Annual reports

Annual report: Surveillance of adverse events following immunisation in Australia, 2007

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Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration for 2007, and describes reporting trends over the 8-year period 2000 to 2007. There were 1,538 AEFI records for vaccines administered in 2007. This is an annual AEFI reporting rate of 7.3 per 100,000 population, the highest since 2003 and an 85% increase compared with 2006 (835 AEFI records; 4.0 records per 100,000 population). The increase was almost entirely due to reports following the commencement of the national 3-dose human papillomavirus (HPV) vaccine program for females aged 12 to 26 years in April 2007 (n=705 reports) and the national infant rotavirus vaccine program in July 2007 (n=72 reports). AEFI reporting rates in 2007 were 2.3 per 100,000 administered doses of influenza vaccine for adults aged ≥18 years, 18.6 per 100,000 administered doses of pneumococcal polysaccharide vaccine for those aged ≥65 years and 12.7 per 100,000 administered doses of scheduled vaccines for children aged <7 years. The majority of the 1,538 AEFI reports for 2007 described non-serious events while 9% (n=141) were classified as serious. Two deaths temporally associated with immunisation were reported; there was no evidence to suggest a causal association. The most significant AEFI reported following HPV vaccine were anaphylaxis (n=11) and convulsion (n=18), mostly associated with syncope. The most commonly reported reactions were allergic reaction, injection site reaction, headache and nausea. The data confirm that, despite the low rate of AEFI reporting in Australia, the passive surveillance system is sufficiently robust to detect safety signals which are expected following changes in the immunisation program, allowing these to be investigated further. *Commun Dis Intell* 2008;32:371–387.

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 31 March 2008. The report focuses on AEFI reported for vaccines administered during 2007 and trends in AEFI reporting for the 8-year period 2000 to 2007.

The aim of passive post-licensure AEFI surveillance is to monitor vaccine and immunisation program safety and to detect population-specific, rare, late-onset or unexpected adverse events that may not be identified in pre-licensure vaccine trials.[1,2] An 'adverse event following immunisation' is defined as any serious or unexpected adverse event that occurs *after* a vaccine has been given, which may be related to the vaccine itself or to its handling or administration. An AEFI can be *coincidentally* associated with the *timing* of immunisation without necessarily being caused by the vaccine or the immunisation process.

In Australia, AEFI are notified to the TGA by state and territory health departments, health professionals, vaccine manufacturers and members of the public.[3,4] All reports are assessed using internationally consistent criteria[5] and entered into the Australian Adverse Drug Reactions System (ADRS) database. All reports for vaccines and complementary medicines, plus all serious reports for drugs, are forwarded to the Adverse Drug Reactions Advisory Committee (ADRAC) for review at regular meetings. ADRAC is an expert committee of the TGA composed of independent medical experts who have expertise in areas of importance to the evaluation of medicine safety.

Passive AEFI surveillance data have been collated in the ADRS database since 2000 and used to monitor trends, detect signals and generate hypotheses. Reports summarising national AEFI surveillance data have been published regularly since 2003.[6–14] Several important changes to vaccine funding and availability occurred in 2007 that impact on the AEFI surveillance data presented in this report.

- A national human papillomavirus (HPV) immunisation program commenced in April 2007 for all girls aged 12 to 18 years, and was extended to the 19 to 26 year age group in July 2007.[15] The program is delivered through a secondary school immunisation program and general practice for those not vaccinated in a school program. In 2007, the funded program delivered only the quadrivalent vaccine (Gardasil®); the bivalent vaccine (Cervarix®) became available on the private market only during 2007. Both vaccines are given as a 3-dose course.
- Rotavirus (RotaTeq® and Rotarix®) vaccine was added to the National Immunisation Program (NIP) for all infants in Australia on 1 July 2007.[15] From August 2006, the vaccine was publicly funded for infants resident in the Northern Territory, and was available on the private market for other infants. Infants receive either a 2-dose schedule (Rotarix®) at 2 and 4 months of age, or a 3-dose schedule (RotaTeq®) at 2, 4 and 6 months of age.

Previous changes to the NIP schedule in 2003 and 2005[3,4,15] also impact on the interpretation of trend data: (i) on 1 January 2003, the meningococcal C conjugate vaccine (MenCCV) immunisation program commenced when the vaccine was introduced into the NIP schedule at 12 months of age with a catch-up program for all those born between 1984 and 2001;[15] (ii) in September 2003, the 4th dose of DTPa vaccine, given at 18 months of age, was removed from the immunisation schedule;[3] (iii) in January 2005, funded national pneumococcal immunisation programs commenced for infants at 2, 4 and 6 months of age (7-valent conjugate vaccine; 7vPCV), and for adults aged ≥65 years (23-valent polysaccharide vaccine; 23vPPV);[15] (iv) in November 2005, varicella vaccine was added to the NIP schedule as a single dose due at 18 months (for children born on or after 1 May 2004) or at 12–13 years of age if they have no evidence of either vaccination or varicella infection; and (v) in November 2005, inactivated poliovirus vaccine (IPV) replaced oral poliovirus vaccine (OPV) for all age groups. All IPV-containing combination vaccines include diphtheria-tetanus-acellular pertussis (DTPa) antigens (i.e. quadrivalent vaccines) and some also include hepatitis B (HepB) and/or *Haemophilus influenzae* type b (Hib) antigens (i.e. pentavalent and hexavalent vaccines). The specific combination vaccines administered at 2, 4, and 6 months of age vary between states and territories but all provide DTPa-IPV quadrivalent vaccine at 4 years of age.[4]

Methods

Adverse events following immunisation data

De-identified information was released to the National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases (NCIRS) for all drug and vaccine adverse event notifications received by the TGA to 31 March 2008. Readers are referred to previous AEFI surveillance reports for a description of the surveillance system and methods used to evaluate reports to the TGA.[6,7]

AEFI 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 and onset occurred between 1 January 2000 and 31 December 2007; *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 2007.

Definitions of 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[5] and the US Vaccine Adverse Events Reporting System.[16] In this report, an AEFI is defined as 'serious' if the record indicated that the person had recovered with sequelae, been admitted to a hospital, experienced a life-threatening event, or died.

The causality ratings of 'certain', 'probable' and 'possible' are assigned to individual AEFI records by the TGA and reviewed by ADRAC. 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 etc) and the spatial correlation (for injection site reactions) of symptoms and signs in relation to vaccination, and whether one or more vaccines were administered.[6] Because children in particular receive several vaccines at the same time, all administered vaccines are usually listed as 'suspected' of involvement in a systemic adverse event as it is usually not possible to attribute the AEFI to a single vaccine.

Typically, each AEFI record listed several symptoms, signs and diagnoses that had been re-coded by TGA staff from the reporter's description into

* The term 'AEFI record' is used throughout this report because a single AEFI notification can generate more than 1 record in the ADRS database. This usually occurs if a notification describes an injection site reaction plus symptoms and signs of a systemic adverse event. Two records will appear in the database: one containing information relevant to the injection site reaction and the other for the systemic adverse event.

standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA®).[17] AEFI reports of suspected anaphylaxis and hypotonic-hyporesponsive episodes (HHE) were reviewed by ADRAC using the Brighton Collaboration case definitions.[18,19] If an AEFI report met any level of the Brighton Collaboration case definition it was coded accordingly.

To simplify data analysis, we grouped MedDRA® coding terms to create a set of reaction categories. Firstly, reaction categories were created that were analogous to the AEFI listed and defined in *The Australian Immunisation Handbook* (8th edition).[3] Additional categories were created for MedDRA® coding terms that were listed in more than 1% of AEFI records (e.g. headache, irritability, cough). 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 9.1.3.[20] The distribution of AEFI records was analysed by age, gender and jurisdiction. 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.

