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Immunization of egg-allergic individuals with egg- or chicken-derived vaccines

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Several vaccines are prepared from viruses propagated in eggs. Some vaccines, such as those for measles and mumps, routinely are administered to infants and children, whereas others, such as the influenza vaccine, are recommended primarily for persons in certain age groups or who have chronic respiratory diseases. Some vaccines, such as those for yellow fever and rabies, are administered only to persons traveling to or living in endemic disease areas or who have sustained animal bites. This article highlights differences in how these vaccines are prepared, with emphasis on the quantitation of residual egg-derived protein in each vaccine, and reviews published studies in which these vaccines were administered to individuals who are allergic to eggs.

Inactivated influenza vaccines

Inactivated parenteral vaccines against influenza were developed during the late 1930s, and their efficacy was demonstrated in large-scale, placebo-controlled studies conducted during World War II. These early vaccines were produced from virus grown in the chorioallantoic fluid of 10-day-old chick embryos [1]. Virus was harvested 48 hours after seeding by opening the embryonic blood vessels and allowing the virus to adsorb to the erythrocytes, which then were isolated. The virus was eluted from the erythrocytes, suspended in saline, concentrated, inactivated with formaldehyde, and preserved with merthiolate.

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Allergic reactions to inactivated influenza vaccines

Early reports of allergic reactions to influenza vaccine were anecdotal. Eaton and Meiklejohn [1] reported allergic reactions in 3 of 1791 persons receiving influenza vaccine during the epidemic of 1942. These reactions involved one case of severe asthma in a person with no history of allergy and two cases of urticaria in which the allergy histories were unknown. Ratner and Untracht [2] reported systemic reactions in two influenza-vaccine recipients. One person developed asthma and generalized urticaria 5 minutes after immunization; he had experienced a previous anaphylactic reaction to typhus vaccine (produced from virus grown in chick yolk sacs) 1 year earlier. The other person, who had a history of egg intolerance, experienced hypotension without respiratory or cutaneous symptoms 13 hours after influenza immunization.

One of the first reported fatal reactions to influenza immunization occurred in a 3-year-old girl with no personal history of allergy to egg or chicken [3]. Four hours after receiving 0.5 mL of influenza A and B vaccine subcutaneously, she developed fever, chills, vomiting, and seizures and died 5 hours after hospitalization. She had no urticaria or wheezing, and postmortem findings showed no upper airway swelling. An egg-allergic child who experienced fatal anaphylaxis after influenza immunization was reported anecdotally by Bierman and colleagues [4].

In 1976, the US federal government established a nationwide surveillance system to monitor adverse events associated with the National Influenza Immunization Program. Nearly 50,000,000 people were immunized during a 10-week period against influenza A/New Jersey/76 [5]. Of 4733 immunization-related illnesses reported, there were 11 cases of anaphylaxis (incidence rate, 0.024 cases per 100,000 vaccinees), none of which was fatal, and none of which occurred in persons allergic to eggs.

Egg protein content of inactivated influenza vaccines

In the 1970s, an attempt to quantitate egg proteins in influenza vaccines was made using radial immunodiffusion assays with rabbit antibody raised to whole embryonated egg homogenates [6]. This antibody preferentially recognized ovalbumin, and the ovalbumin contents of nine lots of influenza vaccine ranged from less than 1.0 $\mu\text{g/mL}$ to 7.4 $\mu\text{g/mL}$. When total protein nitrogen assays rather than immunoassays were used, considerably higher protein levels were measured in influenza vaccines (300–1200 $\mu\text{g/mL}$; $n = 4$), dialyzed infected allantoic fluid (1000 $\mu\text{g/mL}$), and dialyzed uninfected allantoic fluid (1000 $\mu\text{g/mL}$) [7].

There are three types of more recent influenza vaccines: whole virus, split virion (in which the virus is disintegrated by chemical or detergent treatment), and subunit (in which viral surface antigens are separated from other viral proteins by zonal centrifugation). Using the Bradford assay, Chaloupka et al [8] found that the total protein content of three split-virion and three subunit vaccines marketed in Europe ranged from 92 to 198 $\mu\text{g/mL}$. When these vaccine proteins were separated by electrophoresis in polyacrylamide gels containing sodium

dodecylsulfate, 61% to 89% of the protein was estimated to be of viral origin by densitometric scanning of Coomassie blue-stained gels. By ELISA, however, the ovalbumin content of the vaccines varied by more than 30-fold (20–650 ng/mL). Sampson et al [9] developed an inhibition ELISA for ovalbumin and ovomucoid and noted wide variability in the egg protein content of three brands of influenza vaccines marketed in the United States (Table 1) [10].

