



Safety of influenza vaccines

John M. Kelso

Purpose of review

To review recent publications on the safety of influenza vaccines [both the injectable, inactivated trivalent influenza vaccine (TIV) and the intranasal, live attenuated influenza vaccine (LAIV)] and new recommendations regarding their use.

Recent findings

Numerous studies have demonstrated that TIV can be safely administered to patients with egg allergy. Influenza vaccines are very unlikely to cause or exacerbate Guillain-Barré syndrome (GBS). TIV cannot cause asthma exacerbations, whereas there may be some slight risk that LAIV could do so. TIV is well tolerated by patients with immunocompromise. Some brands of influenza vaccine are not indicated for certain age groups due to lack of effectiveness or possible side effects.

Summary

TIV should be administered to patients with egg allergy with appropriate precautions. Influenza vaccines should be withheld from patients with a history of GBS only if the GBS began within 6 weeks of prior influenza immunization. TIV should be given to patients with asthma, but they should not receive LAIV. TIV should be given to immunocompromised patients, but they should not receive LAIV. Contacts of most immunocompromised patients can receive either TIV or LAIV. Age appropriate brands of influenza vaccine should be used.

Keywords

egg allergy, influenza vaccine, safety, side effects

INTRODUCTION

Each year in the United States, approximately 300 000 people are hospitalized due to influenza infection, including 20 000 children less than 5 years of age. More than 20 000 deaths occur annually as a result of the disease, including over 100 children [1]. Influenza vaccines are about 70% effective in preventing infection and can thus have a substantial impact on reducing this morbidity and mortality [2,3]. Routine annual influenza vaccination is recommended for all persons 6 months of age and older [4].

The overwhelming majority of patients receive influenza vaccines uneventfully. However, as with any vaccine, influenza vaccines can cause adverse reactions. There are two types of influenza vaccines approved for use in the United States, specifically the injectable, inactivated trivalent influenza vaccine (TIV) and the intranasal, live attenuated influenza vaccine (LAIV). For safety concerns that apply only to the live vaccine, the inactivated vaccine can often be substituted. The majority of patients who have suffered an adverse reaction to either influenza vaccine, or who have a preexisting medical condition that might increase the risk of

such a reaction, can nonetheless be safely vaccinated with appropriate precautions.

INFLUENZA VACCINE AND EGG ALLERGY

Both TIV and LAIV are grown in chicken eggs and contain residual amounts of egg protein (ovalbumin). In theory, administration of these vaccines to egg-allergic patients could result in systemic allergic reactions (anaphylaxis).

Do influenza vaccines cause systemic reactions when injected into egg-allergic patients?

Seven studies, including six just in the last 2 years, have been published involving more than 1600

Division of Allergy, Asthma and Immunology, Scripps Clinic, San Diego, California, USA

Correspondence to John M. Kelso, MD, Division of Allergy, Asthma and Immunology, Scripps Clinic, 3811 Valley Centre Drive, San Diego, CA 92130, USA. Tel: +1 858 764 9010; fax: +1 858 764 9011; e-mail: kelso.john@scrippshealth.org

Curr Opin Allergy Clin Immunol 2012, 12:383–388

DOI:10.1097/ACI.0b013e328354395d

KEY POINTS

- Trivalent influenza vaccine (TIV) should be administered to patients with egg allergy with appropriate precautions. If egg ingestion caused hives only, TIV can be given under observation in a primary care setting, whereas if egg ingestion caused other systemic allergic symptoms, TIV should be given in an allergist's office.
- Influenza vaccines should be withheld from patients with a history of Guillain-Barré syndrome (GBS) only if the GBS began within 6 weeks of prior influenza immunization.
- TIV should be given to patients with asthma, but they should not receive live attenuated influenza vaccine (LAIV).
- TIV should be given to immunocompromised patients, but they should not receive LAIV. Contacts of most immunocompromised patients can receive either TIV or LAIV.
- Age appropriate brands of influenza vaccine should be used.

egg-allergic patients who have received TIV without any serious reactions (no respiratory distress or hypotension), and with only a low rate of minor reactions (hives, mild wheezing) [5–11]. Further, some studies included control groups and demonstrated comparable rates of reactions among those with and without egg allergy [5,7,8,11]. Thus, if TIV causes systemic allergic reactions in egg-allergic recipients, the rate of such reactions is very low.

