected with BSE in England was likely to have occurred after 1983, and vaccines that contained bovine-derived materials were likely to have been administered to children after 1985. If vaccines that are routinely administered in the first 2 years of life caused vCJD, then no cases of vCJD would have been expected to occur in people who were born before 1985. However, all cases of vCJD occurred in people born who were before 1985 and half before 1970.⁷⁰

MANUFACTURING RESIDUALS

Residual quantities of reagents that are used to make vaccines are clearly defined and well regulated by the FDA. Inactivating agents (eg, formaldehyde), antibiotics, and cellular residuals (eg, egg and yeast proteins) may be contained in the final product.

Inactivating Agents

Inactivating agents separate a pathogen’s immunogenicity from its virulence by eliminating the harmful effects of bacterial toxins or ablating the capacity of infectious viruses to replicate. Examples of inactivating agents include formaldehyde, which is used to inactivate influenza virus, poliovirus, and diphtheria and tetanus toxins; β -propiolactone, which is used to inactivate rabies virus; and glutaraldehyde, which is used to inactivate toxins contained in acellular pertussis vaccines. Formaldehyde deserves special consideration.

Concerns about the safety of formaldehyde have centered on the observation that high concentrations of formaldehyde can damage DNA and cause cancerous changes in cells *in vitro*.^{71,72} Although formaldehyde is diluted during the manufacturing process, residual quantities of formaldehyde may be found in several current vaccines (Table 5). Fortunately, formaldehyde does not seem to be a cause of cancer in humans,⁷³ and animals that are exposed to large quantities of formaldehyde (a single dose of 25 mg/kg or chronic exposure at doses of 80–100 mg/kg/day) do not develop malignancies.^{74,75}

The quantity of formaldehyde contained in individual vaccines does not exceed 0.1 mg (Table 5).

TABLE 5. Formaldehyde Content of Vaccines Licensed for Use in the United States, 2003

Vaccine	Trade Name	Company	Formaldehyde Quantity (per Dose)
Td (adult)	None	Massachusetts Department of Public Health	<0.1 mg
DTaP	Daptacel	Aventis Pasteur	≤0.1 mg
	Infanrix	GlaxoSmithKline	<0.1 mg
	Tripedia	Aventis Pasteur	≤0.1 mg
DTaP-Hepatitis B-Inactivated polio virus	Pediarix	GlaxoSmithKline	≤0.1 mg
	Hepatitis A	Havrix	≤0.05 mg
Hepatitis A-hepatitis B	Vaqta	Merck and Co	<0.0008 mg
	Twinrix	GlaxoSmithKline	≤0.1 mg
Hib-hepatitis B	Comvax	Merck and Co	<0.0002 mg
Polio	IPOL	Aventis Pasteur	0.1 mg
Japanese encephalitis vaccine	JE-Vax	Aventis Pasteur	<0.1 mg

TABLE 6. Neomycin Content in Vaccines Licensed for Use in the United States, 2003

Antibiotic	Vaccine	Trade Name	Company	Quantity (per Dose)
Neomycin	Measles	Attenuvax	Merck and Co	0.025 mg
	Mumps	Mumpsvax	Merck and Co	0.025 mg
	Rubella	Meruvax _{II}	Merck and Co	0.025 mg
	MMR	MMR _{II}	Merck and Co	0.025 mg
	Rabies	Imovax	Aventis Pasteur	<0.15 mg

This quantity of formaldehyde is considered to be safe for 2 reasons. First, formaldehyde is an essential intermediate in human metabolism and is required for the synthesis of thymidine, purines, and amino acids.⁷⁶ Therefore, all humans have detectable quantities of formaldehyde in their circulation (approximately 2.5 μg of formaldehyde/mL of blood).⁷⁷ Assuming an average weight of a 2-month-old of 5 kg and an average blood volume of 85 mL/kg, the total quantity of formaldehyde found naturally in an infant's circulation would be approximately 1.1 mg—a value at least 10-fold greater than that contained in any individual vaccine. Second, quantities of formaldehyde at least 600-fold greater than that contained in vaccines have been given safely to animals.^{74,75}

Antibiotics

Antibiotics are present in some vaccines to prevent bacterial contamination during the manufacturing process. Because antibiotics can cause immediate-type hypersensitivity reactions in children,^{78,79} some parents are concerned that antibiotics that are contained in vaccines might be harmful. However, antibiotics that are most likely to cause immediate-type hypersensitivity reactions (eg, penicillins, cephalosporins, sulfonamides)^{78,79} are not contained in vaccines.

