Annual report: surveillance of adverse events following immunisation in Australia, 2004

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Abstract

This report summarises Australian passive surveillance data on adverse events following immunisation (AEFI) for 2004 and describes reporting trends over the five years, 2000 to 2004. AEFIs are notified to the Adverse Drug Reactions Advisory Committee by state and territory health departments, hospitals, doctors and other health providers, vaccine manufactures, and the public. There were 975 AEFI records for vaccines received in 2004. This is an annual AEFI reporting rate of 4.8 per 100,000 population, the lowest since 2000, and a 33 per cent decrease compared with 2003 (1,460 records; 7.1 AEFI records per 100,000 population). Dose-based AEFI reporting rates in 2004 were 1.8 per 100,000 doses of influenza vaccine for adults aged ≥18 years and 11.8 per 100,000 doses of scheduled vaccines for children aged <7 years. The majority of records described non-serious events while nine per cent (n=88) described AEFIs defined as 'serious'. There were no reports of death related to immunisation. The most frequently reported individual AEFI was injection site reaction in children following a fifth dose of an acellular pertussis-containing vaccine (67 reports per 100,000 doses). The marked reduction in the AEFI reporting rate in 2004 coincided with the removal of the fourth dose of acellular pertussis vaccine, due at 18 months of age, from the vaccination schedule in September 2003 and fewer people receiving meningococcal C vaccine through the national catch-up vaccination program for those aged 1–19 years in 2004, compared with 2003. The consistently low reporting rate of serious AEFIs demonstrates the high level of safety of vaccines in Australia. *Commun Dis Intell* 2005;29:248–262.

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

Introduction

Ongoing surveillance of adverse events following immunisation (AEFI), and regular analysis and reporting of these data, are integral to the management of immunisation programs. The aim of 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 the Adverse Drug Reactions Advisory Committee (ADRAC) by state and territory health departments, health care professionals, vaccine manufacturers and members of the public.[4,5] All reports received by ADRAC are evaluated using internationally consistent criteria[6] and are reviewed at regular meetings. These 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.[7–9] This report summarises AEFI data reported to ADRAC for vaccines received during 2004 and trends in AEFI reporting for the five year period 2000–2004.

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Several important changes both to AEFI surveillance methods and to the Australian childhood vaccination schedule occurred during 2003 and 2004 that affect the AEFI surveillance data presented in this report. In September 2003, the 8th edition of the *Australian Immunisation Handbook*[5] was released. The case definitions of several AEFIs, including those for anaphylactic reaction and allergic reaction, differed from those shown in the 7th edition of the *Australian Immunisation Handbook*.[4] Coinciding with the release of the 8th edition of the Handbook were a number of changes to the immunisation schedule, including the removal of the 4th dose of DTPa (due at 18 months of age) and new recommendations that all children receive three vaccines not included in the funded National Immunisation Program at the time (i.e. 7-valent pneumococcal conjugate vaccine (7vPCV), varicella vaccine and inactivated poliomyelitis vaccine).[5] Also the meningococcal C conjugate vaccine catch-up immunisation program for those aged 1–19 years, which commenced in 2003, was completed for most school-aged and pre-school children during 2004.[10]

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 2005. 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.[7,8]

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 2004 *or* (b) if no vaccination date was recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 31 December 2004.

* 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.

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[6] and the US Vaccine Adverse Events Reporting System (VAERS).[11] In this report, an AEFI is defined as 'serious' if the record indicated 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®).[12] 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).[5] The category created for 'allergic reaction' for this report differs from previous reports to reflect the change in the definition of 'allergic reaction (generalised)' in the 8th edition of the Handbook, where both skin and gastrointestinal symptoms and signs are included.[5] A new category was created, 'severe allergic reaction', to capture reports of a generalised allergic reaction that involved symptoms and signs of the circulatory and/or respiratory system but had not been coded in the dataset as 'anaphylactic reaction'. Reaction categories were not created for two new AEFIs listed in the 8th edition of the Handbook ('extensive limb swelling' and 'nodule') due to the lack of specific MedDRA® coding terms for these AEFIs. Instead, these AEFIs are included in the category of 'injection site reaction'. A separate reaction category was created where symptoms and signs describing a hypotonic-hyporesponsive episode (HHE) or HHE-like event were mentioned but the specific terms of HHE was not present. This definition was *based* on the Brighton Collaboration case definition for HHE (level 2 of diagnostic certainty).[13] A 'possible HHE' in this report is defined as hypotonia plus terms describing colour change (pallor, cyanosis) and/or hyporesponsiveness (somnolence, hypokinesia), in the absence of terms related to other AEFIs such as convulsion.

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 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 8 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 was assessed. For each vaccine, we calculated the age distribution and 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 children aged less than seven years for seven childhood vaccines funded through the National Immunisation Program (DTPa, DTPa-HepB, Hib, Hib-HepB, polio, MMR and MenCCV), and for adults aged 18 years and over for influenza vaccine. The number of administered doses of each of the seven 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.[15] Vaccine doses administered between 1 January and 31 December 2004 were estimated for the age groups <1 year, 1 to <2 years, and 2 to <7 years (i.e. the age at vaccination). The number of administered influenza vaccine doses was estimated from the 2004 annual national influenza coverage survey[16] for the 18–39 years, 40–64 years and ≥65 years age groups. 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.