Administration of inactivated influenza vaccine to egg-sensitive persons

Several published reports deal with egg-allergic persons who were skin tested with influenza vaccine and subsequently immunized (Table 2). Ratner et al [11] first demonstrated that the allergenicity of influenza vaccines was directly proportional to the chick embryo protein contents. Specifically, vaccines prepared from red blood cell eluates, which contained the most chick protein, elicited greater immediate intradermal (ID) skin test reactivity in egg-sensitive children that did centrifuged or alcohol-precipitated influenza vaccines. The skin testing itself elicited an asthma flare-up in one egg-sensitive child. The subcutaneous administration of 0.5-mL undiluted influenza vaccine to another egg-sensitive child evoked generalized urticaria and angioedema 20 minutes later.

Davies and Pepys [7] noted that 22 of 70 atopic children and adults in their study were allergic to egg and that 7 of these 22 subjects had positive prick skin tests to undiluted influenza vaccine. Two of the seven subjects reported previous adverse reactions to influenza immunization, including one with a large immediate local swelling and one with immediate generalized urticaria. None of the seven were given subsequent influenza vaccinations.

Murphy and Strunk [12] administered influenza vaccine to six egg-sensitive children, all of whom had chronic severe asthma. All children had positive puncture skin tests to egg yolk and egg white and had positive ID skin tests to a 1:100 dilution of influenza vaccine. Five children were immunized uneventfully using a sequential graded immunization schedule, whereas the sixth child had mild wheezing after the last graduated dose of vaccine. Serum specimens were

Table 1
Egg protein content in various lots of influenza vaccines

Year	Fluvirin (μg/mL)	Fluogen (μg/mL)	FluShield (μg/mL)
2001–2002	0.06	Not done	29.5, 33.1
2000–2001	Not done	Not done	38.4, 42.4
1999–2000	Undetectable	Not done	Not done
1998–1999	0.8, 0.05	Not done	10.9
1997–1998	Not done	Not done	6.5, 8.3
1996–1997	Not done	0.02	1.0
1995–1996	Not done	1.2	Not done
1994–1995	0.01	0.1	27.2

Egg protein (ovomucoid and ovalbumin) determined by ELISA inhibition [9]. Two values represent analyses from different lots.

From Zeiger RS. Current issues with influenza vaccination in egg allergy. J Allergy Clin Immunol 2002;110:834–40; with permission.

Table 2

Results of skin test for influenza vaccine and response to subsequent immunization in egg-sensitive persons

Study	N	Age	Skin test route	Skin test dilution	Positive skin test (%)	Systemic reactions to vaccine (%)	Symptoms
Ratner et al (1952) [11]	5	4–15 y	ID	Neat	100	40	Urticaria, wheeze
Davies and Pepys (1976) [7]	22	11–66 y	SPT	Neat	32	ND	NA
Murphy and Strunk (1985) [12]	6	4–7 y	SPT	1:10	17	17 ^a	Wheeze
Anolik et al (1992) [13]	8	Children	ID	1:100	100		
			SPT	Neat	13	0 ^a	None
			ID	1:100	100		
James et al (1998) [14]	83	3 y (median)	SPT	Neat	5	0 ^b	None
Zeiger (2002) [10]	28	7 y (mean)	SPT	Neat	11	7 ^a	Cough, hoarseness, rhinitis, urticaria
			ID	1:100	100		

Abbreviations: ID, intradermal; NA, not applicable; ND, not done; SPT, skin prick test.

^a Graded multidoses protocol.

^b Two-dose protocol.

Modified from Zeiger RS. Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol* 2002;110:834–40.

obtained from five children (including the child who experienced mild wheezing) before and after immunization. The specific hemagglutination inhibitory antibody titers that were measured were comparable to those in egg-tolerant children of similar ages who received the vaccine in the routine fashion. Anolik et al [12] used the same sequential graded immunization schedule for eight egg-allergic children, all of whom tolerated the influenza vaccine without symptoms. Antibody levels after vaccination were not measured in this study. The investigators noted that influenza vaccine diluted 1:100 evoked positive ID skin tests in five of eight healthy adult volunteers.