The frequency and age distribution of AEFI outcomes, reaction categories and vaccines listed as 'suspected' of involvement in the reported adverse event were assessed. For each vaccine, the age distribution of vaccinees notified with AEFI was calculated, as well as the proportion of AEFI records where (i) the vaccine was the only suspected vaccine or drug, (ii) the AEFI record was assigned a 'certain' or 'probable' causality rating, and (iii) the AEFI was defined as 'serious'.

AEFI reporting rates per 100,000 administered doses were estimated for influenza vaccine for adults aged ≥18 years, for 23vPPV for adults aged ≥65 years, and for 10 vaccines funded through the NIP for children aged <7 years. These were DTPa-IPV, DTPa-IPV-HepB, DTPa-IPV-HepB-Hib, Hib, Hib-HepB, measles-mumps-rubella (MMR), MenCCV, 7vPCV, varicella and rotavirus vaccines. The 2007 AEFI reporting rates were compared with those for 2006 and 2005.

Denominator data to estimate influenza and 23vPPV AEFI reporting rates were obtained from the biennial national adult coverage survey conducted in 2006 (unpublished) for adults aged ≥65 years and 18 to 64 years (influenza only). The number of administered doses of each of the 10 childhood vaccines was calculated from the Australian Childhood Immunisation Register (ACIR), a national population-based register of approximately 99% of children aged <7 years.[21]

Dose-based AEFI reporting rates could not be calculated for other vaccines and age groups as reliable denominator data for the number of vaccine doses distributed or administered were not available.

Notes on interpretation

Caution is required when interpreting the AEFI data presented in this report. Due to reporting delays and late onset of some AEFI, the data are considered preliminary, particularly for the 4th quarter of 2007. Data published in previous reports for 2000–2006[6–14] differ to that presented in this report for the same period because the data have been updated to include AEFI notified to the TGA during 2007 for vaccines administered in previous years.

The information collated in the ADRS database is intended primarily for signal detection and hypothesis generation. While AEFI reporting rates can be estimated using appropriate denominators, such as the number of vaccine doses administered, they cannot be interpreted as incidence rates due to under-reporting and biased reporting of suspected AEFI, and the variable quality and completeness of information provided in individual AEFI notifications.[6–14,22] In addition, AEFI that were assessed as mild by the health care provider may not be reported to the passive surveillance system, which could impact the comprehensiveness of the report. *The Australian Immunisation Handbook* indicates that immunisation providers need not report common reactions to the TGA.[3,4]

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. Individual database records list symptoms, signs and diagnoses that were used to define a set of reaction categories based on the case definitions provided in the 8th edition of *The Australian Immunisation Handbook*.[3] These reaction categories are similar, but not identical, to the AEFI case definitions.

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. The causality ratings assigned to individual AEFI records describe the likelihood that a suspected vaccine or vaccines was/were associated with the reported reaction at the level of the individual vaccine recipient.

Results

Summary of data

There was a total of 1,538 AEFI records in the ADRS database where the date of vaccination (or onset of an adverse event, if vaccination date was not reported) occurred in 2007. Approximately 2% of AEFI notifications resulted in more than 1AEFI record in the database, usually an injection site reaction (ISR) and a systemic reaction.

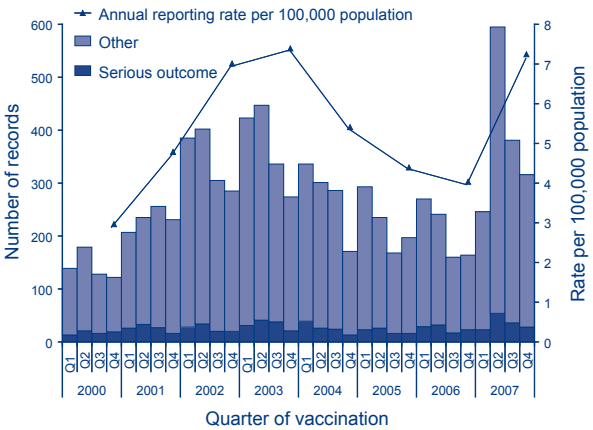
The number of AEFI records for vaccines administered in 2007 is almost twice the 835 AEFI records for vaccines administered in 2006. The increase is largely due to AEFI notifications related to HPV vaccination (n=705) following the commencement of the national school-based HPV immunisation program in April 2007, and to the commencement of the national rotavirus vaccine program in July 2007 (n=72).

One hundred and forty-one (9%) of the 1,538 AEFI records were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threatening event or death). A total of 511 (33%) AEFI records were assigned causality ratings of 'certain' (n=391, 25%) or 'probable' (n=120, 8%).

Reporting trends

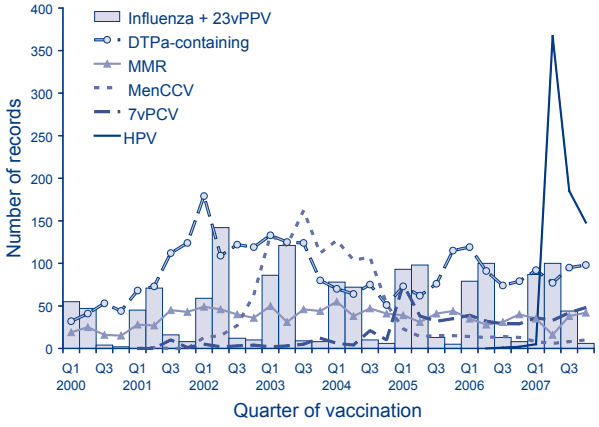
The AEFI reporting rate for 2007 was 7.3 per 100,000 population, compared with 4.0 per 100,000 population in 2006 (Figure 1). This is the second highest reporting rate for the period 2000 to 2007, and is similar to the peak in 2003 that coincided with the national MenCCV catch-up immunisation program for the 1 to 19 year age group. The trends in AEFI notifications shown in Figure 1 are reflected in the trends in vaccines frequently suspected of involvement in reported AEFI (Figure 2), and in the types of reactions frequently reported (Figure 3). Many of these changes correspond in time with changes in the funded NIP schedule. The most recent changes were the commencement of the national school-based HPV immunisation program in April 2007 (which was followed by the highest quarterly peak in AEFI reporting, shown in Figures 1 and 2), and a peak following the commencement of the national infant rotavirus vaccination program in July 2007. Previously, AEFI reporting for MenCCV and 7vPCV increased when the national routine and catch-up programs first commenced in January 2003 (MenCCV) and January 2005 (7vPCV), then stabilised over time (Figure 2). AEFI reports for DTPa-containing vaccines declined following the removal of the 4th dose from the immunisation schedule in the third quarter of 2003, and increased again following the introduction of DTPa and IPV-containing multivalent vaccines in the 4th quarter of 2005.

Figure 1. Adverse events following immunisation, ADRS database, 2000 to 2007, by quarter of vaccination



For reports where the date of vaccination was not recorded, the date of onset was used as a proxy for vaccination date.

Figure 2. Frequently suspected vaccines, adverse events following immunisation, ADRS database, 2000 to 2007, by quarter of vaccination

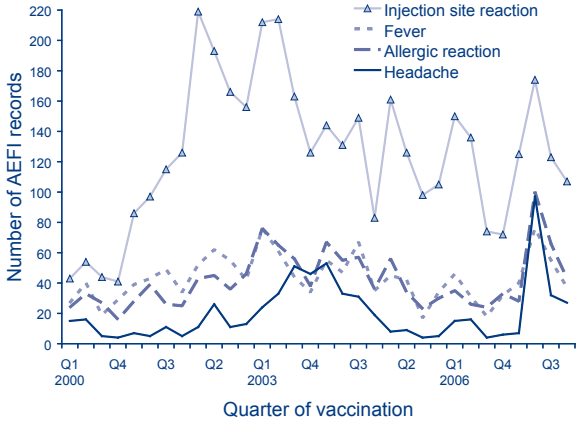


See appendix for abbreviations of vaccine names. DTPa-containing vaccines include DTPa, and the combination vaccines DTPa-HepB, DTPa-IPV, DTPa-IPV-HepB and DTPa-IPV-HepB-Hib.

