

Vaccination and Anaphylaxis

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The incidence of anaphylactic or severe allergic reactions to vaccines is very low, less than one case per million vaccine doses. Larger studies from later years report no deaths. The cause of the reaction is usually not the immunizing antigen itself, but rather some other vaccine ingredient such as egg protein from the production process or gelatin added as a stabilizer. Most people with egg allergy can be vaccinated without any reaction. Vasovagal reactions with or without hyperventilation are common after vaccination. They can be rather dramatic and are often mistaken for anaphylactic reactions. Correct diagnosis is important in making it possible to vaccinate those who might otherwise run the risk of serious infections.

Introduction

According to the original definition, anaphylaxis is a serious and potentially lethal systemic reaction, involving at least two organ systems. Currently, the term anaphylaxis usually is used for any serious, immediate allergic reaction [1].

Anaphylactic reactions may be caused by almost any substance—ingested, inhaled, or injected—and vaccines are no exception. The reaction appears within minutes to 1 hour after vaccination. Skin symptoms such as urticaria are common, combined with respiratory and/or circulatory symptoms (eg, dyspnea, asthma, flushing, low blood pressure).

Case descriptions of anaphylactic reactions to almost all vaccines exist: diphtheria and tetanus toxoids [2], bacilli Calmette-Guérin (BCG) vaccine [3], poliomyelitis and influenza vaccines [4], and vaccines against yellow fever [5], Japanese encephalitis [6], and rabies [7]. Most reports from recent years describe reactions to measles or measles-mumps-rubella (MMR) vaccines, even if the incidence does not seem to be higher than that for other vaccines [8,9].

Judged by the number of reports of cases, the incidence of anaphylactic reactions to vaccines was higher

50 to 60 years ago than it is today. One reason for this may be that the diagnostic criteria are more stringent today. Another explanation can be that many of the reactions were caused by impurities in the vaccines. This is exemplified by a study showing that reactions to several different vaccines were probably caused by allergy to silk from silk filters [4]. These reactions disappeared when the silk filters were substituted by more inert filters in vaccine production. Generally, better purification processes have reduced the amount of allergenic substances in vaccines.

However, even 50 years ago severe systemic allergic reactions to vaccines were rare. Among 158,000 persons vaccinated against diphtheria, tetanus, poliomyelitis, and influenza at Lackland Air Force Base, Texas, USA, only 101 persons (0.06%) were referred for examination because of allergic reactions. In the end, only three persons were unable to receive the scheduled vaccines [2].

Anaphylaxis to Vaccines Today

The risk of anaphylaxis after vaccination is extremely low. An analysis of spontaneously reported “allergic” reactions to 15 different marketed vaccines during the years 1994 to 1998 showed one report per 450,000 doses of vaccine sold [10]. Potentially life-threatening episodes were noted in about one report per 8 million doses sold, and no deaths were documented. A US study including data from four large health maintenance organizations (HMOs) participating in the Vaccine Safety Datalink Project found five cases of potentially vaccine-associated anaphylactic reactions after administration of 7,644,049 vaccine doses, giving a risk of 0.65 cases per million doses [8], and no deaths.

The incidence of anaphylactic or severe allergic reactions varies with different vaccine types. Most reports of anaphylaxis after diphtheria and tetanus vaccines are case reports, and, therefore, the incidence is difficult to estimate. The incidence of anaphylactic reactions to measles virus-containing vaccines reported to the Vaccine Adverse Event Reporting System (VAERS) in the United States between 1991 and 1997 was 1.8 reported cases per million doses [11•]. Other studies give varying incidence figures, but usually in a similar range [8,9]. The incidence of anaphylactic reactions to yellow fever vaccine reported to VAERS from 1990 to 1997 was about one per 131,000 doses [5]. The reaction often occurred

