Surveillance of adverse events following immunisation in Australia, 2012

Deepika Mahajan, Aditi Dey, Jane Cook, Bronwen Harvey, Rob I Menzies, Kristine K Macartney

Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) for 2012. It also describes reporting trends over the 13-year period 1 January 2000 to 31 December 2012. There were 1,897 AEFI records for vaccines administered in 2012, a decrease of 22% from 2,417 in 2011. The decrease in 2012 compared with 2011 was mainly attributable to a drop in the reports following receipt of the 23-valent pneumococcal polysaccharide vaccine (405 reduced to 133). However, reporting rates for some other vaccines such as rotavirus and varicella vaccines were higher in 2012 than 2011. Although an increase was observed in estimated reporting rates for rotavirus and varicella in children aged < 7 years in 2012 compared with 2011, it was not statistically significant. There were 370 AEFI records (37.2 per 100,000 doses) for the pneumococcal conjugate vaccine in 2012, which was fewer than in 2011 (43.4 per 100,000 doses). The most commonly reported reactions were injection site reactions (40%), fever (22%), allergic reactions (19%) and rash (10%). Only 7% of all the reported adverse events were categorised as serious. There were 2 reports of death, which were investigated by the TGA and no clear causal relationship with vaccination was found. *Commun Dis Intell* 2014;38(3):E232–E246.

Keywords: AEFI, adverse events, vaccines, surveillance, immunisation, vaccine safety

Introduction

This report summarises national passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) to 28 February 2013. The report focuses on AEFI reported for vaccines administered during 2012 and trends in AEFI reporting over the 13-year period 1 January 2000 to 31 December 2012.

An adverse event following immunisation is defined as any untoward medical occurrence that follows immunisation and which does not necessarily have a causal relationship with the use of the vaccine.[1] The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.[1]

Thus, AEFI may be caused by a vaccine(s) or may be coincidental. Adverse events may also include conditions that occur following the incorrect handling and/or administration of a vaccine(s). The post-marketing surveillance of AEFI is particularly important for detecting rare, late onset and unexpected events that are difficult to detect in pre-registration vaccine trials.

Reports summarising national AEFI surveillance data have been published regularly since 2003.[2–11] Trends in reported adverse events following immunisation are heavily influenced by changes to vaccine funding and availability provided through the National Immunisation Program (NIP). These changes impact on the interpretation of trend data and have been described in detail elsewhere.[2–11] Recent changes that impact on AEFI surveillance data presented in this report are:

i. Implementation of the 4th dose of Prevenar 13®, (13vPCV, a 13-valent pneumococcal conjugate vaccine) for Indigenous children from October 2012 replacing the booster dose of Pneumovax23®[12] (Table 1).

ii. Replacement of Prevenar® (7-valent pneumococcal conjugate vaccine, 7vPCV) by Prevenar 13® from July 2011. The Northern Territory Government provided a free dose of Prevenar 13® at 18 months for children who previously received a primary course of Synflorix® (10vPCV) or a mixed primary pneumococcal course with Synflorix® and Prevenar®[13] (Table 1).

To assist readers, a glossary of the abbreviations of the vaccines referred to in this report is provided at the end of this report.

Methods

AEFI are notified to the TGA by state and territory health departments, health professionals, vaccine manufacturers and members of the public.[14,15] All reports are assessed using internationally consistent criteria[16] and entered into the Australian Adverse Drug Reactions System (ADRS) database. All serious reports for drugs and vaccines are reviewed by medical officers in the TGA. Other reports are used in data mining and signal detection activities. Where there is insufficient information in a report to determine causality for a serious adverse event the TGA will contact the reporter on up to 3 occasions to elicit further information.

Table 1: Changes to the Australian Standard Vaccination Schedule (2003–2012)[2–11]

Date	Intervention
2003	Commencement of the meningococcal C conjugate vaccine (MenCCV) immunisation program. 18-month dose of DTPa vaccine removed from the National Immunisation Program.
2004	dTpa funded at 15–17 years of age replacing the diphtheria-tetanus dose.
2005	From January 2005, universal funded infant 7-valent pneumococcal conjugate vaccine (7vPCV) program replaced the previous targeted childhood program, with a catch-up program for children aged <2 years. Universal 23-valent pneumococcal polysaccharide vaccine (23vPPV) for adults aged ≥65 years replaced previous subsidy through the Pharmaceutical Benefits Scheme. From November 2005, universal funded immunisation against varicella at 18 months of age with a school-based catch-up program for children at 10–13 years of age not previously vaccinated and without a history of varicella infection (no funded catch-up for children 2–10 years of age). IPV funded to replace OPV, in combination vaccines.
2007	From April 2007, funded immunisation against human papillomavirus for all Australian girls aged 12–13 years delivered through a school-based program, with a temporary catch-up program through schools or primary care providers for females aged 13–26 years until December 2009. From July 2007, universal funded immunisation against rotavirus at 2 and 4 months of age (Rotarix®) or at 2, 4 and 6 months of age (Rotateq®).
2008	Western Australia commenced a seasonal influenza vaccination program for all children aged 6 months to <5 years (born after 1 April 2003). In March 2008, Queensland, South Australia and Victoria changed from using two combination vaccines (quadrivalent DTPa-IPV and Hib-HepB) to the single hexavalent DTPa-IPV-HepB-Hib vaccine.
2009	By late 2009, all states and territories were using the single hexavalent DTPa-IPV-Hib-HepB (Infanrix hexa®) vaccine for all children at 2, 4 and 6 months of age, due to an international shortage of *Haemophilus influenzae* type b (Hib) (PedvaxHib® [monovalent] and Comvax® [Hib-HepB]) vaccines. Influenza A(H1N1)pdm09 vaccine (Panvax®) was rolled out across Australia from 30 September 2009 for people aged ≥10 years. From December 2009, the pandemic vaccine was made available to children aged 6 months to 10 years.
2010	Annual vaccination with seasonal trivalent influenza vaccine (TIV, containing 3 influenza strains: A/H1N1, A/H3N2 and B) was funded under the National Immunisation Program for people aged ≥6 months with medical risk factors (previously subsidised through the Pharmaceutical Benefits Scheme) and all Indigenous people aged ≥15 years (previously all Indigenous adults ≥50 years and 15–49 years with medical risk factors). On 23 April 2010, the use of the 2010 seasonal TIV in children <5 years of age was suspended by Australia's Chief Medical Officer due to an increased number of reports of fever and febrile convulsions post vaccination. A subsequent investigation identified that Fluvax® and Fluvax junior® (CSL Biotherapies), but neither of the other two available brands registered for use in young children, were associated with an unacceptably high risk of febrile convulsions. The recommendation to resume the use of seasonal influenza vaccine in children aged 6 months to 5 years, using brands other than Fluvax® and Fluvax junior®, occurred in August 2010.
2011	From 1 July 2011, Prevenar 13® replaced Prevenar® on the National Immunisation Program for children at 2, 4 and 6 months of age in all states and territories except the Northern Territory, which adopted 13vPCV from 1 October 2011. 1 October 2011 to 30 September 2012 – all children aged between 12–35 months who had completed a primary pneumococcal vaccination course with 7vPCV were eligible to receive a free supplementary dose of Prevenar 13® On 25 March 2011, the Therapeutic Goods Administration issued a recall of Batch N3336 of the 23 valent pneumococcal polysaccharide vaccine 23vPPV, Pneumovax® 23. April 2011 – health professionals were advised not to administer a second or subsequent dose of Pneumovax 23 vaccine. December 2011 – Revised recommendations regarding which patients should be re-vaccinated under the National Immunisation Programwere provided.
2012	From 1 October 2012, a 4th dose of Prevenar 13®, (13vPCV, a 13-valent pneumococcal conjugate vaccine) was listed on the National Immunisation Program for Indigenous children, aged 12–18 months, residing in Queensland, South Australia, Western Australia and the Northern Territory. This replaced the booster dose of Pneumovax23®, (23vPPV, a 23-valent pneumococcal polysaccharide vaccine) administered between 18 and 24 months of age for Indigenous children from these jurisdictions.

