

South African National Essential Medicine List  
Primary Healthcare and Adult Hospital Level of Care Medication Review Process  
Component: Immunization

## MEDICINE REVIEW

**Title:** Inactivated Influenza vaccines and egg allergy: A scoping review

**Date:** 30 May 2023

### Executive Summary

**Date:** 30 May 2023

**Medicine (INN):**Influenza vaccine (inactivated)

**Medicine (ATC):** [http://www.whocc.no/atc\\_ddd\\_index/](http://www.whocc.no/atc_ddd_index/)

**Indication (ICD10 code):**

**Patient population:** Children and Adults with egg-allergies (reported or diagnosed), and requiring influenza vaccination

**Prevalence of condition:** 0.5 - 8.9% in early childhood<sup>1-6</sup>. Egg allergy has a good overall prognosis, with half of children becoming tolerant by 3 years, 66% by 5 years and ~80% by adolescence<sup>7-9</sup>.

**Prescriber Level:** Primary care nurse

**Current standard of Care:** Inactivated Influenza vaccine is contra-indicated in patients with a history of egg allergy

#### **Safety estimates:**

Influenza inactivated Vaccine in egg-allergic populations:

- As many of the studies included were observational direct comparisons are difficult.
- **Risk of anaphylaxis:** 0% in all patient populations in all clinical studies included in the review<sup>(15-24)</sup>
- **Skin reactions:** In one study, 10% of patients with egg allergy (cases) had local reactions (redness of skin) to the vaccine<sup>23</sup>.
- **Other allergic Reactions:** Extremely small numbers reported in all studies

**Motivator/reviewer name(s):** Shelley McGee

**Secretariat support:** Milli Reddy

**ERC Committee support:** Michael McCaul

**AGREE II Appraisal:** Natasha Gloeck & Sumayyah Ebrahim

### Key findings

- ➔ We conducted a scoping review of published primary clinical evidence and clinical practice guidelines in relation to the safety of administration of inactivated influenza vaccines to patients determined to be allergic to egg protein.
- ➔ Ten studies of the safety of inactivated influenza vaccinations in egg-allergic patients were identified. Only one study had an RCT component, whereas another five were prospective cohort studies, and the other four retrospective reviews.

- ➔ The definition of “egg-allergic” patients differed between the studies, as did primary outcomes.
- ➔ No anaphylactic reactions occurred in any of the 2612 patients included in the studies. Some studies reported milder reactions such as skin redness and urticaria, vomiting, and eczema, but reported rates were extremely low.
- ➔ Ten international guidelines including recommendations for influenza vaccination in egg allergic patients were identified. All but two (UK guidelines) recommended that egg allergic patients should receive age-appropriate influenza vaccination. Most referenced some or all of the studies included in this review as their evidence base. The UK guidance recommends that patients may receive inactivated influenza vaccines, unless they have experienced an anaphylactic reaction to egg, which required admission to intensive care.
- ➔ Generally, guidelines have evolved to amend recommendations from contra-indication of influenza vaccination to a permissive approach, based on the evidence documented.
- ➔ Recommendations are predominantly based on the understanding that available influenza vaccines (egg-derived or otherwise) now contain very low quantities of ovalbumin (<1mcg/ml).

## 1. NAME OF AUTHOR(S)/MOTIVATOR(S)

Shelley McGee<sup>1</sup>

## 2. AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS

<sup>1</sup>Ophthalmological Society of South Africa, National Operations Manager

There are no conflicts of interest to declare.

### **Acknowledgments:**

**AGREE II Appraisal:** Natasha Gloeck & Sumayyah Ebrahim (South African Medical Research Council) completed the AGREE II assessments in duplicate. Michael Mccaul provided methodological inputs on the credibility and timeliness scoring of the guidelines and ranking display of the guidelines based on the AGREE II scoring.

**Secretariat Support:** Milli Reddy (Right to Care & Supply Chain Technical Assistance)

NG, SE MM, & MR have no interests related to influenza vaccine.

## 3. BACKGROUND

Egg allergies are among the most common childhood food allergies. The estimated prevalence of egg allergy is 0.5 - 8.9% in early childhood<sup>1-6</sup>. Egg allergy has a good overall prognosis, with half of children becoming tolerant by 3 years, 66% by 5 years<sup>7-9</sup> and ~80% by adolescence.

Influenza vaccines generally contain egg protein (including ovalbumin) because the vaccine virus is cultured in hen's eggs. In theory, patients with egg allergy might be at increased risk of an allergic reaction to influenza

vaccines. In recent years, inactivated influenza vaccines (IIVs) with very low or no ovalbumin content have become available. Observational studies have confirmed the safety of the parenteral monovalent inactivated influenza vaccine (IIV) in children with egg allergy, including those with a history of previous anaphylaxis to egg<sup>10,11</sup> and have led to a relaxation of contraindications relating to egg allergy in some guidelines.<sup>12-14</sup>

A trivalent live attenuated influenza vaccine (LAIV) administered through the intranasal route has been available in the United States for several years and received approval for use in Europe in 2010<sup>34</sup>. This vaccine has not yet become available in South Africa.