Table 1. Potential allergens in vaccines

Potential allergen	Vaccines	Comments
Egg proteins	Influenza, yellow fever, tick-borne encephalitis	May cause serious reactions in persons with anaphylactic reactions to eggs
Gelatin	MMR, yellow fever, acellular pertussis	Probably cause of most severe allergic reactions to MMR
Antibiotics	Many viral vaccines	Today usually neomycin; rarely the cause of general allergic reactions
Thimerosal	Some influenza vaccines (removed from most vaccines)	Probably not cause of general allergic reactions
Aluminum salts	As adjuvant in many vaccines	Probably not cause of general allergic reactions
Formaldehyde	Trace amounts in many vaccines	Probably not cause of general allergic reactions
Latex	May be found in packaging material	Only one report in literature of anaphylactic reaction to vaccination in a latex-allergic individual

MMR—measles, mumps, and rubella.

after the first vaccine dose, which indicates that ingredients other than the immunizing vaccine antigen were possibly the cause of the allergic reaction.

Most viral vaccines are still “traditional vaccines,” consisting of live attenuated or inactivated viruses, or parts of inactivated viruses. The production starts with growing of the virus in some kind of cellular system. Subsequently, the virus is either killed or attenuated by several growth passages. The vaccines go through one or several purification processes, aiming to remove as much of remaining foreign substances as possible from the cell cultures, the growth media, and the inactivation process, but the vaccine still may contain trace amounts of substances from all the production steps. Other substances may be added to stabilize the vaccine or make it more immunogenic (adjuvants). The substances from the production processes and the added substances are all potential allergens: egg proteins, gelatin and antibiotics, thimerosal, aluminum salts, formaldehyde, colorants, and residues of different growth media. Another possible allergen is latex from rubber stoppers or syringes (Table 1).

Reactions to Egg Proteins

Vaccines against influenza, yellow fever, and tick-borne encephalitis are grown in embryonated eggs. These vaccines may contain small amounts of egg proteins (ovomucoid-ovalbumin). The quantity varies, in influenza vaccines more than three orders of magnitude, from undetectable to as high as 42 µg/mL [12]. Egg allergy is one of the more common food allergies in childhood and has been considered a risk and a contraindication to vaccination with egg-grown virus vaccines. Several studies have shown, however, that most people with egg allergy, documented by skin

prick tests, radioallergosorbent test (RAST), and clinical symptoms, will tolerate influenza vaccine without problems [13]. According to most recommendations, previous anaphylactic reactions to egg are still considered a real contraindication to egg-grown vaccines, but procedures have been described that may make it acceptable to give the vaccine if the indications for vaccination are very strong [5,14•,15]. This is of increasing importance as influenza vaccination now is generally recommended for children between the ages of 6 and 24 months in several countries.

Anaphylactic reactions to the first injection of duck embryo rabies vaccine have also been described in those with strong allergic reactions to hen's egg [16]. Cross-sensitivity between duck and hen's egg protein may be the cause of such reactions.

Egg allergy as a possible contraindication to measles-containing vaccines, including the MMR vaccine, has been a topic for discussion for many years. It is important to decide if anaphylactic reactions to egg really represent an increased risk for anaphylactic and other severe allergic reactions to the vaccine. Egg allergy as a contraindication to MMR-vaccine would increase the difficulties in reaching the high population coverage that is necessary to eliminate the diseases. The measles and mumps components of the MMR vaccine are grown in cell cultures of chicken embryo fibroblasts. Therefore, the MMR vaccine may contain trace amounts of egg proteins, even if the quantity and associated risk are much smaller than in egg-grown vaccines. During the past 20 years, many studies have shown that almost all children will tolerate measles or MMR vaccines, in spite of strong allergic reactions to egg as judged by clinical symptoms, skin testing, and RAST [17–19]. Further examination of children with anaphylactic reactions to measles or MMR vaccine has rarely documented egg allergy as the most probable cause of the reaction [20,21•]. Today, almost

all countries recommend that children with egg allergy are routinely vaccinated with the MMR vaccine [15,22]

Reactions to Gelatin

Gelatin is used as a stabilizer in several vaccines, among them MMR and yellow-fever vaccines. Japanese studies of children with severe allergic reactions to MMR vaccine have shown that most of these children have allergic reactions to gelatin when tested [23]. It has been difficult to understand how the children have been sensitized to gelatin at an early age. A possible explanation is that the acellular pertussis component in the diphtheria-tetanus-pertussis vaccines (DTaP), used in Japan since the beginning of the 1980s, contained small amounts of gelatin from the production process of pertussis toxin [24]. The minimum incidence of severe anaphylaxis to gelatin-containing live virus vaccines in Japan was estimated to be about seven per million vaccine doses before 1997. Thereafter, Japanese vaccine manufacturers started eliminating gelatin from their products [25].

