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Original Article

Increased reactions to pediatric influenza vaccination following concomitant pneumococcal vaccination

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Background Influenza in children causes significant morbidity and hospitalizations and also some mortality particularly in children <5 years of age. Influenza vaccination in children has been shown to be safe and effective, but in 2010 the pediatric influenza vaccination program was suspended in Western Australia after the rate of febrile convulsions observed (9/1000 doses) was 55 times the previously reported rate.
In 2009, over 80% of all children in New Brunswick were vaccinated with an adjuvanted monovalent H1N1 vaccine shown to have very high effectiveness, raising the prospect of potential hyper-responsiveness because of residual protection. We conducted enhanced post-marketing surveillance to monitor local and general reactions.

Methods Parents of participating children seen at dedicated vaccination clinics were given influenza vaccine survey kits to record local and general symptoms up to 3 days following receipt of season influenza vaccine.

Results Febrile reactions of ≥38° occurred in <10% of children who received a first dose of seasonal influenza vaccine (n = 660) and severe febrile incidents with fever ≥39° were uncommon. Concurrent administration of other vaccine(s) including conjugated pneumococcal vaccine appeared to increase reactogenicity. No child in the study had a febrile convulsion.

Conclusion Influenza vaccines in children are safe, and this study provides a baseline for rapid assessment studies at the start of a vaccine season. Parents should be aware of increased fevers with concurrent vaccine administration, and antipyretics should be considered.

Keywords Children, febrile convusions, influenza, pneumococcal vaccine, reactogenicity, safety, vaccination.

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Introduction

Influenza in children is under-recognized, and its importance underestimated. Available data suggest that influenza causes significant morbidity and hospitalizations and also some mortality particularly in children <5 years of age.[1–5] Prospective studies from the USA of laboratory-proven influenza have shown that in a single influenza season, up to 12% of outpatient clinic and emergency room visits in children <5 years of age are attributable to influenza and about one child <5 years of age in 1000 with laboratory-confirmed influenza is admitted to hospital.[6] In a South Australian study, 81% of children aged <5 years admitted to hospital with influenza had no documented risk factor that increased their risk of serious outcome following infection.[7] Children are also likely to shed virus for longer periods and to be an important contributor to continued propagation of influenza in the community.[8]

Influenza vaccination in children has been shown to be safe and to be effective if two doses are initially given so that young children are immunologically primed.[9,10] Also some studies have shown that yearly immunization against influenza in children is cost-effective.[11,12]

In Western Australia, all children up to 59 months of age have been offered free influenza vaccination since 2008 after a cluster of influenza-related deaths in 2007 prompted a review of vaccination benefits.[13]

On April 22, 2010, the Western Australian Health Department suspended the pediatric influenza vaccination program after they noted an increase in the number of febrile convulsions in children <5 years of age. Following a detailed review of case reports of affected children, the Australian Government Therapeutic Goods Administration (TGA) concluded that there were 99 confirmed cases of febrile convulsions in children under the age of 5 years across Australia causally related to seasonal influenza

vaccination with Fluvax (CSL Biotherapies).[14–17] The rate of febrile convulsions observed in Western Australia (9/1000 doses) was 55 times the rate reported by the United States Centers for Disease Control and Prevention (US CDC) from 2005–2006 to 2009–2010 (0·16/1000 doses) quoted in a TGA review.[18]

In 2010, in the province of New Brunswick, Canada, the trivalent split virion seasonal influenza vaccines Fluviral (GlaxoSmithKline) and Vaxigrip (Sanofi Pasteur) were offered to children aged 6 months to 18 years through the publicly funded immunization program. [16] Both vaccines were standard unadjuvanted compositions that year (15 μg of A/California/7/2009 (H1N1)-like virus; A/Perth/16/2009 (H3N2)-like virus; B/Brisbane/60/2008-like virus). In light of the Australian observations, the potential for an increased reactogenicity to seasonal influenza vaccine was of concern to local Health authorities.