Dose-based AEFI reporting rates for vaccines received in 2004 were compared to 2003 reporting rates and to the average annual reporting rate for the four years 2000 to 2003 inclusive.

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 2004. 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.[7,8,17]

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*.[5] These reaction categories are similar to but not identical to 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. 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 was administered.[7] Because children in particular receive several different vaccines at the same time, all vaccines tend to be listed as 'suspected' of involvement of a systemic adverse event, as it is usually not possible to ascribe the AEFI to a single vaccine.

Results

Summary of data

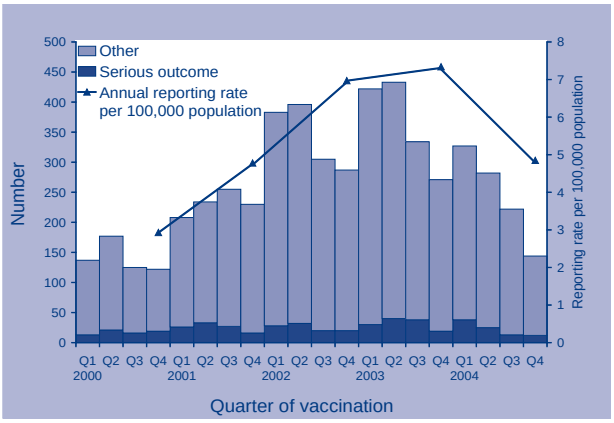
There were a total of 975 AEFI records in the ADRAC database for 2004. This is a decrease of 33 per cent compared with 2003 when there were 1,460 AEFI records. In 2004, approximately four per cent of AEFI notifications resulted in more than one AEFI record in the database (usually of an injection site reaction and a systemic reaction). This was lower than in 2003 when approximately 10 per cent of notifications resulted in more than one AEFI record.[8]

Eighty-eight (9%) of the 975 AEFI records for 2004 were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threatening event or death). A total of 444 (46%) AEFI records were assigned causality ratings of 'certain' (n=363, 37%) or 'probable' (n=81, 8%).

Adverse events following immunisation reporting trends

The AEFI reporting rate for 2004 was 4.8 per 100,000 population and was lower than for the previous three years (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).

Figure 1. Adverse events following immunisation, ADRAC database, 2000 to 2004, 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.

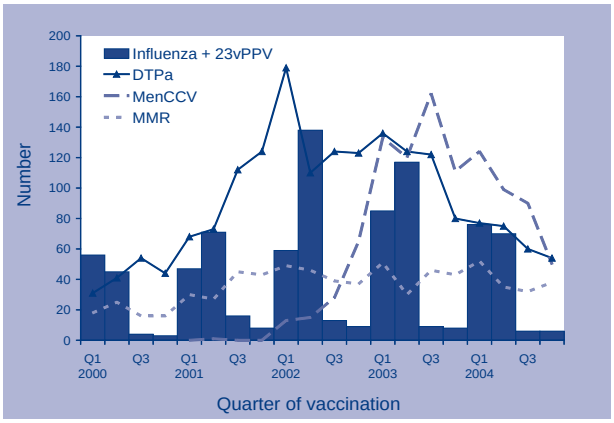
A seasonal pattern of AEFI reporting was apparent in 2004 and previous years, with the highest number of AEFI notifications for vaccinations administered in the first half of the year (Figure 1). The seasonal peak corresponds to the months when more vaccinations are administered in Australia, particularly among 5-year-old children receiving DTPa and MMR vaccines prior to commencing school in February and older Australians receiving influenza and pneumococcal vaccines during the autumn months (March to June) (Figure 2).

Age and gender distribution

The AEFI reporting rate in 2004 was highest among children aged <1 year (40.9 per 100,000 population), the age group that receive the greatest number of vaccinations. The annual AEFI reporting rate decreased for all age groups in 2004 compared with 2003 (Figure 4). The largest decrease was among children aged 2 to <7 years (91.1 and 23.1 per 100,000 population in 2003 and 2004, respectively).

The overall male to female ratio was 1.0:1.2. There were more reports for females in all age groups except the 2 to <7 year age group (male:female 1.0:0.9).

Figure 2. Frequently suspected vaccines, adverse events following immunisation, ADRAC database, 2000 to 2004, by quarter of vaccination



See appendix for abbreviations of vaccine names.

Figure 3. Selected frequently reported adverse events following immunisation, ADRAC database, 2000 to 2004, by quarter of vaccination

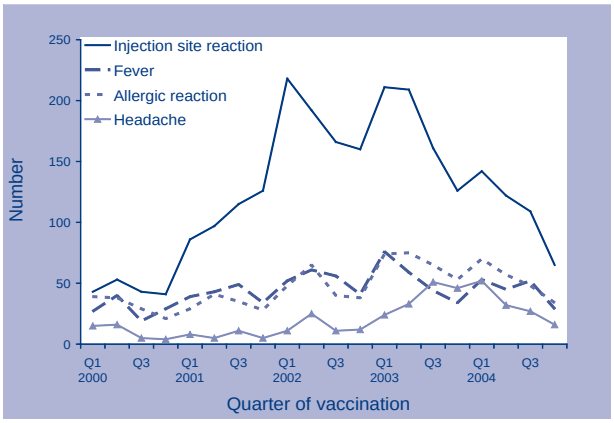
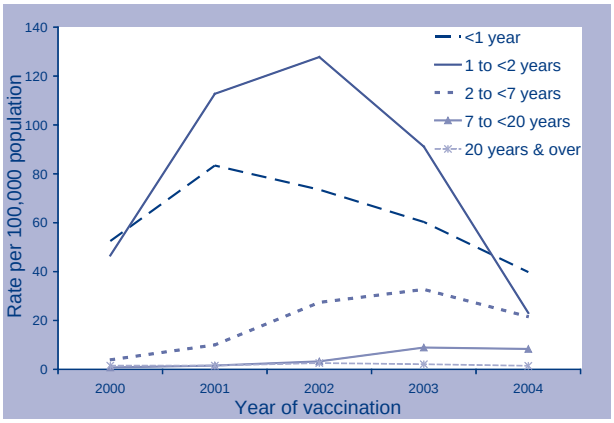


