Annual reports

Annual report: surveillance of adverse events following immunisation in Australia, 2011

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

Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) for 2011, and describes reporting trends over the 12-year period 2000 to 2011. There were 2,327 AEFI records for vaccines administered in 2011, a decrease of 40% from 3,894 in 2010. The decrease in 2011 was attributable to a decline in reporting following seasonal influenza (2,354 to 483) and pandemic H1N1 (pH1N1) influenza vaccines (514 to 2). However, reporting rates for some other vaccines were higher in 2011 compared with 2010. The 13-valent pneumococcal conjugate vaccine (13vPCV) replaced the 7-valent pneumococcal conjugate vaccine (7vPCV) and was suspected of involvement in 236 AEFI cases (48 per 100,000 doses). An increase in the number of reports following rotavirus (from 40 to 56 per 100,000 doses), and the hexavalent infant vaccine (from 27 to 40 per 100,000 doses), may have been due at least in part to co-administration with 13vPCV. Reports following DTPa-IPV also increased (from 94 to 139 per 100,000 doses), continuing a trend since 2009. AEFI reports following receipt of the 23-valent pneumococcal vaccine also increased markedly in those aged ≥65 years, from 155 to 288 records. In response to the increase in reports following 23vPPV, boosters are no longer recommended for those without medical risk factors. The most commonly reported reactions were injection site reactions, fever, allergic reactions and malaise. Only 7% of all the reported adverse events were categorised as serious, as per the database definitions, although some events classified as non-serious may have caused severe illness. Three deaths were temporally associated with vaccination; however, all were attributed to causes other than vaccination. The increase in 2011 was predominately due to reports of injection site reactions (49% increase in 2011). Increases in some instances may also be partly attributable to an increasing propensity to report AEFI. *Commun Dis Intell* 2012;36(4):E315–E332.

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 2012. The report focuses on AEFI reported for vaccines administered during 2011 and trends in AEFI reporting over the 12-year period 1 January 2000 to 31 December 2011.

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, which are difficult to detect in pre-registration vaccine trials.

Reports summarising national AEFI surveillance data have been published regularly since 2003. Trends in reported adverse events following immunisation are heavily influenced by changes to vaccines provided through the National Immunisation Program (NIP). Changes in previous years have been reported elsewhere.[2–10] Recent changes that impact on AEFI surveillance data presented in this report are:

i. From 1 July 2011, Prevenar 13® (13-valent pneumococcal conjugate vaccine, 13vPCV) replaced Prevenar® (7-valent pneumococcal conjugate vaccine, 7vPCV) on the NIP 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).[11] In addition, children aged between 12 and 35 months, who had completed a primary pneumococcal vaccination course with 7vPCV were eligible to receive a free supplementary dose of Prevenar 13® from 1 October 2011 to 30 September 2012. The Northern Territory Gov-

ernment 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®.[12]

ii. On 25 March 2011, TGA issued a recall of Batch N3336 of the 23 valent pneumococcal polysaccharide vaccine (23vPPV, Pneumovax® 23), as a precautionary measure following an increased number of reports of adverse reactions in patients who had received the vaccine.[13] Further advice to health professionals not to administer a second or subsequent dose of Pneumovax 23 vaccine was provided in April 2011.[14] Revised recommendations regarding which patients should be re-vaccinated under the NIP was provided in December 2011.[15]

A number of other important changes to vaccine funding and availability that impact on the interpretation of trend data have been described in detail in previous reports published regularly since 2003.[2–10] These are listed in Table 1 in chronological order. To assist readers, at the end of this report is a glossary of the abbreviations of the vaccines referred to in this report.

Methods

AEFI are notified to the TGA by state and territory health departments, health professionals, vaccine manufacturers and members of the public.[16,17] All reports are assessed using internationally consistent criteria[18] and entered into the Australian Adverse Drug Reactions System (ADRS) database. All serious reports for drugs and vaccines are reviewed by the TGA. Other reports are used in data mining and signal detection activities.

AEFI data

De-identified information on all AEFI reported to the TGA from 1 January 2000 to 28 February 2012 and stored in the ADRS database were released to the National Centre for Immunisation Research and Surveillance (NCIRS). 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 2011, 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 2011.

Study definitions of AEFI outcomes and reactions

AEFI were defined as 'serious' or 'non-serious' based on information recorded in the ADRS database and criteria similar to those used by the World Health Organization[18] and the US Vaccine Adverse Events Reporting System (VAERS).[19] In this report, an event is defined as 'serious' if the record indicated that the person had recovered with sequelae, was admitted to a hospital, experienced a life-threatening event, or died.

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 correlation of symptoms and signs in relation to vaccination (for injection site reactions), and whether one or more vaccines were administered, and 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 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®).[20]

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).[17] Where MedDRA® coding terms could not be categorised into Handbook categories, 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

* The term 'AEFI record' is used throughout this report because a single AEFI notification/report to the Medicine Safety Monitoring Unit can generate more than one 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 as biologically plausible.

Table 1: Changes to the Australian Standard Vaccination Schedule (2003–2010)[2–10]

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 from April 2007, 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. Pandemic H1N1 2009 influenza 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 NIP 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. From 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, TGA issued a recall of Batch N3336 of the 23 valent pneumococcal polysaccharide vaccine 23vPPV, Pneumovax® 23. In April 2011 health professionals were advised not to administer a second or subsequent dose of Pneumovax 23 vaccine.In December 2011 revised recommendations regarding which patients should be re-vaccinated under the National Immunisation Program were provided.

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.[21] 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.

Reporting rates per 100,000 administered doses were estimated where reliable information was available on the number of doses administered. This was done for 12 vaccines funded through the NIP for children aged <7 years, for influenza vaccine in adults aged ≥18 years, and for 23vPPV in adults aged ≥65 years.

Denominator data to estimate reporting rates for influenza and 23vPPV vaccines were obtained from a national adult coverage survey conducted in 2009.[22] For 23vPPV, the number of people vaccinated in 2011 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 (ACIR), a national population-based register of approximately 99% of children aged <7 years.[23]

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 fourth quarter of 2011. Data published in previous reports for 2000–2010[2–10] 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. Data can also differ because reports 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.[2–10,24]

It is important to note that this report is based on vaccine and reaction term information collated in the ADRS database and not on comprehensive clinical notes or case reviews. The reaction categories are created from available information and are similar, but not identical, to *The Australian Immunisation Handbook*[17] AEFI case definitions.

Comparison with online Database of Adverse Events Notifications

In August 2012, the TGA made a searchable database, the Database of Adverse Event Notifications (DAEN) publicly available on its web site. DAENS contains data of all adverse event reports for medicines (including vaccines).[25] This annual report includes data from the ADRS database sent to NCIRS by TGA in March 2012, and includes more detailed data than those provided by DAEN. The numbers published in this report may be different to the numbers in the DAEN database, due to different dates of data extraction. 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 2,327 records where the date of vaccination (or onset of adverse event, if vaccination date was not reported) was between 1 January and 31 December 2011.