In 2009, over 80% of all children in New Brunswick had been vaccinated with an adjuvanted monovalent H1N1 vaccine shown to have very high vaccine effectiveness after one dose, and half of these children received two doses of the monovalent H1N1 vaccine (Arepanrix™ GlaxoSmithKline Inc. Mississauga, ON, Canada 09 H1N1 and an AS03 adjuvant composed of DL-a-tocopherol, squalene and polysorbate 80 as an oil-in-water emulsion).[19] A previous Hong Kong study showed vaccine efficacy with a non-adjuvanted vaccine lasted 3 years in children,[20] so there was a high likelihood of residual protection in children who had received the highly effective adjuvanted H1N1 vaccine. This raised the prospect of potential increased reactogenicity, as all the trivalent inactivated influenza vaccines (TIV) licensed for use in Canada for the 2010–2011 influenza season contained the A/California/7/2009 (H1N1)-like pandemic strain.[21]

Strong support by parents for vaccination during the pandemic produced a very high monovalent H1N1 vaccine coverage in children in the province. It was hoped that this awareness could be built upon to entrench the importance of pediatric seasonal influenza vaccination in the minds of parents, but this aim was at risk if increased reactogenicity ensued.

Accordingly, we conducted enhanced post-marketing surveillance of the two publicly funded TIV in New Brunswick to monitor and review local and general reactions in children aged six to 59 months.

Methods

Participants

Dedicated clinics to vaccinate children against influenza were organized by public health staff throughout the province of New Brunswick, Canada commencing October 13, 2010. Children aged 6–59 months on the day of vaccination were recruited by research assistants trained by the Communicable Disease Control Branch of the Office of the Chief Medical Officer of Health. Written informed consent was obtained from the parent, guardian, or caregiver of each participating child.

Procedures

Parents of participating children were given influenza vaccine survey kits containing a diary card, diary card instruction sheet, participant information and consent form, pen, digital thermometer, measuring tape, and return envelope. Parents were educated on how to complete the diary card by recording their child's local and general symptoms on the evening of the day the vaccine was given and for the following three days.

Local symptoms measured included pain, redness, and swelling at the injection site. General symptoms measured included temperature, nausea/vomiting, diarrhea, loss of appetite, and irritability. The variables pain, nausea/vomiting, diarrhea, loss of appetite, and irritability were assessed using a grading scale of 0–3, with zero being absence of symptoms and three being considered severe symptoms. Redness and swelling were measured by taking the widest diameter of reaction at the injection site. Axillary temperature was taken using the digital thermometer provided in the survey kit. Parents were also asked to record on the diary card if symptoms were ongoing after the evening of the fourth day, if medical advice was sought, and/or if medication was taken for a specific event.

Participant information on age, sex, previous influenza vaccination (both 2009 pandemic and seasonal), and medical condition(s) was collected by research assistants at the time of recruitment. Information on receipt of concurrent vaccine(s) was obtained through the New Brunswick Client Service Delivery System (CSDS) which records all childhood vaccinations. Data collected at the time of 2010 seasonal influenza immunization and data retrieved from CSDS were merged prior to analysis.

As per the National Advisory Committee on Immunization recommendations, children aged 6–35 months received 0·25 ml of vaccine, while children 36–59 months of age received 0·5 ml of vaccine.

Data analysis

Observations were linked to doses of seasonal influenza vaccine administered to children between the ages of 6 and 59 months. Analysis was restricted to first dose of vaccine administered between October 13 and December 17, 2010. The primary outcome of interest was whether or not the child experienced fever following immunization. Localized pain, redness and/or swelling, nausea, diarrhea, loss of appetite, and irritability were measured as secondary outcomes. Independent factors assessed included sex, vaccine type (Fluviral or Vaxigrip), age group, receipt of a previous

H1N1 or seasonal influenza vaccine, and receipt of concurrent vaccine(s).

For analysis, concurrent vaccines administered were separated into three groups, children who received 13 valent pneumococcal vaccine (Prevnar 13®, Pfizer Canada Inc, Kirkland, QC, Canada) with or without other vaccines, children who received at least one other vaccine with or without Prevnar 13®, and finally children who received at least one other vaccine but not including Prevnar 13®. Two consolidated age group variables were included in the analysis: firstly 6–23 versus 24–59 months, and secondly 6–11, 12–23, 24–35, 36–47, and 48–59 months as groupings.

