

Vaccination of the egg-allergic individual

Summary

- Egg allergic individuals may be safely vaccinated with the **measles mumps rubella (MMR)**, the **measles mumps rubella varicella (MMR-V)** vaccine (which contains no egg protein) and the **influenza** vaccine (which may contain minute traces of egg protein).
- Special precautions such as split dosing, prior allergy testing with the vaccines, allergy specialist review before vaccination or prolonged waiting times after administration are not required.
- The **yellow fever** and **Q fever** vaccines potentially contain higher amounts of egg protein and allergy specialist evaluation is recommended before vaccination.

Introduction

Vaccination is an important method of reducing the risk of developing a number of infectious diseases. Before mass vaccination campaigns in Australia, **measles** was a significant contributor to hospitalization, morbidity (such as pneumonia, meningitis and encephalitis) and sometimes death www.health.gov.au/internet/main/publishing.nsf/content/cda-cdi3901a.htm.

Influenza is also a significant cause of morbidity and mortality in Australia, accounting for over 1% of staff absenteeism in winter, and an estimated 3089 deaths per year from combined influenza/pneumonia between 2001 and 2006 (1). In 2007 there were 2,623 deaths with influenza and pneumonia as the underlying cause of death. In 2007, influenza and pneumonia was the 13th leading cause of death in Australia (2). Laboratory confirmed influenza resulted in 3 deaths in otherwise healthy preschool children in Western Australia in 2007.

Notification and hospitalisation rates related to influenza infection are highest in children aged 0-5 years (the age group most affected by egg allergy 3, 4) and in adults aged 70+ years www.health.gov.au/flureport. While egg protein-free influenza vaccines grown in mammalian cell lines exist (e.g. *Celvapan*® and *Flublok*®), called recombinant influenza vaccines (RIV), the current influenza vaccines distributed in Australia and New Zealand are inactivated influenza vaccines (IIV) which are derived from influenza virus grown in hen's egg, thus the vaccine potentially may contain minute traces of egg protein. Live attenuated influenza vaccine (LAIV) is not available in Australia or New Zealand and is not currently recommended. The ability to safely vaccinate egg-allergic individuals (particularly in the context of potentially pandemic infection) is an important public health issue.

Older vaccination guidelines and the vaccine Product Information (PI) recommended avoidance of influenza vaccination in egg-allergic individuals based on case reports of anaphylaxis 30 years ago, when the amounts of egg protein were much higher than currently (5, 6). A number of studies over the last ten years have shown no greater risk of influenza vaccine allergy in those with or without egg allergy (7). This is not surprising given that the amount of egg ovalbumin present in Australian and New Zealand vaccines is currently ~ 1ug or less/dose, substantially less than the estimated 130 ug egg protein taken orally considered likely to trigger reactions in egg allergic patients (8).

Aims

These guidelines aim to provide updated recommendations for vaccination of egg-allergic individuals, consistent with international and current Australian and New Zealand Guidelines (9-12). Since the MMR vaccine contains no egg protein and egg-containing vaccines such as the Yellow Fever and Q Fever are specialist vaccines, this document will concentrate on the safety of administering the influenza vaccine in the egg allergic individual. The

ASCIA Guidelines - Influenza vaccination of the egg allergic individual

information applies to the vaccines currently available in Australia and New Zealand. Since vaccine manufacture is subject to change and may vary between countries, this information may or may not be applicable to vaccines available in other countries. In drafting these guidelines, the authors have examined recent published studies of vaccination safety (Table 1) published international recommendations, product information sheets and relevant Australian and New Zealand vaccination guidelines. As with any form of medical intervention, the benefits of vaccination (protection against infection) need to be balanced against the very low risk of adverse reactions.

Minor short-lived side effects from vaccination are common

Injection site reactions (local pain, redness and swelling), fever, muscle aches, irritability or worsened eczema a day or so later are common vaccine side effects and do not represent vaccine allergy but rather the initiation of an immune response. Measles mumps and rubella (MMR) and Varicella vaccines can occasionally be followed by delayed rash (usually 4-12 days after vaccination) but this is also *not* due to a vaccine allergy. An exception to these may be a delayed (type 3) response characterised by urticaria and/or joint pain observed several hours to several days after vaccination. This type of reaction does not increase the risk of anaphylaxis and does not contraindicate subsequent vaccination.