Allergy to gelatin in children with severe allergic or anaphylactic reactions to live virus vaccines has also been reported from Europe [21•] and the United States [11•], but the incidence seems to be much lower than that in Japan. One reason for this might be that acellular pertussis vaccine was not part of the vaccination program in western countries before 1995. Children in Europe and the United States would, therefore, not run the risk of being sensitized by gelatin-containing DTaP, as the Japanese children were. However, Pool et al. [11•] showed that the incidence did not increase after acellular pertussis vaccine was included in the US vaccination program in 1997. A better explanation may be that the kind of gelatin used is different. Japanese vaccines contain bovine gelatin. Vaccines produced in the United States and Europe contain porcine gelatin, which is much more hydrolyzed, and therefore less allergenic [11•]. Gelatin allergy is an important cause of anaphylactic reactions to MMR vaccines, but the incidence is very low.

Reactions to Antibiotics and Other Excipients

Antibiotics are added to some viral vaccines to prevent bacterial growth. Fifty years ago, several antibiotics were used. Some of them, such as streptomycin, were also used for systemic antibiotic treatment. Sensitization through treatment might lead to the risk for severe allergic reactions to small amounts of antibiotics in vaccines. Currently, neomycin is the only antibiotic used in vaccines. Neomycin is not used for systemic treatment in humans, and "neomycin allergy" is almost always contact allergy. Contact allergy to neomycin will presumably not increase the risk for severe systemic allergic reactions after vaccination.

Formaldehyde is used for inactivation of bacteria and viruses during vaccine production. Most of it is removed

in the purification steps, but trace amounts may remain. As with allergy to neomycin, allergy to formaldehyde is almost always contact allergy, which is not associated with severe systemic reactions to vaccines.

Thimerosal is a mercury-containing preservative, once added to many vaccines to prevent bacterial growth. Allergy to thimerosal is known, but the risk for severe reactions to vaccines is not higher in those who are allergic to thimerosal [26]. However, thimerosal has lately been accused of causing other serious adverse events, such as neurologic disorders [27]. Although most studies do not substantiate this, the accusations have resulted in the elimination of thimerosal from vaccines. Almost all vaccines are now produced without this substance.

Aluminum salts have until recently been the only accepted adjuvants in vaccines. Allergy to aluminum salts exists, and may result in long-lasting subcutaneous nodules with itching after subcutaneous injections [28]. Severe systemic allergic reactions to aluminum salts have not been reported.

Reactions to Latex

During the past 20 years, there has been an increasing awareness of latex as a substance that may cause serious allergic reactions. Latex was once the most common substance in rubber stoppers in vials, plungers in syringes, and sometimes for caps covering injection needles. However, there is only one report in the literature describing a case of anaphylaxis to vaccination in a latex-sensitive person [29], and generally the risk for vaccination reactions in those who are allergic to latex seems to be very small [30]. As most manufacturers are now substituting latex-containing material with synthetic packaging material whenever possible, the risk should be further reduced.

Differential Diagnosis

Two other reaction types are easily mistaken for anaphylaxis: anaphylactoid and vasovagal reactions [31,32]. Anaphylactoid reactions have been mostly described in German literature. They appear most often with aluminum-adsorbed vaccines and are probably caused by intravascular injection. Applying a correct injection technique should prevent recurrences. Similar to real anaphylactic reactions, anaphylactoid reactions are very rare [31].

Vasovagal reactions, however, are not rare at all. They are caused by the combination of pain, fear, and excitement at the time of vaccination, and may be provoked by warm rooms, strange smells, and the general conditions of the vaccination setting. Adolescents are especially prone to this kind of reaction, which may spread like an "epidemic" through the group in school vaccination sessions. Feeling faint or fainting are the primary and well-known symptoms, but the reactions are often much more dramatic than mere fainting. Nausea and hyperven-

tilation are common. When hyperventilating, the person feels breathless, and complaints of breathlessness may be misdiagnosed as dyspnea. Hyperventilation leads to other symptoms, such as tingling sensations in hands and feet and even convulsions. According to a study of adolescents in the United States, as many as 30% of the reactions may feature convulsions as one of the symptoms [32].