Antibiotics that are used during vaccine manufacture include neomycin, streptomycin, polymyxin B, chlortetracycline, and amphotericin B. Only neomycin is contained in vaccines in detectable quantities (Table 6). However, immediate-type hypersensitivity reactions to the small quantities of neomycin contained in vaccines has not been clearly documented.^{80,81} Although neomycin-containing products have been found to cause delayed-type hypersensitivity reactions,^{82,83} these reactions are not a contraindication to receiving vaccines.

Cellular Residuals

Egg Proteins

Egg allergies occur in approximately 0.5% of the population and in approximately 5% of atopic children.⁸⁴ Because influenza and yellow fever vaccines both are propagated in the allantoic sacs of chick embryos (eggs), egg proteins (primarily ovalbumin) are present in the final product. Residual quantities of egg proteins found in the influenza vaccine (approximately 0.02–1.0 μg /dose) are sufficient to induce severe and rarely fatal hypersensitivity reactions in children with egg allergies.^{85,86} Unfortunately, children with egg allergies also have other diseases (eg, asthma) that are associated with a high risk of severe and occasionally fatal influenza infec-

tion.^{87,88} For this reason, children who have egg allergies and are at high risk of severe influenza infection should be given influenza vaccine via a strict protocol.^{86–90}

In contrast to influenza vaccine, measles and mumps vaccines are propagated in chick embryo fibroblast cells in culture. The quantity of residual egg proteins found in measles- and mumps-containing vaccines is approximately 40 pg—a quantity at least 500-fold less than those found for influenza vaccines.⁹¹ The quantity of egg proteins found in measles- and mumps-containing vaccines is not sufficient to induce immediate-type hypersensitivity reactions, and children with severe egg allergies can receive these vaccines safely.⁹²

Yeast Proteins

Hepatitis B vaccines are made by transfecting cells of *Saccharomyces cerevisiae* (baker's yeast) with the gene that encodes hepatitis B surface antigen, and residual quantities of yeast proteins are contained in the final product. Engerix-B (GlaxoSmithKline, Research Triangle Park, NC) contains no more than 5 mg/mL and Recombivax HB (Merck and Co) contains no more than 1 mg/mL yeast proteins.

Immediate-type hypersensitivity reactions have been observed rarely after receipt of hepatitis B vaccine (approximately 1 case per 600 000 doses).⁹³ However, yeast-specific IgE has not been detected in patients with immediate-type hypersensitivity^{94–96} or in nonallergic patients⁹⁷ after receipt of hepatitis B vaccine. Therefore, the risk of anaphylaxis after receipt of hepatitis B vaccine as a result of allergy to baker's yeast is theoretical.

CONCLUSION

Parents should be reassured that quantities of mercury, aluminum, and formaldehyde contained in vaccines are likely to be harmless on the basis of exposure studies in humans or experimental studies in animals. Although severe anaphylactic reactions may occur rarely after receipt of vaccines that contain sufficient quantities of egg proteins (eg, influenza, yellow fever) or gelatin (eg, MMR_{II}), children who are at risk for severe infection with influenza can be desensitized to influenza vaccine, and gelatin-specific allergies are very rare. Immediate-type hypersensitivity reactions to neomycin or yeast proteins have not been clearly documented and remain theoretical.

