australasian society of clinical immunology and allergy inc.

Guidelines for medical practitioners
Influenza vaccination of the egg-allergic individual

September 2010

Introduction

Vaccination is an important method of reducing the risk of developing a number of infectious diseases. Influenza in particular is a significant source of morbidity and mortality in Australia, accounting for over 1% of staff absenteeism in winter, an estimated 3089 deaths per year from combined influenza/pneumonia between 2001 and 2006 (1). In 2007 (the latest year for which data is available) 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 three deaths in otherwise healthy preschool children in Western Australia in 2007. It is important to note that mortality figures likely underestimate the influence the impact of influenza infection, due to inherent difficulties in assigning causes of death appropriate disease classification (ICD) codes.

Notification and hospitalisation rates related to influenza infection are highest in children aged 0-5 years, the group also most commonly affected by egg allergy (3, 4). While egg protein-free influenza vaccines grown in mammalian cell lines exist, the current influenza vaccines distributed in Australia and New Zealand are derived from influenza virus grown in hen's egg. The ability to safely vaccinate egg-allergic individuals (particularly in the context of potentially pandemic infection) will thus remain an important public health issue, well after current concerns regarding non-allergic adverse reactions to vaccination in this age group subside.

Product information and current Australian/New Zealand vaccination guidelines currently list egg anaphylaxis as an absolute contraindication to influenza vaccination (5, 6 and http://www.immune.org.nz/?t=889) yet recent studies suggest that most can be safely vaccinated. The majority of reported cases of anaphylaxis following influenza vaccination of egg allergic individuals occurred over 20 years ago, when the amount of egg protein in vaccines was substantially higher. By contrast, the amount of egg ovalbumin present in Australian and New Zealand vaccines in recent years has been ~ 1ug or less/dose (manufacturer data source), substantially less than the estimated 130 ug egg protein taken orally considered likely to trigger reactions in egg allergic patients (7).

Aims

These guidelines aim to provide recommendations for vaccination of egg-allergic individuals. The 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 (8-10) and unpublished studies (listed below) examining the safety of vaccinating egg-allergic individuals, published international recommendations (11-16) and published information on known vaccine ingredients (17), product information sheets and relevant Australian and New Zealand vaccination guidelines (18, 19 and http://www.immune.org.nz/?t=889). 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, 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 be followed by delayed skin rash (usually 4-12 days after vaccination) but this is also *not* due to a vaccine allergy. As exception to these may be a delayed (type 3) response characterised by urticarial rash and/or joint pain observed several hours to several days after vaccination. This type of reaction neither increases the risk of anaphylaxis nor constitutes a contraindication for a subsequent dose of vaccine.

Serious allergic reactions to vaccination are very rare

The risk of serious allergic reaction to vaccination (anaphylaxis) is very low, estimated at between 1 and 4 cases per million doses administered (20) and 1 per 4.4 million does of the influenza vaccine (21), although it is likely that many egg-allergic subjects were excluded from vaccination in this 1976 survey. To minimise the consequences of adverse reactions, all vaccines should be administered according to national guidelines (10, 11) followed by an observation period of 15 minutes (Australia) or 20 minutes (New Zealand). Vaccine providers should also be able to recognise anaphylaxis and have the facilities and staff to assess and treat adverse reactions.

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; (18) 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)*****
- DPT (Diptheria, Pertussis, Tetanus)
- IPV (Inactivated polio vaccine)
- HiB (*Hemophilus influenzae* type B)
- Pneumococcus
- Meningococcal C
- Chickenpox (Varicella) vaccines
- 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, specifically gelatin (22-25).

Egg allergy and vaccination

Allergy to hen's egg occurs in an estimated 2-3% of young children. 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 eggs (e.g. H1N1, seasonal influenza vaccine, Yellow Fever and Q fever) raising the possibility that the final product may contain small amounts of egg protein. To enhance safety, attempts have been made in recent years to limit the amount of egg ovalbumin in the H1N1 and seasonal influenza vaccines to less than 1ug of egg protein per vaccine dose. It is important to note, however, that the actual amount may vary by manufacturer, year of production and batch and country of origin.