Severe allergic reactions to vaccination are very rare

The risk of a severe allergic reaction to vaccination (anaphylaxis), to inactivated influenza vaccine is very low, estimated at 1.35 per million doses (10, 13). Immunisation guidelines recommend an observation period of 15 minutes (Australia) or 20 minutes (New Zealand) post-vaccination. The first symptoms of anaphylaxis may occur 20 minutes or longer after vaccination. However, because anaphylaxis is a very rare event it is not considered routine practice for vaccinated individuals to be observed beyond these specified times.

Vaccination providers should be able to recognise and manage anaphylaxis.

Most vaccines do not contain food allergens

There are no traces of dairy products, peanut, tree nuts, wheat, soy, seeds or seafood in vaccines. The following vaccines, as currently recommended on the Australian Childhood Vaccination Schedule (14) do not contain food-derived protein allergens and can be given to any patient with food allergy, even those with food-induced anaphylaxis:

- MMR (measles, mumps, rubella)*
- MMR-V (measles, mumps, rubella varicella)
- DPT (Diphtheria, Pertussis, Tetanus)
- IPV (Inactivated polio vaccine)
- HiB (*Hemophilus influenzae* type B)
- Pneumococcus
- Meningococcal C
- Chickenpox (Varicella) vaccines (which contain neither egg nor chicken protein)
- Rotaviral vaccine

* **Note:** The MMR vaccine is cultured on chicken fibroblast cell cultures, contains no residual egg allergen and has been safely administered to large numbers of egg-allergic individuals. The rare allergic reactions to MMR vaccination that have occurred have been attributed to non-egg ingredients such as gelatin (15).

The following vaccines may contain residual egg protein

Egg allergy is common, with up to 8.9% of Australian infants having challenge proven allergy to raw egg and likely a smaller proportion reacting to well cooked egg (4). Most outgrow their allergy by primary school, although with occasional persistence or development of new egg allergy during adult life. Some vaccines are grown in

ASCIA Guidelines - Influenza vaccination of the egg allergic individual

eggs (see below). Older vaccination guidelines recommended avoidance of influenza vaccination in egg-allergic individuals based on case reports of anaphylaxis 30 years ago when the amounts of egg protein were much higher than currently (5, 6). To enhance safety, attempts have been made in recent years to limit the amount of egg ovalbumin in the pandemic and seasonal inactivated influenza vaccines to less than 1 ug of egg protein per vaccine dose.

- Seasonal inactivated influenza vaccine (s)
- Pandemic inactivated influenza vaccine(s) (e.g. H1N1, bird or swine flu vaccines).
- Yellow Fever vaccine (important for travelers and those living in an endemic area)
- Q fever vaccine (important in occupational setting)

The amount of residual egg protein in Yellow fever and Q fever vaccines is generally higher than in seasonal influenza and H1N1 vaccines, although administration of these vaccines to egg allergic individuals has been described (16). *Egg allergic patients in whom Yellow fever or Q fever vaccines are indicated should be referred to an allergy/immunology specialist for assessment.* The remaining discussion pertains to egg-allergic individual in whom seasonal/pandemic influenza vaccination is indicated.

What is known about the safety of egg-containing influenza vaccines?

In the only case report of a death following influenza vaccine in 1969 (17), few details have been published, and the causative relationship with egg allergy is unclear. More useful information has been obtained from recent prospective studies using H1N1 or seasonal influenza vaccines where the amount of residual egg ovalbumin has been limited to 1ug/dose or less. A recent review of 28 studies comprising 4,315 subjects with egg allergy (including 656 subjects with a history of egg anaphylaxis) showed no severe reactions after influenza vaccination (7) as summarized in Table 1 (smaller older studies where the amount of ovalbumin is unknown are omitted). Mild and occasional side-effects such as local itching, mild hives, throat irritation, wheezing or abdominal pain have been observed but not anaphylaxis. Comparison of graded administration of vaccination (“split dosing”) has shown no differences in the rate of adverse reactions (Table 1). Results of allergy testing with the vaccine prior to administration have shown no correlation with outcomes in terms of adverse reactions (18).