Product package inserts in relation to the inactivated trivalent and quadrivalent influenza vaccines currently available in South Africa, state that the vaccinations should not be administered to patients with a history of egg allergy, as does the South African Medicines Formulary 2023. This status quo has been challenged by allergy experts in the country, and there is a need to review the evidence and guidelines available in relation to the administration of influenza vaccinations to egg-allergic individuals.

In other countries, most influenza vaccine manufacturers provide information in the package inserts about the vaccine ovalbumin concentration. The vaccine ovalbumin content is typically expressed in micrograms per 0.5 mL dose. 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. However, the quantity of ovalbumin in local vaccines is not currently reported in South African Package inserts.

Following an appeal submitted to the National Essential Medicines List Committee (NEMLC) following the publication of the Immunization Chapter of the Primary Standard Treatment Guideline, the NEMLC has expressed concerns about a proposed removal of the contra-indication to egg allergy, citing the possibility of medico-legal challenges, as well as limited skills to manage allergic reactions in the primary care setting, where vaccines are routinely delivered.

Hence, in order to consider any changes to the current recommendations, a full review of the evidence available was necessary.

#### **4. OBJECTIVE AND RESEARCH QUESTION:**

“What is the evidence for the safety of inactivated influenza vaccines when administered to egg-allergic individuals”.

##### **Objectives**

- Map the evidence base and safety for different influenza vaccine type
- Assess the relative safety of the inactivated influenza vaccines in the egg-allergic patient population

## 5. METHODS

### Search strategy

We considered all studies in relation to influenza vaccine and egg allergy. We performed an initial limited search of MEDLINE to identify randomised controlled trials and observational studies on the topic. We only included studies published in English unless a translated version of a non-English text was readily available after performing a free-text search on the internet. Having recognised that much of the academic discussion around the topic started in the early 2010's, studies were limited to 2010 to 2023. Grey literature was not considered unless it was brought to the reviewers' attention while searching reference lists.

### Guidelines and National Recommendations

In addition, several international guidelines were identified through the literature search, or through referrals from other guidance and documents.

Guidelines were subjected to the AGREE II tool in order to evaluate their quality and relevance to the research question. Two reviewers (NG & SE) completed the AGREE II in duplicate (Appendix 3). Furthermore, relevant guidelines were ranked in terms of credibility (based on the AGREE II score), timeliness (whether it is likely to be up to date) and the use of GRADE methods in order for reviewers to focus on the most trustworthy guidance available.

## 6. RESULTS:

### Studies in egg-allergic individuals

Our initial database search (Appendix 1) yielded 121 articles. 6 studies were excluded because of language; and 30 were unrelated to the research question. 5 studies were excluded as they involved the Live attenuated influenza vaccine, and a further 4 which examined adverse events from the recombinant influenza vaccination. Twenty-nine studies were narrative reviews of the topic, and a further 26 were guideline documents or position statements.

10 studies were thus included in this review, as well as a further 10 international guidelines (the most recent in their series).

The 10 included studies are summarised in Appendix 2<sup>15-24</sup>. Only one study was defined as an RCT, while the others were prospective cohort studies (5) and retrospective reviews (4). Primary outcomes were often not well-defined in the studies, although many reported on anaphylaxis, and other allergy related reactions, following vaccination. The definition of "egg-allergy" differed between studies, and many considered egg-allergy the reported history of a reaction to egg ingestion. Some others also confirmed egg allergy through a skin prick test.

Overall, there were no cases of anaphylaxis reported in any of the populations (2 612 patients in total in all the studies in the review). Other, minor reactions were reported in some of the cohorts, namely skin erythema and swelling and small numbers of urticarias and other allergy related reactions.

### National Guidance and recommendations

We identified ten national guidelines in respect of influenza vaccines. These are summarised in Appendix 2<sup>25-33</sup>.

Guidance published by vaccine advisory committees in the United States, Canada and the WHO recommend that based on the evidence available, egg-allergic individuals can receive age-appropriate influenza vaccine doses. The United Kingdom is somewhat more reserved, recommending Inactivated influenza vaccines that are egg-free or have a very low ovalbumin content (<0.12 micrograms/ml - equivalent to <0.06 micrograms for a 0.5 ml dose) may be used safely in individuals with egg allergy. Similar recommendations were made by an expert group for Europe. Guidelines in Australia / New Zealand also recommend that none of the available influenza vaccines contain >1 µg of ovalbumin and that people with egg allergy, including a history of anaphylaxis, can be safely vaccinated with any influenza vaccines (including egg-based and cell-based vaccines) unless they have reported a serious adverse reaction to influenza vaccines.

Very few of the guidelines identified specified the levels of evidence, or strength of recommendations made. The American College of Allergy, Asthma & Immunology made strong recommendations on the basis of level A/B evidence that influenza vaccines should be administered to individuals with egg allergy of any severity, just as they would be to individuals without egg allergy, and that no special precautions beyond those recommended for the administration of any vaccine to any patient are necessary for administration of influenza vaccine to egg allergic individuals.

