

The safety of seasonal influenza vaccines in Australian children in 2013

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Fever and febrile convulsions in young Australian children were widely reported after vaccination with one brand of influenza vaccine (Fluvax and Fluvax Junior; bioCSL) in 2010.¹ This unexpected increase in risk (estimated incidence of 4.4 seizures per 1000 doses) was confirmed in several studies.²⁻⁶ The method of manufacture of the Fluvax vaccine, which unknowingly preserved strain-specific viral components of new influenza strains in 2010, appears to have been responsible for the higher rate of fever in children.^{7,8} Despite reassuring data on the safety of other brands of influenza vaccine^{6,9} and the recommendation that Fluvax vaccine not be administered to young children,^{10,11} there has been a loss of confidence in the safety of influenza vaccines. In Western Australia, where influenza vaccine is available free of charge for all children aged 6 months to <5 years, influenza (but not other routine) vaccine uptake was substantially reduced in children during 2010–2012.¹²

To provide more information on the safety of influenza vaccines in children, the Australian Government Department of Health funded a national pilot of active postmarketing surveillance of influenza vaccines registered by the Therapeutic Goods Administration for use in children. As influenza vaccines can vary in composition each year, studies to ensure that each annual vaccine has a consistently low rate of side effects are important. Further, a government review after the adverse events of 2010 suggested that additional surveillance mechanisms to ensure vaccine safety be evaluated.¹³ Here, we report the results of prospective active surveillance of influenza vaccine safety in children using solicited parent and carer reporting in 2013.

Methods

Parents and carers of all children aged 6 months to <10 years who received

Abstract

Objective: To examine influenza vaccine safety in Australian children aged under 10 years in 2013.

Design, participants and setting: Active prospective surveillance study conducted with parents or carers of children who received influenza vaccine in outpatient clinics at six tertiary paediatric hospitals or from selected primary health care providers between 18 March and 19 July 2013.

Main outcome measures: Parental-reported frequency of systemic reactions (fever, headache, nausea, abdominal symptoms, convulsions, rash, rigors and fatigue), injection site reactions (erythema, swelling and/or pain at the injection site), use of antipyretics or analgesics, and medical attendance or advice within 72 hours after vaccination.

Results: Of 981 children enrolled in the surveillance, 893 children aged 6 months to <10 years were eligible for inclusion. These children received 1052 influenza vaccine doses. Fever was reported in 5.5% (95% CI, 4.1%–7.3%) and 6.5% (95% CI, 3.5%–10.9%) of children after Doses 1 and 2, respectively. One febrile convulsion occurred in a child with a known seizure disorder. Injection site reactions occurred in 21.2% (95% CI, 18.5%–24.1%) and 6.0% (95% CI, 3.1%–10.2%) after Doses 1 and 2, respectively; most were mild. Very few parents sought medical follow-up for their child's reaction: 22 (2.6%; 95% CI, 1.6%–3.9%) after Dose 1, and 11 (5.5%; 95% CI, 2.8%–9.6%) after Dose 2.

Conclusions: These results are consistent with clinical trials and other observational studies of influenza vaccines currently registered for use in young children in Australia and can reassure parents and health care providers that influenza vaccination is safe and well tolerated.

influenza vaccine in outpatient clinics at six paediatric hospitals in Australia (the Children's Hospital at Westmead, Sydney; Royal Children's Hospital, Melbourne; Monash Medical Centre, Melbourne; Women's and Children's Hospital, Adelaide; Princess Margaret Hospital for Children, Perth; and Royal Children's Hospital, Brisbane) and from primary health care providers (Central Immunisation Clinic, Perth; and general practices in the Western Sydney Medicare Local, Sydney) were invited to participate in the study. Participation rate was not formally recorded across the sites. In WA, the upper age limit for inclusion was 59 months (<5 years).

