Allergic Reactions to Vaccine Constituents

Subjects: Allergy

Contributor: Ming-Han Tsai, Chih-Yung Chiu

Vaccination is an essential public health measure that helps to reduce the burden of infectious diseases in children. Although vaccines have an excellent safety record and the association of severe allergic reactions is rare, public concerns about vaccine safety can lead to incomplete vaccination coverage in children with or without allergies. Therefore, it is important to understand the mechanisms and implications of allergic reactions to vaccines and define strategies to manage them to provide the safest care for vaccine recipients. Unlike drugs, which are the primary cause of immediate allergic reactions, vaccine excipients (i.e., substances used to formulate a vaccine) are the main cause of specific IgE and immediate reactions associated with vaccines. Pre-existing allergies to vaccine excipients, such as antigens, adjuvants, stabilizers, preservatives, emulsifiers, leached packaging components, residual antibiotics, cell culture materials, and inactivating ingredients, are the primary contributors to immediate allergic reactions during vaccination. In contrast, drug-related anaphylaxis is usually caused by the active drug itself rather than excipients.

Keywords: allergic reaction ; vaccines ; children

1. Gelatin

Gelatin is used as a stabilizer in several vaccines. It has been identified as a cause of many anaphylactic reactions to measles, mumps, rubella (MMR), and varicella vaccines [1][2]. A retrospective study that collected sera from individuals who had experienced anaphylaxis after receiving the MMR vaccine found that 27% of them had anti-gelatin IgE, whereas none of the vaccinated subjects who did not experience adverse events had detectable levels of this antibody [3]. Further research has shown that patients who experience anaphylaxis due to the MMR vaccine may also be sensitized to gelatin present in the diphtheria–tetanus–acellular pertussis (DTaP) vaccine [4]. Gelatin is also a source of alpha-gal, a carbohydrate allergen that causes meat allergies. Children with an alpha-gal allergy may experience anaphylaxis after receiving an MMR or varicella vaccine [5].

Thus, children with allergic reactions to gelatin upon ingestion should be evaluated by an allergist before receiving gelatin-containing vaccines. If there is a history of an immediate-type allergic reaction to gelatin, which is confirmed by skin tests or serum-specific IgE antibody tests, it is advisable to test such children for gelatin-containing vaccines prior to administration. If the vaccine skin tests are negative, the vaccine can be administered in the usual manner. However, children should be observed for at least 30 min after vaccine administration. If the vaccine skin tests are positive, the vaccine can be administered in incremental doses under observation [6].

2. Egg

Egg proteins are present in some influenza, MMR, and yellow fever vaccines because they are cultured in chicken embryo fibroblasts or embryonated chicken eggs [7][8]. Egg allergy is common in children, but studies have shown that influenza and MMR vaccines can be safely administered to children with egg allergies [9][10]. In particular, children with egg allergies, including those who experienced anaphylaxis, successfully received yellow fever vaccines without any serious adverse events [11]. According to the ACIP guidelines, individuals with mild egg allergies can receive any licensed age-appropriate influenza vaccine and no longer need to be observed for 30 min after vaccination, as severe allergic reactions to these vaccines are rare [7]. However, individuals with severe egg allergies should only receive influenza vaccines under the supervision of a healthcare provider capable of recognizing and managing serious allergic conditions. For children with egg allergies, the current practice for the yellow fever vaccine is to undergo skin testing before administration. If the vaccine skin test results are negative, the vaccine can be administered in the usual manner. However, the children should be observed for at least 30 min. If the skin test results are positive, the vaccine can be administered safely in graded doses [12].

3. Milk Protein

Casein, a protein found in cow milk, has been implicated in anaphylaxis to DTP-containing vaccines in a small number of children with severe milk allergies [13]. These vaccines are prepared using a medium derived from cow milk protein, and trace amounts of casein are found in these preparations. However, there is no evidence to suggest that DTP vaccines contribute to the development of allergic diseases or that atopy is a contraindication for these vaccines [14].

4. Preservatives/Adjuvants (Thimerosal, Aluminum, and Phenoxyethanol)

Thimerosal, aluminum, and phenoxyethanol are added to some vaccines as preservatives. However, thimerosal, which contains mercury, is rarely used as a preservative in vaccines, and its role as an allergen remains unclear [15]. A risk assessment study found no evidence of harm caused by thimerosal in vaccines, except for local hypersensitivity reactions [16]. Additionally, it should be noted that thimerosal is a mercury-based organic compound, and therefore does not possess any toxic characteristics for mammals. These preservatives are not known to cause immediate-type allergic reactions and immediate-type skin testing is not necessary.