The largest study to determine whether influenza vaccine could be administered safely to egg-sensitive children was a multicenter prospective trial that was conducted from 1994 through 1997 [14]. The study group contained 83 children with positive clinical histories of egg allergy and positive prick tests to egg extract, including 27 children with egg-induced anaphylaxis. The control group contained 124 children, of whom 109 had negative clinical histories of egg allergy and negative prick skin tests to egg extract; 13 had positive histories of egg allergy but negative egg skin tests; and two children had equivocal histories, positive egg skin tests, but negative blinded oral challenges with egg. The influenza vaccines contained between 0.02 and 1.2 µg/mL egg protein, as measured by inhibition

immunoassay, and only four children in the study group and one child in the control group had a positive prick skin test to the vaccine. Children in the study group initially received one-tenth dose of influenza vaccine, followed 30 minutes later by a nine-tenth dose. All children tolerated the vaccine without allergic reaction. Thirty-four egg-allergic children aged 8 years or younger returned 1 month later and tolerated a single booster dose of vaccine without incident. The investigators cautioned that influenza vaccines containing higher levels of egg proteins might not be as well tolerated by egg-sensitive children.

Inactivated influenza vaccines marketed in the United States include Fluzone (Aventis Pasteur, Swiftwater, PA), Fluvirin (Evans Vaccines, Liverpool, England), and FluShield (Wyeth-Lederle Vaccines, Philadelphia) [15]. Despite the encouraging multicenter trial results summarized earlier, the American Academy of Pediatrics Committee on Infectious Diseases recommends that inactivated influenza vaccines not be administered to children demonstrating anaphylactic reactivity to chicken or egg proteins [15].

Live, attenuated, cold-adapted influenza vaccine

A live, attenuated, cold-adapted, trivalent intranasal viral vaccine (FluMist, MedImmune, Gaithersburg, MD) is awaiting Food and Drug Administration approval. This vaccine also contains trace quantities of egg protein and in clinical trials has not been administered to egg-sensitive individuals.

Vaccines for measles, mumps, and rubella

The vaccines which have received the most scrutiny relative to egg allergy are measles and mumps, which often are administered with the rubella vaccine. As far back as 1963, reports appeared describing the uneventful administration of measles vaccine to egg-allergic children [16–18]. Other authors noted that the vaccines are “grown in tissue cultures of chick fibroblasts which are antigenically distinct from egg proteins” [19], and that the “vaccines are not prepared in ovo, but are prepared in cell cultures free of the contaminating egg proteins” [20]. Beginning in 1980, reports of anaphylactic reactions to measles vaccine appeared, but the subjects were not allergic to eggs, and most subjects had negative skin tests for the vaccine [21,22].

In 1983, Herman et al reported the cases of two boys who had anaphylactic reactions to measles vaccine [23]. One patient developed generalized urticaria, angioedema, wheeze, and respiratory distress 1 minute after a measles, mumps, and rubella (MMR) immunization at age 15 months. At age 5 months, he had developed generalized urticaria and wheezing 5 minutes after ingestion of “a food product containing egg white.” The second patient developed generalized urticaria, angioedema, and wheezing 2 minutes after an MMR immunization at age 15 months. He had a history of an episode of generalized urticaria, angioedema, and stridor at age 3 months while breast feeding. His only possible exposure to egg would have

been from the mother's breast milk or from a cooked egg placed nearby. By immunoassay, both patients had IgE antibodies to ovalbumin and to MMR vaccine. Although the vaccine was reported to have 0.5 to 1.0 ng of "ovalbumin-reacting protein," no inhibition studies were performed to indicate that the binding of the subjects' IgE antibodies to ovalbumin could be inhibited with the vaccine. The history for egg allergy in the second case does not seem certain.