Adverse event following immunisation data

De-identified information on all AEFI reported to the TGA from 1 January 2000 to 28 February 2013 and stored in the ADRS database were released to the National Centre for Immunisation Research and Surveillance (NCIRS) in March 2013. Readers are referred to previous AEFI surveillance reports for a description of the surveillance system.[2,3]

Records* contained in the ADRS database were eligible for inclusion in the analysis if a vaccine was recorded as 'suspected'† of involvement in the reported adverse event and *either*

a. the vaccination occurred between 1 January 2000 and 31 December 2012, or
b. for records where the vaccination date was not recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 31 December 2012.

Study definitions of adverse event following immunisation outcomes and reactions

AEFI were defined as 'serious' or 'non-serious' based on information in the report sent to the TGA and criteria similar to those used by the World Health Organization[16] and the US Vaccine Adverse Events Reporting System (VAERS).[17] In this report, an AEFI is defined as 'serious' if it meets one or more of the following criteria: (1) results in death (2) is life-threatening (3) requires inpatient hospitalisation or prolongation of existing hospitalisation (4) results in persistent or significant disability/incapacity (5) is a congenital anomaly/birth defect, or (6) is a medically important event or reaction.

The causality ratings of 'certain', 'probable' and 'possible' are assigned to individual records by the TGA. They describe the likelihood that a suspected vaccine or vaccines was/were associated with the reported reaction at the level of the individual vaccine recipient. Factors that are considered in assigning causality ratings include the timing (minutes, hours), the spatial relationship between symptoms and signs and the vaccination (for injection site reactions), and whether one or more vaccines were administered. These factors are outlined in more detail elsewhere.[3] However, in many instances a causal association between vaccines administered to an individual and events that subsequently occurred cannot be clearly ruled in or out. In addition, children in particular often receive several vaccines at the same time. Therefore, all administered vaccines are usually listed as 'suspected' of involvement in a systemic adverse event as it is usually not possible to attribute the event to a single vaccine.

Typically, each record lists several reaction terms, that is symptoms, signs and/or diagnoses that have been coded by TGA staff from the reporter's description into standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA®).[18]

To analyse reported AEFI, MedDRA® coding terms were grouped to create a set of reaction categories. Firstly, reaction categories were created that were analogous to the reactions listed and defined in the *Australian Immunisation Handbook,* 9th edition.[15] Where MedDRA® coding terms could not be categorised into categories as per the Immunisation Handbook, additional categories were created for those that were listed in more than 1% of records (e.g. headache, dizziness, change in heart or respiratory rate or rhythm). Reaction terms listed in less than 1% of records were grouped into broader categories based on the organ system where the reaction was manifested (e.g. gastrointestinal, neurological).

Data analysis

All data analyses were performed using SAS software version 9.3.[19] Average annual population-based reporting rates were calculated for each state and territory and by age group using population estimates obtained from the Australian Bureau of Statistics.[20]

Reporting rates per 100,000 administered doses were estimated where information was available on the number of doses administered. This was done for vaccines funded through the NIP for children aged < 7 years.

Denominator data to estimate reporting rates for influenza and 23vPPV for people aged ≥ 18 years were obtained from a national adult coverage survey conducted in 2009.[21] For 23vPPV, the number of people vaccinated in 2012 was derived from the number of people who reported receipt of the vaccine within the previous 5 years, divided by five. The number of administered doses of each of the 10 childhood vaccines was obtained from the Australian Childhood Immunisation Register, a national population-based register of approximately 99% of children aged < 7 years.[22]

* The term 'AEFI record' is used throughout this report because a single AEFI notification or report to the Office of Product review can generate more than 1 record in the ADRS database. This may occur if there is a time sequence of separate adverse reactions in a single patient, such as systemic and local reactions.

† Records are classified as 'suspected' if the report contains sufficient information to be valid and the relationship between reported reactions and drugs are deemed to be biologically plausible.

Notes on interpretation

Caution is required when interpreting the data presented in this report. Due to reporting delays and the late onset of some AEFI, the data are considered preliminary, particularly for the 4th quarter of 2012. Data published in previous reports for 2000–2011[2–11] may differ from that presented in this report for the same period because this report has been updated to include delayed notifications to the TGA that were not included in prior publications and data may be updated and recoded when follow-up information is received.

The information collated in the ADRS database is intended primarily for signal detection and hypothesis generation. While reporting rates can be estimated using appropriate denominators, they cannot be interpreted as incidence rates due to under-reporting and biased reporting of suspected events, and the variable quality and completeness of information provided in individual notifications.[2–11,23]

It is important to note that this report is based on information collated in the ADRS database and not on comprehensive clinical notes or case reviews. The reported symptoms, signs and diagnoses in each AEFI record in the ADRS database are temporally associated with vaccination but are not necessarily causally associated with a vaccine or vaccines.

Comparison with online Database of Adverse Events Notifications

In August 2012, the TGA made a searchable database, the Database of Adverse Event Notifications (DAEN) available on its web site. DAEN contains reports of all adverse event reports for medicines (including vaccines).[24] The data in this report are more detailed than that available on DAEN, and were provided to NCIRS by the TGA from the ADRS database. The numbers published in this report may be different to the numbers in the DAEN database, due to different dates of data extraction and amendment to reports where further information has become available. In addition, this report provides several features that are not available from the DAEN database, including long-term trends and population and dose-based reporting rates, put in the context of changes in vaccine policy and use, and reporting practices.

Results

The ADRS database included a total of 1,897 records where the date of vaccination (or onset of adverse event, if vaccination date was not reported) was between 1 January and 31 December 2012.

In 2012, 84% of AEFI (n = 1,599) were reported to the TGA via states and territories (except Tasmania where all AEFIs are directly reported to the TGA), while the rest were reported directly to the TGA; 10% (n = 193) by doctors or health care providers, 3% (n = 50) by members of the public, 1% (n = 23) by hospitals, and 2% (n = 32) by drug companies.

Reporting trends

The overall reporting rate for 2012 was 8.4 per 100,000 population, compared with 10.8 in 2011. The rate was lower compared with the previous years following a peak in 2010 (17.4) predominantly due to reports in children following vaccination with the 2010 seasonal trivalent influenza vaccine; in 2009 (11.0) associated with the influenza A(H1N1)pdm09 vaccine program; and in 2011 (10.8) following an increase in reports following 23vPPV in adults.[9,10,11]

There was a decline in the reported events and reporting rate per 100,000 population during 2012 and the vast majority of reported events from all reporter types, were of a non-serious nature similar to the previous years (Figure 1).[10,11] There were marked variations in reporting levels in association with previous changes to the NIP from 2000 onwards (Figures 2a, 2b, 2c). The drop in reports in 2012 was predominantly associated with a drop in reports following 23vPPV vaccines in adults (Figure 2a). However, an increase was observed in estimated reporting rates for rotavirus and varicella in children aged < 7 years in 2012 compared with 2011, but it was not statistically significant (Table 2, Figure 2c).

