Surveillance of adverse events following immunisation: Australia, 2000–2002

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Abstract

The Adverse Drug Reactions Advisory Committee (ADRAC) database collates notifications of adverse events following immunisation (AEFI) from across Australia. The data were analysed for vaccines received between 1 January 2000 and 30 September 2002. Dose-based AEFI reporting rates were calculated using denominator data from the Australian Childhood Immunisation Register and annual national influenza vaccination coverage surveys. The majority of the 2,409 AEFI records analysed described non-serious events, principally injection site reactions; 10.5 per cent (n=253) described AEFIs with outcomes defined as 'serious'. Ten deaths were recorded but only one, following yellow fever vaccine, was causally related to immunisation. The average annual population-based reporting rate was 4.5 per 100,000 population. Vaccine dose-based AEFI reporting rates were 2.2 per 100,000 doses of influenza vaccine for adults aged 40 years and over and 14.6 per 100,000 doses of all scheduled vaccines for children aged less than 7 years. The most frequently reported type of adverse event was injection site reaction following receipt of an acellular pertussis-containing vaccine, particularly among children in the age groups scheduled to receive their fourth or fifth doses of the vaccine (overall reporting rate 67 per 100,000 doses). The data highlight the safety of vaccines in Australia, and illustrate both the utility of available immunisation coverage data to estimate dose-based AEFI reporting rates and the value of the ADRAC database as a surveillance tool for monitoring AEFIs nationally. *Commun Dis Intell* 2003;27:307–323.

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

Introduction

The term 'adverse event following immunisation (AEFI)' describes any serious or unexpected adverse event that occurs after immunisation that may be related to the vaccine itself or to its handling or administration.[1] An adverse event may be *coincidentally* associated with the *timing* of immunisation without necessarily being caused by the vaccine or the immunisation process.

Routine ongoing surveillance of AEFIs after a vaccine is licensed allows the detection of rare, late-onset, unexpected and population-specific adverse events that are difficult to detect in pre-licensure vaccine trials.[1,2] Surveillance also helps identify specific problems related to the manufacture, storage or administration of a vaccine, and allows monitoring of trends over time. AEFI surveillance and the regular reporting of surveillance data help build and maintain public confidence in immunisation programs.[1,2,3] This is increasingly important as the incidence of vaccine preventable diseases declines[4] as a result of successful immunisation programs, and the community focuses more on vaccine safety.[3]

Overview of passive AEFI surveillance in Australia

Australia has had a passive AEFI surveillance system in place for many years, which has undergone a number of changes over time. The Adverse Drug Reactions Unit (ADRU), which is part of the Therapeutic Goods Administration and provides the secretariat for the Adverse Drug Reactions Advisory Committee (ADRAC), has been responsible for the collation and review of all Australian AEFI notifications since May 2000. Notifications are either sent directly to the ADRU by reporters, or via state and territory health departments (Figure 1).

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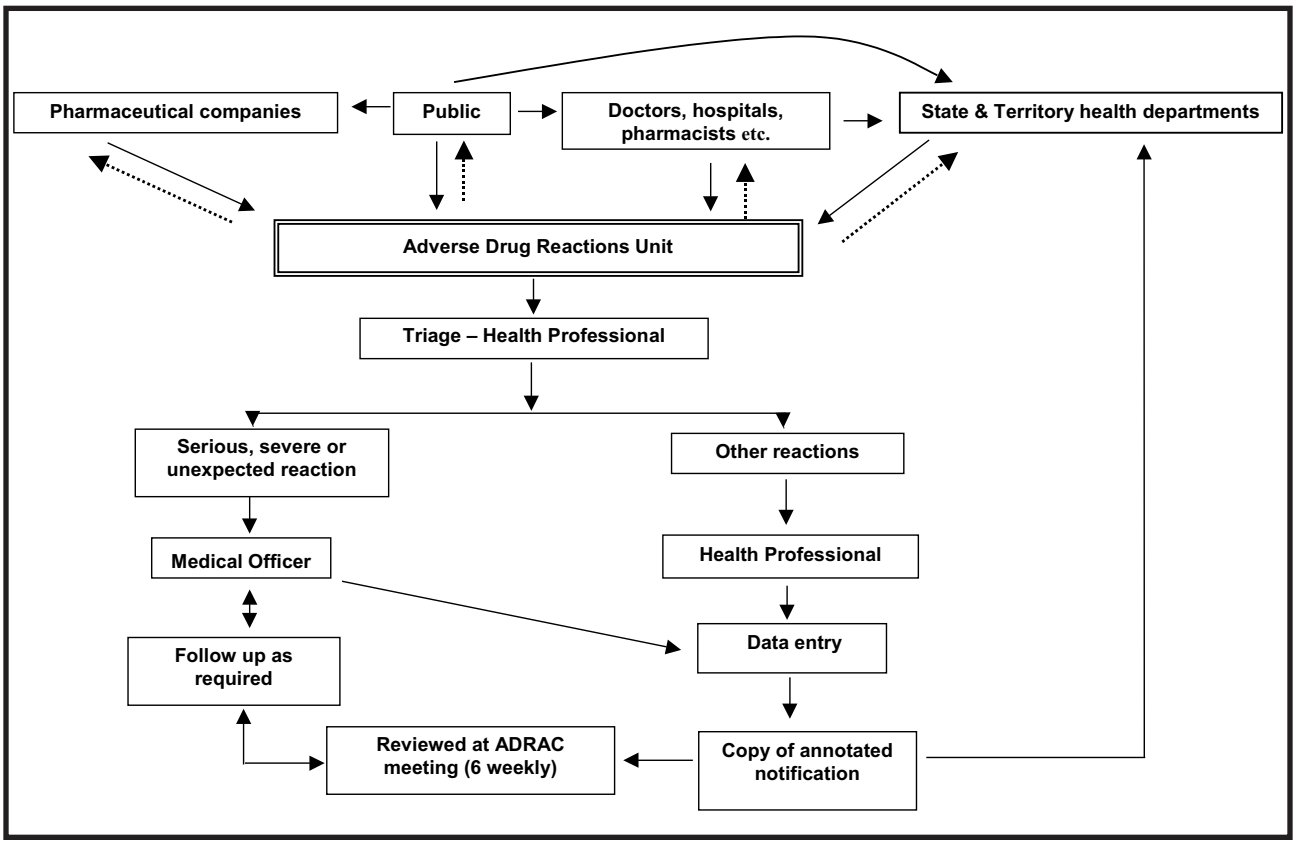
Figure 1. Flow diagram of Adverse Event Following Immunisation surveillance in Australia



Arrows indicate the directions of information transfer. Dotted lines indicate acknowledgment of receipt of an AEFI notification by the Adverse Drug Reactions Unit. All notifications are reviewed by the Adverse Drug Reactions Advisory Committee which meets at six-weekly intervals.

All state and territory health departments encourage doctors, other health professionals and members of the public to notify suspected AEFIs to a relevant authority and request notification of specific AEFIs that are listed and defined in the *Australian Immunisation Handbook*.[5] However, AEFI surveillance methods differ somewhat between the states and territories. Legislation in New South Wales, Queensland, the Northern Territory and Western Australia requires doctors and hospitals to notify the respective health department of suspected AEFIs[5] and notifications are investigated by local public health staff. In South Australia and the Australian Capital Territory, notification of AEFIs is not a legislated requirement although both jurisdictions request notification to their respective health departments and investigate notified cases. Victoria and Tasmania require all suspected AEFIs to be notified directly to the ADRU.