AGREE II appraisals are outlined in Appendix 3.

Seven of the 10 guidelines were rated as high quality (score greater than 60% assessed using the AGREEII tool in duplicate). Where guidelines fell short, this was mainly in terms of the description and outlining of the methodologies followed for the rigorous development of an evidence base, or their applicability to their environment (odd as most of the guidance for vaccines was developed by country health authorities). Six of the 10 guidelines scored relatively high quality for rigour of their development, all of which recommended, based on evidence assessments, that a history of egg allergy is not a contraindication to patients receiving the influenza vaccine.

A secondary appraisal of the guidelines for overall timeliness and credibility was also conducted, based on the recommendations of the ERC. The top-scoring guidance in this assessment were the Australian Technical Advisory Group on Immunisation (ATAGI): The Australian Immunisation Handbook – Influenza (flu); followed by the 2022-

2023 Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States. Both of these guidelines recommend administration of the inactivated Influenza vaccine to egg-allergic individuals with no additional measures or cautions in place.

## **7. DISCUSSION**

This scoping review aimed to assess the body of evidence relating to the safety of inactivated influenza vaccines in adults and children suffering from allergy to hens eggs.

In general studies done in this area have all been prospective cohort studies or retrospective record reviews. Very limited information is available from randomised controlled trials. Most of the studies conducted have utilised locally available vaccinations known to have low quantities of ovalbumin (<1mcg/ml). Different studies have used differing definitions of egg-allergy, varying from reported history to allergy prick testing prior to receipt of the influenza vaccination.

There have been no reports of anaphylaxis in egg-allergic patients in any of the studies, although other less serious reactions were documented. Because of the study designs it is not possible to gauge whether reactions happened more frequently in the egg-allergic population than a non-egg-allergic group (no comparator arm in most of the studies).

It must be recognised that anaphylactic reactions are a rare occurrence in all vaccination administrations, and the sample sizes in the observational studies may have been insufficient to identify the rare adverse event. When expanded to a large real-world vaccination population, these events may occur. Immunisation centres should be sufficiently equipped to manage an anaphylactic reaction should this occur.

The levels of evidence seem to have been sufficient to convince guideline groups that contra-indications and even additional cautions around egg allergic individuals receiving the inactivated influenza vaccines are not warranted, and several international guidelines recommend vaccination of individuals with reported egg allergies. The guidelines in the United Kingdom are the exception, specifically tailoring their recommendations for safe use to those vaccines with a low ovalbumin content (<1.2 mcg/ml).

Most of the guidelines recommend that any vaccination centres are adequately equipped to manage anaphylaxis and other vaccine reactions, as these may occur, although rarely, in relation to any vaccine component.

## **8. CONCLUSION**

Inactivated influenza vaccine safety has been evaluated in several cohort studies, which have indicated overall safety in egg-allergic patients. A caveat may be ovalbumin concentration in administered egg-derived vaccines, and it may be necessary to ensure that local vaccines contents are as low as those used in the studies, prior to adapting any general advice about the administration of the vaccines to egg-allergic individuals. Generally international guidelines

from both public health institutions and immunology societies have accepted the levels of evidence as strong enough to recommend the inactivated egg-derived influenza vaccinations can be safely administered to egg-allergic individuals.

The most cautious guidance recommends that patients with severe allergy histories should be referred to specialist centres for vaccination, or vaccinated in an environment assured to be able to manage a severe allergic reaction, and that patients should be observed for a reasonable time post-vaccination.

Version	Date	Reviewer(s)	Recommendation and Rationale
1	May 2023	SM	There is a large amount of evidence that the influenza vaccine can be given to patients with a history of egg allergy. The evidence is reasonably strong and the reduced amounts of ovalbumin in influenza vaccines has contributed to the safety of these vaccines in egg allergic patients. However, studies do have different definitions of egg allergy, and generally report on anaphylaxis as the primary end-point, with little emphasis on other reactions.

### **NEMLC RECOMMENDATION 20 July 2023:**

NEMLC accepted the Primary Health Care and Adult Hospital Level Expert Committee Recommendation and Rationale.

