Journal of the Postgraduate Institute of Medicine 2019; 6 (1): E 93: 1-7
doi: http://dx.doi.org/10.4038/jpgim.8258

Invited Article

EVIDENCE UPDATE

Evidence update on vaccine allergy

W M D K Dasanayake[1], N R de Silva[2]

[1]Teaching Hospital, Kandy, Sri Lanka, [2]Medical Research Institute, Sri Lanka

Keywords: adverse event, vaccine allergy, anaphylaxis, immunization, vaccination, vaccine

Corresponding Author: W M D K Dasanayake, E-mail: <dhanushkadasanayake@yahoo.com > https://orcid.org/0000-0001-6351-9983
Competing Interests: Authors have declared that no competing interests exist

Introduction

Vaccines are intended to provide active immunity to specific microbes in the recipient. They are biological preparations that contain weakened, non-pathogenic or killed microorganisms, toxins, surface protein or polysaccharide capsules.

Immunisation has proven to be one of the most effective public health interventions by reducing the morbidity and mortality of many vaccine preventable diseases. In addition, this protection may extend to the non-vaccinated individuals via herd immunity. Many countries have national immunisation programmes in place and in the United States children receive 10 vaccines to protect against 16 diseases before the age of 2 years [1] In Sri Lanka, the national immunisation programme offers 7 types of vaccines, free of charge, to all eligible children less than 2 years [2]. This is expected to provide immunity to diseases caused by 11 pathogens. One of the main obstacles in sustaining immunisation programmes is vaccine hesitancy or refusal [3]. This is increasingly common in a setting where the actual disease incidence is low, and parents are concerned about vaccine safety.

Most reported vaccine-associated adverse reactions are not immunologically mediated and are not reproducible on re-exposure [1]. Rarely, immunologically mediated reactions such as type l hypersensitivity reactions, including anaphylaxis, can occur. Anaphylaxis is the most feared vaccine reaction as it can lead to fatality if it is not managed accurately. Therefore, clinicians need to be proficient in detecting vaccine recipients who are at a higher risk of developing hypersensitivity reactions, minimising occurrence of reactions and managing reactions effectively. This will contribute to strengthening the confidence of the public regarding safety of vaccines.

Allergic reactions to vaccines

Immunologically mediated reactions can be classified as immediate or delayed reactions [4]. Most immediate reactions are due to pre-formed IgE antibodies to vaccine components. Symptoms and signs may be limited to the vaccine site or a single organ system. Examples are, bronchoconstriction, urticaria and angioedema occurring as the

sole clinical feature. These usually occur within 4 hours of vaccination. In anaphylaxis, there is involvement of several organ systems. It occurs within minutes following vaccination. Rarely, biphasic or protracted anaphylaxis may occur following vaccination. Type III and IV hypersensitivity reactions may also occur. Manifestations are skin rash, fever, malaise, polyarthralgia or polyarthritis and injection site nodules [1].

Anaphylaxis to specific vaccines

Virtually all vaccines have the potential to trigger anaphylaxis. Incidence of anaphylaxis to most commonly used vaccines is approximately 1: 1,000,000 doses administered. The highest incidence of anaphylaxis is reported with the measles mumps rubella (MMR) vaccine, at a rate of 5.14 per million doses. Other implicated vaccines are varicella, influenza, hepatitis B, DTaP, meningococcal and human papillomavirus vaccines [1]. Hypersensitivity reactions can occur to any of the vaccine constituents including the antigen itself, residual media, stabilizers, preservatives or excipients [4].

Vaccine components and allergy

Microbial antigen

Although there have been case reports of systemic hypersensitivity to tetanus and diphtheria toxoids and pertussis and influenza antigens, these reactions are considered to be rare [5,6]. Comprehensive allergy testing has not been carried out in many such cases. Delayed urticaria, angioedema or both and nonspecific skin rashes are reported in about 5% to 13% of recipients of toxoid vaccines [1].