Figure 4. Reporting rates of adverse events following immunisation per 100,000 population, ADRAC database, 2000 to 2003, by age group and quarter of vaccination



Geographical distribution

As seen in previous years, AEFI reporting rates varied between the states and territories for vaccines received during 2004 (Table 1). The Australian Capital Territory and Northern Territory had the highest reporting rates (35.9 and 17.5 per 100,000 population, respectively) while Tasmania and Victoria had the lowest rates (1.2 and 2.5 per 100,000 population, respectively). Reporting rates were lower in 2004, compared with 2003,[8] for all states and territories except the Australian Capital Territory where the overall reporting rate increased from 23.0 to 35.9 per 100,000 population and the rate for children aged <7 years increased from 151 to 180 per 100,000 population. The majority of the increase in reports from the Australian Capital Territory in 2004 described adverse events following MenCCV among school-aged children.

Adverse events following immunisation outcomes

Fifty-nine per cent of reported AEFIs in 2004 were defined as 'non-serious' while nine per cent were defined as 'serious' (Table 2) – the same as seen in 2003. No deaths related to immunisation were reported in 2004. Fewer 'serious' AEFIs were assigned 'certain' or 'probable' causality ratings compared with 'non-serious' AEFIs (21% versus 50%).

Vaccines and adverse events following immunisation

Twenty-three vaccines were recorded as 'suspected' of involvement in the adverse events described in the 975 AEFI records for vaccines received in 2004 (Table 3). They included all vaccines recommended in the ASVS, plus vaccines recommended to travellers and specific risk groups.

The most frequently suspected individual vaccine was MenCCV with 363 (37%) records (Table 3). Vaccines containing pertussis, diphtheria and tetanus antigens (i.e. DTPa, DTPa-HepB and dTpa) were suspected in 342 (35%) reports. The proportion of reports where only one vaccine was suspected of involvement in the adverse event differed by vaccine, as did the proportion assigned causality ratings of 'certain' or 'probable', and the proportion defined as 'serious' (Table 3).

AEFI reporting trends differed by vaccine (Figure 2). The number of reports of AEFIs where DTPa vaccine was suspected declined in 2004 following a peak in the first quarter of 2002. Reports related to MMR vaccine remained relatively constant while reports for MenCCV increased in 2003 following the addition of this vaccine to the national immunisation program and delivery of a catch-up campaign through provider and school-based immunisation programs, then declined during 2004 as the catch-up programs were completed for most of those aged 1–19 years (Figure 5).

Table 1. Adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2004, by jurisdiction

Jurisdiction	AEFI records		Annual reporting rate per 100,000 population*			
	n	%	Overall	'Certain' or 'probable' causality rating†	'Serious' outcome‡	Aged <7 years
Northern Territory	35	4	17.5	9.0	1.50	74.3
Queensland	170	17	4.4	2.1	0.49	25.4
South Australia	127	13	8.3	4.2	0.39	50.7
Tasmania	6	1	1.2	0.2	0.21	0.0
Victoria	123	13	2.5	1.0	0.18	13.9
Western Australia	59	6	3.0	1.1	0.40	21.5
Other§	21	2	na	na	na	na
Total	975	100	4.8	2.2	0.44	24.5

* Average annual rates per 100,000 population calculated using mid-2004 population estimates (Australian Bureau of Statistics).

† See previous report[7] for criteria used to assign causality ratings.

‡ Adverse events following immunisation 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, including AEFIs notified by pharmaceutical companies (n = 17).

na Not available.

Table 2. Outcomes of adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2004

Outcome	AEFI records		'Certain' or 'probable' causality rating†		Age group‡			
					< 7 years		≥ 7 years	
	n	%*	n	%§	n	%§	n	%§
Non-serious	577	59	286	50	269	47	297	51
Not recovered at time of report	222	23	96	43	90	41	129	58
Not known (missing data)	88	9	41	47	46	52	38	43
Serious:	88	9	21	24	36	41	49	56
recovered with sequelae	(2)		(1)		(0)		(2)	
hospital treatment – admission	(81)		(20)		(35)		(46)	
life-threatening event	(5)		(0)		(1)		(4)	
death	(0)		(0)		(0)		(0)	
Total	975	100	444	46	437	45	513	53

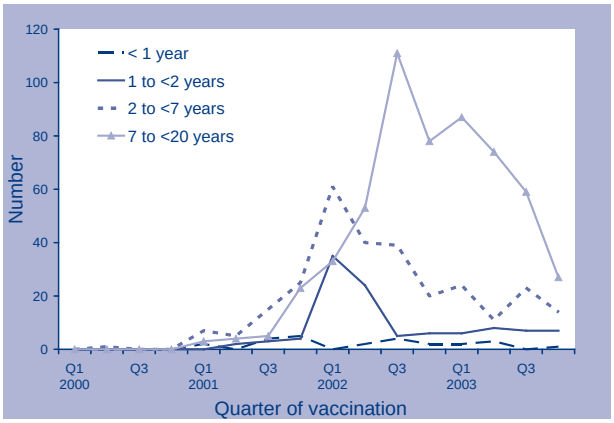
* Percentages relate to the total number of adverse events following immunisation records (n=975).