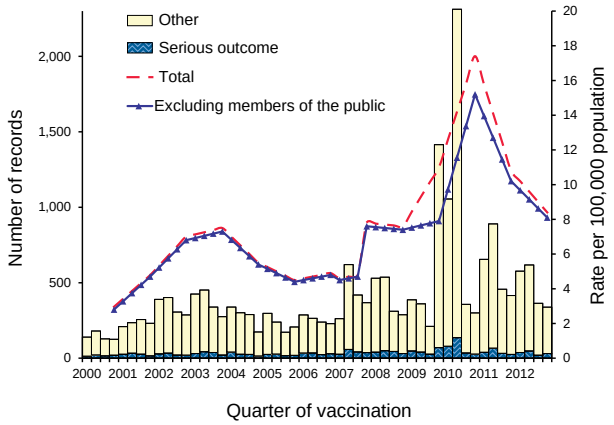
A seasonal pattern of AEFI reporting was apparent in 2012 and previous years, with the highest number of AEFI notifications for vaccinations administered in the first half of the year (Figure 1). The usual seasonal pattern of AEFI reporting in adults, with peaks in the first half of the year, was also apparent in 2012 (Figure 2a), corresponding to the months when older Australians receive the 23vPPV and influenza vaccines (March to June). However, more AEFI reports following influenza vaccine were received in 2011 and 2012 than in the years prior to 2009 (pre-pandemic era) (Figure 2a).

Age distribution

In 2012, the highest population-based AEFI reporting rate occurred in infants < 1 year of age and 1 to < 2 years of age, the age groups that received the highest number of vaccines (Figure 3). Compared with 2011, AEFI reporting rates per 100,000 population increased among the < 1 year age group (5% increase from 134.9 to 142.3 per 100,000 population in 2011 and 2012 respectively),

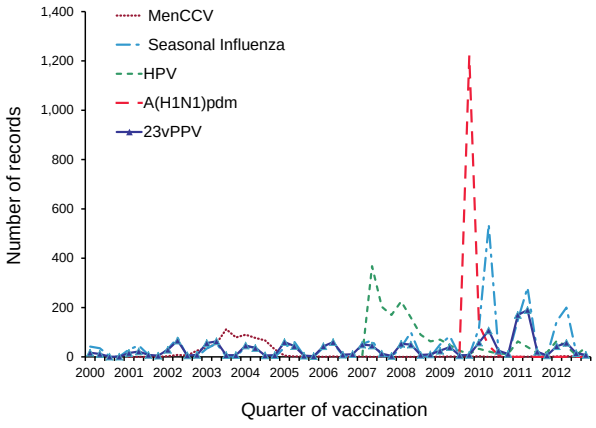
and the 1 to <2 year age group (5% increase, 53.8 to 56.7 per 100,000). Rates declined for all other age groups especially in the ≥65 years age group (60% decline, 12.1 to 4.9 per 100,000).

Figure 1: Adverse events following immunisation, Australian Adverse Drug Reactions System database, 2000 to 2012, by quarter of vaccination



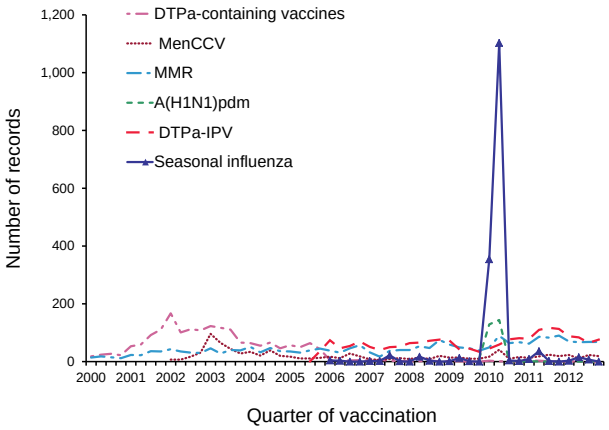
For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Figure 2a: Adverse events following immunisation for people aged ≥7 years for frequently reported vaccines, Australian Adverse Drug Reactions System database, 2000 to 2012, by quarter of vaccination



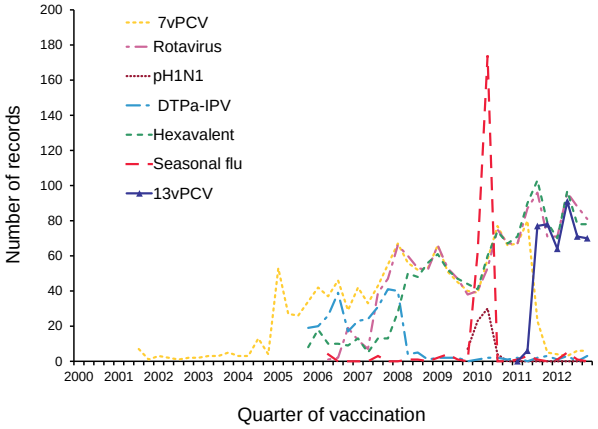
For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Figure 2b: Adverse events following immunisation for children aged 1 to <7 years for frequently reported vaccines, Australian Adverse Drug Reactions System database, 2000 to 2012, by quarter of vaccination



For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Figure 2c: Adverse events following immunisation for children aged <1 year for frequently suspected vaccines,* Australian Adverse Drug Reactions System database, 2000 to 2012, by quarter of vaccination



* Meningococcal C conjugate vaccine was introduced into the National Immunisation Program schedule on 1 January 2003; 7-valent pneumococcal conjugate vaccine on 1 January 2005; DTPa-IPV and DTPa-IPV-HepB-Hib (hexavalent) vaccines in November 2005; rotavirus (RotaTeq® and Rotarix®) vaccines on 1 July 2007; pH1N1 influenza vaccine for children 6 months to 10 years on December 2009; seasonal trivalent influenza vaccine in 2010; and the 13-valent pneumococcal conjugate vaccine (13vPCV) on 1 July 2011 (Table 1).