Hens' egg

Egg allergy is frequently encountered in western countries. Therefore, residual egg protein, especially ovalbumin, which is found in varying concentration in vaccines, has drawn a lot of attention as a possible trigger of hypersensitivity reactions in vaccine recipients. The concentration of ovalbumin is lower in chicken fibroblast cell culture vaccines, such as the MMR and purified chick embryo (PCEC) rabies vaccine [1]. Therefore, these vaccines are given to children with pre-existing egg allergy under standard care. Concentrations are higher in embryonated chicken egg vaccines such as influenza and yellow fever [4]. The amount of ovalbumin is deemed clinically significant in the yellow fever vaccine. Therefore, it is contraindicated in persons with a history of anaphylaxis to eggs [2]. However, there are instances where yellow fever vaccine desensitization is carried out in individuals with severe egg sensitivity, who need the vaccine due to a travel destination specific risk [4].

The number of doses of influenza vaccine administered annually have increased since 2010 [1]. Therefore, the possibility of reactions following influenza vaccine has been studied in great detail. All influenza vaccines, with the exception of recombinant inactivated influenza vaccine, may contain traces of egg protein. Currently, most vaccine manufacturers provide the concentration of ovalbumin in the package inserts. All currently available influenza vaccines claim to contain less than 1 µg of ovalbumin per 0.5 mL dose [10]. The current recommendations for vaccination has been based on these claims. The American Academy of Paediatrics recommendation for prevention and control of influenza in children for 2018- 2019 states that children with egg allergies can

receive any licensed and recommended age-appropriate influenza vaccine without any additional precautions beyond those recommended for all vaccines [11]. However, the CDC guidelines recommend that patients with severe egg allergy should be vaccinated in a medical setting under supervision [12].

Gelatine

Gelatine is contained as a vaccine stabilizer in most vaccines. It is of bovine or porcine origin. In 1993, Kelso *et al* reported a case of an anaphylactic reaction after MMR in a patient with IgE to gelatine. Since then, gelatine has been identified as a trigger in a number of allergic reactions following immunisation with the MMR, varicella and Japanese encephalitis vaccines [13]. Many cases were reported from Japan and sensitisation to gelatine was partly attributed to genetic characteristics in this population. This led to the production of gelatine-free preparations of certain vaccines in Japan. Subsequently, similar cases of vaccine allergy attributed to gelatine have been reported from several European countries [1].

Alpha gal allergy

Alpha gal or galactose- α -1,3galactose is a sugar molecule found in most mammals except humans, old world monkeys and apes. This is a recently reported allergen, initially reported from south-eastern United States and causally linked to bites from the lone star tick. Evidence suggests that natural exposure to alpha gal present in the saliva of ticks induces production of IgE antibodies in some people. Sensitized subjects may develop delayed anaphylaxis on exposure to mammalian red meat containing alpha-Gal (on glycoproteins or glycolipids) as late as three to six hours after ingestion [1]. As certain mammalian products, including gelatine, are present in vaccines, there is a possibility of vaccine allergies in such individuals. Anaphylaxis has been reported in an alpha gal sensitised individual following zoster vaccine [14]. The occurrence of an immediate rather than the delayed reactions observed with alpha gal was attributed to difference in the route of exposure.

Residual media

Residual media can be found in both inactivated and live vaccines. There have been reports of probable or possible anaphylaxis following hepatitis B and human papilloma virus vaccines in people sensitised to yeast [1,4]. These vaccines are recombinant vaccines grown in *Saccharomyces cerevisiae* or baker's yeast and residual yeast protein may be present in the vaccine [15].

Cows' milk

Cows' milk is used as stabilizers in many vaccines, such as DTaP and Tdap vaccines [1]. Although cows' milk allergy is frequently encountered in infants around the world, the number of allergic reactions to these vaccines in such individuals are low [4]. This could be attributed to the presence of only nanogram quantities of bovine casein in vaccines. [1] However, anaphylaxis has been rarely reported. Therefore, caution is advised when booster doses of vaccines are administered to highly sensitive children with cows' milk allergy.

Adjuvants

Aluminum hydroxide and aluminum phosphate are commonly used vaccine adjuvants. These boost T cell immunity and increase helper T cell function. Immediate hypersensitivity reactions have not been documented due to adjuvants. However, contact allergy, formation of small granulomas or nodules with persistent urticaria at the site can occur. These are not contraindications to future vaccination [1].

Antimicrobials

Many antimicrobials such as gentamicin, tetracycline, neomycin, streptomycin and polymyxin B, which have been added to prevent bacterial or fungal growth, can be found in vaccines [1]. Although, systemic hypersensitivity reactions have been reported with these during therapy, reactions following vaccines not been well documented. This could be due to the presence of only trace amounts in vaccines.