Many additional reports appeared of egg-allergic subjects who uneventfully received the vaccine [9,23–30]. Lack of clinical reaction to vaccination was found among those who had positive skin tests to the vaccine [9,23,26,27]. In one such study, all 114 children had convincing recent histories of immediate-type allergic reactions to egg and positive egg skin tests [27]. Skin tests were performed with the MMR vaccine by the prick method with the vaccine diluted 1:10; if this test was negative, an ID test with the vaccine diluted 1:100 was performed. Ninety (79%) subjects had negative skin tests to the vaccine and were immunized with MMR vaccine in a single dose in the usual manner without reaction. Twenty-four subjects had positive vaccine skin tests and were given the vaccine in graded doses. During the procedure, three subjects had urticaria without other symptoms that did not require treatment. Another study evaluated 140 children who had positive double-blind, placebo-controlled food challenges to egg or convincing recent histories of anaphylaxis to egg ingestion and positive egg skin tests [9]. Sixty-nine children already had received uneventfully the MMR vaccine, and the other 71 children were immunized prospectively. None had any reaction to the vaccine. This report also included an assay for ovalbumin in the MMR vaccine and found 37 pg per dose.

Reports also appeared describing a few anaphylactic reactions to the vaccine in nonegg-allergic subjects [9,31,32]. A 1993 report of an anaphylactic reaction to MMR vaccine in a nonegg-allergic subject determined the responsible allergenic vaccine component to be gelatin [31]. Many subsequent reports demonstrated gelatin allergy to be responsible for a large number of anaphylactic reactions to this and to other vaccines containing gelatin [33–36].

The issue was clouded further by three reports of immediate-type generalized reactions in egg-allergic children given the MMR vaccine [37–39]. Since 10 months of age, one patient had a history of generalized urticaria and angioedema of the lips and eyelids after ingestion of egg or egg-containing foods [38]. Egg skin tests and radioallergosorbent tests were positive. At 15 months of age, a prick skin test with MMR vaccine diluted 1:10 was negative; however, an ID skin test with the vaccine diluted 1:100 gave a "4+" reaction, and the patient developed generalized urticaria at the time of the skin test. Another patient had a history of "generalized anaphylaxis and respiratory arrest" at 4 months of age after ingestion of egg [38]. At 10 months of age, after ingestion of an egg-containing food, she developed hives, angioedema, and asthma. An immunoassay demonstrated elevated levels of egg-specific IgE antibodies. An ID skin test with MMR vaccine diluted 1:100 caused greater than 5 cm of local swelling, and within 30 minutes of the skin test she had severe wheezing and dyspnea. In a separate report, a 19-month-old boy was described with a history of vomiting, urticaria, and

rhinitis within minutes of egg ingestion [39]. Skin prick test to egg was positive (4+). Prick skin test to the MMR vaccine was negative, but an ID skin test to MMR vaccine diluted 1:100 gave a 4+ positive reaction. During a desensitization protocol (in which the vaccine was administered in graded doses), he developed urticaria and a drop in oxygen saturation, but no change in pulse or blood pressure. He was treated with oxygen, intravenous fluids, and diphenhydramine, and his desensitization protocol was completed without further reaction. Another report describes a 15-month-old child who had a history of worsening eczema 24 hours after egg ingestion [37]. It was not stated whether the child had egg-specific IgE antibody by skin test or immunoassay, but a prick skin test with undiluted vaccine resulted in a 10-mm wheal. Despite the positive prick skin test, an ID test with the vaccine was performed 20 minutes later, resulting in a 15-mm local reaction and generalized urticaria, diarrhea, and hypotension.

Such isolated reports of reactions to the vaccine in egg-allergic children continued to be overwhelmed by hundreds of reports of egg-allergic children who uneventfully received the vaccine [37,39–44]. In 1994, two reports were published describing a total of 738 children with histories of immediate-type allergic reactions to egg and positive egg skin tests, all of whom received the vaccine without allergic reaction [41,42]. The reports of patients allergic to egg who were given the measles or MMR vaccine are summarized (Table 3).

Collectively, the reports of allergic reactions to the measles, mumps, or MMR vaccine reveal that:

Most egg-allergic subjects uneventfully receive the MMR vaccine as a single dose in the usual manner.

Although the vaccine may contain picogram or nanogram quantities of egg protein, this quantity of allergen seems to be insufficient to cause allergic reactions in egg-allergic vaccinees.

Most anaphylactic reactions to the MMR vaccine occur in nonegg-allergic recipients.

Skin tests with the vaccine do not reliably predict reactions to the vaccine.