In 2011, 83% of AEFI (n=1,933) were reported to the TGA via states and territories, while the rest were reported directly to the TGA; 13% (n=291) by doctors or health care providers, 2% (n=42) by members of the public, 1% (n=29) by hospitals, and 1% (n=32) by drug companies. The proportion reported directly to the TGA by members of the public during 2011 (2%; n=42) was substantially lower than in 2009 (28%; n=664) and 2010 (13%; n=502) mainly because of the active promotion of the direct reporting of AEFI to TGA following the monovalent pandemic H1N1 influenza (pH1N1) vaccine in 2009, as well as a high level of public interest in both the pH1N1 and seasonal TIV vaccines during 2009 and 2010.

Reporting trends

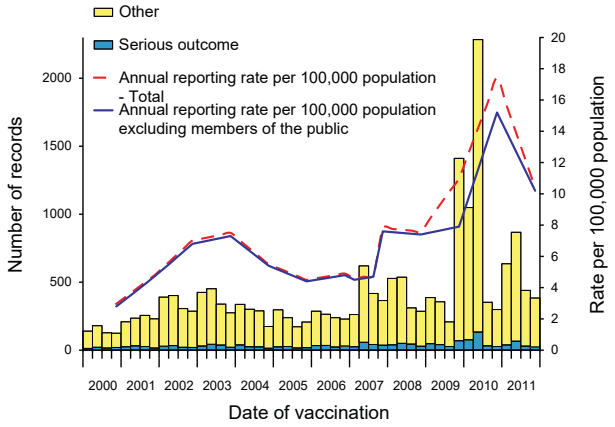
The overall AEFI reporting rate for 2011 was 10.4 per 100,000 population, compared with 17.4 in 2010. The AEFI reporting rate was the third highest for the period 2000 to 2011, after peaks in 2010 (17.4) predominantly due to reports in children following vaccination with the 2010 seasonal TIV, and in 2009 (11.0) following the commencement of the pandemic (pH1N1) influenza vaccine program.[9,10]

There was a substantial drop in reported events as well as reporting rate per 100,000 population during 2011, and the vast majority of reported events (from all reporter types) were of a non-serious nature (Figure 1). There were marked variations in reporting levels in association with previous changes to the NIP from 2000 onwards (Figures 2a, 2b and 2c). There was an increase in the number of in reports following the receipt of 7vPCV, 13vPCV, and DTPa-containing vaccines in children aged <7 years compared with previous years (Figures 2b and 2c). There was a spike in reports following 23vPPV vaccination in adults. However, this was consistent with the usual seasonal pattern of reporting from older Australians who typically receive 23vPPV and influenza vaccine during the autumn months (March–June) (Figure 2a).

Age distribution

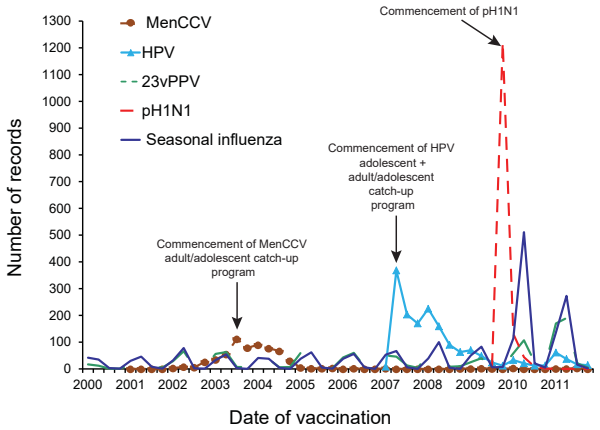
In 2011, the AEFI reporting rate per 100,000 population declined for all age groups <65 years com-

Figure 1: Adverse events following immunisation, ADRS database, 2000 to 2011, by date of vaccination



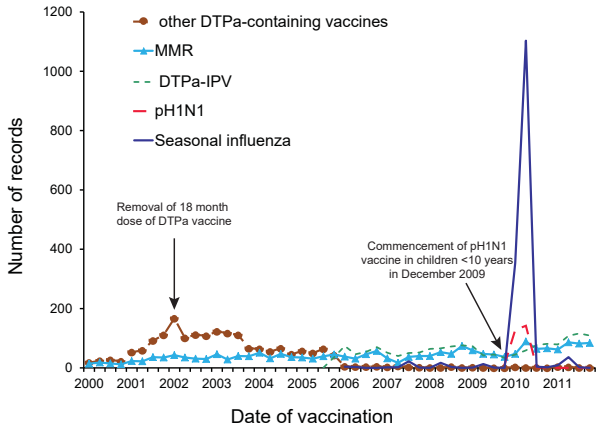
For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Figure 2a: Adverse events following immunisation for people aged ≥7 years for frequently reported vaccines, ADRS database, 2000 to 2011, by date of vaccination



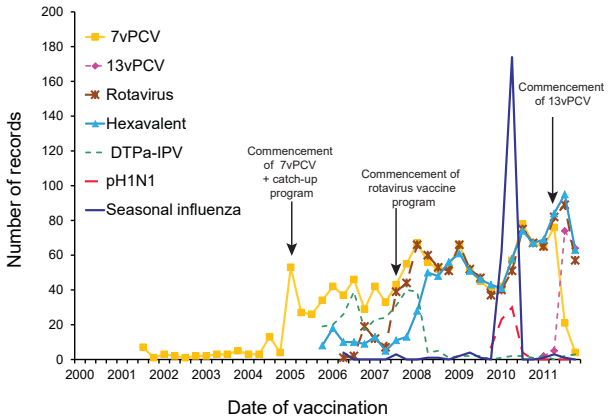
For reports where the date of vaccination was not recorded, the date of onset or the date the event was reported to the Therapeutic Goods Administration was used as a proxy for vaccination date.

Figure 2b: Adverse events following immunisation for children aged 1 to <7 years for frequently reported vaccines, ADRS database, 2000 to 2011, by date 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: Frequently suspected vaccines,* adverse events following immunisation for children aged <1 year, ADRS database, 2000 to 2011, by date of vaccination



* Meningococcal C conjugate vaccine (MenCCV) was introduced into the NIP schedule on 1 January 2003; 7-valent pneumococcal conjugate vaccine (7vPCV) 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.

pared with 2010 (Figure 3). These decreases were almost entirely related to the decline in the number of reports following the receipt of the influenza vaccine; primarily seasonal influenza vaccine. An increase was observed in reporting rates per 100,000 doses of certain vaccines and age groups as shown in Table 2. Reporting rates per 100,000 doses were higher in 2011 compared with 2010 for all age groups, but the increase was significant in children aged 2 to <7 years (80.2 vs 44.7) compared with children aged <1 years (17.6 vs 12.8) and 1 to <2 years (14.2 vs 9.2). The increase in reporting of AEFI in children aged 2 to <7 years in 2011 is primarily because of increased reporting of injection site reaction (ISR) following vaccination with DTPa-IPV