For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Table 2: Vaccine types listed as 'suspected' of involvement in records of adverse events following immunisation, Australian Adverse Drug Reactions System database, 2012,* by age group

Vaccines†	AEFI records‡ n	Vaccine doses§ n	Reporting rate per 100,000 doses‖ (95% CI) 2012	2011
<7 years				
DTPa-containing vaccines	664	1,153,117	57.6 (53.3–62.1)	66.7 (62.0–71.6)
DTPa-IPV	320	298,769	107.1 (95.7–119.5)	138.9 (125.9–152.9)
Pentavalent (DTPa-IPV-HepB)	1	274	364.9 (10.9–2032.8)	396.8 (11.9–2222.2)
Hexavalent (DTPa-IPV-HepB-Hib)	343	854,074	40.2 (36.0–44.6)	40.4 (36.2–45.0)
Pneumococcal conjugate - PCV	370	993,880	37.2 (33.5–41.2)	48.3 (42.3–54.8)
Rotavirus vaccine	338	537,171	62.9 (56.4–70.0)	56.3 (50.0–63.1)
Measles-mumps-rubella	283	591,536	47.8 (42.4–53.8)	54.8 (49–61.1)
Meningococcal C conjugate	79	297,603	26.6 (21.0–33.1)	26.3 (20.8–32.8)
Varicella	67	280,568	23.9 (18.5–30.3)	21.7 (16.6–27.9)
Haemophilus influenzae type b	66	284,223	23.2 (18.0–29.5)	25.5 (19.9–32.1)
Seasonal influenza	32	na	na	na
Total (<7 years)¶	973	4,138,379	23.5 (22.1–25.0)	27.6 (26.0–29.3)
7–17 years				
HPV	151	na	na	na
Hepatitis B	124	na	na	na
dTpa	98	na	na	na
Varicella	39	na	na	na
Seasonal influenza	17	na	na	na
Total (7–17 years)	317	na	na	na
18–64 years				
Seasonal influenza**	271	3,170,300	8.6 (7.9–9.6)	7.1 (6.2–8.1)
dTpa	67	na	na	na
23vPPV**	40	132,520	30.2 (21.6–41.1)	63.4 (50.6–78.4)
Total (18–64 years)††	311	3,302,820	9.4 (8.4–10.5)	9.4 (8.4–10.5)
≥65 years				
Seasonal influenza**	78	2,176,000	3.6 (2.8–4.5)	5.9 (4.9–7.0)
23vPPV**	77	317,400	24.3 (19.2–30.3)	90.7 (80.6–101.8)
dTpa	17	na	na	na
Total (≥65 years)††	155	2,493,400	6.2 (5.3–7.3)††	16.7 (15.2–18.4)††

AEFI Adverse events following immunisation.

* Influenza A(H1N1)pdm09 was reported in the table in previous reports but is not shown in this table as it is no longer in use and no reports were received.

† Records where at least one of the vaccines shown in the table was suspected of involvement in the reported adverse event.

‡ Number of AEFI records in which the vaccine was coded as 'suspected' of involvement in the reported adverse event and the vaccination was administered between 1 January and 31 December 2012. More than one vaccine may be coded as 'suspected' if several were administered at the same time.

§ Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 January and 31 December 2012.

‖ The estimated reporting rate per 100,000 vaccine doses recorded.

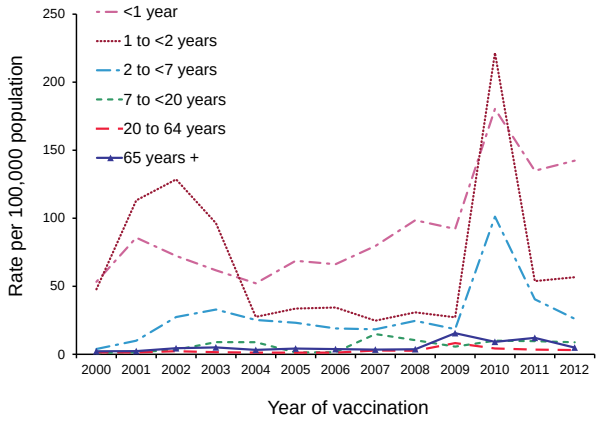
¶ Number of AEFI records excluding influenza vaccines.

** Number of administered doses of seasonal influenza vaccine estimated from the 2009 Australian Institute of Health and Welfare national adult vaccination survey.[21]

†† Seasonal influenza and 23vPPV only.

na Not applicable

Figure 3: Reporting rates of adverse events following immunisation per 100,000 population, Australian Adverse Drug Reactions System database, 2000 to 2012, by age group and year of vaccination



For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Reporting rates per 100,000 doses (excluding influenza due to the absence of reliable dose data) decreased overall and for most individual vaccines in children aged < 7 years in 2012 compared with 2011 except for rotavirus and varicella vaccines (Table 2).

Reporting rates per 100,000 vaccine doses were lower overall in 2012 compared with 2011 for adults aged ≥65 years (down to 6.2 in 2012 from 16.7 in 2011) and especially for 23vPPV (down to 24.3 in 2012 from 90.7 in 2011) (Table 2).

Geographical distribution

Population-based reporting patterns varied between states and territories during 2012 (Table 3) as in previous years.[2–11] The highest reporting rates were from the Northern Territory, the Australian Capital Territory, Western Australia and Victoria (20.0, 13.1, 11.7, 11.5, respectively) while New South Wales had the lowest rate (4.4). Reporting rates dropped in most jurisdictions in 2012 compared with 2011 except in Western Australia, which experienced an increase that was not statistically significant (Table 3).

Vaccines

Thirty-two different vaccines were included in the 1,897 records received in 2012 (Table 4). The percentage of records where only 1 vaccine was reported as being the suspected vaccine differed by the vaccine administered, typically varying according to whether multiple vaccines were routinely co-administered for the patient's age. The percentage of records assigned causality ratings of 'certain' or 'probable' also varied. Adverse events such as

Table 3: Adverse events following immunisation, Australian Adverse Drug Reactions System database, 2012, by state or territory

State or territory	AEFI records		Annual reporting rate per 100,000 population*			
	n	%	Overall	'Certain'/ 'probable' causality rating†‡	'Serious' outcome	Aged <7 years
Australian Capital Territory	49	3	13.1 (9.7–17.3)	2.7	0.3	5.3
New South Wales	321	17	4.4 (3.9–4.9)	0.8	0.6	1.7
Northern Territory	47	2	20.0 (14.7–26.6)	6.0	1.3	10.2
Queensland	328	17	7.2 (6.4–8.0)	1.9	0.5	3.5
South Australia	142	7	8.6 (7.2–10.1)	1.1	0.4	3.9
Tasmania	42	2	8.2 (5.9–11.1)	1.6	0.4	1.8
Victoria	650	34	11.5 (10.7–12.5)	2.0	0.6	7.7
Western Australia	285	15	11.7 (10.4–13.2)	2.5	0.7	5.4
Other§	33	2	na	na	na	na
Total		100	8.4 (8.0–8.7)	1.6	0.5	4.3

AEFI Adverse events following immunisation.

* Average annual rates per 100,000 population calculated using the Australian Bureau of Statistics mid-2011 population estimates.[20]

† Causality ratings were assigned to AEFI records using criteria described previously.[2,3]

‡ AEFI records defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening or death).

§ Records where the jurisdiction in which the AEFI occurred was not reported or was unclear. AEFI records in this category were notified mainly by pharmaceutical companies (n = 32), and General Practioners (n = 1).