All data were entered into Microsoft Access 2007 (Microsoft Corporation, Redmond, WA, USA) and analyzed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA).

In the univariate analysis, the chi-square test was used to test for an overall association between each of the factors of interest and four outcomes: (i) fever of ≥38° on the evening following immunization; (ii) fever of ≥39° on the evening following immunization; (iii) fever of ≥38° up to 3 days following the day of immunization; and (iv) fever of ≥39° up to 3 days following day of immunization. Fisher's two-tailed exact test was used to test for differences where expected cell counts were ≤5.

Factors significant at the $P < 0{\cdot}05$ level, as well as potential confounders, were then included in the multivariate analysis. Poisson regression models were used to estimate the relative risk and 95% confidence interval for having fever according to sex, age group (6–23, 24–59 months only), having previous seasonal influenza vaccine, having adjuvanted monovalent H1N1 vaccine, influenza vaccine type, receipt of concurrent vaccines including Prevnar 13® and receipt of at least one other vaccine with or without Prevnar 13®). The third vaccine group ($n = 134$) who had other concomitant vaccines but not Prevnar 13® were a subset of the group at least one other vaccine ($n = 215$). This third vaccine group variable was thus not included in the multivariate regression as it was not independent, and the model became unstable.

Because likelihood ratio confidence intervals are more reliable than the Wald confidence intervals for small and moderate sample size, they were provided for all primary outcomes of interest. However, because no children who received previous seasonal influenza vaccine experienced a body temperature of ≥39° up to 3 days following day of vaccine receipt, this led to quasi-complete separation in the regression models and no likelihood ratio confidence intervals could be produced. Instead, 95% Wald confidence intervals were provided. All the p-values from the regression model were based on likelihood ratio tests.

Proc GENMOD in SAS was used for multivariate analyses. All tests were two-tailed, where $P < 0{\cdot}05$ indicated statistical significance.

Results

Participants

Influenza vaccine survey kits were given to 1516 parents of vaccinated children during the immunization program. Returned diary cards for 790 doses of seasonal influenza vaccine (52%) administered to 706 children were initially included in the analysis: 592 children who received a first dose only, 84 children who received both a first and second dose, and 33 children for whom only the second dose was captured. Six hundred and seventy-three ($n = 673$) of the 790 total doses were first doses. After removal of 13 vaccination episodes for whom no information was available on concurrent vaccine administration, 777 vaccine dose recipients remained of which 660 were first-dose episodes. The latter were included in more detailed analysis.

Of the 660 first-dose children, an almost equal number of observations were collected for boys (52%) and girls (48%), and just over half (56%) of the observations were in children under 24 months of age. Fifty-eight percent (58%) received the Fluviral vaccine, while the remaining 42% received the Vaxigrip vaccine. Similar proportions were seen in the analysis of all doses. No significant differences were seen in vaccine type administered between gender or age groups.

Concomitant vaccines administered included Prevnar 13® (85), MMR11® (88), Pediacel® (131), Recombivax HB® (75), Quadracel® (47), Varilrix® (30), Menjugate® (29), Hib® (1), and Imovax Polio® (1).

Frequency of non-febrile adverse events

The frequency of non-febrile adverse events on the evening following immunization or up to 3 days following immunization for the first dose is shown in Table 1. Both pain and irritability were common, occurring in over a third of vaccine recipients at some time. Other adverse events were less

Table 1. Frequency of having a non-febrile adverse event $N = 660$

Adverse event	Day 1*		≤Day 4**	
	n	%	*n*	%
Pain	234	35·5	270	41·0
Nausea	21	3·2	43	6·5
Diarrhea	30	4·6	82	12·4
Loss of appetite	74	11·2	136	20·6
Irritability	179	27·1	258	39·1
Redness (>3 cm)	2	0·3	37	5·6
Swelling (>3 cm)	2	0·3	17	2·6

*Evening following immunization.
**In the 3 days following immunization.

common. Non-febrile events at 4 days or more following immunization were reported for <4% of observations (n = 29) and included nausea, diarrhea, loss of appetite, and/or irritability.

