

SPECIAL ARTICLE

Guidelines for measles vaccination in egg-allergic children

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The vaccines currently in use in the United Kingdom for measles-mumps-rubella (MMR) vaccination contain the Enders Edmonston strain of measles [1]. The attenuated measles and mumps vaccine viruses are grown in cultures of chick embryo fibroblasts, hence the concern about the possible presence of egg protein in the vaccine and its administration to egg-allergic individuals. A measles vaccine grown in human fibroblasts has been shown to have much lower immunogenicity than one grown in chick fibroblast culture [2], and thereby does not present a viable alternative.

We present a review of the evidence for egg as the agent responsible for allergic reactions to measles vaccine and propose recommendations based on the evidence. The arguments presented in this paper also apply to the single mumps vaccine and indeed to all vaccines derived from egg. The recommendations presented have been reviewed and endorsed by The Royal College of Paediatrics and Child Health Committee on Infection and Immunisation and The British Society of Allergy and Clinical Immunology. The search strategy for the relevant literature was carried out using Medline (covering 1966–1999), which revealed 51 references, and a search of the Cochrane Library 1999 Volume 3 which gave no references. We also reviewed the reference list of each identified study. Thirty-four of these studies were relevant in dealing either with allergic reactions to measles vaccine in egg and nonegg allergic individuals or with the potential allergic components of the measles vaccine. None of the studies involved any form of randomization or case-control as they consisted of reports of isolated or consecutive cases, although there were reports from respected authorities and expert committee reports [3].

UK immunization policy is that all children, except those with a valid contraindication, should receive two doses of MMR vaccine, given shortly after the first birthday and before school entry [1]. There are currently in the region of 640 000 livebirths per year in England and Wales with an uptake of the first dose by age 2 years of 90% [4], but less than 50% for the preschool dose [5]. This represents

approximately 576 000 doses of the vaccine given each year in the 1–2-year-old age group. The prevalence of egg allergy in early childhood has been estimated to be 1–4% [6–8], and up to 6–8% in atopic children [9,10]. Even taking the lower prevalence rate of 1%, 5760 MMR vaccinations are given to egg-allergic children between ages 1 and 2 years in England and Wales. These figures are lower for the preschool dose when uptake rates are lower and many children will have outgrown their egg allergy. Between 10 and 25% of these children will have had severe reactions to egg (anaphylaxis or difficulty in breathing) [9,11].

Current recommendations

The United Kingdom Immunization against Infectious Diseases 1996 edition states '... over 99% of children who are allergic to eggs can safely receive MMR vaccine. Dislike of egg, or refusal to eat it, is not a contraindication. If there is concern, paediatric advice should be sought with a view to immunization under controlled conditions such as admission to hospital as a day case' [1]. The advice from the Health Education Authority in 1997 [12] is that 'if a child has had a serious reaction when eating eggs, or food containing egg, then the parent should talk to their doctor about making special arrangements for the child's immunization. This can usually be done as a day-case at the Paediatric Department of the local hospital.' The definition of a serious reaction is not provided nor are the specific precautions for vaccination in these patients defined. This has resulted in inconsistent and widely differing local practices across the country, with inevitable caution leading to inappropriate admissions and unnecessary intravenous cannulation. A lack of focus on the individuals who are at greatest risk may lead to their inadequate supervision.

The American Academy of Paediatrics' guidelines [13] are similar to those in the UK, with no further clarity given. Critical reviews of the subject, most notably by James *et al.* [14] led to the Academy reversing its previous stance of advising skin prick and intradermal testing with the measles vaccine followed by a desensitization procedure if either was positive. The Canadian National Advisory Committee on Immunization advises special precautions only 'in individuals with histories of anaphylactic hypersensitivity to

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Recommendations endorsed by The Royal College of Paediatrics and Child Health Committee on Infection and Immunization and The British Society of Allergy and Clinical Immunology.

hens' eggs' although the distinction between allergy and anaphylaxis is not clear [15].

