

# VIRAL VACCINATION AND ALLERGY

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## ABSTRACT

Childhood immunisation is one of the greatest public health successes of the last century. Adverse vaccine reactions are uncommon and may be caused by the vaccine itself, by preservatives, adjuvants and stabilisers, or by contaminants acquired during the manufacturing process or administration of the vaccine. Influenza vaccine contains significant amounts of egg protein and may cause allergic reactions in egg-sensitive individuals. Adverse reactions are classified as IgE-mediated, delayed hypersensitivity reactions, or non-allergic, manifesting as pyrexia and local reactions. The history is vital in the assessment of an adverse vaccine reaction, particularly in respect of the onset of symptoms in relation to the administration of the vaccine. Skin-prick testing and intradermal testing are useful in assessing IgE-mediated reactions where future vaccination is required.

The overwhelming evidence is that childhood immunisations are not causally related to asthma and allergic disease, and are safe. Influenza vaccination is recommended in asthmatics and is safe, but the evidence for its efficacy in preventing asthma exacerbations is not convincing, and it has not been shown to be cost-effective.

Parents should be encouraged to have their children immunised against childhood diseases as the benefits far outweigh the risks.

## INTRODUCTION

Childhood immunisation has been credited with being responsible for reducing childhood morbidity and mortality over the past 40-50 years.<sup>1</sup> It was the first item on the list of the Centers for Disease Control (CDC) for the 'Ten great public health achievements' of the 20th century.<sup>2</sup> The viral diseases smallpox and poliomyelitis were eradicated in the United States of America as a result of vaccination, with a substantial reduction in morbidity and mortality from measles, mumps and rubella.<sup>3</sup> The new South African Expanded Programme on Immunisation schedule includes immunisation against the viral diseases hepatitis B and rotavirus, and vaccines against hepatitis A, varicella, influenza and human papillomavirus (HPV) are also available.

It is logical to speculate that such extensive vaccine coverage with a direct effect on the immune system of children should impact on other conditions having their origin in immune dysfunction. One of the components of the 'hygiene hypothesis' to explain the increase in allergic conditions is that immunisation may programme the immune system from a Th1 to a Th2 pre-

dominant phenotype, with resultant expression of allergic disease.

The theme of this journal issue is viruses and allergy, and this article addresses some aspects of the interaction between viral vaccines and allergic disease, with specific reference to the following: (i) adverse vaccine reactions, their diagnosis and management; (ii) the relationship between vaccination and allergic disease; and (iii) influenza vaccine and asthma.

## VIRAL VACCINES AND ADVERSE REACTIONS

The possibility of allergic reactions following vaccination is low and the risk must be weighed against the impact of and benefit from immunisation. Where the vaccine-preventable infectious disease is serious with the potential to cause severe consequences, vaccination side-effects may be deemed acceptable and tolerable. As soon as the disease becomes controlled and thus less of a threat, side-effects are less easily accepted.<sup>4</sup> Current vaccination programmes expose infants to multiple simultaneous vaccines, with concerns being expressed that their immune systems may be overwhelmed as a result.<sup>5</sup>

Vaccine reactions may be local or systemic and of immediate or delayed onset.<sup>5</sup> Reactions may result from the vaccine (vaccine reaction) or from a mistake in the immunisation process (programme error).<sup>6</sup> Vaccine reactions may occur to the vaccine itself or to preservatives, adjuvants and stabilisers, thus making it difficult to quantify the risk.<sup>5</sup> Moreover, the composition of many vaccines has changed during the past few years, making it difficult to compare studies of adverse reactions.

A functional classification of immunologically mediated vaccine reactions is to assess whether the onset of the reaction is immediate or delayed. Most of the immediate reactions are IgE-mediated and occur within a few minutes, or usually within 4 hours, of vaccination.<sup>7</sup> IgE-mediated reactions most commonly present with urticaria and angio-oedema, but may also involve wheezing, stridor, abdominal symptoms and hypotension.<sup>7</sup> Anaphylaxis can also occur after vaccination.<sup>8</sup> Delayed hypersensitivity reactions usually occur hours to days after the vaccination, although they may even occur 2-3 weeks later.<sup>7</sup> The most common manifestation of delayed hypersensitivity is a skin rash, which may present as a maculopapular rash, urticaria or erythema multiforme. Other delayed vaccine reactions may not be immunologically mediated, such as irritant local reactions to vaccine constituents such as aluminium.

What follows applies to vaccines in general, but I will confine the discussion of specific vaccines to viral vaccines.