The usual seasonal pattern of AEFI reporting, with peaks in the 1st half of the year, was less apparent in 2007 following the commencement of the national HPV program in the second quarter of the year, where 3 doses were delivered over a period of several months (Figure 1). The seasonal peaks generally correspond to the months when more vaccinations are administered in Australia, particularly among 4- and 5-year-old children receiving MMR and DTPa-containing vaccines prior to commencing

school in February and older Australians receiving 23vPPV and influenza vaccine during the autumn months (March to June) (Figure 2).

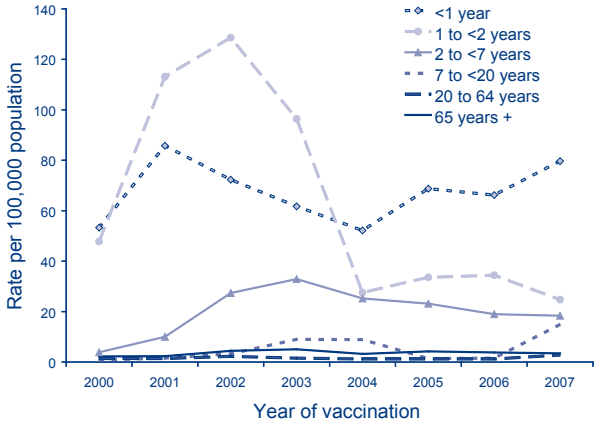
Figure 3. Selected frequently reported adverse events following immunisation, ADRS database, 2000 to 2007, by quarter of vaccination



Age distribution

In 2007, the highest population-based AEFI reporting rate occurred in infants <1 year of age, the age group that received the highest number of vaccines (Figure 4). Compared with 2006, AEFI reporting rates increased among the <1 year age group (from 66.2 to 79.6 per 100,000 population), the 7 to 19 year age group (1.5 to 14.8 per 100,000) and the 20 to 64 year age group (1.2 to 2.8 per 100,000). Rates were stable or declined slightly for other age groups. The changes over time reflect the introduction or removal of scheduled vaccines for specific age groups.

Figure 4. Reporting rates of adverse events following immunisation per 100,000 population, ADRS database, 2000 to 2007, by age group and year of vaccination



Geographical distribution

As in previous annual reports,[6,7,9,11,13] AEFI reporting patterns varied between states and territories for vaccines received during 2007 (Table 1). The Northern Territory, South Australia and the Australian Capital Territory had the highest reporting rates (20.9, 19.8 and 18.2 per 100,000 population, respectively) while Tasmania and New South Wales had the lowest rates (4.7 and 4.5 per 100,000 population, respectively). AEFI reporting rates increased in all jurisdictions in 2007, largely related to the commencement of the school-based HPV program. An increase in the reporting rate for Victoria (from 3.7 per 100,000 in 2006 to 6.7 in 2007) also followed the implementation of a new AEFI reporting and evaluation system in that state in April 2007.[23]

Outcomes

Sixty per cent of reported AEFI in 2007 were defined as 'non-serious' while 9% were defined as 'serious' (Table 2), similar to the proportions observed in previous years. Fewer 'serious' AEFI were assigned certain or probable causality ratings compared with 'non-serious' AEFI (20% versus 35%) (Table 2). Vaccines listed as 'suspected' of involvement in reported AEFI and with outcomes defined as 'serious' are shown in Table 3.

Two deaths were recorded as temporally associated with receipt of vaccines. One was a 16-month-old child who had received influenza and varicella vaccines 3 days prior to death. The child had Down Syndrome and a pre-existing cardiac condition; autopsy was inconclusive. The other reported death was a 55-year-old who died 1 day after receiving influenza vaccine. Further information was requested by the TGA and has not been provided by the reporter.

Vaccines

Thirty-one vaccines were recorded as 'suspected' of involvement in the adverse events described in the 1,538 AEFI records for vaccines received in 2007 (Table 3). The percentage of records where only 1 vaccine was suspected of involvement in the adverse event differed by vaccine, as did the percentage assigned causality ratings of 'certain' or 'probable', and with outcomes defined as 'serious'. This is to be expected as vaccines are routinely co-administered at specific ages in the immunisation schedule.

HPV vaccine was the most frequently reported vaccine (705 records; 46%) (Table 3). Vaccines containing diphtheria, tetanus and acellular pertussis antigens (including combination vaccines and dTpa) were suspected in 391 (25%) records (Table 3) with DTPa-IPV the most frequently suspected vaccine in

Table 1. Adverse events following immunisation (AEFI), ADRS database, 1 January to 31 December 2007, by jurisdiction

Jurisdiction	AEFI records		Annual reporting rate per 100,000 population*			
	n	%	Overall	'Certain' or 'probable' causality rating†	'Serious' outcome‡	Aged <7 years
Australian Capital Territory	62	4	18.2	4.1	0.6	64.8
New South Wales	313	20	4.5	1.7	0.5	9.8
Northern Territory	45	3	20.9	12.6	2.3	120.1
Queensland	228	15	5.5	1.8	0.4	14.0
South Australia	313	20	19.8	5.3	0.9	91.2
Tasmania	23	1	4.7	1.4	0.2	16.2
Victoria	347	23	6.7	2.4	0.6	39.4
Western Australia	129	8	6.1	2.2	0.7	21.2
Other§	78	5	na	na	na	na
Total	1,538	100	7.3	2.4	0.7	28.3

* Average annual rates per 100,000 population calculated using mid-2007 population estimates (Australian Bureau of Statistics).

† See previous report[6] for criteria used to assign causality ratings.

‡ AEFI records defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening or death – see Table 2).

§ Records where the jurisdiction in which the AEFI occurred was not reported or was unclear. AEFI records in this category were notified by pharmaceutical companies (n=67), members of the public (8), general practitioners (2) and from a hospital (1).

Table 2. Outcomes of adverse events following immunisation (AEFI), ADRS database, 2007

Outcome	AEFI records		'Certain' or 'probable' causality rating†		Age group‡			
					<7 years		≥7 years	
	n	%*	n	%§	n	%§	n	%§
Non-serious	920	60	321	35	318	35	591	64
Not recovered at time of report	328	21	119	36	95	29	229	70
Not known (missing data)	149	10	43	29	50	34	93	62
Serious:	141	9	28	20	63	45	78	55
recovered with sequelae	(3)		(2)		(0)		(3)	
hospital treatment – admission	(125)		(24)		(59)		(66)	
life-threatening event	(11)		(2)		(3)		(8)	
death (maybe drug)	(2)		(0)		(1)		(1)	
Total	1,538	100	511	33	526	34	991	64

* Percentages relate to the total number of AEFI records (n=1538).

† Causality ratings were assigned to AEFI records using criteria described previously.[6]

‡ AEFI records where both age and date of birth were not recorded are not shown (21 missing).

§ Percentages relate to the number of AEFI records with the specific outcome, e.g. of 920 AEFI records with a 'non-serious' outcome, 35% had causality ratings of 'certain' or 'probable' and 35% were for children aged <7 years.

this group (288 records; 19%). Influenza vaccine and 23vPPV were among the more common vaccines listed as suspected of involvement in reported AEFI, particularly where only 1 vaccine was listed as suspected (Table 3). The relative frequency of reports for specific vaccines relates both to the number of doses administered and the types of AEFI reported for each vaccine.