What about patients with severe egg allergy?

Most studies have specifically included patients with histories of severe anaphylaxis to egg ingestion [5,7,8,10,11]. Collectively 185 such patients have been immunized with TIV and these patients also tolerate the vaccine. So, even these patients do not appear to be at risk of serious reaction.

Does skin testing with the vaccine help predict a reaction?

In most studies in which skin testing with the vaccine was performed, either by prick or intradermal method, patients were vaccinated irrespective of their skin test results. Vaccinated skin test positive patients had no reactions, or no greater rate of reactions, than skin test negative patients [5,6,8,10,11]. The rate (low) of reactions (minor) is the same whether skin testing is included in the protocol or not [6]. So, vaccine skin test results do not predict vaccine reactions and are thus

unnecessary. Vaccine skin testing is appropriate in the evaluation of a patient who has had an apparent allergic reaction to influenza vaccination itself as opposed to egg ingestion [12[•]].

Does dividing the vaccine dose reduce the rate of reactions?

In some studies administering influenza vaccine to egg-allergic patients, 10% of the dose was given and the patient was observed for 30 min and, if they had no reaction, the remaining 90% of the dose was given with an additional 30 min of observation. As the vast majority of patients ultimately tolerate the 10–90%, most authors have concluded that the vaccine could have been administered as a single dose [5–11]. Studies wherein the vaccine has been administered as a single dose also report no serious reactions [7,8,10,11]. Thus, dividing the vaccine dose is not required.

Why are there no serious reactions being reported?

In those studies reporting the ovalbumin level, influenza vaccines administered to egg-allergic patients have contained as much as 0.7 mcg per 0.5 ml dose without serious reactions, so at least that much appears well tolerated [5,7–11]. Such data on 'safe' ovalbumin levels are based on analyzing content of vaccines used in various studies, not dose-response studies. Thus, it is not known what amount of ovalbumin per dose might be associated with a higher rate of reactions or more severe reactions. Three of the four manufacturers of TIV report the maximum amount of ovalbumin in the package insert and the other manufacturer will provide the information on request. The claimed amounts are all less than 1 mcg per 0.5 ml dose. When the amount of ovalbumin contained in the vaccines has been measured in independent laboratories, the actual amounts are typically much lower than the claimed amounts [13–15]. So the reason that the vaccine is tolerated in egg-allergic patients is likely that there is not enough ovalbumin in the vaccine to cause a reaction.

What about live attenuated influenza vaccine?

Although LAIV contains a low amount of ovalbumin, all published studies to date have evaluated TIV, and thus TIV rather than LAIV should be used for egg-allergic recipients. Also LAIV should not be used in children with asthma, which often coexists with egg allergy.

Changes to vaccine recommendations

The evidence outlined above has led the Centers for Disease Control and Prevention's (CDC) Advisory Committee on Immunization Practices (ACIP) [4] and the American Academy of Pediatrics' (AAP) Committee on Infectious Diseases ('Red Book' committee) [16] to revise recommendations on the administration of influenza vaccine to patients with egg allergy. These guidelines state that patients with egg allergy should receive TIV, but do so in a setting where anaphylaxis could be recognized and treated should it occur, and that such patients should be observed for 30 min after vaccination. If the reaction to the ingestion of eggs involves hives only, TIV can be administered in a primary care setting, whereas if the reaction to the ingestion of eggs involved respiratory or cardiovascular symptoms or recurrent emesis, these patients should be referred to an allergist for TIV administration.