5. Antibiotics

Antibiotics, including neomycin, polymyxin B, kanamycin, gentamicin, and streptomycin, can cause allergic reactions ranging from mild to severe, including anaphylaxis. For example, an individual who received the MMR vaccine containing neomycin was reported to have experienced anaphylaxis shortly after vaccination [17]. In addition, one case of anaphylaxis has been reported following the use of eye drops containing polymyxin B, an excipient found in DTaP, and other vaccines [18]. To the best of the knowledge, no other antibiotic has been linked to vaccine-associated anaphylaxis. A commonly used preservative in cosmetics and vaccines is 2-phenoxyethanol. There are favorable reports about this compound for its broad-spectrum antimicrobial activity and good tolerability [7][19].

6. Latex

The use of rubber in vaccine vial stoppers or syringe plungers can cause allergic reactions in some individuals. A report of an anaphylactic reaction following the administration of the hepatitis B vaccine to a latex-allergic patient has been attributed to the rubber in the vaccine stopper [20]. However, a review of 160,000 reports from the Vaccine Adverse Event Reporting System (VAERS) found only 28 cases of possible immediate-type allergic reactions following the administration of a vaccine containing dry natural rubber [21]. Patients with a history of anaphylaxis to latex can safely receive vaccines with non-latex packaging. However, if the only available option contains latex, the vaccine can still be administered. In such cases, the patient must be observed for at least 30 min afterward.

7. Yeast

There are relatively few reported instances of anaphylaxis following vaccination in individuals with known allergies to yeast proteins. Between 1990 and 2004, only 15 such cases were reported, 11 of which occurred after administration of the hepatitis B vaccine. This vaccine contained trace amounts of yeast proteins [7]. According to a report from VAERS, 107 adverse events were reported in individuals with a pre-existing yeast allergy. Of them, 11 were probable or possible anaphylactic events following administration of the hepatitis B vaccine [22]. It has been reported that individuals with yeast allergies may experience reactions to vaccines containing yeast proteins. If a patient has a history of reaction to baker's or brewer's yeast and has a positive skin test for *Saccharomyces cerevisiae*, it is recommended to test with yeast-containing vaccines before administration [6][23]. If the vaccine skin test result is negative, the vaccine can be administered as usual, with the patient being observed for at least 30 min. If the vaccine skin test is positive, the vaccine can be administered in incremental doses, with the patient being monitored.

8. Dextran

The use of dextran as a medium nutrient or stabilizer in some vaccines, including the MMR vaccine previously used in Italy and Brazil, has been linked to allergic reactions [24]. These reactions were attributed to the presence of IgG antibodies to dextran and activation of the complement system, leading to the release of anaphylatoxins. This brand of MMR vaccine has been removed from the market. However, dextran can still be found in some other vaccines such as rotavirus vaccines.

9. Polyethylene Glycol

The Pfizer-BioNTech BNT162B2 and the Moderna mRNA-1273 vaccines are lipid nanoparticles that contain messenger ribonucleic acid (mRNA) coding for the spike protein of the coronavirus [7]. Lipid nanoparticles stabilize and improve the solubility of mRNA vaccines in water and act as adjuvants. These vaccines contain polyethylene glycol (PEG) 2000, a high-molecular-weight version of PEG. This is used as an emulsifier in a variety of products, including vaccines, pharmaceuticals, cosmetics, and foods. PEG and its derivatives are commonly found in household products [7]. There is evidence that sensitivity to PEG may lead to IgE-mediated anaphylaxis after the administration of PEG-conjugated biologics, and severe allergic reactions to PEG have been linked to pre-existing anti-PEG antibodies induced by PEG-containing household products. Although more research is needed to understand the higher rate of anaphylaxis observed with COVID-19 vaccines compared to other vaccines, PEG 2000, a component of mRNA vaccines such as Pfizer-BioNTech BNT162B2 and Moderna mRNA-1273, is considered the most likely cause of allergic reactions. Here, **Table 1** shows the components implicated in allergic reactions and related adverse events.

Table 1. Immediate component-mediated reactions and associated vaccines in children.

