Annual report: surveillance of adverse events following immunisation in Australia, 2005

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Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Adverse Drug Reactions Advisory Committee for 2005, and describes reporting trends over the six year period 2000 to 2005. There were 839 AEFI records for vaccines received in 2005. This is an annual AEFI reporting rate of 4.1 per 100,000 population, the lowest since 2000 and a 22 per cent decrease compared with 2004 (1,081 records; 5.4 AEFI records per 100,000 population). The decrease was not consistent across age groups. Reporting of AEFI increased for children aged <1 year in 2005 (60.7 versus 50.3 per 100,000 population) and decreased for the 7 to <20 year age group (0.9 versus 8.9 per 100,000 population). Dose-based AEFI reporting rates in 2005 were 11.0 per 100,000 doses of scheduled vaccines for children aged <7 years and 2.0 per 100,000 doses of influenza vaccine for adults aged ≥18 years. The majority of records described non-serious events while 9 per cent (n=72) described AEFIs defined as serious. There was one report of death in an older person following influenza vaccine and one of non-polio acute flaccid paralysis in an infant, both temporally associated with immunisation. The most frequently reported individual AEFI was injection site reaction in children following a fifth dose of diphtheria-tetanus-acellular pertussis vaccine (79 reports per 100,000 doses). The increase in the population-based AEFI reporting rate for children aged <1 year in 2005 coincided with the introduction of national immunisation programs for conjugate pneumococcal vaccine in January 2005 and inactivated poliovirus vaccine in November 2005. The fall in reporting rates for older children and adolescents follows the completion of the national meningococcal C catch-up program in early 2005. The consistently low reporting rate of serious AEFIs demonstrates the high level of safety of vaccines in Australia. *Commun Dis Intell* 2006;30:319–333.

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 Adverse Drug Reactions Advisory Committee (ADRAC) by 31 March 2006. The report focuses on AEFI reported for vaccines administered during 2005 and trends in AEFI reporting for the six year period 2000 to 2005.

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 detected in pre-licensure vaccine trials.[1–3] An 'adverse event following immunisation' is defined as any serious or unexpected adverse event that occurs *after* a vaccination has been given which may be related to the vaccine itself or to its handling or administration.[1] An AEFI can be *coincidentally* associated with the *timing* of immunisation without necessarily being caused by the vaccine or the immunisation process.

In Australia, AEFIs are notified to ADRAC (an expert committee of the Therapeutic Goods Administration) by state and territory health departments, health care professionals, vaccine manufacturers and members of the public.[4] All reports received by ADRAC are evaluated using internationally consistent criteria[5] and are reviewed at regular meetings. Passive AEFI surveillance data have been collated in the ADRAC database since 2000 and are used to monitor trends, detect signals and generate hypotheses. Reports summarising national AEFI surveillance data have been published regularly since 2003.[6–10]

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There were several important changes to the Australian National Immunisation Program Schedule (NIPS) in 2005[11] that impact on the AEFI surveillance data presented in this report:

(i) A national childhood pneumococcal conjugate vaccine program commenced on 1 January 2005. Since then, infants routinely receive the vaccine at 2, 4 and 6 months of age while children born from 1 January to 31 December 2004 were to receive a catch-up schedule with the number of doses dependent on the child's age.

(ii) Anational adult pneumococcal polysaccharide vaccine program commenced on 1 January 2005 for those aged 65 years and over. This was in addition to the funded program for Indigenous adults aged 50 years and over.

(iii) On 1 November 2005, inactivated poliovirus vaccine (IPV) replaced oral poliovirus vaccine (OPV) for all age groups. All states and territories introduced multi-component vaccines to deliver IPV in combination with other antigens to children at 2, 4 and 6 months and 4 years of age. All these IPV-containing combination vaccines include diphtheria-tetanus-acellular pertussis (DTPa) antigens (i.e. quadrivalent vaccines) and some also include hepatitis B and/or *Haemophilus influenza* 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 vaccine at 4 years of age.

(iv) A national varicella program commenced on 1 November 2005 with doses due at 18 months of age or at 12–13 years of age.

(v) Diphtheria-tetanus-acellular pertussis (adult formulation) (dTpa) vaccine was recommended in place of the adult formulation of diphtheria-tetanus (dT) vaccine for young adolescents in routine school-based immunisation programs.

Changes to the NIPS in 2003 also impact on the interpretation of trend data. On 1 January 2003, the meningococcal C conjugate immunisation program commenced when the vaccine was introduced into the schedule at 12 months of age, with a catch-up program for all those born between 1984 and 2001.[11] Also, in September 2003, the dose of DTPa at 18 months of age was removed from the schedule. Since then, DTPa has been given at 2, 4 and 6 months, and 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 for all drug and vaccine adverse event notifications received by ADRAC between 1 January 2000 and 31 March 2006. Readers are referred to previous AEFI surveillance reports for a description of the AEFI surveillance system and methods used to evaluate AEFI reports received by ADRAC.[6,7]

ADRAC database records* were eligible for inclusion in the analysis if:

- a vaccine was recorded as 'suspected' of involve- ment in the reported adverse event *and* either
  - (a) the vaccination occurred between 1 January 2000 and 31 December 2005 *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 2005.

Study definitions of adverse events following immunisation outcomes and reactions

AEFIs were defined as 'serious' or 'non-serious' based on information recorded in the ADRAC database and criteria similar to those used by the World Health Organization[5] and the US Vaccine Adverse Events Reporting System.[12] In this report, an AEFI is defined as 'serious' if the record indicated that the person had recovered with sequelae, been admitted to hospital, experienced a life-threatening event, or died.

Typically, each AEFI record listed several symptoms, signs and diagnoses that had been re-coded from the reporter's description into standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA®).[13] 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 AEFIs listed and defined in the *Australian Immunisation Handbook* (8th edition).[4] Additional categories were created for MedDRA® coding terms that were listed in more than one per cent of AEFI records (e.g. headache, irritability, cough). Reaction terms listed in less than one per cent of records were grouped into broader

*. The term 'AEFI record' is used throughout this report because a single AEFI notification to ADRAC can generate more than one record in the database. For example if a notification describes an injection site reaction plus symptoms and signs of a systemic adverse event (e.g. fever or generalised allergic reaction), two records will appear in the database: one record containing information relevant to the injection site reaction and one record for the systemic adverse event.

categories based on the organ system where the reaction was manifested (e.g. gastrointestinal, neurological).

Data analysis

All data analyses were performed using the SAS version 9 computer program.[14] 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 AEFIs 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'. Because many AEFI records listed more than one suspected vaccine and several reaction terms to describe an adverse event, column totals in the relevant tables exceed the number of AEFI records analysed.

Dose-based AEFI reporting rates were estimated for influenza vaccine for adults aged 18 years and over and for eight childhood vaccines funded through the National Immunisation Program (i.e. DTPa, DTPa-HepB, Hib, Hib-HepB, polio, MMR, MenCCV, 7vPCV) for children aged <7 years. Dose-based AEFI reporting rates for vaccines received in 2005 were compared to 2004 reporting rates and to the average annual reporting rate for the four years 2001 to 2004. Dose-based AEFI reporting rates were not determined for other vaccines and age groups due to the lack of reliable denominator data for the number of vaccine doses distributed or administered.

Denominator data to estimate influenza AEFI reporting rates in 2005 were obtained from the 2004 national influenza coverage survey[15] for the 18–39 years, 40–64 years and ≥65 years age groups as a survey was not conducted in 2005. The number of administered doses of each of the eight childhood vaccines was calculated from the Australian Childhood Immunisation Register (ACIR), a national population-based register of approximately 99 per cent of children aged <7 years.[16] Vaccine doses administered between 1 January and 31 December 2005 were estimated for the age groups <1 year, 1 to <2 years, and 2 to <7 years (i.e. the age at vaccination). Reporting rates were not calculated for vaccines introduced into NIPS in November 2005 (i.e. IPV combination vaccines and varicella vaccine) due to inaccurate numerator and denominator data in the very early stages of these programs.

Notes on interpretation

Caution is required when interpreting the AEFI data presented in this report. Due to reporting delays and late onset of some AEFIs, the data are considered preliminary, particularly for the fourth quarter of 2005. Data published in previous reports for 2000–2004[6–10] differ to that presented in this report for the same period because the data are updated to include AEFIs notified to ADRAC for vaccines administered before 2005.

The information collated in the ADRAC database is intended primarily for signal detection and hypothesis generation. While reporting rates of AEFIs 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 AEFIs, and the variable quality and completeness of information provided in individual notifications.[6–10,17]

It is also important to note that this report is based on vaccine and reaction term information collated in a 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*.[4] These reaction categories are similar, but not identical, to case the definitions of adverse events.

The reported symptoms, signs and diagnoses in each AEFI record in the ADRAC database are temporally associated with vaccination but are not necessarily causally associated with a vaccine or vaccines. The causality ratings of 'certain', 'probable' and 'possible' assigned to individual AEFI records describe the likelihood that a suspected vaccine was or vaccines were associated with the reported reaction at the level of the individual. 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 different vaccines at the same time, all administered vaccines are often listed as 'suspected' of involvement of a systemic adverse event as it is usually not possible to attribute the AEFI to a single vaccine.

Results

Summary of data

There were a total of 839 AEFI records in the ADRAC database where the date of vaccination or onset of an adverse event, if vaccination date was not reported,

occurred between 1 January and 31 December 2005. This is a decrease of 22 per cent compared with 2004 when there were 1,081 AEFI records. In 2005, approximately four per cent of AEFI notifications resulted in more than one AEFI record in the database (usually of an injection site reaction and a systemic reaction). This was the same as in 2004 and lower than previous years when approximately 10 per cent of notifications resulted in more than one AEFI record.[6,7,9]

Seventy-two (9%) of the 839 AEFI records for 2005 were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threatening event or death). A total of 401 (48%) AEFI records were assigned causality ratings of 'certain' (n=272, 44%) or 'probable' (n=29, 3%).

Adverse events following immunisation reporting trends

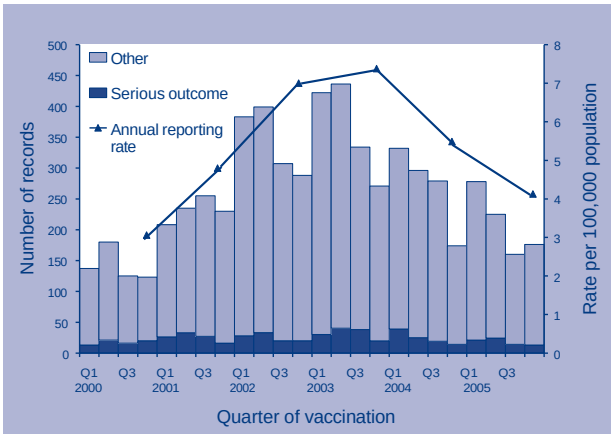
The AEFI reporting rate for 2005 was 4.1 per 100,000 population and was the lowest since 2000 (Figure 1). The trends in AEFI notifications shown in Figure 1 are reflected in the trends in vaccines frequently suspected of involvement in reported AEFIs (Figure 2), and in the types of reactions frequently reported (Figure 3). The decline in the number of AEFI records for vaccines administered in 2005 compared with earlier years follows reductions in the number of AEFIs notified that involved DTPa vaccine or MenCCV (Figure 2).

A seasonal pattern of AEFI reporting, seen in previous years, was apparent in 2005 with the highest number of AEFI notifications for vaccinations administered in the first half of the year (Figure 1). The seasonal peak corresponds to the months when more vaccinations are administered in Australia, particularly among 5-year-old children receiving DTPa and measles-mumps-rubella (MMR) vaccines prior to commencing school in February and older Australians receiving influenza and pneumococcal polysaccharide (23vPPV) vaccines during the autumn months (March to June) (Figure 2). There was also a peak in the first quarter of 2005 following the introduction of the 7-valent pneumococcal conjugate vaccine (7vPCV) into the childhood schedule.

Age and gender distribution

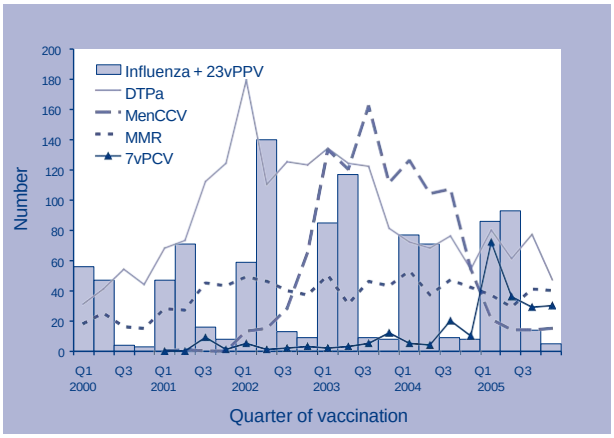
Sixty-three per cent (n=530) of AEFI records for 2005 were for children aged <7 years, compared with 45 per cent in 2004. The AEFI reporting rate in 2005 was highest among children aged <1 year (60.7 per 100,000 population), the age group that receives the greatest number of vaccinations. While the overall population-based reporting rate declined in 2005 compared with 2004 (4.1 versus 5.4 per 100,000), the trend varied by age group (Figure 4). There was

Figure 1. Adverse events following immunisation, ADRAC database, 2000 to 2005, by quarter of vaccination



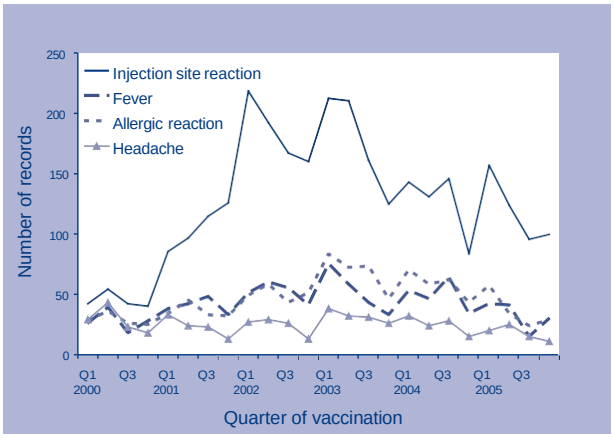
For reports where the date of vaccination was not recorded, the date of onset was used as a proxy for vaccination date.

Figure 2. Frequently suspected vaccines, adverse events following immunisation, ADRAC database, 2000 to 2005, by quarter of vaccination



See appendix for abbreviations of vaccine names.

Figure 3. Selected frequently reported adverse events following immunisation, by quarter of vaccination, ADRAC database, 2000 to 2005



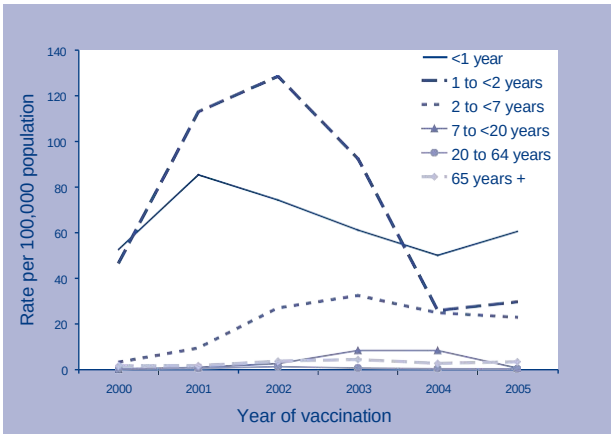
an increase among children aged <1 year (60.7 versus 50.3 per 100,000 population in 2005 and 2004 respectively), children aged 1 to <2 years (30.1 versus 26.3 per 100,000 population) and adults aged ≥65 years (4.0 versus 3.3 per 100,000 population). The reporting rate decreased in other age groups with the largest decrease in the 7 to <20 year age group (0.9 versus 8.9 per 100,000 population) (Figure 4).

The overall male to female ratio was 1:1.2, similar to previous years. The gender ratio varied by age group with slightly lower AEFI reporting rates for females aged <7 years (male:female 1:0.8) and higher reporting rates for females aged ≥7 years (male:female 1:3.1).

Geographical distribution

As noted in previous reports,[6,7,9] the AEFI reporting rate varied between states and territories for vaccines received during 2005 (Table 1). The Australian Capital Territory and the Northern Territory had the highest reporting rates (16.3 and 13.8 per 100,000 population, respectively) while New South Wales, Queensland and Western Australia had the lowest rates (2.7, 2.8 and 2.8 per 100,000 population, respectively). Reporting rates were higher in 2005 compared with those published for 2004[9] for South Australia (11.7 versus 8.3 per 100,000 population), Tasmania (4.3 versus 1.2 per 100,000 population) and Victoria (3.9 versus 2.5 per 100,000 population) and lower in the other states and territories. The increase in reporting rates for South Australia, Tasmania and Victoria appears to be partly related to changes in AEFI surveillance and reporting practices in 2005 compared with 2004 (see Discussion).

Figure 4. Reporting rates of adverse events following immunisation per 100,000 population, ADRAC database, 2000 to 2005, by age group and year of vaccination



Adverse events following immunisation outcomes

Fifty-nine per cent of reported AEFIs in 2005 were defined as 'non-serious' while nine per cent were defined as 'serious' (Table 2)—the same percentage as occurred in 2003 and 2004. One death was recorded as temporally related to influenza vaccine and/or another medication. Fewer 'serious' AEFIs

Table 1. Adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2005, 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	53	6	16.3	6.2	0.92	123.4
New South Wales	185	22	2.7	1.1	0.31	16.4
Northern Territory	28	3	13.8	6.4	0	87.2
Queensland	110	13	2.8	1.2	0.25	18.3
South Australia	180	21	11.7	6.4	0.71	102.3
Tasmania	21	3	4.3	3.3	0.62	18.6
Victoria	194	23	3.9	2.2	0.18	31.3
Western Australia	56	7	2.8	1.1	0.40	19.2
Other§	12	1	na	na	na	na
Total	839	100	4.1	2.0	0.32	29.7

* Average annual rates per 100,000 population calculated using mid-2005 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. All AEFI records in this category were notified by pharmaceutical companies.

were assigned 'certain' or 'probable' causality ratings compared with 'non-serious' AEFIs (21% versus 51%) (Table 2). Vaccines listed in records where the outcome was defined as 'serious' are shown in Table 3.

Vaccines and adverse events following immunisation

Twenty-eight vaccines were recorded as 'suspected' of involvement in the adverse events described in the 839 AEFI records for vaccines received in 2005 (Table 3). The most frequently suspected individual vaccine was DTPa with 257 (31%) records (Table 3). Vaccines containing diphtheria, tetanus and acellular pertussis antigens (including combination vaccines and dTpa) were suspected in 381 (45%) records. The second most frequently reported vaccine was 7vPCV with 171 (20%) records. The percentage of records where only one vaccine was suspected of involvement in the adverse event differed by vaccine, as did the percentage assigned causality ratings of 'certain' or 'probable', and defined as 'serious' (Table 3).

AEFI reporting trends differed by vaccine (Figure 2). Reports related to the MMR vaccine remained relatively stable. The number of reports where DTPa vaccine was suspected of involvement in the reported AEFI declined further in 2005 following a peak in the first quarter of 2002, and particularly after the dose due at 18 months of age was removed from the schedule in September 2003. Records listing MenCCV as a suspected vaccine decreased and stabilised in 2005 following a peak in 2003, which coincided with the commencement of the routine (at 12 months of age) and catch-up (aged 1–19 years) MenCCV programs. Records listing 7vPCV as a suspected vaccine peaked at 72 in the first quarter of 2005, following the commencement of the universal infant program on 1 January 2005, then stabilised to approximately 30 records per quarter (Figure 2).

Adverse events following immunisation reactions

The distribution and frequency of reactions listed in AEFI records for 2005 are shown in Tables 4 and 5. In Table 4, only the reaction categories analogous to those listed in the *Australian Immunisation Handbook*[4] are shown. In Table 5, other reaction categories are listed in descending order of frequency.

The most frequently reported adverse events were injection site reaction (57% of 839 AEFI records) followed by allergic reaction (18%), fever (16%) and rash (9%) (Table 4). Injection site reactions were the most commonly reported adverse event following receipt of 23vPPV (84%; 99/118), DTPa (79%; 202/257), MMR (59%; 87/147) and influenza (45%; 42/94) vaccines, administered alone or in combination with other vaccines.

More severe AEFIs included reports of anaphylactic reaction (n=7), severe allergic reaction involving the respiratory and/or circulatory system (n=13), hypotonic-hyporesponsive episode (HHE, n=11), thrombocytopenia (n=3), encephalitis (n=1) and convulsion (n=14), acute flaccid paralysis (AFP; n=1), Guillain-Barré syndrome (GBS; n=1) and sudden death (n=1). The death occurred in a 75-year-old

Table 2. Outcomes of adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2005

Outcome	AEFI records		'Certain' or 'probable' causality rating†		Age group‡			
					<7 years		≥7 years	
	n	%*	n	%§	n	%§	n	%§
Non-serious	496	59	254	51	333	67	155	31
Not recovered at time of report	201	24	90	45	116	58	81	40
Not known (missing data)	70	8	42	60	46	52	38	43
Serious:	72	9	15	21	35	49	34	47
recovered with sequelae	(1)		(0)		(0)		(1)	
hospital admission	(60)		(20)		(31)		(26)	
life-threatening event	(10)		(0)		(4)		(6)	
death	(1)		(0)		(0)		(1)	
Total	839	100	401	48	530	63	291	35

* Percentages relate to the total number of AEFI records (n=839).

† 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.

§ Percentages relate to the number of AEFI records with the specific outcome e.g. of 496 AEFI records with a 'non-serious' outcome, 51 per cent had causality ratings of 'certain' or 'probable' and 67 per cent were for children aged less than 7 years.

Table 3. Vaccine types listed as 'suspected' in records of adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2005

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	%¶
DTPa	257	146	57	143	56	11	4	254	99	0	–
7vPCV**	171	62	36	31	18	19	11	169	99	1	1
MMR	147	30	20	28	19	10	7	142	97	4	3
23vPPV	118	97	82	83	70	10	8	6	5	108	92
Influenza	94	71	76	33	35	17	18	1	1	92	98
Polio	92	3	3	2	2	12	13	87	95	4	4
Hib	74	4	5	3	4	6	8	72	97	1	1
MenCCV	64	18	28	12	19	7	11	53	83	11	17
DTPa-hepatitis B	57	3	5	3	5	1	2	57	100	0	–
DTPa-IPV††	47	26	55	25	53	4	9	45	96	0	–
Hib-hepatitis B	47	2	4	2	4	11	23	46	98	1	2
dTpa	37	28	76	19	51	1	3	0	–	33	89
Hepatitis B	29	18	62	9	31	3	10	7	24	22	76
Varicella††	20	13	65	3	15	1	5	15	75	4	20
dT	14	12	86	8	57	0	–	0	–	14	100
Hepatitis A	12	9	75	4	33	2	17	3	25	9	75
DTPa-IPV-hepB-hib††	8	2	25	0	–	2	25	8	100	0	–
Hepatitis A-typhoid	6	6	100	2	33	1	17	0	–	6	100
Japanese encephalitis	6	3	50	1	17	1	17	1	17	5	83
Hepatitis A + B	5	3	60	0	–	3	60	0	0	5	100
BCG	3	1	33	1	33	1	33	1	33	2	67
DTPa-IPV-hepB††	3	0	–	0	–	0	–	3	100	0	–
Men4PV	3	1	33	0	–	1	33	0	–	3	100
Rabies	3	3	100	1	33	0	–	0	–	2	67
Tetanus	3	2	67	1	33	1	33	0	–	3	100
Typhoid	2	1	50	0	–	1	50	0	–	2	100
Yellow fever	2	2	100	0	–	0	–	0	–	1	50
Q fever	1	1	100	0	–	1	100	0	–	1	100
Total‡‡	839	567	68	401	48	72	9	530	63	291	35

* See appendix for abbreviations of vaccine names.

† 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.[6]

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

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

¶ Percentages are calculated for the number of AEFI records where the specific vaccine was suspected of involvement in the AEFI, e.g. DTPa was listed as 'suspected' in 257 AEFI records; this was the only suspected vaccine in 57 per cent of the 257 AEFI records, 55 per cent had 'certain' or 'probable' causality ratings, 4 per cent were defined as 'serious' and 99 per cent were for children aged less then 7 years.

** Pneumococcal conjugate vaccine added to the National Immunisation Program Schedule on 1 January 2005.

†† Varicella vaccine and combination vaccines containing inactivated poliovirus were added to the National Immunisation Program Schedule on 1 November 2005.

‡‡ 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.

Table 4. Reaction categories of interest* mentioned in records of adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2005

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	477	312	65	359	75	312	65	157	33
Allergic reaction¶	148	42	28	38	26	97	66	48	32
severe allergic reaction¶	13	0	–	1	8	3	23	10	77
Fever	132	4	3	39	30	89	67	42	32
Rash	75	21	28	18	24	60	80	14	19
Abnormal crying	30	5	17	4	13	29	97	1	3
Arthralgia	14	2	14	5	36	2	14	11	79
Convulsions	14	8	57	3	21	10	71	3	21
HHE**	11	5	45	1	9	11	100	0	–
Lymphadenopathy/itis††	8	1	13	3	38	3	38	5	63
Anaphylactic reaction	7	2	29	1	14	2	29	5	71
Parotitis	3	1	33	0	–	3	100	0	–
Thrombocytopenia	3	1	33	0	–	3	100	0	–
Abscess	1	1	100	1	100	0	–	1	100
Acute flaccid paralysis	1	0	–	0	–	1	100	0	–
Arthritis	1	1	100	0	–	0	0	1	100
Death	1	0	–	0	–	0	–	1	100
Encephalitis	1	0	–	0	–	0	–	1	100
Guillain-Barré syndrome	1	0	–	0	–	0	–	1	100
Osteomyelitis	1	0	–	0	–	1	–	0	–
Brachial neuritis	0	–	–	–	–	–	–	–	–
Encephalopathy	0	–	–	–	–	–	–	–	–
Meningitis	0	–	–	–	–	–	–	–	–
Orchitis	0	–	–	–	–	–	–	–	–
Osteitis	0	–	–	–	–	–	–	–	–
Sepsis	0	–		–	–	–	–	–	–
SSPE‡‡	0	–	–	–	–	–	–	–	–
Toxic shock syndrome	0		–	–	–	–	–	–	–
Total§§	839	448	53	401	48	530	63	291	35

* Reaction categories were created for the AEFIs of interest listed and defined in the *Australian Immunisation Handbook*, (8th edition, p 22–3 and 271–5)[4] 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.[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 477 AEFI records listing injection site reaction, 65 per cent listed only one type of reaction while 75 per cent had a causality rating of 'certain' or 'probable' and 65 per cent were for children aged less than 7 years.

¶ Allergic reaction includes skin and/or gastrointestinal (e.g. diarrhoea, vomiting) symptoms and signs.[4] The category 'severe allergic reaction' includes allergic reaction with involvement of the circulatory and/or respiratory system but not recorded in the ADRAC database as 'anaphylactic reaction'.[4]

†† Includes lymphadenitis following BCG 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 one reaction term.

Table 5. 'Other'* reaction terms listed in records of adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2005

Reaction term*	AEFI records	Only reaction reported†		Certain/probable causality rating‡		Age group§			
						<7 years		≥7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Malaise	48	0	0	20	42	21	44	26	54
Oedema	38	5	13	22	58	19	50	17	45
Pain	37	0	–	19	51	9	24	27	73
Nausea	28	0	–	12	43	7	25	20	71
Respiratory rate/rhythm change	28	2	7	3	11	14	50	14	50
Irritability	27	0	–	6	22	27	100	0	–
Headache	24	10	42	12	50	5	21	18	75
Pallor	22	0	–	5	23	15	68	6	27
Myalgia	19	1	5	4	21	1	5	18	95
Syncope	19	5	26	9	47	1	5	17	89
Increased sweating	17	0	–	7	41	3	18	12	71
Dizziness	16	0	–	8	50	0	0	14	88
Heart rate/rhythm change	15	1	7	1	7	9	60	6	40
Anorexia	13	0	–	5	38	8	62	5	38
Reduced sensation	13	2	15	3	23	0	0	13	100
Cough	10	0	–	2	20	4	40	5	50
Other									
General non-specific	31	2	6	11	35	12	39	19	61
Neurological	19	2	11	6	32	8	42	11	58
Psychological	18	2	11	7	39	11	61	7	39
Cardiovascular	17	1	6	3	18	8	47	9	53
Gastrointestinal	14	2	14	2	14	5	36	8	57
Haematological	14	0	–	3	21	7	50	6	43
Eye or ear	13	1	8	4	31	6	46	7	54
Respiratory	13	3	23	2	15	4	31	9	69
Skin	13	3	23	2	15	8	62	5	38
Musculoskeletal	11	2	18	3	27	2	18	9	82
Metabolic/endocrine	10	2	20	1	10	6	60	1	10
Infection	7	0	–	2	29	8	114	2	29
Renal/urogenital	5	1	20	2	40	1	20	4	80

* Reaction terms not listed in the *Australian Immunisation Handbook*[4] but included in AEFI records in the ADRAC database. The top part of the table shows reaction terms included in one per cent or more of AEFI records; the bottom part of the table shows reaction terms grouped by organ system that were included in less than one per cent of AEFI records.

† AEFI records where only one 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 477 AEFI records listing injection site reaction, 65 per cent listed only one type of reaction while 75 per cent had a causality rating of 'certain' or 'probable' and 65 per cent were for children aged less than 7 years.

person who became unwell two days after receiving an influenza vaccine and died eight days later. Both influenza vaccine and a prescription medication were coded as 'possibly' related to the person's death. The single case of GBS was in a 57-year-old person following receipt of influenza vaccine. The case of AFP (transverse myelitis) occurred in a 6-month-old child following receipt of oral polio vaccine and was reported by the Australian AFP Surveillance Program.[18] The Polio Expert Committee classified the case as 'non-polio AFP'.

Five of the seven AEFI reports of anaphylactic reaction were for adults—three following influenza vaccine and two following receipt of a combined hepatitis A and B vaccine. Of the 14 reports of convulsion, 10 were in children aged <7 years following routinely scheduled combinations of vaccines. The most commonly suspected vaccines were MMR (n=4) and polio (n=4). All 11 reports of HHE listed 7vPCV as suspected of involvement, usually in combination with other routine childhood vaccines.[9,10,19] DTPa-containing vaccines were listed as suspected of involvement in the HHE for nine of the 11 children.

Reactions mentioned in fewer than one per cent of AEFI records in 2005 are shown in the lower portion of Table 5, grouped by organ system categories. The most commonly reported category was coded as 'general non-specific' reactions, which included reaction terms such as 'feeling hot', 'feeling cold' and 'discomfort'.

The trends in the most frequently reported types of reactions changed over time (Figure 3). Overall, there were fewer reports of injection site reaction in 2005 compared with previous years. Reports of allergic reaction, fever and rash were less variable over time and reports of headache were lower in 2005 compared with 2004 and 2003, consistent with the decrease in reporting of adverse events following MenCCV as the adolescent catch-up program was concluded.

Although there were fewer reports of injection site reaction in 2005, the percentage of reports for 23vPPV that listed injection site reaction as an AEFI has increased over time. This is particularly evident for adults aged ≥65 years where the percentage of reports for 23vPPV that listed injection site reaction, increased from 50 per cent of reports in 2001 to 87 per cent in 2005 (Figure 5).

Dose-based adverse events following immunisation reporting rates

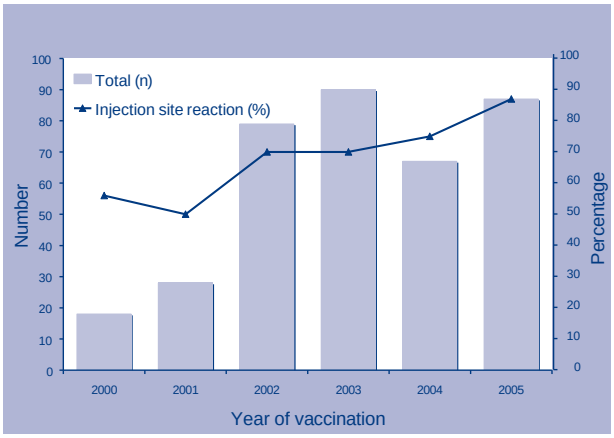
Influenza vaccine and adults aged ≥18 years

In 2005, influenza vaccine was suspected of involvement in 91 AEFI records for people aged ≥18 years. The dose-based AEFI reporting rates (using 2004 coverage data), by age group, are shown in Table 6. As seen previously,[6,7,9] the AEFI reporting rate in 2005 was lower among influenza vaccinees aged ≥65 years than for younger vaccinees (Table 6). The most frequently reported adverse events were injection site reaction, fever and allergic reaction (0.9, 0.3 and 0.3 per 100,000 doses, respectively). The estimated reporting rate of injection site reactions in 2005 was approximately 50 per cent higher than seen than in 2004 for all age groups. Again, the highest reporting rate of injection site reactions was among younger vaccinees aged 18–39 years (1.5 per 100,000 doses) compared with the 40–64 year and ≥65 year age groups (1.1 and 0.5 per 100,000 doses, respectively). The single report of GBS following influenza vaccination in a person aged 40–64 years (Table 4) corresponds to a reporting rate of 0.06 per 100,000 doses for persons aged 40–64 years and 0.02 per 100,000 doses for persons aged ≥40 years, compared with 0.03 per 100,000 doses in 2004.[9]

Scheduled vaccines for children aged <7 years

Dose-based AEFI reporting rates for eight NIPS vaccines administered during 2005 to children aged <7 years are shown in Table 7 (by vaccine) and Table 8 (by age group). The reporting rate for 7vPCV, which was added to the NIPS in January 2005, was 14.7 per 100,000 doses recorded on the ACIR. Dose-based AEFI reporting rates for most vaccines were

Figure 5. Trends in reporting of all adverse events and injection site reactions following 23vPPV for adults aged ≥65 years, ADRAC database, 2000 to 2005, by year of vaccination



similar to, or lower than, 2004 estimates although there was an increase in the AEFI reporting rates for DTPa and Hib-HepB (Table 7).

The reporting rate across all vaccines for children aged <7 years declined slightly in 2005 (11.0 versus 13.0 per 100,000 doses) (Table 7), and varied by age group (Table 8). The rate increased among children aged <1 year (5.9 versus 5.5 per 100,000 doses), was stable for children aged 1 to <2 years and decreased slightly for children aged 2 to <7 years (Table 8). This age group had the highest dose-based reporting rate among children aged <7 years (30.1 per 100,000 doses). The main contributor to this was injection site

Table 6. Reporting rate of adverse events following immunisation (AEFI) per 100,000 doses of influenza vaccine,* 18 years and over, ADRAC database, 2005

AEFI category†	Age group	AEFI records‡ (n)	Vaccine doses* (n)	Rate per 100,000 doses§		Ratio of 2005 to 4-yr mean‖
				2005	2004	
Overall	≥18 years	91	4,447,500	2.0	1.8	–¶
	18–39 years	19	732,700	2.6	2.7	–¶
	40–64 years	48	1,653,300	2.9	2.2	1.0
	≥65 years	24	2,061,500	1.2	1.1	0.9
Serious	≥18 years	16	4,447,500	0.36	0.27	–¶
	18–39 years	1	732,700	0.14	0.0	–¶
	40–64 years	9	1,653,300	0.54	0.54	1.8
	≥65 years	6	2,061,500	0.29	0.24	1.0

* Number of administered doses of influenza vaccine estimated from the 2004 national influenza survey.[15]

† 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 2005.

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

‖ Ratio of the reporting rate per 100,000 doses for 2005 and the average (mean) reporting rate per 100,000 doses for the previous 4 years (2001–2004).

¶ Influenza immunisation rates for the 18–39 year age group were not estimated before 2004, therefore the 4-year average AEFI reporting rates and rate ratios for this age group have not been estimated.

Table 7. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* by vaccine, children aged less than 7 years, ADRAC database, 1 January to 31 December 2005

Suspected vaccine type†	AEFI records (n)	Vaccine doses* (n)	Rate per 100,000 doses‡		Ratio of 2005 to 4-yr mean§
			2005	2004	
DTPa	254	474,852	53.5	47.9	0.9
DTPa-HepB	57	388,029	14.7	15.4	0.7
Hib	72	408,237	17.6	20.4	0.6
Hib-HepB	46	283,650	16.2	9.1	1.5
Polio	87	856,211	10.2	10.3	0.8
7vPCV	169	1,156,487	14.7	–	–
MenCCV	53	304,969	17.4	30.8	–
MMR	142	505,333	28.1	33.6	0.9

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 January and 31 December 2005.

† AEFI records where the vaccine was one of those listed as 'suspected' of involvement in the reported adverse event. See appendix for abbreviations of vaccine names.

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

§ Ratio of the AEFI reporting rate per 100,000 doses for 2005 and the average (mean) reporting rate per 100,000 doses for the previous four years (2001–2004). The reporting rate ratio was not estimated for vaccines funded by the National Immunisation Program for less then five years.

reactions following DTPa vaccine (reporting rate of 79.0 per 100,000 doses). The reporting rate of injection site reactions following DTPa vaccine in this age group has been stable at 76–80 per 100,000 doses for the four years 2003–2005.

For all age groups, the dose-based reporting rates of AEFI defined as 'serious' were lower in 2005 compared with 2004 and the average rate for the four years 2001–2004 (Table 8). The reporting rate for HHE following 7vPCV was 1.35 per 100,000 doses for children aged <1 year. This is similar to the combined reporting rates of HHE following DTPa or DTPa-HepB vaccine (1.33 per 100,000 doses) and to rates estimated previously for DTPa containing vaccines (1.23 per 100,000 doses).[9]

Discussion

The data show an overall decrease in AEFI reports in 2005 compared with the three previous years (2002–2004), although this was not consistent across age groups, vaccines or states and territories. A number of factors may explain the observed AEFI reporting trends including several significant changes to the funded NIPS in the past few years and known differences in AEFI surveillance and reporting practices between states and territories and over time. Importantly, the proportion of reports coded as 'serious' remained stable at nine per cent, while the dose-based reporting rate of serious AEFIs for children aged <7 years decreased from 1.0 to 0.7 per 100,000 doses (Table 8).

The largest increase in AEFI reports in 2005 occurred among children aged <1 year and coincided with the introduction of the universally funded 7vPCV program for children in this age group from 1 January 2005. As frequently observed following the introduction of new vaccines or the expansion of an immunisation program,[3,7,9,20] AEFI reports where 7vPCV was suspected of involvement peaked in the first quarter of 2005 then stabilised in the next three quarters (Figure 3). Observed increases in the dose-based reporting rates of DTPa and Hib-HepB vaccines in 2005, compared with 2004 (Table 7), may relate to increased reporting of AEFI following 7vPCV as the vaccines are given to children at the same time points in the immunisation schedule.

Table 8. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* ADRAC database, 1 January to 31 December 2005, by age group, for children aged less than 7 years

AEFI category†	Age group	AEFI records‡ (n)	Vaccine doses* (n)	Rate per 100,000 doses§		
				2005	2004	Ratio of 2005 to 4–yr mean‖
All records	Total	482	4,374,768	11.0	13.0	0.6
	<1 year	150	2,535,194	5.9	5.5	0.8
	1 to <2 years	65	951,887	6.8	6.8	0.2
	2 to <7 years	267	887,687	30.1	33.8	1.0
'Serious' outcome†	Total	30	4,374,768	0.7	1.0	0.6
	<1 year	15	2,535,194	0.6	0.9	0.6
	1 to <2 years	9	951,887	0.9	1.0	0.5
	2 to <7 years	6	887,687	0.7	1.2	0.8
'Certain' or 'probable' causality rating†	Total	206	4,374,768	4.7	5.3	0.6
	<1 year	20	2,535,194	0.8	0.8	0.5
	1 to <2 years	16	951,887	1.7	1.0	0.1
	2 to <7 years	170	887,687	19.2	18.2	1.1

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 January and 31 December 2005.

† AEFI category includes all records (i.e. total), those assigned 'certain' or 'probable' causality ratings, and those defined as 'serious' where at least one of the seven vaccines shown in the table was suspected of involvement in the reported adverse event. Causality ratings were assigned using the criteria described previously.[6] The definition of a 'serious' outcome is described in the Methods section.

