Surveillance of adverse events following immunisation: Australia 2002 to 2003

Glenda Lawrence,[1] Ian Boyd,[2] Peter McIntyre,[1] David Isaacs[3]

Abstract

Reports of suspected adverse events following immunisation (AEFI) are reviewed by the Adverse Drug Reactions Advisory Committee and collated in a central database. We analysed AEFI records for vaccines administered during October 2002 to December 2003, and assessed AEFI reporting trends for 2000 to 2003. AEFI reporting rates were calculated using denominator data from the Australian Childhood Immunisation Register and the annual national influenza vaccination coverage survey. A total of 1,744 AEFI records were analysed for October 2002 to December 2003. The majority described non-serious events; 9 per cent (n=149) described AEFIs defined as 'serious'. Four deaths were reported but none were causally related to immunisation. Dose-based AEFI reporting rates were 2.1 per 100,000 doses of influenza vaccine for adults aged 40 years or over and 19.8 per 100,000 doses of scheduled vaccines for children aged <7 years. The most frequently reported individual AEFI was injection site reaction in children after a fourth or fifth dose of an acellular pertussis-containing vaccine (54 and 98 reports per 100,000 doses respectively). The most frequently suspected vaccine was meningococcal C conjugate vaccine (34% of reports—mostly injection site reactions, gastrointestinal symptoms and headaches). The average annual reporting rate was 7.0 per 100,000 population, the highest to date. The increase in the AEFI reporting rate was due to a greater number of children becoming eligible to receive a fourth or fifth consecutive dose of acellular pertussis vaccine and the introduction of the meningococcal C vaccination program in January 2003 for those aged 1–19 years. The low reporting rate of serious AEFIs demonstrates the high level of safety of vaccines in Australia. *Commun Dis Intell* 2004;28:324–338.

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

Introduction

An adverse event following immunisation (AEFI) 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 may be *coincidentally* associated with the *timing* of immunisation without necessarily being caused by the vaccine or the immunisation process. AEFI surveillance is an integral component of all vaccination programs to monitor vaccine safety and detect rare, late-onset, unexpected and population-specific adverse events that are difficult to detect in pre-licensure vaccine trials.[2,3]

In Australia, passive AEFI surveillance is conducted by state and territory health departments and the Adverse Drug Reactions Unit (ADRU), which is part of the Australian Government Therapeutic Goods Administration and provides the secretariat for the Adverse Drug Reactions Advisory Committee (ADRAC).[4,5,6] Immunisation providers, other health care professionals, vaccine manufacturers, parents and members of the public report suspected AEFIs to the ADRU, either directly or via the relevant state or territory health department as required.[5,6] At the ADRU, all reports are evaluated using internationally consistent criteria[7] and are reviewed by the ADRAC at regular meetings. The data collected by these passive surveillance methods are used to monitor trends, detect signals and generate hypotheses.

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

Corresponding author: Dr Glenda Lawrence, National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, University of Sydney and The Children's Hospital at Westmead, Locked Bag 4001, Westmead NSW 2145. Telephone: +61 2 9845 0520. Facsimile: +61 2 9845 3082. Email: glendal@chw.edu.au

The first AEFI surveillance report using national data collated in the ADRAC database was published in September 2003 and focussed on AEFIs reported for vaccines administered between 1 January 2000 and 30 September 2002.[4] It provided the first estimates of national dose-based AEFI reporting rates for the most commonly used vaccines in Australia and demonstrated an increase over time in reports of injection site reactions following a fourth or fifth dose of acellular-pertussis containing vaccines.

This report focuses mainly on AEFIs reported to ADRAC for vaccines administered between 1 October 2002 and 31 December 2003 and compares reporting trends for the four years 2000 to 2003. Several important surveillance and immunisation program initiatives occurred during the October 2002 to December 2003 timeframe which impact on the AEFI surveillance data presented in this report. A new data management system was implemented by the ADRU in November 2002 to replace the original system that dated from 1972. At the same time the ADRU changed from the World Health Organization Adverse Reaction Terminology (WHO-ART) coding system to the Medical Dictionary of Regulatory Activities (MedDRA®) system. This is an international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.[8] During implementation of the new data management system, reaction terms in reports entered into the database between January 2000 and November 2002 were converted from the WHO-ART terms to the most closely related term in the MedDRA® reaction term coding system.