### *IgE-mediated reactions to vaccines*

Anaphylaxis after vaccine administration is rare, and the rate is estimated at between 0.65 and 1.53 per million doses.<sup>9</sup> Identification of the specific vaccine responsible for an anaphylactic event is difficult because of the simultaneous administration of a number of vaccines. Bohlke *et al.*<sup>9</sup> discussed anaphylaxis following vaccination in 5 children; only 1 child had had

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a single vaccine, viz. measles-mumps-rubella (MMR). Two of the 5 children in their study had a history of asthma with/without eczema, but the numbers were too small to be able to associate atopy with vaccine-induced anaphylaxis. Other studies have reported anaphylaxis associated with MMR, hepatitis B and varicella vaccination.<sup>9</sup>

A recent study from Germany reported on 38 patients aged between 13 and 79 years referred for assessment with a diagnosis of vaccine-induced anaphylaxis.<sup>10</sup> Eight of the patients had received hepatitis A or B vaccines, 7 were vaccinated against tick-borne encephalitis, and 6 had received influenza vaccine. The work-up included skin-prick tests (SPTs) and challenge tests; all the SPTs were negative and those patients who were later challenged tolerated the procedure.

### ***IgE-mediated reactions to vaccine constituents***

Vaccine components that may cause allergic reactions include gelatin, neomycin, egg and yeast, and latex in syringes and vial stoppers may also cause vaccine-associated anaphylaxis.<sup>4,5,9,10</sup> Gelatin is used as a stabiliser in many vaccines, and anti-gelatin IgE was demonstrated in children who had an immediate systemic reaction to live virus vaccines.<sup>11</sup> Genetic susceptibility to gelatin allergy is suggested by the demonstration of an association between gelatin allergy and HLA-DR9, which is unique to Asians.<sup>12</sup> Elimination of the gelatin from vaccines such as MMR and varicella has significantly decreased the number of severe vaccine reactions in Japan.<sup>10</sup>

Many vaccines are developed in chick embryos, thus causing concern that egg-allergic individuals may react to these vaccines. Examples of viral vaccines developed in this way include measles, mumps, rabies, influenza and yellow fever.<sup>4</sup> However, measles and mumps are grown in chick embryo fibroblast cultures, and contain no or very little egg protein. In fact, most MMR vaccine reactions are caused by gelatin allergy. The current recommendation is that measles and MMR vaccines can safely be given to egg-allergic children.<sup>5,13,14</sup> The Institute for Vaccine Safety website lists currently used vaccines together with possible allergens contained in them ([www.vaccinesafety.edu](http://www.vaccinesafety.edu)).

### ***Specific vaccines***

#### ***Influenza vaccine***

Influenza vaccine contains measurable amounts of egg protein (ovomucoid-ovalbumin) as it is grown in the allantoic fluid of embryonated chicken eggs.<sup>4,15</sup> The American Academy of Pediatrics recommendation regarding influenza vaccine and egg-allergic children is that it should not be given to children who have had anaphylactic reactions to egg.<sup>5</sup> The reasoning behind this recommendation is that the vaccine has to be administered every year and antiviral therapy for influenza exists, so the risk outweighs the potential benefits. Zeiger<sup>15</sup> recommends that patients with a history of egg allergy who would benefit from influenza vaccine should be referred to an allergist for skin-prick testing to egg and influenza vaccine if the former is positive.

The British Society for Allergy and Clinical Immunology (BSACI) guidelines state that influenza vaccine for administration to egg-allergic children should contain a stated maximum egg content <1.2 µg/ml (0.6 µg/dose), that the anticipated benefits of the vaccine should outweigh the risks of an adverse reaction, and that the vaccine should be administered in a centre that is experienced in the management of anaphylaxis.<sup>16</sup>

### ***Human papillomavirus vaccine***

One of the newer vaccines administered to adolescents and young adults is the human papillomavirus (HPV) vaccine. Anaphylaxis following HPV vaccine has been reported but is rare.<sup>17</sup> The quadrivalent HPV vaccine was implemented free of charge for all women between the ages of 12 and 26 years in Australia in 2007. Twelve cases of anaphylaxis to the HPV vaccine were reported soon afterwards, and 8 cases were classified as anaphylactic reactions; 6 occurred after the first dose and 2 after the second.<sup>17</sup> The overall anaphylaxis rate was 2.6 per 100 000 doses administered, higher than reported for other vaccines. Four of the participants had negative skin tests to intradermal quadrivalent HPV vaccine. The explanation for the anaphylactic reactions is not clear – possibly a reaction to remaining yeast protein or the stabiliser polysorbate 80 in the vaccine.<sup>17</sup> The package insert of the vaccine has been adapted to reflect the reports of anaphylaxis with HPV vaccination, but subsequent analysis does not suggest that the rate of anaphylaxis is higher than that of other vaccines (1 case per one million doses).<sup>18</sup>