Table 2: Vaccine types recorded as 'suspected' of involvement in adverse events following immunisation, ADRS database, 2011, by selected age group

Vaccines*	AEFI records† (n)	Vaccine doses‡ (n)	Reporting rate per 100,000 doses§ (95% CI)	
			2011	2010
<7 years				
DTPa-containing vaccines	757	1,135,635	66.7 (62.0–71.6)	44.0 (40.2–48.1)
DTPa-IPV	419	301,607	138.9 (125.9–152.9)	94.1 (83.2–106.2)
Pentavalent (DTPa-IPV-HepB)	1	252	396.8 (11.9–2222.2)	1033.6 (281.7–2646.0)
Hexavalent (DTPa-IPV-HepB-Hib)	337	833,776	40.4 (36.2–45.0)	26.5 (23.2–30.3)
Haemophilus influenzae type b	72	282,350	25.5 (19.9–32.1)	31.9 (25.6–39.2)
Measles-mumps-rubella	324	591,059	54.8 (49–61.1)	48.2 (42.6–54.2)
Meningococcal C conjugate	78	296,320	16.9 (20.8–32.8)	28.6 (22.8–35.4)
Pneumococcal conjugate –7vPCV	176	460,353	33.7 (32.8–44.3)	26.3 (22.9–30.0)
Pneumococcal conjugate –13vPCV	236	488,896	48.3 (42.3–54.8)	na
Rotavirus vaccine	294	522,638	56.3 (50.0–63.1)	39.8 (34.6–45.6)
Varicella	61	280,837	21.7 (16.6–27.9)	35.2 (28.5–42.9)
Seasonal influenza	52	na	na	na
pH1N1	2	na	na	na
Total‖ (<7 years)¶	1,121	4,058,431	27.6 (26.0–29.3)	19.3 (18.0–20.8)
7–17 years				
HPV	128	na	na	na
Hepatitis B	96	na	na	na
dTpa	93	na	na	na
Varicella	31	na	na	na
Seasonal influenza	66	na	na	na
pH1N1	–	na	na	na
Total 7–17 years)	346	na	na	na
18–64 years				
Seasonal influenza**	226	3,170,300	7.1 (6.2–8.1)	10.8 (9.7–12.0)
pH1N1	–	na	na	na
dTpa	108	na	na	na
23vPPV¶	84	132,520	63.4 (50.6–78.4)	22.6 (15.3–32.3)
Total‖ (18–64 years)††	467	3,302,820	9.4 (8.4–10.5)	11.3 (10.2–12.5)
≥65 years				
23vPPV**	288	317,400	90.7 (80.6–101.8)	48.8 (41.4–57.2)
Seasonal influenza**	129	2,176,000	5.9 (4.9–7.0)	7.0 (6.0–8.2)
pH1N1	–	na	na	na
dTpa	27	na	na	na
Total‖ (≥65 years)††	363	2,493,400	16.7 (15.2–18.4)††	12.4 (11.0–13.8)††

* 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 2011. 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 (ACIR) and administered between 1 January and 31 December 2011.

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

‖ 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 one reaction term.

¶ Number of AEFI records excluding influenza vaccines

** Number of administered doses of seasonal influenza vaccine estimated from the 2009 AIHW national adult vaccination survey.[24]

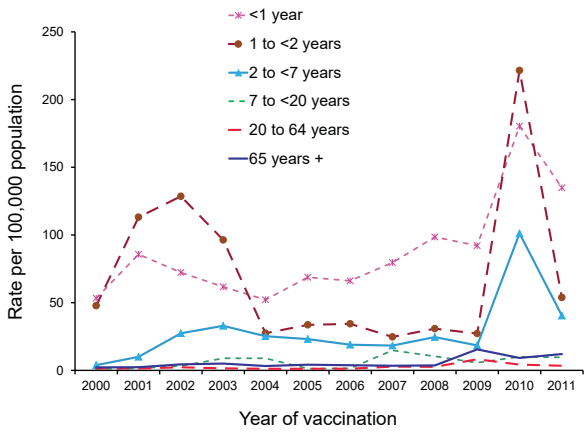
†† Seasonal influenza and 23vPPV only

Na Not applicable

containing vaccines and 13vPCV. The increase was largely seen in Victoria followed by Queensland and New South Wales.

There were reductions in population-based reporting rates in all age groups over the age of 7 years in 2011 compared with 2010, with the exception of the ≥65 year age group in which rates increased from 9.2 to 12.1 per 100,000. Also, reporting rates per 100,000 vaccine doses were higher overall in 2011 compared with 2010 for the ≥65 years age group (from 12.4 to 16.7) especially for 23vPPV (from 48.8 to 90.7) (Table 2).

Figure 3: Reporting rates of adverse events following immunisation per 100,000 population, ADRS database, 2000 to 2011, 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.

Geographical distribution

Population-based reporting patterns varied between states and territories during 2011 (Table 3) as in previous years.[2–10] The highest rates were in the Northern Territory, the Australian Capital Territory and South Australia (27.7, 17.4, 15.1, respectively), while New South Wales had the lowest rate (6.2). Reporting rates dropped in most jurisdictions in 2011 compared with 2010. There was a 75% decline in Western Australia (from 42.1 to 10.5); 57% decline in South Australia (from 34.9 to 15.1) and a more than 45% decline in Tasmania (from 15.6 to 8.4) and the Australian Capital Territory (from 32.6 to 17.4).

Vaccines

Thirty-one different vaccines were included in the 2,327 records received in 2011 (Table 4). The percentage of records where only one vaccine was reported differed by vaccine, 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, in accordance with the frequency of injection site reactions, for which

Table 3: Adverse events following immunisation, ADRS database, 1 January to 31 December 2011, by state or territory

	AEFI records		Annual reporting rate per 100,000 population*			
State or territory	n	%	Overall	'Certain'/'probable' causality rating†	'Serious' outcome‡	Aged <7 years
Australian Capital Territory	64	3	17.4 (13.4–22.2)	3.8	1.4	7.3
New South Wales	449	19	6.2 (5.7–6.8)	1.4	0.6	2.1
Northern Territory	64	3	27.7 (21.3–35.3)	7.8	3.5	14.7
Queensland	433	18	9.7 (8.8–10.6)	3.1	0.8	5.1
South Australia	248	11	15.1 (13.3–17.1)	2.7	0.5	7.4
Tasmania	43	2	8.4 (6.1–11.3)	2.2	0.0	3.3
Victoria	738	31	13.3 (12.4–14.3)	2.6	0.7	7.6
Western Australia	248	11	10.5 (9.3–11.9)	2.1	0.6	4.7
Other§	40	2	na	na	na	na
Total	2,327	100	10.4 (10.0–10.9)	2.3	0.7	5.0

* Average annual rates per 100,000 population calculated using mid-2010 population estimates (Australian Bureau of Statistics).

† See previous reports[2,3] for criteria used to assign causality ratings.

‡ Adverse events following immunisation (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), members of the public (n=6), and health care providers (n=2).