Component	Function in Vaccines	Relevant Vaccines	Allergic Reactions	Ref.
Gelatin	Stabilizer	MMR and varicella	Anaphylaxis and urticaria	[1][2]
Egg protein (albumin)	Residual medium and stabilizer	MMR, influenza, and yellow fever	Anaphylaxis	[7][8]
Milk protein (casein)	Medium nutrient	DTaP	Anaphylaxis	[13]
Thimerosal	Preservative	Influenza and Td	Local reaction	[15][16]
Aluminum	Adjuvant	DTaP, Hib, hepatitis A/B, HPV, Japanese encephalitis, meningococcal, pneumococcal, and Tdap	Local reaction	[7]
Neomycin	Antimicrobial	DTaP, hepatitis A, influenza, MMR, polio, and varicella	Anaphylaxis	[18]
Phenoxyethanol	Preservative	DTaP, influenza, polio, and Tdap	Local reaction	[19]
Latex	Pharmaceutical closure	DTaP, hepatitis A/B, influenza, meningococcal, rotavirus, Tdap, Td, and yellow fever	Anaphylaxis and urticaria	[20][21]
Yeast	Medium nutrient	DTaP, hepatitis B, HPV, meningococcal, and pneumococcal	Anaphylaxis	[7][22]
Dextran	Medium nutrient and stabilizer	MMR [a] and rotavirus	Anaphylaxis	[24]
Polyethylene glycol	Surfactant of mRNA	COVID-19	Anaphylaxis	[25][26][27]

[a] MMR vaccines containing dextran have been withdrawn from the market. MMR, measles–mumps–rubella; DTaP, diphtheria–tetanus–acellular pertussis; Td, tetanus–diphtheria; Tdap, tetanus-diphtheria-acellular pertussis; Hib, *Hemophilus influenzae* type b; HPV, human papillomavirus.

References

1. Kelso, J.M.; Jones, R.T.; Yunginger, J.W. Anaphylaxis to measles, mumps, and rubella vaccine mediated by IgE to gela tin. J. Allergy Clin. Immunol. 1993, 91, 867–872.
2. Sakaguchi, M.; Yamanaka, T.; Ikeda, K.; Sano, Y.; Fujita, H.; Miura, T.; Inouye, S. IgE-mediated systemic reactions to g elatin included in the varicella vaccine. J. Allergy Clin. Immunol. 1997, 99, 263–264.
3. Pool, V.; Braun, M.M.; Kelso, J.M.; Mootrey, G.; Chen, R.T.; Yunginger, J.W.; Jacobson, R.M.; Gargiullo, P.M.; VARES T eam. Prevalence of anti-gelatin IgE antibodies in people with anaphylaxis after meals-mumps rubella vaccine in the Uni ted States. Pediatrics 2002, 110, e71.