Recruitment commenced on 18 March 2013 and concluded on 19 July 2013. Data on age, sex, presence of any pre-existing chronic medical conditions for which annual influenza vaccine is highly recommended,¹⁴ brand of influenza vaccine, and concomitant vaccines received were recorded. Information was collected in a brief telephone interview conducted by surveillance nurses 3–5 days after vaccination.

Antipyretic or analgesic medications were not routinely recommended for children before or after vaccination; their use was at the discretion of the parent or carer.

Approval for this surveillance was granted by the human research ethics committees of each participating hospital and by the Australian Government Department of Health.

Vaccines

Influenza vaccination is recommended and in most cases funded under the National Immunisation Program (NIP) for people in Australia aged ≥6 months with conditions predisposing to severe outcomes from influenza infection. Additionally, in WA, influenza vaccine is offered free of charge to all children aged 6–59 months. Influenza vaccines used in 2013 contained the vaccine virus strains: A(H1N1) — an A/California/7/2009(H1N1)-like virus; A(H3N2) — an A/Victoria/361/2011(H3N2)-like virus; and B — a B/Wisconsin/1/2010-like virus. The four vaccines registered and recommended for use in children

aged 6 months to <10 years were Fluarix (GlaxoSmithKline Australia), Vaxigrip (Sanofi Pasteur), Influvac (Abbott Australasia) and Agrippal (Novartis Australia). The vaccines funded under the NIP were Fluarix and Vaxigrip. Fluvax was not included in this study as it is not registered for use in children aged <5 years and is not recommended for routine use in children aged 5 to <10 years.¹⁵

Outcome measures

Primary outcomes were the frequency within 72 hours after vaccination of systemic reactions (fever, headache, nausea, abdominal symptoms, convulsions, rash, rigors and fatigue) and injection site reactions (erythema, swelling and/or pain at the injection site). All outcome measures were recorded according to information provided by the parent or carer. Fever (or feeling hot) was recorded either by parental report (yes/no) or, if temperature was measured, fever was defined as $\geq 37.5^{\circ}\text{C}$ by any route. Severity of injection site reactions was recorded for non-WA sites only and was classified on the basis of parental description as: "severe" when erythema or swelling was estimated as ≥ 50 mm diameter and/or pain prevented normal everyday activities or required medical attention; "moderate" when diameter was > 10 to < 50 mm; and "mild" when diameter was ≤ 10 mm. Information was also collected on use of antipyretics or analgesics after vaccination, and whether medical attention or advice was sought.

Sample size calculation and data analysis

The number of study participants was determined from power calculations using estimates of the expected percentage of fever in vaccinees (5%–10%).^{16,17} A sample size of 865 was calculated to achieve the point estimate with 95% confidence intervals of 2%–5% absolute precision.

Data were recorded in a REDCap online database,¹⁸ and Stata/SE version 12.0 (StataCorp) was used for analysis. Subgroup analyses were performed for dose number (1 versus 2), concomitant versus sole administration of influenza vaccine, and vaccine brand received. To test the

difference between binomial variables, the χ^2 test was used for independent samples, and the McNemar test for paired samples. The Wilcoxon rank-sum test was used to compare the median values of non-normal continuous variables.

Results

Of 981 children enrolled in the surveillance, 88 (9.0%) were excluded from the analysis: eight of these were aged ≥ 10 years; influenza vaccine was inadvertently given just below the age of 6 months for one; and parents were unable to be contacted for 79 (non-response rate of 8.1%). Of the 893 children eligible for inclusion in the analysis, 419 (46.9%) were from WA, and 474 (53.1%) from other states.

Data on participant characteristics and vaccines received are shown in Box 1. The 893 children received 1052 influenza vaccinations: data were obtained after a single dose (Dose 1) for 693 children; after two doses (Doses 1 and 2) for 159 children; and after

Dose 2 only for 41 children (totals: Dose 1, 852; Dose 2, 200). The mean age was 3.6 years (median, 3.1 years), and 484 children (54.2%) had at least one chronic medical condition. Of these, 196 (40.5%) had a respiratory condition and 55 (11.4%) had a cardiac condition. More children aged ≥ 3 years had a chronic medical condition than those aged < 3 years (61.2% v 47.0%).