Table 4: Vaccine types listed as 'suspected' in records of adverse events following immunisation, ADRS database, 2011

Suspected vaccine type*	AEFI records	One suspected vaccine or drug only†		'Certain'/ 'probable' causality rating‡		'Serious' outcome§		Age group‖ <7 years		Age group‖ ≥7 years	
	n	n	%¶	n	%¶	n	%¶	n	%¶	n	%¶
Influenza	483	356	74	68	14	34	7	52	11	427	88
DTPa-IPV	426	198	46	161	38	16	4	419	98	4	1
23vPPV	405	281	69	106	26	17	4	16	4	386	95
MMR	348	34	10	14	4	20	6	324	93	22	6
DTPa-IPV-HepB-Hib	339	28	8	16	5	40	12	337	99	2	1
Rotavirus	296	31	10	7	2	36	12	294	99	1	0.3
13vPCV	236	78	33	43	18	20	8	235	99.6	1	0.4
dTpa	235	173	74	73	31	13	6	4	2	229	97
7vPCV	176	8	5	6	3	24	14	176	100	0	0
Hepatitis B	140	54	39	9	6	9	6	11	8	127	91
HPV	133	58	44	9	7	4	3	1	0.8	129	97
Varicella	96	55	57	10	10	8	8	61	64	35	36
MenCCV	83	3	4	0	0	9	11	78	94	5	6
Hib	73	2	3	0	0	9	12	72	99	1	1
Hepatitis A	25	3	12	1	4	3	12	6	24	19	76
DTPa	24	15	63	8	33	4	17	11	46	12	50
Typhoid	21	4	19	0	0	3	14	0	0	21	100
dT	19	13	68	6	32	1	5	0	0	19	100
Yellow fever	16	6	38	1	6	6	38	1	6	15	94
Hepatitis A + B	14	6	43	0	0	1	7	1	7	13	93
Rabies	13	6	46	0	0	4	31	2	15	11	85
10vPCV	11	2	18	0	0	1	9	9	82	2	18
Hepatitis A-Typhoid	9	2	22	0	0	2	22	2	22	7	78
Q fever	7	7	100	2	29	0	0	0	0	7	100
BCG	6	5	83	2	33	0	0	6	100	0	0
IPV	4	0	0	0	0	0	0	1	25	3	75
Japanese encephalitis	4	1	25	0	0	1	25	0	0	4	100
Men4PV	4	0	0	0	0	2	50	1	25	3	75
Cholera	2	2	100	0	0	2	100	0	0	2	100
dTpa-IPV	2	0	0	0	0	0	0	0	0	2	100
DTPa-IPV-HepB	1	0	0	0	0	0	0	1	100	0	0
Total**	2,327	1,421	61	523	22	158	7	1,121	48	1,189	51

* See appendix for abbreviations of vaccine names.

† Adverse events following immunisation (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 133 AEFI records; this was the only suspected vaccine in 44% of the 133 AEFI records, 7% had 'certain' or 'probable' causality ratings, 3% were defined as 'serious' and 97% 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 one vaccine.

the attribution of causality is more straightforward. There were also slight variations in the numbers with outcomes defined as 'serious', which have remained low as in previous years.

The individual vaccines most frequently suspected to have been related to AEFI events were seasonal influenza vaccine with 483 records (21%), followed by DTPa-IPV (n=426; 18%) and 23vPPV (n=405; 17%) (Table 4).

Reactions

The distribution and frequency of reactions listed in records for vaccines received in 2011 are shown in Tables 5a and 5b. In Table 5a, only the reaction categories analogous to those listed in *The Australian Immunisation Handbook*[17] are shown. In Table 5b, other reaction categories are listed in descending order of frequency.

The most frequently reported adverse events were ISR (46%), fever (24%), allergic reaction (18%), malaise (10%), rash, headache and pain (8% each) (Tables 5a and 5b; Figure 4).

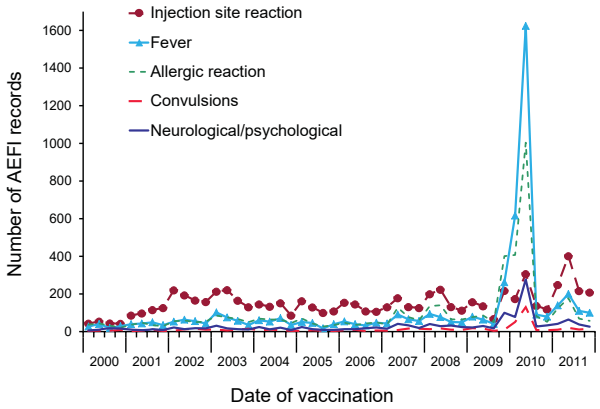
Of the 1,073 cases of ISR, 531 (49%) were children aged less than 7 years. The vaccines most commonly suspected to have been related to AEFI for the <7 years age group related to ISR were: DTPa-IPV (n=345); MMR (n=183); 13vPCV (n=77); hexavalent vaccine (n=61) and 7vPCV (n=24). For the ≥7 years age group (n=533), these were 23vPPV (n=269); seasonal influenza vaccine (n=163); and dTpa (n=116) either given alone or co-administered with other vaccines. As expected, reports for 23vPPV and seasonal influenza vaccine were predominantly in the ≥65 years age group (72% and 39% respectively), while dTpa was commonly reported in the 12–17 years (26%) and 18–64 years age groups (58%).

The number of reports in each reaction category has changed over time (Figure 4). In previous years, reports of allergic reactions peaked in 2003 and 2007, coinciding with the national school-based MenCCV immunisation program and the human papillomavirus school program. Much of the variation in reporting of ISR over time is 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 vaccine.[2–10,26,27] 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. However, by far the largest peaks in reports since 2000 have been associated with the pH1N1 and seasonal influenza 2010 vaccines. In particular, there were large peaks of reports of fever and allergic reactions in 2009 associated with the pH1N1 vaccine, and in 2010 associated with both the pH1N1 and seasonal influenza vaccines. Reports of convulsions peaked in 2010, mainly associated with the seasonal influenza vaccine but also to a lesser extent with pH1N1. The peaks in neurological/psychological conditions in both years were mainly related to the pH1N1 and seasonal influenza vaccine. In 2011, the increase in ISR was associated with non-influenza vaccines, particularly 23vPPV and DTPa-containing vaccines.

Severity of outcomes

Summary data on outcomes are presented in Table 6. Fifty-eight per cent of reported events in 2011 were defined as 'non-serious' while 7% were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threatening event or death) (Table 6). This is similar to the proportion of serious AEFI observed in previous years.[9,10] A further 22% were recorded as not fully recovered at the time of reporting; 41% of these reports came from Victoria, followed by Western Australia (20%) and Queensland (15%). Ninety-three per cent of cases recorded as 'not fully recovered' had missing information in various fields including hospitalisation; 77% were reported by states and territories, 17% by health care providers, 3% by members of the public, and 1% each by hospital, pharmacist and drug companies. Information on severity could not be determined for 14% (n=316) of records due to insufficient data and the majority of these reports came from states and territories (77%). Forty-four per cent of these reports were reported by Victoria. Of those without information describing severity,

Figure 4: Selected frequently reported adverse events following immunisation, ADRS database, 2000 to 2011, by date 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.

the most commonly reported adverse reactions were: ISR (49%); fever (23%); and allergic reactions (15%).