Preservatives

Thimerosal, 2-phenoxyethanol and phenol have been traditionally used as preservatives especially in multidose vials to prevent bacterial growth. However, thimerosal was removed from many vaccine preparations due to the theoretical risk of mercury toxicity [1]. Although there have been reports of contact allergy following vaccines due to thimerosal, immediate reactions have not been reported. Injection site reactions or delayed hypersensitivity to thimerosal is not a considered a contraindication to future vaccines [9].

During the 2011 and 2012 outbreaks of influenza in Japan, a few cases of anaphylaxis linked to 2-phenoxyethanol containing influenza vaccine were reported. Follow-up investigations also implicated it in a possible role although the exact immunologic mechanism was not described [1]. There have been a few single case reports of late onset contact dermatitis and maculopapular rash attributed to phenol in vaccines [1]. However, immediate hypersensitivity has not been reported.

Extrinsic substances

Natural latex in rubber stoppers and on plungers in prefilled vaccine syringes have been associated with rare case reports of acute hypersensitivity in vaccine recipients sensitised to latex [16]. However, specific studies were not carried out in most cases. Synthetic rubber has replaced natural rubber in most vaccine vials [1].

Carrier proteins

The first case report of anaphylaxis following the pneumococcal conjugate vaccine was reported in 2016. Carrier protein CRM 197 was suggested to be the trigger [17]. This was further supported by skin testing and the basophil activation test.

Vaccine allergy in Sri Lanka

In a study conducted by the Department of Immunology, Medical Research Institute, vaccine allergy accounted for 11.8% of instances of anaphylaxis [18]. In this study, 238 episodes of anaphylaxis, in 188 patients who attended the clinic from 2012 to 2017, were assessed. This may not reflect the actual incidence as vaccine allergy tends to be referred

for investigation more frequently compared to other allergies. Out of the 28 episodes of anaphylaxis due to vaccines investigated, 14 were due to the MMR vaccine, three were due to the Japanese encephalitis vaccine and the PCEC rabies vaccine accounted for 3 episodes. Other vaccines implicated were DT, DPT, Hepatitis A/B and the pentavalent vaccine. The majority of vaccine allergic patients were sensitised to either mammalian meat or cows' milk [18].

This led to a second study by the same unit, where 20 patients with immediate hypersensitivity to vaccine with bovine or porcine excipients along with four control groups with red meat allergy, cows' milk allergy, without vaccine reactions and non-atopic controls were assessed [19]. Out of the vaccine allergic patients 80% had allergy to either cows' milk or red meat. Only one patient had IgE to gelatine, whereas 73% had IgE to bovine serum albumin (BSA). Sensitisation to BSA is not reported frequently among cows' milk allergic patients in other countries. Therefore, this study highlighted the possibility of BSA in vaccine being the trigger for vaccine allergies in this cohort.

Investigation of suspected vaccine allergies

The EACCI 2017 position paper on practical aspects of vaccine allergy states that mast cell tryptase level (MCT) should be measured in clinically diagnosed cases of anaphylaxis. Levels should be determined within 2 hours after the onset of reaction and a baseline level should be obtained at least 48 hours after the episode [4]. The predictive values of this assay for vaccine associated anaphylaxis has not been established. However, a significant increase in MCT level from baseline is considered a strong indicator of anaphylaxis [4].

Where possible, all culprit allergens should be detected as it will be important for the future management of the patient as well as be of use to the population as a whole. Sensitisation to components in the vaccine should be assessed [4]. Skin prick testing with the vaccine can also be carried out although, this may sometimes lead to false positive results due to irritation [4].

If further doses are recommended in the immunisation schedule, the actual need for vaccination may be assessed by testing for protective levels of antibodies where the protective levels have been described [1,4]. However, it should be discussed with the vaccine recipient or the guardian that the degree and duration of protection provided by the complete vaccine course may not be provided by these incomplete schedules.
If the vaccine is deemed necessary, it may be given via split dose and graded dose protocols [15]. Although, a person may be temporary desensitised by such protocols, this is not permanent. Therefore, they require reassessment if further doses or boosters are required.

In summary, vaccine recipients who are at a higher risk of immediate hypersensitivity reactions may be recognised to some extent based on the investigation of previous reactions to vaccines as well as reactions to vaccine constituents. However, the currently available tools may not be able to predict all severe allergic reactions that can occur.