Most vaccinations given were Vaxigrip or Vaxigrip Junior (776; 73.8%). No children were recorded as receiving Agrippal. Concomitant vaccines were administered with influenza vaccine in 60 of 1052 encounters (5.7%), all of which were with Dose 1 of the influenza vaccine. The median age of children receiving concomitant vaccines was lower than that for those receiving influenza vaccine only (2.7 v 3.3 years, $P=0.033$ with Wilcoxon rank-sum test).

Safety outcome data

Data on the frequency of systemic and injection site reactions are shown

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1 Characteristics of study participants and influenza vaccines administered, by age group*

Characteristic	Age		Total†
	6 months to < 3 years	3 to < 10 years	
Total children	436	456	893
Male‡	158/298 (53.0%)	92/173 (53.2%)	250/471 (53.1%)
Mean age, years (SD)	1.7 (0.7)	5.3 (1.9)	3.6 (2.4)
Median age, years (interquartile range)	1.6 (1.0–2.3)	4.7 (3.7–6.8)	3.1 (1.6–4.8)
Previous influenza vaccine			
At least one dose in previous 3 years	91 (20.9%)	209 (45.8%)	300 (33.6%)
Never received	344 (78.9%)	247 (54.2%)	592 (66.3%)
Not recorded	1 (0.2%)	0	1 (0.1%)
Chronic medical conditions			
At least one chronic medical condition	205 (47.0%)	279 (61.2%)	484 (54.2%)
No chronic medical conditions	231 (53.0%)	177 (38.8%)	409 (45.8%)
Data on doses recorded			
Dose 1	283 (64.9%)	409 (89.7%)	693 (77.6%)
Dose 2	35 (8.0%)	6 (1.3%)	41 (4.6%)
Both Doses 1 and 2	118 (27.1%)	41 (9.0%)	159 (17.8%)
Total vaccines administered	553	498	1052
Fluarix	30 (5.4%)	100 (20.1%)	131 (12.5%)
Influvax or Influvac Junior	54 (9.8%)	55 (11.0%)	109 (10.4%)
Vaxigrip or Vaxigrip Junior	444 (80.3%)	332 (66.7%)	776 (73.8%)
Not recorded	25 (4.5%)	11 (2.2%)	36 (3.4%)

* Age groups were chosen to coincide with the ages at which children are recommended to receive different doses of influenza vaccine, as per the *Australian immunisation handbook* (children aged 6 months to < 3 years receive a 0.25 mL dose, and children aged 3 to < 10 years receive a 0.5 mL dose).¹⁴ Percentages may not sum to 100% due to rounding. † Totals include one child whose age was not recorded. This child had never received influenza vaccine, had no chronic medical conditions and received Dose 1 of Fluarix. ‡ Information on sex was received for 471 participants (data not collected in Western Australia). ◆