A total of 523 (22%) records were assigned causality ratings of either 'certain' (n=466; 20%) or 'probable' (n=57; 2%) and the rest (78%) were rated as 'possible'.

Table 5a: Reaction categories of interest* mentioned in records of adverse events following immunisation, ADRS database, 2011

	AEFI records	Only reaction reported†		'Certain'/'probable' causality rating‡		Age group§			
						<7 years		≥7 years	
Reaction category*	n	n	%‖	n	%‖	n	%‖	n	%‖
Injection site reaction	1,073	244	23	481	45	531	49	533	50
Fever	549	11	2	34	6	301	55	245	45
Allergic reaction¶	426	53	12	14	3	173	41	250	59
Rash**	190	66	35	1	1	134	71	54	28
Syncope	106	64	60	12	11	19	18	84	79
Abnormal crying	82	3	4	5	6	79	96	3	4
Convulsions	56	31	55	1	2	44	79	12	21
Lymphadenopathy/lymphadenitis††	42	4	10	13	31	7	17	35	83
Hypotonic-hyporesponsive episodes	38	29	76	1	3	38	100	0	0
Arthralgia	36	3	8	4	11	3	8	33	92
Abscess	16	5	31	6	38	4	25	12	75
Anaphylactic reaction	13	11	85	1	8	2	15	11	85
Arthritis	12	1	8	2	17	5	42	7	58
Intussusception	6	6	100	0	0	6	100	0	0
Guillain-Barré syndrome	3	2	67	1	33	0	0	3	100
Death	3	2	67	0	0	1	33	2	67
Brachial neuritis	1	1	100	0	0	0	0	1	100
Parotitis	1	0	0	0	0	0	0	1	100
Thrombocytopenia	1	1	100	0	0	1	100	0	0
Encephalitis	0	0	0	0	0	0	0	0	0
Encephalopathy	0	0	0	0	0	0	0	0	0
Orchitis	0	0	0	0	0	0	0	0	0
Osteitis	0	0	0	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	0	0
Total‡‡	2,327	1,421	61	523	22	1,121	48	1,189	51

* Reaction categories were created for the Adverse events following immunisation (AEFI) of interest listed and defined in *The Australian Immunisation Handbook*, (9th edition, p 58–65 and 360–3)[17] 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 1,073 AEFI records listing injection site reaction, 23% listed only one type of reaction while 45% had a causality rating of 'certain' or 'probable' and 49% 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 like abdominal pain, nausea, flatulence, abnormal faeces, hematochezia etc. Does not include anaphylaxis.

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

†† Includes lymphadenitis following Bacille Calmette-Guérin 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 one reaction term.

Table 5b: 'Other'* reaction terms listed in records of adverse events following immunisation, ADRS database, 2011

Reaction term*	AEFI records	Only reaction reported†		'Certain'/'probable' causality rating		Age group§ <7 years		Age group§ ≥7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Malaise	240	0	0	16	7	80	33	160	67
Headache	180	4	2	6	3	19	11	59	88
Pain	176	6	3	2	1	16	9	159	90
Neurological/psychological	169	1	0.6	6	4	133	79	36	21
Oedema	146	9	6	2	1	35	24	110	75
Nausea	126	0	0	9	7	6	5	118	94
Myalgia	121	5	4	6	5	12	10	110	89
Erythema	118	16	14	2	2	41	35	77	65
Gastrointestinal – RVV¶	107	8	7	3	3	106	99	0	0
Abdominal pain	91	4	4	4	4	45	49	45	49
Respiratory	88	12	13	4	5	39	44	49	56
Dizziness	75	1	1	3	4	2	3	73	97
Reduced sensation	44	1	2	4	9	1	2	43	98
Increased sweating	39	0	0	0	0	7	18	32	82
Somnolence	39	0	0	3	8	28	72	11	28
Pallor	35	0	0	2	6	22	63	13	37
ENT**	32	1	3	4	13	5	16	27	84
Circulatory	25	2	8	1	4	7	28	18	72
Weakness	21	0	0	0	0	2	10	19	90
Flushing	17	1	6	2	12	2	12	15	88
Tremor	17	1	6	2	12	4	24	12	71
Vision impaired	16	0	0	1	6	5	31	11	69
Other	242	22	9	15	6	111	46	130	54
eye or ear	25	0	0	2	8	12	48	13	52
cardiovascular	14	0	0	1	7	5	6	9	64
general non-specific	38	10	26	3	8	16	42	22	58
infection	20	3	15	0	0	10	50	10	50
respiratory	10	0	0	0	0	5	50	5	50
psychological	15	0	0	3	20	8	53	7	47
neurological	14	4	29	1	7	7	50	7	50
skin††	17	2	12	2	12	9	53	8	47
renal/urogenital	11	0	0	0	0	1	9	10	91
gastrointestinal‡‡	15	0	0	1	7	8	53	6	40
musculoskeletal	11	2	18	0	0	2	18	9	82
metabolic/endocrine	15	0	0	1	7	9	60	6	40
pregnancy/congenital	5	1	20	1	20	1	20	4	80
miscellaneous	3	0	0	1	33	2	67	1	33
haematological	5	0	0	0	0	3	60	2	40

* Reaction terms not listed in *The Australian Immunisation Handbook*[17] but included in adverse events following immunisation (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.

† 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 1,073 AEFI records listing injection site reaction, 23% listed only one type of reaction while 45% had a causality rating of 'certain' or 'probable' and 49% were for children aged <7 years.

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

** Includes all the conditions related to ear, nose and throat

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

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

The reactions recorded as 'serious' (n=158) were ISR (n=40; 25%); fever (n=37; 23%); allergic reactions (n=23; 15%); convulsions (n=18; 11%), including 11 febrile convulsions; diarrhoea/vomiting (n=11; 7%); hypotonic-hyporesponsive episode (HHE) (n=6; 4%); anaphylaxis (n=4; 3%); Guillain-Barré syndrome (GBS) (n=3; 2%); intussusception (n=3; 2%); 3 cases of syncope (2%); 3 reports of death (2%); and 1 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 their outcome and/or hospitalisation status, included: convulsion (n=38; 38/56=68%), including 20 febrile convulsions; HHE (n=32; 32/38=84%); anaphylaxis (n=9; 9/13=69%); and intussusception (n=3; 3/6=50%).

All the reported cases of HHE (38) were from children aged <7 years. Seventeen reports (45%) were following co-administration of hexavalent, 7vPCV and rotavirus vaccines while 11 reports were following hexavalent, 13vPCV and rotavirus vaccines. Another 10 cases were following vaccination with MenC, MMR, BCG and DTPa/IPV administered simultaneously or individually.