Univariate analysis

Fifty-six children (8·5%) reported having any fever up to 3 days following receipt of first dose of seasonal influenza vaccine. Of these, 24 (3·6%) had a fever of ≥38° on the evening following immunization, and 7 (1·1%) had a fever of ≥39° on the evening following day of immunization.

The prevalence of fever by all independent factors of interest in first-dose recipients on the evening following the day of immunization is shown in Table 2. Sex, vaccine type, age group, receipt of previous H1N1 vaccine, and receipt of previous seasonal influenza vaccine were not associated with an increase in fever.

Among children reporting any fever on the evening following receipt of first dose of 2010 seasonal influenza vaccine, 58% (14/24) received at least one concurrent vaccine. Receipt of concurrent vaccine(s) was significantly associated with fever, but the effect appeared to be principally related to receipt of Prevnar 13®. Children who received Prevnar 13® were more likely to have a fever of ≥38° on the evening following immunization (P < 0·001). Receipt of other vaccine(s) when Prevnar 13® was not included was not associated with fever.

Twenty-seven of the children who received a first dose of influenza vaccine had a co-morbidity described. Only asthma (n = 6) and symptoms related to teething (n = 4) had more than two children in a co-morbidity category. No difference was found for any of the fever outcomes for any co-morbidity although the numbers were very small.

Multivariate analysis

Sex, vaccine type, age group, previous seasonal or H1N1 influenza vaccine, and concurrent receipt of at least one other vaccine with or without Prevnar 13® were not significantly associated with febrile episodes on the evening of immunization in first-dose recipients in the multivariate analysis (Table 3).

The only factor that was significantly associated with fever outcomes was the concurrent administration of Prevnar 13® vaccine. Those children who received one or more concurrent vaccines including Prevnar 13® were over four times as likely to have a febrile episode ≥38° on the evening following immunization (RR = 4·26, 95% CI: 1·24–15·74, P = 0·02) and almost three times as likely to have a febrile episode of ≥38° up to 3 days following day of immunization (RR = 2·73, 95% CI: 1·17–6·47, P = 0·02).

Receipt of one or more concurrent vaccines including Prevnar 13® was also significantly associated with fever of ≥39° up to 3 days following day of immunization (RR = 17·20, 95% CI: 1·61–228·99, P = 0·02). However, the confidence intervals were large as the numbers involved were small. The addition of children without Prevnar 13® weakened the strength of the association with fever.

Table 2. Frequency of having a fever on the evening following immunization (n = 660)

	Fever ≥38 (n = 24)			Fever ≥39 (n = 7)		
	n	%		n	%	
Sex						
Male (n = 341)	12	3·5		4	1·2	
Female (n = 319)	12	3·8		3	0·9	
Vaccine type						
Fluviral (n = 384)	10	2·6		4	1·0	
Vaxigrip (n = 276)	14	5·1		3	1·1	
Age group 1 (months)						
6–11 (n = 166)	3	1·8		0	0·0	
12–23 (n = 202)	12	5·9		5	2·5	
24–35 (n = 96)	1	1·0		0	0·0	
36–47 (n = 90)	3	3·3		1	1·1	
48–59 (n = 106)	5	4·7		1	0·9	
Age group 2 (months)						
6–23 (n = 368)	15	4·1		5	1·4	
24–59 (n = 292)	9	3·1		2	0·7	
Prev H1N1 vaccine*						
Yes (n = 402)	16	4·0		6	1·5	
Prev seasonal flu vaccine*						
Yes (n = 138)	2	1·4		0	0·0	
Concomitant vaccines received on same day*						
Prevnar 13® ± other vaccines (n = 85)	10	11·8	P < 0·001	4	4·7	P < 0·01
Any concomitant vaccine ± Prevnar 13® (n = 215)	14	6·5	P < 0·01	4	1·9	
Any concomitant vaccine except Prevnar 13® (n = 134)	4	3·0		0	0·0	

*Binary variables for which the number and percent in those without the factor are not shown.

