Real-time safety surveillance of seasonal influenza vaccines in children, Australia, 2015

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Increased febrile reactions in Australian children from one influenza vaccine brand in 2010 diminished confidence in influenza immunisation, highlighting the need for improved vaccine safety surveillance. *AusVaxSafety*, a national vaccine safety surveillance system collected adverse events in young children for 2015 influenza vaccine brands in real time through parent/carer reports via SMS/email. Weekly cumulative data on 3,340 children demonstrated low rates of fever (4.4%) and medical attendance (1.1%). Fever was more frequent with concomitant vaccination.

In 2014, a multi-jurisdictional national system, *AusVaxSafety,* was established to undertake enhanced influenza vaccine safety surveillance and report real-time adverse events in children aged six months to four years. This collaborative system was funded by the Australian Government Department of Health. Surveillance (n = 782 children) demonstrated the safety of 2014 seasonal influenza vaccines in a matter of weeks, although most children received one vaccine brand (Vaxigrip, Sanofi Pasteur; 86.2%; n = 674 children) [1,2]. Expansion of the programme in 2015 to incorporate a new data management platform and more participating general practice (GP) sites (GPs provide more than 70% of vaccines given nationally [3]) has enabled reporting of the safety of 2015 southern hemisphere trivalent influenza vaccines for thousands of children receiving multiple manufacturers' vaccines. Here we report the results of our surveillance conducted during the 2015 Australian influenza season.

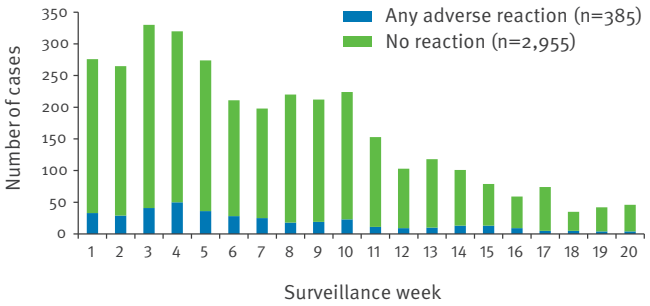
The *AusVaxSafety* vaccine safety surveillance system

In Australia (population 23 million [4]), influenza vaccination is funded under the National Immunisation Program for children aged six months to four years who have medical conditions pre-disposing them to complications and/or for Indigenous children. Only one state, Western Australia (WA), has funded influenza vaccination for this age group since 2008.

For the purposes of *AusVaxSafety* surveillance, children aged six months to four years receiving seasonal influenza vaccine from participating GP sites (n = 54), hospitals (n = 6), public clinics (n = 2) and primary healthcare providers such as Aboriginal Medical Services (n = 7) in four states (New South Wales (NSW), Victoria, South Australia and WA) were eligible for inclusion. Parent/carer-reported adverse events in children were solicited within three days of vaccination using two computer-based data management platforms, Vaxtracker [5] and SmartVax [6]. Both systems sent automated SMS messages (and/or emails for Vaxtracker) and received parent/carer-completed questionnaire responses via reply SMS with a URL link to smartphone survey (SmartVax)

Figure

AusVaxSafety participants with and without post-vaccine reaction, by week of vaccination, and cumulative percentage of participants, Australia, 1 April–31 August 2015 (n = 3,340)



Surveillance Week 1 included all participants vaccinated prior to the official rollout of the influenza vaccine for the 2015 season (20 April 2015) and captured children vaccinated from 1 to 19 April 2015. After that, each surveillance week consisted of seven days, with Week 2 including 20–26 April, etc. Week 20 included eight days (24–31 August 2015).

or web-based survey (Vaxtracker). Demographic details were obtained, as well as information regarding vaccine brand, medical conditions, concomitant vaccines, reactions and healthcare consultations required after vaccination (including follow-up visit to a GP, emergency department (ED) or hospitalisation).

Serious adverse events (SAE) were categorised according to predefined criteria, which included any untoward medical event that resulted in death, was life-threatening or required hospitalisation [7]. We also included seizures requiring medical attendance (ED and/or hospitalisation) as medically important events. SAEs were reported to state/territory health departments and the Therapeutic Goods Administration as required by legislation. For this report, data were compiled from 1 April through 31 August 2015 and cumulative data reported to health authorities weekly. After week 4 of surveillance, progressive results were periodically made publically available online and shared via immunisation provider networks.

For rapid signal detection, fast initial response cumulative summation (FIR CUSUM) and Bayesian methods [8,9] were employed weekly to estimate the probability that any potential safety signal was true or false based on predetermined expected and threshold rates of two objective outcome measures (fever and medical advice/attendance sought) in relation to the number of reports received. Expected and threshold rates were set according to previous surveillance results and published studies. For fever, the expected rate was 6% and the threshold rate for triggering a signal was 13% [5,10-12].

Results

Approximately 75% of the 4,441 parents/carers invited agreed to participate, resulting in 3,340 post-vaccination reports (Figure). The majority of parent/carers responded within two hours of being queried. Descriptive details of participants are presented in Table 1.