### ***Non-IgE-mediated reactions to vaccines and vaccine constituents***

Any vaccine may cause non-allergic reactions such as pyrexia and local erythema, swelling and tenderness at the injection site. Delayed hypersensitivity vaccine reactions to neomycin, thimerosal (thiomersol) and aluminium contained in the vaccine may also occur.<sup>4,5</sup> Rashes, fever and febrile convulsions have been reported with measles and MMR vaccines.

### ***Approach to a patient with a suspected vaccine reaction***

It is important to note the presenting symptoms and their timing in relation to the vaccine. Immediate hypersensitivity reactions usually present soon after administration of the vaccine and are therefore easier to diagnose than delayed reactions. In the latter it is important to consider other causes of the symptoms, e.g. infection.<sup>7</sup>

In South Africa adverse vaccine reactions must be reported as an adverse event following immunisation (AEFI) to the district and provincial vaccine co-ordinators. Health care professionals should also report any adverse reactions to the National Adverse Drug Event Monitoring Centre (NADEMC) of the Medicines Control Council (MCC).

The Hypersensitivity Working Group of the Clinical Immunization Safety Assessment (CISA) Network has prepared an algorithm for the approach to a suspected vaccine reaction. The history is crucial in deciding whether the patient's symptoms and signs are consistent with an IgE-mediated vaccine, as detailed in Table 1.<sup>7</sup> Figure 1<sup>7</sup> outlines an algorithm for the approach to a suspected IgE-mediated vaccine reaction.

If the history suggests that the patient had an IgE-mediated vaccine reaction and that the vaccine will be required in future, allergy testing is indicated. Most of the time only the whole vaccine is available for testing, but occasionally the constituents and adjuvants are also obtainable.<sup>7</sup> Controversy exists as to whether skin-prick testing or intradermal testing should be done.<sup>4,5</sup> The recommendation of the Working Group is to start with a 1:10 dilution of the vaccine or its constituents as an SPT. Positive and negative controls should be used as references, and a wheal of 3 mm greater than the negative control surrounded by a flare is considered to be positive. Only if the SPT is negative or if a wheal without a flare is present, should the SPT be repeated

**Table I. Key historical data**

Patient's age  
 Specific symptoms that were noted  
 Timing of onset of the symptoms relative to the administration of the vaccine  
 Other exposures to possible allergens  
 Any information from office visits/emergency department visits  
 Treatment that was administered  
 Duration of symptoms, time course of resolution  
 Previous vaccine history  
 History of other atopic disease, including food allergy, drug allergy, atopic dermatitis, asthma, and allergic rhinitis  
 Specific vaccine(s) that was(were) administered, including the manufacturer and lot number

From Wood *et al.*<sup>7</sup>

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with the undiluted vaccine or constituent. If the prick testing is negative, then intradermal testing should be done with a 1:100 dilution, followed by a 1:10 dilution if that is negative.<sup>7</sup> A recent study done in children with other atopic diseases suggested that intradermal testing with a 1:10 diluted vaccine is more reliable than SPT

with undiluted vaccine for both measles and influenza vaccines.<sup>19</sup> Skin testing of vaccines and vaccine components should be done by an allergologist who should assess whether a positive test is clinically relevant or false-positive.

If the skin test is negative without a history of anaphylaxis, the vaccine can be administered and the patient observed for an hour afterwards. If the skin test is negative but a history of anaphylaxis is present, then the first vaccine dose should be administered as 10% of the vaccine strength and the patient observed for 30 minutes to an hour. If no reaction occurs, then the rest of the vaccine can be administered and the patient watched for 1 hour. If the skin test is positive for the vaccine and/or its constituents and the vaccine is considered essential, then a protocol using graded doses can be utilised.<sup>4,7</sup>

**DOES VACCINATION PREDISPOSE CHILDREN TO THE DEVELOPMENT OF ALLERGIC DISEASE?**

The 'hygiene hypothesis' was developed in an attempt to explain the global increase in allergic disease. It proposes that this increase is due to an altered regulation of the immune system as a result of decreased exposure to infections in childhood, and that this is due to general improvements in hygiene and sanitation, smaller families with decreased exposure to childhood ill-