Several constituents of the measles vaccine may cause allergic reactions

Many different preparations of the measles vaccine are available, all containing at most small amounts of the egg protein ovalbumin. Analysis of one of the most commonly used vaccines, MMR II (Pasteur Merieux, Maidenhead, UK), has shown it to contain between none [16], picogram [17] and 0.5–1 nanogram [18] quantities of ovalbumin per 0.5 mL dose. These discrepancies may reflect either lack of standardization between batches of the vaccine, or may be due to different methods of assaying for egg protein which include enzyme-linked immunosorbent assay [17,18] and radial immunodiffusion [16]. In most double-blind, placebo-controlled food challenges the minimum oral doses eliciting objective reactions are between 50 and 100 mg, although occasionally as low as 2 mg [19]. Therefore the amount of ovalbumin in the vaccine appears to be far too small to cause an allergic reaction in the majority of individuals even allowing for the parenteral route of exposure.

However, each 0.5 mL of MMR II also contains 14.5 mg of gelatine and 25 µg of neomycin sulphate [20], both agents well known to cause severe allergic reactions [21–23] and present in larger doses, thereby more likely to induce such reactions.

Reactions to measles vaccine are not confined to children with egg allergy

Although acute allergic reactions after measles vaccine are well recognized, accurate figures for their rate of occurrence are not available. The only study that truly describes type I hypersensitivity following measles vaccine in the general population is from Kalet *et al.* [24] describing 2789 doses of the measles vaccine. Five allergic reactions (facial swelling [1], wheezing [3], urticaria [1]) are reported – two children had other vaccines at the same time. Co-existent egg allergy was not assessed in this study.

There are only 16 children with egg allergy reported in the literature as having systemic allergic reactions to measles vaccine [11,18,25–29]. Ten of these involved severe (cardiorespiratory) reactions and six involved generalized urticaria. Of these 16 children, five are reported by Sakaguchi *et al.* [25] and had evidence of raised specific immunoglobulin (Ig) E to gelatine as well as to ovalbumin. There are reports of seven other children with raised specific IgE to gelatine who suffered cardiorespiratory allergic reactions to measles vaccine [25,30,36]. Three of these children had no evidence of egg allergy, which was not assessed in the other four children. One case of possible

neomycin allergy is reported in a patient receiving MMR vaccine [21]. Furthermore, there are 37 other children reported in the literature [14,17,24,25,30–36] with systemic allergic reactions to the measles vaccine, and 36 of these involved cardiorespiratory reactions. Egg allergy was not present in eight children, but this was not assessed in the other children. Whilst these figures do not reflect true incidence rates in the general population, the larger number of reported severe reactions to measles vaccine in nonegg-allergic children suggests that predicting children at risk of allergic reactions is difficult since reactions are not limited to those with egg allergy.

There is insufficient evidence that egg causes allergic reactions to measles vaccine

There are few reports of systemic allergic reactions to measles vaccine in egg-allergic children

Since 1963 there have been numerous published reports looking at the incidence of allergic reactions to measles vaccination in egg-allergic children [11,14,17,18,25–29,37–48]. These document a total of 1803 patients, of whom 14 experienced mild local reactions (erythema, weal or induration at the injection site), puffy eyes, facial swelling, flushing, perioral and localized urticaria and vomiting. Sixteen systemic reactions are also reported, of which 10 involved cardiorespiratory compromise and six involved only distant/generalized urticaria. Only eight of these 16 reactions occurred following a single dose of the vaccine, and five occurred in children with coexistent gelatine allergy. Many of the reports suffer from a lack of definition regarding the nature of the allergic reaction or the egg allergy. Herman *et al.* [18] and Puvvada *et al.* [28] alone give adequate reports of cardiorespiratory allergic reactions to measles vaccine in three egg-allergic children. All three reactions occurred in children in whom previous egg exposure had led to a life-threatening reaction or who had a history of coexistent asthma. This agrees with the reports that coexistent asthma is a risk factor for anaphylaxis [17,49].

Half of the reported systemic reactions (eight out of 16 cases) occurred following diagnostic skin/intradermal testing (three cases) or during preventative desensitization (five cases) with the measles vaccine [11,26,28,29,38], procedures which we argue should be abandoned (see below).