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## APPENDIX 1: SEARCH STRATEGY

**Database: PubMed**

Date: 18 May 2023

Table 1: Search Strategy

Search	Query	Results
Influenza vaccine and egg allergy	(influenza vaccine) AND (egg allergy)	N = 121

**APPENDIX 2: SUMMARY OF STUDIES INCLUDED**

**TABLE 2. DETAILS FROM RANDOMISED CONTROLLED TRIALS**

Author (year); Title	Population	Sample size	Methodology	Intervention & Comparator	Outcomes & Key Findings
<p>Greenhawt MJ, et al<sup>18</sup></p> <p>Safe administration of the seasonal trivalent influenza vaccine (TIV) to children with severe egg allergy. <i>Ann Allergy Asthma Immunol.</i> 2012 Dec;109(6):426-30.</p>	<p>Included a history of a severe reaction, including anaphylaxis, to the ingestion of egg and a positive skin test result or evidence of serum specific IgE antibody to egg.</p>	<p>N=31 were prospectively evaluated in the randomized controlled trial (group A, single dose 14; group B graded challenge, 17); 45.1% had a history of anaphylaxis after egg ingestion. N= 112 were retrospectively evaluated (n=87 with the single dose and n=25 with the split dose); 77.6% of participants had a history of anaphylaxis after egg ingestion.</p>	<p>Phase 1 consisted of a randomized, prospective, double-blind, placebo-controlled trial of TIV administration to egg allergic children, using a 2-step approach;</p> <p>Phase 2 was a retrospective analysis of single dose vs split-dose administration of TIV in eligible study participants who declined participation in the randomized controlled trial.</p>	<p>Group A received 0.1 mL of influenza vaccine, followed in 30 minutes if no reaction with the remainder of an age-appropriate dose, whereas group B received an injection of normal saline followed in 30 minutes if no reaction with the full 100% of the age-appropriate dose.</p>	<p>Primary Outcome Measures was Categorical Reactivity to Vaccine as it Was Administered [ Time Frame: 48 hours</p> <p>]All participants (143) in both phases received TIV without developing an allergic reaction. In the Phase 1 prospective group there were no systemic reactions (n=31) although mild, transient, induration at injection site occurred in 3 patients in group A and 4 patients in group B.</p>

**TABLE 3. DETAILS FROM OBSERVATIONAL STUDIES**

Author (year); Title	Population	Sample size	Methodology	Intervention & Comparator	Outcomes & Key Findings
Gagnon et al 2010 <sup>15</sup>  Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine  J Allergy Clin Immunol. 2010 Aug;126(2):317-23	IgE-mediated egg allergy was defined as a minimum of 1 sign or symptom occurring within 60 minutes of egg ingestion and confirmation of sensitization to eggs.	N = 830 Egg allergic children	Prospective observational study included patients with confirmed egg allergy and a group of control subjects without egg allergy of the same age	Monovalent H1N1 Inactivated Influenza vaccination	Primary outcome was the occurrence of an anaphylactic reaction according to the criteria of the Brighton Collaboration. The Brighton Collaboration criteria for anaphylaxis require the sudden onset and rapid progression of signs and symptoms involving more than 1 system.  None of the patients with confirmed egg allergy had anaphylaxis (risk, 0/830; 95% CI, 0% to 0.4%).
Siret-Alatrasta A, et al 2011 <sup>16</sup>  The 2009-2010 H1N1 vaccination campaign for patients with egg allergy in a region of France.  Allergy. 2011 Feb;66(2):298-9	Subjects aged 8 months to 76 years (median 5 years) having either initiated egg avoidance because of positive skin prick tests (39, 37.5%) or because of egg allergy after egg ingestion (40, 38.5%)	N= 107 (72 had positive skin and +ve IGE; 35 had positive skin test but negative IGE)	Prospective Observational study	Monovalent H1N1 Inactivated Influenza vaccination. Subjects with a positive skin test received the single dose in two divided doses 30 minutes apart	No primary outcome of interest was specified in the manuscript. All patients tolerated the vaccination in a simple or double-dose protocol without any significant allergic reaction in this series.
Des Roches A, et al <sup>17</sup>  Egg-allergic patients can be safely vaccinated against influenza. J Allergy Clin Immunol. 2012 Nov;130(5):1213-1216.e1.	Children over the age of 2 years with egg allergy. Egg allergy defined as a history of at least 1 sign or symptom of allergy (cutaneous, ocular, respiratory, gastrointestinal, or cardiovascular symptoms) occurring within 60 minutes of egg ingestion, and the confirmation of persistent sensitization to egg (within 6 months of vaccination) shown by a skin prick test response to egg at least 3 mm larger than that of the saline control within 10 to 15 minutes, or an egg-specific IgE level of 0.35 kU/L	367 patients among whom 132 (153 doses) had a history of severe allergy to egg	Prospective observational cohort study	Trivalent inactivated influenza vaccine	Primary outcome was the occurrence of anaphylaxis according to the Brighton Collaboration definition.  No cases of anaphylaxis.  n=4 patients reported mild allergic-like symptoms after previous influenza vaccination (1 urticaria, 2 vomiting, and 1 eczema).