At the ADRU, AEFI notifications are investigated and managed following internationally consistent protocols[6,7] (Figures 1 and 2). A causality rating is assigned to each AEFI using the criteria described in the Box, which describes the level of certainty that suspected vaccines or drugs caused the reported AEFI. All AEFI notifications are reviewed by ADRAC at six-weekly committee meetings and summary data are forwarded to the World Health Organization (WHO) annually and as required.

Scope of this report

This report provides an overview of the AEFI notification data collected in the ADRAC database for vaccines received between 1 January 2000 and 30 September 2002 (33 months). The study period was chosen based on the transition to the centralised collation of all Australian AEFI reports in the ADRAC database in May 2000, and the changeover to a new ADRAC database in mid-November 2002. The time frame encompasses several important changes in childhood immunisation in Australia:

(i) universal hepatitis B vaccination was introduced into the Australian Standard Vaccination Schedule (ASVS) for babies born on or after 1 May 2000,[5]

(ii) in May 2001, the 7-valent pneumococcal conjugate vaccine (7vPCV) was added to the ASVS for children in specific risk groups;[5] and

(iii) the varicella vaccine and meningococcal C conjugate vaccine (MenCCV) became available for use in Australia in early 2000 and late 2001, respectively.

Methods

Data source

De-identified information was released to the National Centre for Immunisation Research and Surveillance for all drug and vaccine adverse event notifications entered into the ADRAC database between 1972 and 18 November 2002.

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

- a vaccine was recorded as 'suspected' of involvement in the reported adverse event *and*
- either

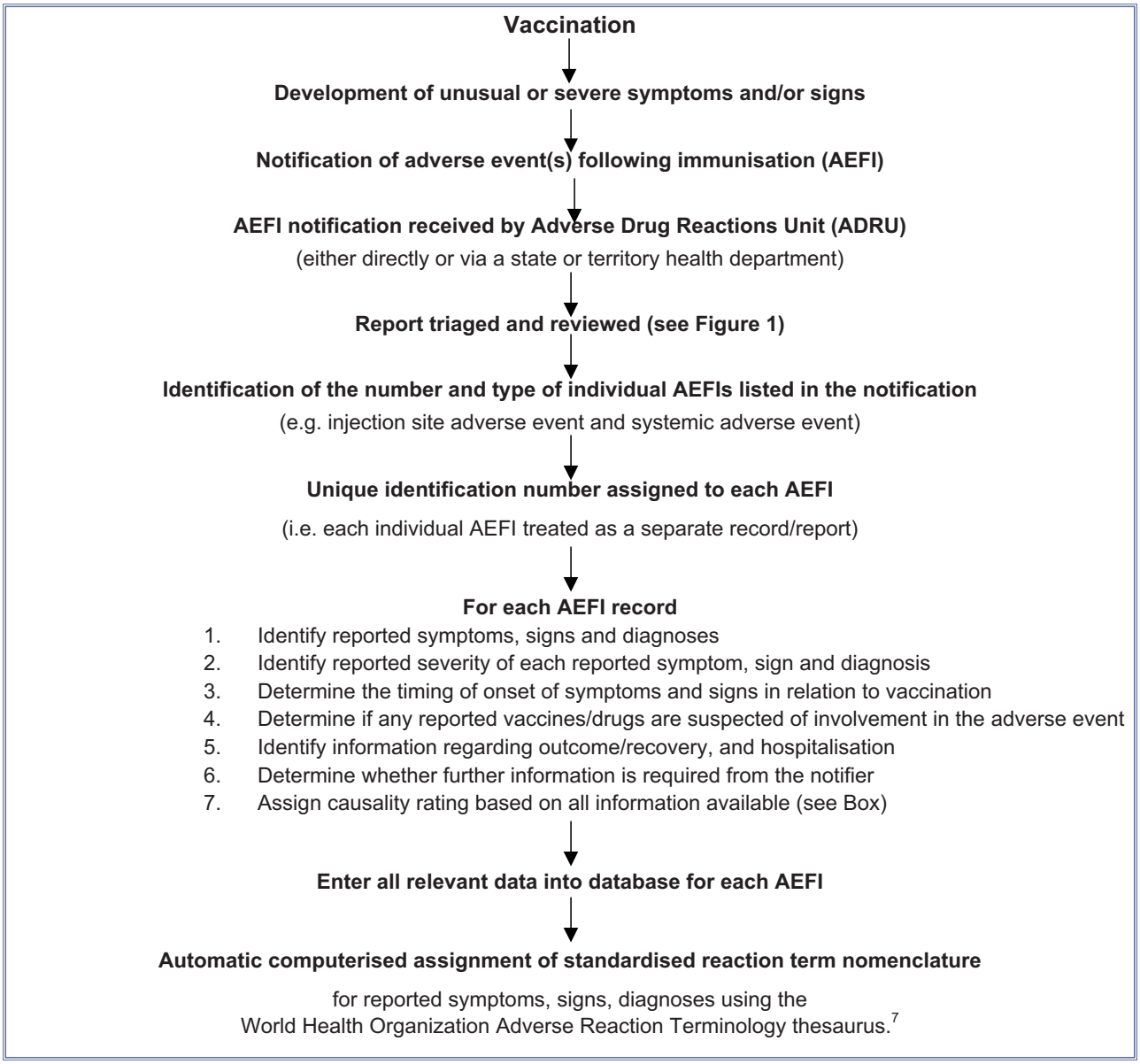
  a) the vaccination occurred between 1 January 2000 and 30 September 2002

  or

  b) if no vaccination date was recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 30 September 2002.

It was not possible to identify and link AEFI records* that arose from the same AEFI notification. Nevertheless, the number of notifications that generated the AEFI records included in the analysis was estimated from information provided by ADRU staff and by comparison of the dates of birth, onset and notification for a subset of AEFI records in the database.

Figure 2. Flow chart showing processing of notifications of adverse events following immunisation by staff of the Adverse Drug Reactions Unit



* Note that the terms 'AEFI record' and 'AEFI notification' have specific meanings in this report. One 'AEFI notification' (a report to a relevant authority) may generate more than one 'AEFI record' in the ADRAC database if a number of adverse events are described in the notification (e.g. a local injection site adverse event and a systemic adverse event – Figure 2). This report is based on 'AEFI records'.

Box. Criteria used to determine the causality rating* of a notified adverse event

The basic criteria used by the Adverse Drug Reactions Advisory Committee in determining causality ratings are consistent with international World Health Organization criteria and are as follows:

Certain

(a) A reaction in association with a single drug/vaccine which is confirmed by re-challenge; or

(b) reaction in association with a single drug/vaccine which is confirmed by laboratory data specifically implicating that drug/vaccine; or

(c) reaction whose onset is immediately following the administration of a single drug/vaccine (within five minutes if injection was the method of administration); or

(d) reaction with a precise spatial correlation with the administration of a single drug/vaccine (e.g. at the exact site of injection).

Probable

(a) A reaction with a close temporal or spatial (e.g. skin) correlation with the administration of a single drug/vaccine; or

(b) reaction is in reasonable temporal association with a single drug/vaccine and recovery on withdrawal of the drug/vaccine if no other drug/vaccine is withdrawn and no therapy given; or

(c) an uncommon clinical phenomenon associated with the administration of a single drug/vaccine and the reasonable exclusion of other factors.