While egg protein-free influenza vaccines grown in mammalian cell lines exist (Celvapan, distributed by Baxter Bioscience in Australia), egg-free influenza vaccines are not currently available in Australia

or New Zealand without individual patient approval for non-registered products. In Australia, this requires SAS Category B approval. While the likely amount of egg protein in influenza vaccines is relatively small compared to the estimated minimum dose of 130ug egg protein considered likely to trigger and allergic reaction via the oral route (7), injection of allergen is generally considered to convey a higher risk of an allergic reaction than oral exposure. A more cautious approach has been historically taken in vaccinating patients with egg allergy with a potentially egg-containing vaccine.

The following vaccines may contain residual egg protein

- Seasonal influenza vaccine (s)
- Pandemic influenza vaccine(s) (e.g. H1N1, bird or swine flu vaccines).
- Yellow Fever vaccine (important for travellers 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 that present in seasonal influenza and H1N1 vaccines. *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?

Recent reviews highlight the very low risk of vaccinating egg-allergic subjects with the influenza vaccine (11-13, 26, 27). While a USA population study (11 cases of non-fatal anaphylaxis, none reporting egg allergy, after 48 million doses of influenza vaccine) is often quoted to support a low risk, it is also highly likely that many egg allergic patients were excluded (21). In the only case report of a death following influenza vaccine in 1969 (28), few details have been published, and the causative relationship with egg allergy is unclear. Importantly, most cases of anaphylaxis after influenza vaccination in individuals with egg allergy occurred over 20 years ago when the amounts of egg protein in vaccines were substantially higher than now. More useful information is 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.

In an American study of 83 egg-allergic subjects (27 with anaphylaxis) and 124 controls, positive vaccine allergy tests were detected in 4/83 egg-allergic patients and 1/124 controls, yet all tolerated split-dose vaccination (10% vaccine dose, then the remaining 90% dose 30 minutes later if the first was tolerated; (8). Of the egg allergic group, one patient experienced mild throat itching and cough, which resolved without treatment and tolerated the second recommended dose uneventfully. A second patient experienced mild cough and wheeze that resolved with a bronchodilator, and tolerated the second dose uneventfully.

An Italian study demonstrated the safety of vaccination of 44 children (mean age 6±3.3 years) with asthma and egg allergy (10 anaphylaxis; 9) and 44 non egg-allergic children; one in each group had wheeze within a few hours of vaccination but anaphylaxis was not observed. Following the death of three otherwise healthy West Australian preschoolers with influenza in 2007, 165 egg-allergic children aged 6 months to 16 years (48 with anaphylaxis) were vaccinated and a similar safety profile was demonstrated. One patient developed mild facial urticaria yet tolerated the second full vaccine dose a few weeks later, as presented thus far in abstract form (http://www3.interscience.wiley.com/journal/121509789/issue; http://www3.interscience.wiley.com/journal/122594036/issue). In a study (at the time of writing), 164/171 patients aged 6 months to 18 years with non-anaphylactic egg allergy underwent split-dose

vaccination. Six experienced urticaria *or* wheeze after 10% vaccine dose; one had flushing/hives alone after the second 90% dose (10).

In the largest and most recent study published, 830 Canadian egg-allergic children were given the H1N1 vaccine; nine patients developed rashes treated with antihistamines and three required bronchodilator administration using a split-dose protocol; none progressed to anaphylaxis (29). Following initial experience, the same group expanded their vaccination programme to include 3640 individuals with a history of self-reported egg allergy (not medically confirmed by the researchers. Adverse reactions were reported in 71 (1.9%) of subjects; none had anaphylaxis. Adrenaline was administered in two cases; one adult female with tingling of the mouth and throat without objective evidence of respiratory or cardiovascular compromise and one male 3 year old with crying and respiratory distress 30 minutes after vaccination. Of the remaining 69 patients, 42 complained of rash, 17 complained of a sensation of throat tingling or tightness and 7 reported cough. All these patients were treated with antihistamines and 4/7 of those reporting cough were given a bronchodilator.

Is allergy testing with vaccines worthwhile?

In a prospective study of 83 egg-allergic and 124 control subjects, all tolerated a split dose regimen of 10% of the vaccine dose followed 30 minutes later by the remaining 90%, despite positive skin allergy tests with the vaccine in 4/83 and 1/124 subjects, respectively (8). Similar tolerance to vaccination was demonstrated in the Western Australian studies described above despite approximately 20% of subjects having positive tests. Finally, the incidence of local and systemic adverse reactions was similar in 171 patients aged 6 months to 18 years with non-anaphylactic egg allergy, independent of the results of prior vaccine allergy testing (10).