	or more (UniCAP, Pharmacia)				
Webb L, et al. <sup>19</sup> Single-dose influenza vaccination of patients with egg allergy in a multicenter study. <i>J Allergy Clin Immunol.</i> 2011 Jul;128(1):218-9.	Thirty-four (22%) of the 152 patients had a convincing history of anaphylaxis to egg involving a drop in blood pressure or a combination of respiratory compromise, skin involvement, or prolonged gastrointestinal symptoms Eighty-seven (57%) patients had a history of immediate-type allergic reaction to egg affecting the skin or gastrointestinal system alone.	N = 152	Retrospective review of the safety of seasonal and H1N1 influenza vaccinations in patients with egg allergy at 4 university-based allergy and immunology clinics during the 2009 to 2010 influenza season		There were no systemic reactions in any of the patients undergoing vaccination, including those with severe egg allergy.
Upton JE, et al. <sup>20</sup> No systemic reactions to influenza vaccination in egg-sensitized tertiary-care pediatric patients. <i>Allergy Asthma Clin Immunol.</i> 2012 Mar 2;8(1):2.	Patients above 0 years old. N= 77; Egg allergy was confirmed with skin testing.	N = 77	Prospective Cohort study	Adjuvunated 2009 H1N1 influenza A vaccine with < 0.165 mcg/ml ovalbumin.	All patients administered the vaccine tolerated it with no systemic adverse event. No patient had any significant reaction to the vaccine.
Forsdahl BA. <sup>21</sup> Reactions of Norwegian children with severe egg allergy to an egg-containing influenza A (H1N1) vaccine: a retrospective audit. <i>BMJ Open.</i> 2012 Jan 5;2(1):e000186.	Paediatric patients diagnosed with sensitisation to egg demonstrated by a positive SPT or positive serum specific IgE (SSiGE)-mediated egg allergy.	N = 80	Retrospective audit	Monovalent influenza A (H1N1) vaccine that had an ovalbumin content <0.33 µg/ml.	Of the 80 patients enrolled in the programme, only four displayed symptoms shortly after vaccination. There were no systemic reactions within the egg-allergic group
Schuler JE, et al. <sup>22</sup> Administration of the adjuvanted pH1N1 vaccine in egg-allergic children at high risk for influenza A/H1N1 disease. <i>Can J</i>	Patients were considered at high risk for egg allergy on the basis of their clinical history along with a positive skin prick test and/or	N= 62	Prospective observational cohort study	H1N1 vaccine containing less than 165 ng/mL (0.165 mcg/mL)	Of the 62 children receiving the first pH1N1 vaccine dose, there were no reactions following the test dose. When given the remaining dose, two children developed hives and were treated with Benadryl and one patient developed a vasovagal response requiring symptomatic management.

Public Health. 2011 May-Jun;102(3):196-9.	a positive serum egg IgE antibody level as documented by an allergist				
Tozandehjani S, Nasiri Kalmarzi R, Khodabandehloo M, Kashefi H. <sup>23</sup> Safety of Inactivated Influenza Vaccine in Patients with Egg Allergy in Kurdistan Province, Iran. Iran J Public Health. 2019 Apr;48(4):758-763.		N=635 with egg allergy (cases) and N=241 without egg allergy (controls)	Case-control study	Seasonal trivalent inactivated influenza vaccine (IIV3), subunit vaccine (INFULVAC, Abbott Biologicals, Netherlands)	<ul style="list-style-type: none"> <li>• No anaphylactic reactions or shocks were seen after administration of seasonal injectable inactivated influenza vaccine in both groups.</li> <li>• However, there were some minor reactions to the vaccine. 63 out of 635 patients with egg allergy (cases) had local reactions (redness of skin) to the vaccine.</li> <li>• There were no local reactions to the vaccine in patients without egg allergy (controls).</li> <li>• Difference of the local reactions between case and control groups was statistically significant (P=0.001).</li> </ul>
Fung I, Spergel JM. <sup>24</sup> Administration of influenza vaccine to pediatric patients with egg-induced anaphylaxis. J Allergy Clin Immunol. 2012 Apr;129(4):1157-9. doi: 10.1016/j.jaci.2011.11.038. Epub 2012 Jan 10. PMID: 22236726.		In total, 119 vaccinations were performed on n=56 patients with egg-induced anaphylaxis	Retrospective review of patients who received influenza vaccination at the Children's Hospital of Philadelphia allergy clinics between 2007 and 2009.	Seasonal trivalent inactivated influenza vaccine (H1N1 vaccinations specifically excluded)	<ul style="list-style-type: none"> <li>• In 119 vaccinations there were 3 cases of skin-limited reactions and no systemic reactions.</li> </ul>