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REFERENCES

- Wilson GS. *The Hazards of Immunization*. New York, NY: The Althone Press; 1967:75–84
- General Biologics Product Standards; Constituent materials. Ingredients, preservatives, diluents, and adjuvants. 21 CFR: 610.15 (a)
- 21 USC 397 Section 413
- Stratton K, Gable A, McCormick MC, eds. *Immunization Safety Review: Thimerosal-Containing Vaccines and Neurodevelopmental Disorders*. Washington, DC: National Academy Press; 2001
- Goldstein BD. The precautionary principle also applies to public health actions. *Am J Public Health*. 2001;91:1358–1361
- Hay WJ, Rickerts AG, McMenemey WH, Cumings JN. Organic mercurial encephalopathy. *Neurol Neurosurg Psychiatry*. 1963;26:199–202
- Axton JHM. Six cases of poisoning after a parenteral organic mercury compound (Merthiolate). *Postgrad Med J*. 1972;48:417–421
- Fagan DG, Pritchard JS, Clarkon TW, Greenwood MR. Organ mercury levels in infants with omphaloceles treated with organic mercury anti-septic. *Arch Dis Child*. 1977;52:962–964
- Cinca I, Dumitrescu I, Onaca P, et al. Accidental ethyl mercury poisoning with nervous system, skeletal muscle, and myocardium injury. *J Neurol Neurosurg Psychiatry*. 1979;43:143–149
- Rohyans J, Walson PD, Wood GA, MacDonald WA. Mercury toxicity following merthiolate ear irrigations. *J Pediatr*. 1984;104:311–313
- Pfab R, Muckter H, Roeder G, Zilker T. Clinical course of severe poisoning with thiomersal. *Clin Toxicol*. 1996;34:453–460
- Marsh DO, Clarkson TW, Cox C, et al. Fetal methylmercury poisoning: relationship between concentration in single strands of maternal hair and child effects. *Arch Neurol*. 1987;44:1017–1022
- Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet*. 2002;360:1737–1741
- Strömland K, Nordin V, Miller M, et al. Autism in thalidomide embryopathy: a population study. *Dev Med Child Neurol*. 1994;36:351–356
- Rodier PM. The early origins of autism. *Sci Am*. 2000;February:56–63
- Chess S, Fernandez P, Korn S. Behavioral consequences of congenital rubella. *J Pediatr*. 1978;93:699–703
- Deykin EY, MacMahon B. Viral exposure and autism. *Am J Epidemiol*. 1979;109:628–638
- American Academy of Pediatrics. Committee on Infectious Diseases and Committee on Environmental Health. Thimerosal in vaccines—an interim report to clinicians. *Pediatrics*. 1999;104:570–574
- Centers for Disease Control and Prevention. Impact of the 1999 AAP/USPHS joint statement on thimerosal in vaccines on infant hepatitis B vaccination practices. *MMWR Morb Mortal Wkly Rep*. 2001;50:94–97
- Hurie MB, Saari TN, Davis JP. Impact of the joint statement by the American Academy of Pediatrics/US Public Health Service on thimerosal in vaccines on hospital infant hepatitis B vaccination practices. *Pediatrics*. 2001;107:755–758
- Brayden RM, Pearson KA, Jones JS, et al. Effect of thimerosal recommendations on hospitals' neonatal hepatitis B vaccination policies. *J Pediatr*. 2001;138:752–755
- Watson B. Comment. In: *Transcript of the National Vaccine Advisory Committee Workshop on Thimerosal in Vaccines*. Bethesda, MD: US Government Printing Office; August 12, 1999
- Centers for Disease Control and Prevention. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. *MMWR Morb Mortal Wkly Rep*. 1999;48:996–998
- Freed GL, Andreae M. Presentation to Immunization Safety Review Committee. History of Thimerosal Concern and Comparative Policy Actions; Cambridge, Massachusetts; July 16, 2001
- Shirodkar S, Hutchinson RL, Perry DL, et al. Aluminum compounds used as adjuvants in vaccines. *Pharm Res*. 1990;7:1282–1288
- Glenny AT, Pope CG, Waddington H, Wallace U. The antigenic value of toxoid precipitated by potassium alum. *J Pathol Bacteriol*. 1926;29:38–39
- Volk VK, Bunney WE. Diphtheria immunization with fluid toxoid and alum-precipitated toxoid. *Am J Public Health*. 1942;32:690–699
- Barr M, Glenny AT, Hignett S, et al. Antigenic efficiency of fluid and precipitated diphtheria prophylactics in very young babies and lambs. *Lancet*. 1952;2:803–805
- Barr M, Glenny AT, Butler NR. Immunization of babies with diphtheria-tetanus-pertussis prophylactic. *Br Med J*. 1955;2:635–639