2 Safety outcomes and management of children aged 6 months to < 10 years who received influenza vaccines*

Outcome	Dose 1 (n = 852)							Dose 2 (n = 200)
	Total	Chronic medical conditions		Previous influenza vaccine		Age		Total
		Yes	No	Yes	No	6 m to < 3 y	3 to < 10 y	
Systemic reaction of any severity								
Fever	47 (5.5%) [4.1%–7.3%]	29 (6.1%) [4.1%–8.7%]	18 (4.7%) [2.8%–7.4%]	20 (6.7%) [4.1%–10.1%]	27 (4.9%) [3.2%–7.0%]	26 (6.4%) [4.3%–9.4%]	21 (4.7%) [2.9%–7.0%]	13 (6.5%) [3.5%–10.9%]
Headache	26 (3.1%) [2.0%–4.4%]	19 (4.0%) [2.4%–6.2%]	7 (1.8%) [0.7%–3.8%]	15 (5.0%) [2.8%–8.1%]	11 (1.9%) [1.0%–3.5%]	1 (0.2%) [0.01%–1.4%]	25 (5.6%) [3.6%–8.1%]	1 (0.5%) [0.01%–2.8%]
Nausea, vomiting or abdominal pain	39 (4.6%) [3.3%–6.2%]	23 (4.9%) [3.1%–7.2%]	16 (4.2%) [2.4%–6.8%]	14 (4.7%) [2.6%–7.7%]	25 (4.5%) [2.9%–6.6%]	18 (4.5%) [2.7%–7.0%]	21 (4.7%) [2.9%–7.0%]	5 (2.5%) [0.8%–5.7%]
Convulsion	1 (0.1%) [0.01%–0.7%]	1 (0.2%) [0.01%–1.2%]	0 (0) [0–1.0%]	1 (0.3%) [0.01%–1.8%]	0 (0) [0–0.7%]	0 (0) [0–0.9%]	1 (0.2%) [0.01%–1.2%]	0 (0) [0–1.8%]
Rash	15 (1.8%) [1.0%–2.9%]	11 (2.3%) [1.2%–4.1%]	4 (1.1%) [0.3%–2.7%]	8 (2.7%) [1.2%–5.2%]	7 (1.2%) [0.5%–2.6%]	7 (1.7%) [0.7%–3.6%]	8 (1.8%) [0.8%–3.4%]	1 (0.5%) [0.01%–2.8%]
Rigors	6 (0.7%) [0.3%–1.5%]	5 (1.1%) [0.3%–2.4%]	1 (0.3%) [0.01%–1.5%]	2 (0.7%) [0.1%–2.4%]	4 (0.7%) [0.2%–1.8%]	3 (0.7%) [0.2%–2.2%]	3 (0.7%) [0.1%–1.9%]	0 (0) [0–1.8%]
Fatigue	73 (8.6%) [6.8%–10.7%]	48 (10.1%) [7.6%–13.2%]	25 (6.6%) [4.3%–9.6%]	24 (8.0%) [5.2%–11.7%]	49 (8.8%) [6.6%–11.5%]	35 (8.7%) [6.2%–11.9%]	38 (8.4%) [6.0%–11.4%]	6 (3.0%) [1.1%–6.4%]
Any systemic reaction†	157 (18.4%) [15.9%–21.2%]	92 (19.4%) [15.9%–23.3%]	65 (17.2%) [13.5%–21.3%]	60 (20.1%) [15.7%–25.1%]	97 (17.5%) [14.4%–20.9%]	77 (19.2%) [15.5%–23.4%]	80 (17.8%) [14.3%–21.6%]	33 (16.5%) [11.6%–22.4%]
Injection site reaction of any severity								
Swelling or lump	49 (5.8%) [4.3%–7.5%]	34 (7.2%) [5.0%–9.9%]	15 (4.0%) [2.2%–6.4%]	26 (8.7%) [5.8%–12.5%]	23 (4.2%) [2.6%–6.2%]	12 (2.9%) [1.6%–5.2%]	37 (8.2%) [5.9%–11.2%]	6 (3.0%) [1.1%–6.4%]
Pain or tenderness	158 (18.5%) [16.0%–21.3%]	106 (22.4%) [18.7%–26.4%]	52 (13.7%) [10.4%–17.6%]	72 (24.1%) [19.3%–29.3%]	86 (15.5%) [12.6%–18.8%]	27 (6.7%) [4.5%–9.6%]	131 (29.1%) [25.0%–33.5%]	7 (3.5%) [1.4%–7.1%]
Any injection site reaction‡	181 (21.2%) [18.5%–24.1%]	119 (25.1%) [21.3%–29.3%]	62 (16.4%) [12.8%–20.5%]	83 (27.7%) [22.8%–33.2%]	98 (17.7%) [14.6%–21.1%]	39 (9.7%) [7.0%–13.1%]	142 (31.6%) [27.3%–36.1%]	12 (6.0%) [3.1%–10.2%]
Management								
Analgesic or antipyretic after vaccination§	164 (19.2%) [16.7%–22.1%]	103 (21.7%) [18.1%–25.7%]	61 (16.1%) [12.5%–20.2%]	69 (23.1%) [18.4%–28.3%]	95 (17.1%) [14.1%–20.6%]	85 (21.2%) [17.3%–25.5%]	79 (18.3%) [14.5%–21.9%]	35 (17.5%) [12.5%–23.5%]
Sought medical attention¶	22 (2.6%) [1.6%–3.9%]	14 (2.9%) [1.6%–4.9%]	8 (2.1%) [0.9%–4.1%]	10 (3.3%) [1.6%–6.1%]	12 (2.2%) [1.1%–3.8%]	11 (2.7%) [1.4%–4.9%]	11 (2.5%) [1.3%–4.4%]	11 (5.5%) [2.8%–9.6%]