**APPENDIX 3: TABLE 2. DETAILS FROM GUIDELINES / RECOMMENDATIONS IDENTIFIED**

Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
Vaccines against influenza: WHO position paper No 19, 2022, 97, 185–208 May 2022	World Health Organisation	Although there have been concerns that egg-based IIV could trigger anaphylaxis in people who are allergic to eggs, such reactions have not been documented. Rates of anaphylaxis after IIV are within the expected range of 0.2–1.5 cases per million doses and individuals with egg allergy are not more likely than others to have anaphylaxis.	No strength given	
Leech, SC, Ewan, PW, Skypala, IJ, et al. BSACI 2021 guideline for the management of egg allergy. Clin Exp Allergy. 2021; 51: 1262– 1278. <a href="https://doi.org/10.1111/cea.14009">https://doi.org/10.1111/cea.14009</a>	British Society for Allergy and Clinical Immunology (Great Britain)	Children with egg allergy can receive the nasal live attenuated influenza vaccine (LAIV) and most children and adults can receive the intramuscular influenza vaccine in primary care, unless they have had anaphylaxis to egg requiring admission to intensive care.	(Grade of recommendation = B).	Few study references – referral to the British Green Book on vaccination
Influenza: the green book, chapter 19 Influenza immunisation information including updates for public health professionals.	UK Health Security Agency	In all settings providing vaccination, facilities should be available and staff trained to recognise and treat anaphylaxis. Inactivated influenza vaccines that are egg-free or have a very low ovalbumin content (<0.12 micrograms/ml - equivalent to <0.06 micrograms for a 0.5 ml dose) are available and studies show they may be used safely in individuals with egg allergy (des Roches et al., 2012) JCVI has advised that egg-allergic children aged less than 2 years can be offered the quadrivalent inactivated egg-free vaccine, QIVc	No strength provided	Refer to the Des Roches study for this recommendation.
Grohskopf LA, Blanton LH, Ferdinands JM, et al. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season. MMWR Recomm Rep	United States Advisory Committee on Immunization practices	Persons with a history of egg allergy who have experienced only urticaria (hives) after exposure to egg should receive influenza vaccine. Any	No strength provided	

Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
<p>2022;71(No. RR-1):1–28. DOI: <a href="http://dx.doi.org/10.15585/mmwr.rr7101a1">http://dx.doi.org/10.15585/mmwr.rr7101a1</a></p>		<p>licensed, recommended influenza vaccine (i.e., any IIV4, RIV4, or LAIV4) that is otherwise appropriate for the recipient’s age and health status can be used.</p> <p>Persons who report having had reactions to egg involving symptoms other than urticaria (e.g., angioedema or swelling, respiratory distress, light-headedness, or recurrent vomiting) or who required epinephrine or another emergency medical intervention can similarly receive any licensed, recommended influenza vaccine (i.e., any IIV4, RIV4, or LAIV4) that is otherwise appropriate for their age and health status. If a vaccine other than cIIIV4 or RIV4 is used, the selected vaccine should be administered in an inpatient or outpatient medical setting, including but not necessarily limited to hospitals, clinics, health departments, and physician offices. Vaccine administration should be supervised by a health care provider who is able to recognize and manage severe allergic reactions.</p>		
<p>Greenhawt M, Turner PJ, Kelso JM Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017. SO Ann Allergy Asthma Immunol. 2018;120(1):49.</p>	<p>American College of Allergy, Asthma &amp; Immunology</p>	<p><b>Summary Statement 1:</b> Influenza vaccines should be administered to individuals with egg allergy of any severity, just as they would be to individuals without egg allergy.</p> <p><b>Summary Statement 2:</b> No special precautions beyond those recommended for the administration of any vaccine to any patient are necessary for administration of influenza vaccine to egg allergic individuals.</p>	<p>Strength of recommendation: strong. Evidence level: A/B.</p> <p>Strength of recommendation: strong. Evidence level: A/B.</p>	<p>References most of the clinical trials which were included in this scoping review as the evidence for the safety of the vaccines in egg-allergic individuals.</p>



Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
		<p><b>Summary Statement 3:</b> Use of non-egg-based influenza vaccines (ccIV3, RIV3, or RIV4) in egg allergic individuals in the age groups for which they are approved is acceptable but not medically necessary or preferred.</p> <p><b>Summary Statement 4:</b> Live attenuated influenza vaccine (LAIV) may be administered to patients with egg allergy of any severity in the age group for which it is approved (ages 2–49 years), in particular, countries and seasons when LAIV is recommended as an agent (based on effectiveness in prior seasons).</p>	<p>Strength of recommendation: moderate. Evidence level: C/D.</p> <p>Strength of recommendation: strong. Evidence level: A/B.</p>	
<p>National Advisory Committee on Immunization (NACI): Canadian immunization guide chapter on influenza and statement on seasonal influenza vaccine for 2022-2023 (2022)</p> <p><a href="https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2022-2023.html">https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2022-2023.html</a></p>	<p>National Advisory Committee on Immunization (NACI) - Canada</p>	<p>Egg allergy is not a contraindication for influenza vaccination, as there is a low risk of adverse events (AEs) associated with the trace amounts of ovalbumin allowed in some influenza vaccines manufactured using eggs. Egg-allergic individuals may be vaccinated against influenza using any age-appropriate product, including LAIV, without prior influenza vaccine skin test and with the full dose, irrespective of a past severe reaction to egg, and in any setting where vaccines are routinely administered. The IIV4-cc and RIV4 are completely egg-free (ovalbumin-free).</p> <p>As with any vaccine product, vaccine providers should be prepared for managing possible allergic reactions including anaphylaxis, and have the necessary equipment to respond to a vaccine emergency at all times.</p>	<p>No strength of evidence provided</p>	<p>The recommendation is based on the fact that the amount of trace ovalbumin allowed in influenza vaccines that are authorized for use in Canada is associated with a low risk of AE, and in addition, two of the authorized products do not contain any ovalbumin.</p>

Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
<p>Australian Technical Advisory Group on Immunisation (ATAGI): The Australian Immunisation Handbook – Influenza (flu)</p> <p><a href="https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/influenza-flu">https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/influenza-flu</a></p>	<p>Australian Technical Advisory Group on Immunisation (ATAGI)</p>	<p>None of the available influenza vaccines contain &gt;1 µg of ovalbumin.</p> <p>People with egg allergy, including a history of anaphylaxis, can be safely vaccinated with any influenza vaccines (including egg-based and cell-based vaccines) unless they have reported a serious adverse reaction to influenza vaccines.</p> <p>People with a history of anaphylaxis to egg should: receive a full age-appropriate vaccine dose; do not split the dose into multiple injections (for example, a test and then the rest of the dose) 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.</p> <p>Several published reviews, guidelines and reports suggest a very low risk of anaphylaxis associated with influenza vaccination of egg-allergic people. A 2012 review of published studies included 4172 egg-allergic patients. 513 of these patients reported a history of severe allergic reaction to egg. The review found no cases of anaphylaxis after receiving an inactivated influenza vaccine. The largest study in the review included 830 egg-allergic patients. 164 of these patients reported a history of severe allergic reaction to egg. Only 17 (2%) of these patients</p>	<p>No evidence strength provided – simply a narrative of some of the studies in this review which have shown no risk of anaphylaxis in egg-allergic individuals following vaccination with egg-derived vaccines.</p>	

Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
		<p>experienced any adverse event. All adverse events were mild, and included abdominal pain, hives and respiratory symptoms such as wheezing.</p> <p>People with a history of egg allergy (non-anaphylaxis) can receive an age-appropriate full dose of vaccine in any immunisation setting. This includes sensitised children (that is, children who are skin-prick or RAST-test positive) who have not yet eaten egg.</p>		
<p>ASCIA Guidelines - Influenza vaccination of the egg allergic individual.  <a href="https://www.allergy.org.au/hp/papers/vaccination-of-the-egg-allergic-individual">https://www.allergy.org.au/hp/papers/vaccination-of-the-egg-allergic-individual</a></p>	<p>Australasian Society of Clinical immunology and Allergy</p>	<p>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.</p> <p>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.</p> <p>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 suspected anaphylaxis following administration of the influenza vaccine itself,</p>	<p>No strength of evidence provided for the recommendations</p>	<p>The guidelines note that they vary from the product PI:</p> <p>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.</p>

Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
		<p>further vaccination should be avoided without specialist allergy assessment.</p> <p>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.</p>		
<p>Chua GT, Li PH, Ho MH, Lai E, Ngai V, Yau FY, Kwan MY, Leung TF, Lee TH. Hong Kong Institute of Allergy and Hong Kong Society for Paediatric Immunology Allergy &amp; Infectious Diseases joint consensus statement 2018 on vaccination in egg-allergic patients. Hong Kong Med J. 2018 Oct;24(5):527-531.</p>	<p>Hong Kong Institute of Allergy and Hong Kong Society for Paediatric Immunology Allergy &amp; Infectious Diseases</p>	<p>As the quantity of ovalbumin in influenza vaccines is <math>\leq 1 \mu\text{g}/\text{dose}</math>, such a level of egg protein in influenza vaccines is very unlikely to trigger an allergic response in this group of patients. Thus, despite the product information recommendations and the trace amounts of ovalbumin present in these influenza vaccines, they should be safe for egg-allergic individuals, including those with a history of anaphylaxis to egg proteins.</p> <p>Influenza vaccines can be safely administered, and are recommended, for disease prevention in egg-allergic individuals. They are recommended to be administered in an out-patient or ambulatory setting. Only those patients who have previously required admission to an intensive care unit for severe anaphylaxis to egg should be referred to an allergist for further evaluation prior to influenza vaccination.</p>	<p>No level of evidence provided</p>	<p>Guideline acknowledges that the recommendation is at odds with the Product information provided by manufacturers</p>
<p>Kassianos G, Blank P, Falup-Pecurariu O, Kuchar E, Kyncl J, Ortiz De Lejarazu R, Nitsch-Osuch A, Van Essen GA. Influenza</p>	<p>This document has been written by a</p>	<p>Severe egg allergy (only for egg-containing vaccines). Note that</p>	<p>No level of evidence provided</p>	

Guideline source / title	Entity	Recommendation	Strength of recommendation	Notes
<p>vaccination: key facts for general practitioners in Europe—a synthesis by European experts based on national guidelines and best practices in the United Kingdom and the Netherlands. <i>Drugs in Context</i> 2016; 5: 212293.</p>	<p>group of European experts, with financial support from Sanofi Pasteur and Sanofi Pasteur MSD for medical writing, meeting costs, and layout</p>	<p>vaccines that contain only low levels or no egg protein (with an ovalbumin content &lt;0.12 µg/mL, i.e., &lt;0.06 µg for a 0.5 mL dose) may be administered to individuals with mild to moderate sensitivity to egg protein at the discretion of the physician following a risk–benefit assessment. Patients with severe allergy should ideally be referred to specialist centres for vaccination in accordance with existing national recommendations in the prescribing country and should be observed for a reasonable time post-vaccination</p>		