- Greenberg L, Benoit R. Control of potency and the dosage of diphtheria and tetanus toxoids. *JAMA*. 1956;160:108–113
- Glenny AT, Butler AH, Stevens MF. Rate of disappearance of diphtheria toxoid injected into rabbits and guinea pigs: toxoid precipitated with alum. *J Pathol Bacteriol*. 1931;34:267–275
- Mannhalter JW, Neychev HO, Zlabinger GJ, et al. Modulation of the immune response by the non-toxic and non-pyrogenic adjuvant aluminum hydroxide: effect on antigen uptake and antigen presentation. *Clin Exp Immunol*. 1985;61:143–151
- Ulanova M, Tarkowski A, Hahn-Zoric M, Hanson LA. The common vaccine adjuvant aluminum hydroxide upregulates accessory properties of human monocytes via an interleukin-4-dependent mechanism. *Infect Immun*. 2001;69:1151–1159
- Ramanathan VD, Badenoch-Jones P, Turk JL. Complement activation by aluminum and zirconium compounds. *Immunology*. 1979;37:881–888
- Gupta RK, Rost BE, Relyveld E, Siber GR. Adjuvant properties of aluminum and calcium compounds. In: Powell MF, Newman MJ, eds. *Vaccine Design: The Subunit and Adjuvant Approach*. New York, NY: Plenum Press; 1995:229–248
- Koo WWK, Kaplan LA, Krug-Wispe SK. Aluminum contamination of infant formulas. *J Parenteral Nutr*. 1988;12:170–173
- Weintraub R, Hams G, Meerkin M, Rosenberg AR. High aluminum content of infant milk formulas. *Arch Dis Child*. 1986;61:914–916
- Simmer K, Fudge A, Teubner J, James SL. Aluminum concentrations in infant milk formulae. *J Paediatr Child Health*. 1990;26:9–11
- Hawkins NM, Coffey S, Lawson MS, Delves HT. Potential aluminum toxicity in infants fed special infant formula. *J Paediatr Gastroenterol Nutr*. 1994;19:377–381
- Mandic ML, Grgic J, Grgic Z, et al. Aluminum levels in human milk. *Sci Total Environ*. 1995;170:165–170
- Keith LS, Jones DE, Chou C. Aluminum toxicokinetics regarding infant diet and vaccination. *Vaccine*. 2002;20:S13–S17
- Golub MS, Donald JM, Gershwin ME, Keen CL. Effects of aluminum ingestion on spontaneous motor activity of mice. *Neurotoxicol Teratol*. 1989;11:231–235
- Toxicological Profile for Aluminum*. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry; 1999
- Kelso JM, Jones RT, Yunginger JW. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gelatin. *J Allergy Clin Immunol*. 1993;91:867–872
- Herman JJ, Radin R, Schneiderman R. Allergic reactions to measles (rubeola) vaccine in patients hypersensitive to egg proteins. *J Pediatr*. 1983;102:196–199
- Sakaguchi M, Ogura H, Inouye S. IgE antibody to gelatin in children with immediate-type reactions to measles and mumps vaccines. *J Allergy Clin Immunol*. 1995;96:563–565
- Centers for Disease Control and Prevention. Update: vaccine side effects, adverse reactions, contraindications, and precautions. *MMWR Morb Mortal Wkly Rep*. 1996;45:1–35
- Sakaguchi M, Nakayama T, Fujita H, et al. Minimum estimated incidence in Japan of anaphylaxis to live virus vaccines including gelatin. *Vaccine*. 2001;19:431–436
- Sakai Y, Yamoto R, Onuma M, et al. Non-antigenic and low allergic gelatin produced by specific digestion with enzyme-coupled matrix. *Biol Pharm Bull*. 1998;21:330–334
- Nakayama T, Aizawa C. Change in gelatin content of vaccines associated with reduction in reports of allergic reactions. *J Allergy Clin Immunol*. 2000;106:591–592
- Sakaguchi M, Nakayama T, Inouye S. Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. *J Allergy Clin Immunol*. 1996;98:1058–1061
- Sakaguchi M, Yamanaka T, Ikeda K, et al. IgE-mediated systemic reactions to gelatin included in the varicella vaccine. *J Allergy Clin Immunol*. 1997;99:263–264
- Sakaguchi M, Hori H, Ebihara T, et al. Reactivity of the immunoglobulin E in bovine gelatin-sensitive children to gelatins from other animals. *Immunology*. 1999;96:286–290
- Centers for Disease Control and Prevention. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR Morb Mortal Wkly Rep*. 2002;51:17
- Tyler KL. Prions and prion diseases of the central nervous system (transmissible neurodegenerative diseases). In Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practices of Infectious Diseases*. Philadelphia, PA: Churchill Livingstone; 2000