Table 4: Vaccine types listed as 'suspected' in records of adverse events following immunisation, Australian Adverse Drug Reactions System database, 2012

Suspected vaccine type*	AEFI records	One suspected vaccine or drug only†		'Certain'/ 'probable' causality rating‡		'Serious' outcome§		Age group‖			
								<7 years		≥7 years	
	n	n	%¶	n	%¶	n	%¶	n	%¶	n	%¶
Influenza	406	342	84	56	14	37	9	32	8	366	90
PCV	370	35	10	19	5	34	10	370	100	0	0
DTPa-IPV-HepB-Hib	344	21	6	19	6	33	10	343	99	1	1
Rotavirus	338	52	15	11	3	44	13	338	100	0	0
DTPa-IPV	324	133	41	113	35	10	3	320	99	2	1
MMR	298	31	10	13	4	14	5	283	95	14	5
dTpa	186	132	71	47	25	10	5	2	1	182	98
Hepatitis B	160	53	33	13	8	7	4	10	6	150	94
HPV	155	62	40	12	8	9	6	0	0	155	100
23vPPV	133	80	60	43	32	9	7	10	8	122	92
Varicella	111	59	53	6	5	9	8	67	60	41	37
MenCCV	87	6	7	5	6	6	7	79	91	8	9
Hib	67	0	0	0	0	6	9	66	99	1	1
Typhoid	20	5	25	1	5	3	15	2	10	18	90
dT	16	10	63	5	31	0	0	0	0	16	100
BCG	15	15	100	10	67	0	0	15	100	0	0
Hepatitis A	14	3	21	2	14	3	21	4	29	10	71
Hepatitis A-Typhoid	13	6	46	1	8	0	0	0	0	13	100
Yellow fever	12	4	33	0	0	2	17	1	8	11	92
DTPa	11	8	73	5	45	1	9	2	18	9	82
Hepatitis A + B	11	8	73	1	9	0	0	1	9	10	91
Rabies	8	4	50	3	38	0	0	1	12	7	88
IPV	6	3	50	0	0	0	0	1	17	5	83
dTpa-IPV	5	3	60	2	40	0	0	0	0	5	100
10vPCV	3	0	0	0	0	0	0	2	67	1	33
Q fever	3	3	100	0	0	1	33	0	0	3	100
Japanese encephalitis	2	1	50	1	50	0	0	0	0	2	100
Men4PV	2	0	0	0	0	0	0	0	0	2	100
Cholera	2	1	50	1	50	0	0	0	0	2	100
Tetanus	2	2	100	0	0	0	0	0	0	2	100
DTPa-IPV-HepB	1	1	100	0	0	0	0	1	100	0	0
Total**	1,897	1,078	57	374	20	137	7	973	51	908	48

AEFI Adverse events following immunisation.

* The abbreviations of vaccine names are included at the end of this report.

† AEFI records where only one vaccine was suspected of involvement in a reported adverse event.

‡ Causality ratings were assigned to AEFI records using criteria described previously.[2,3]

§ 'Serious' outcomes are defined in the Methods section.

‖ AEFI records are not shown if both age and date of birth were not reported.

¶ Percentages are calculated for the number of AEFI records where the vaccine was suspected of involvement in the AEFI, e.g. HPV was 'suspected' in 155 AEFI records. This was the only suspected vaccine in 40% of the 155 AEFI records. Eight per cent had 'certain' or 'probable' causality ratings, 6% were defined as 'serious' and 100% were for those aged ≥7 years.

** Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and an AEFI record may list more than 1 vaccine.

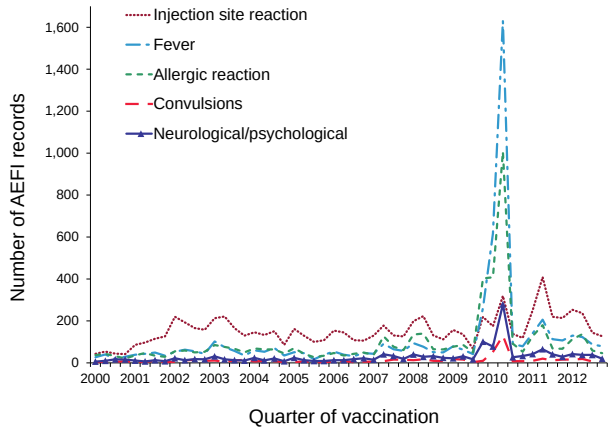
injection site reactions, for which the attribution of causality is more straightforward, were more often reported as certain or probable. There were also slight variations in the number with outcomes defined as 'serious', which have remained low as in previous years.

The individual vaccines most frequently suspected to have been involved in AEFI events were seasonal influenza vaccine (n = 406,21%), 13vPCV (n = 350, 18%) and hexavalent DTPa-IPV-HepB-Hib (n = 344, 18%) (Table 4).

Reactions

The most frequently reported adverse events in 2012 were injection site reactions (ISRs) (n = 761, 40%), fever (n = 420, 22%), allergic reaction (n = 355, 19%), and rash (n = 195, 10%) (Tables 5a and 5b, Figure 4). Some of the severe reactions included convulsions (n = 54, 3%) including 25 cases of febrile convulsion, hypotonic-hyporesponsive episode (HHE) (n = 33, 2%), anaphylactic reaction (n = 16, 1%), intussusception (n = 16, 1%), thrombocytopenia (n = 2, 0.1%), and Guillain-Barrè syndrome (GBS) (n = 1, 0.05%) (Table 5a).

Figure 4: Selected frequently reported adverse events following immunisation, Australian Adverse Drug Reactions System database, 2000 to 2012, by quarter of vaccination



For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Of the 761 cases of ISR, 385 (51%) were in children aged < 7 years. The vaccines most commonly suspected of involvement in AEFI for children aged < 7 years were: DTPa-IPV (n = 257); MMR (n = 149); 13vPCV (n = 55); and hexavalent vaccine (n = 52). For those aged ≥7 years (n = 370), these were seasonal influenza vaccine (n = 149), 23vPPV (n = 104) and dTpa (n = 84) either given alone or co-administered with other vaccines. As expected, reports for 23vPPV were predominantly in those aged ≥65 years (63%), while AEFI with seasonal influenza vaccine was commonly reported in the 18–64 years age group (70%). The dTpa vaccine was most commonly recorded as causing ISR in AEFI records in the 12–17 years age group (40%) and the 18–64 years age group (40%).

The number of reports in each reaction category has changed over time (Figure 4). Much of the variation in reporting of ISR related to specific changes in the immunisation schedules for vaccines that are known to have higher rates of ISR, including DTPa-containing vaccines, MenCCV, 23vPPV and HPV vaccines.[2–11,25,26]

The increase in ISR during 2012 was predominantly associated with non-influenza vaccines, particularly 23vPPV and DTPa-containing vaccines. In children aged 2 to < 7 years, ISR was mainly associated with DTPa-IPV vaccine (86%, n = 251). In the 18–64 years age group, it is associated with seasonal influenza vaccine (60%, n = 109), while in the 12–17 years age group, the increase in ISR was associated with adult dTpa vaccine (44%, n = 186), HepB (34%, n = 160), and HPV (30%, n = 155).

Increases in reports of fever were largely associated with time periods when new vaccines were added to the NIP in the reporting period, such as rotavirus and HPV in 2007 and the extension of seasonal influenza vaccine from the elderly to others at high risk in 2010.