Egg allergy is poorly defined

The majority of the reports lack a true definition of egg allergy. Only 233 of the reported 1803 cases had their egg allergy confirmed by an open food challenge or double-blind placebo-controlled food challenge. In the other children, egg

allergy was defined on scientifically weaker criteria of positive history and/or skin testing. None of the children in whom egg allergy was confirmed by food challenge experienced an acute allergic reaction to measles vaccination.

Other relevant allergens have not been excluded

Egg allergy is a marker for many other allergies in children [50]. In only five of the 16 children with possible egg allergy who experienced allergic reactions to the measles vaccine were assessments carried out to look for evidence of allergy to other components of the vaccine. These five all had raised specific IgE to gelatine [25].

Predicting and preventing allergic reactions to the measles vaccine

Skin testing with measles vaccine is of limited value and causes allergic reactions

Skin prick and intradermal testing with measles vaccine have been advocated in the prediction of type I hypersensitivity on the basis of cutaneous reactivity [18,28]. However most reports confirm that in practice skin prick and intradermal testing have poor positive and negative predictive values in assessing the risk of an allergic reaction to the measles vaccine [32,37,51]. Furthermore, such practice is self-defeating since systemic reactions to measles vaccine in egg-allergic children have occurred as a result of this diagnostic procedure [26,28,29].

Desensitization to measles vaccine is not effective and causes allergic reactions

Desensitization of skin test-positive children has been performed in an attempt to prevent an acute allergic reaction to measles vaccine in egg-allergic children. This involves administration of five increasing subcutaneous doses of the vaccine given at 15- to 20-min intervals with the aim of inducing tolerance to the egg protein [13]. The rationale for this procedure is dubious, as there is no evidence in the literature of successful desensitization to egg. Furthermore, the maximum amount of ovalbumin in a dose of measles vaccine is only 1 nanogram [18], which is one-thousandth part of the minimum recommended dose for allergen desensitization [52]. Of the 16 reported systemic allergic reactions to measles vaccine in egg-allergic children, five cases occurred during desensitization [11,38]. Desensitization is therefore also associated with a substantial risk of allergic reaction that it is supposed to prevent.

Guidelines for measles vaccination in egg-allergic children

On the arguments presented, a case can be made for having

no special precautions for measles vaccination in egg-allergic children. In practice the vast majority of children can safely be given the measles vaccine regardless of whether the child has egg allergy. As with all vaccines, Department of Health guidelines which advise the availability of adrenaline must be followed [53]. For all vaccines there are special cases when the vaccination protocol needs to be modified. In the specific case of measles vaccine it is advisable to take special precautions for a small subgroup of children in whom there is the remote possibility that an allergic reaction may occur. Children with previous life-threatening reactions to foods or children with food allergy and active chronic asthma may be at risk for future life-threatening reactions upon renewed exposure to the food [49]. Theoretically these children might also have a lower threshold for reacting to very low doses of allergen. Although the numbers are small, a review of the literature shows that only children with a history of life-threatening reactions to egg, or egg allergy *and* coexistent asthma, suffered cardiorespiratory reactions after the measles vaccine (see above). We therefore advise the following guidelines for measles vaccination in egg-allergic children, developed in conjunction with The Royal College of Paediatrics and Child Health Committee on Infection and Immunization and The British Society of Allergy and Clinical Immunology, which we believe represent safe practice and will allay parental anxiety.

- The vast majority of children can be safely vaccinated with measles vaccine with no extra precautions regardless of whether or not they have egg allergy.
- Children in whom egg ingestion has led to cardiorespiratory signs or symptoms (difficulty in breathing, noisy breathing, stridor, hoarseness, cyanosis, change in conscious level, pallor and hypotension) should be vaccinated in a hospital paediatric department, as day-cases or outpatients. A small group of children with egg allergy (regardless of severity) who have active chronic asthma with regular symptoms requiring inhaled steroids or other prophylaxis for symptoms should also be vaccinated in a hospital paediatric department. This does not include the majority of infants who have viral-induced wheezing.
- Other children with egg allergy causing oral, gastrointestinal or cutaneous reactions including urticaria and angioedema and who do not have active chronic asthma do not require any special precautions.
- Children awaiting further specialist paediatric or allergy assessment for their egg allergy should not have their measles vaccine delayed.
- In the small subgroup requiring extra supervision, monitoring for an allergic reaction must include cardiorespiratory parameters for 2 h post-vaccination [54]. This should be performed by a suitably qualified paediatric nurse, with continuous observation for the first 20 min

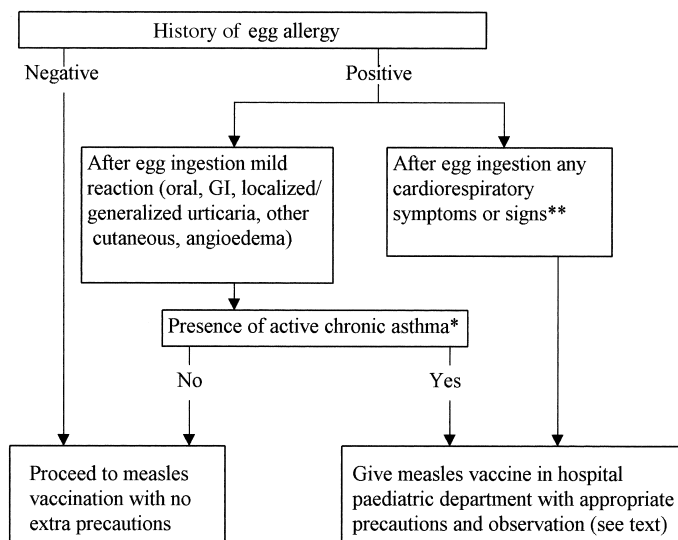


Fig. 1. Flowchart for the administration of measles vaccine in egg-allergic children.

*Active chronic asthma defined as children with regular symptoms requiring inhaled steroid or other prophylaxis for symptom control – this does not include the majority of infants who have viral-induced wheeze.

**Cardiorespiratory symptoms or signs include any difficulty in breathing, noisy breathing, stridor, hoarseness, cyanosis, change in conscious level, pallor, hypotension

after vaccination, and an assessment prior to discharge. Resuscitation facilities and an anaphylaxis management protocol must be available, but routine siting of an intravenous cannula is not required.

These guidelines are summarized in Fig. 1.

Evaluation of allergic reactions to measles vaccine

Future studies must contain better reporting on the exact timing and nature of any allergic reaction to the measles vaccine, and exclusion of all possible allergens. We propose that any systemic reaction to measles vaccine should be referred for specialist evaluation to include:

- A detailed history of the reaction to any known food allergen
- Skin testing and specific IgE testing to allergens
- Confirmation of egg, gelatine or neomycin allergy by an open food challenge or double-blind placebo-controlled food challenge, if appropriate.

Conclusions

Despite previous guidelines, there are varying practices throughout the UK for the administration of measles vaccine in egg-allergic children. There is little clear data on the incidence of allergic reactions to the measles vaccine. The amount of ovalbumin in the vaccine is so small as to be highly unlikely to cause a serious allergic reaction in the majority of individuals. The role of allergens other than egg in the aetiology of systemic allergic reactions with measles vaccine is supported by the larger number of these reactions reported in nonegg-allergic children than in those with egg allergy. Only a few of the reports have looked for other potential allergens, such as neomycin and gelatine, which

are present in larger quantities and known to cause serious reactions in the context of measles vaccination. Skin testing to the vaccine lacks specificity and sensitivity in predicting a serious allergic response, and desensitization in this context is a procedure that lacks scientific rationale. Both procedures are associated with a risk of allergic reaction and should be abandoned. Children with a past history of a cardiorespiratory reaction to egg or with coexistent active chronic asthma are the only small subgroups of egg-allergic children who require hospital paediatric supervision during measles vaccination. Measles vaccine (MMR vaccine) is as safe as any other vaccine, and children with egg allergy must not have their vaccination delayed.

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