Re-assessing reactions to influenza vaccination initially classified as vaccine allergies

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Although rare, vaccine-associated hypersensitivity reactions classified as allergies can hamper vaccination programs. As it can be difficult to distinguish influenza vaccine-associated anaphylaxis — estimated by one American study to affect 1.35 people per one million doses[1] — from the much more numerous immunisation stress-related responses[2] — affecting 4–7% of influenza vaccine recipients[3] — the latter may be misdiagnosed as allergies.

We therefore reviewed the clinical records of all adults (18 years or older) with diagnoses of influenza vaccine allergies who attended the Monash Health adult vaccine allergy service during 1 April 2017 – 31 August 2021. The Monash Health Human Research Ethics Committee approved the study as a quality and service improvement activity (QA/66280).

An allergist assessed each participant before challenge with influenza vaccine (depending on current availability: Afluria Quad or Fluad Quad [Sequirus] or Vaxigrip Tetra [Sanofi]). Vaccine allergy centres typically prefer split dose challenges; that is, administering 10% of the vaccine dose and observing the patient for an hour before administering the remaining 90%.[4] Our clinic undertook full dose challenges unless the allergist noted objective signs consistent with anaphylaxis in the record of the index reaction, such as visualised hives or urticaria, hypoxia, or hypotension. Intradermal testing was not offered because it is unreliable.[5] The vaccine brand associated with the index reaction was often unknown; in such cases, the person was invited for challenges in successive years with different brands, to control for differences in excipients. We assessed index reactions and challenge responses with the Brighton criteria, a non-clinical research tool for assessing the likelihood of anaphylaxis in vaccinations.[6]

1 Demographic characterstics of the 49 people with diagnoses of influenza vaccine allergies referred to the Monash Health adult vaccine allergy service, 1 April 2017 – 31 August 2021

Characteristic	All participants
Sex (women)	43 (88%)
Age at initial reaction (years), median (range)	47 (8–76)
Age at clinic presentation (years), median (range)	53 (19–77)
Time from reaction to clinic presentation (years), median (IQR)	3 (9)
Age group (years)	
Under 65	38 (78%)
65 or older	11 (22%)
Health care workers	20 (41%)
History of atopic disease*	20 (41%)

IQR = interquartile range. * Asthma, eczema, allergic rhinitis, or anaphylaxis to another allergen. ◆

2 Index reactions to influenza vaccine and challenge outcomes* for 49 adults with diagnoses of influenza vaccine allergies

Characteristic	Number
Index reaction	
Brighton anaphylaxis criteria[6]	
Level 1	1 (2%)
Level 2	6 (12%)
Level 3	0
Criteria not met	42 (86%)
Index reaction: symptoms†	
Respiratory, minor	24 (49%)
Respiratory, major	4 (8%)
Dermatological, minor	19 (39%)
Dermatological, major	15 (31%)
Gastrointestinal	4 (8%)
Cardiac, minor	1 (2%)
Cardiac, major	1 (2%)
Challenge reaction	
Split dose challenges	10 (20%)
Symptoms	5 [50%]
Full dose challenges	39 (80%)
Symptoms	15 [38%]
Symptoms (split and full dose)	20 (41%)
Pruritus	8 (16%)
Sensation in throat or dyspnoea	7 (14%)
Rash or generalised flushing	6 (12%)
Localised tingling	4 (8%)
Gastrointestinal symptoms	3 (6%)
Anaphylaxis	0

* For the first influenza vaccine challenge. † Nineteen patients had multiple symptoms during the index reaction. ◆

The index reactions of seven of the 49 participants (including 43 women; Box 1) met the Brighton criteria for anaphylaxis; the most frequent symptoms were dermatologic (70%) or respiratory reactions (57%). Following split dose (ten participants) or full dose challenges (39 participants), 20 people had symptoms consistent with immunisation stress-related responses, but none met the Brighton criteria for anaphylaxis (Box 2). Thirteen of the

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twenty were de-labelled (ie, deemed safe for further influenza vaccinations) because their symptoms were mild; the other seven were also de-labelled after challenge with a different influenza vaccine the following year.

Conditions that mimic vaccine anaphylaxis are more common than anaphylaxis itself, and our findings suggest that influenza vaccine allergy may be over-diagnosed. Our preference for full dose challenges partially reflected our experience with recognising immunisation stress-related responses, but the outcomes suggest that they could be a safe, efficient alternative to split dose challenge testing.

Our study was limited by its small size, but our approach could be cautiously applied to assessing responses to other vaccines, including those for preventing coronavirus disease 19 (COVID-19). Another limitation was the long delay between index reactions and presentation to our clinic (mean, seven years; standard deviation, 10.6 years), and the index vaccine could often not be identified. However, the fact that none of our participants experienced reactions to two different vaccines administered a year apart (in each case one vaccine formulation included polysorbate 80), suggests that excipient-related reactions were unlikely.

Distinguishing between anaphylaxis and an acute stress response in acute health care is difficult, despite World Health Organization guidance.[2] We recommend that reactions be treated as allergic if clinically suspected, but also that the patient be promptly referred to an allergist for further assessment. It will probably be safe to de-label many patients because their reactions do not meet anaphylaxis criteria.

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Competing interests: Samar Ojaimi sat on the CSL Behring advisory board on secondary immunodeficiency in haematological malignancies (December 2019). Kymble Spriggs has served on the Seqirus advisory board for the allergen immunotherapy products Acarizax and Grazax. ■

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