Discussion

Our study has shown that febrile reactions to the 2010/11 northern hemisphere seasonal influenza vaccine occurred in <10% of children and severe febrile incidents with fevers >39 degrees were uncommon (<2%). No child in the study had a febrile convulsion.

Table 3. Factors significantly associated* with having a fever on the evening following immunization (n = 660)

	Fever ≥38			Fever ≥39		
	Risk ratio	**95% confidence interval***	***P* Value**	**Risk ratio**	**95% confidence interval***	***P* value**
Sex						
Boys	1·07	(0·47–2·42)	0·88	1·62	(0·35–0·87)	0·53
Girls	–	–	–	–	–	–
Vaccine type						
Fluviral	—	–	–	–	–	–
Vaxigrip	1·83	(0·82–4·27)	0·14	0·87	(0·17–4·05)	0·86
Age, months						
6–23	–	–	–	–	–	–
24–59	1·68	(0·52–5·51)	0·39	0·76	(0·07–8·18)	0·81
Previous seasonal vaccine						
Yes	0·33	(0·05–1·20)	0·10	–	–	–
No	–	–	–			
Previous H1N1 vaccine						
Yes	1·22	(0·44–3·56)	0·71	4·25	(0·59–86·48)	0·16
No	–	–	–	–	–	–
Concomitant Prevnar 13® vaccine ± other vaccines						
Yes	4·26	(1·24–15·74)	0·02	12·09	(0·83–235·36)	0·07
No	–	–	–	–	–	–
Any concomitant vaccine received ± Prevnar 13®						
Yes	1·46	(0·46–4·22)	0·51	0·61	(0·06–6·68)	0·70
No	–	–	–	–	–	–

*$P < 0·05$.

As just over half the parents returned cards, a participation bias may have been present. However, if present, we expect such a bias would have over-estimated febrile reactions because parents with unaffected children may have been less likely to submit diary cards.

Phone calls to a random sample of 50 parents who did not return forms revealed five children who may have experienced fevers (10%), suggesting that those children for whom diary cards were not returned did not differ significantly from those who were included in the sample.

Our data found an increase in febrile episodes in children receiving concurrent administration of other vaccines including Prevnar 13® at the time of influenza vaccination. Because of small numbers, we were unable to assess fever in children who received only Prevnar 13® concurrently with seasonal influenza vaccine (n = 4). However, our finding of increased febrile events associated with concurrent vaccination with at least Prevnar 13® is aligned with the January 2011 announcement by the US Food and Drug Administration (FDA) of an increase in the number of reports to the USCDC and FDA's Vaccine Adverse Events Reporting System (VAERS) of febrile seizures following vaccination with Fluzone manufactured by Sanofi Pasteur, Inc. again in association with concurrent receipt of Prevnar 13®. These reported febrile seizures were primarily seen in children younger than 2 years of age. No change to vaccination policy in the USA occurred following this initial signal. However, those findings lend weight to our data that suggested an increase in febrile responses with concurrent administration in a Canadian population.[22]

For the 2011 Southern winter, the Australian TGA restricted the use of CSL vaccine to those children 5 years and over and required CSL to conduct a preliminary study of 600 children aged 5–18 years looking for reactions in the first 3 days. Subsequently, this requirement was extended to other manufacturers with pediatric influenza vaccines not previously licensed in Australia.

The CSL vaccine was previously studied in 298 children in a multicentre study in Australia in 2005 and 2006. Higher rates of fever were seen in that study than here with 22% of children under 3 years of age reporting fever. However, the ''case definition'' criteria for fever in the Australian study included axillary temperatures over 37·5 degrees potentially explaining this higher rate as an ascertainment

issue rather than a continued tendency for CSL vaccines to be more reactogenic.[23]

In the United Kingdom where another CSL vaccine is in use for children, the Medicines and Healthcare products Regulatory Agency (MHRA) calculated background rates of febrile convulsion after influenza vaccines from 2008/09 and 2009/10 with data from the General Practice Research Database.