All the 3 cases of GBS were in people aged >60 years. All of the three reports were following receipt of the seasonal influenza vaccine (2 following vaccination with Fluvax®, and one with Vaxigrip®).The timing in relation to administration of vaccine and onset of symptoms varied between same day to 7 weeks.

Of the 6 reports of intussusception, 5 were from infants (<1 year of age): 3 were following hexavalent, 7vPCV and rotavirus vaccines and 2 were following hexavalent, 13vPCV and rotavirus vaccines administered together. One report of intussusception was from a 19-month-old child following varicella vaccine administered alone. Five of the 13 reports of anaphylaxis in 2011 occurred following receipt of one of the influenza vaccines administered alone or in combination with other vaccines, while another 5 reports were following adult dTpa vaccine administered alone or in combination with other vaccines. Other individual vaccines leading to anaphylaxis were rotavirus, 13vPCV, and typhoid vaccine.

Three deaths were recorded as temporally associated with receipt of vaccines; two were following receipt of seasonal influenza vaccine.

- One was an infant who had received hexavalent, 13vPCV and rotavirus vaccine 3 days prior to death. The cause of death was recorded as sudden infant death syndrome.
- The second reported death was a middle-aged person, with motor neurone disease, who died 4 days after receiving the seasonal influenza vaccine. He developed flu-like-illness after vaccination and had a cardiac arrest. The cause of the death was documented as complications of motor neurone disease.
- The third death was of a very elderly person, who developed progressive neurological dysfunction and died 29 days after receiving sea-

Table 6: Outcomes of adverse events following immunisation, ADRS database, 2011

Outcome	AEFI records		'Certain'/ 'probable' causality rating†		Age group‡ <7 years		Age group‡ ≥7 years	
	n	%*	n	%§	n	%§	n	%§
Non-serious:	1,341	58	290	22	611	46	720	54
Not recovered at time of report	512	22	119	23	248	48	258	50
Not known (missing data) – total	316	14	87	28	172	54	144	46
Serious:	158	7	27	17	90	57	67	42
recovered with sequelae	1		–		–		1	
hospital treatment – admission	148		25		89		58	
life-threatening event	6		2		–		6	
Death	3		–		1		2	
Total	2,327	100	523	22	1,121	48	1,189	51

* Percentages relate to the total number of adverse events following immunisation (AEFI) records (n=2,327).

† 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 (17 missing).

§ Percentages relate to the number of AEFI records with the specific outcome, e.g. of 1,341 AEFI records with a 'non-serious' outcome, 22% had causality ratings of 'certain' or 'probable' and 46% were for children aged <7 years.

sonal influenza vaccine. The cause of the death was documented as acute disseminated encephalomyelitis (ADEM).

All deaths were investigated by the TGA and no clear causal relation to vaccination was found.

Pneumococcal conjugate vaccine

In 2011, pneumococcal conjugate vaccines (7vPCV and 13vPCV) were suspected of involvement in 412 records (236 for 13vPCV and 176 for 7vPCV) for people aged <7 years with 44 cases being coded as serious (24 for 7vPCV and 20 for 13vPCV). Eighty-five per cent of the 7vPCV reports were from the first half of the year and 97% of 13vPCV in the second half, consistent with their usage, with 13vPCV replacing 7vPCV in July 2011. The AEFI reporting rates in people aged < 7 years were 48.3 per 100,000 doses for 13vPCV and 33.7 per 100,000 doses for 7vPCV (Table 2). The rate for 7vPCV was about 28% higher in 2011 than in 2010 (26.3) and 33% higher than in 2009 (25.4). The majority of the 7vPCV vaccines were co-administered with hexavalent and rotavirus vaccines and only 5% were administered alone while in the case of 13vPCV, 29% (n=68) cases were administered alone. Of the 68 cases, 95% (n=65) of children were between 12 months and <36 months, who received vaccine under the catch-up program offered to children between 12 months and 35 months.

The most frequently reported reactions for 7vPCV were vomiting/diarrhoea (n=46, 26% each); fever (n=39, 22%); rash (n=34, 19%); screaming (n=31, 18%); allergic reactions (n=26, 15% each); ISR (n=24, 14%) and 1 case of syncope (Figure 5a). All reports recorded the co-administration of other vaccines.

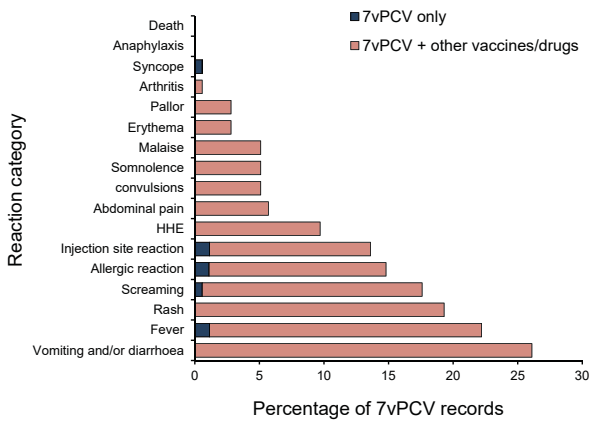
The spectrum of reactions for 13vPCV included 77 (33%) reports of ISR; 66 (28%) of fever; 43 (18%) of rash; 37 (16%) of vomiting/diarrhoea; 31 (13%) of allergic reactions; 2 case of syncope; 1 case of anaphylaxis and 1 reported death following co-administration of hexavalent, 13vPCV and rotavirus vaccine (Figure 5b).

Pneumococcal polysaccharide vaccine (23vPPV)

A single dose of 23vPPV is recommended for all non-Indigenous persons aged ≥65 years and all Indigenous persons aged ≥50 years. A second dose, 5 years later, should only be given to non-Indigenous persons aged ≥65 years with specified medical conditions that put them at increased risk of invasive pneumococcal disease, and to Indigenous persons who received their 1st dose at age ≥50 years.

There were a total of 405 records for 2011 where 23vPPV was listed as a suspected vaccine. Twenty-seven records were from those aged <18 year (16 in the 0–6 years and 11 in the 8–17 years age groups). There were 375 records for adults aged ≥18 years, with 13 cases coded as serious. There were 288 reports for older adults (≥65 years) including 194 (67%) reports of ISR, 76 (26%)

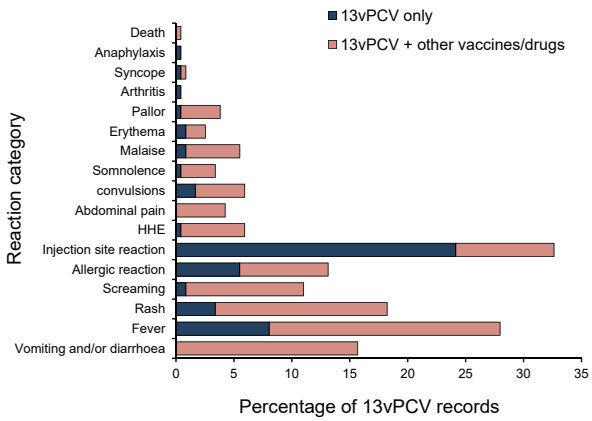
Figure 5a: Percentage of reported adverse events following immunisation with 7vPCV,* 2011, by reaction type and vaccine suspected of involvement in the reported event



* Per cent of 176 adverse events following immunisation records where 7vPCV was listed as suspected of involvement in the reported adverse event following immunisation.