In January 2003 the meningococcal C conjugate vaccine (MenCCV) was introduced into the Australian Standard Vaccination Schedule (ASVS). Children born on or after 1 January 2002 became eligible for a single dose of the vaccine at 12 months of age and a provider and school-based catch-up campaign was implemented for older children and adolescents up to 19 years of age through the National Immunisation Program.[6] The exact timing of the catch-up campaign varied between jurisdictions. In September 2003, the fourth dose of diphtheria-tetanus-acellular pertussis (DTPa) vaccine, due at 18 months of age, was removed from the ASVS.[6]

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 1 January 2000 and 7 April 2004. The AEFI surveillance system and methods used by ADRU to evaluate AEFI reports are described in detail in the first AEFI surveillance report.[4]

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 31 December 2003 *or* (b) if no vaccination date was recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 31 December 2003.

Study definitions of AEFI 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[7] and the United States of America (USA) Vaccine Adverse Events Reporting System (VAERS).[9] In this report, an AEFI is defined as 'serious' if the record indicated the person had recovered with sequelae, was hospitalised, experienced a life-threatening event, or died.

Typically, each AEFI record listed several symptoms, signs and diagnoses. We used the MedDRA® terms to create a set of reaction categories for analysis. Initially, reaction terms were grouped to create reaction categories analogous to the AEFIs listed and defined in the *Australian Immunisation Handbook* (7th edition).[5] Reaction categories were then created for the remaining reaction terms that were listed in more than one per cent of AEFI records. Finally, terms listed in less than one per cent of records were grouped into broader categories mainly based on the organ system where the reaction was manifested (e.g. gastrointestinal, neurological). The impact of the change in reaction term coding from the WHO-ART to MedDRA® systems was assessed by comparing the frequencies of reaction categories created for the 2,409 AEFI

* 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).[4] This report is based on 'AEFI records'

records that were coded using both systems and analysed previously.[4] The frequencies for all reaction categories based on AEFIs listed in the *Australian Immunisation Handbook*[5] were comparable for the two reaction term coding systems.

Data analysis

All data analyses were performed using the SAS version 8 computer program.[10] 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 <7 years for seven childhood ASVS vaccines funded through the National Immunisation Program (DTPa, DTPa-hepB, Hib, Hib-hepB, polio, MMR and MenCCV), 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 approximately 99 per cent of children aged <7 years. Vaccine doses administered between 1 October 2002 and 31 December 2003 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 2003 annual national influenza coverage survey[11] and mid-2003 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.

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 2003. 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.[4,12]

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 7th edition of the *Australian Immunisation Handbook*.[5] However, these reaction categories are 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 were administered.[4] Assigning a causality rating to an individual report is not the same as the epidemiological concept of 'causality' which applies at the population level and requires a specific epidemiological study with an appropriate control group to investigate. Signals and hypotheses generated from passive surveillance inform the need for such studies.

Results

Summary of data

A total of 1,744 AEFI records were entered in the ADRAC database where the date of vaccination or onset of an adverse event occurred between 1 October 2002 and 31 December 2003. This corresponded to approximately 1,575 individual AEFI notifications, with 11 per cent of AEFI notifications generating more than one AEFI record.

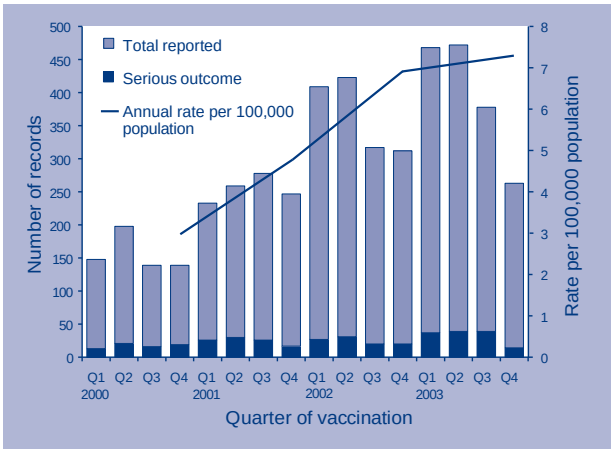
One hundred and forty nine AEFI records (9%) were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threat-

ening event or death). A total of 897 (51%) AEFI records were assigned causality ratings of 'certain' (n=745) or 'probable' (n=152).