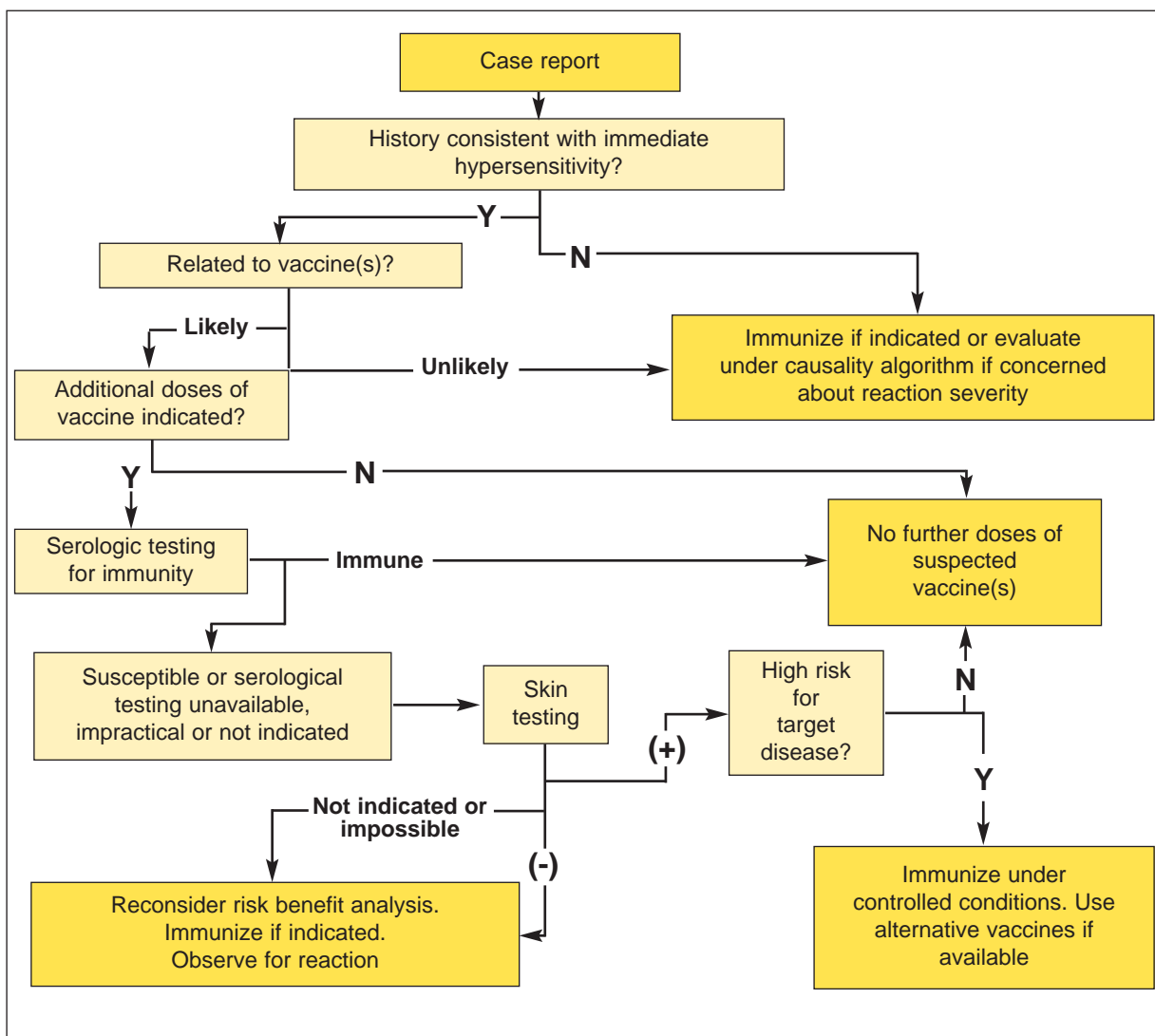


Fig. 1. An algorithm for the management of suspected allergic reactions to vaccines. (From Wood *et al.*<sup>7</sup> Reproduced with permission from *Pediatrics* volume 122, pages 771-777, copyright © 2008 by the AAP).

nesses, and immunisation.<sup>20,21</sup> The theory is that immunisation may stimulate Th1-type immunity directly, or that Th1-type immunity may be enhanced as a result of the prevention of infections.<sup>22</sup>

The relationship between atopic disease and immunisation has been studied for various vaccines, particularly for BCG, measles and pertussis. The International Study of Asthma and Allergies in Childhood (ISAAC study) looked at this relationship in its Phase 1 study and found 'no statistically significant associations' between symptoms of wheezing, rhinoconjunctivitis and eczema, and national immunisation rates.<sup>22</sup>

### **Measles and measles vaccination**

Findings regarding the influence of measles and measles vaccination on the development of atopy differ according to the method and the setting of the study. A 1994 study of young adults in Guinea-Bissau revealed that a documented history of measles infection was associated with decreased atopy as measured by skin-prick testing for house-dust mite.<sup>23</sup> This relationship remained even after correction for potential confounders. However, the study was performed on survivors of a severe measles epidemic, and it is difficult to know how this may have influenced these results. Lewis *et al.*<sup>24</sup> studied a British cohort of children and found varying results depending on the number of siblings and the position of the study child in the family. Measles vaccine was associated with increased hay fever and measles infection with reduction in hay fever by univariate analysis. However, in children with many older siblings, both measles infection and measles immunisation were significantly associated with decreased hay fever. The ISAAC study confirmed the absence of a relationship between measles immunisation or infection and increased atopy.<sup>22</sup>

A systematic review published in 2004 reviewed the epidemiological evidence for an association between childhood immunisation and allergic disease, and found that 'current infant vaccines do not cause allergic diseases.'<sup>25</sup> The authors analysed nine studies of measles and/or MMR vaccines, and concluded that 'measles vaccination is not associated with an increased risk of atopic disease.' Subsequent studies in various cohorts of children have also failed to demonstrate an association between childhood vaccination with measles and/or MMR and allergic disease.<sup>26-29</sup>

### **Other viral vaccines**

Bager *et al.*<sup>30</sup> could find no association between smallpox vaccination in childhood and subsequent atopy or allergic rhinitis, although there appeared to be a small reduction in the risk of asthma. Hepatitis B immunisation at birth was associated with allergic sensitisation to aeroallergens and increased total serum IgE, and varicella vaccination was inversely associated with elevated total IgE and atopy in the study by Grüber *et al.* but the authors caution against over-interpretation of the significance of these results.<sup>28</sup>

## **SHOULD INFLUENZA VACCINATION BE GIVEN TO CHILDREN WITH ASTHMA?**

Most guidelines suggest that influenza vaccine should be recommended to all children with asthma requiring regular therapy, yet only about a quarter of asthmatic children are actually vaccinated.<sup>31</sup> So, should influenza vaccine be given to children with asthma? This question could be structured differently: does influenza vaccination in children with asthma reduce asthma exacerbations?<sup>31</sup> Data are available that influenza increases

paediatric admissions to hospital, but there is little evidence that asthmatic children have an added risk.<sup>32</sup> In the only available randomised, placebo-controlled trial of influenza vaccine in asthmatic children, the number and severity of asthma exacerbations were not significantly reduced by influenza vaccine; the duration of influenza-related asthma exacerbations was 3 days less in the vaccine group, but did not reach statistical significance.<sup>33</sup> In a cohort study of influenza vaccine in asthmatic children, benefit was shown for children younger than 6 years in preventing acute respiratory disease, but this benefit did not extend to older children.<sup>34</sup>

What are the risks of administering influenza vaccine to asthmatic children? A large randomised, double-blind, placebo-controlled, crossover study enrolled 2 032 patients with asthma, and could only demonstrate negligible increases in asthma exacerbations following influenza vaccination, and no significant adverse effects occurred in any of the groups.<sup>35</sup> In the study performed by Bueving *et al.*<sup>33</sup> no difference in airway symptoms could be demonstrated during the week following vaccination. As previously stated, influenza vaccine may contain significant amounts of egg protein and therefore has the potential to cause allergic reactions in egg-sensitive individuals.<sup>4,15</sup>

Finally, a recent Cochrane review concluded that 'uncertainty remains about the degree of protection vaccination affords against asthma exacerbations that are related to influenza infection.' It also concluded that there is no evidence that influenza vaccine is associated with increased asthma exacerbations in the immediate period following vaccination.<sup>36</sup>

## **CONCLUSION**

Childhood immunisation programmes have made a significant contribution to the health of children globally. The available evidence suggests that immunisation is safe in the vast majority of cases and is not causally associated with allergic disease. Parents should be encouraged to have their children immunised as it is in their children's best interests as well as in the interests of the community. Current guidelines recommend that asthmatic children be vaccinated against influenza and it appears to be safe, but the evidence for its efficacy and cost-effectiveness is lacking.<sup>32</sup>

### **Declaration of conflict of interest**

The author declares no conflict of interest in respect of the content of this article.

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