Severity of outcomes

Fifty-three per cent (n = 999) of reported events in 2012 were defined as 'non-serious', 7% (n = 137) were defined as 'serious' (i.e. requiring hospitalisation, resulting in persistent or significant disability or incapacity; medically important reaction or event; experiencing a life-threatening event or death); 26% (n = 495) were recorded as not fully recovered, while information on severity could not be determined due to insufficient data for 14% (n = 266) of events (Table 6). This was similar to the proportions of serious AEFI in previous years.[9,10,11] Of the reported events recorded as not fully recovered at the time of reporting, the largest proportion were from Victoria (39%, n = 191), followed by Western Australia (21%, n = 106) and Queensland (16%, n = 77). Ninety-three per cent of cases recorded as 'not fully recovered' had missing information in various fields including

Table 5a: Reaction categories of interest* mentioned in records of adverse events following immunisation, Australian Adverse Drug Reactions System database, 2012

Reaction category*	AEFI records	Only reaction reported†		'Certain'/'probable' causality rating‡		Age group§			
						<7 years		≥7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Injection site reaction	761	273	36	321	42	385	51	370	49
Fever	420	8	2	9	2	239	57	175	42
Allergic reaction¶	355	60	17	12	3	163	46	191	54
Rash**	195	72	37	8	4	142	73	52	27
Syncope	125	84	67	13	10	29	23	96	77
Abnormal crying	74	10	14	0	0	72	97	1	1
Arthralgia	64	4	6	2	3	5	8	59	92
Convulsions	54	28	52	0	0	40	74	14	26
Lymphadenopathy/itis††	46	12	26	14	30	22	22	34	74
Hypotonic-hyporesponsive episodes	33	26	79	1	3	33	100	0	0
Anaphylactic reaction	16	12	75	3	19	5	31	11	69
Intussusception	16	14	88	2	13	1	100	0	0
Abscess	10	3	30	5	50	8	80	2	20
Arthritis	5	0	0	1	20	0	0	5	100
Brachial neuritis	2	1	50	0	0	0	0	2	100
Death	2	1	50	0	0	1	50	1	50
Thrombocytopenia	2	0	0	1	50	1	50	1	50
Encephalitis	1	0	0	0	0	1	100	0	0
Encephalopathy	1	0	0	0	0	1	100	0	0
Guillain-Barré syndrome	1	0	0	0	0	0	0	1	100
Parotitis	1	0	0	0	0	1	100	0	0
Orchitis	1	0	0	0	0	1	100	0	0
Osteitis	0	0	0	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	0	0
Total‡‡	1,897	734	39	374	20	973	51	908	48

AEFI Adverse events following immunisation.

* Reaction categories were created for the AEFI of interest listed and defined in *The Australian Immunisation Handbook* 9th edition (p 58–65 and 360–363)[15] as described in the Methods section.

† AEFI records where only one reaction was reported.

‡ Causality ratings were assigned to AEFI records using criteria described previously.[2,3]

§ Not shown if neither age nor date of birth were recorded.

‖ Percentages relate to the number of AEFI records in which the specific reaction term was listed, e.g. of 761 AEFI records listing injection site reaction, 36% listed only one type of reaction while 42% had a causality rating of 'certain' or 'probable' and 51% were for children aged <7 years.

¶ Allergic reaction includes skin reactions including pruritus, urticaria, periorbital oedema, facial oedema, erythema multiforme etc. (excludes skin reactions presented elsewhere in this table); and/or gastrointestinal (e.g. diarrhoea, vomiting) symptoms and signs but does not include other abdominal symptoms such as abdominal pain, nausea, flatulence, abnormal faeces, hematochezia etc. and does not include anaphylaxis.

** Includes general terms of rash but does not include pruritic rash.

†† Includes lymphadenitis following Bacille Calmette-Guérin BCG vaccination and the more general term of 'lymphadenopathy'.

‡‡ Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and an AEFI record may list more than 1 reaction term.

Table 5b: 'Other'* reaction terms listed in records of adverse events following immunisation, Australian Adverse Drug Reactions System database, 2012

Reaction term*	AEFI records	Only reaction reported†		'Certain'/'probable' causality rating		Age group§			
						<7 years		≥7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Malaise	152	3	2	5	3	47	31	102	67
Headache	139	2	1	6	4	8	6	130	94
Neurological/psychological	138	3	2	3	2	87	63	48	35
Gastrointestinal – RVV¶	122	15	12	3	2	122	100	0	0
Nausea	111	1	1	6	5	5	5	105	95
Dizziness	98	4	4	4	4	2	2	94	96
Myalgia	72	2	3	5	7	9	13	61	85
Pain	69	0	0	3	4	6	9	61	88
Abdominal pain	60	2	3	4	7	31	52	29	48
Reduced sensation	60	5	8	2	3	0	0	58	97
Respiratory	47	5	11	1	2	15	32	31	66
Erythema	38	5	13	1	3	23	61	14	37
Pallor	37	1	3	1	3	26	70	10	27
ENT	26	2	8	2	8	5	19	20	77
Oedema	27	0	0	0	0	14	52	12	44
Somnolence	25	1	4	0	0	16	64	9	36
Circulatory	24	2	8	4	13	12	50	12	50
Increased sweating	21	0	0	2	10	6	29	13	62
Tremor	18	1	6	1	6	2	11	16	89
Vision impaired	16	1	6	1	6	2	13	14	88
Weakness	11	0	0	0	0	0	0	11	100
Flushing	9	0	0	0	0	1	11	8	89
Other	225	32	14	20	9	111	49	109	48
general non-specific	38	7	18	5	13	22	58	16	42
infection	19	7	37	0	0	8	42	10	53
neurological	19	9	47	2	11	9	47	10	53
eye or ear	17	3	8	1	6	8	47	9	53
metabolic/endocrine	16	0	0	1	6	14	88	2	12
cardiovascular	15	1	7	3	20	9	0	6	40
musculoskeletal	13	0	0	0	0	2	15	11	85
gastrointestinal††	12	0	0	0	0	5	42	7	58
respiratory	12	1	8	0	0	5	42	7	58
skin**	11	2	18	0	0	7	64	3	27
psychological	9	0	0	1	11	4	44	5	56
renal/urogenital	7	0	0	0	0	3	43	4	57
haematological	7	2	29	1	14	2	29	5	71
miscellaneous	4	0	0	0	0	1	25	2	50
pregnancy/congenital	2	0	0	0	0	2	100	0	0

AEFI Adverse events following immunisation.

* Reaction terms not listed in *The Australian Immunisation Handbook 9th edition*[15] but included in AEFI records in the ADRS database. The top part of the table shows reaction terms included in 1% or more of AEFI records, the bottom part of the table shows reaction terms, grouped by organ system, that were included in less than 1% of AEFI records.

§ Not shown if neither age nor date of birth were recorded.

‖ Percentages relate to the number of AEFI records in which the specific reaction term was listed, e.g. of 152 AEFI records listing malaise, 2% listed only 1 type of reaction while 3% had a causality rating of 'certain' or 'probable' and 31% were for children aged <7 years.

¶ Gastrointestinal – RVV includes gastrointestinal reactions following rotavirus vaccination only.

** Other, skin includes purpura, petechie, blister, burning, dermatitis, dry skin etc. but does not include skin reactions.

†† Other, gastrointestinal does not include reaction categories coded as gastrointestinal reactions or Gastrointestinal – RVV signs and symptoms.

hospitalisation. For reports where not 'fully recovered' was recorded, 83% (n = 409) were reported by states and territories, 11% (n = 56) by health care providers, 4% (n = 19) by members of the public, 1% each by pharmacist (n = 4) and drug companies (n = 5), and 0.4% (n = 2) by hospitals. Of those without information describing severity, the most commonly reported adverse reactions were ISR (41%, n = 110), fever (22%, n = 58) and allergic reactions (20%, n = 52).