* Data are number (%) [95% CI]. Some children reported more than one symptom. † Missing data for Dose 1, n = 1. ‡ Missing data for Dose 1, n = 5. § Any injection site reaction† includes erythema. ¶ Missing data for Dose 1, n = 1. † Missing data for Dose 1, n = 2.

in Box 2. Overall, reactions occurred in about one in five influenza vaccine recipients. Injection site reactions were more common after Dose 1 than Dose 2 (21.2% v 6.0%), whereas frequency of systemic reactions was similar after Doses 1 and 2 (18.4% v 16.5%). Fever was reported in 47 of 852 children (5.5%) after Dose 1, with a similar rate after Dose 2 (13/200; 6.5%) ($P=0.61$). Among the 159 vaccinees with data available for both doses, no obvious differences in the risk of adverse events after vaccination compared with the whole cohort analysis were evident (data not shown).

Overall, there were 60 children whose parents or carers reported fever (either measured temperature elevation or feeling hot) during the 3 days of observation (Box 2). After Dose 1, most children experienced fever on Day 1 (29/47; 61.7% [95% CI,

46.4%–75.5%]), with fewer having fever on Day 2 (18/47; 38.3% [95% CI, 24.5%–53.6%]). After Dose 2, fever occurred on Day 1 in seven of 13 children (53.8% [95% CI, 25.1%–80.8%]). There was no significant difference in fever between age groups.

After Dose 1, older children (aged 3 to < 10 years) had significantly higher rates than younger children of injection site reactions (31.6% v 9.7%; $P<0.001$), as did children who had received influenza vaccine previously compared with vaccine-naive children (27.7% v 17.7%; $P=0.001$).

Certain adverse events were more common after influenza vaccine was given concomitantly with other vaccines than after influenza vaccine given alone. For occurrence of fever with concomitant versus sole administration (13.3% [95% CI, 5.9%–24.6%] v 4.9% [3.5%–6.7%]; $P=0.013$), the

relative risk (RR) was 2.7 (95% CI, 1.3–5.5). Systemic reactions (36.7% [95% CI, 24.6%–50.1%] v 17.0% [95% CI, 14.5%–19.8%]; $P<0.001$) and analgesic or antipyretic use (30.0% [95% CI, 18.8%–43.2%] v 18.4% [95% CI, 15.8%–21.3%]; $P=0.04$) were also more common after concomitant administration with other vaccines (RR, 2.2 [95% CI, 1.5–3.1] and 1.6 [95% CI, 1.1–2.5], respectively).

There were some differences between vaccine brands, but they were not consistent across all outcome measures and age groups. Fever rates did not exceed 6.7% for any of the three vaccine brands (data not shown).

Severity of adverse events

Of the 181 injection site reactions reported after Dose 1, severity was reported for 154, and only 11 of these

(7.1%) were reported as severe. Of the 60 children for whom fever was reported, 46 had their temperature recorded: four (defined as having fever based on parental report) had a temperature less than 37.5°C, 22 were between 37.5°C and 38.5°C, 18 were between 38.6°C and 39.5°C, and two were >39.5°C. One child had a febrile convulsion after Dose 1. This child was known to have a seizure disorder and had a history of seizures after vaccination. Despite administration of paracetamol after vaccination, he had a seizure on Day 1 and was hospitalised, but made a complete recovery. Nearly one in five children used analgesics or antipyretics within 3 days of vaccination (Box 2).