Source: Adverse Drug Reactions Reporting System database, Therapeutic Goods Administration.

Figure 5b: Percentage of reported adverse events following immunisation with 13vPCV,* 2011, by reaction type and vaccine suspected of involvement in the reported event



* Per cent of 236 AEFI records (13vPCV) where 13vPCV was listed as suspected of involvement in the reported adverse event following immunisation.

Source: Adverse Drug Reactions Reporting System database, Therapeutic Goods Administration.

oedema, 60 (21%) fever, 43 (15%) erythema, 4 reports of syncope, and 1 report of anaphylaxis (Figure 6.). Using the 2009 estimate of the number of doses of 23vPPV administered to people aged ≥65 years (n=317,400), the reporting rate was 90.7 per 100,000 doses, with rates of 3.2 for events classified as serious and 61.0 for ISR. This is substantially higher than the overall rate reported for 2010 (from 48.8 to 90.7). Reporting rates for ISR also increased substantially (from 39.7 per 100,000 to 61.0 per 100,000).

An initial increase in reports of adverse events following vaccination with 23vPPV was noted in early 2011 up to 25 March 2011, which was much greater than the historical average (Figure 7). These initial reports triggered a national investigation, which led to a batch recall on 25 March and a subsequent increase in reporting.

Figure 7: Injection site reactions following 23vPPV immunisation for individuals aged ≥65 years, 2002 to 2011, by week of vaccination (2002–2010)* and week of report (2011)†

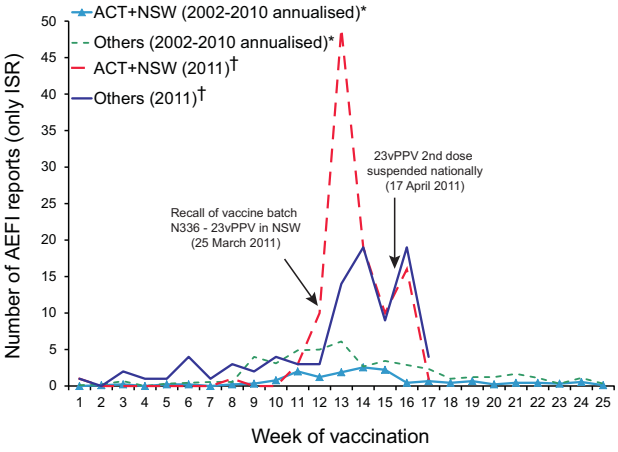
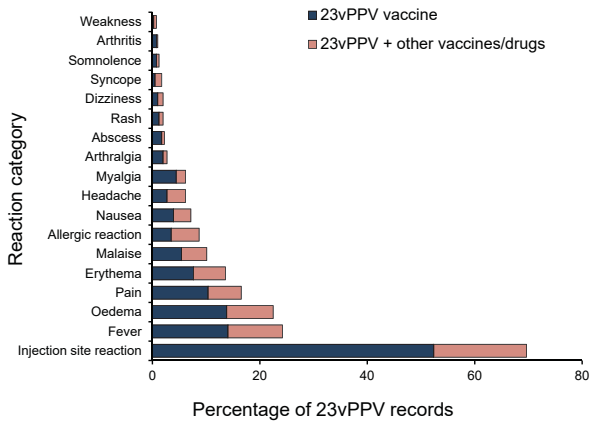


Figure 6: Percentage of reported adverse events following immunisation with pneumococcal polysaccharide (23vPPV),* 2011, by reaction type and vaccines suspected of involvement in the reported event



* Per cent of 405 adverse events following immunisation records where the pneumococcal polysaccharide vaccine (23vPPV) was listed as suspected of involvement in the reported adverse event following immunisation.

Source: Adverse Drug Reactions Reporting System database, Therapeutic Goods Administration

Discussion

In 2011 there was a substantial drop in the total number of reports of AEFI and population-based reporting rates compared with 2010, predominantly due to a large decline in reports following vaccination with seasonal influenza vaccine and pH1N1 influenza vaccines. The reduction in reports follows the temporary suspension of the Western Australia vaccination program for children under 5 years and the national vaccination program for at-risk children under age 5 years in 2010 and the subsequent recommendations against using the CSL vaccine (Fluvax®) in young children (<10 year),[28,29] which was associated with fever and febrile convulsions in children <5 years and has been discussed in detail elsewhere.[30]

However in 2011, reporting rates per 100,000 doses, which excluded influenza vaccine in children due to unreliable dose data, increased in all age groups except those aged 18–64 years, as shown in Table 2. The increase in reports for children aged 2 to <7 years is primarily due to ISR following vaccination with DTPa-IPV and 13vPCV. The increase was largely seen in Victoria, Queensland and New South Wales.

Data from the clinical studies of Prevenar 13® demonstrated an increase in ISR and systemic reactions following the 4th dose of 7vPCV or 13vPCV vaccine in the second year of life compared with earlier doses.[31] 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®,[11] and the increased reporting rate of ISR for 13vPCV may be in part because it is being given as a fourth dose of a PCV vaccine. It may also be attributed to the 'Weber effect',[32] which describes increased reporting frequently observed following the introduction of new vaccines.

The reporting rate of ISR in children aged 2 to <7 years has declined in recent years, as was expected following the removal of the dose of DTPa-IPV due at 18 months of age from the NIP schedule in September 2003. However, an increase in ISR following DTPa-IPV was observed in 2011.

The reasons for the increase in 2011 are not entirely clear but are at least partly due to general changes in AEFI surveillance. One additional suggested hypothesis is that some ISR's are 'Arthus reactions' caused by the presence of high levels of prevaccination IgG antibody in the vaccinees, which have been associated with higher rates of ISR.[33,34] Possible causes of higher pre-vaccination antibody levels include immunity induced by natural infection during the pertussis epidemic from 2008, which was notable for high notification rates in pre-school aged children,[35] as well as the earlier age of administration of the pre-school DTPa-IPV booster since the change of eligibility rules for provider and parent incentive payments.[36]

The higher overall numbers of reports in 2011 (excluding influenza vaccines) is also suggestive of generally increased propensity to report by providers in 2011, and may also reflect changes in the proportion of reports that were sent to TGA from individual state or territory surveillance systems. For example, in 2011, Victoria changed to submitting all reports to TGA, irrespective of severity, whereas previously minor/expected AEFI reports had not been submitted [personal communication: Dr Nigel Crawford, Surveillance of Adverse Events Following Vaccination In the Community (SAEFVIC), Victoria].