4. Sakaguchi, M.; Inouye, S. Systemic allergic reactions to gelatin included in vaccines as a stabilizer. Jan. J. Infect. Dis. 2000, 53, 189–195.
5. Stone, C.A., Jr.; Commins, S.P.; Choudhary, S.; Vethody, C.; Heavrin, J.L.; Wingerter, J.; Hemler, J.A.; Babe, K.; Phillips, E.J.; Norton, A.E. Anaphylaxis after vaccination in a pediatric patient: Further implicating alpha-gal allergy. J. Allergy Clin. Immunol. Pract. 2019, 7, 322–324.e2.
6. Dreskin, S.C.; Halsey, N.A.; Kelso, J.M.; Wood, R.A.; Hummell, D.S.; Edwards, K.M.; Caubet, J.-C.; Engler, R.J.M.; Gold, M.S.; Ponvert, C.; et al. International Consensus (ICON): Allergic reactions to vaccines. World Allergy Organ J. 2016, 9, 32.
7. Sampath, V.; Rabinowitz, G.; Shah, M.; Jain, S.; Diamant, Z.; Jesenak, M.; Rabin, R.; Vieths, S.; Agache, I.; Akdis, M.; et al. Vaccines and allergic reactions: The past, the current COVID-19 pandemic, and future perspectives. Allergy 2021, 76, 1640–1660.
8. Magista, S.; Albanesi, M.; Chaoul, N.; Bona, D.D.; Leo, E.D.; Nettis, E.; Caiaffa, M.F.; Macchia, L. Safety of measles, mumps, and rubella vaccine in egg allergy: In vivo and in vitro management. Clin. Mol. Allergy 2020, 18, 21.
9. Upton, J.E.M.; Hummel, D.B.; Kasprzak, A.; Atkinson, A.R. No systemic reactions to influenza vaccination in egg-sensitized tertiary-care pediatric patients. Allergy Asthma Clin. Immunol. 2012, 8, 2.
10. Kang, J.H. Effectiveness and safety of seasonal influenza vaccination in children with underlying respiratory diseases and allergy. Korean J. Pediatr. 2014, 57, 164–170.
11. Sharma, K.; Perrett, K.P.; Wood, N. Yellow fever vaccination in egg-allergic children. Pediatr. Infect. Dis. J. 2020, 39, e76–e78.
12. Gerhardt, C.M.B.; Castro, A.P.B.M.; Pastorino, A.C.; Dorna, M.B.; Nunes-Santos, C.J.; Aquilante, B.P.; Miyaji, K.T.; Lopes, M.H. Safety of yellow fever vaccine administration in confirmed egg-allergic patients. Vaccine 2020, 38, 6539–6544.
13. Kattan, J.D.; Konstantinou, G.N.; Cox, A.L.; Nowak-Wegrzyn, A.; Gimenez, G.; Sampson, H.A.; Sicherer, S.H. Anaphylaxis to diphtheria, tetanus, and pertussis vaccines among children with cow's milk allergy. J. Allergy Clin. Immunol. 2011, 128, 215–218.
14. Nilsson, L.; Brockow, K.; Alm, J.; Cardona, V.; Caubet, J.C.; Gomes, E.; Jenmalm, M.C.; Lau, S.; Netterlid, E.; Schwarze, J.; et al. Vaccination and allergy: EAACI position paper, practical aspects. Pediatr. Allergy Immunol. 2017, 28, 628–640.
15. McMahon, A.W.; Iskander, J.K.; Haber, P.; Braun, M.M.; Ball, R. Inactivated influenza vaccine (IIV) in children <2 years of age: Examination of selected adverse events reported to the Vaccine Adverse Event Reporting System (VAERS) after thimerosal-free or thimerosal-containing vaccine. Vaccine 2008, 26, 427–429.
16. Ball, L.K.; Ball, R.; Pratt, R.D. An assessment of thimerosal use in childhood vaccines. Pediatrics 2001, 107, 1147–1154.
17. Kwittken, P.L.; Rosen, S.; Sweinberg, S.K. MMR vaccine and neomycin allergy. Am. J. Dis. Child 1993, 147, 128–129.
18. Henao, M.P.; Ghaffari, G. Anaphylaxis to polymyxin B-trimethoprim eye drops. Ann. Allergy Asthma Immunol. 2016, 116, 372.
19. Dreno, B.; Zuberbier, T.; Gelmetti, C.; Gontijo, G.; Marinovich, M. Safety review of phenoxyethanol when used as a preservative in cosmetics. J. Eur. Acad. Dermatol. Venereol. 2019, 33, 15–24.
20. Lear, J.T.; English, J.S. Anaphylaxis after hepatitis B vaccination. Lancet 1995, 345, 1249.
21. Russell, M.; Pool, V.; Kelso, J.M.; Tomazic-Jezic, V.J. Vaccination of persons allergic to latex: A review of safety data in the Vaccine Adverse Event Reporting System (VAERS). Vaccine 2004, 23, 664–667.
22. DiMiceli, L.; Pool, V.; Kelso, J.M.; Shadomy, S.V.; Iskander, J.; Team VAERS. Vaccination of yeast sensitive individuals: Review of safety data in the US vaccine adverse event reporting system (VAERS). Vaccine 2006, 24, 703–707.
23. Kelso, J.M.; Greenhawt, M.J.; Li, J.T.; Nicklas, R.A.; Bernstein, D.I.; Blessing-Morre, J.; Cox, L.; Khan, D.; Lang, D.M.; Oppenheimer, J.; et al. Adverse reactions to vaccines practice parameter 2012 update. J. Allergy Clin. Immunol. 2012, 130, 25–43.
24. Zanoni, G.; Puccetti, A.; Dolcino, M.; Simone, R.; Peretti, A.; Ferro, A.; Tridente, G. Dextran-specific IgG response in hypersensitivity reactions to measles-mumps-rubella vaccine. J. Allergy Clin. Immunol. 2008, 122, 1233–1235.
25. Cabanillas, B.; Akdis, C.; Novak, N. Allergic reactions to the first COVID-19 vaccine: A potential role of polyethylene glycol? Allergy 2020, 76, 1617–1618.
26. Pfaar, O.; Mahler, V. Allergic reactions to COVID-19 vaccinations-unveiling the secret(s). Allergy 2021, 76, 1621–1623.

27. Povsic, T.J.; Lawrence, M.G.; Lincoff, A.M.; Mehran, R.; Rusconi, C.P.; Zelenkofske, S.L.; Huang, Z.; Sailstad, J.; Armstrong, P.W.; Steg, P.G.; et al. Pre-existing anti-PEG antibodies are associated with severe immediate allergic reactions to pegnivacogin, a PEGylated aptamer. J. Allergy Clin. Immunol. 2016, 138, 1712–1715.