These considerations have led the American Academy of Pediatrics Committee on Infectious Diseases to state that “children with egg allergy routinely may be given MMR, measles, or mumps vaccine without previous skin testing” [45].

Yellow fever vaccine

Of the various vaccines that are grown in eggs, the yellow fever vaccine may have the greatest likelihood of causing allergic reactions in egg-allergic recipients. The virus is grown in chick embryos, as opposed to extraembryonic allantoic fluid (influenza) or chick embryo fibroblast cell cultures (measles, mumps, and purified chick embryo rabies). The embryos are homogenized and centrifuged. The resultant virus-containing supernatant is freeze-dried as the

Table 3

Results of skin tests to measles or measles, mumps, and rubella vaccine and response to subsequent immunization in egg-sensitive persons

Study	N	Positive skin test	Generalized, apparently mast cell-mediated reactions
Kamin et al (1963) [16]	11	0	0
Kamin et al (1965) [17]	11	NR	0
Brown and Wolfe (1967) [18]	1	0	0
Herman et al (1983) [23]	2	2	2 ^a
Herman et al (1983) [23]	6	6	0 ^b
Miller et al (1983) [26]	4	3	0
Greenberg and Bix (1988) [25]	15	0	0
Lavi et al (1990) [27]	114	24	3 ^{b,c}
Kemp et al (1990) [28]	32	NR	0
Bruno et al (1990) [30]	23	NR	0
Beck et al (1991) [29]	15	0 of 13	0
Businco et al (1991) [24]	60	0	0
Fasano et al (1992) [9]	71	2	0
Puvvada et al (1993) [38]	10	4	2 ^{b,d}
Tounian et al (1993) [40]	16	2 of 10	0 ^b
Aickin et al (1994) [42]	238	17 of 96 ^e	0
Freigang et al (1994) [41]	500	NR	0
Trotter et al (1994) [39]	12	3	1
James et al (1995) [43]	54	3 of 17	0
Baxter et al (1996) [37]	200	5	1 ^f
Bruno et al (1997) [44]	19	NR	0
Total	1414	71 of 642	9 of 1414

Abbreviation: NR; not reported.

^a One subject had a questionable history of egg allergy.

^b Vaccine given in graded doses to patients with positive skin tests.

^c Three of the 24 subjects with positive skin tests had urticaria only on vaccine administration.

^d Two of the four subjects with positive vaccine skin tests had anaphylactic reactions to ID skin testing.

^e Seventeen of 96 subjects with positive prick skin tests to egg also had positive intradermal skin tests to vaccine (at least 5 mm larger than negative control skin tests). It was unclear how many of the 96 subjects had histories of clinical reaction to ingestion of egg.

^f One of 200 subjects had an anaphylactic reaction to ID skin testing (performed despite a positive prick skin test) but questionable history for egg allergy.

vaccine [46,47]. In an assay that quantified residual host protein in vaccines by radial immunodiffusion, the yellow fever vaccine was found to have 15.6 µg/mL of ovalbumin, compared with the influenza vaccine (1.0–7.4 µg/mL) and measles vaccine (undetectable) [6].

The earliest report of anaphylaxis after administration of the yellow fever vaccine dates from 1943 and describes a 27-year-old man who developed generalized hives and shortness of breath and lost consciousness minutes after receiving cholera and yellow fever vaccines [48]. He had a history of similar reactions after eating eggs and chicken. Skin tests were positive to egg, chicken, and yellow fever vaccine but negative to cholera vaccine. A report from 1945 describes a 20-year-old man who, 15 minutes after receiving his first yellow fever

vaccine, developed severe asthma, facial edema, and generalized urticaria and required treatment with five doses of epinephrine [49]. He had a history of egg allergy from infancy. He also had positive skin tests to egg, chicken, and the vaccine. A third report from the 1940s describes a 19-year-old man who developed angioedema and chest tightness shortly after receiving typhus fever and yellow fever vaccines [50]. He reported that he did not eat eggs because they caused him to vomit. Skin tests were positive to egg, yellow fever vaccine, typhus fever vaccine, and egg but negative to chicken.