† Causality ratings were assigned to AEFI records using criteria described previously.[7]

‡ 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 577 AEFI records with a 'non-serious' outcome, 50 per cent had causality ratings of 'certain' or 'probable' and 47 per cent were for children aged less than 7 years.

Figure 5. Number of adverse events following immunisation records for meningococcal C conjugate vaccine, ADRAC database, 2001 to 2004, by age group and quarter of vaccination



Adverse events following immunisation reactions

The distribution and frequency of reactions listed in AEFI records for 2004 are shown in Tables 4 and 5. In Table 4, only the reaction categories analogous to those listed in the *Australian Immunisation Handbook*[5] 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 (45% of 975 AEFI records) followed by allergic reaction (23%), fever (18%) headache (14%) and rash (9%) (Tables 2 and 5). The relationship between the most frequently reported vaccines and adverse events is shown in Figure 6. Injection site reactions were the most commonly reported adverse event following receipt of MenCCV, DTPa, MMR, 23vPPV and influenza vaccines – over 60 per cent of reports for both DTPa (176/237) and 23vPPV (62/93) listed injection site reaction. Headache was mainly reported following receipt of MenCCV (88/363).

Figure 6. Most frequently suspected vaccines, records of adverse events following immunisation, ADRAC database, by most frequent reaction categories

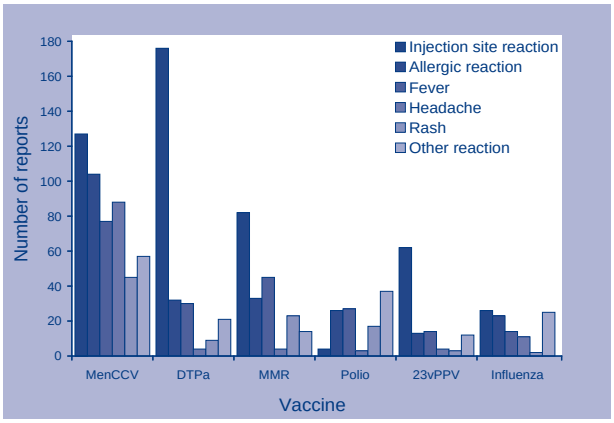


Table 3. Vaccine types listed as 'suspected' in records of adverse events following immunisation (AEFI), ADRAC database, 1 January to 31 December 2004

Suspected vaccine type*	AEFI records	One suspected vaccine or drug only†		'Certain' or 'probable' causality rating‡		'Serious' outcome§		Age group‖ < 7 years		Age group‖ ≥ 7 years	
	n	n	%¶	n	%¶	n	%¶	n	%¶	n	%¶
MenCCV	363	280	77	168	46	33	9	106	29	250	69
DTPa	237	114	48	103	43	6	3	221	93	0	-
MMR	157	23	15	15	10	11	7	146	93	7	4
Polio	93	2	2	1	1	13	14	88	95	2	2
23vPPV	93	71	76	59	63	4	4	1	1	88	95
Influenza	83	63	76	27	33	15	18	1	1	80	96
Hib	77	2	3	2	3	11	14	75	97	1	1
DTPa-hepatitis B	66	12	18	9	14	12	18	65	98	0	-
Hepatitis B	52	28	54	13	25	8	15	8	15	43	83
dTpa	39	31	79	20	51	1	3	0	-	39	100
7vPCV	29	17	59	6	21	6	21	28	97	0	-
Hib-hepatitis B	24	3	13	3	13	2	8	19	79	0	-
Varicella	23	19	83	1	4	4	17	13	57	9	39
dT	15	13	87	9	60	1	7	1	7	14	93
Rabies	13	9	69	3	23	0	-	0	-	13	100
JE	9	6	67	4	44	1	11	1	11	8	89
Hepatitis A	7	1	14	0	-	4	57	2	29	4	57
Q fever	7	7	100	2	29	4	57	0	-	6	86
Hepatitis A + B	5	3	60	0	-	0	-	0	-	4	80
BCG	2	2	100	1	50	0	-	2	100	0	-
Typhoid	2	0	-	0	-	1	50	0	-	1	50
Yellow fever	2	2	100	0	-	0	-	0	-	2	100
Tetanus	1	1	100	1	100	0	-	0	-	1	100
Total**	975	709	73	444	46	88	9	437	45	513	53

* See appendix for abbreviations of vaccine names.

† Adverse events following immunisation 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.[7]

§ '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. MenCCV was listed as 'suspected' in 363 AEFI records; this was the only suspected vaccine in 77 per cent of the 363 AEFI records, 46 per cent had 'certain' or 'probable' causality ratings, 9 per cent were defined as 'serious' and 29 per cent were for children aged less than 7 years.

** Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and one 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 2004

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	438	272	23	324	74	233	53	196	45
Allergic reaction¶	197	23	12	58	29	69	35	123	62
Severe allergic reaction¶	12	0	0	2	17	4	33	8	67
Fever	179	6	3	54	30	88	49	83	46
Rash	92	35	38	24	26	52	57	34	37
Abnormal crying	28	4	14	3	11	26	93	2	7
Convulsions	27	8	30	17	63	8	30	19	70
Arthralgia	26	3	12	13	50	1	4	24	92
Lymphadenopathy/itis**	21	4	19	9	43	7	33	12	57
HHE††	7	0	–	7	100	7	100	0	–
Possible HHE††	10	0	–	0	–	10	100	0	–
Abscess	6	0	–	1	17	6	100	0	–
Arthritis	4	0	–	0	–	1	25	3	75
Anaphylactic reaction	2	0	–	0	–	0	–	1	50
Brachial neuritis	2	0	–	1	50	0	–	2	100
Guillain-Barré syndrome	2	0	–	1	50	1	50	1	50
Encephalitis	1	0	–	0	–	1	100	0	–
Parotitis	1	0	–	0	–	1	100	0	–
Sepsis	1	0	–	0	–	0	–	1	100
Thrombocytopenia	1	0	–	1	100	0	–	1	100
Acute flaccid paralysis	0	–		–		–		–	
Death	0	–		–		–		–	
Encephalopathy	0	–		–		–		–	
Meningitis	0	–		–		–		–	
Orchitis	0	–		–		–		–	
Osteitis	0	–		–		–		–	
Osteomyelitis	0	–		–		–		–	
SSPE‡‡	0	–		–		–		–	
Toxic shock syndrome	0	–		–		–		–	
Total§§	975	415	43	444	46	437	45	513	53

* Reaction categories were created for the adverse events following immunisation of interest listed and defined in the *Australian Immunisation Handbook*, (8th edition, p 22–3 and 271–5)[5] as described in Methods section.

† Adverse events following immunisation records where only one reaction was reported.

‡ Causality ratings were assigned to AEFI records using criteria described previously.[7]

§ Not shown if both age and date of birth were not recorded.

‖ Percentages relate to the number of AEFI records in which the specific reaction term was listed e.g. of 438 AEFI records listing injection site reaction, 62 per cent listed only one type of reaction while 74 per cent had causality ratings of 'certain' or 'probable' and 53 per cent were for children aged less than 7 years.

¶ Allergic reaction includes skin and/or gastrointestinal (e.g. diarrhoea, vomiting) symptoms and signs.[5] The category 'severe allergic reaction' includes allergic reaction with symptoms and signs indicating involvement of the circulatory and/or respiratory system but not recorded in the ADRAC database as 'anaphylactic reaction'. [5]

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

†† Hypotonic-hyporesponsive episode (HHE). The separate reaction term of 'possible HHE' indicates records where 'HHE' was not listed but other terms describing an HHE or similar event were (e.g. hypotonia plus pallor or cyanosis or somnolence or hypokinesia not coded as convulsion).[13]

‡‡ Subacute sclerosing panencephalitis.

§§ Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and one 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 2004

Reaction term*	AEFI records	Only reaction reported†		Certain/probable causality rating‡		Age group§ < 7 years		Age group§ ≥ 7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Headache	127	10	8	53	42	7	6	116	91
Malaise	86	0	–	25	29	31	36	53	62
Oedema	62	9	15	29	47	28	45	32	52
Pain	52	2	4	16	31	7	13	43	83
Nausea	48	0	–	22	46	2	4	46	96
Myalgia	42	0	–	17	40	2	5	39	93
Syncope	33	3	10	16	52	3	10	28	90
Irritability	30	1	3	6	20	22	73	6	20
Dizziness	29	0	–	14	48	0	–	29	100
Anorexia	23	0	–	7	30	11	48	12	52
Reduced sensation	22	0	–	12	55	0	–	22	100
Pallor	21	1	5	8	38	7	33	13	62
Erythema	20	2	10	5	25	10	50	9	45
Somnolence	15	1	7	6	40	7	50	7	25
Increased sweating	15	0	–	6	40	4	27	11	73
Cough	14	0	–	4	29	5	36	8	57
Pharyngitis	11	0	–	3	27	3	27	8	73
Fatigue	11	0	–	5	45	0	–	10	91
Weakness	11	0	–	1	9	2	18	8	73
Heart rate/rhythm change	10	1	10	2	20	5	50	5	50
Influenza-like illness	10	0	–	3	30	1	10	9	90
Other									
general non-specific	43	1	2	15	35	11	26	29	67
respiratory	34	4	12	8	24	9	26	24	71
eye or ear	33	1	3	12	36	8	24	25	76
cardiovascular	28	1	4	15	54	7	25	21	75
neurological	27	4	15	8	30	8	30	8	30
psychological	26	0	–	6	23	13	50	13	50
skin	19	4	21	6	32	7	37	12	63
gastrointestinal	12	3	25	1	8	5	42	7	58
infection	11	3	27	0	–	3	27	6	55
musculoskeletal	11	2	18	5	45	1	9	1	9
metabolic/endocrine	6	0	–	0	–	4	67	1	17
renal/urogenital	4	0	–	4	100	0	–	4	100
haematological	3	0	–	1	33	0	–	3	100
miscellaneous	1	0	–	1	100	0	–	1	100
pregnancy/congenital	1	0	–	0	–	0	–	1	100

* Reaction terms not listed in the *Australian Immunisation Handbook*[5] but included in adverse events following immunisation 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.[7]

§ Not shown if both age and date of birth were not recorded.