As of Feb 15, 2011, MHRA had received only two reports of febrile convulsions in children younger than 5 years after influenza immunization. At least 72 000 children had been vaccinated in this age group at this time, among whom up to ten cases of febrile convulsions were expected to have occurred. The observed-to-expected ratio for the age group was 0·19 (95% CI: 0·02–0·67). Brian and Seabroke concluded that, taking into account the possibility of under-reporting, there remained no indication that other influenza vaccines are associated with a large increase in risk of febrile convulsions as seen in Australia.[24]

Influenza vaccine is protective and important for all children. Seizures occur in 1% of children under 5 years of age with laboratory-confirmed influenza and 9% of children who are hospitalized because of influenza infection.[6] Our study reinforces previous work on the safety of influenza vaccine in children.[25]

However, to continue vaccinating children each year parents will need to be convinced, influenza vaccine is less harmful than contracting influenza itself, not the situation in 2010 in Australia.[15] Rapid studies, such as the study described here, on cohorts of children at the start of vaccination programs enable assessments that would prevent the use of vaccines associated with high rates of complications. Our study provides a baseline of levels of reactogenicity to seasonal influenza vaccines in subsets of young children in actual practice which can be used to assess future vaccine responses in rapid trials at the commencement of vaccine programs. Study data were collected over an 8-week period in this review but increasing the number of study sites included can reduce this time substantially.

Concurrent use of conjugated pneumococcal vaccine increases reactogenicity and, although this was not associated with a demonstrable increase in febrile convulsions, the sample size of our study may have been be too small to exclude this possibility. In jurisdictions such as New Brunswick where pneumococcal programs are delivered as a ''two plus one'' schedule with the booster dose at 12 months, the febrile risk may be higher. Concurrent use of quadrivalent Measles Mumps Rubella Varicella (MMRV) vaccine at the same time, also associated with fevers and convulsions, may further exacerbate reactogenicity although the fevers associated with MMRV occur some days after vaccination.[26] Therefore, further studies investigating reactogenicity associated with concurrent vaccines at time of seasonal influenza vaccination are warranted. Consideration should be given to prophylactic antipyretics with concurrent vaccinations to children aged 6–59 months which include influenza and conjugated pneumococcal vaccines, and parents should be advised to monitor for fevers.

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Authors contribution

All authors were involved in the development of the study design. PVB, GF, FWT, and BF cleaned and analyzed the data and led the writing of the manuscript. JVB, AR, and CJ were involved in developing diary cards, consent forms and information sheets and collation and review of data. All authors revised the manuscript critically and approved the final version that was submitted.

Disclaimer

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References

1 Espositi S, Marchisio P, Principi N. The global state of influenza in children. Paediatr Infec Dis J 2008; 27:S149–S153.
2 Neuzil KM, Mellen BG, Wright PF *et al.* The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000; 342:225–231.
3 Coffin SE, Zaoutis TE, Rosenquist AB *et al.* Incidents, complications and risk factors for prolonged stay in children hospitalized with community-acquired influenza. Pediatrics 2007; 119:740–748.
4 Bhat N, Wright JG, Broder KR *et al.* Influenza-associated deaths among children in the United States, 2003-2004. N Engl J Med 2005; 353:2559–2567.
5 Silvennoinen H, Peltola V, Vainionpää R, Ruuskanen O, Heikkinen T. Incidence of Influenza Related Hospitalizations in different age groups of children in Finland: a 16 year study. Pediatr Inf Dis J 2011; 30:e24–e28.
6 Poehling KA, Edwards KM, Weinberg GA *et al.* The under-recognised burden of influenza in young children. N Engl J Med 2006; 355:31–40.

7 D'Onise K, Raupach JC. The burden of influenza in health children in South Australia. Med J Aust 2008; 188:510–513.

8 Vynnycky E, Pitman R, Siddiqui R *et al.* Estimating the impact of childhood influenza vaccination programmes in England and Wales. Vaccine 2008; 41:5321–5330.

9 Eisenberg KW, Szilagyi PG, Fairbrother G *et al.* Vaccine effectiveness against laboratory-confirmed influenza in children 6 to 59 months of age during the 2003–2004 and 2004–2005 influenza seasons. Pediatrics 2008; 122:911–919.