No additional reports of anaphylaxis appeared until a 1999 review of the Vaccine Adverse Event Reporting System (VAERS) database [51]. During 1990 through 1997, 243 VAERS reports describing adverse events after the administration of yellow fever vaccine were submitted. Forty (16%) reports described probable or possible anaphylactic events, indicating that, despite the paucity of previous reports, anaphylactic reactions occur after yellow fever vaccination. Based on the number of doses distributed, the report estimated the rate of such reactions to be 1 case in 131,000 doses. The constituent of yellow fever vaccine that may cause allergic reactions was not determined. With only one exception, the reactions occurred after the first dose of yellow fever vaccine, making the yellow fever viral proteins unlikely to be the cause of these reactions. Patients to be given the vaccine typically are asked if they are allergic to eggs or chicken; however, it is possible that some of the reactions in these studies were caused by egg or chicken allergy. The vaccine also contains gelatin as a stabilizer [47] that has been implicated as the allergen in many allergic reactions to other gelatin-containing vaccines [31,33–36].

Yellow fever vaccine may contain chicken proteins other than those from eggs. The package insert indicates that “since the yellow fever virus is propagated in chicken embryos, it should not be administered to an individual with a history of hypersensitivity to egg, chicken protein, or to any other component of the vaccine” [47]. Two of the three reports of anaphylaxis caused by yellow fever vaccine in the 1940s (described earlier) involved subjects who were allergic to chicken and egg proteins. A 1999 report describes three military recruits who were allergic to chicken but not to egg who required yellow fever vaccine [52]. The recruits had positive skin tests to various avian meats, and immunoblots demonstrated IgE antibodies to avian meat proteins. Skin test results were positive to yellow fever vaccine, but IgE could not be demonstrated to vaccine components on immunoblots. The vaccine was administered successfully in graded doses.

Another potential issue with yellow fever and other egg-containing vaccines is raw egg allergy. Patients have been described who tolerate the ingestion of hard-boiled eggs but have systemic immediate-type allergic reactions to foods containing raw eggs and whose skin tests demonstrate less reactivity to boiled, as opposed to raw, eggs [53]. In another report relating this phenomenon to a vaccine reaction, a 37-year-old woman developed total body itching and frank hives within 4 hours of receiving yellow fever vaccination [54]. She stated that she routinely ate eggs without any reaction; before the vaccination, she stated that she was not allergic to eggs. Further questioning revealed that when she ate

Table 4

Evaluation of patients with anaphylactic reactions to yellow fever vaccine

Study	n	Other vaccines given at same time/skin test result	Skin tests		
			Yellow fever vaccine	Egg	Chicken
Swartz (1943) [48]	1	Cholera/–	+	+	+
Sprague and Barnard (1945) [49]	1	None	+	+	+
Rubin (1946) [50]	1	Typhus/+	+	+	–
Kelso et al (1999) [51]	40	18 of 40/ND	ND	ND	ND
Kelso (2000) [54]	1	None	+	+	–

Abbreviation: ND, not determined.

cookie dough containing raw egg, she developed immediate oral itching. Prick skin tests were positive for yellow fever vaccine, commercial whole egg extract, and raw egg but were negative for the same materials after they had been heated or cooked and for commercial chicken extract. This patient is probably allergic to some heat-labile allergen in egg. Yellow fever vaccine is not heated at any time during the manufacturing process, and the residual egg proteins could include some that are heat labile. Perhaps some of the other reported anaphylactic reactions to the vaccine are caused by an unrecognized raw egg allergy. This same phenomenon could account for some allergic reactions to influenza vaccines, particularly to lots containing higher amounts of egg protein.

Unlike measles, mumps, and influenza vaccines [14,43], there are no reports of the prospective administration of yellow fever vaccine to egg-allergic patients. The likelihood of such patients having anaphylactic reactions to the vaccine is unknown. Anaphylactic reactions to yellow fever vaccine do occur, and some reactions that have been investigated have implicated egg or chicken as the responsible allergen (Table 4). It seems prudent to inquire about egg allergy (and chicken and gelatin allergies) before the administration of yellow fever vaccine. Patients who indicate such an allergy should be referred to an allergist for evaluation. A suggested approach to these patients is outlined in Appendix 1.