‖ Percentages relate to the number of AEFI records in which the specific reaction term was listed e.g. of 438 AEFI records listing injection site reaction, 62 per cent listed only one type of reaction while 74 per cent had causality ratings of 'certain' or 'probable' and 53 per cent were for children aged less than seven years.

More severe AEFIs reported included anaphylactic reaction (n=2), severe allergic reaction involving the respiratory and/or circulatory system (n=12), hypotonic-hyporesponsive episode (HHE, n=7), possible HHE (n=10), thrombocytopenia (n=1), encephalitis (n=1) and convulsion (n=27). The two reports of anaphylactic reaction were for adults: one following 23vPPV and one following receipt of typhoid and hepatitis A vaccines. DTPa-HepB vaccine was the most commonly suspected vaccine in AEFI records of HHE (5/7, 71%) and possible HHE (7/10, 70%). Of the 27 reports of convulsion, 17 (63%) listed MenCCV and 3 (11%) listed dTpa as a suspected vaccine: 19/27 (70%) vaccinees were aged 7 to <20 years and had received one or more of MenCCV, dTpa and hepatitis B vaccines.

Reactions mentioned in fewer than one per cent of AEFI records for 2004 are shown grouped by higher or organ system categories in the lower portion of Table 5. The most commonly reported category was 'general non-specific', 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). There were fewer reports of injection site reaction in 2004 compared with previous years. Reports of allergic reaction, fever and rash were less variable over time and reports of headache were lower in 2004 compared with 2003, consistent with the decrease in reporting of adverse events following MenCCV.

Dose-based adverse events following immunisation reporting rates

Influenza vaccine and adults aged ≥18 years

Influenza vaccine was suspected of involvement in 78 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 lower among influenza vaccinees aged ≥65 years than for younger vaccinees (Table 6), as seen previously.[7,8] The most frequently reported adverse events were injection site reaction, fever and allergic reaction (0.6, 0.3 and 0.3 per 100,000 doses, respectively). The reporting rate of injection site reactions was highest among younger vaccinees aged 18–39 years (1.2 per 100,000 doses) than for the 40–64 year and ≥65 year age groups (0.4 and 0.3 per 100,000 doses, respectively). There was one report of Guillain-Barré syndrome following influenza vaccination in a person aged 65 years or more. This corresponds to a reporting rate of 0.05 per 100,000 doses for persons aged 65 years or more and 0.03 per 100,000 doses for persons aged 40 years or more, the same as in previous years.[7,8]

Table 6. Dose-based reporting rates of adverse events following immunisation (AEFI) with influenza vaccine,* 18 years and over, ADRAC database

AEFI category†	Age group	AEFI records‡ n	Vaccine doses n	Rate per 100,000 doses§		
				2004	2003	Ratio of 2004 to 4-year mean‖
Overall	≥ 18 years	78	4,447,500	1.8	– ¶	–
	18 to 39 years	20	732,700	2.7	–	–
	40 to 64 years	36	1,653,300	2.2	2.8	0.7
	≥ 65 years	22	2,061,500	1.1	1.6	0.7
Serious	≥ 18 years	12	4,447,500	0.3	–	–
	18 to 39 years	0	732,700	0.0	–	–
	40 to 64 years	7	1,653,300	0.4	0.2	2.5
	≥ 65 years	5	2,061,500	0.2	0.3	1.2

* Number of administered doses of influenza vaccine estimated from the 2004 national influenza survey.[16]

† Adverse events following immunisation (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 2004.

§ 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 2004 and the average (mean) reporting rate per 100,000 doses for the previous 4 years (2000–2003).

¶ Influenza immunisation rates for the 18–39 year age group were not estimated before 2004, therefore AEFI reporting rates for this age group have not been estimated for 2000–2003.

Scheduled vaccines for children aged <7 years

Dose-based AEFI reporting rates are shown in Table 7 for seven funded vaccines received during 2004 by children aged less than seven years. The overall reporting rate and those for all vaccines and categories decreased in 2004 compared with 2003. The highest AEFI reporting rate and largest change in reporting rate was for DTPa vaccine (Table 7). The reporting rate for MMR vaccine was slightly higher than the average annual rate for the previous four years (2000–2003) (Table 7).

Dose-based reporting rates of the most commonly reported AEFIs differed by vaccine type (Figure 7). Injection site reaction following DTPa vaccine was reported at a rate of 32.9 per 100,000 doses of DTPa vaccine for children aged <7 years, down from 47.9 per 100,000 doses for 2003.[8] The decrease was greatest among children aged 1 to <2 years following the removal from the immunisation schedule of the 4th dose of the vaccine, due at 18 months of age, in September 2003 (Figure 8). In 2004, only one report of a local reaction following DTPa was received for a child in this age group. The reporting rates of injection site reaction for the <1 year and 2 to <7 year age groups were 1.1 and 66.7 per 100,000 doses of DTPa vaccine, respectively.

The reporting rate of injection site reaction following MMR vaccine was highest among children aged 2 to <7 years (30 per 100,000 doses). Over 85 per cent (65/75) of these children had received DTPa and/or other vaccines at the same time as MMR but the specific injection sites of each of the vaccines were not reported or could not be differentiated.