Reports related to MMR vaccine remained relatively stable over time (Figure 2), while there have been peaks in AEFI reporting for vaccines recently introduced into the routine childhood immunisation schedule, followed by a reduction and stabilisation in reporting over time (Figure 5). This pattern has been particularly evident with the introduction of the scheduled MenCCV dose at 12 months of age

Table 3. Vaccine types listed as 'suspected' in records of adverse events following immunisation (AEFI), ADRS database, 2007

Suspected vaccine type*	AEFI records	One suspected vaccine or drug only†		'Certain' or 'probable' causality rating‡		'Serious' outcome§		Age group‖			
								<7 years		≥7 years	
	n	n	%¶	n	%¶	n	%¶	n	%¶	n	%¶
HPV**	705	674	96	203	29	43	6	0	–	689	98
DTPa-IPV	288	128	44	113	39	24	8	287	100	1	0
7vPCV	159	7	4	9	6	26	16	158	99	1	1
Influenza	150	111	74	45	30	21	14	30	20	116	77
MMR	131	27	21	16	12	15	11	118	90	13	10
23vPPV	118	87	74	73	62	10	8	4	3	112	95
Hib-Hepatitis B	118	118	100	4	3	14	12	118	100	0	–
Rotavirus††	90	26	29	5	6	19	21	90	100	0	–
Hepatitis B	53	22	42	7	13	5	9	7	13	46	87
Varicella	44	32	73	8	18	6	14	28	64	16	36
DTPa-IPV-HepB-Hib	39	2	5	2	5	9	23	39	100	0	–
MenCCV	32	4	13	3	9	1	3	30	94	2	6
dTpa	29	18	62	10	34	2	7	0	–	29	100
DTPa	27	7	26	5	19	2	7	27	100	0	–
Hib	17	1	6	1	6	2	12	17	100	0	–
dT	15	9	60	7	47	2	13	0	–	15	100
Hepatitis A	13	4	31	2	15	2	15	5	38	8	62
Hepatitis A + B	9	7	78	2	22	3	33	0	–	9	100
DTPa-IPV-HepB	8	2	25	2	25	2	25	8	100	0	–
Yellow fever	8	3	38	0	–	3	38	0	–	8	100
Men4PV	5	2	40	1	20	2	40	0	–	5	100
BCG	4	3	75	1	25	1	25	4	100	0	–
IPV	4	0	–	0	–	2	50	1	25	3	75
Q fever	4	4	100	1	25	0	–	0	–	4	100
Hepatitis A-Typhoid	3	2	67	1	33	0	–	0	–	3	100
Rabies	3	0	–	0	–	2	67	1	33	2	67
Typhoid	3	1	33	1	33	1	33	1	33	2	67
dTpa-IPV	1	0	–	0	–	1	100	0	–	1	100
Cholera	1	0	–	0	–	1	100	0	–	1	100
Japanese encephalitis	1	0	–	0	–	1	100	1	100	0	–
Tetanus	1	1	100	0	–	0	–	0	–	1	100
Total‡‡	1,538	579	38	515	33	141	9	526	34	991	64

* See appendix for abbreviations of vaccine names.

† AEFI records where only 1 vaccine was suspected of involvement in a reported adverse event.

‡ Causality ratings were assigned to AEFI records using criteria described previously.[6]

§ 'Serious' outcomes are defined in the Methods section (see also Table 2).

‖ 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 705 AEFI records; this was the only suspected vaccine in 96% of the 705 AEFI records, 29% had 'certain' or 'probable' causality ratings, 6% were defined as 'serious' and 98% were for those aged ≥7 years.

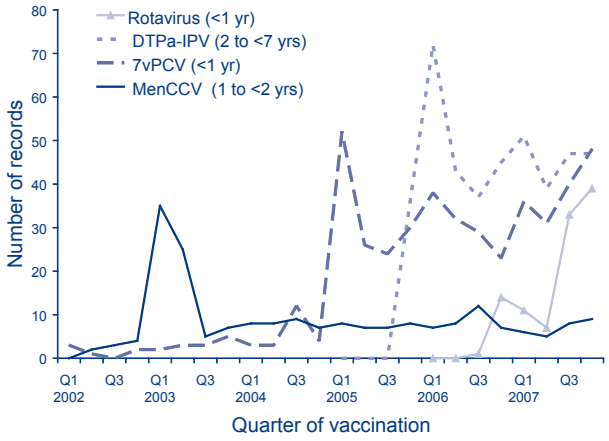
** Human papillomavirus vaccine was added to the National Immunisation Program schedule on 1 April 2007.[15]

†† Rotavirus vaccine was added to the National Immunisation Program schedule on 1 July 2007.[15]

‡‡ 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.

in January 2003, 7vPCV at 2, 4, and 6 months of age in January 2005, and the DTPa-IPV containing vaccines at 2, 4, 6 months and 4 years of age in November 2005. The most recent peak evident is shown for rotavirus vaccine from the second quarter of 2007. Smaller peaks in 7vPCV AEFI reporting coincide with the later introduction of the infant DTPa-IPV and rotavirus programs (Figure 5), presumably related to the simultaneous administration of the 3 vaccines at 2, 4 and 6 months of age.

Figure 5. Reports of adverse events following immunisation, ADRS database, 2002 to 2007, for vaccines recently introduced into the funded National Immunisation Program,* by quarter of vaccination



* Meningococcal C conjugate vaccine (MenCCV) was introduced into the National Immunisation Program on 1 January 2003, 7-valent pneumococcal conjugate vaccine (7vPCV) on 1 January 2005, both DTPa-IPV and combination vaccines on 1 November 2005, and rotavirus vaccine on 1 July 2007.

Reactions

The distribution and frequency of reactions listed in AEFI records for 2007 are shown in Tables 4 and 5. In Table 4, only the reaction categories analogous to those listed in *The Australian Immunisation Handbook*[3] are shown. In Table 5, other reaction categories are listed in descending order of frequency.

The most frequently reported adverse events were ISR (34% of 1,538 AEFI records) followed by allergic reaction (17%), fever (14%), rash (11%), headache (11%) and malaise (10%) (Tables 4 and 5). ISR was the most commonly reported individual adverse event following receipt of 23vPPV (78%; 92/118), MMR (60%; 71/118), DTPa-containing vaccines (52%; 202/391), and influenza vaccine (37%; 56/150), administered alone or in combination with other vaccines. Twenty per cent (143/705) of HPV vaccine-related AEFI records listed ISR.

More severe AEFI included reports of anaphylactic reaction (n=13), HHE (n=37), thrombocytopenia (n=2), encephalitis (n=2), convulsion (n=35), Guillain-Barré syndrome (GBS; n=7) and death (n=2; described previously in this report). The 7 records coded as GBS included 2 reports in adolescent girls following HPV vaccine, and 5 reports following influenza vaccine in adults aged 23 to 72 years.

Ten of the 13 reports of anaphylaxis in 2007 occurred in women following receipt of HPV vaccine; two had also received dTpa.[24] There were a total of 35 reports of convulsion, including syncopal and febrile convulsions. Twelve were for children aged <7 years. The most commonly suspected vaccines were HPV (n=18), 7vPCV (n=6) and MMR (n=6).

The majority (34/37) of HHE were notified by Victoria (22), South Australia (6) and Queensland (6). DTPa-containing vaccines were listed as suspected in 30 reports, with DTPa-IPV suspected in 27 reports. 7vPCV (n=31) and Hib-HepB (n=26) were also commonly suspected vaccines in HHE reports.

Reactions shown in Table 5 include headache, malaise, nausea, dizziness and reduced sensation (paraesthesia). The most commonly reported categories for grouped reactions involved the gastrointestinal, neurological and musculoskeletal organ systems.