Diagnosis and Treatment

Although the risk for severe allergic reactions is very low, it is commonly recommended that inoculated individuals should be kept under observation for 15 to 20 minutes after vaccination. Almost all serious allergic reactions will occur during this period. If a person reacts with something that might be an anaphylactic reaction, the standard immediate treatment is an injection of adrenalin. This may be life-saving if the patient really has an anaphylactic reaction, and is harmless if the reaction is caused by other mechanisms. Even a vasovagal reaction may improve after an injection of adrenalin. Therefore, having observed an effect of adrenalin should not be regarded as a proof that the reaction really was allergic.

Further treatment will depend on the symptoms and the severity of the reaction, but will usually include intravenous fluids, steroids, and antihistamines.

Many vaccination regimens will need more than one dose to give good protection against the disease, or a booster dose after some years may be recommended to maintain the immunity. This may be a dilemma when the person has had a possible anaphylactic reaction to an earlier dose. Often a thorough case history will show that the reaction most probably was not anaphylaxis, but rather something more common, such as a vasovagal reaction. In that case, the vaccination series should be completed. However, further vaccination should take place in a setting in which one is well prepared to treat a possible reaction satisfactorily. This is in itself a preventive measure, as anxiety in the vaccinated individual will increase the risk for further reactions.

If the case history indicates that the reaction really was anaphylactic, a diagnostic process with the aim of finding the underlying cause of the reaction may be the best solution. Skin prick test or intradermal tests have been used to clarify the mechanisms after reactions to different vaccines: toxoid vaccines, pneumococcal vaccines, and skin testing for egg and gelatin allergy [14,33]. Most allergists recommend skin testing before use of egg protein-containing vaccines in patients with anaphylactic reactions to egg. Skin testing with the vaccines themselves is of more doubtful value, as several studies have found poor positive or negative predictive values [18,19]. In a few cases, severe allergic reactions to the testing have also been reported [17]. RAST tests are useful when tests are available, such as for egg and gelatin, two of the substances most often suspected to be the cause of anaphylactic vaccine reactions.

The physician will have to decide which is the greater risk: to remain unprotected against the disease or to risk a new reaction after vaccination. This depends most of all on the risk of infection and the seriousness of the disease. If the vaccination is a part of post-exposure rabies treatment, there are no real contraindications to continuing vaccination, as the disease is lethal in all cases. The challenge is to construct a setting in which the risk from vaccination is minimized. In other situations, the risk for disease may be small, and, consequently, being unvaccinated is the best choice. The physician in charge will have to find the best solution in each situation. However, it is worth remembering that most studies of persons who have experienced severe allergic reactions to vaccines show that very few have similar reactions to the next dose. In most cases, completing the vaccination in an adequate setting will therefore be a good option.

Conclusions

Anaphylactic reactions to vaccines exist, but the incidence is very low. Potentially life-threatening episodes have been reported in less than one case per million vaccine doses, and larger studies from later years report no deaths. There are case reports of anaphylactic or severe allergic reactions after most vaccines, but during the later years, such reactions have most often been reported after viral vaccines such as measles-containing vaccines, yellow-fever vaccine, or influenza vaccine. The cause of the reaction is rarely the immunizing antigen itself, but rather some other vaccine ingredient, such as egg protein from the production process or gelatin added as a stabilizer. Most people with egg allergy can be vaccinated without any reaction. Only those with previous anaphylactic reactions to egg will need special precautions, and even they will almost always tolerate the MMR vaccine.

Vasovagal reactions with or without hyperventilation are common after vaccination. They can be rather dramatic and are often mistaken for anaphylactic reactions. A detailed case history will usually give the correct diagnosis. This is important, as it makes it possible to offer the protection of vaccination to persons who might otherwise run the risk of serious infections.

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