INFLUENZA VACCINE AND GUILLAIN-BARRÉ SYNDROME

Some studies have suggested an association between influenza vaccination and GBS.

What does Guillain-Barré syndrome have to do with infection or vaccination?

Guillain-Barré syndrome is an acute inflammatory demyelinating polyradiculoneuropathy. It is often preceded by infection, most commonly with *Campylobacter jejuni*, but also with other infectious organisms including influenza [17,18]. The pathophysiology is thought to be autoimmune through molecular mimicry, whereby the immune response generated toward specific elements on the infectious agent also attack coincidentally similar elements on peripheral nerves [17]. GBS has also been temporally associated with receipt of various vaccinations, most commonly influenza vaccine [19].

What happened with the 'swine flu' vaccine in 1976?

In 1976, influenza A H1N1 virus isolates from Army recruits at Fort Dix New Jersey demonstrated similarity to the 'swine flu' virus that caused the 1918 pandemic, and public health authorities initiated a special mass immunization program in the United States [20]. However, an increased number of cases of GBS after vaccination were reported and, after more than 40 million people had been immunized, the program was discontinued. Epidemiologic studies estimated the risk to be one per 100 000 vaccines [21].

Has Guillain-Barré syndrome been associated with influenza vaccine in other years?

Because of the 1976 experience, influenza vaccination programs in subsequent years, including the special mass immunization program in 2009 against H1N1 'swine flu', have been carefully monitored for an association between vaccination and GBS. These studies have demonstrated either no association, or a risk in the order of one case per million vaccines [17,22]. In a report published in 2011, the Institute of Medicine stated that, except for the 1976 vaccine, epidemiologic studies 'generally report a null association', that the mechanistic evidence regarding the association is 'weak', and concluded that 'the evidence is inadequate to accept or reject a causal relationship between influenza vaccine and GBS' [23]. It should also be appreciated that influenza disease itself may also trigger GBS [18], and thus influenza immunization may well prevent some cases of GBS.

Can influenza vaccine be given to patients with a history of Guillain-Barré syndrome?

Nonetheless, because of the possible increased risk, however small, for GBS after influenza vaccination, and because GBS is recurrent in a small percentage of cases, persons who have had the onset of GBS within 6 weeks of influenza vaccination should avoid subsequent immunization with influenza vaccine [24]. However, for those with a history of GBS without a temporal association to influenza vaccine, the benefits of vaccination likely outweigh any risks [24].

INFLUENZA VACCINE IN PATIENTS WITH ASTHMA

Several studies have addressed the safety of both inactivated and live attenuated influenza vaccines in patients with asthma.

Can trivalent influenza vaccine safely be given to patients with asthma?

TIV contains killed virus or viral subunits and cannot cause influenza [24]. Further, the vaccine does not cause asthma exacerbations in children or adults with the disease [24,25].

Can live attenuated influenza vaccine safely be given to patients with asthma?

LAIV contains live attenuated virus that has been cold adapted. It can replicate in the cooler

temperature of the nose where it is administered, but cannot survive in the higher temperature of the lungs. The package insert for LAIV states that it 'should not be administered to any individuals with asthma or children less than 5 years of age with recurrent wheezing because of the potential for increased risk of wheezing postvaccination'; however the data supporting this potential risk are not very strong. In a study [26] wherein LAIV was administered to 9689 children, medical utilization was monitored for 42 days after vaccination. Sixteen/728 LAIV recipients' age 18–35 months had asthma events compared with two of 369 placebo recipients [RR 4.06 (1.29, 17.86)]. However, the asthma events were not clustered at any particular time point after vaccination and there was no increased risk when the diagnoses of wheezing and shortness of breath were included with asthma. There was also no increased risk among children with a previous diagnosis of asthma or in any other age group. In another study [27] wherein the vaccine was administered to over 11 000 children annually for 4 years, children age 18 months to 4 years had a higher risk for asthma events 15–42 days after vaccination only in the 1st year of vaccination that was just barely of statistical significance [RR 2.85 (1.01–8.03)]. However, even in this age group there was no increased risk for asthma events 0–14 days after vaccination or at any time point in other years. In both of these studies, the large number of comparisons made raises the possibility that these associations occurred by chance [27]. Other studies that have specifically administered the vaccine to children with asthma have not seen an increase in asthma events after vaccine administration [28,29]. The CDC states that 'although FDA licensure of LAIV excludes children aged 2–4 years with a history of asthma or recurrent wheezing, the precise risk, if any, of wheezing caused by LAIV among these children is unknown,' but nonetheless concludes that TIV, rather than LAIV, should be used for patients with asthma [24].