10 Vesikari T, Fleming DM, Aristequi JF *et al.* Safety, efficacy, and effectiveness of cold-adapted influenza vaccine-trivalent against community-acquired, culture-confirmed influenza in young children attending day care. J Pediatrics 2006; 118:2298–2312.

11 Salo H, Kilpi T, Sintonen H, Linna M, Peltola V, Heikkinen T. Cost effectiveness of influenza vaccination of healthy children. Vaccine 2006; 24:4934–4941.

12 Fairbrother G, Cassidy A, Ortega-Sanchez IR *et al.* High costs of influenza: direct medical costs of influenza disease in young children. Vaccine 2010; 28:4913–4919.

13 Van Buynder PG, Carcione D, Rettura V, Daly A, Wood E. Marketing paediatric influenza vaccination: results of a major metropolitan trial. Influenza Other Respir Viruses 2010; 5:33–38.

14 Therapeutic Goods Administration. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. Woden: Department of Health and Ageing. 24 September 2010. Available from: http://www.tga.gov.au/alerts/medicines/fluvaccine-report100702.pdf

15 Kelly H, Carcione D, Dowse G, Effler P. Quantifying benefits and risks of vaccinating Australian children aged six months to four year with trivalent inactivated seasonal influenza vaccine in 2010. Euro Surveill 2010; 15:pil1 + 9661, Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19661.

16 Armstrong PK, Dowse GK, Effler PV *et al.* Epidemiological study of severe febrile reactions in young children in Western Australia caused by a 2010 trivalent influenza vaccine. BMJ Open 2011; 25:25–25, 1:e000016 doi:10.1136/bmjopen-2010-000016.

17 Blyth CC, Currie AJ, Wiertsema SP *et al.* Trivalent Influenza vaccine and febrile adverse events in Australia 2010: clinical features and potential mechanisms. Vaccine 2011; 32:5107–5113.

18 Australian Government. Review of the management of adverse events associated with Panvax and Fluvax, Available from: http://www.health.gov.au/internet/immunise/publishing.nsf/Content/adverse-event-l~adverse-event-l-ch5.

19 Van Buynder PG, Dhaliwal JK, Van Buynder JL *et al.* Protective effect of single-dose adjuvanted pandemic influenza vaccine in children. Influenza and Other Respiratory Viruses 2010; 4:171–178.

20 Ochiai H, Shibata M, Kamimura K, Niwayama S. Evaluation of the efficacy of split-product trivalent A(h1N1), A(N3N2) and B influenza vaccines: reactogenicity, immunogenicity, and persistence of antibodies following two doses of vaccine. Microbiol Immunol 1986; 30:1141–1149.

21 Public Health Agency of Canada. Statement on seasonal trivalent inactivated influenza vaccine (TIV) for 2010–2011. Can Commun Dis Rep 2010; 6:1–49, http://www.phac-aspc.gc.ca/publicat/ccdr-rmtc/10vol36/acs-6/index-eng.php.

22 Centers for Disease Control and Prevention. Update on febrile seizures in children following vaccination with influenza vaccines and pneumococcal vaccines. Centers for Disease Control and Prevention, Available from: http://www.cdc.gov/vaccinesafety/Concerns/FebrileSeizures.html.

23 Nolan T, Richmond P, McVernon J *et al.* Safety and Immunogenicity of an inactivated thimerosal-free influenza vaccine in infants and children. Influenza and Other Resp Viruses 2009; 3:315–325.

24 Bryan P, Seabroke S No increased risk of febrile convulsions after seasonal influenza immunisation in UK. Lancet 2011; 377:904, Doi:10.1016/S0140-6736(11)60352-8.

25 Hambridge SJ, Glanz KM, France EK *et al.* Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old. JAMA 2006; 296:1990–1997.

26 Centers for Disease Control Prevention. Use of combination measles, mumps, rubella, and varicella vaccine: recommendations of the advisory committee on immunization practices. MMWR 2010; 59:RR–3, Available from: http://www.cdc.gov/mmwr/pdf/rr/rr5903.pdf.