Possible

(a) An alternative explanation exists; or

(b) more than one drug/vaccine is suspected† in association with the adverse event; or

(c) data are incomplete; or

(d) recovery follows withdrawal of more than one drug/vaccine; or

(e) the time relationship is not clear; or

(f) the outcome of the reaction is not recorded; or

(g) recovery follows therapy in addition to withdrawal of the drug/vaccine.

* Modified from information provided by the Adverse Drug Reactions Advisory Committee.

† ADRAC will always code as suspected, the drug/vaccine implicated by the notifier of the suspected adverse event. On some occasions, however, the Committee may suspect other drugs/vaccines whose commencement has a reasonable temporal relationship with the onset of the event.

Study definitions of AEFI outcomes and reactions

AEFI outcomes were defined as 'serious' or 'non-serious' using information recorded in the ADRAC database and criteria similar to those used by the World Health Organization[6] and the United States of America (US) Vaccine Adverse Events Reporting System (VAERS).[8] An AEFI was defined as 'serious' if the record indicated that the person had recovered with sequelae, required attendance or treatment at a hospital, experienced a life-threatening event, or died.

Typically, each AEFI record listed multiple symptoms, signs and diagnoses, and their equivalent World Health Organization standardised adverse reaction terms. The WHO standardised terms were used to create a set of reaction categories for analysis. First, reaction terms were grouped to create reaction categories analogous to the AEFIs listed and defined in the *Australian Immunisation Handbook*.[5] The categories were less specific than those defined in the *Australian Immunisation Handbook* because the investigators had to rely on information recorded in the ADRAC database rather than complete clinical notes. Specific reaction categories were then created for all remaining WHO reaction terms that were mentioned in more than 1 per cent of AEFI records. Finally, terms mentioned in less than 1 per cent of AEFI records were grouped into broader reaction categories based on the organ system where the reaction was manifested (e.g. other-gastrointestinal, other-neurological). A panel of four clinicians with expertise in AEFIs and two epidemiologists reviewed the reaction category definitions.

Data analysis

All data analyses were performed using the SAS version 8.02 computer program.[9] The distribution of AEFI records was analysed by age, gender, jurisdiction and type of reporter (e.g. health department, doctor, public). Average annual population-based reporting rates were calculated for each state or territory and by age group using 2001 mid-year census data obtained from the Australian Bureau of Statistics.

The frequency and age distribution of AEFI outcomes and reaction term categories were calculated. The frequency of each vaccine listed as 'suspected' of involvement in the reported adverse event was also calculated. The age distribution and the proportion of AEFI records for each vaccine was calculated 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 7 years for seven childhood ASVS vaccines (DTPa, DTPa-hepB, Hib, Hib-hepB, hepB, polio and MMR), and for adults aged 40 years and over for influenza vaccine. The number of administered doses of each of the seven childhood ASVS vaccines was calculated from the Australian Childhood Immunisation Register (ACIR), a national population-based register of >99 per cent of children aged less than 7 years. Vaccine doses administered between 1 January 2000 and 30 September 2002 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 2000, 2001 and 2002 annual national influenza coverage surveys[10,11,12] and mid-2001 population estimates for the 40–64 years and 65 years age groups. Dose-based AEFI reporting rates could not be determined for other vaccines and age groups due to the lack of reliable denominator data for the number of vaccine doses distributed or administered.

Results

There were 2,409 AEFI records entered into the ADRAC database where the date of vaccination or onset of a reported adverse event occurred between 1 January 2000 and 30 September 2002. This corresponded to approximately 2,050 AEFI notifications, and indicates that approximately 15 per cent of AEFI notifications generated more than one AEFI record.

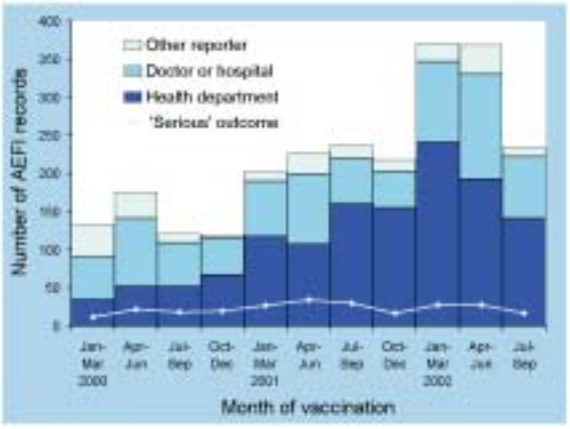
Two hundred and fifty-three AEFI records (10.5%) were defined as 'serious' (i.e. recovery with sequelae, requiring hospital treatment, experiencing a life-threatening event or death). In total, 1,041 (43%) AEFI records were assigned causality ratings of 'certain' (n=939) or 'probable' (n=102).

AEFI reporting sources and trends

The distribution, sources and population-based reporting rates of AEFIs for each state or territory are shown in Table 1. The overall average annual AEFI reporting rate was 4.5 per 100,000 population. This increased from 2.8 per 100,000 population for the 12 months January–December 2000 to 6.1 per 100,000 population for the 12 months October 2001–September 2002. The average annual population-based AEFI reporting rates varied considerably between the states and territories. Generally, the more populous jurisdictions (i.e. New South Wales, Victoria, Queensland) had the lowest AEFI reporting rates. Reporting rates for AEFIs assigned a 'certain' or 'probable' causality rating, or those defined as 'serious', were less variable across jurisdictions than the overall AEFI reporting rates. The relative contribution of each type of reporter (i.e. health department, doctor/hospital, other) varied by jurisdiction and was related to jurisdictional differences in AEFI notification requirements.

The distribution of AEFI records by quarter of vaccination is shown in Figure 3. The number per quarter ranged from 133 records in January–March 2000 to 371 in January–March 2002 (median: 218). Trends over time by type of reaction category and vaccine type are shown in Figures 4 and 5 and described later in the report. Although the proportion

Figure 3. Reporter type and outcome records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002, by month of vaccination



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

Table 1. Distribution and population-based reporting rates of adverse events following immunisation ADRAC database, 1 January 2000 to 30 September 2002, by jurisdiction

Jurisdiction	AEFI records		Rate per 100,000 population*			Reporter type		
			Overall	'Certain' or 'probable' causality rating†	'Serious' outcome‡	Health department	Doctor or hospital	Other§
	n	%				%	%	%
Australian Capital Territory	194	8.1	22.5	5.8	0.8	93	7	<1
New South Wales	544	22.6	3.0	1.3	0.5	53	43	3
Northern Territory	86	3.6	15.8	7.0	1.3	81	13	6
Queensland	305	12.7	3.1	1.3	0.3	48	47	5
South Australia	448	18.6	10.8	5.7	0.5	78	22	<1
Tasmania	30	1.2	2.3	1.2	0.2	0	97	3
Victoria	349	14.5	2.6	1.1	0.3	11	78	12
Western Australia	299	12.4	5.7	2.9	0.4	83	15	2
Australia¶	154	6.4	na	na	na	na	na	na
Total	2,409	100	4.5	2.0	0.5	55	35	10

AEFI Adverse event following immunisation.

* Average annual rates per 100,000 population, calculated using 2001 mid-year population census data (Australian Bureau of Statistics).

† See the Box for criteria used to assign causality ratings.

‡ AEFI records defined as 'serious' (see Methods and Table 3).