Taken as a whole, skin allergy testing (skin prick testing and/or intradermal testing) of egg-allergic individuals before vaccination has shown poor correlation between results of testing and vaccine tolerance. Since most individuals are able to tolerate vaccination even when skin tests are positive (reviewed in 11-13), allergy testing with the vaccine prior to vaccination is not recommended.

International guidelines for vaccinating the egg-allergic individual

UK, USA, European and Canadian Consensus Guidelines (11-16) suggest that most egg-allergic subjects can safely receive seasonal and H1N1 vaccines if precautions are undertaken to minimise risk, specifically recommending vaccines containing no more than 1ug/dose of egg ovalbumin. International recommendations are summarised in the Table 1.

ASCIA Guidelines for vaccinating the egg-allergic individual

The Australasian Society for Clinical Immunology and Allergy concurs with these views, as summarised in the accompanying Table 1. We acknowledge that these proposals are at variance with current Australian and New Zealand guidelines that list egg anaphylaxis as an absolute contraindication (5, 6 and http://www.immune.org.nz/?t=889). Our recommendations specifically apply to vaccines containing no more than 1 ug egg ovalbumin per dose and are summarised in Figure 1. The current egg content of influenza vaccines available in Australia and New Zealand is summarised in Table 2. Recent reviews have examined the variable levels of egg ovalbumin in influenza vaccines available in the USA (30, 31).

Allergy testing with the vaccine

Allergy testing with the vaccine prior to administration is not recommended due to poor correlation between test results and vaccine tolerance.

Risk assessment

Those presenting for immunisation may be considered in three potential risk groups.

(1) No additional risk

The first group are those considered to be at no additional risk to the general population risk of vaccination: family (but not personal) history of egg allergy, non-egg food allergy, past egg allergy (but now able to eat whole egg) or those reacting to raw egg only but tolerate at least a teaspoon of scrambled/hard boiled egg. 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 15-20 minute waiting period. Importantly, egg allergy is not a contraindication for the measles mumps rubella vaccine, which contains no egg protein (see discussion above).

(2) Lower risk

The second group encompasses those with non-anaphylactic reactions to egg/egg-containing food who are able to tolerate at least a teaspoon of lightly cooked egg (e.g. scrambled/boiled). Based on current published evidence, we suggest that vaccination can be safely administered in a primary care (general practitioner) setting as a single dose with a 30-minute waiting period (instead of the standard 15 [Australia]-20 [New Zealand] minutes). *The immediate availability of medical practitioner care is recommended.*

(3) Higher risk group

The third group includes patients with (a) non-anaphylactic reactions to egg who are avoiding all dietary egg, (b) those with past egg anaphylaxis or (c) those who have never ingested egg but have egg sensitization on skin prick or specific IgE serology testing.. These patients merit special consideration as a higher risk group since it is difficult to assess current risk of anaphylaxis. The decision to vaccinate should include a discussion of the risk *vs.* benefit of vaccination, allergy specialist consultation (*including telephone contact initially for advice*), and vaccination in a medically supervised environment that may include a community or hospital-based vaccination or allergy clinic and use of a split dose protocol (10%/90% given 30 minutes apart if the first dose is tolerated), with a final 30-minute wait period after the final dose.

Subsequent doses

Subsequent doses administered in the same year can be given as a single dose if the first is tolerated. Tolerance one year does not guarantee the safety for the next (due to potential year-to-year variation in the amount of egg present in the vaccine) and we recommend that the same process be followed yearly in those considered to still be at risk of egg allergy. In the setting of pandemic influenza infection, whereby a new vaccine for a new strain of influenza virus becomes available, the new vaccine should be administered according to the protocols described above.

Important note

Documented anaphylaxis to influenza vaccination is a contraindication to further administration, independent of egg allergy status.

Conclusions

Current evidence is that the vast majority of 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. Since it is not possible in egg allergic subjects to totally eliminate the very small risk of anaphylaxis to egg protein in the vaccine, vaccines should always be administered in facilities with staff able to recognise and treat anaphylaxis.