AEFI reporting trends

The average annual AEFI reporting rate for the period October 2002 to December 2003 was 7.0 per 100,000 population. The rate and number of AEFIs reported in 2003 was higher than in previous 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). The commencement of the MenCCV immunisation program in 2003 contributed to an overall increase in population-based AEFI reporting rates in 2003 compared with previous years.

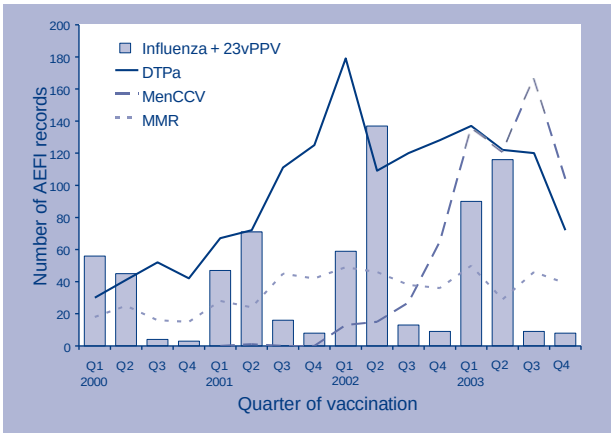
Figure 1. Adverse events following immunisation, ADRAC database, 2000 to 2003, by quarter of vaccination



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

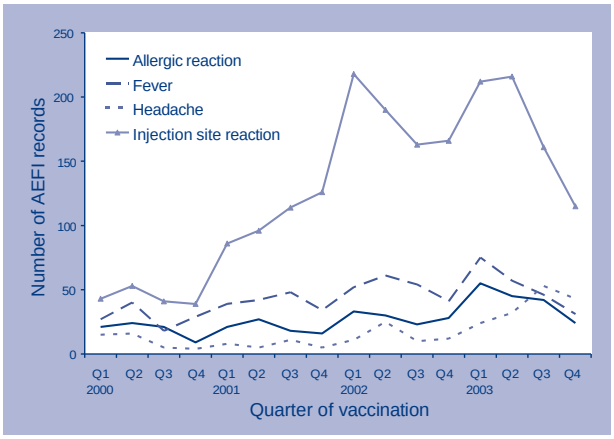
A clear seasonal pattern of AEFI reporting was apparent with the highest number of AEFI notifications for vaccinations administered in the first half of each year (Figure 1). These seasonal peaks correspond to the months when more vaccinations are administered in Australia, particularly among five year old children receiving DTPa and measles-mumps-rubella (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).

Figure 2. Frequently suspected vaccines, adverse events following immunisation, ADRAC database, 2000 to 2003, by quarter of vaccination



Note: see appendix for abbreviations of vaccine names.

Figure 3. Selected frequently reported reactions, by quarter of vaccination, ADRAC database, 2000 to 2003

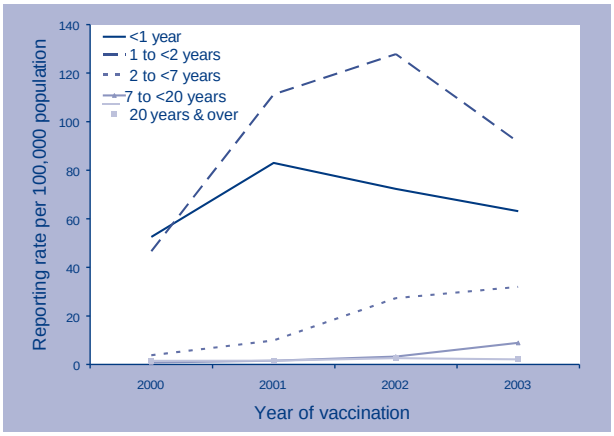


Age and gender distribution

The AEFI reporting rate in 2003 was highest among children aged <1 year and 1 to <2 years (63.1 and 91.5 per 100,000 population, respectively) (Figure 4), the age groups that receive the greatest number of vaccinations. The average annual AEFI reporting rates for these age groups decreased in 2003 compared with 2002, but increased among older age groups.