§ Includes reports from pharmacists (n=21), the public (n=78) and pharmaceutical companies (n=143).

|| Percentages were calculated using the number of reports for the specific jurisdiction as the denominator e.g. 93 per cent of the 194 AEFI reports from the Australian Capital Territory were reported to ADRAC by the health department, 7 per cent by doctors or hospitals and < 1 per cent by other reporters.

¶ Records where the jurisdiction in which the AEFI occurred was not reported or was unclear. These included AEFIs notified by pharmaceutical companies (n = 143) and by the Australian Vaccination Network (n=11).

na Not applicable

of AEFIs reported by state and territory health departments increased from May 2000 onwards, when jurisdictional reporting to the ADRU commenced, the number defined as 'serious' remained relatively constant (median 22; range 12–34 per quarter).

Age and gender distribution

In all, 62 per cent (n=1,496) of AEFI records involved children aged less than 7 years. The average annual population-based reporting rates were highest for children aged less than two years, the age group that receives the greatest number vaccinations (Table 2). Overall, there were more AEFI records for females, although the male to female ratio differed by age group (Table 2).

AEFI outcomes and reactions

The majority of records were defined as 'non-serious' (55%) while 10.5 per cent had outcomes defined as 'serious' (Table 3). Fewer 'serious' AEFIs were assigned 'certain' or 'probable' causality ratings compared with 'non-serious' AEFIs (23% versus 46%). Death was recorded as the outcome in

Table 2. Age and gender distribution of records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002

Age group (years)	Total		Male to female ratio	Rate* per 100,000 population
	n	%		
<1	442	18.3	1:0.8	62.5
1 to <2	632	26.2	1:0.8	89.7
2 to <7	422	17.5	1:0.8	11.7
7 to <20	152	6.3	1:1.4	1.6
20 to <65	503	20.9	1:3.0	1.6
65	209	8.7	1:2.2	3.1
Unknown	49	2.0	1:2.3	na
Total	2,409	100.0	1:1.2	4.5

* Average annual rate estimated using mid-2001 population census data (Australian Bureau of Statistics).

na Not applicable.

10 AEFI records (Table 3). Only one death (an adult who received a yellow fever vaccination) was thought to be causally related to vaccination[13,14] Thirty-four per cent of AEFI records were either missing relevant information (10%) or indicated that the person had not recovered at the time of notification (24%). Many of the latter group are likely to be reports of injection site reactions that had not resolved at the time of the notification.

The distribution and frequency of reactions mentioned in AEFI records 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. Injection site reactions were the most commonly mentioned category of reaction (n=1,072 or 42% of AEFI records), both overall and among the AEFIs of interest listed in the *Australian Immunisation Handbook*[5] (Table 4). This was followed by fever (18%), rash (16%) and allergic reactions (10%). There was a large increase over time in the number of AEFI records involving injection site reactions compared with those involving fever, rash and allergic reactions (Figure 4). The peak in notifications of injection site reactions for vaccines received in the first six months of 2002, shown in Figure 4, corresponds in time with the peak in the number of AEFI records shown in Figure 3.

Figure 4. Frequently reported reactions by month of vaccination, records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002

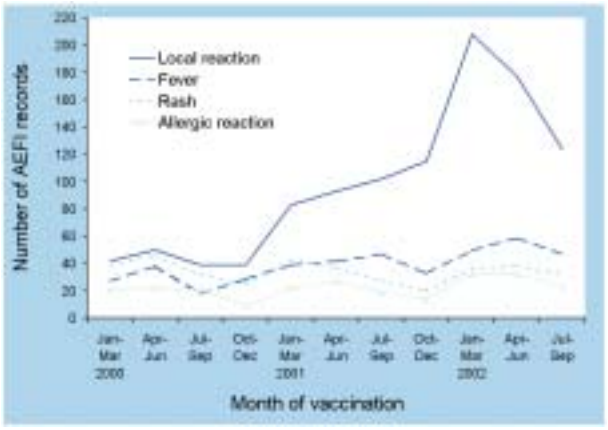


Table 3. Outcomes shown in records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002

Outcome	AEFI records		'Certain' or 'probable' causality rating†		Age group‡			
					< 7 years		7 years	
	n	%	n	%§	n	%§	n	%§
Non-serious: total	1,333	55.3	611	46	885	66	430	32
Not recovered at time of report	576	23.9	259	45	309	54	253	44
Not known (missing data)	247	10.3	113	46	160	65	78	32
Serious	253	10.5	58	23	142	56	103	41
recovered with sequelae	7		4		3	43	4	57
hospital admission	210		46		120	57	84	40
emergency department	21		8		12	57	8	38
life-threatening event	29		6		13	45	15	52
death	10		1		5	50	5	50
Total	2,409	100	1,041	43	1,496	62	864	36

AEFI Adverse event following immunisation.

* Percentages relate to the total number of adverse event following immunisation (AEFI) records (n=2,409).

† Causality ratings were assigned to AEFI records using criteria described in the Box.

‡ AEFI records where age or date of birth was not recorded are not shown.

§ Percentages relate to the number of AEFI records with the specific outcome, e.g. of 1,333 AEFI records with a 'non-serious' outcome, 46 per cent had causality ratings of 'certain' or 'probable' and 66 per cent were for children aged less than 7 years.

|| Categories are not mutually exclusive; an AEFI record may be counted in more than one 'serious' category (e.g. 'life-threatening event' and 'hospital treatment').

Table 4. Reactions of interest* listed in records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002

Reaction*	AEFI records	Single reaction reported†		Certain/probable causality rating‡		Age group§			
						<7 years		7 years	
	n	n	%	n	%	n	%	n	%
Injection site reaction	1,072	767	72	885	83	753	70	305	28
Fever	429	48	11	59	14	294	69	125	29
Rash	377	85	23	96	25	256	68	117	31
Allergic reaction	242	64	26	58	24	110	45	127	52
Abnormal crying	123	32	26	11	9	122	99	0	0
Convulsions	70	16	23	9	13	58	83	11	16
Lymphadenopathy/itis¶	54	13	24	18	33	22	41	30	56
Arthralgia	51	4	8	9	18	5	10	44	86
HHE**	33	13	39	8	24	30	91	1	3
hypotonia/hypokinesia**	41	3	7	4	10	36	88	3	7
Anaphylactoid reaction††	20	8	40	7	35	3	15	13	65
Arthritis	20	5	25	0	0	1	5	19	95
Abscess	16	12	75	13	81	11	69	5	31
Thrombocytopenia	11	1	9	1	9	5	45	6	55
Death	10	4	36	1	9	5	45	5	45
Encephalopathy	9	2	22	3	33	3	33	6	67
Brachial neuritis	4	2	50	1	25	0	0	4	100
Meningitis	4	2	50	0	0	3	75	1	25
Orchitis	4	2	50	0	0	0	0	4	100
Encephalomyelitis	3	0	0	0	0	1	33	2	67
Guillain-Barré syndrome	3	1	33	0	0	0	0	3	100
Parotitis	3	2	67	0	0	2	67	1	33
Sepsis	2	0	0	1	50	0	0	2	100
Osteomyelitis	1	0	0	0	0	1	100	0	0
Acute flaccid paralysis	0	0	0	0	0	0	0	0	0
Osteitis	0	0	0	0	0	0	0	0	0
SSPE‡‡	0	0	0	0	0	0	0	0	0
Toxic shock syndrome	0	0	0	0	0	0	0	0	0

AEFI Adverse event following immunisation.