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

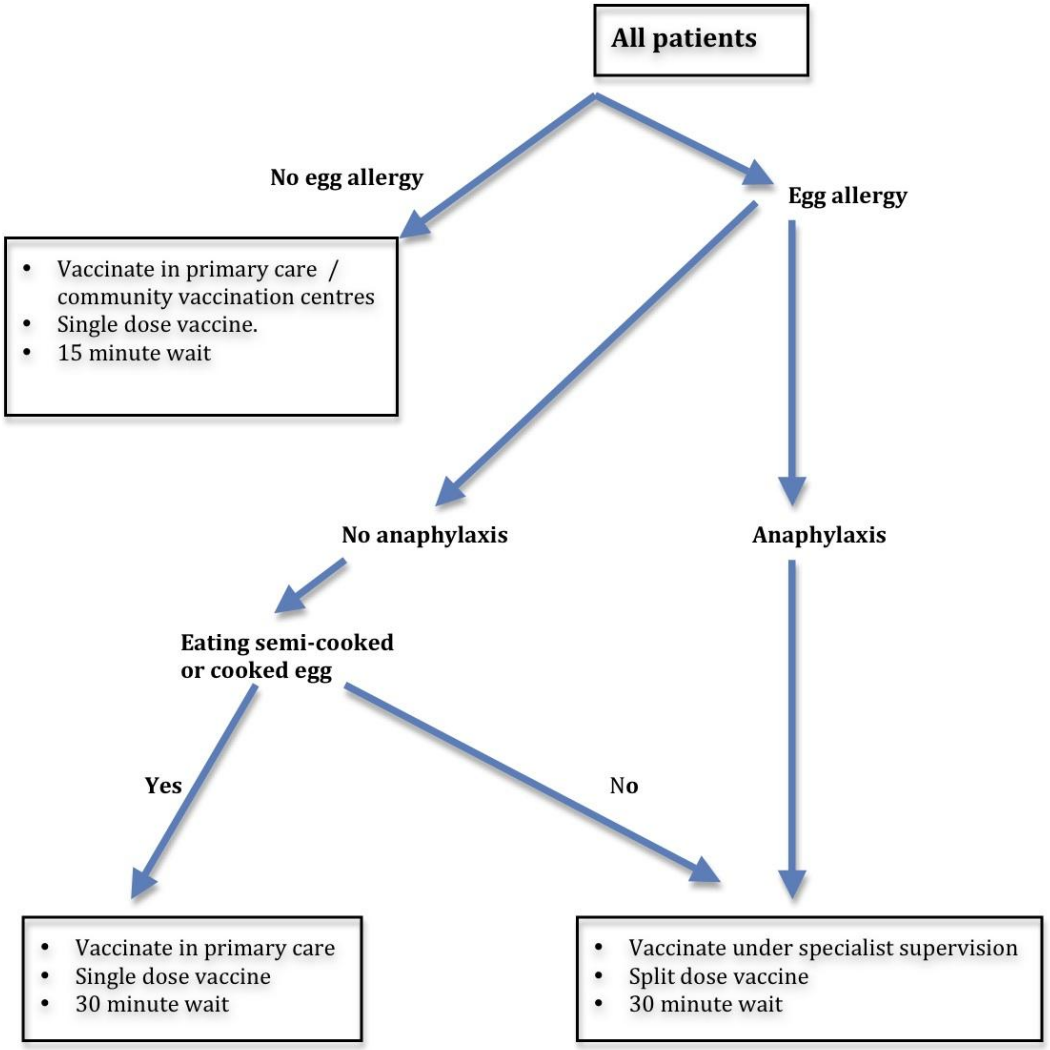
Adverse events following immunisation should document the timing of onset, the nature and severity of symptoms experienced, the likelihood of whether the adverse event occurred as a direct result of vaccination and details regarding underlying health issues (including known atopic disease) and be reported to the Advisory Committee on the Safety of Medicines (ACSOM) in Australia and Medsafe in New Zealand. Blood for tryptase measurements should be taken if possible to assist in the confirmation of possible anaphylaxis.

Table 2. Reported levels of Egg ovalbumin "seasonal" and swine flu (H1N1) vaccines available in Australia and New Zealand 2010.