The overall male to female ratio was 1:1.2 although, as seen previously,[4] this differed by age group. There were more reports for males than females among children aged 1 to <7 years (1:0.8) and fewer reports for males than females aged 20 to 64 years (1:2).

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

AEFI reporting rates varied between the states and territories for the period October 2002 to December 2003 (Table 1). The Australian Capital Territory and Northern Territory had the highest reporting rates (23.0 and 20.6 per 100,000 population, respectively) while Tasmania and Victoria had the lowest rates (3.9 and 4.5 per 100,000 population, respectively). In general, reporting rates of AEFIs assigned a 'certain' or 'probable' causality rating and those defined as 'serious' were less variable across jurisdictions. The greatest variation in population-based reporting rates between jurisdictions was for children aged <7 years (Table 1).

AEFI outcomes

The majority of reported AEFIs for the period October 2002 to December 2003 were defined as 'non-serious' (60%) while nine per cent were defined as 'serious' (Table 2). Fewer 'serious' AEFIs were assigned 'certain' or 'probable' causality ratings compared with 'non-serious' AEFIs (32% versus 55%). Death was recorded as the outcome in four AEFI records (Table 2). Although temporally related, none of these deaths was found to be causally related to vaccination.

Vaccines and AEFI

Twenty-five vaccines were recorded as 'suspected' of involvement in the adverse events described in the 1,744 AEFI records for the period October 2002 to December 2003 (Table 3). They included all vaccines recommended in the ASVS, plus vaccines recommended to travellers and specific risk groups.

Table 1. Adverse events following immunisation (AEFI), ADRAC database, October 2002 to December 2003, by jurisdiction

Jurisdiction	AEFI records		Annual reporting rate per 100,000 population*			
	n	%	Overall	'Certain' or 'probable' causality rating†	'Serious' outcome‡	Aged < 7 years
Australian Capital Territory	93	5.3	23.0	8.7	0.7	151.0
New South Wales	539	30.9	6.4	3.3	0.7	33.1
Northern Territory	51	2.9	20.6	9.3	2.4‖	83.0
Queensland	249	14.3	5.2	2.3	0.4	35.7
South Australia	308	17.7	16.1	9.3	0.8	155.2
Tasmania	23	1.3	3.9	2.5	0.2	14.9
Victoria	277	15.9	4.5	2.6	0.3	26.7
Western Australia	147	8.4	6.0	3.3	0.6	43.6
Other§	57	3.3	na	na	na	na
Total	1,744	100.0	7.0	3.6	0.6	45.2

* Average annual rates per 100,000 population calculated using mid-2003 population estimates (Australian Bureau of Statistics).

† See previous report[4] for criteria used to assign causality ratings.

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

§ Records where the jurisdiction in which the AEFI occurred was not reported (n=17) or was unclear (n=40). These included AEFIs notified by pharmaceutical companies (n = 35).

‖ Based on 6 reports.

Table 2. Outcomes shown in records of adverse events following immunisation (AEFI), ADRAC database, October 2002 to December 2003

Outcome	AEFI records		'Certain' or 'probable' causality rating†		Age group‡			
					< 7 years		≥ 7 years	
	n	%*	n	%§	n	%§	n	%§
Non-serious	1041	60	576	55	635	61	381	37
Not recovered at time of report	393	22	196	50	201	51	182	46
Not known (missing data)	161	9	77	48	105	65	53	33
Serious:	149	9	48	32	68	46	80	54
recovered with sequelae	0	0	–	–	–	–	–	–
hospital admission	132	8	45	34	61	45	71	54
life-threatening event	13	<1	3	23	5	38	7	54
death	4	<1	0	0	2	50	2	50
Total	1,744	100	897	51	1,009	58	696	40

* Percentages relate to the total number of AEFI records (n=1744).