Figure 7. Reporting rates of adverse events following immunisation per 100,000 doses of vaccine recorded on the Australian Childhood Immunisation Register, children aged <7 years, ADRAC database, 2004

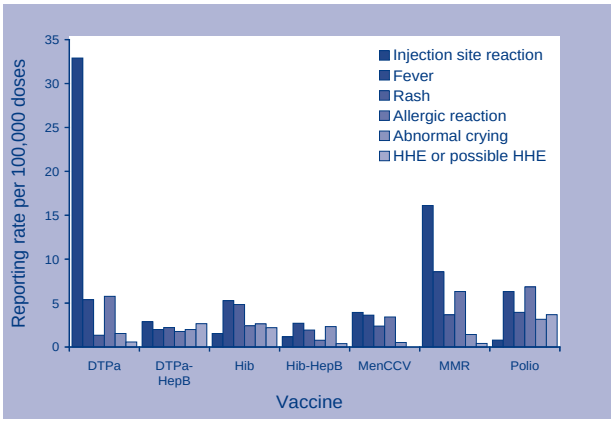


Table 7. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* children aged less than 7 years, ADRAC database

Suspected vaccine type† or AEFI category‡	AEFI records n	Vaccine doses n	Rate per 100,000 doses§		
			2004	2003	Ratio of 2004 to 4–year mean‖
DTPa	221	519,708	42.5	63.3	0.9
DTPa-HepB	65	451,793	14.4	18.5	0.6
Hib	75	454,667	16.5	21.0	0.7
Hib-HebB	19	258,483	7.4	10.7	0.5
Polio	88	964,591	9.1	14.6	0.7
MMR	146	490,500	29.8	32.0	1.2
MenCCV	106	380,023	27.9	33.3	na
Total‡	400	3,519,765	11.4	18.5	0.7
'Serious' outcome‡	30	3,519,765	0.9	1.1	0.7
'Certain' or 'probable' causality rating‡	160	3,519,765	4.5	9.2	0.6

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 January and 31 December 2004.

† Adverse events following immunisation (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.

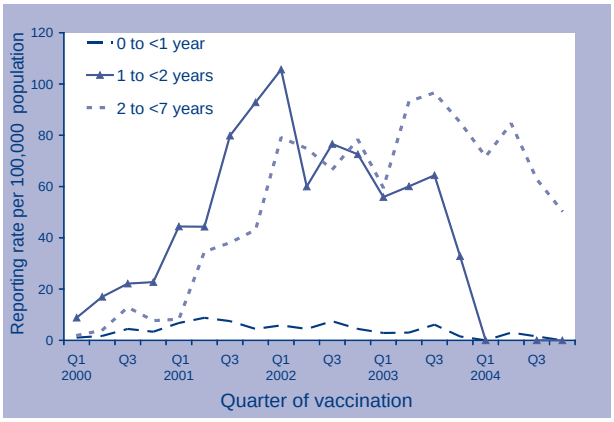
‡ AEFI category includes all records (i.e. total), those assigned 'certain' or 'probable' causality ratings, and those defined as 'serious' where at least one of the seven vaccines shown in the table was suspected of involvement in the reported adverse event. Causality ratings were assigned using the criteria described previously.[4] The definition of a 'serious' outcome is described in the Methods section.

§ 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 2004 and the average (mean) reporting rate per 100,000 doses for the previous 4 years (2000–2003).

na Not estimated as the program commenced on 1 January 2003.

Figure 8. Reporting rate of injection site reaction per 100,000 doses of DTPa vaccine, by age group and quarter of vaccination, ADRAC database, 2000 to 2004



The reporting rate for HHE following DTPa-HepB vaccine was 1.13 per 100,000 doses for children aged <1 year. This is the same as for the previous three-year period (2001–2003) of 1.12 per 100,000 doses of DTPa-HepB vaccine and 1.23 per 100,000 doses of DTPa vaccine. Only one report of HHE following DTPa vaccine was received in 2004.

Discussion

The data show that there was a significant decrease in reports of AEFIs to ADRAC in 2004 compared with 2002 and 2003. This was evident across all age groups and all states and territories except the Australian Capital Territory, and was most apparent in reports of adverse events following DTPa among children aged 1 to <2 years and MenCCV among people aged 2 to <20 years. This decrease coincides with the removal of the 4th dose of DTPa vaccine (due at 18 months of age) from the ASVS in September 2003 and the completion in most states and territories of the catch-up MenCCV immunisation program for older children and adolescents during 2004 (Figures 2 and 5).

The data demonstrate a high level of safety of vaccines in Australia, with the majority of AEFIs reported being injection site reaction and other non-serious events. The reporting rate of AEFIs defined as serious remains low (0.9 per 100,000 doses of vaccines for children aged <7 years and 0.3 per 100,000 for influenza vaccinees aged ≥18 years), while the proportion of all reported AEFIs that are defined as serious has remained at 9–10 per cent over the past five years.

Although the number of AEFI reports for MenCCV and DTPa were substantially lower in 2004 than 2003 (363 and 237 in 2004 vs 536 and 416 in 2003), they remained the most frequently suspected vaccines with injection site reactions still the most often commonly reported AEFI for both vaccines. The types of adverse events reported for both vaccines is consistent with those detected in other AEFI surveillance systems and in observational studies.[18–20] Any impact that removal of the DTPa dose due at 18 months of age from the ASVS might have on rates of injection site reaction among children receiving DTPa at 4–5 years of age will not be seen in the national AEFI surveillance data until 2006 when the first cohort of children affected by the schedule change become due for their 4th dose prior to school entry. It is expected that the total number of AEFI reports for MenCCV will decline in 2005 when the catch-up program is completed. Reporting has stabilised for the age group who receive MenCCV as part of the routine immunisation schedule at 12 months of age with six to eight reports per quarter for the 1 to <2 year age group during 2004 (Figure 5).

There has been a decrease in AEFI reporting for children aged <1 year each year for 2002–2004, following a peak in 2001 (Figure 4). The reason for this decease is unclear, as it has occurred in all states and territories and for all vaccines scheduled for this age group (data not shown). Immunisation coverage rates have not changed substantially for this age group over that time.[15] The decrease since 2001 could relate to increased reporting during 2001 following a major change to the ASVS in May 2000 with the introduction of the universal hepatitis B vaccination program (given as a monovalent vaccine at birth and combined with either DTPa or Hib at two, four and six months of age). An increase in reporting of AEFIs often occurs after the introduction of a new vaccine, followed by a decrease in reporting as providers become more familiar with the vaccine.[2,17,21]

The recent addition of 7vPCV to the National Immunisation Program in January 2005 for all children[22] and further changes to be implemented in November 2005 are likely to be reflected in AEFI reporting patterns. These changes include a national childhood varicella vaccination program[23] and replacement of the current monovalent and combination vaccines used in the infant schedule (i.e. DTPa, DTPa-HepB, Hib, Hib-HepB and polio) with a single hexavalent vaccine at two, four and six months of age.[24]

The implementation of the nationally funded 7vPCV program for all children from January 2005 has seen an increase in AEFI reports mentioning this vaccine compared with previous years (45 reports were received in the first three months of 2005 compared with a total of 72 reports for 2000–2004; data not shown). The frequency and type of adverse events following 7vPCV reported to ADRAC since 2000 are similar to those reported to the US VAERS with injection site reaction, fever, allergic reaction and irritability or fussiness the most frequently reported adverse events.[25] Data for adverse events following 7vPCV reported to ADRAC will be included in future surveillance reports.

Differences in AEFI surveillance practices among key stakeholders also affect the interpretation of AEFI trend data. In November 2002 there were major changes with the implementation of a new database and the MedDRA® dictionary used to code reaction terms. In September 2003, the definitions of some AEFIs listed in the *Australian Immunisation Handbook*, which many reporters use as a guide to notify an AEFI, were changed to reflect current opinion. These mainly affected coding and reporting of anaphylactic reaction and allergic reaction. Our assessment of the data suggests that these changes have had little impact on AEFI trends.

AEFI surveillance practices differ markedly between the states and territories and are reflected in their reporting rates (Table 1). Victoria and Tasmania consistently have the lowest AEFI reporting rates – both states request general practitioners and others to report directly to ADRAC. In contrast, the Australian Capital Territory and South Australia have significantly higher reporting rates, particularly for children aged <7 years, and have similar systems where reporting of AEFIs to the state or territory health department is requested and reporting by parents is encouraged.

AEFI surveillance is complex compared with most public health surveillance systems as there are multiple exposures and multiple outcomes of interest.[2,3,17] Further, the association between the reported exposure(s) and outcome(s) is temporal but not always causal. The quality of the information contained in AEFI notifications to ADRAC is very important as inadequate or misleading information can impact on the interpretation of AEFI surveillance data. For example, based on data from clinical trials and observational research, the apparently high reporting rate of injection site reaction following MMR vaccine in children aged 2 to <7 years could, at least partly, be attributed to co-administration of a 5th dose of DTPa vaccine and insufficient information reported to ADRAC about the sites of injection of the co-administered vaccines.

Conclusions

The benefits of immunisation in preventing disease continue to significantly outweigh the risks of immunisation-related adverse events for the Australian population. Disease notification data consistently show low rates of vaccine preventable diseases in Australia and the substantial impact of national immunisation programs in reducing the incidence, morbidity and mortality of diseases such as Hib, invasive pneumococcal disease, meningococcal C disease and measles.[26–30] AEFI surveillance data over a five year period also show consistently low reporting rates of serious AEFIs and that the most frequently reported AEFIs in Australia are injection site reaction, allergic reaction, fever and other non-serious and transient events.

This is the fourth regular report analysing AEFIs in Australia detected by the national passive surveillance system.[7–9] Regular analysis and reporting of national AEFI surveillance data collated in the ADRAC database is an important aspect of the management of Australia's immunisation programs. The data reported here demonstrate that the system is sufficiently sensitive to detect both known rarer adverse events, including HHE and thrombocytopenia, and expected changes in AEFI reporting trends, such as those related to changes in immunisation programs for DTPa and MenCCV. It is expected that the system will provide valuable information to assist in the management of the hexavalent and varicella immunisation programs that are to commence in November 2005.

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Appendix

Abbreviations of vaccine types

BCG	Bacille Calmette-Guèrin
dT	diphtheria-tetanus
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
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
Hib-HepB	combined *Haemophilus influenzae* type b and hepatitis B
JE	Japanese encephalitis virus
Men4PV	meningococcal polysaccharide tetravalent vaccine
MenCCV	meningococcal C conjugate vaccine
MMR	measles-mumps-rubella
7vPCV	7-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine
polio	poliomyelitis (oral and inactivated)

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