Table 1a: Major studies of influenza vaccination of egg-allergic individuals: parenteral (injected) vaccines

| Study | Ref | Location | No. participants | Outcome | Split/full dose | Design |
|--------------------------------------|-----|----------|----------------------|---|-----------------|--|
| Shimizu et al, Aregugi 2016 | 19 | Japan | 17 | No systemic reactions | Split | Prospective |
| Gagnon et al 2010 | 20 | Canada | 830 | No anaphylaxis; 17 had mild hives, wheeze or abdominal pain | Both | Prospective: 2+ years |
| Siret-Alatrasta et al 2011 | 21 | France | 178 (72 had +ve IgE) | No systemic reactions | Full | Prospective: 2-50 years |
| Des Roches et al, JACI 2012 | 22 | Canada | 367 | No anaphylaxis; 1 case each of hives, vomiting or aggravated eczema | Both | Prospective; |
| Greenhawt et al, Annals Allergy 2012 | 23 | USA | 142 | No systemic reactions | Both | Mixed randomized and retrospective observational |
| Webb et al, JACI 2011 | 24 | USA | 152 | No systemic reactions | Both | Prospective; 1-30 years |

ASCIA Guidelines - Influenza vaccination of the egg allergic individual

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|---|----|--------|----|-----------------------|-------|----------------------------|
| Upton et al, Allergy Asthma Clin Immunol 2012 | 25 | Canada | 77 | No systemic reactions | Split | Prospective: 0+ years |
| Forsdahl BMJ Open 2012 | 26 | Norway | 80 | No systemic reactions | Both | Retrospective: 1- 17 years |
| Schuler et al. Can J Public Health 2011 | 27 | Canada | 62 | No systemic reactions | Both | Prospective |
| James et al, J Ped 1998 | 28 | USA | 83 | No systemic reactions | Both | Prospective |

Table 1b: Studies of influenza vaccination of egg-allergic individuals: live attenuated intranasal vaccines (LAIV; not currently available in Australia/New Zealand)

| Study | Ref | Location | No. participants | Outcome | Split/full dose | Design |
|--------------------------------|-----|----------|------------------|-----------------------|---------------------------------|------------------------------|
| Turner et al, BMJ 2015 | 29 | UK | 779 | No systemic reactions | Full; <i>intranasal vaccine</i> | Prospective: age 2-18 years |
| Turner et al, JACI 2015 | 30 | UK | 433 | No systemic reactions | Full; <i>intranasal vaccine</i> | Prospective: age 2-17 years |
| Des Roches et al, JACI-IP 2015 | 31 | Canada | 69 | No systemic reactions | Full; <i>intranasal vaccine</i> | Prospective: age 2-16 years. |

International guidelines for vaccinating the egg-allergic individual

UK, USA, European and Canadian Consensus Guidelines recommend that most egg-allergic subjects can safely receive seasonal and pandemic vaccines if precautions are undertaken to minimise risk, specifically recommending vaccines containing no more than 1ug/dose of egg ovalbumin as summarised in [Table 2](#).

Table 2. International guidelines for vaccinating the egg-allergic individual*

| Country | Organisation | Web link |
|-----------|------------------------------|--|
| Canada | | www.phac-aspc.gc.ca/naci-ccni/flu-2016-grippe-addendum-eggs-oeufs-eng.php |
| USA | CDC | www.cdc.gov/flu/protect/vaccine/egg-allergies.htm |
| UK | BSACI | www.bsaci.org/Guidelines/Flu%20jab%20egg%20allergic%20kids.pdf |
| Australia | Department of Health | www.health.gov.au/internet/immunise/publishing.nsf/content/Handbook10-home |
| NZ | Immunisation Advisory Centre | www.immune.org.nz/immunisation |
| Other | World Allergy Organisation | www.waojournal.biomedcentral.com/articles/10.1186/s40413-016-0120-5 |

*Last accessed 14 April 2017

ASCIA Guidelines for vaccinating the egg-allergic individual

The Australasian Society of Clinical Immunology and Allergy (ASCIA) concurs with these views. Our recommendations specifically apply to vaccines containing no more than 1 ug ovalbumin per dose and are summarized below.