The trends in the most frequently reported types of reactions changed over time (Figure 3). Reports of allergic reaction, fever and rash were less variable compared with reports of ISR. Reports of headache peaked in 2003 and again in 2007, coinciding with the national school-based MenCCV immunisation program in 2003 and the HPV program in 2007. Much of the variation in reporting of ISR relates to specific changes in the immunisation schedules for vaccines that are known to have higher rates of ISR, including DTPa-containing vaccines, MenCCV, 23vPCV and HPV vaccine.[6–14,25,26]

Dose-based reporting rates

Influenza vaccine and adults aged ≥18 years

In 2007, influenza vaccine was suspected of involvement in 109 AEFI records for people aged ≥18 years. The AEFI reporting rate was 2.3 per 100,000 administered doses, similar to the rate in 2005 and 2006 (Table 6). As seen in previous years, both the overall and serious AEFI reporting rates were higher for vaccinees aged 18 to 64 years than among older vaccinees.

Table 4. Reaction categories of interest* mentioned in records of adverse events following immunisation (AEFI), ADRS database, 2007

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	529	293	55	366	69	235	44	288	54
Allergic reaction¶	269	46	17	48	18	68	25	198	74
Fever	208	7	3	25	12	92	44	115	55
Rash	164	52	32	23	14	71	43	91	55
Abnormal crying	52	1	2	1	2	47	90	5	10
HHE**	37	18	49	2	5	37	100	0	–
Convulsions	35	8	23	4	11	12	34	22	63
Arthralgia	25	1	4	4	16	0	–	25	100
Lymphadenopathy/itis††	21	6	29	2	10	5	24	16	76
Anaphylactic reaction	13	0	–	10	77	2	15	11	85
Arthritis	7	3	43	0	–	1	14	6	86
Guillain-Barré syndrome	7	5	71	0	–	0	–	7	100
Abscess	4	3	75	2	50	3	75	1	25
Death	2	2	100	0	–	1	50	1	50
Encephalitis	2	1	50	0	–	1	50	1	50
Orchitis	2	0	–	0	–	1	50	1	50
Parotitis	2	0	–	0	–	0	–	2	100
Thrombocytopenia	2	1	50	0	–	1	50	1	50
Meningitis	1	0	–	0	–	0	–	1	100
Sepsis	1	0	–	0	–	0	–	1	100
Acute flaccid paralysis	0	–		–		–		–	
Brachial neuritis	0	–		–		–		–	
Encephalopathy	0	–		–		–		–	
Osteitis	0	–		–		–		–	
Osteomyelitis	0	–		–		–		–	
SSPE‡‡	0	–		–		–		–	
Toxic shock syndrome	0			–		–		–	
Total§§	1,538	579	38	515	33	526	34	991	64

* Reaction categories were created for the AEFI of interest listed and defined in *The Australian Immunisation Handbook,* (8th edition, p 22–23 and 271–275)[3] as described in Methods section.

† AEFI records where only 1 reaction was reported.

‡ Causality ratings were assigned to AEFI records using criteria described previously.[6]

§ 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 529 AEFI records listing injection site reaction, 55% listed only 1 type of reaction while 69% had a causality rating of 'certain' or 'probable' and 44% were for children aged <7 years.

¶ Allergic reaction includes skin and/or gastrointestinal (e.g. diarrhoea, vomiting) symptoms and signs.[3]

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

** Hypotonic-hyporesponsive episode.

‡‡ Subacute sclerosing panencephalitis.

§§ 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 5. 'Other'* reaction terms listed in records of adverse events following immunisation (AEFI), ADRS database, 2007

Reaction term*	AEFI records	Only reaction reported†		Certain/probable causality rating‡		Age group§			
						<7 years		≥7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Headache	163	15	9	29	18	3	2	153	94
Malaise	159	1	1	21	13	28	18	129	81
Nausea	149	2	1	34	23	3	2	142	95
Dizziness	125	2	2	36	29	0	–	122	98
Reduced sensation	71	9	13	19	27	0	–	70	99
Syncope	69	18	26	19	28	0	–	68	99
Pain	62	2	3	9	15	3	5	59	95
Resp. rate/rhythm change	62	3	5	14	23	24	39	38	61
Myalgia	42	0	–	3	7	2	5	40	95
Oedema	42	4	10	17	40	13	31	29	69
Irritability	39	0	–	0	–	36	92	3	8
Pallor	39	2	5	10	26	17	44	22	56
Gastrointestinal – RVV	37	9	24	3	8	37	100	0	–
Weakness	36	0	–	7	19	1	3	35	97
Heart rate/rhythm change	31	1	3	6	19	13	42	18	58
Increased sweating	29	0	–	5	17	4	14	25	86
Somnolence	29	1	3	4	14	11	38	17	59
Anorexia	23	0	–	3	13	11	48	11	48
Flushing	21	0	–	7	33	1	5	18	86
Visual disturbance	21	1	5	4	19	0	–	20	95
Abdominal pain	20	0	–	3	15	2	10	18	90
Erythema	20	1	5	4	20	7	35	12	60
Tremor	16	1	6	6	38	1	6	15	94
Genital/menstrual – HPV	15	7	47	0	–	0	–	15	100
Other	721	51	12	73	17	104	25	311	74
gastrointestinal	61	9	15	9	15	21	34	40	66
neurological	59	3	5	13	22	10	17	49	83
musculoskeletal	46	2	4	12	26	4	9	42	91
psychological	46	3	7	6	13	11	24	33	72
respiratory	44	6	14	10	23	13	30	28	64
general non-specific	37	1	3	3	8	4	11	32	86
eye or ear	35	0	–	5	14	6	17	28	80
cardiovascular	33	2	6	13	39	6	18	27	82
skin	33	5	15	6	18	6	18	27	82
infection	23	7	30	23	100	13	57	10	43
metabolic/endocrine	16	0	–	16	100	7	44	9	56
renal/urogenital	14	1	7	3	21	3	21	11	79
haematological	12	2	17	1	8	1	8	11	92
miscellaneous	4	2	50	0	–	0	–	4	100
pregnancy/congenital	1	1	100	0	–	0	–	1	100

* Reaction terms not listed in *The Australian Immunisation Handbook*[3] but included in AEFI records in the ADRAC 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.

Please see Table 4 for the description of other footnotes.

The most frequently reported adverse events were ISR, allergic reaction, fever, and malaise (1.1, 0.5, 0.5 and 0.4 per 100,000 doses, respectively). Reporting rates for each of these reactions were higher in the 18 to 64 year age group. There were 5 reports of GBS following influenza vaccination in 2007 giving a reporting rate of 0.11 per 100,000 doses. This is higher than in recent years, when only 1 or 2 reports were received annually,[11,13] but well within the expected reporting rates.

Pneumococcal vaccine and adults aged ≥65 years

There were 82 AEFI reports for older adults where 23vPPV was listed as suspected of involvement in the reported adverse event, with 6 reports coded as serious and 64 reports of ISR. Using the 2006 estimate of the number of doses of 23vPPV administered to people aged ≥65 years (n=429,500), the AEFI reporting rate was 18.6 per 100,000 doses, with 1.4 serious and 14.9 ISR reports per 100,000 doses. This is similar to the reporting rates estimated for 2006.[13]

Scheduled vaccines for children aged <7 years

There was a total of 526 AEFI records for vaccines administered in 2007 for children aged <7 years. Of these, 470 records listed as suspected one of the 10 vaccines for which ACIR data could be used to estimate AEFI reporting rates per 100,000 administered doses (Table 7). Vaccines for which reliable denominator data were not available included Bacille Calmette-Guèrin (n=4), influenza (n=30), 23vPPV (n=4), hepatitis A (n=5) and hepatitis B (n=7) (Table 3). Eighteen reports for rotavirus vaccine administered prior to the commencement of the national program on 1 July 2007 were also excluded from the assessment due to lower reliability of denominator data recorded on the ACIR for this time period.

The overall reporting rate for the 10 NIP vaccines was 12.7 per 100,000 administered doses, while the reporting rate for serious AEFI was 1.5 per 100,000 doses (Table 7). Reporting rates were similar to, or lower than, those in 2006 for most vaccine types including MenCCV, MMR and DTPa-containing vaccines (Table 7). The apparent increase in the reporting rates for Hib-HepB and 7vPCV vaccines may be related to reporting of AEFI for rotavirus vaccine as the vaccines are all given at 2 and 4 months of age.[15]

Reporting rates for the different DTPa-IPV combination vaccines varied by vaccine type and age group. The reporting rate for pentavalent vaccine is likely to be inaccurate due to the small number of reports and some under-reporting to the ACIR of doses administered. AEFI reports following quadrivalent DTPa-IPV include both children aged <1 year who were scheduled to receive the vaccine at 2, 4, and 6 months of age (reporting rate of 24.6 per 100,000 doses) and the 2 to <7 year age group (reporting rate of 73 per 100,000 doses). The reporting rate of ISR following DTPa-IPV in this older age group was 63 per 100,000 doses compared with 70 per 100,000 doses in 2006 and 76–80 per 100,000 doses of DTPa vaccine over the 2002–2005 period.

The AEFI reporting rate for children aged <1 year was higher for quadrivalent DTPa-IPV compared with the hexavalent DTPa-IPV-HepB-Hib vaccine (24.6 vs 10.3 reports per 100,000 administered doses) (Table 7). Reporting rates among infants for most reaction categories were approximately 2 to 3 times

Table 6. Reporting rate of adverse events following immunisation (AEFI) per 100,000 doses of influenza vaccine,* 18 years and over, ADRS database, 2007

AEFI category†	Age group	AEFI records‡ (n)	Vaccine doses* (n)	Rate per 100,000 doses§		
				2007	2006	2005
Overall	≥18 years	109	4,746,900	2.3	1.9	2.1
	18 to 64 years	79	2,626,400	3.0	2.5	2.8
	≥65 years	30	2,120,500	1.4	1.1	1.2
Serious	≥18 years	14	4,746,900	0.29	0.19	0.37
	18 to 64 years	11	2,626,400	0.42	0.27	0.49
	≥65 years	3	2,120,500	0.14	0.09	0.27

* Number of administered doses of influenza vaccine estimated from the 2006 national survey (unpublished).

† AEFI category includes all records, and those defined as 'serious' where influenza vaccine was suspected of involvement in the reported adverse event. The definition of a 'serious' outcome is shown in the Methods section.

‡ Number of AEFI records in which influenza vaccine was 'suspected' and the vaccination was administered in 2007.

§ The estimated reporting rate of adverse events per 100,000 administered doses of influenza vaccine.

higher for DTPa-IPV, except for HHE which was 12-fold higher for DTPa-IPV (6.6 per 100,000 doses; 95% CI 4.3–9.6) compared with DTPa-IPV-HepB-Hib (0.5 per 100,000 doses; 95% CI 0.1–2.0). The differing reporting rates and surveillance practices by jurisdiction (Table 1) need to be borne in mind as higher reporting jurisdictions (South Australia and Victoria) use quadrivalent DTPa-IPV for this age group.

New National Immunisation Program schedule vaccines

Rotavirus vaccine

There were a total of 90 AEFI records for 2007 where a rotavirus vaccine was listed as a suspected vaccine (Table 3). Of these, 72 were for the period following the commencement of the national program in July 2007 (reporting rate of 33.2 per 100,000 doses; Table 7). As expected, the majority (71%) of the 90 rotavirus vaccine AEFI reports also listed other vaccines as suspected of involvement in the reported adverse event, as most infants now receive rotavirus vaccine at the same time as other scheduled vaccines at 2, 4 and 6 months of age. Six per cent of the 90 rotavirus AEFI records had a certain or probable causality rating and 21% described events that met the definition of 'serious'.

The most commonly reported AEFI were vomiting/diarrhoea (n=37; 41%), abnormal crying (n=19; 21%) and other gastrointestinal events (n=16; 18%)

Table 7. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* children aged less than 7 years, ADRS database, 2007

	AEFI records‡ (n)	Vaccine doses* (n)	Reporting rate per 100,000 doses§ 2007	2006	2005
Vaccine†					
DTPa-containing vaccines	334	1,064,713	31.4	32.3	34.8
DTPa-IPV	287	669,451	42.9	43.0	–
Pentavalent (DTPa-IPV-HepB)	8	17,862	44.8	37.4	–
Hexavalent (DTPa-IPV-HepB-Hib)	39	377,400	10.3	12.9	–
Haemophilus influenzae type b	17	111,389	15.3	22.1	17.8
Haemophilus influenzae type b-hepatitis B	118	422,838	27.9	24.8	18.9
Measles-mumps-rubella	118	527,082	22.4	24.4	29.0
Meningococcal C conjugate	30	282,527	10.6	18.4	17.7
Pneumococcal conjugate	158	825,018	19.2	15.8	15.1
Rotavirus vaccine¶	72	219,791	33.2	–	–
Varicella	28	251,766	11.1	18.5	–
Age group					
<1 year	195	1,790,663	9.0	8.6	6.6
1 to <2 years	56	990,723	5.9	9.3	7.7
2 to <7 years	219	488,695	38.3	39.5	32.0
AEFI category†					
Total	470	3,702,124	12.7	13.9	12.0
'Certain' or 'probable' causality rating	150	3,702,124	4.1	5.4	5.3
'Serious' outcome	53	3,702,124	1.48	1.35	0.76

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register (ACIR) and administered between 1 January and 31 December 2007.

† Records where at least one of the vaccines shown in the table was suspected of involvement in the reported adverse event. AEFI category includes all records (i.e. total), those assigned 'certain' or 'probable' causality ratings, and those with outcomes defined as 'serious'. Causality ratings were assigned using the criteria described previously.6 A 'serious' outcome is defined as recovery with sequelae, hospitalisation, life-threatening event or death.[6]

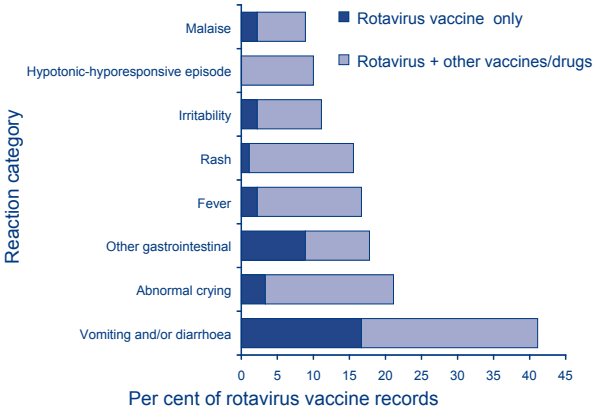
‡ Number of AEFI records in which the vaccine was coded as 'suspected' of involvement in the reported adverse event and the vaccination was administered between 1 January and 31 December 2007. More than 1 vaccine may be coded as 'suspected' if several were administered at the same time.

§ The estimated AEFI reporting rate per 100,000 vaccine doses recorded on the ACIR.

¶ Rotavirus vaccine AEFI reporting rate estimated for July–December 2007 only, the period where the vaccine was included in the funded National Immunisation Program schedule.

(Figure 6). Other gastrointestinal events included 3 reports of intussusception (reporting rate of 1.4 per 100,000 administered doses). The intervals between receipt of rotavirus vaccine and onset for the 3 cases of intussusception were 6, 16 and 31 days.

Figure 6. Most frequently reported adverse events following rotavirus immunisation,* ADRS database, 2007, by number of vaccines suspected of involvement in the reported adverse event



* Per cent of 90 adverse events following immunisation (AEFI) records where rotavirus vaccine was listed as suspected of involvement in the reported AEFI.

Human papillomavirus vaccine

A total of 705 AEFI reports were received for 2007 where HPV vaccine was the suspected vaccine. The age range was 11 to 31 years with a median of 16 years. HPV vaccine was the only suspected vaccine in 674 (96%) records, 203 (29%) had causality ratings of 'certain' or 'probable' and 43 (6%) were defined as 'serious' (Table 3). No deaths were reported.

The most frequently reported categories of reactions associated with HPV administration are shown in Figure 7. They included non-anaphylactic allergic reactions (23%; n=161), ISR (20%), headache (19%), nausea (16%), dizziness (14%) and malaise (13%).

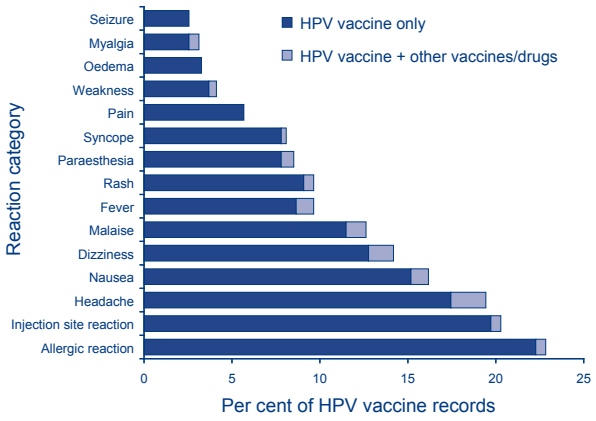
There were a total of 11 reports of anaphylactic reaction (in 2 cases, dTpa had also been administered)[24] and 18 reports of convulsion, mainly associated with syncope. The 2 cases initially reported as GBS were subsequently assigned alternate or uncertain diagnostic labels and, in 1 case, *Mycoplasma* infection was identified as the probable antecedent.

More recent information about AEFI and HPV vaccine reported up to June 2008 can be obtained from the TGA website.[27]

Discussion

As in previous years, the majority of AEFI reported to the TGA in 2007 were mild, transient and well-recognised vaccine side-effects. There was a large increase in the number of AEFI reports received for 2007 compared with recent years, mainly related to

Figure 7. Most frequently reported adverse events following HPV immunisation,* ADRS database, 2007, by number of vaccines suspected of involvement in the reported adverse event



* Per cent of 705 AEFI records where human papillomavirus (HPV) vaccine was listed as suspected of involvement in the reported AEFI

the commencement of the national HPV vaccine immunisation program in April 2007 for women aged 12 to 26 years. Other factors that may have contributed to the increase in reporting include the commencement of the national rotavirus immunisation program on 1 July 2007 and enhanced AEFI surveillance in the state of Victoria from April 2007.[23] Although the number of AEFI reports increased substantially, the proportion defined as serious remained stable at around 9%.

There was a higher than expected number of anaphylactic reactions following HPV vaccine detected in New South Wales.[24,27] An expert multidisciplinary panel was convened by NSW Health to investigate all reports of anaphylaxis and severe allergic reaction following HPV vaccine. The panel found that the rate of anaphylaxis in New South Wales was significantly higher for the school-delivered HPV vaccination program compared with the 2003 school-delivered MenCCV program.[24] However, the overall rate was low, and all cases were managed appropriately without serious sequelae.[24,27,28] The results of the study were shared nationally and internationally. It

is recommended that vaccine recipients be observed for 15 minutes following administration of HPV vaccine[4,15,24,28] and that any symptoms and/or signs that may suggest anaphylaxis are clearly documented to allow an accurate assessment of the AEFI report using Brighton Collaboration case definitions.[18]

The majority of the 705 AEFI reports for HPV vaccine during 2007 were mild vaccine side-effects that had been identified in pre-licensure clinical trials.[25,26] These included mainly injection site reactions and milder allergic reactions. A range of non-specific symptoms were also reported, including headache, nausea, dizziness, malaise and weakness. (Table 5; Figure 7).[27,29] These symptoms have previously been reported to the TGA for secondary school students following receipt of MenCCV as part of the national catch-up program in 2003 and 2004.[9,11] This constellation of symptoms, which are likely to be due to a conversion reaction, are known to be associated with the event of vaccination rather than any specific vaccine.[4] They are more commonly reported in settings such as schools where many people are being vaccinated at the same time and can lead to a mass psychogenic response.[29,30] Immunisation providers of mass campaigns in this age group need to be aware of this response and attempt to put measures in place to prevent these events from occurring.[29]

The rotavirus vaccines used in Australia (RotaTeq® and Rotarix®) underwent extensive pre-licensure clinical trials which involved over 140,000 infants in developed and developing countries.[4,31,32] The major reason for these larger than usual clinical trials related to an apparent association between intussusception within 21 days of receipt of a previously licensed rotavirus vaccine, RotaShield, which was licensed in the United States of America (USA) in 1998 and withdrawn soon afterwards.[33,34] In the pre-licensure clinical trials for both RotaTeq® and Rotarix®, there was no difference in the rate of intussusception among vaccine recipients and the placebo group, while vaccine recipients were found to have an increased risk of up to 3% for gastrointestinal symptoms, predominately diarrhoea and vomiting, within 1 week of vaccination.[31,32] The most commonly reported AEFI to the TGA following rotavirus vaccine was gastrointestinal symptoms, predominantly diarrhoea and vomiting (41%). Post-licensure analysis of USA passive and active AEFI surveillance data for RotaTeq® indicated no association with intussusception.[35] The overall passive reporting rate of intussusception in Australia of 1.4 per 100,000 administered doses is similar to the rate estimated for the US passive surveillance system of 1.3 per 100,000 administered doses (calculated from data presented in the published paper of 160 reports and administration of 75% of 9.1 million distributed doses).[35]

After excluding reports for HPV and rotavirus vaccines, the number and patterns of AEFI reported to the TGA in 2007 was generally similar to that seen in 2006,[13] both for the older age groups receiving influenza vaccine and 23vPPV, and among children aged <7 years for scheduled vaccines. The only substantive changes identified for children were a further reduction in reported ISRs among 4- and 5-year-old children receiving DTPa-containing vaccines, and a significantly higher reporting rate of HHE among infants receiving DTPa-IPV compared with DTPa-IPV-HepB-Hib vaccines.

Children born after 1 April 2002 were due to receive their 4th dose of acellular pertussis-containing vaccines at 4 years of age following the removal of the dose due at 18 months of age from the immunisation schedule in September 2003.[3] The rate of ISR following acellular pertussis-containing vaccines in the 2 to <7 year age group has declined from a consistent reporting rate of approximately 80 per 100,000 doses during the 4 years 2002–2005[11] to 70 per 100,000 in 2006 and 63 per 100,000 in 2007. This suggests that the removal of the dose due at 18 months of age is having an impact on extensive limb swelling following receipt of a 4th versus 5th scheduled dose of vaccine prior to school entry.[36,37] However, other surveillance and schedule-related factors may also be impacting on the observed reporting trends, including the change to DTPa-IPV quadrivalent vaccine in November 2005, increased reporting and awareness that usually follows the introduction of new vaccines, and commencement of enhanced AEFI surveillance in Victoria in April 2007.