Manufacturer	Vaccine	Egg ovalbumen/dose	Countries available
CSL	H1N1	<1ug	Aust/
CSL	FluVax	<1ug	Aust/
Solvay	Influvac	<1ug	Aust/NZ
Sanofi Pasteur	Intanza	<0.05 ug	Aust/NZ
Sanofi Pasteur	Vaxigrip	<0.05 ug	Aust/NZ
Celvapan monovalent	H1N1	Nil	NZ
Novartis	Fluad	< 2ug	Aust
GlaxoSmithKline	Fluarix	<1ug	Aust
Medeva	Fluvirin	<1ug	Aust

Abbreviations

AAP	American Academy of Pediatrics
ASCIA	Australasian Society of Clinical Immunology and Allergy
AVP	Australian Vaccination Handbook
BSACI	British Society for Clinical Immunology and Allergy
CSACI	Canadian Society of Clinical Immunology and Allergy
EAACI	European Academy of Allergy and Clinical Immunology
JTFPP	Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology.
SEICAP	Food Allergy Committee of the Sociedad Espanola de Inmunologia Clinicica y Alergologia Prediatrica



Influenza vaccination of the egg allergic individual - flow diagram

REFERENCES

(1) Australian Government, Department of Health and Aging. Australian Influenza Report 2009. http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm Last accessed 2 May 2010.

(2) Australian Bureau of Statistics 2007. Causes of Death 2007. http://www.health.gov.au/internet/main/Publishing.nsf/Content/cda-surveil-ozflu-flucurr.htm

(3) Eggesbo M, Botten G, Halvorsen R, Magnus P. The prevalence of allergy to egg: a population-based study in young children. *Allergy* 2001; **56**: 403–11.

(4) Loblay R, Soutter V, Swain A, Pintol E, Mullins RJ. Prevalence of reported food allergies in childcare in Central Sydney (CSAHS) and the Australian Capital Territory (ACT). Internal Med J 2006; 36 (Suppl 6): A209.

(5) Australian Government, Department of Health and Aging. The Australian Immunisation Handbook 9th Edition 2008 . http://www.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook-home. Last accessed 2 May 2010.

(6) Policy Statement—Recommendations for the Prevention and Treatment of Influenza in Children, 2009 –2010. American Academy of Pediatrics. Pediatrics 2009; 124: 1216–1226 http://aappolicy.aappublications.org/cgi/reprint/pediatrics;124/4/1216.pdf. Last accessed 1 May 2010.

(7) Moneret-Vautrin DA, Kanny G. Update on threshold doses of food allergens: implications for patients and the food industry. Curr Opin Allergy Clin Immunol. 2004; 4: 215-9.

(8) James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, Schwartz HJ, Sampson HA, Windom HH, Machtinger SB, Lensing S. Safe administration of influenza vaccine to patients with egg allergy. J Pediatr. 1998; 133: 624-8.

(9) Esposito S; Gasparini C; Martelli A; Zenga A; Tremolati E; Varin E; Marseglia GL; Fiocchi A; Principi N. Safe administration of an inactivated virosomal adjuvanted influenza vaccine in asthmatic children with egg allergy. Vaccine. 2008; 26 (36): 4664-8.

(10) Chung EY, Huang L, Schneider L. Safety of Influenza Vaccine Administration in Egg-Allergic Patients. Pediatrics 2010; 125: 1024-1030.

(11) Kelso JM, Li JT, Nicklas RA, Blessing-Moore J, Cox L, Lang DM, Oppenheimer J, Portnoy JM, Randolph C, Schuller DE, Spector SL, Tilles S, Wallace D, Ballas ZK, Baker JR, Bellanti JA, Ein D, Grammer LC; Joint Task Force on Practice Parameters; Joint Task Force on Practice Parameters for Allergy & Immunology. Adverse reactions to vaccines. Ann Allergy Asthma Immunol. 2009; 103(4 Suppl2): S1-14.

(12) Kelso JM. Administration of influenza vaccines to patients with egg allergy. J Allergy Clin Immunol. 2010; 125: 800-802.

(13) Erlewyn-Lajeunesse M, Brathwaite N, Lucas JS, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. BMJ 2009; 339: b3680. http://www.bmj.com/cgi/content/full/339/sep15_3/b3680?view=long&pmid=19755545. Last accessed 1 April 2010.

(14) EAACI (European Academy of Allergy and Clinical Immunology) recommendations for health professionals regarding seasonal and swine influenza vaccination in egg-allergic patients. http://www.eaaci.net/attachments/1282_091026_EAACI_Release_%20H1N1_Egg%20Allergy_pub%20-%20Health%20Professionals.pdf . Last accessed 1 April 2010.