Recommended

- Based on prospective and retrospective studies of influenza vaccination in those with and without egg allergy (including egg anaphylaxis), the presence of egg allergy does not increase the risk of allergic reactions to the influenza vaccine.
- The entire vaccine can be administered in community vaccination clinics (which may or may not have direct medical practitioner supervision) as a single dose followed by the recommended 15 (Australia) or 20 (New Zealand) minute waiting period.
- In making this recommendation, we are aware that some guidelines (e.g. CDC 2017) recommend a longer waiting period of 30 minutes in those with past egg anaphylaxis and that occasionally allergic reactions to vaccination may commence later than 20-30 minutes after administration *The immediate availability of medical practitioner care is recommended and staff should be familiar with the recognition and treatment of anaphylaxis.*
- In individuals who have had anaphylaxis following administration of the influenza vaccine itself, further vaccination should be avoided without specialist allergy assessment.
- If there is significant parental or health professional anxiety, the vaccine may be administered in primary care settings with a longer waiting period of 30 minutes.

Not recommended

- “Split dosing”
- Allergy testing with the vaccine or to egg prior to administration
- Ingestion of egg as a pre-condition to administering the vaccine (relevant in infants);
- Vaccination in specific hospital-based vaccination clinics
- Allergy specialist review before influenza vaccination *unless anaphylaxis to the influenza vaccine itself has occurred previously*

ASCIA Guidelines for vaccinating the egg-allergic individual and the Product Information (PI)

These guidelines are at variance with those contained in the Product Information (PI). In regard to egg allergy the ASCIA and the Australian Immunisation Handbook should be followed and not the PI. This is only one example of a number of variations to product information that can be found in the Australian Immunisation Handbook.

If adverse reactions to vaccination occur

If a sudden collapse occurs after immunisation a vaso-vagal event needs to be distinguished from anaphylaxis (see www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part2~handbook10-2-3)

If the diagnosis is in doubt the vaccine recipient should be managed for anaphylaxis which includes the administration of intra-muscular adrenaline (epinephrine). Guidelines to anaphylaxis management can be found at www.resus.org.au/glossary/anaphylaxis-guideline-9-2-7/ and www.allergy.org.au/health-professionals/papers/acute-management-of-anaphylaxis-guidelines

After the event, adverse events following immunisation should be reported to the Therapeutic Goods Administration (TGA) (www.tga.gov.au/reporting-medicine-and-vaccine-adverse-events-0) in Australia and Medsafe in New Zealand (www.medsafe.govt.nz/).

It is important to document the timing of onset, the nature and severity of symptoms experienced, the likelihood of whether the adverse event occurred as a direct result of vaccination and details regarding underlying health issues (including known atopic disease). Blood for tryptase measurements should be taken if possible to assist in the confirmation of possible anaphylaxis.

Conclusions

Current evidence is that patients with egg allergy (including anaphylaxis) for whom influenza vaccine is indicated can be vaccinated safely as long as the amount of residual egg ovalbumin is limited to 1ug or less per dose. This requires checking the egg ovalbumin content for any planned vaccine prior to administration, although at the time of writing (2017) all vaccines licensed for use in Australia and New Zealand contain less than 1ug egg ovalbumin. Split dosing and prior allergy testing with the vaccine is no longer recommended. Egg allergy does not increase the risk of anaphylaxis to the influenza vaccine but anaphylaxis to other components may occur. Vaccines should always be administered in facilities with staff able to recognise and treat anaphylaxis.

These recommendations are based on current available evidence, and subject to change as additional evidence becomes available.

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ASCIA Guidelines - Influenza vaccination of the egg allergic individual

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