### APPENDIX 3: AGREE II APPRAISAL

Using an approach used in Mc Allister *et al.* Advancing guideline quality through country-wide and regional appraisal of CPGs: a scoping review, 22 September 2022, PREPRINT (Version 1) available at Research Square [<https://doi.org/10.21203/rs.3.rs-1850020/v1>], the domains for the Quality of Clinical Practice Guidelines were ranked as follows: Low quality: RED < 40%; Moderate quality: YELLOW 40%-59%, High quality: GREEN ≥ 60%.

No	Guideline	Scope and purpose Domain 1	Stakeholder involvement Domain 2	Rigour of development Domain 3	Clarity of presentation Domain 4	Applicability Domain 5	Editorial independence Domain 6	Overall Assessment Score
1	Influenza vaccination: key facts for general practitioners in Europe—a synthesis by European experts based on national guidelines and best practices in the United Kingdom and the Netherlands	76%	55%	31%	79%	68%	64%	67%
2	Hong Kong Institute of Allergy and Hong Kong Society for Paediatric Immunology Allergy & Infectious Diseases joint consensus statement 2018 on vaccination in egg-allergic patients	74%	55%	32%	74%	32%	96%	58%
3	ASCIA Guidelines - Influenza vaccination of the egg allergic individual	71%	19%	33%	74%	34%	36%	50%
4	Australian Technical Advisory Group on Immunisation (ATAGI): The Australian Immunisation Handbook – Influenza (flu)	79%	79%	78%	88%	63%	61%	83%
5	National Advisory Committee on Immunization (NACI): Canadian immunization guide chapter on influenza and statement on seasonal influenza vaccine for 2022-2023 (2022)	81%	69%	71%	81%	43%	68%	83%
6	Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017	88%	50%	60%	76%	36%	75%	67%
7	Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices – United States, 2022–23 Influenza Season	79%	60%	67%	74%	45%	57%	75%
8	Influenza: the green book, chapter 19 Influenza immunisation information including updates for public health professionals	48%	38%	36%	69%	46%	57%	50%

No	Guideline	Scope and purpose Domain 1	Stakeholder involvement Domain 2	Rigour of development Domain 3	Clarity of presentation Domain 4	Applicability Domain 5	Editorial independence Domain 6	Overall Assessment Score
9	BSACI 2021 guideline for the management of egg allergy	76%	67%	76%	86%	41%	21%	67%
10	Vaccines against influenza: WHO position paper No 19, 2022, 97, 185–208 May 2022	81%	79%	81%	83%	79%	57%	92%

#### Assessment of Timeliness and Credibility of Guidelines

No	Guideline	Timeliness	Credibility	Use of GRADE	Overall Assessment Score
1	Influenza vaccination: key facts for general practitioners in Europe—a synthesis by European experts based on national guidelines and best practices in the United Kingdom and the Netherlands	1	3	1	5
2	Hong Kong Institute of Allergy and Hong Kong Society for Paediatric Immunology Allergy & Infectious Diseases joint consensus statement 2018 on vaccination in egg-allergic patients	1	3	1	5
3	ASCIA Guidelines - Influenza vaccination of the egg allergic individual	3	3	1	7
4	Australian Technical Advisory Group on Immunisation (ATAGI): The Australian Immunisation Handbook – Influenza (flu)	3	5	2	10
5	National Advisory Committee on Immunization (NACI): Canadian immunization guide chapter on influenza and statement on seasonal influenza vaccine for 2022-2023 (2022)	3	3	2	8
6	Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017	1	3	2	6
7	Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022–23 Influenza Season	3	3	3	9

No	Guideline	Timeliness	Credibility	Use of GRADE	Overall Assessment Score
8	Influenza: the green book, chapter 19 Influenza immunisation information including updates for public health professionals	3	1	1	5
9	BSACI 2021 guideline for the management of egg allergy	3	3	2	8
10	Vaccines against influenza: WHO position paper No 19, 2022, 97, 185–208 May 2022	3	3	2	8

### Key to Scoring:

#### Timeliness (CPG level)

- Guideline is out-of-date and likely to miss important recent evidence 1
- Guideline is recent and unlikely to miss recent important evidence 3

#### Credibility (CPG level)

- Guideline is not credible (e.g., < 60% overall for Domain 1, 3 and 6) 1
- Guideline is credible but has significant limitations (e.g., > 60% in either D1, D3 or D6) 3
- Guideline is credible (e.g., high overall scores across domains) 5

#### Use of GRADE (CPG Level)

- Does not use/report GRADE or GRADE EtD 1
- Guidelines uses GRADE 2
- Guidelines reported GRADE EtD tables 3