INFLUENZA VACCINE IN IMMUNOCOMPROMISED PATIENTS

The safety of influenza vaccines in patients with immune compromise has been evaluated in a number of studies.

Can trivalent influenza vaccine safely be given to immunocompromised patients?

Because TIV contains killed virus or viral subunits, it cannot replicate, and therefore cannot cause disease in immunocompromised recipients. Immunosuppression may dampen appropriate immune responses to the vaccine making it less effective,

although most such patients do achieve protective antibody titers and protection from disease [30–34]. Although there are anecdotal reports of transplant rejection after influenza vaccination, [35] influenza infection has also been associated with rejection [30,35] and most studies have not linked vaccination and rejection [24,30]. Although some studies have demonstrated a transient rise in HIV RNA in HIV-infected influenza vaccine recipients, there have been no adverse consequences of this reported [24,30] and the vaccine has demonstrated effectiveness in HIV-infected patients [36]. TIV is specifically recommended for patients who 'are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus)' [24].

Can live attenuated influenza vaccine safely be given to immunocompromised patients?

Because LAIV contains live attenuated virus that might be allowed to replicate and cause disease in immunocompromised patients, it should not be administered to such patients, although there are no reports of adverse outcome in immunocompromised patients inadvertently vaccinated with LAIV [37,38^{*}]. Healthcare providers and household contacts of patients who are so severely immunocompromised that they required a protected environment (such as a bone marrow transplant unit) should not receive LAIV due to the theoretical risk of transferring the virus to such patients. However, contacts of patients with a lesser degree of immunosuppression (such as with HIV infection or on chemotherapy) can receive LAIV [24].

AGE APPROPRIATE INFLUENZA VACCINES

Each of the influenza vaccines approved for use in the United States has a specific age range for approval.

Is it necessary to choose a particular influenza vaccine for a particular age group?

In some cases the vaccine is not approved for a given age group simply because it has not been studied in that age group. In other cases it is not approved for a specific age group because it was not demonstrated to be effective or demonstrated decreased immune responsiveness in the age group. One vaccine was also associated with an increased risk of febrile seizures in a certain age group [39]. Thus, an age appropriate vaccine (Table 1) should always be administered.

Table 1. Choice of influenza vaccines by age group, 2011±2012 season

Manufacturer/brand	CSL biotherapies	GlaxoSmith Kline	ID biomedical	MedImmune	Novartis	Sanofi Pasteur		
Age	Afluria	Fluarix	FluLaval	FluMist	Fluvirin	Fluzone	Fluzone high-dose	Fluzone intradermal
< 6 months	Influenza vaccine not recommend							
6 months - 23 months	Increased risk of febrile seizures	Decreased immune response	Not studied	Increased wheezing	Decreased immune response	Approved	Not studied	Not studied
24 months - 35 months		Approved (if no asthma)						
36 - 47 months								
4 years - 8 years								
9 years - 17 years	Approved	Approved	Approved	Not effective	Approved	Approved	Approved	Not studied
18 years - 49 years								
50 years - 64 years								
≥ 65 years								

CONCLUSION

TIV should be administered to patients with egg allergy with appropriate precautions. Influenza vaccines should be withheld from patients with a history of GBS only if the GBS began within 6 weeks of prior influenza immunization. TIV should be given to patients with asthma, but they should not receive LAIV. TIV should be given to immunocompromised patients, but they should not receive LAIV. Contacts of most immunocompromised patients can receive either TIV or LAIV. Age appropriate brands of influenza vaccine should be used.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 442).