Only 20% of records (n = 374) were assigned causality ratings of either 'certain' (n = 347, 18%) or 'probable' (n = 27, 2%), and the rest (80%) were rated as 'possible'.

The 'serious' reactions (n = 137) were ISR (n = 21, 15%); fever (n = 25, 18%); allergic reactions (n = 17, 12%); convulsions (n = 21, 15%), including 12 febrile convulsions; diarrhoea/vomiting (n = 16, 12%); HHE (n = 7, 5%); anaphylaxis (n = 6, 4%); GBS (n = 1, 1%); intussusception (n = 9, 7%); 11 cases of syncope (8%); and 2 reports of death (2%), one of which was a case of idiopathic thrombocytopenic purpura. Other relatively severe reactions that were not classified as 'serious', either because they did not satisfy the criteria, or due to a lack of information about the outcome and/or hospitalisation status, included: convulsion (n = 33, 61%), including 13 febrile convulsions; HHE (n = 26, 79%); anaphylaxis (n = 10, 63%); and intussusception (n = 9, 56%).

All the reported cases of HHE (33) were from children aged < 7 years. Twenty-eight reports (85%) followed co-administration of hexavalent, PCV and rotavirus vaccines. Another 2 cases followed vaccination with Hib, MenC and MMR while a further 3 cases followed the vaccines administered simultaneously in combinations of: DTPa, PCV and rotavirus; DTPa-IPV, PCV and rotavirus; and PCV, Hep A and varicella vaccine.

The single reported case of GBS was in a person aged > 60 years following co-administered seasonal influenza (Fluvax®) and 23vPPV vaccines. The person experienced corrhyzal symptoms for 4 days after receiving the vaccines and developed symptoms of GBS approximately 11 days post vaccination.

All of the 16 reports of intussusception were from infants (< 1 year of age). Fifteen reports (94%) were following hexavalent, 13vPCV and rotavirus vaccines administered together, while 1 report was following rotavirus vaccine administered alone.

Five of the 16 reports of anaphylaxis were in children aged < 7 years. Three cases were infants and two were following hexavalent and 13vPCV vaccine administered together, while one reported anaphylaxis following hexavalent alone. Another 2 cases in children aged < 7 years were following vaccination with DTPa-IPV and MMR administered together. Eight of the 11 cases of anaphylaxis in those aged > 7 years followed receipt of one of the influenza

Table 6: Outcomes of adverse events following immunisation, Australian Adverse Drug Reactions System database, 2012

Outcome	AEFI records		'Certain'/ 'probable' causality rating*		Age group†			
					<7 years		≥7 years	
	n	%‡	n	%§	n	%§	n	%§
Non-serious	999	53	171	17	498	50	494	49
Not recovered at time of report	495	26	140	28	247	50	245	49
Not known (missing data) – total	266	14	52	20	153	58	109	41
Serious:	137	7	11	8	75	55	60	44
recovered with sequelae	1		–		–		1	
hospital treatment – admission	125		11		72		51	
life-threatening event	9		–		2		7	
Death	2		–		1		1	
Total	1,897	100	374	20	973	51	908	48

AEFI Adverse events following immunisation.

* Causality ratings were assigned to AEFI records using criteria described previously.[2,3]

† AEFI records where both age and date of birth were not recorded are not shown (16 missing).

‡ Percentages relate to the total number of AEFI records (n = 1,897).

§ Percentages relate to the number of AEFI records with the specific outcome, e.g. of 999 AEFI records with a 'non-serious' outcome, 17% had causality ratings of 'certain' or 'probable' and 50% were for children aged < 7 years.

vaccines administered alone or in combination with other vaccines, while one each of the remaining three followed adult dTpa vaccine, HepB vaccine and 23vPPV vaccine administered alone.

Two deaths were recorded as being temporally associated with receipt of vaccines:

- A 19-month-old child who had received varicella vaccine 7 weeks prior to death. Seven weeks after vaccination the child presented with vomiting, fever and drowsiness. The cause of death was recorded as encephalitis.

- A 28-year-old person, who became unwell 2–3 days post vaccination with an unspecified influenza vaccine. The person developed thrombotic thrombocytopenic purpura (TTP) and died 2 days after onset of symptoms. The cause of the death was documented as TTP.

Both deaths were investigated by the TGA and no clear causal relationship with vaccination was found.

Pneumococcal conjugate vaccine

In 2012, there were 370 reports of adverse events following pneumococcal conjugate vaccine in people aged < 7 years, with 34 of these cases being coded as serious.

The reporting rates were 37.2 per 100,000 doses for PCV (Table 2). Seven per cent of reports involving PCV (n = 26) were for PCV administered alone. Of the 26 cases, 92% (n = 24) were children between 12 months and < 36 months, who received vaccine under the catch-up program offered to children between 12 months and 35 months of age. Seventy-three per cent (n = 269) of the reports involving PCV vaccines were for PCV co-administered with rotavirus vaccine.

The spectrum of reactions for PCV included 91 (25%) reports each of vomiting or diarrhoea and fever; 73 (20%) of rash; 61 of allergic reactions (17%); 55 ISR (16%); 56 screaming (15%); 29 cases of HHE (8%); 18 cases of convulsions (including 6 febrile convulsions) (5%); 6 case of syncope (2%); and 2 cases of anaphylaxis (0.5%). The total number of AEFIs don't add up as some reports had multiple reactions.

Discussion

There was an overall drop in the total number of AEFI reports and population-based reporting rates in 2012 compared with 2011, predominantly due to a large decline in reports following vaccination with the 23vPPV vaccine.

Reporting rates per 100,000 doses for children aged < 1 years and 1 to < 2 years were similar to the corresponding period in 2011, but significantly lower for children aged 2 to < 7 years [54 (95% CI: 48.5–59.4) vs 80 (73.7–87.0)]. The decrease in overall reporting of AEFI in children aged 2 to < 7 years in 2012 is primarily due to a drop in the reporting of ISR following vaccination with DTPa-IPV in that age group in 2012 compared with 2011. Although reporting rates for DTPa-IPV vaccines were lower in 2012 compared with 2011, reporting rates remained higher than for other years (92 in 2008; 72 in 2009; 94 in 2010).[9,10]

The increase in the reports following rotavirus vaccine may be because in the majority of the records (77%), rotavirus vaccine was administered with PCV. The likelihood of developing at least 1 AEFI with the administration of multiple vaccines is greater than with just 1 vaccine. From October 2011, children aged between 12 and 35 months who had completed a primary pneumococcal vaccination course with 7vPCV have been eligible to receive a free supplementary dose of Prevenar 13®.[13] The increased AEFI reports following PCV administration in toddlers might be in part because it is being given as a 4th dose of PCV vaccine. Data from the clinical studies of Prevenar 13® demonstrated similar rates of injection site reactions when comparing 7vPCV with 13vPCV, with an increase following the 4th dose of either 7vPCV or 13vPCV (in the 2nd year of life) compared with earlier doses in infancy. A similar trend was also observed for the other systemic reactions.[27] Some may also be attributed to the 'Weber effect',[28] which describes increased reporting frequently observed following the introduction of new vaccines.

Conclusion

The total number of reported AEFI in 2012 was reduced by 22% compared with 2011.