* Reaction term variables were created for the AEFIs of interest listed in the *Australian Immunisation Handbook*, 7th edition, p 22–3 and 271–5[5] as described in Methods section.

† AEFI records where only one reaction was reported.

‡ See the Box for causality criteria.

§ AEFI records not shown if age or date of birth was missing.

|| Percentages relate to the number of AEFI records in which the specific reaction term was listed, e.g. of 1,072 AEFI records listing injection site reaction, 72 per cent listed only one type of reaction while 83 per cent had causality ratings of 'certain' or 'probable' and 70 per cent were for children aged less than 7 years.

¶ Includes lymphadenitis following BCG vaccination (n=2) and the more general term of 'lymphadenopathy'.

** Hypotonic-hyporesponsive episode (HHE). The separate reaction term of 'hypotonia/hypokinesia' indicates records where 'HHE' was not listed but other terms describing an HHE or similar event were.

†† Includes anaphylactoid reactions plus events reported as 'anaphylaxis' but coded in the database as 'anaphylactoid reaction'.

‡‡ Subacute sclerosing panencephalitis.

Table 5. 'Other'* reactions listed in records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002

Reaction*	AEFI records	Single reaction reported†		Certain/probable causality rating‡		Age group§			
						<7 years		7 years	
	n	n	%	n	%	n	%	n	%
Vomiting	117	5	4	10	9	72	62	43	37
Headache	110	5	5	19	17	8	7	99	90
Malaise	109	8	7	21	19	31	28	72	66
Fatigue	100	1	1	20	20	36	36	60	60
Nausea	97	3	3	22	23	9	9	81	84
Pain (nos)	85	2	2	60	71	34	40	50	59
Irritability	78	5	6	10	13	78	100	0	0
Pallor	78	2	3	16	21	58	74	18	23
Myalgia	75	3	4	11	15	4	5	69	92
Oedema (nos)	62	3	5	43	69	36	58	26	42
Diarrhoea	52	10	19	6	12	30	58	19	37
Increased sweating	50	0	0	16	32	10	20	40	80
Dizziness	46	3	7	15	33	1	2	44	96
Anorexia	45	0	0	6	13	31	69	13	29
Somnolence	42	1	2	5	12	33	79	9	21
Coughing	41	1	2	3	7	21	51	20	49
Varicella or herpes zoster	41	18	44	0	0	25	61	13	32
Purpura	38	5	13	20	53	32	84	6	16
Dyspnoea	37	1	3	9	24	14	38	21	57
Abdominal pain	35	0	0	3	9	11	31	23	66
Rhinitis	35	2	6	3	9	18	51	16	46
Syncope	34	5	15	9	26	10	29	21	62
Paraesthesia	30	3	10	9	30	0	0	29	97
Influenza-like illness	29	4	14	5	17	9	31	18	62
Pharyngitis	28	1	4	1	4	10	36	17	61
Agitation	27	3	11	3	11	23	85	3	11
Flushing	27	0	0	12	44	7	26	20	74
Chest pain	24	1	4	6	25	0	0	23	96
Other – neurological	105	7	7	19	18	48	46	56	53
Cardiovascular	80	5	6	16	20	38	48	38	48
Body as a whole	62	5	8	12	19	20	32	41	66
Special senses	61	2	3	9	15	17	28	40	66
Respiratory	58	7	12	7	12	33	57	24	41
Gastrointestinal	49	5	10	10	20	12	24	35	71
Psychological	33	2	6	7	21	13	39	19	58
Skin	31	2	6	7	23	14	45	17	55
Inflammation	21	2	10	3	14	13	62	8	38
Metabolic/endocrine	19	2	11	1	5	7	37	12	63
Musculo-skeletal	17	1	6	5	29	4	24	13	76
Haematological	14	1	7	2	14	2	14	12	86
Renal/urogenital	9	0	0	1	11	1	11	8	89
Miscellaneous	7	3	43	0	0	5	71	2	29

* Reaction terms not listed in the *Australian Immunisation Handbook*[5] but included in adverse event following immunisation (AEFI) records in the ADRAC database. The top part of the table shows reaction terms included in 1 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 1 per cent of AEFI records.

† AEFI records where only one reaction was reported.

‡ See the Box for causality criteria.

§ AEFI records not shown if age or date of birth was missing.

|| Percentages relate to the number of AEFI records in which the specific reaction term was listed e.g. of 1,072 AEFI records listing injection site reaction, 72 per cent listed only one type of reaction while 83 per cent had causality ratings of 'certain' or 'probable' and 70 per cent were for children aged less than 7 years.

nos Not otherwise specified.

Of reactions not listed in the *Australian Immunisation Handbook,* gastrointestinal symptoms of nausea, vomiting and diarrhoea were the most frequently recorded (Table 5). Reactions mentioned in less than 1 per cent of AEFI records are shown grouped by organ system category in the lower portion of Table 5. Neurological symptoms and signs were the most commonly reported category; the most frequent were hypoaesthesia (n=13) and tremor (n=11).

Vaccines and AEFI

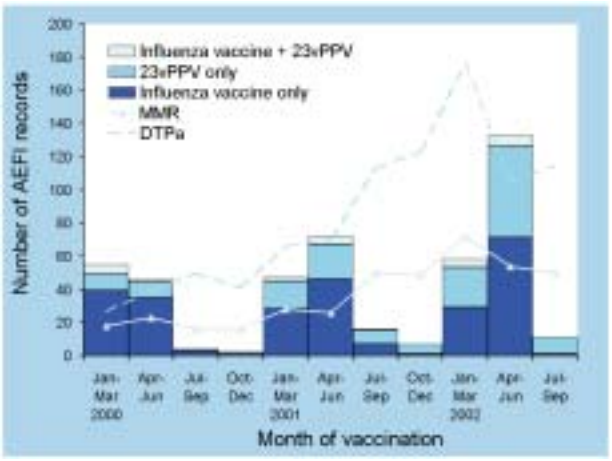
Twenty-nine vaccines were recorded as 'suspected' of involvement in the adverse events described in the 2,409 AEFI records analysed (Table 6). They included all vaccines recommended in the ASVS, plus vaccines recommended to travellers and specific risk groups (e.g. hepatitis A, Japanese encephalitis and Q fever vaccines) and the more recently licensed vaccines such as the varicella and meningococcal C conjugate vaccines.

The most frequently suspected group of vaccines were those containing pertussis, diphtheria and tetanus antigens (i.e. DTPa and DTPa-hepB); suspected in 1,163 (48%) reports (Table 6). Influenza (n=289) and 23-valent polysaccharide pneumococcal (23vPPV) (n=173) vaccines were suspected in the majority of AEFI records for people aged 7 years and over. The proportion of AEFI records where only one vaccine was suspected of involvement in the reported adverse event differed by vaccine, as did the proportion assigned causality ratings of 'certain' or 'probable', or defined as 'serious' (Table 6).

Table 7 focuses on AEFIs defined as 'serious'. The proportion of 'serious' AEFI records assigned causality ratings of 'certain' or 'probable' varied by vaccine. While Hib and polio vaccines were among the most frequently listed vaccines in 'serious' AEFI records, only a small proportion of these records were assigned 'certain' or 'probable' causality ratings (Table 7).