Rabies vaccine

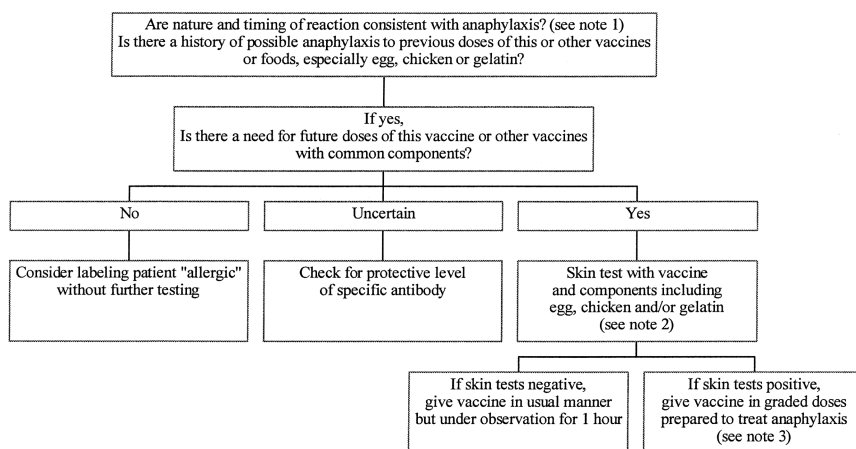
Three inactivated rabies vaccines are marketed in the United States. One vaccine is produced from virus propagated on human diploid cells (Imovax, Aventis Pasteur, Swiftwater, PA), and a second vaccine is propagated on fetal rhesus lung diploid cells (Rabies Vaccine Adsorbed, BioPort Corporation, Lansing, MI). Neither of the vaccines contains egg proteins. The third vaccine is grown on chicken fibroblasts (RabAvert, Chiron Corporation, Emeryville, CA) and contains less than 3 ng of ovalbumin per 1-mL dose [55]. Among approximately 12 million doses of this vaccine distributed worldwide, two cases

of anaphylactic shock have been reported. No safety data exist regarding the use of RabAvert in persons with anaphylactic egg allergies.

Smallpox vaccine

Techniques for large-scale production of smallpox vaccine in embryonated eggs were developed in the late 1930s by the Texas State Health Department [56]. Routine immunization of children with smallpox vaccine was discontinued in the early 1970s, and residual stocks of smallpox vaccine from that era were prepared from calf lymph, not eggs. This vaccine does not pose increased risks to egg-sensitive persons, provided that the persons do not have eczema.

Appendix 1. Suggested approach to suspected immediate-type allergic reactions to vaccines



Note 1. Are nature and timing of reaction consistent with anaphylaxis?

Probable anaphylactic reaction: reaction occurring within 4 hours of vaccine administration to include signs and/or symptoms from > 1 system as below:

- Dermatologic: pruritus, urticaria, angioedema, flushing
- Respiratory: dyspnea, bronchospasm, glossal/pharyngeal edema, hoarseness, nose/eye symptoms: nasal congestion, rhinorrhea, sneezing, red, itchy, watery eyes
- Cardiovascular: hypotension, tachycardia, palpitations, lightheadedness, loss of consciousness.
- Gastrointestinal: nausea, vomiting, diarrhea

Possible anaphylactic reaction:

- Signs and/or symptoms from only one system as above
- Signs and/or symptoms from greater than one of the systems as above, but happened more than 4 hours after vaccination

Note 2. Skin tests with vaccine and components including egg, chicken and/or gelatin*Vaccine skin tests:*

- Prick test with full strength vaccine (consider dilution if history of life-threatening reaction)
- If prick test with full strength vaccine negative, ID test with 0.02 cc vaccine 1:100
- Note: Vaccine skin tests may cause false (or clinically irrelevant) positives.

Vaccine component/food skin tests:

- Prick tests with commercial extracts of egg (influenza and yellow fever vaccines) and chicken (yellow fever vaccine)
- Prick test with sugared gelatin (eg, Jell-O: dissolve 1 teaspoon of gelatin powder in 5 cc normal saline). Vaccines that contain gelatin: DTaP (some brands), influenza (some brands), Japanese encephalitis, measles, mumps, rabies (some brands), rubella, typhoid (oral, in the capsule), varicella, yellow fever

Note 3. Vaccine administration in graded doses

For a vaccine where usual dose is 0.5 ml, administer graded doses of vaccine at 15 minute intervals: 0.05 ml of 1:100 dilution, 0.05 ml of 1:10 dilution, 0.05 ml of full strength, 0.10 ml of full strength, 0.15 ml of full strength, 0.20 ml of full strength

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