Therefore, all vaccinating units need to be equipped with the expertise and material needs for treating anaphylaxis at all times.

References

1. McNeil M, DeStefano F. Vaccine-associated hypersensitivity. Journal of Allergy and Clinical Immunology. 2018 February; 141(2): 463-472 https://doi.org/10.1016/j.jaci.2017.12.971
2. SLMA guidelines and information on vaccines. 6th edition 2017 Editorial Vaccine hesitancy: a generation at risk. The Lancet Child & Adolescent Health. May 01, 2019 Volume 3, issue 5, P281 https://doi.org/10.1016/S2352-4642(19)30092-6
3. Dreskin et al. International Consensus (ICON): allergic reactions to vaccines. World Allergy Organization Journal. 2016; 9:32 https://doi.org/10.1186/s40413-016-0120-5
4. Nilsson et al. Vaccination and allergy: EAACI position paper, practical aspects. Paediatric Allergy and Immunology. 2017;28:628-640 https://doi.org/10.1111/pai.12762
5. Skov et al. Hypersensitivity to the diphtheria component in the Di-Te-Pol vaccine. A type I allergic reaction demonstrated by basophil histamine release. Paediatric Allergy and Immunology 1997; 8:156 https://doi.org/10.1111/j.1399-3038.1997.tb00171.x
6. O'Brien et al. Quantitation of residual host protein in chicken embryo-derived vaccines by radial immunodiffusion. Applied Microbiology. 1971; 21:780
7. Ruggeberg et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. Vaccine. 2007; 25(31):5675-84 https://doi.org/10.1016/j.vaccine.2007.02.064
8. Kroger AT, Duchin J, Vázquez M. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). https://www.cdc.gov/vaccines/hcp/acip-recs/generalrecs/index.html Accessed on January 10, 2019.
9. Kelso J.M. Drug and vaccine allergy. Immunology and allergy clinics of north America. 2015; Volume 35, Issue 1, Pages 221-230 https://doi.org/10.1016/j.iac.2014.09.013
10. Grohskopf et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices-United States, 2017-18 Influenza Season. MMWR. 2017;66 (RR-2):1-24 https://doi.org/10.15585/mmwr.rr6602a1
11. Committee on Infectious Diseases. Recommendations for prevention and control of influenza in children, 2018-2019. Pediatrics. 2018 Oct;142(4) https://doi.org/10.1542/peds.2018-2367
12. Kelso J.M. The gelatine story. Journal of Allergy and Clinical Immunology. 1999;103,2 https://doi.org/10.1016/S0091-6749(99)70490-2

13. Stone et al. Anaphylaxis after zoster vaccine: Implicating alpha-gal allergy as a possible mechanism. Journal of Allergy and Clinical Immunology. 2017;139: 1710-3.e2 https://doi.org/10.1016/j.jaci.2016.10.037
14. Kelso JM, Greenhawt M, Li JT. Adverse reactions to vaccine practice parameter 2012. Journal of Allergy and Clinical Immunology. 2012;130:26-43 https://doi.org/10.1016/j.jaci.2012.04.003
15. Lear JT, English JS. Anaphylaxis after hepatitis B vaccination. Lancet 1995; 345:1249 https://doi.org/10.1016/S0140-6736(95)92039-0
16. Arroabarren E, Anda M, Sanz ML. Anaphylaxis to pneumococcal vaccine; CRM (197): novel cause of vaccine allergy. Pediatric Allergy and Immunology. 2016;27:433-437 https://doi.org/10.1111/pai.12548
17. de Silva NR, Dasanayake WMDK, Karunatilake CH, Wickramasingha GD , De Silva BD, Malavige GN, Aetiology of anaphylaxis in patients referred to an immunology clinic in Colombo, Sri Lanka. Allergy, Asthma Clinical Immunology 2018; 14:81 https://doi.org/10.1186/s13223-018-0295-0
18. de Silva NR, Dasanayake WMDK, Karunatilake CH, Wickramasingha GD , Weerasinghe N, Gunasekara P, Malavige GN, Sensitization to bovine serum albumin as a possible cause of allergic reactions to vaccines. Vaccine. 2017 ; vol 35:1494-1500 https://doi.org/10.1016/j.vaccine.2017.02.009