Reports of adverse events following 23vPPV vaccination in those aged ≥65 years increased substantially in 2011 compared with 2010 in all AEFI (from 48.8 to 90.7 per 100,000 doses). This increase may have been due to a larger number of people receiving second doses (recommended 5 years after the second dose) following the commencement of nationally funded vaccine in 2005. However, the current method of estimating the number of doses administered does not allow the detection of changes in vaccinations by year and cannot distinguish between the first and subsequent doses. In response to the continued increase in reports of severe ISR reports, in April 2011, the TGA issued advice to health professionals not to administer a second or subsequent dose of Pneumovax 23 vaccine.[14] An expert multidisciplinary working group was convened to investigate all reports of ISR following 23vPPV. Revised recommendations regarding which patients should be re-vaccinated under the NIP was provided in December 2011, with revaccination no longer recommended for those in the ≥65 years age group without predisposing medical conditions.[15]

Conclusion

There was a decline of 40% in the number of AEFI reported in 2011 compared with 2010 when a large number of reports were submitted in association with influenza vaccination. However, reporting rates for selected vaccines were higher in various age groups in 2011, mainly due to reports of ISR. Increases in reports in infants were related to the introduction of 13vPCV onto the schedule from July 2011, particularly including the supplementary booster dose for children aged 12–35 months, which as a booster dose, is known to be associated with increased ISRs. Increases in the 2 to <7 year age group were related to the DTP-IPV vaccine, and continue the trend of increasing reports since 2009. There was also an increase in the 12–17 year age group associated with dTPa. Increases in reactions in the ≥65 years age group were mostly of ISR following 23vPPV, many of which may have been second doses. The increase in the reporting rate for most vaccines might also be due to the greater propensity by providers to report in 2011 due to the heightened awareness of adverse events following influenza vaccine safety issues in 2010.

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, NCIRS, 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 and Ageing, the NSW Department of Health and The Children's Hospital at Westmead, Australia.

Author details

Deepika Mahajan[1]
Jane Cook[2]
Aditi Dey[1]
Kristine Macartney[1]
Rob Menzies[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;27:307–323.
3. Lawrence G, Boyd I, McIntyre P, Isaacs D. Surveillance of adverse events following immunisation: Australia 2002 to 2003. *Commun Dis Intell* 2004;28:324–338.
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):248–62.
5. Lawrence G, Boyd I, McIntyre P, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2005. *Commun Dis Intell* 2006;30:319–333.
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;31:269–282.
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;32:371–387.
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. 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 16 August 2012. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-pneumococcal
12. Northern Territory Government, Department of Health. NT Immunisation Schedule. Accessed on 16 August 2012. Available from: http://www.health.nt.gov.au/library/scripts/objectifyMedia.aspx?file=pdf/10/78.pdf&siteID=1&str_title=Childhood Vaccination Schedule.pdf
13. Australian Government Department of Health and Ageing, TGA. Pneumovax® 23: Recall of vaccine batch N3336. 25 March 2011.Accessed on 16 August 2012. Available from: http://www.tga.gov.au/safety/alerts-medicine-pneumovax-110325.htm.
14. Australian Government Department of Health and Ageing, TGA. Pneumovax 23 – Recommendation about revaccination. 18 April 2011. Accessed on 16 August 2012. Available from: http://www.tga.gov.au/safety/alerts-medicine-pneumovax-110416.htm
15. Australian Government Department of Health and Ageing, Immunise Australia program. Australian Technical Advisory Group on Immunisation (ATAGI) Statement – Updated recommendations for revaccination of adults with 23-valent pneumococcal polysaccharide vaccine (23vPPV), Pneumovax 23®. December 2011. Accessed on 16 August 2012. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/pneumo23-atagi-statement-cnt.htm
16. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 8th edn. Canberra: Australian Government Department of Health and Ageing, 2003.
17. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 9th edn. Canberra: Australian Government Department of Health and Ageing, 2008.
18. Adverse Events following Immunisation (AEFI): Causality assessment. WHO. Accessed on 6 December 2012. Available from: http://www.who.int/vaccines-documents/DocsPDF05/815.pdf
19. 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;52(6):113]. *MMWR Morb Surveill Summ* 2003;52(SS–1):1–24.
20. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;20:109–117.
21. The SAS system for Windows [computer program]. Version 9.3. Cary, N.C.: SAS Institute Inc, 2012.
22. Australian Institute of Health and Welfare. 2009 Adult Vaccination Survey: summary results. Cat. No. PHE 135 Canberra: AIHW, 2011.
23. Additional reports – Childhood immunisation coverage. *Commun Dis Intell* 2008;32:288–289.
24. 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;23:287–294.
25. Australian Government Department of Health and Ageing, TGA. Database of Adverse Event Notifications. 1 August 2012. Accessed on 28th August 2012. Available from: http://www.tga.gov.au/safety/daen.htm
26. 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;369:1693–1702.
27. 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;26:201–209.
28. Australian Government Department of Health and Ageing, TGA. Seasonal influenza vaccines: safety advisory. 11 March 2011. Accessed on 1 June 2012. Available from: http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-110310.htm
29. Australian Government Department of Health and Ageing, Immunise Australia program. Chief Medical Officer advice: Seasonal influenza vaccination. 7 March 2011. Accessed on 1 June 2012. Available from: http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/immunise-cmo
30. Blyth CC. Currie AJ. Wiertsema SP. Conway N. Kirkham LA. Fuery A. et al. Trivalent influenza vaccine and febrile adverse events in Australia, 2010:clinical features and potential mechanisms. *Vaccine* 2011;29(32):5107–13.

31. Australian Government Department of Health and Ageing, TGA. Australian Public Assessment Report for Pneumococcal Polysaccharide Conjugate Vaccine (Prevenar 13®). Accessed on 16 August 2012. Available from: http://www.tga.gov.au/pdf/auspar/auspar-prevenar13.pdf

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

33. Rennels MB. Extensive swelling reactions occurring after booster doses of Diphtheria-tetanus-Acellular Pertussis vaccines. Seminars in *Pediatr Infect Dis J* 2003;14(3):196–198.

34. Liese JG, Stojanov S, Zink TH, et al. Safety and immunogenicity of Biken acellular pertussis vaccine in combination with diphtheria and tetanus toxoid as a fifth dose at four to six years of age. *Pediatr Infect Dis J* 2001;20:981–988.

35. NNDSS Annual report writing group. Australia's notifiable disease status, 2009: Annual report of the National Notifiable Disease Surveillance System. *Commun Dis Intell* 2011;35(2):61–131.

36. Hull B, Dey A, Mahajan D, Menzies, RI, McIntyre PB. Immunisation coverage annual report, 2009. *Commun Dis Intell* 2011;35(2):132–148.

Abbreviations for vaccine types

BCG	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
7vPCV	7-valent pneumococcal conjugate vaccine
10vPCV	10-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine