Annual report on surveillance of adverse events following immunisation in Australia, 2006

Glenda L Lawrence, Padmasiri E Aratchige, Ian Boyd, Peter B McIntyre, Michael S Gold

Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Adverse Drug Reactions Advisory Committee for 2006, and describes reporting trends over the seven-year period 2000 to 2006. There were 779 AEFI records for vaccines administered in 2006. This is an annual AEFI reporting rate of 3.8 per 100,000 population, the lowest since 2002 and a 10% decrease compared with 2005 (869 AEFI records; 4.3 records per 100,000 population). Dose-based AEFI reporting rates in 2006 were 1.9 per 100,000 doses of influenza vaccine for adults aged ≥18 years, 19.1 per 100,000 doses of pneumococcal polysaccharide vaccine for those aged ≥65 years and 12.5 per 100,000 doses of scheduled vaccines for children aged <7 years. Trend data showed transient increases in reporting of AEFI following the introduction of DTPa-IPV combination vaccines in November 2005 for children aged <7 years. The majority of the 779 AEFI records for 2006 described non-serious events while 11% (n=85) described AEFIs defined as serious. There was one report of death temporally associated with receipt of dTpa-IPV and typhoid vaccines in an adult with a history of a chronic medical condition. The most frequently reported individual AEFI was injection site reaction in children following a fourth or fifth dose of acellular pertussis-containing vaccine (70 reports per 100,000 doses). The data confirm the low rate of AEFI reported in Australia and demonstrate the ability of the system to detect and investigate signals such as those associated with changes in immunisation programs. *Commun Dis Intell* 2007;31:269–283.

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) to 31 March 2007. The report focuses on AEFI reported for vaccines administered during 2006 and trends in AEFI reporting for the seven-year period 2000 to 2006.

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.[1–3] An 'adverse event following immunisation' is defined as any serious or unexpected adverse event that occurs after a vaccine has been given that 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 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.[6–13]

Several important changes to vaccine funding and availability occurred in 2005 and 2006 that impact on the AEFI surveillance data presented in this

report. Major changes to the funded Australian National Immunisation Program (NIP) Schedule[12] in November 2005 included:

(i) Inactivated poliovirus vaccine (IPV) replaced oral poliovirus vaccine 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 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.

(ii) 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.

In 2006, rotavirus (RotaTeq® and Rotarix®) and human papillomavirus (HPV) (Gardasil®) vaccines were registered by the Therapeutic Goods Administration and became available in the private market throughout Australia. In October 2006, the Northern Territory commenced a funded rotavirus immunisation program for infants. Both rotavirus and HPV vaccines were added to the funded NIP Schedule during 2007.[13]

Previous changes to the NIP Schedule in 2003 and 2005 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 routine schedule at 12 months of age with a catch-up program for all those born between 1984 and 2001.[13] Also in September 2003, the fourth dose of DTPa vaccine, given at 18 months of age, was removed from the immunisation schedule.[4] In January 2005, funded national pneumococcal immunisation programs commenced for infants at 2, 4 and 6 months of age, and for adults aged 65 years or over.[13]

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 2007. 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 involvement in the reported adverse event *and*
- *either*

  (a) the vaccination occurred between 1 January 2000 and 31 December 2006 *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 2006.

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 (VAERS).[14] 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 or hospitalisation was prolonged; 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®).[15] 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 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 the SAS version 9 computer program.[16] The distribution of AEFI records was analysed by age, gender and jurisdiction. Average annual population-based reporting

* 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.

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'.

Dose-based AEFI reporting rates were estimated for influenza vaccine for adults aged ≥18 years, pneumococcal polysaccharide vaccine (23vPPV) for adults aged ≥65 years, and nine vaccines (i.e. DTPa-IPV, DTPa-IPV-HepB, DTPa-IPV-HepB-Hib, Hib, Hib-HepB, MMR, MenCCV, 7vPCV and varicella) funded through the NIP for children aged <7 years. The 2006 AEFI reporting rates per 100,000 doses of these vaccines were compared with those for 2005 and 2004 where denominator data were available.

Denominator data to estimate influenza and 23vPPV AEFI reporting rates were obtained from the 2006 draft national adult coverage survey report (unpublished) for adults aged ≥65 years and 18–64 years (influenza only). The number of administered doses of each of the nine childhood vaccines was calculated from the Australian Childhood Immunisation Register (ACIR), a national population-based register of approximately 99% of children aged <7 years.[17]

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

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 2006. Data published in previous reports for 2000–2005[6–11] differ to that presented in this report for the same period because the data have been updated to include AEFIs notified to ADRAC during 2006 for vaccines administered in previous years.

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 AEFI individual notifications.[6–12,18]

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 the case 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 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.

Results

Summary of data

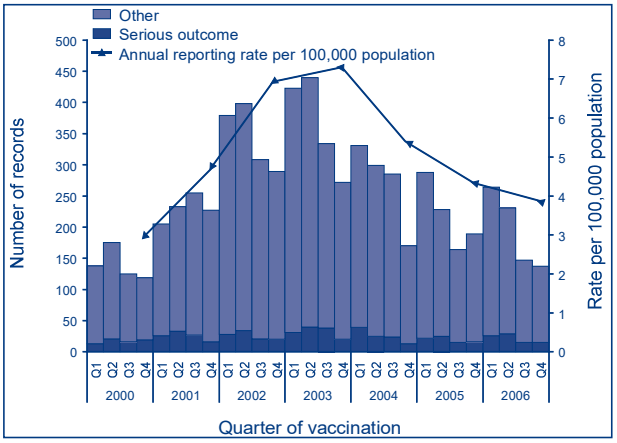
There were a total of 779 AEFI records in the ADRAC database where the date of vaccination (or onset of an adverse event, if vaccination date was not reported) occurred between 1 January and 31 December 2006. This is a decrease of 10% compared with 2005 when there were 869 AEFI records. In 2006, approximately 2% of AEFI notifications resulted in more than one AEFI record in the database (usually of an injection site reaction and a systemic reaction).

Eighty-five (11%) of the 779 AEFI records for 2006 were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threatening event, or death). A total of 345 (44%) AEFI records were assigned causality ratings of 'certain' (n=288, 37%) or 'probable' (n=57, 7%).

Adverse events following immunisation reporting trends

The AEFI reporting rate for 2006 was 3.8 per 100,000 population, down from 4.3 per 100,000 population in 2005 and the lowest since 2001 (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). Many of these changes correspond in time to changes in the funded NIP Schedule. Reports for meningococcal C conjugate vaccine (MenCCV) and pneumococcal conjugate vaccine (7vPCV) increased when the national routine and catch-up programs first commenced in January 2003 (MenCCV) and January 2005 (7vPCV), then stabilised over time. AEFI reports for DTPa-containing vaccines declined following the removal of the fourth dose from the immunisation schedule in the third quarter of 2003, and increased again following the introduction of the new DTPa-IPV containing multivalent vaccines in the fourth quarter of 2005.

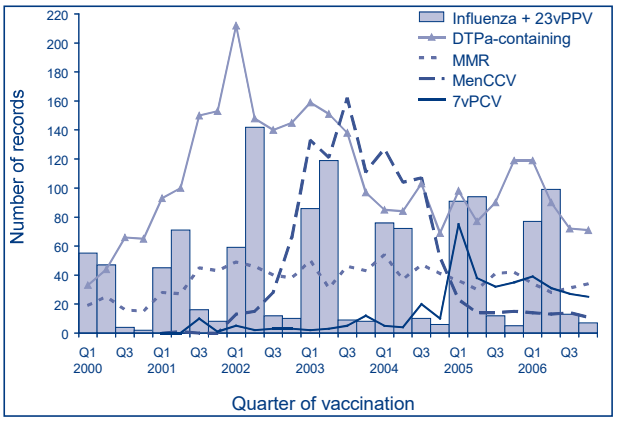
Figure 1. Adverse events following immunisation, ADRAC database, 2000 to 2006, by quarter of vaccination



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

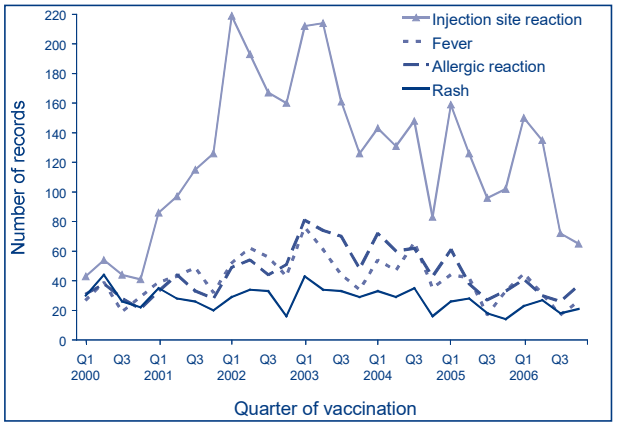
A seasonal pattern of AEFI reporting, seen in previous years, was apparent in 2006 with the highest number of AEFI notifications for vaccinations administered in the first half of the year (Figure 1). The seasonal peak corresponds to the months when more vaccinations are administered in Australia, particularly among 4 and 5-year-old children receiving measles-mumps-rubella (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 2. Frequently suspected vaccines, adverse events following immunisation, ADRAC database, 2000 to 2006, 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.

Figure 3. Selected frequently reported adverse events following immunisation, ADRAC database, 2000 to 2006, by quarter of vaccination

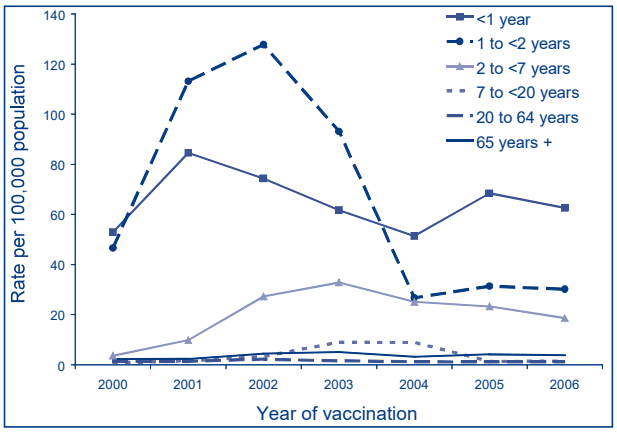


Age and gender distribution

In 2006, the highest AEFI reporting rate occurred in the <1 year age group, which received the highest number of vaccines (Figure 4). Compared with 2005, AEFI reporting rates declined in the <1 year (from 68.5 to 62.6 per 100,000 population), the 2 to <7 year (23.2 to 18.6 per 100,000) and ≥65 year (4.2 to 3.8 per 100,000) age groups and were stable for other age groups.

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 <1 year (male to female 1:0.8) and higher relative reporting rates for females aged ≥20 years (male to female 1:2.6).

Figure 4. Reporting rates of adverse events following immunisation per 100,000 population, ADRAC database, 2000 to 2006, by age group and year of vaccination



Geographical distribution

As noted in previous reports,[6,7,9,11] AEFI reporting rates varied between states and territories for vaccines received during 2006 (Table 1). The Northern Territory and the Australian Capital Territory had the highest reporting rates (18.2 and 16.6 per 100,000 population, respectively) while New South Wales and Queensland had the lowest rates (1.8 and 2.4 per 100,000 population, respectively). AEFI reporting rates either declined or were similar to those in 2005 in all jurisdictions except the Northern Territory where the reporting rate increased from 14.8 to 18.2 (30 to 37 records). The biggest decrease in reporting rates occurred in New South Wales, from 2.8 to 1.8 per 100,000 population in 2005 and 2006, respectively (188 to 125 records).

Adverse events following immunisation outcomes

Sixty-two per cent of reported AEFIs in 2006 were defined as 'non-serious' while 11% were defined as 'serious' (Table 2), similar to the percentages observed in the previous three years (59% and 9%, respectively). Fewer 'serious' AEFIs were assigned certain or probable causality ratings compared with 'non-serious' AEFIs (29% versus 50%) (Table 2). Vaccines listed in records where the outcome was defined as 'serious' are shown in Table 3.

One death was recorded as temporally associated with receipt of combined dTpa-IPV and typhoid vaccines in an adult with a chronic medical condition. The autopsy report indicated that the cause of death was not known.

Vaccines and adverse events following immunisation

Thirty-two vaccines were recorded as 'suspected' of involvement in the adverse events described in the 779 AEFI records for vaccines received in 2006 (Table 3). 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 with outcomes defined as 'serious'.

Table 1. Adverse events following immunisation (AEFI), ADRAC database, January to December 2006, by state or territory

State or territory	AEFI records		Annual reporting rate per 100,000 population*			
	n	%	Overall	'Certain' or 'probable' causality rating†	'Serious' outcome‡	Aged <7 years
Australian Capital Territory	54	7	16.6	3.7	0	112.8
New South Wales	125	16	1.8	0.9	0.15	8.5
Northern Territory	37	5	18.2	8.4	1.97	124.6
Queensland	94	12	2.4	1.1	0.23	18.1
South Australia	165	21	10.7	5.3	0.84	92.7
Tasmania	15	2	3.1	1.2	0.21	21.0
Victoria	187	24	3.7	1.6	0.46	26.4
Western Australia	61	8	3.0	1.4	0.45	27.1
Other§	41	5	na	na	na	na
Total	779	100	3.8	1.7	0.42	26.6

* 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 – Table 2).

§ Records where the jurisdiction in which the AEFI occurred was not reported or was unclear. Most (37/41) AEFI records in this category were notified by pharmaceutical companies while three were from the public and one from a nurse.

Vaccines containing diphtheria, tetanus and acellular pertussis antigens (including combination vaccines and dTpa) were suspected in 380 (49%) records (Table 3). DTPa-IPV was the most frequently suspected vaccine (278 records; 36%), followed by MMR (127 records;16%), 7vPCV (122 records; 16%) and 23vPPV (121 records; 16%). There were 10 reports of AEFI where rotavirus vaccine was suspected and two for HPV vaccine (Table 3).

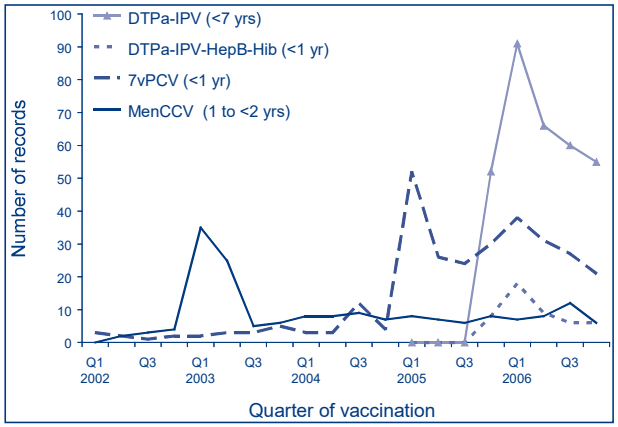
As described previously in this report, AEFI reporting trends differed by vaccine (Figure 2). Reports related to MMR vaccine remained relatively stable over time while AEFI reporting for vaccines recently introduced into the routine childhood schedule has stabilised over time, following peaks shortly after the programs commenced (Figure 5). This pattern has been evident following the introduction of the routine MenCCV dose at 12 months of age 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.

Adverse events following immunisation reactions

The distribution and frequency of reactions listed in AEFI records for 2006 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 (ISR; 54% of 779 AEFI records) followed by allergic reaction (17%), fever (15%) and rash (11%) (Table 4). Injection site reactions were the most commonly reported adverse event following receipt of 23vPPV (85%; 103/121), DTPa-containing vaccines (61%; 230/380), MMR (53%; 67/127) and influenza vaccine (38%; 39/103), administered alone or in combination with other vaccines.

Figure 5. Reports of adverse events following immunisation, ADRAC database, 2002 to 2006, for vaccines recently introduced into the funded National Immunisation Program*



* Meningococcal C conjugate vaccine (MenCCV) was introduced into the NIP on 1 January 2003, 7-valent pneumococcal conjugate vaccine (7vPCV) on 1 January 2005, and both DTPa-IPV and DTPa-IPV-HepB-Hib combination vaccines on 1 November 2005.

Table 2. Outcomes of adverse events following immunisation (AEFI), ADRAC database, 2006

Outcome	AEFI records		'Certain' or 'probable' causality rating†		Age group‡			
					< 7 years		≥ 7 years	
	n	%*	n	%§	n	%§	n	%§
Non-serious	484	62	240	50	310	64	171	35
Not recovered at time of report	158	20	60	38	72	46	85	54
Not known (missing data)	52	7	20	39	37	71	15	29
Serious:	85	11	25	29	56	66	28	33
recovered with sequelae	(1)		(1)		(0)		(1)	
hospital treatment – admission	(72)		(24)		(51)		(20)	
life-threatening event	(11)		(0)		(5)		(6)	
death	(1)		(0)		(0)		(1)	
Total	779	100	345	44	475	61	299	38

* Percentages relate to the total number of AEFI records (n=779).

† 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 484 AEFI records with a 'non-serious' outcome, 50% had causality ratings of 'certain' or 'probable' and 64% 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, 2006

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-IPV**	278	141	51	133	48	28	10	272	98	0	–
MMR	127	22	17	19	15	11	9	122	96	5	4
7vPCV	122	3	2	8	7	22	18	122	100	0	–
23vPPV	121	87	72	74	61	6	5	6	5	114	94
Influenza	103	72	70	27	26	13	13	8	8	93	90
Hib-hepatitis B	97	7	7	11	11	20	21	96	99	1	1
MenCCV	52	5	10	6	12	7	13	50	96	2	4
DTPa-IPV-hepB-hib**	46	13	28	12	26	6	13	46	100	0	–
Hepatitis B	38	28	74	12	32	4	11	4	11	34	89
Varicella**	36	25	69	11	31	1	3	27	75	9	25
dTpa	25	17	68	13	52	0	–	1	4	24	96
Hib	23	1	4	3	13	4	17	23	100	0	–
DTPa	20	5	25	4	20	2	10	20	100	0	–
dT	17	12	71	7	41	3	18	0	–	17	100
Hepatitis A	12	2	17	1	8	1	8	6	50	6	50
Hepatitis A + B	11	7	64	6	55	4	36	1	9	10	91
Rotavirus††	10	8	80	3	30	2	20	10	100	0	–
BCG	8	0	–	7	88	3	38	8	100	0	–
DTPa-IPV-hepB**	7	0	–	1	14	1	14	7	100	0	–
Japanese encephalitis	7	6	86	2	29	0	–	0	–	7	100
IPV	7	1	14	0	–	1	14	3	43	4	57
Typhoid	7	1	14	1	14	0	–	0	–	7	100
Q fever	5	5	100	2	40	2	40	0	–	5	100
Men4PV	4	0	–	0	–	1	25	0	–	4	100
Rabies	4	1	25	0	–	0	–	0	–	4	100
dTpa-IPV	3	1	33	0	–	1	33	0	–	3	100
Cholera	3	0	–	2	67	0	–	0	–	3	100
Yellow fever	3	2	67	0	–	1	33	0	–	3	100
Hepatitis A-typhoid	2	0	–	0	–	0	–	0	–	2	100
HPV vaccine††	2	2	100	0	–	1	50	0	–	2	100
DTPa-hepatitis B	1	0	–	0	–	0	–	1	100	0	–
Tetanus	1	1	100	1	100	0	–	0	–	1	100
Total‡‡	779	486	62	345	44	85	11	475	61	299	38

* 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 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. DTPa-IPV was 'suspected' in 278 AEFI records; this was the only suspected vaccine in 51% of the 278 AEFI records, 48% had 'certain' or 'probable' causality ratings, 10% were defined as 'serious' and 98% were for children <7 years.

** Varicella vaccine and combination vaccines containing inactivated poliovirus were added to the National Immunisation Program Schedule on 1 November 2005.[13]

†† Rotavirus vaccine and human papillomavirus vaccines were registered for use in Australia by the Therapeutic Goods Administration in 2006.

‡‡ 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, 2006

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	422	260	61	281	67	266	63	152	36
Fever	119	1	1	39	33	76	64	43	36
Allergic reaction¶	117	22	19	30	26	72	62	45	38
severe allergic reaction¶	17	0	–	4	24	4	24	12	71
Rash	89	23	26	19	21	67	75	22	25
Abnormal crying	24	1	42	6	25	24	100	0	–
HHE**	20	7	35	2	10	20	100	0	–
Arthralgia	19	0	–	5	26	0	–	19	100
Convulsion	16	8	50	3	19	12	75	4	25
Lymphadenopathy/itis††	7	0	–	2	29	2	29	5	71
Abscess	6	2	33	5	83	5	83	1	17
Anaphylactic reaction	3	0	–	2	67	0	–	3	100
Arthritis	3	2	67	1	33	0	–	3	100
Guillain-Barré syndrome	2	0	–	0	–	0	–	2	100
Thrombocytopenia	2	2	100	0	–	1	50	1	50
Brachial neuritis	1	1	100	0	–	0	–	1	100
Death	1	0	–	0	–	0	–	1	100
Encephalitis	1	0	–	0	–	0	–	1	100
Encephalopathy	1	0	–	0	–	0	–	1	100
Orchitis	1	0	–	0	–	0	–	1	100
Parotitis	1	1	100	0	–	1	100	0	–
Acute flaccid paralysis	0	0	–	0	–	0	–	0	–
Meningitis	0	0	–	0	–	0	–	0	–
Osteomyelitis	0	0	–	0	–	0	–	0	–
Osteitis	0	0	–	0	–	0	–	0	–
Sepsis	0	0	–	0	–	0	–	0	–
SSPE‡‡	0	0	–	0	–	0	–	0	–
Toxic shock syndrome	0	0	–	0	–	0	–	0	–
Total§§	779	366	47	345	44	475	61	299	38

* Reaction categories were created for the AEFIs of interest listed and defined in *The Australian Immunisation Handbook*, (8th edition, p 22–23 and 271–275)[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 422 AEFI records listing injection site reaction, 61% listed only one type of reaction while 67% had a causality rating of 'certain' or 'probable' and 63% 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]

** Hypotonic-hyporesponsive episode.

†† Includes lymphadenitis following BCG vaccination and the more general term of 'lymphadenopathy'.

‡‡ 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, 2006

Reaction term*	AEFI records	Only reaction reported†		Certain/probable causality rating‡		Age group§			
						< 7 years		≥ 7 years	
	n	n	%¶	n	%¶	n	%¶	n	%¶
Malaise	43	0	–	17	40	10	23	33	77
Oedema	39	3	8	18	46	28	72	11	28
Headache	39	0	–	12	31	3	8	36	92
Respiratory rate/rhythm change	35	1	3	6	17	22	63	11	31
Pallor	34	2	6	8	24	28	82	6	18
Irritability	29	0	–	6	21	29	100	0	–
Nausea	29	0	–	2	7	2	7	27	93
Anorexia	27	0	–	6	22	22	81	5	19
Heart rate/rhythm change	25	0	–	4	16	17	68	8	32
Myalgia	24	0	–	8	33	2	8	22	92
Increased sweating	23	0	–	8	35	3	13	19	83
Dizziness	22	0	–	5	23	0	–	22	100
Reduced sensation	18	1	6	8	44	0	–	18	100
Syncope	18	3	17	5	28	3	17	15	83
Pain	16	0	–	4	25	3	19	13	81
Erythema	14	2	14	0	–	10	71	4	29
Cough	9	0	–	2	22	5	56	4	44
Other	144	19	13	36	25	63	44	81	56
neurological	30	7	23	1	3	9	30	21	70
general non-specific	24	2	8	12	50	11	46	13	54
cardiovascular	22	1	5	7	32	5	23	15	68
respiratory	19	5	26	5	26	5	26	14	74
eye or ear	16	0	–	1	6	8	50	8	50
psychological	16	0	–	4	25	9	56	7	44
musculoskeletal	14	2	14	3	21	1	7	13	93
skin	11	2	18	4	36	6	55	5	45
gastrointestinal	8	0	–	1	13	5	63	3	37
infection	8	1	13	3	38	4	50	4	50
haematological	2	0	–	0	–	1	50	1	50
renal/urogenital	2	0	–	0	–	0	–	2	100
pregnancy/congenital	2	2	100	0	–	0	–	2	100
metabolic/endocrine	1	0	–	1	100	0	–	1	100

* 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 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.

Note: Please see Table 4 for the description of other footnotes.

More severe AEFIs included reports of anaphylactic reaction (n=3), severe allergic reaction involving the respiratory and/or circulatory system (n=17), hypotonic-hyporesponsive episode (HHE, n=20), thrombocytopenia (n=2), encephalitis (n=1) convulsion (n=16), Guillain-Barré syndrome (GBS; n=2) and death (n=1; described previously in this report). The two records coded as GBS were for a 63-year-old following receipt of influenza vaccine and 13-year-old following hepatitis B vaccine, although the diagnosis of GBS was apparently not confirmed for the latter report.

Two of the three reports of anaphylaxis occurred in adults following receipt of influenza vaccine and one occurred in a 13-year-old after receiving both HepB and Men4PV vaccines. Of the 16 reports of convulsion, 12 were in children aged <7 years following

routinely scheduled combinations of vaccines. The most commonly suspected vaccines were 7vPCV (n=5) and MMR (n=4). The majority (16/20) of HHE were reported by Victoria and South Australia, and the most commonly suspected vaccines were the ones used in these states including DTPa-IPV (n=14), 7vPCV (n=14) and Hib-HepB (n=13). DTPa-containing vaccines were listed for 18 of 20 reports of HHE.

Reactions shown in Table 5 include changes in respiratory rate/rhythm (n=35) and heart rate/rhythm (n=25). These include 16 reports of bradycardia combined with apnoea or respiratory depression in infants receiving vaccines due at two months of age. Eleven of these reports were for pre-term or very pre-term infants who had received their immunisations in a hospital setting at a chronological age of >8 weeks. An increase in reports of this type was observed following the introduction of the DTP-IPV containing vaccines in November 2005.[13] Before this time, an average of 2–3 reports of bradycardia combined with apnoea or respiratory depression in infants were received each year. The number of reports increased to a peak of six in the fourth quarter of 2005, then declined to four per quarter for the first half of 2006 and only one and two reports in each of the third and fourth quarters, respectively.

Reactions mentioned in fewer than 1% of AEFI records in 2006 are shown in the lower portion of Table 5, grouped by organ system categories. The most commonly reported categories were coded as 'neurological' and '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). Reports of allergic reaction, fever and rash were less variable compared with reports of ISR. 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 and 23vPCV.[6–12] The percentage of reports for 23vPPV that list ISR has increased over time, particularly for adults aged ≥65 years.[11] This has increased from 50% of 26 reports in 2001 to 88% of 82 reports in 2006.

Dose-based reporting rates of adverse events following immunisation

Influenza vaccine and adults aged ≥ 18 years

In 2006, influenza vaccine was suspected of involvement in 89 AEFI records for people aged ≥18 years. The dose-based AEFI reporting rates, by age group, are shown in Table 6. The AEFI reporting rate was 1.9 per 100,000 doses, similar to the rate in 2004 and 2005, while the reporting rate for serious AEFI declined. Both the overall and serious AEFI reporting rates were higher for vaccinees aged 18–64 years than among older vaccinees.

The most frequently reported adverse events were ISR, fever, headache and allergic reaction (0.8, 0.4, 0.4 and 0.3 per 100,000 doses, respectively). Rates of each of these reactions were higher in the 18–64 year age group. There was one report of GBS (in a 63-year-old) following influenza vaccination in 2006, the same as in previous years.[9]

Table 6. Reporting rate of adverse events following immunisation (AEFI) per 100,000 doses of influenza vaccine,* 18 years and over, ADRAC database, 2006

AEFI category†	Age group	AEFI records‡	Vaccine doses*	Rate per 100,000 doses§		
		n	n	2006	2005	2004
Overall	≥ 18 years	89	4,746,900	1.9	2.1	1.8
	18 to 64 years	65	2,626,400	2.5	2.8	2.4
	≥ 65 years	24	2,120,500	1.1	1.2	1.1
Serious	≥ 18 years	9	4,746,900	0.19	0.37	0.36
	18 to 64 years	7	2,626,400	0.27	0.49	0.46
	≥ 65 years	2	2,120,500	0.09	0.27	0.24

* 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 2006.

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

Pneumococcal vaccine and adults aged ≥ 65 years

It was estimated that approximately 429,500 doses of 23vPPV were administered to people aged >65 years in 2006 (unpublished). There were 82 reports of AEFI for this age group where 23vPPV was listed as suspected of involvement in the reported adverse event, with four reports coded as serious and 72 as ISR. The dose-based reporting rates were 19.1 AEFI reports per 100,000 doses, with 0.93 serious and 16.8 ISR reports per 100,000 doses of 23vPPV.

Scheduled vaccines for children aged <7 years

A total of 475 AEFI records for vaccines administered in 2006 were for children aged <7 years. Of these, 442 records listed one of the nine vaccines for which ACIR data could be used to estimate AEFI reporting rates per 100,000 vaccine doses, as the suspected vaccine (Table 7). Vaccines for which reliable denominator data were not available included rotavirus (n=10), BCG (n=8), influenza (n=8), 23vPPV (n=6), hepatitis A (n=6), and hepatitis B (n=4) (Table 3).

The AEFI reporting rates per 100,000 vaccine doses recorded on the ACIR were similar to, or lower than, those in 2005 for most vaccine types, including MenCCV, 7vPCV, MMR and DTPa-containing vaccines (Table 7). The apparent increase in the reporting rate for Hib-HepB and Hib vaccines may be related to reporting of AEFIs for the newer quadrivalent and pentavalent DTP-IPV combination vaccines among children aged <1 year, as the two vaccines are both given at 2 and 4 months of age.[13]

Reporting rates for the different DTPa-IPV combination vaccines varied by vaccine type. 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

Table 7. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* children aged less than 7 years, ADRAC database, 2006

	AEFI records‡	Vaccine doses*	Reporting rate per 100,000 doses§		
	n	n	2006	2005	2004
Vaccine†					
DTPa–containing vaccines	325	1,201,873	27.0	34.8	32.9
DTPa-IPV	272	827,510	32.9	–	–
Pentavalent (DTPa-IPV-HepB)	7	17,938	39.0	–	–
Hexavalent (DTPa-IPV-HepB-Hib)	46	356,425	12.9	–	–
Haemophilus influenzae type b	23	100,361	22.9	17.8	20.4
Haemophilus influenzae type b-hepatitis B	96	408,687	23.5	18.2	9.1
Measles-mumps-rubella	122	512,018	23.8	27.8	33.6
Meningococcal C conjugate	50	277,358	18.0	17.4	30.8
Pneumococcal conjugate	122	789,610	15.5	15.1	–
Varicella	27	233,912	11.5	–	–
Age group					
<1 year	144	1,850,721	7.8	6.6	5.5
1 to <2 years	72	1,089,218	6.6	7.2	6.9
2 to <7 years	226	583,972	38.7	31.7	33.6
AEFI category†					
Total	442	3,523,914	12.5	11.3	13.0
'Certain' or 'probable' causality rating	179	3,523,914	5.1	6.9	5.3
'Serious' outcome	45	3,523,914	1.28	0.71	0.97

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register (ACIR) and administered between 1 January and 31 December 2006.

† 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 2006. More than one 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.

administered. The reporting rate for quadrivalent DTPa-IPV includes reports for children aged <1 year who were scheduled to receive the vaccine at 2, 4 and 6 months of age (reporting rate of 19.6 per 100,000 doses) and the 2 to <7 year age group (reporting rate of 78 per 100,000 doses). The reporting rate of ISR following DTPa-IPV in this older age group was 70 per 100,000 doses compared with 76–80 per 100,000 doses of DTPa vaccine over the four years 2002–2005.

Although the number of AEFI reports for children aged <1 year and 2 to <7 years was lower in 2006 than in 2005, AEFI reporting rates per 100,000 vaccine doses increased for children in these two age groups (Table 7). The reporting rate for AEFIs defined as serious also increased from 0.7 in 2005 to 1.3 in 2006. Reasons for these changes are discussed below and relate to a number of factors including a reduction in the denominator following the introduction of multivalent vaccines in November 2005.

Discussion

The data show a decrease in the number of AEFI reports received for 2006, the lowest since 2002. The reduction in AEFI reporting occurred mainly in the age groups that receive the most vaccines – the <1 year, 2 to <7 year and the ≥65 year age groups. The percentage of reports of serious AEFI increased slightly compared with previous years, from 9% to 11%, particularly among children aged <1 year. This appears to have been related to increased vigilance in reporting following the introduction of DTPa-IPV combination vaccines in November 2005, with a peak in the first quarter of 2006, and a reduction back to baseline later in the year.

An important contributor to the increase in serious AEFI reports in late 2005 and early 2006 was reports of bradycardia and respiratory depression among pre-term and very pre-term infants who received vaccines in hospital settings at around 8 weeks of age. Cardio-respiratory events are known and manageable AEFIs among hospitalised pre-term infants.[19–21] The total number of reports of serious AEFI is low and the increase in reports may be related to the usual increase in reporting following the introduction of new vaccines in Australia (Figure 5) and the United States of America (USA).[22,23] It may also be related to increased awareness among providers following published reports in Germany that suggested an increased risk of sudden unexpected death in children aged <2 years following receipt of a hexavalent vaccine marketed in Germany.[24,25] It is important to note that a large case-control epidemiological study found no link between the use of hexavalent vaccines and sudden unexpected death;[26] that the Global Advisory Committee on Vaccine Safety (convened by the World Health Organization) concluded that hexavalent vaccines are safe;[27] and that the German vaccine is not used in Australia.

The majority of AEFI reported to ADRAC in 2006 were mild transient and expected vaccine side-effects. Injection site reactions remain the most commonly reported AEFI. Two groups are of interest in this regard – children receiving a school entry booster dose of an acellular pertussis-containing vaccine[28,29] and adults receiving booster doses of 23vPPV.[30,31]

The 2006 AEFI data include the first cohorts of children (born after 1 April 2002) who received their fourth dose of acellular pertussis-containing vaccines at 4–5 years of age following the removal from the schedule, in September 2003, of the dose due at 18 months.[4] The rate of ISR following acellular pertussis-containing vaccines in the 2 to <7 year age group has declined slightly in 2006 to 70 per 100,000 doses, down from the consistent reporting rate of 76–80 per 100,000 doses for 2002–2005.[11] As more children receive their fourth dose at 4–5 years of age, it is expected that the reporting rate of AEFI will decline further.

The second group of interest regarding ISR are older adults who receive 23vPPV. Both the total number of reports and the proportion of reports of ISR following 23vPPV in adults aged ≥65 years has continued to increase since 2001. Although dose number is poorly recorded, approximately two-thirds of those where dose information was available indicated that the dose was not a first dose. Increased reporting of ISR following second and third doses of 23vPPV has been suggested previously,[30] however, a recent USA study found little difference in the rate of ISR for first versus subsequent doses.[31] Importantly, ISR does not represent a contraindication to revaccination for age groups that are recommended 23vPPV.[4,29,30]

Available unpublished data on the number of doses of 23vPPV administered in Australia to the ≥65 year age group allowed the first dose-based AEFI reporting rate to be calculated. The availability of 23vPPV coverage data from future regular adult vaccination surveys will allow monitoring of dose-based AEFI reporting rates over time.

The largest population group where dose-based AEFI reporting rates have not been included in this report is adolescents receiving funded vaccines through school-based programs. These programs have expanded considerably in recent years and include routine immunisation with HepB, dTpa and varicella vaccines and, from April 2007, HPV vaccine.[13] At this stage, coverage data are not routinely collated at a national level to allow routine

estimation of dose-based AEFI reporting rates for these vaccines among adolescents. It is anticipated that these data will become available in time.

Conclusion

The benefits of immunisation in reducing morbidity and mortality due to vaccine preventable diseases outweighs the risks of immunisation-related adverse events in Australia. Notification data show the impact of immunisation on reducing the number of cases of many severe infections,[32,33] including significant impacts on the incidence of both invasive meningococcal disease[34] and invasive pneumococcal disease[35] following the introduction of these national immunisation programs in 2003 and 2005.

During 2006, an estimated 9–10 million vaccine doses were administered in Australia and a total of 779 reports of AEFI were received by ADRAC. While under-reporting is a known disadvantage of passive surveillance systems,[1–3,18] the Australian national AEFI passive surveillance system is sufficiently sensitive to detect expected changes in AEFI reporting associated with changes in immunisation programs, and signals of rarer adverse events like the transient increase in reporting of bradycardia and respiratory depression among pre-term infants that occurred in late 2005 and early 2006. Processes are in place to investigate signals and monitor trends in AEFI reporting. 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 six months of 2007.

Acknowledgments

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

Author details

Glenda L Lawrence[1]
Padmasiri E Aratchige[1]
Ian Boyd[2]
Peter B McIntyre[1]
Michael S Gold[3]

1. National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, University of Sydney and The Children's Hospital at Westmead, Sydney, New South Wales
2. Adverse Drug Reactions Unit, Therapeutic Goods Administration, Canberra, Australian Capital Territory
3. Adverse Drug Reactions Advisory Committee and the Women's and Children's Hospital, Adelaide, South Australia

Corresponding author: Dr G Lawrence, NCIRS, Locked Bag 4001, Westmead NSW 2145. Telephone: +61 2 9845 1433. Facsimile: +61 2 9845 1418. Email: glendal@chw.edu.au

References

1. Mansoor O, Shin S, Maher C, and the Immunization Focus of WPRO. Immunization safety surveillance: guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization. Manila: World Health Organization Regional Office for the Western Pacific; 1999.
2. Duclos P. A global perspective on vaccine safety. *Vaccine* 2004;22:2059–2063.
3. 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.
4. National Health and Medical Research Council. *The Australian Immunisation Handbook*, 8th edition. Canberra: Australian Government Publishing Service, 2003.
5. Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. Available from: http://www.who-umc.org Accessed September 2007.
6. Lawrence GL, 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. 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 G, Boyd I, McIntyre P, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2004. [published erratum 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 for 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 GL, Boyd I. Supplementary report: surveillance of adverse events following immunisation for children aged less than 7 years in Australia, 1 January to 30 June 2006. *Commun Dis Intell* 2006;30:438–442.
13. Australian Government Department of Health and Ageing. Immunisation programs and initiatives. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/programs Accessed August 2007.
14. 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. [published erratum in *MMWR Morb Mortal Wkly Rep* 2003;52:113.] *MMWR Surveill Summ* 2003;52 SS–1:1–28.
15. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Safety* 1999;20:109–117.

16. The SAS system for Windows [computer program]. Version 9.1.3. Cary, NC: SAS Institute Inc.; 2005.

17. Australian Government Department of Health and Ageing. Additional reports – Childhood immunisation coverage. *Commun Dis Intell* 2007;31:333–334.

18. 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.

19. Botham SJ, Isaacs D, Henderson-Smart DJ. Incidence of apnoea and bradycardia in pre-term infants following DTPa and Hib immunization: a prospective study. *J Paediatr Child Health* 1997;33:418–421.

20. Schulzke S, Heininger U, Lucking-Famira M, Fahenstich H. Apnoea and bradycardia in preterm infants following immunisation with pentavalent and hexavalent vaccines. *Eur J Pediatr* 2005; 164:432–435.

21. Faldella G, Galletti S, Corvaglia L, Ancora G, Alessandroni R. Safety of DTaP-IPV-Hib-HBV hexavalent vaccine in very premature infants. *Vaccine* 2007;25:1036–1042.

22. Wise R, Iskander J, Pratt R, Campbell S, Ball R, Pless R, et al. Post licensure safety surveillance for 7-valent pneumococcal conjugate vaccine. *JAMA* 2004;292:1702–1710.

23. Wise RP, Salive ME, Braun MM, Mootrey GT, Seward JF, Rider LG, et al. Postlicensure safety surveillance for varicella vaccine. [published erratum in *JAMA* 2000;284:3129.] *JAMA* 2000;284:1271–1279.

24. Von Kries R, Toschke AM, Strassburger K, Kundi M, Kalies H, Nennsteil U, et al. Sudden and unexpected deaths after administration of hexavalent vaccines (DTPa-IPV-HBV-Hib): is there a signal? *Eur J Pediatr* 2005;164:61–69.

25. Zinka B, Rauch E, Buettner A, Penning R, Rueff F. Unexplained cases of sudden infant death shortly after hexavalent vaccination. *Vaccine* 2006;24:5779–5780.

26. Vennemann MMT, Butterfass-Bahloul T, Jorch G, Brinkmann B, Findeisen M, Sauerland C, et al. Sudden infant death syndrome: no increased risk after immunisation. *Vaccine* 2007;25:336–340.

27. Global Advisory Committee on Vaccine Safety. Safety of hexavalent vaccines. *Wkly Epidemiol Rec* 2005;28:245–246. Available from: http://www.who.int/vaccine_safety/reports/June_2005/en/index.html Accessed August 2007.

28. 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.

29. 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.

30. Jackson L, Benson P, Sneller V-P, Butler J, Thompson RS, Chen RT, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999;281:243–248.

31. Jackson L, Nelson J, Whitney C, Neuzil K, Benson P, Malais D, et al. Assessment of the safety of a third dose of pneumococcal polysaccharide vaccine in the Vaccine Safety Datalink population. *Vaccine* 2006;24;151–156.

32. 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:i–S152.

33. Owen R, Roche PW, Yohannes K, Hope K, Yohannes K, Roberts A, et al. Australia's notifiable diseases status, 2005: Annual report of the National Notifiable Diseases Surveillance System. *Commun Dis Intell* 2007;31:1–70.

34. The Australian Meningococcal Surveillance Programme. Annual report of the Australian Meningococcal Surveillance Programme, 2006. *Commun Dis Intell* 2007;31:185–121.

35. Roche P, Krause V, Cook H. Invasive pneumococcal disease in Australia, 2005. *Commun Dis Intell* 2007;31:86–100.

Appendix

Abbreviations of vaccine types

7vPCV	7-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine
BCG	Bacille Calmette-Guérin (i.e. tuberculosis)
dT	diphtheria-tetanus – adolescent and adult formulation
DTPa	diphtheria-tetanus-pertussis (acellular) – paediatric formulation
dTpa	diphtheria-tetanus-pertussis (acellular) – adolescent and adult formulation
dTpa-IPV	combined dTpa and inactivated poliovirus
DTPa-hepB	combined diphtheria-tetanus-pertussis (acellular) and hepatitis B
DTPa-IPV	combined diphtheria-tetanus-pertussis (acellular) and inactivated poliovirus (quadrivalent)
DTPa-IPV-hepB	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus and hepatitis B (pentavalent)
DTPa-IPV-hepB-hib	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b (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