Medical attention or advice was sought in the 72 hours after influenza vaccination for 22 children (2.6%) after Dose 1, and 11 (5.5%) after Dose 2 (Box 2). Of the children for whom medical attention was sought after Dose 1, eight attended a hospital emergency department, 10 went to their local medical practitioner, and telephone or email advice was sought for four. The eight children who attended an emergency department included one child with a febrile seizure, two with urticarial rashes, two with croup or bronchitis, one with diarrhoea, one with headache and vomiting, and one with unspecified illness. Two children saw their local medical practitioner because of parental concern about fever. The reasons for medical presentations after Dose 2 were not recorded.

Discussion

This is the first time that active surveillance of influenza vaccine safety has been conducted across multiple states in Australia. The results from this large cohort offer reassurance to parents and health care providers that the seasonal influenza vaccines recommended for use in young children are safe. We found that a low proportion of children (5.5%–6.5%) had fever after vaccination, and recorded temperature elevations were generally low-grade. Although injection site and systemic reactions occurred in about one in five vaccine recipients, these were generally mild.

Our data are similar to two smaller Australian studies in children aged <5 years: one in WA in 2011, in which 6.9% of children (10/144) reported fever;¹⁹ and another in New South Wales in 2010–2011, in which the prevalence of fever was 6.3%–7.1% after use of non-bioCSL vaccine.⁶ A recent systematic review found a similar overall rate of fever in children aged 6 to <36 months. After one dose of influenza vaccine, the median average weekly risk of any fever was 8.2% (range, 5.3%–28.3%) in published reports and 26.0% (range, 10.3%–70.0%) in unpublished trials.¹⁶ The latter estimate included results from bioCSL Fluvax studies, including a Phase IV clinical trial conducted in 2009 but not published until 2013 (in which 28.6% of children aged 6 months to <3 years and 19.5% of children aged 3 to <9 years experienced fever).²⁰

Although one in five parents in our study reported injection site reactions after Dose 1, very few of these were considered severe. Injection site reactions were more common in older children and in those previously vaccinated; however, this may be confounded by older children being more likely to verbally report pain and tenderness. Similar to previous studies,^{6,19} very few families sought medical advice after vaccination, and in some instances this was for events that were likely to be unrelated to vaccination.

Our study suggests that the risk of fever and other systemic reactions is increased in those who are given influenza vaccine on the same day as other routine vaccines. Similarly, a prospective cohort study in the United States demonstrated that children aged 6–23 months who received influenza vaccine concomitantly with 13-valent pneumococcal conjugate vaccine (PCV13) had higher rates of fever (37.6%) than children who received influenza vaccine (7.5%) or PCV13 (9.5%) on separate days.²¹ Another study showed an increased, albeit low, absolute risk of febrile seizure associated with concurrent administration of influenza vaccine and PCV13.²²

The strengths of this surveillance included the prospective follow-up of vaccinated children, with a short

interval between receipt of influenza vaccine and collection of safety outcome data. However, the use of nurse phone calls for soliciting parental reports was labour-intensive. Recently, the use of mobile phone text messaging and web-based technology to contact patients or parents has been shown to be effective for follow-up after vaccination.^{23–25} Although potential variability in data quality due to parental reporting may limit detailed analysis and interpretation, the consistency of our findings with multiple other studies for outcome measures such as fever suggests this was not a limitation.

Vaccination providers and the public can feel confident that a range of measures, including surveillance that employs parent and carer reporting of adverse events, provide information on the safety of the influenza vaccines currently recommended for use in Australian children. This surveillance is ongoing in 2014 and has continued to provide reassuring data on the current season's influenza vaccines.²⁶

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