56. Britton TC, Al-Sarraj S, Shaw C, et al. Sporadic Creutzfeld-Jacob disease in a 16-year-old in the UK. *Lancet*. 1995;346:1155
57. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeld-Jacob disease in the UK. *Lancet*. 1996;347:921-925
58. Zeidler M, Stewart GE, Barraclough CR, et al. New variant Creutzfeld-Jacob disease: neurologic features and diagnostic tests. *Lancet*. 1997;350:903-907
59. Schonberger L. New variant Creutzfeld-Jacob disease and bovine spongiform encephalopathy. *Infect Dis Clin North Am*. 1998;12:111-121
60. Anderson RM, Donnelly CA, Ferguson NM, et al. Transmission dynamics and epidemiology of BSE in British cattle. *Nature*. 1996;382:779
61. Delys J-P, Lasmexas CI, Streichenberger N, et al. New variant Creutzfeld-Jacob disease in France. *Lancet*. 1997;349:30-31
62. Collinge J, Sidle KCL, Meads J, et al. Molecular analysis of prion strain variation and the aetiology of 'new variant' CJD. *Nature*. 1996;383:685-690
63. Parchi P, Capellari S, Chen SG, et al. Typing prion isoforms. *Nature*. 1997;386:232
64. Bruce ME, Will RG, Ironside JW, et al. Transmissions to mice indicate that 'new variant' CJD is caused by BSE agent. *Nature*. 1997;389:498-501
65. Marwick C. FDA calls bovine-based vaccines currently safe. *JAMA*. 2000;284:1231-1232
66. Petersen M, Winter G. 5 drug makers use material with possible mad cow link. *New York Times*. 2001;February 8:C1
67. Brown P. Can Creutzfeld-Jacob disease be transmitted by transfusion? *Curr Opin Hematol*. 1995;2:472-477
68. Collins S, Law MG, Fletcher A, et al. Surgical treatment and risk of sporadic Creutzfeld-Jacob disease: a case-control study. *Lancet*. 1999;353:693-697
69. Esmonde TF, Will RG, Slattey JM, et al. Creutzfeld-Jacob disease and blood transfusion. *Lancet*. 1993;341:205-207
70. Minor PD, Will RG, Salisbury D. Vaccines and variant CJD. *Vaccine*. 2001;19:409-410
71. Goldmacher VS, Thilly WG. Formaldehyde is mutagenic for cultured human cells. *Mutat Res*. 1983;116:417-422
72. Ragan DL, Boreiko CJ. Initiation of C3H/10T1/2 cell transformation by formaldehyde. *Cancer Lett*. 1981;13:325-331
73. Epidemiology of chronic occupational exposure to formaldehyde: report of the ad hoc panel on health aspects of formaldehyde. *Toxicol Ind Health*. 1988;4:77-90
74. Natarajan AT, Darroudi F, Bussman CJM, van Kesteren-van Leeuwen AC. Evaluation of the mutagenicity of formaldehyde in mammalian cytogenetic assays *in vivo* and *in vitro*. *Mutat Res*. 1983;122:355-360
75. Til HP, Woutersen RA, Feron VJ, et al. Two-year drinking-water study of formaldehyde in rats. *Food Chem Toxicol*. 1989;27:77-87
76. Huennekens FM, Osborne MJ. Folic acid coenzymes and one-carbon metabolism. *Adv Enzymol*. 1959;21:369-446