- Estimates of deaths associated with seasonal influenza: United States, 1976–2007. *MMWR Morb Mortal Wkly Rep* 2010; 59:1057–1062.
- Monto AS, Ohmit SE, Petrie JG, *et al.* Comparative efficacy of inactivated and live attenuated influenza vaccines. *N Engl J Med* 2009; 361:1260–1267.
- Fiore AE, Uyeki TM, Broder K, *et al.* Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2010; 59:1–62.

The most recent comprehensive review of ACIP recommendations on the administration of influenza vaccines.

- Prevention and Control of Influenza with Vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2011. *MMWR Morb Mortal Wkly Rep* 2011; 60:1128–1132.

The most recent ACIP recommendations on the administration of influenza vaccine to patients with egg allergy.

- James JM, Zeiger RS, Lester MR, *et al.* Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998; 133:624–628.
- Chung EY, Huang L, Schneider L. Safety of influenza vaccine administration in egg-allergic patients. *Pediatrics* 2010; 125:e1024–e1030.
- Gagnon R, Primeau MN, Des Roches A, *et al.* Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol* 2010; 126:317–323.
- Greenhawt MJ, Chernin AS, Howe L, *et al.* The safety of the H1N1 influenza A vaccine in egg allergic individuals. *Ann Allergy Asthma Immunol* 2010; 105:387–393.
- Owens G, Macginnitie A. Higher-ovalbumin-content influenza vaccines are well tolerated in children with egg allergy. *J Allergy Clin Immunol* 2011; 127:264–265.
- Webb L, Petersen M, Boden S, *et al.* Single-dose influenza vaccination of patients with egg allergy in a multicenter study. *J Allergy Clin Immunol* 2011; 128:218–219.
- Howe LE, Conlon AS, Greenhawt MJ, Sanders GM. Safe administration of seasonal influenza vaccine to children with egg allergy of all severities. *Ann Allergy Asthma Immunol* 2011; 106:446–447.
- Kelso JM, Li JT, Nicklas RA, *et al.* Adverse reactions to vaccines. *Ann Allergy Asthma Immunol* 2009; 103:S1–S14.

The most recent practice parameter on adverse reactions to all vaccines.

- Waibel KH, Gomez R. Ovalbumin content in 2009 to 2010 seasonal and H1N1 monovalent influenza vaccines. *J Allergy Clin Immunol* 2010; 125:749–751; 51 e1.
- Li JT, Rank MA, Squillace DL, Kita H. Ovalbumin content of influenza vaccines. *J Allergy Clin Immunol* 2010; 125:1412–1413.
- McKinney KK, Webb L, Petersen M, *et al.* Ovalbumin content of 2010–2011 influenza vaccines. *J Allergy Clin Immunol* 2011; 127:1629–1632.
- Recommendations for prevention and control of influenza in children, 2011–2012. *Pediatrics* 2011; 128:813–825.

The most recent AAP recommendations on the administration of influenza vaccine, including to patients with egg allergy.

- Lehmann HC, Hartung HP, Kieseier BC, Hughes RA. Guillain-Barre syndrome after exposure to influenza virus. *Lancet Infect Dis* 2010; 10:643–651.
- Sivadon-Tardy V, Orlikowski D, Porcher R, *et al.* Guillain-Barre syndrome and influenza virus infection. *Clin Infect Dis* 2009; 48:48–56.
- Souayah N, Nasar A, Suri MF, Qureshi AI. Guillain-Barre syndrome after vaccination in United States a report from the CDC/FDA Vaccine Adverse Event Reporting System. *Vaccine* 2007; 25:5253–5255.
- Sencer DJ, Millar JD. Reflections on the 1976 swine flu vaccination program. *Emerg Infect Dis* 2006; 12:29–33.

21. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, *et al.* Guillain-Barre syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol* 1979; 110:105–123.
 22. Centers for Disease Control and P. Preliminary results: surveillance for Guillain-Barre syndrome after receipt of influenza A (H1N1) 2009 monovalent vaccine – United States, 2009–2010. *MMWR Morb Mortal Wkly Rep* 2010; 59:657–661.
 23. Institute of Medicine. *Adverse Effects of Vaccines: Evidence and Causality* Washington, DC: The National Academies Press; 2011.
 24. Fiore AE, Uyeki TM, Broder K, *et al.* Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2010; 59:1–62.
 25. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001; 345:1529–1536.
 26. Bergen R, Black S, Shinefield H, *et al.* Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. *Pediatr Infect Dis J* 2004; 23:138–144.
 27. Piedra PA, Gaglani MJ, Riggs M, *et al.* Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial. *Pediatrics* 2005; 116:e397–e407.
 28. Fleming DM, Crovari P, Wahn U, *et al.* Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J* 2006; 25:860–869.
 29. Gaglani MJ, Piedra PA, Riggs M, *et al.* Safety of the intranasal, trivalent, live attenuated influenza vaccine (LAIV) in children with intermittent wheezing in an open-label field trial. *Pediatr Infect Dis J* 2008; 27:444–452.
 30. Kunisaki KM, Janoff EN. Influenza in immunosuppressed populations: a review of infection frequency, morbidity, mortality, and vaccine responses. *Lancet Infect Dis* 2009; 9:493–504.
 31. Nailescu C, Xu X, Zhou H, *et al.* Influenza vaccine after pediatric kidney transplant: a Midwest Pediatric Nephrology Consortium study. *Pediatr Nephrol* 2011; 26:459–467.
 32. Issa NC, Marty FM, Gagne LS, *et al.* Seroprotective titers against 2009 H1N1 influenza A virus after vaccination in allogeneic hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant* 2011; 17:434–438.
 33. Goldschmidt I, Pfister ED, Becker M, *et al.* Acceptance and adverse events of the 2009 H1N1 vaccination in immunosuppressed pediatric liver transplant recipients. *J Pediatr* 2011; 158:329–333.
 34. Mackay HJ, McGee J, Villa D, *et al.* Evaluation of pandemic H1N1 (2009) influenza vaccine in adults with solid tumor and hematological malignancies on active systemic treatment. *J Clin Virol* 2011; 50:212–216.
 35. Fabio V, Daniele F, Monica de D, *et al.* Pancreas rejection after pandemic influenzavirus A(H1N1) vaccination or infection: a report of two cases. *Transpl Int* 2011; 24:e28–e29.
 36. Madhi SA, Maskew M, Koen A, *et al.* Trivalent inactivated influenza vaccine in African adults infected with human immunodeficient virus: double blind, randomized clinical trial of efficacy, immunogenicity, and safety. *Clin Infect Dis* 2011; 52:128–137.
 37. Tennis P, Toback SL, Andrews E, *et al.* A postmarketing evaluation of the frequency of use and safety of live attenuated influenza vaccine use in non-recommended children younger than 5 years. *Vaccine* 2011; 29:4947–4952.
 38. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 2011; 60:1–64.
- Most recent comprehensive ACIP recommendations on vaccination in general.
39. Update: Recommendations of the Advisory Committee on Immunization Practices (ACIP) regarding use of CSL seasonal influenza vaccine (Afluria) in the United States during 2010–11. *MMWR Morb Mortal Wkly Rep* 2010; 59:989–992.