Reports of ISR following DTPa-IPV at 4 years decreased in 2012 compared with 2011 but remained higher than in previous years. Reporting rates for most of the vaccines were similar to 2011 or lower in 2012, particularly in the 2 to < 7 year age group.

The majority of AEFIs reported to the TGA were mild transient events and the data reported here are consistent with an overall high level of safety for vaccines included in the NIP schedule.

Acknowledgements

We thank Brynley Hull and Donna Armstrong, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, for assisting in the preparation of this report.

The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases is supported by the Australian Government Department of Health, the New South Wales Ministry of Health and The Children's Hospital at Westmead, New South Wales.

Author details

Deepika Mahajan[1]
Aditi Dey[1]
Jane Cook[2]
Bronwen Harvey[2]
Rob Menzies[1]
Kristine Macartney[1]

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, University of Sydney and The Children's Hospital at Westmead, Sydney, New South Wales
2. Office of Product Review, Therapeutic Goods Administration, Canberra, Australian Capital Territory

Corresponding author: Dr Deepika Mahajan, National Centre for Immunisation Research and Surveillance, Locked Bag 4001, WESTMEAD NSW 2145. Telephone: +61 2 9845 1433. Facsimile: +61 2 9845 1418. Email: Deepika.mahajan@health.nsw.gov.au

References

1. Council for International Organizations of Medical Sciences (CIOMS) c/o World Health Organization. Definition and Application of Terms for Vaccine Pharmacovigilance: Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance. 2012. Accessed on 16 August 2012. Available from: http://www.cioms.ch/frame_vaccine_pharmacovigilance.htm
2. Lawrence G, Menzies R, Burgess M, McIntyre P, Wood N, Boyd I, et al. Surveillance of adverse events following immunisation: Australia, 2000–2002. *Commun Dis Intell* 2003;27(3):307–323.
3. Lawrence G, Boyd I, McIntyre P, Isaacs D. Surveillance of adverse events following immunisation: Australia 2002 to 2003. *Commun Dis Intell* 2004;28(3):324–338.
4. Lawrence GL, Boyd I, McIntyre PB, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2004. *Commun Dis Intell* 2005;29(3):248–262.
5. Lawrence G, Boyd I, McIntyre P, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2005. *Commun Dis Intell* 2006;30(3):319–333.
6. Lawrence GL, Aratchige PE, Boyd I, McIntyre PB, Gold MS. Annual report on surveillance of adverse events following immunisation in Australia, 2006. *Commun Dis Intell* 2007;31(3):269–282.
7. Lawrence G, Gold MS, Hill R, Deeks S, Glasswell A, McIntyre PB. Annual report: surveillance of adverse events following immunisation in Australia, 2007. *Commun Dis Intell* 2008;32(4):371–387.
8. 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(4):365–381.
9. Mahajan D, Roomiani I, Gold M, Lawrence G, McIntyre P, Menzies R. Annual report: surveillance of adverse events following immunisation in Australia, 2009. *Commun Dis Intell* 2010;34(3):259–276.
10. Mahajan D, Cook J, McIntyre P, Macartney K, Menzies R. Annual report: surveillance of adverse events following immunisation in Australia, 2010. *Commun Dis Intell* 2011;35(4):263–280.
11. Mahajan D, Cook J, Dey A, Macartney K, Menzies R. Annual report: surveillance of adverse events following immunisation in Australia, 2011. *Commun Dis Intell* 2012;36(4):E315–E332.
12. Australian Government Department of Health and Ageing. Immunise Australia program. Pneumococcal Disease: Recent changes to pneumococcal vaccine for children Program providing a supplementary dose of Prevenar 13®. Accessed on 7 August 2013. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-pneumococcal
13. Centre for Disease Control. Change to Northern Territory Childhood Immunisation Schedule to introduce 13 valent pneumococcal vaccine 1 October 2011. *Northern Territory Disease Control Bulletin* 2011;18:37.
14. Australian Technical Advisory Group on Immunisation. *The Australian Immunisation Handbook*. 8th edn. Canberra: Australian Government Department of Health and Ageing, 2003.
15. National Health and Medical Council. *The Australian Immunisation Handbook*. 9th edn. Canberra: Australian Government Department of Health and Ageing, 2008.
16. Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. Accessed on 30 August 2010. Available from: http://www.who-umc.org/
17. Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)–United States, 1991–2001. [Erratum appears in *MMWR Morb Mortal Wkly Rep* 2003(06):113]. *MMWR Morb Mortal Wkly Rep* 2003;52(SS–1):1–24.
18. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;20(2):109–117.
19. The SAS system for Windows [computer program]. Version 9.3. Cary, N.C.: SAS Institute Inc, 2012.
20. Australian Bureau of Statistics. *Population by Age and Sex, Australian States and Territories, June 2011*. Australian Bureau of Statistics: Cat no. 31010DO002_201106; 2011.
21. Australian Institute of Health and Welfare. *2009 Adult Vaccination Survey: summary results*. Cat. No. PHE 135 Canberra: Australian Institute of Health and Welfare; 2011.
22. Additional reports – Childhood immunisation coverage. *Commun Dis Intell* 2008;32(2):288–289.
23. Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J* 2004;23(4):287–294.
24. Therapeutic Goods Administration. Database of Adverse Event Notifications. 1 August 2012. Accessed on 28 August 2012. Available from: http://www.tga.gov.au/safety/daen.htm

25. Joura EA, Leodolter S, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet* 2007;369(9574):1693–1702.

26. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. *Pediatr Infect Dis J* 2007;26(3):201–209.

27. Therapeutic Goods Administration. *Australian Public Assessment Report for Pneumococcal Polysaccharide Conjugate Vaccine (Prevenar 13®)*. Accessed on 7 August 2013. Available from: http://www.tga.gov.au/pdf/auspar/auspar-prevenar13.pdf

28. Simon LS. Pharmacovigilance: towards a better understanding of the benefit to risk ratio. *Ann Rheum Dis* 2002;61(Suppl II):ii88–ii89.

Abbreviations of vaccine types

7vPCV	7-valent pneumococcal conjugate vaccine
10vPCV	10-valent pneumococcal conjugate vaccine
13vPCV	13-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccineBCG Bacille Calmette-Guérin (i.e. tuberculosis)
dT	diphtheria-tetanus – adolescent and adult formulation
DTPa	diphtheria-tetanus-pertussis (acellular) – paediatric formulation
dTpa	diphtheria-tetanus-pertussis (acellular) – adolescent and adult formulation
dTpa-IPV	combined dTpa and inactivated poliovirus
DTPa-HepB	combined diphtheria-tetanus-pertussis (acellular) and hepatitis B
DTPa-IPV	combined diphtheria-tetanus-pertussis (acellular) and inactivated poliovirus (quadrivalent)
DTPa-IPV-HepB	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus and hepatitis B (pentavalent)
DTPa-IPV-HepB-Hib	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccine (hexavalent)
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
Hib-HepB	combined *Haemophilus influenzae* type b and hepatitis B
HPV	human papillomavirus
IPV	inactivated poliovirus vaccine
Men4PV	meningococcal polysaccharide tetravalent vaccine
MenCCV	meningococcal C conjugate vaccine
MMR	measles-mumps-rubella
pH1N1	pandemic H1N1 influenza 2009