77. Heck H, Casanova-Schmitz M, Dodd PB, et al. Formaldehyde (CH₂O) concentrations in the blood of humans and Fischer-344 rats exposed to CH₂O under controlled conditions. *Am Ind Hyg Assoc J*. 1985;46:1-3
78. Anderson JA, Adkinson NF. Allergic reactions to drugs and biologic agents. *JAMA*. 1987;258:2891-2899
79. Yunginger JW. Anaphylaxis. *Curr Probl Pediatr*. 1992;22:130-146
80. Goh CL. Anaphylaxis from topical neomycin and bacitracin. *Aust J Dermatol*. 1986;27:125-126
81. MacDonald PL, Rosen S, Sweinberg SK. MMR vaccine and neomycin allergy. *Am J Dis Child*. 1993;147:128-129
82. Leyden JJ, Kligman AM. Contact dermatitis to neomycin sulfate. *JAMA*. 1979;242:1276-1278
83. MacDonald RH, Beck M. Neomycin: a review with particular reference to dermatological usage. *Clin Exp Dermatol*. 1983;8:249-258
84. Ratner B, Untracht S. Egg allergy in children. *Am J Dis Child*. 1952;83:309-316
85. Bierman CW, Shapiro GG, Pierson WE, et al. Safety of influenza vaccination in allergic children. *J Infect Dis*. 1977;136:S652-S655
86. James JM, Zeiger RS, Lester MR, et al. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr*. 1998;133:624-628
87. Glezen WP. Serious morbidity and mortality associated with influenza epidemics. *Epidemiol Rev*. 1982;4:25-44
88. Glezen WP, Greenberg SB, Atmar RL, et al. Impact of respiratory virus infection on persons with underlying conditions. *JAMA*. 2000;283:499-505
89. Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. *J Pediatr*. 1985;106:931-933
90. Zieger RS. Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol*. 2002;110:834-840
91. Fasano MB, Wood RA, Cooke SK, Sampson HA. Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine. *J Pediatr*. 1992;120:878-881
92. James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. *N Engl J Med*. 1995;332:1262-1266
93. Lear JT, English JS. Anaphylaxis after hepatitis B immunization. *Lancet*. 1995;345:1249
94. Hudson TJ, Newkirk M, Gervais F, Shuster J. Adverse reaction to the recombinant hepatitis B vaccine. *J Allergy Clin Immunol*. 1991;88:821-822
95. Barbaud A, Tréchet P, Reichert-Pénétrat S, et al. Allergic mechanisms and urticaria/angioedema after hepatitis B immunization. *Br J Dermatol*. 1998;139:916-941
96. Brightman CA, Scadding GK, Dumbreck LA, et al. Yeast-derived hepatitis B vaccine and yeast sensitivity. *Lancet*. 1989;i:903
97. Wiederman G, Scheiner O, Ambrosch F, et al. Lack of induction of IgE and IgG antibodies to yeast in humans immunized with recombinant hepatitis B vaccines. *Int Arch Allergy Appl Immunol*. 1988;85:130-132

IMPOTENT METHODOLOGISTS

“I’m not going to do any methodology [in this course on economics]. The methodologists are like eunuchs in a harem. They know everything about love, but they can’t do anything about it.”

Alex Gerschenkron quoted in Dawidoff N. *The Fly Swatter*. Pantheon; 2002

Submitted by Student