The significantly higher reporting rate of HHE in children aged <1 year following DTPa-IPV versus DTPa-IPV-HepB-Hib is difficult to interpret due to confounding related to changes in surveillance practices, the higher overall AEFI reporting rates from the South Australia and Victoria, and in the application of the Brighton Collaboration case definition for HHE by the TGA.[19] There were 2 reports of HHE following hexavalent DTPa-IPV-HepB-Hib in both 2006 and 2007 (from New South Wales and Western Australia) compared with 13 reports following DTPa-IPV in 2006 and 27 in 2007. The increase in 2007 was predominantly from Victoria and Queensland (16 Victoria, 6 South Australia and 5 Queensland in 2007 vs 8 Victoria, 4 South Australia and 1 Queensland in 2006). While most other jurisdictions use the hexavalent DTPa-IPV-HepB-Hib vaccine at 2, 4 and 6 months of age, these 3 states use quadrivalent DTPa-IPV vaccine at 2, 4 and 6 months plus Hib-HepB vaccine at 2 and 4 months. In 2007, Queensland changed the formulation of DTPa-IPV vaccine to the same as that used in Victoria and South Australia. Taken

together, the available information suggests that the higher HHE reporting rate following quadrivalent DTPa-IPV vaccine and Hib-HepB might be related to differences in surveillance practices (including enhanced clinical referral and assessment processes in Victoria from April 2007), as well as a true difference in HHE rates. Differences in reporting of HHE by vaccine type will continue to be monitored. A recent study in The Netherlands identified reporting rates of HHE through enhanced passive surveillance mechanisms to be up to 10 times higher than that identified from TGA data.[38]

Conclusion

The benefits of immunisation in reducing morbidity and mortality due to vaccine preventable diseases outweigh the risks of immunisation-related adverse reactions in Australia. Disease notification data show the impact of immunisation on reducing the number of cases of many severe infections,[39,40] including significant impacts on the incidence of both invasive meningococcal disease and invasive pneumococcal disease following the introduction of these national immunisation programs in 2003 and 2005.

While under-reporting is a known disadvantage of passive surveillance systems,[1,2,16,22] the Australian national AEFI passive surveillance system is sufficiently sensitive to detect expected changes in AEFI reporting associated with changes in immunisation programs, such as higher apparent reporting of anaphylaxis following receipt of HPV vaccine. Processes are in place to investigate signals and monitor trends in AEFI reporting.[24,27] The regular analysis and publication of national AEFI surveillance data collated in the ADRAC database remains an important aspect of Australia's immunisation programs. The next report will present AEFI data for children <7 years of age for vaccines administered in the first 6 months of 2008.

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References

1. Duclos P. A global perspective on vaccine safety. *Vaccine* 2004;22:2059–2063.
2. Chen RT, DeStefano F, Pless R, Mootrey G, Kramarz P, Hibbs B. Challenges and controversies in immunization safety. *Infect Dis Clin North Am* 2001;15:21–39.
3. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 8th edn. Canberra: Australian Government Department of Health and Ageing, 2003.
4. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 9th edn. Canberra: Australian Government Department of Health and Ageing, 2008.
5. Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. Available from: http://www.who-umc.org/ Accessed on 27 July 2005.
6. 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.
7. 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.
8. Lawrence G, Boyd I. Surveillance of adverse events following immunisation for children aged less than 7 years, 1 January to 30 June 2004. *Commun Dis Intell* 2004;28:490–492.
9. Lawrence GL, Boyd I, McIntyre PB, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2004. [erratum appears in *Commun Dis Intell* 2005;29:416. *Commun Dis Intell* 2005;29:248–262.
10. Lawrence G, Boyd I. Supplementary report: surveillance of adverse events following immunisation among children aged less than 7 years in Australia, 1 January to 30 June 2005. *Commun Dis Intell* 2005;29:413–416.
11. 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.

12. Lawrence G, Boyd I. Supplementary report: surveillance of adverse events following immunisation among children aged <7 years in Australia, 1 January to 30 June 2006. *Commun Dis Intell* 2006;30:438–442.

13. 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.

14. Lawrence GL, Aratchige PE, Hill R. Supplementary report: surveillance of adverse events following immunisation among children aged less than 7 years in Australia, 1 January to 30 June 2007. *Commun Dis Intell* 2007;31:379–382.

15. Australian Government Department of Health and Ageing. Immunisation programs and initiatives. 2007. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/programs Accessed on 1 August 2007.

16. 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 ;52:113.] *MMWR Morb Surveill Summ* 2003;52:1–24.

17. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;20:109–117.

18. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25:5675–5684.

19. Bonhoeffer J, Gold MS, Heijbel H, Vermeer P, Blumberg D, Braun M, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine* 2004;22:563–568.

20. The SAS system for Windows [computer program]. Version 9.1.3. Cary, N.C.: SAS Institute Inc, 2005.

21. Australian Government Department of Health and Ageing. Additional reports—Childhood immunisation coverage. *Commun Dis Intell* 2008;32:288–289.

22. 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.

23. State Government of Victoria, Department of Human Services. SAEFVIC: Surveillance of adverse events following vaccination in the community. Available from: http://www.health.vic.gov.au/immunisation/general/saefvic Accessed on 1 October 2008.

24. Brotherton JM, Gold MS, Kemp AS, McIntyre PB, Burgess MA, Campbell-Lloyd S, et al. Anaphylaxis following quadrivalent human papillomavirus vaccination. *CMAJ* 2008;179:525–533.

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;369:1693–1702.

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;26:201–209.

27. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Human papillomavirus vaccine (GARDASIL). Updated 4 July 2008. Available from: http://www.tga.gov.au/alerts/medicines/gardasil.htm Accessed on 1 October 2008.

28. Halsey NA. The human papillomavirus vaccine and risk of anaphylaxis. *CMAJ* 2008;179:509–510.

29. Buttery JP, Madin S, Crawford NW, Elia S, La Vincente S, Hanieh S, et al. Mass psychogenic response to human papillomavirus vaccination. *Med J Aust* 2008;189:261–262.

30. Clements CJ. Mass psychogenic illness after vaccination. *Drug Saf* 2003;26:599–604.

31. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, Abate H, Breuer T, Costa Clemens S, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med* 2006;354:11–22.

32. Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med* 2006;354:23–33.

33. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. [erratum appears in *N Engl J Med* 2001;344:1564.] *N Engl J Med* 2001;344:564–572.

34. Kramarz P, France EK, DeStefano F, Black SB, Shinefield H, Ward JI, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J* 2001;20:410–416.

35. Haber P, Patel M, Izurieta HS, Baggs J, Gargiullo P, Weintraub E, et al. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. *Pediatrics* 2008;121:1206–1212.

36. Rennels MB, Deloria MA, Pichichero ME, Losonsky GA, Englund JA, Meade BD, et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. *Pediatrics* 2000;105:e12.

37. Gold MS, Noonan S, Osbourn M, Precepa S, Kempe AE. Local reactions after the fourth dose of acellular pertussis vaccine in South Australia. *Med J Aust* 2003;179:191–194.

38. Vermeer-de Bondt PE, van der Maas NA. The effect of age and dose number on the risk of collapse (hypotonic-hyporesponsive episode) after pertussis vaccination. *Pediatr Infect Dis J* 2008;27:355–357.

39. Brotherton J, Wang H, Schaffer A, Quinn H, Menzies R, Hull B, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2003 to 2005. *Commun Dis Intell* 2007;31(Suppl):viii–S152.

40. Begg K, Roche P, Owen R, Liu C, Kaczmarek M, Hii A, et al. Australia's notifiable diseases status, 2006: annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2008;32:139–207.

Abbreviations of vaccine types

7vPCV	7-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine
BCG	Bacille Calmette-Guèrin (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
RRV	rotavirus vaccine