AEFI reporting trends over time differed by vaccine (Figure 5). The peaks in reported adverse events following vaccination in the first six months of 2002, shown in Figure 3, corresponded with a seasonal peak in AEFIs reported for influenza and/or 23vPPV vaccines among adults (Figure 5) and an increasing number of AEFIs reported for DTPa vaccine among children. The peaks in AEFIs reported for DTPa and MMR vaccinations in January–March 2002 corresponds to the commencement of the school year. A larger number of vaccinations are given at this time of the year than at other times (data not shown).

Figure 5. Selected frequently suspected vaccine types records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002, by month of vaccination



Abbreviations of vaccine types are listed in the appendix.

Dose-based AEFI reporting rates

Scheduled vaccines for children aged <7 years

Dose-based AEFI reporting rates for children aged less than 7 years for seven scheduled vaccines are shown in Table 8. Reporting rates differed by age and vaccine type. Much of the difference in reporting rates across age groups was attributable to DTPa vaccine. The apparently high AEFI reporting rate for children aged less than one year for MMR vaccine (54.2 records per 100,000 recorded doses) was estimated from only 15 records, all for children aged 11 months at the time of vaccination. Similarly, the rate for DTPa-hepB vaccine for children aged 1 to <2 years was estimated from only 10 AEFI records (Table 8).

Dose-based rates of the most commonly reported reaction types differed by vaccine type (Figure 6). Injection site reactions were reported for DTPa vaccine at a rate of 27.9 per 100,000 recorded doses, compared with rates of less than 8 per 100,000 recorded doses for other vaccines. The higher overall dose-based AEFI reporting rates for DTPa vaccine and for children aged over one year were related to injection site reactions (Figure 7). Dose-based reporting rates of injection site reactions following DTPa vaccination were 69 per 100,000 for children aged 1 to <2 years and 64 per 100,000 for children aged 2 to <7 years. These ages correspond to the timing of the fourth and fifth doses, respectively, of a DTPa vaccine.

Table 6. Vaccine types listed as 'suspected' in records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002

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	923	565	61	498	54	54	6	915	99	4	< 1
Hib	419	31	7	37	9	67	16	412	98	0	0
MMR	336	125	37	49	15	49	15	293	87	37	11
Polio	326	8	2	9	3	50	15	299	92	22	7
Influenza	289	257	89	110	38	43	15	0	0	275	95
DTPa-hepatitis B	240	58	24	54	23	36	15	234	98	1	< 1
23vPPV	173	144	83	99	57	19	11	8	5	160	92
Hepatitis B	145	117	81	51	35	23	16	37	26	101	70
Varicella	128	109	85	15	12	19	15	89	70	35	27
dT	100	85	85	63	63	5	5	2	2	96	96
Hib-hepatitis B	59	10	17	8	14	6	10	59	100	0	0
MenCCV	46	46	100	18	39	5	11	30	65	15	33
Q fever	37	37	100	21	57	5	14	1	3	36	97
Hepatitis A	34	19	56	2	6	6	18	2	6	32	94
Hepatitis A+B	32	25	78	7	22	1	3	2	6	28	88
Typhoid	27	10	37	1	4	6	22	0	0	27	100
JE	26	18	69	6	23	3	12	0	0	26	100
Pneumococcal (nos)	22	16	73	11	50	3	14	5	23	17	77
Rabies	17	10	59	1	6	2	12	0	0	17	100
Yellow fever	14	5	36	1	7	5	36	0	0	14	100
Tetanus	10	10	100	6	60	0	0	1	10	8	80
BCG	7	6	86	2	29	0	0	3	43	3	43
Men4PV	6	1	17	0	0	2	33	0	0	6	100
7vPCV	5	0	0	0	0	1	20	5	100	0	0
Cholera	4	1	25	1	25	0	0	0	0	4	100
Measles-mumps	4	0	0	0	0	0	0	3	75	1	25
Meningococcal (nos)	4	2	50	1	25	0	0	2	50	2	50
Rubella	2	2	100	1	50	0	0	1	50	1	50
Pertussis	1	1	100	0	0	1	100	1	100	0	0
Total**	2,409	1,717	71	1,041	43	253	11	1,496	62	864	36

AEFI Adverse event following immunisation.

* See appendix for abbreviations of vaccine types.

† 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 in the Box.

§ 'Serious' outcomes are defined in the Methods section (see Table 3 also).

|| AEFI records not shown if age or date of birth was missing.

¶ Percentages are calculated for the number of AEFI records where the specific vaccine was suspected of involvement in the AEFI, e.g. DTPa vaccine was listed as 'suspected' in 923 AEFI records; this was the only suspected vaccine in 61 per cent of the 923 AEFI records, 54 per cent had 'certain' or 'probable' causality ratings, 6 per cent were defined as 'serious' and 99 per cent were for people aged less then 7 years.

** Total number of AEFI records analysed, not the total in each column.

Table 7. Causality ratings of adverse events following immunisation defined as 'serious', ADRAC database, January 2000 to September 2002, by suspected vaccine type and age group

Suspected vaccine type*	'Serious' outcome†	'Certain' or 'probable' causality rating‡		Total
		Age group§		
		< 7 years	7 years	
	n	n	n	n
Hib	67	4	0	4
DTPa	54	10	0	10
Polio vaccine	50	1	0	1
MMR	49	5	0	6§
Influenza	43	0	7	9§
DTPa-hepB	36	5	0	5
HepB	23	2	6	8
23vPPV	19	0	7	7
Varicella	19	2	2	4
HepA	6	0	0	0
Hib-hepB	6	0	0	0
Typhoid	6	0	0	0
Q fever	5	0	2	2
dT	5	0	1	1
MenCCV	5	1	0	1
Yellow fever	5	0	1	1
JE	3	0	1	1
Pneumococcal¶	3	0	1	1
Meningococcal¶	2	0	1	1
Rabies	2	0	0	0
Hepatitis A + B	1	0	1	1
Pertussis	1	0	0	0
7vPCV	1	0	0	0
Total	253	27	28	58§

AEFI Adverse event following immunisation

* The vaccine type was recorded as 'suspected' of involvement in the reported adverse event. See appendix for abbreviations of vaccine types.

† AEFI records defined as 'serious' (see Table 3 and Methods).

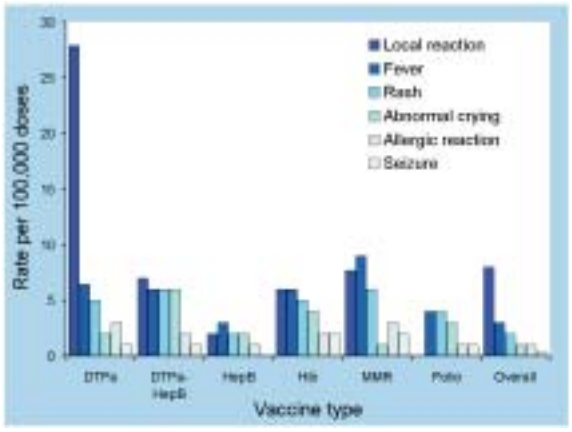
‡ Causality ratings were assigned to AEFI records using the criteria described in the Box.

§ AEFI records not shown where age or date of birth was missing.

Total number of AEFI records analysed, not the total in each column.

¶ Not otherwise specified.

Figure 6. Rates of frequently reported reactions per 100,000 vaccine doses administered to children aged less than 7 years for recommended vaccine types, records of adverse events following immunisation, ADRAC database, 1 January 2000 to 30 September 2002



Abbreviations of vaccine types are listed in the appendix.