(15) Statement: Administration of h1n1 and seasonal influenza vaccine to egg allergic individuals. The Canadian Society of Allergy and Clinical Immunology. http://www.csaci.ca/include/files/CSACI_H1N1_Statement.pdf. Last accessed 1 April 2010.

(16) Piquer-Gibert M, Plaza-Martín A, Martorell-Aragonés A, Ferré-Ybarz L, Echeverría-Zudaire L, Boné-Calvo J, Nevot-Falcó S; Food Allergy Committee of the Sociedad Española de Inmunología Clínica y Alergología Pediátrica. Recommendations for administering the triple viral vaccine and antiinfluenza vaccine in patients with egg allergy. Allergol Immunopathol (Madr). 2007 ;35(5):209-12. Last accessed 1 May 2010.

(17) Barbara E Eldred, Angela J Dean, Treasure M McGuire and Allan L Nash. Vaccine components and constituents: responding to consumer concerns. MJA 2006; 184 (4): 170-175. http://www.mja.com.au/public/issues/184_04_200206/eld10500_fm.html . Last accessed 1 April 2010.

(18) Australian Immunisation Schedule. http://www.health.gov.au/internet/immunise/publishing.nsf/content/nips2. Last accessed 1 May 2010.

(19) New Zealand Immunisation Schedule. http://www.moh.govt.nz/moh.nsf/indexmh/immunisation-schedule . Last accessed 1 May 2010.

(20) Menzies R, Mahajan D, Gold MS, Roomiani I, McIntyre P, Lawrence G. Annual report: surveillance of adverse events following immunisation in Australia, 2008. Commun Dis Intell. 2009; 33: 365-81.

(21) Retailliau HF, Curtis AC, Storr G, Caesar G, Eddins DL, Hattwick MA. Illness after influenza vaccination reported through a nationwide surveillance system, 1976–1977. Am. J. Epidemiol. 1980; 111: 270–8.

(22) Ainsworth E, Debenham P, Carrol ED, Riordan FA. Referrals for MMR immunization in hospital. Arch Dis Child. 2010 Apr 6. [Epub ahead of print]

(23) Goodyear-Smith F, Wong F, Petousis-Harris H, Wilson E, Turner N. Follow-up of MMR vaccination status in children referred to a pediatric immunization clinic on account of egg allergy. Hum Vaccin. 2005; 1: 118-22.

(24) James JM, Burks AW, Roberson PK, Sampson HA. Safe administration of the measles vaccine to children allergic to eggs. N Engl J Med. 1995; 332: 1262-6.

(25) Freigang B, Jadavji TP, Freigang DW. Lack of adverse reactions to measles, mumps, and rubella vaccine in egg-allergic children. Ann Allergy. 1994; 73: 486-8.

(26) Zeiger RS. Current issues with influenza vaccination in egg allergy. J Allergy Clin Immunol. 2002; 110: 834-40.

(27) Kelso JM, Yunginger JW. Immunization of egg-allergic individuals with egg- or chicken-derived vaccines. Immunol Allergy Clin North Am. 2003; 23: 635-48

(28) Bierman CW, Shapiro GG, Pierson WE, Taylor JW, Foy HM, Fox JP. Safety of influenza vaccination in allergic children. J Infect Dis 1977;136(suppl):S652-5.

(29) Gagnon R, Primeau MN, Roches AD, Lemire C, Kagan R, Carr S, et al. PHAC-CIHR influenza Research Network (PCIRN). Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. J Allergy Clin Immunol. 2010 (in press).

(30) Waibel KH, Gomez R. Ovalbumin content in 2009 to 2010 seasonal and H1N1 monovalent influenza vaccines. J Allergy Clin Immunol. 2010; 125: 749-51

(31) Li JT, Rank MA, Squillace DL, Kita H. Ovalbumin content of influenza vaccines. J Allergy Clin Immunol. 2010 Jun;125(6):1412-3

The Australasian Society of Clinical Immunology and Allergy (ASCIA) is the peak professional body of Clinical Immunologists and Allergists in Australia and New Zealand.

Website: www.allergy.org.au
Email: education@allergy.org.au
Postal address: PO Box 450 Balgowlah, NSW Australia 2093

Disclaimer

ASCIA guidelines and position papers are reviewed by ASCIA members and represent the available published literature at the time of review. The content of this document is not intended to replace professional medical advice and any questions regarding a medical diagnosis or treatment should be directed to a medical practitioner.

Content last updated September 2010