‡ Number of AEFI records in which the vaccine was coded as 'suspected' and the vaccination was administered between 1 January and 31 December 2005.

§ The estimated rate of adverse events records per 100,000 vaccine doses recorded on the ACIR.

‖ Ratio of the reporting rate per 100,000 doses for 2005 and the average (mean) reporting rate per 100,000 doses for the previous four years (2001–2004). The reporting rate ratio was not estimated for vaccines included in the National Immunisation Program for less then five years.

The overall dose-based reporting rate for 7vPCV was 14.7 per 100,000 doses, lower than for most of the vaccines given to children <7 years where dose-based reporting rates can be estimated (Table 7). The types of reactions following 7vPCV were similar to those reported in the USA for 7vPCV including mild allergic reaction, rash, fever and fussiness.[10,19] Reports of HHE following administration of 7vPCV have occurred in the USA and Australia, although a causal relationship has not been established between the vaccine and HHE.[19]

There was a significant decrease in the number of AEFI reports in 2005 for children aged 7 to <20 years following the completion of the school-based MenCCV catch-up program at the end of 2004. The majority of AEFI reports mentioning MenCCV vaccine were for children aged 1 to <2 years who received the vaccine as part of the routine childhood schedule at approximately 12 months of age. Reporting of adverse events following MenCCV appear to have stabilised with an average of 13 reports received per quarter in 2005, down from a peak of 96 reports in first quarter of 2003 when the program commenced (Figure 2).

Children aged 2 to <7 years continue to have the highest dose-based AEFI reporting rates of all age groups with injection site reactions following a 5th dose of acellular pertussis-containing vaccines being the largest contributor. Injection site reactions and extensive limb swelling are a known and relatively frequent adverse event associated with 4th and 5th doses of acellular pertussis-containing vaccines.[21,22] Studies show that children recover without sequelae.[21,22] The reporting rate has stabilised at 76–80 reports of injection site reaction per 100,000 doses of DTPa vaccine over the four years to 2005. This trend may be influenced in the future by the removal of the 4th dose of DTPa (due at 18 months of age) from the schedule in September 2003[4] and replacement of DTPa with DTPa-IPV for the dose due at 4 years of age in November 2005.[11]

The AEFI reporting rate for adults ≥65 years of age increased slightly between 2004 and 2005 from 3.3 to 4.0 per 100,000 population, while the dose-based AEFI reporting rate for influenza vaccine remained stable at 1.2 per 100,000 (using 2004 denominator data). Most of the increase in AEFI reporting for this age group between 2004 and 2005 appears to be related to an increase in the number of reports of injection site reaction following 23vPPV (Figure 5). Published data suggest that the incidence of injection site reactions following a second dose of 23vPPV is higher than for the first dose,[23] although one study from the US Vaccine Safety Datalink project found there was relatively little difference in the rate of medical consultation for injection site reaction following a first versus second dose of 23vPPV.[24] Dose number was recorded for only 45 per cent of AEFI records in the ADRAC database for injection site reaction following 23vPPV among those aged ≥65 years. However, of these, approximately two-thirds indicated that the reaction followed a second dose of 23vPPV.

States and territories differ markedly in AEFI surveillance practices and reporting practices. Previously, clear patterns were evident where differences in population-based AEFI reporting rates generally corresponded to the type of AEFI reporting requirements in each state and territory.[7,9] Specifically, Victoria and Tasmania, which both request that general practitioners and other reporters notify AEFI directly to ADRAC, had lower reporting rates than other states and territories. However, in 2005, population-based AEFI reporting rates increased for both Victoria and Tasmania while the overall reporting rate and that for most states and territories decreased (Table 1). The change appears to be related to increased reporting of AEFIs by nurse immunisers in Victoria and Tasmania and coincides with changes to the nurse immuniser accreditation program in Victoria in 2004 to emphasise AEFI reporting (H Pitcher, personal communication), and an increase in the number of nurse immunisers in Tasmania in 2005 (A Misrachi, personal communication). The higher reporting rate for South Australia in 2005 compared with the published rate for 2004[9] is related to increased timeliness of reporting to ADRAC by the cut-off date for inclusion of data in the annual report (31 March of each year).

Conclusions

The data presented in this report indicate that the majority of AEFIs that occur in Australia and are reported to ADRAC are mild, transient and expected vaccine side-effects such as injection site reaction, fever and minor allergic reaction. There was one report of death in an older person following influenza vaccine and another medication and one of non-polio acute flaccid paralysis in an infant. Both were temporally associated with immunisation, and causation was assessed as possible. Serious AEFIs remained stable at nine per cent of all reports to ADRAC and the overall rate of serious AEFI per 100,000 vaccine doses declined among children aged <7 years.

The benefits of immunisation in preventing disease significantly outweigh the risks of immunisation-related adverse events for the Australian population. Immunisation coverage and disease notification data continue to show high immunisation coverage levels[16,25] and low rates of vaccine preventable diseases with significant reductions on the incidence, morbidity and mortality of diseases such as Hib, invasive pneumococcal disease, meningococcal C disease and measles.[25–29]

This is the sixth regular report analysing AEFIs in Australia detected by the national passive surveillance system.[6–10] The data reported here demonstrate that the system is able to detect both known rarer adverse events and expected changes in AEFI reporting trends following changes to the NIPS. The next planned report, analysing AEFI data for children aged <7 years to 30 June 2006, will provide further information on AEFIs reported for new vaccines introduced into the schedule for children aged <7 years from November 2005, including IPV combination vaccines and varicella vaccine.

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Appendix

Abbreviations of vaccine types

23vPPV: 23–valent pneumococcal polysaccharide vaccine

7vPCV: 7–valent pneumococcal conjugate 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-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

Men4PV: meningococcal polysaccharide tetravalent vaccine

MenCCV: meningococcal C conjugate vaccine

MMR: measles-mumps-rubella

polio: poliovirus (oral and inactivated vaccine)