Figure 7. Rates of selected frequently reported adverse per 100,000 administered doses of DTPa, ADRAC database, 1 January 2000 to 30 September 2002, by age group (DTPa dose number)

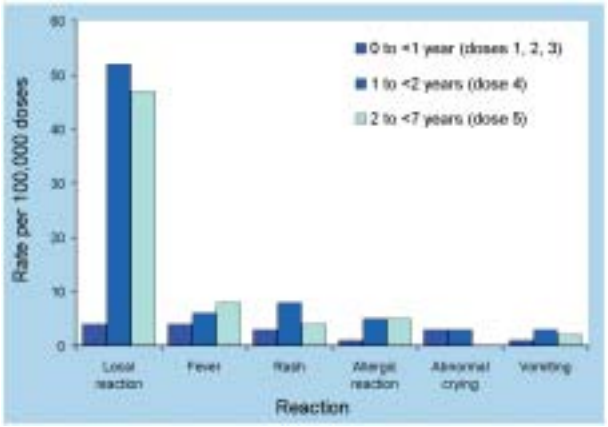


Table 8. Reporting rates of adverse events following immunisation per 100,000 vaccine doses* for children aged less than 7 years, ADRAC database, 1 January 2000 to 30 September 2002

Suspected vaccine type† or AEFI category‡		Age group (years)			Overall
		<1	1 to <2	2 to <7	
DTPa	AEFI records (n)§	153	451	311	915
	Vaccine doses (n)*	1,026,027	650,740	483,820	2,160,587
	Rate per 100,000 doses	14.9	69.3	64.3	42.3
DTPa-hep B	AEFI records (n)	217	10	na	227
	Vaccine doses (n)	891,482	10,237	na	901,719
	Rate per 100,000 doses	24.3	97.7	na	25.2
Hib	AEFI records (n)	239	162	11	412
	Vaccine doses (n)	1,518,623	596,402	34,983	1,784,257
	Rate per 100,000 doses	15.7	27.2	31.4	23.1
Hib-hebB	AEFI records (n)	44	13	na	57
	Vaccine doses (n)	365,751	103,676	na	469,427
	Rate per 100,000 doses	12.0	12.5	na	12.1
HepB¶	AEFI records (n)	21	6	10	37
	Vaccine doses (n)	212,871	75,415	66,671	354,957
	Rate per 100,000 doses	9.9	8.0	15.0	10.4
Polio	AEFI records (n)	230	8	64	302
	Vaccine doses (n)	1,914,883	34,630	446,130	2,395,643
	Rate per 100,000 doses	12.0	23.1	14.3	12.6
MMR	AEFI records (n)	15	129	150	294
	Vaccine doses (n)	27,678	629,062	448,458	1,105,198
	Rate per 100,000 doses	54.2	20.5	33.4	26.6
Total‡	AEFI records (n)	409	589	345	1,339
	Vaccine doses (n)	5,591,564	2,100,162	1,480,062	9,168,788
	Rate per 100,000 doses	7.3	28.0	23.3	14.6
'Certain' or 'probable' causality rating‡	AEFI records (n)	86	306	194	586
	Vaccine doses (n)	5,591,564	2,100,162	1,480,062	9,168,788
	Rate per 100,000 doses	1.5	14.6	13.1	6.4
'Serious' outcome‡	AEFI records (n)	61	50	19	130
	Vaccine doses (n)	5,591,564	2,100,162	1,480,062	9,168,788
	Rate per 100,000 doses	1.1	2.4	1.3	1.4

AEFI Adverse event following immunisation

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 January 2000 and 30 September 2002.

† 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 shown in the Box1. The definition of a 'serious' outcome is described in the Methods section.

§ Number of AEFI records in which the vaccine was coded as 'suspected' and the vaccination was administered between 1 January 2000 and 30 September 2002.

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

¶ Includes the birth dose of hepatitis B vaccine.

na Not applicable as the vaccine is not recommended in the Australian Standard Vaccination Schedule for children aged 2 to < 7 years.

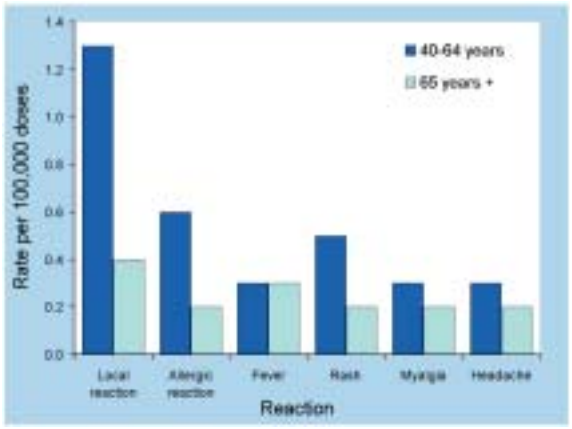
Influenza vaccine and adults aged ≥ 40 years

Influenza vaccine was suspected of involvement in 289 AEFI records. Of these, 205 (71%) were for people aged 40 years and over. The dose-based AEFI reporting rates are shown in Table 9 and Figure 8. Rates were higher among vaccinees aged 40 to 64 years than among the older age group. The most frequently reported adverse events following influenza vaccination were injection site reactions and allergic reactions (0.7 and 0.4 per 100,000 doses, respectively). There were three reports of Guillain-Barré syndrome following influenza vaccination (Table 4).[8] This is a reporting rate of approximately 0.03 per 100,000 doses or 3.2 per 10 million doses.

Discussion

This report analysing AEFI notifications to the ADRU over a period of 33 months highlights the safety of vaccines in Australia. Over 9 million doses of seven ASVS vaccines were administered to children aged less than 7 years and a similar number of influenza vaccine doses were administered to adults 40 years and over during the 33-month period. The corresponding dose-based AEFI reporting rates were 14.6 per 100,000 doses of scheduled vaccine doses for children under 7 years and 2.2 per 100,000 doses of influenza vaccines for adults aged 40 years and over. The majority of AEFIs reported were injection site reactions and non-serious systemic events.

Figure 8. Rates per 100,000 doses of the most frequently reported adverse events following influenza vaccination, ADRAC database, 1 January 2000 to 30 September 2002, by age group



There were two major findings of this study. The first estimates of national dose-based AEFI reporting rates for the most commonly used vaccines in Australia allows direct comparisons of AEFI reporting rates over time, between vaccines and between surveillance systems. The observed increase over time in ADRAC notifications related to injection site reactions following receipt of a fourth or fifth dose of a DTPa vaccine shows that the surveillance system, despite its limitations, is sufficiently sensitive to detect this known AEFI.

Table 9. Dose-based reporting rates of adverse events following immunisation with influenza vaccine,* ADRAC database, January 2000 to September 2002, by age group

AEFI category†		Age group (years)		Overall
		40 to 64	65	
Total	AEFI records (n)‡	124	81	205
	Vaccine doses (n)*	3,761,200	5,589,700	9,350,900
	Rate per 100,000 doses§	3.3	1.4	2.2
'Certain' or 'probable' causality rating†	AEFI records (n)	51	23	74
	Vaccine doses (n)	3,761,200	5,589,700	9,350,900
	Rate per 100,000 doses	1.4	0.4	0.8
'Serious' outcome†	AEFI records (n)	11	16	27
	Vaccine doses (n)	3,761,200	5,589,700	9,350,900
	Rate per 100,000 doses	0.3	0.3	0.3

AEFI Adverse events following immunisation

* Number of administered influenza vaccine doses estimated from the 2000, 2001 and 2002 annual national influenza coverage surveys,[10,11,12] and mid-2001 census data (Australian Bureau of Statistics).