Weekly analysis using FIR CUSUM and Bayesian methods (conducted 1 April through 5 July 2015) did not demonstrate a safety signal at any time. After the third week of surveillance (n = 877 cumulative reports), fever rates remained less frequent than 5% each week and medical advice/attendance rates remained lower than 2%.

Parent/carer-reported fever was recorded by 4.4% (n = 148); medical advice/attendance was sought by 1.1% (n = 35). Details on reactions and medical advice/attendance sought are included in Table 2.

Of the 35 children who received medical advice/attendance, 23 reported fever. Five children experienced seizures, four of whom had a history of seizures (three: underlying neurological conditions; one: previous febrile seizures). The fifth seizure case occurred in a child diagnosed with a febrile viral illness. Only three of the children with seizures sought medical attendance and were thus classified as having SAEs; all attended an ED only. One additional SAE was recorded in a child hospitalised with an influenza-like illness and fever. Two of the four children experiencing an SAE had received Vaxigrip, one had received Fluarix and the other received Influvac. All reported improvement within days.

No significant difference was identified between children who had received one of the two most commonly used vaccine brands, Vaxigrip or Fluarix, and who experienced fever or sought medical advice/attendance. All other brands had been administered in insufficient numbers to reliably report on differences (Table 3). Children receiving other vaccines concomitantly were significantly more likely to experience fever (60/687; 8.7%) than those who did not (87/2,618; 3.3%) (p = 0.000). There was no difference between children with and without an underlying condition regarding fever (29/400 (7.3%) vs 56/721 (7.8%)) or medical advice/attendance sought (9/400 (2.3%) vs 17/721 (2.4%)).

Discussion

Our novel system of active, prospective vaccine safety surveillance, *AusVaxSafety,* has demonstrated in real time that 2015 southern hemisphere influenza vaccines registered for use in young Australian children were safe and well-tolerated. Adverse event rates reported by parents/carers remained low and within expected ranges throughout the surveillance period. The fever rate was lower than the pooled estimate (6.7%) in a recent systematic review of randomised control trials of children aged six to 35 months receiving the first dose of a trivalent influenza [12].

Table 1

Demographic details of *AusVaxSafety* participants, Australia, 1 April–31 August 2015 (n = 3,340)

Variable	Response	Number	Percentage
Median age (range)	23.0 months (6.0–59.9)		
Sex [a]	Male	1,781/3,314	53.7%
Ethnicity [b]	Indigenous	119/2,519	4.7%
Underlying medical condition [c]	Yes	400/1,121	35.7%
Concomitant vaccine(s) received [d]	Yes	687/3,305	20.8%

[a] Sex unknown for 26 of 3,340 participants.

[b] Ethnicity unknown for 821 of 3,340 participants.

[c] Underlying medical condition not available for 2,219 of 3,340 participants (SmartVax data management system does not currently collect this variable).

[d] Data on whether concomitant vaccine was received unknown for 35 of 3,340 participants.

Table 2

Adverse events reported by 2015 *AusVaxSafety* participants within three days of vaccination, Australia, 1 April–31 August 2015 (n = 3,340)

Adverse event		Number	Percentage
Any adverse event		385/3,340	11.5%
Fever		148/3,340	4.4%
Seizure [a]		5/3,340	0.2%
Injection site reaction		67/3,340	2.0%
Vomiting/abdominal pain		41/3,340	1.2%
Rash		36/3,340	1.1%
Participants who sought any medical advice and/or required any medical attendance		35/3,340	1.1%
Highest medical advice and/or attendance reported	Participants attending a medical facility for consultation with a general practitioner or other medical practitioner	23/3,340	0.7%
	Participants telephoning a medical facility or a medically staffed helpline for advice	4/3,340	0.1%
	Participants presenting to an emergency department (not admitted) [a]	6/3,340	0.2%
	Participants hospitalised [b]	2/3,340	0.1%

[a] Of the five children with seizures reported, three presented to an emergency department and were thus classified as having a serious adverse event.

[b] One child was hospitalised with an unrelated condition not deemed a serious adverse event. The other hospitalised child had an influenza-like illness.

Active, prospective vaccine safety surveillance is superior to traditional post-marketing vaccine safety surveillance which typically relies on passive reporting. In Australia, SMS technology has also been used to study vaccine reactions among healthcare workers and pregnant women [13,14]. One study in the United States also used SMS follow-up of parents, detecting increased fever rates in children who had concomitantly received trivalent influenza vaccine and 13-valent pneumococcal vaccine compared with those who received each vaccine alone [15]. Similarly, we reported an increased (although low) rate of fever when influenza vaccine was administered together with other vaccines. This was also associated with a significantly higher likelihood of seeking medical advice and warrants further investigation.

Because large volumes of influenza vaccine are distributed annually within short, defined periods, active surveillance provides the opportunity to gain early, reliable assessments of the safety profiles of new vaccines. As the number of available influenza vaccines increases, obtaining timely safety data becomes more important, particularly as strain composition may vary from season to season. In 2010 in Australia, an unexpected increase in febrile reactions following receipt of influenza vaccination in young children led to a three month suspension of all national paediatric influenza immunisation programmes [16]. Epidemiological and laboratory studies linked these reactions to one manufacturer's vaccine (Fluvax or Afluria, bioCSL) which is no longer registered for use in young children [16,17]; however, confidence in all influenza vaccines was negatively impacted [18,19]. In response to these safety concerns which have resulted in low uptake of

Table 3

Details of influenza vaccines administered to *AusVaxSafety* participants, Australia, 1 April–31 August 2015 (n = 3,340)

Brand[a] (manufacturer)	Vaccine type	Number of vaccines administered (n = 3,336)		Number of participants with fever by brand		Number of participants who sought medical advice/attendance by brand	
		n	%	n/N	%	n/N	%
Vaxigrip (Sanofi-Pasteur)	Trivalent	3,075	92.2	133/3,075[c]	4.3%	28/3,075[d]	0.9%
Fluarix (GlaxoSmithKline)	Trivalent	189	5.7	9/189	4.8	4/189	2.1
Influvac (BGP Products)	Trivalent	47	1.4	5/47	NR	2/47	NR
Agrippal (Novartis Vaccines and Diagnostics)	Trivalent	11	0.3	0/11	NR	0/11	NR
FluQuadri[b] (Sanofi Pasteur)	Quadrivalent	14	0.4	1/14	NR	1/14	NR

NR: not relevant.

[a] Brand unknown for four participants.

[b] All administered vaccines except for FluQuadri were trivalent. Quadrivalent vaccines (FluQuadri/ FluQuadri Junior and Fluarix Tetra (GlaxoSmithKline)) were available for use for the first time in Australia in 2015 but were not funded under the National Immunisation Program.

[c] p = 0.775 for rates of fever among those who received Vaxigrip (4.3%) compared with those who received Fluarix (4.8%) calculated using Pearson's chi-square test.

[d] p = 0.102 for rates of medical advice/attendance sought among those who received Vaxigrip (0.9%) compared with those who received Fluarix (2.1%) calculated using Fisher's exact test.

seasonal influenza vaccines in children, *AusVaxSafety* surveillance data have been able to provide reassuring results.

Data obtained from parental reporting should be interpreted with care. Consequently, *AusVaxSafety* reports on outcomes which are the most objective: fever and medical advice/attendance sought within three days of vaccination. Although these provide less precision than results obtained in more formal follow-up such as clinical trials, this is unlikely to reduce our system's sensitivity for detecting SAEs, of which medical advice/attendance sought can be considered a good proxy. This was demonstrated in the epidemiological investigation of the 2010 increase in febrile reactions [16].

An advantage of our system is its potential adaptability for monitoring new vaccines, such as live attenuated influenza vaccine, although this is not yet available in the southern hemisphere. Another advantage is its ability to provide rapid real-time feedback to inform programme rollout and vaccine promotion. In addition, *AusVaxSafety*'s flexibility may be valuable in situations where vaccine safety data are limited, such as for pandemic vaccines. The timeliness of our results also makes them valuable beyond Australia; our data may be of interest to counterparts in the northern hemisphere preparing for 2015/16 vaccination using vaccines comprised of the strains administered in the 2015 southern hemisphere season.

Our system, which is able to report adverse events within days of vaccination, is as near to real time as possible. Such timeliness is feasible thanks to the strong collaboration with parents/carers and providers and the use of SMS technology for reporting reactions. We anticipate being able improve our system by including more participants in future years. To our knowledge, *AusVaxSafety* is the only active influenza vaccine safety surveillance system for young children analysing and reporting data on a weekly basis, allowing safety deliberations on vaccines within mere weeks of influenza vaccination commencing. Our ability to provide early and reliable safety profiles of seasonal influenza vaccines for children is likely to improve public confidence and vaccine uptake, which we will continue to assess.

AusVaxSafety 2015 surveillance team

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Conflict of interest

None declared.

Authors' contributions

AP served as *AusVaxSafety* surveillance coordinator for 2015, drafted the manuscript, and conducted data analysis and interpretation of results. PC contributed to the design and implementation of the *AusVaxSafety* surveillance system, served as coordinator/recruiter of the Hunter New England area surveillance sites, reviewed and contributed to the manuscript draft. AL contributed to the design and implementation of the *AusVaxSafety* surveillance system, recruited general practice site participants, reviewed and contributed to the manuscript draft. AR contributed to the design and implementation of the *AusVaxSafety* surveillance system, served as a coordinator of the Western Australia surveillance sites, conducted data collection and analysis, and reviewed and contributed to the manuscript draft. DW served as a coordinator of the Western Australia surveillance sites, conducted data collection and analysis, and reviewed and contributed to the manuscript draft. TS contributed to the design and implementation of the *AusVaxSafety* surveillance system, conducted data analysis, and reviewed the manuscript draft. CB contributed to the design and implementation of the *AusVaxSafety* surveillance system and reviewed and contributed to the draft manuscript. NC contributed to the design and implementation of the *AusVaxSafety* surveillance system and reviewed and contributed to the draft manuscript. KM contributed to the design, implementation and coordination of the *AusVaxSafety* surveillance system, and drafted the manuscript.

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