† AEFI category includes all records, those assigned 'certain' or 'probable' causality ratings, and those defined as 'serious' where influenza vaccine was suspected of involvement in the reported adverse event. Causality ratings were assigned using the criteria shown in the Box. 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 between 1 January 2000 and 30 September 2002.

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

Several studies have shown higher rates of severe injection site reactions, particularly extensive limb swelling, following receipt of a fourth or fifth dose of acellular pertussis-containing vaccines (e.g. DTPa) than after the first three doses of these vaccines or following fourth or fifth doses of the previously used whole cell pertussis vaccines (DTPw).[8,15,16,17] These injection site reactions are characteristic of the acellular pertussis vaccines. Despite being extensive, they are usually associated with minimal discomfort, resolve without sequelae and should not contraindicate further vaccination. Importantly, studies show that rates of systemic adverse reactions are lower among children receiving acellular pertussis vaccines than whole cell pertussis vaccines.[8,15,17]

The trend and disproportionate increase in AEFI notifications following receipt of a DTPa vaccine, compared with MMR vaccine (which is given at similar ages as the fourth and fifth doses of DTPa) (Figure 5), reflects changes in the DTPa vaccine funding policy for different jurisdictions and birth cohorts.[4] In South Australia and the Northern Territory, all children received free DTPa vaccines instead of DTPw for all five scheduled doses from August 1997. There, children started receiving their fourth dose of DTPa from early 1999 and fifth dose from mid-2001 onwards. The other states and territories commenced funding all five doses of DTPa in February 1999. These children started receiving their fourth DTPa dose from mid-2001 and fifth dose from early 2003. Extensive injection site reactions following the fourth, then fifth, dose of a DTPa vaccine were first observed in South Australia and the Northern Territory and have now been seen in all jurisdictions as more children have received four doses of a DTPa vaccine. Further increases in the number of notifications of injection site reactions are expected as more children progress to receive their fifth dose of a DTPa vaccine.

AEFI notification rates

The overall average annual population-based AEFI reporting rate for the 33-month period analysed was 4.5 per 100,000 population. This was similar to that averaged over 11 years for the US VAERS system of 4.4 per 100,000 population.[8] In general, the more populous Australian States and Territories had lower population-based reporting rates than the less populous ones. This has also been observed in the USA and Canada.[8,18] Reasons are unclear but the rates of AEFIs with outcomes defined as 'serious' or assigned ADRAC causality ratings of 'certain' or 'probable' were less variable across jurisdictions than overall reporting rates (Table 1). This pattern suggests large differences in the sensitivity of the individual state and territory AEFI surveillance systems. This is likely to be related, to some extent, to known differences in notification and case investigation procedures. Further study to evaluate and compare AEFI surveillance methods across jurisdictions would help to elucidate this.

The proportion of AEFI records with outcomes defined as 'serious' was comparable with US VAERS data (14.5% compared with 10.5% for ADRAC data), although there are differences between the two systems in the methods used to estimate numerator and denominator data.[8] There were also similarities between the two systems in dose-based AEFI reporting rates for specific vaccines. In 2001, the highest VAERS dose-based reporting rate was for the DTPa vaccines (27.5 per 100,000 distributed doses).[8] The USA data also showed an increasing trend in the number of reports for acellular pertussis-containing vaccines per 100,000 distributed doses, and the number of reports for injection site reactions following fourth or fifth doses of acellular pertussis vaccines.[8]

Limitations of passive AEFI surveillance

Caution is required when interpreting the AEFI data presented here. The AEFI reporting rates cannot be interpreted as true incidence rates. Like all passive surveillance data, AEFI data are subject to under-reporting, over-reporting and reporting biases that are difficult to measure.[1,2,3] There is under-reporting of less serious adverse events and of those sustained by adults. In contrast, there is over-reporting of serious events *coincidentally* associated with the timing of immunisation, particularly for newer vaccines and among children. AEFI records assigned ADRAC causality ratings of 'certain' or 'probable' fulfil stricter criteria than those rated as 'possible', and usually involve only one vaccine (see Box). There are a wide range of reasons why a reported AEFI might be assigned a 'possible' causality rating including insufficient information, the existence of a plausible alternative explanation or more than one vaccine or drug being administered at a time, as is frequently the case in infants and the elderly. The causality rating assigned to each AEFI record describes the likelihood that a suspected vaccine(s) was associated with the reported adverse event at the level of the individual patient. This is not the same as the epidemiological concept of 'causality', which applies at the population level. Specific epidemiological studies are required to investigate the broader question of whether a vaccine is causally associated with a specific adverse event at the population level. Such studies are often implemented as a result of 'signals' detected through passive AEFI surveillance.[15,19]

In Australia, passive AEFI surveillance is complemented by specialist clinics in several jurisdictions[17] that function as sentinel surveillance sites for more serious AEFIs. Enhanced AEFI surveillance during ad-hoc immunisation campaigns, such as the 1998 Measles Control Campaign, also

plays an important role.[20] Data linkage methods, similar to the US Vaccine Safety Datalink methods[21] are currently being piloted in Australia. If successful, they will provide an important adjunct to passive AEFI surveillance. Internationally, the Brighton Collaboration is developing and evaluating standardised AEFI case definitions and guidelines for AEFI surveillance, which may be applicable in Australia.[22]

Conclusions

The data reported here illustrate the high level of vaccine safety in Australia, particularly at a time of high vaccination coverage rates and resulting low rates of vaccine preventable diseases.[4] Recent examples include the dramatic decline in hospitalisations and deaths among children since 1993, following the introduction of Hib vaccine into the ASVS, and the large reductions in measles and rubella infection rates following changes to the MMR vaccination schedule in the mid-late 1990s.[4] The benefits of immunisation far outweigh the risks of adverse events following immunisation, particularly since the majority of those reported are not serious, and many that are serious are only coincidentally associated with immunisation.

The ADRAC database provides a valuable resource of Australian AEFI surveillance data. The data have been assessed using protocols consistent with international practice allowing comparison with AEFI surveillance data from other countries particularly the USA. Routinely collected immunisation coverage data from the ACIR and the annual national influenza coverage surveys have allowed the estimation of national dose-based AEFI reporting rates for the first time. As denominator data become available about the number of doses administered or distributed for other vaccines, the estimation of dose-based AEFI reporting rates will become more complete. While continued effort is required to maintain and improve AEFI surveillance in Australia, regular analysis and reporting of the data and dose-based AEFI reporting rates will provide important information for immunisation service providers, program managers and the general public.

Acknowledgments

We thank Brynley Hull for calculating vaccine doses from ACIR data. The National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases is supported by the Commonwealth Department of Health and Ageing, the New South Wales Department of Health and the Children's Hospital at Westmead, Australia.

Appendix

Abbreviations of vaccine types

BCG	Bacille Calmette-Guèrin (i.e. tuberculosis)
dT	diphtheria and tetanus
DTPa	diphtheria-tetanus-pertussis (acellular)
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
MenCCV	meningococcal C conjugate
MMR	measles-mumps-rubella
7vPCV	7-valent pneumococcal conjugate
23vPPV	23-valent pneumococcal polysaccharide
polio	poliomyelitis (oral and inactivated)

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