† Causality ratings were assigned to AEFI records using criteria described previously.[4]

‡ 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 1041 AEFI records with a 'non-serious' outcome, 55% had causality ratings of 'certain' or 'probable' and 61% were for children aged <7 years.

The most frequently suspected individual vaccine was MenCCV with 591 (34%) of reports (Table 3). Vaccines containing pertussis, diphtheria and tetanus antigens (i.e. DTPa and DTPa-hepB) were suspected in 687 (39%) reports. 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', and the proportion defined as 'serious'.

AEFI reporting trends over time differed by vaccine (Figure 2). The number of reports of AEFIs for DTPa vaccine declined during 2003 following a peak in the first quarter of 2002. MMR reports remained relatively constant while reports for MenCCV vaccine increased following the addition of this vaccine to the National Immunisation Program and delivery through provider and school-based immunisation programs in 2003.

AEFI reactions

The distribution and frequency of reactions listed in AEFI records for October 2002 to December 2003 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 common category of reaction (n=870 or 50% of AEFI records) (Table 4) followed by fever (14%), allergic reactions (11%) and rash (10%). DTPa, MenCCV and 23-valent pneumococcal polysaccharide vaccine (23vPPV) were the most frequently suspected vaccines in the 870 AEFI records listing injection site reaction (50%, 21% and 12% respectively). DTPa and MenCCV were also the most frequently suspected vaccines in AEFI records listing fever (24% and 42% respectively) and allergic reaction (23% and 44% respectively).

More serious AEFIs included anaphylactic reaction (n=9), hypotonic-hyporesponsive episode (HHE, n=12), thrombocytopenia (n=6) and convulsions (n=52). The most commonly suspected vaccines in the reports of anaphylactic reaction were influenza (n=3) and MenCCV (n=3). DTPa was the most commonly suspected vaccine in reports listing HHE (10/12, 83%), while MMR was the most commonly suspected vaccine in reports listing thrombocytopenia (4/6, 67%). Of the 52 reports listing convulsions as a reaction term, 32 (62%) listed MenCCV and 13 (25%) listed DTPa as a suspected vaccine.

Of reactions not listed in the Australian Immunisation Handbook,[5] oedema (13%), headache (9%), vomiting (6%) and malaise (6%) were the most frequently recorded (Table 5). DTPa and MenCCV were the most commonly suspected vaccines in 225 AEFI records where oedema was listed as a reaction (52% and 23% respectively), while MenCCV was suspected of involvement in 73% (n=120) of the 164 AEFI records that listed headache as a reaction. MenCCV was also suspected in the majority of AEFI records that listed syncope (26/38, 68%) or loss of consciousness (15/27, 55%) as a reaction term.

Table 3. Vaccine types listed as 'suspected' in records of adverse events following immunisation (AEFI), ADRAC database, October 2000 to December 2003

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	%¶
MenCCV	591	469	79	249	42	63	11	277	47	305	52
DTPa	579	390	67	354	61	22	4	564	97	5	1
MMR	200	32	16	23	12	16	8	189	95	7	4
Polio	180	4	2	6	3	24	13	176	98	2	1
23vPPV	151	132	87	97	64	9	6	4	3	136	90
Hib	126	11	9	12	10	17	13	125	99	0	0
DTPa-hepatitis B	108	18	17	16	15	12	11	106	98	1	1
Influenza	98	81	83	42	43	13	13	2	2	94	96
dT	73	47	64	34	47	2	3	5	7	67	92
Hepatitis B	58	39	67	27	47	10	17	18	31	39	67
Varicella	40	36	90	10	25	3	8	22	55	17	43
Hib-hepatitis B	36	4	11	3	8	10	28	36	100	0	0
Q fever	28	28	100	18	64	2	7	1	4	25	89
7vPCV	25	12	48	6	24	6	24	25	100	0	0
Hepatitis A + B	13	9	69	3	23	2	15	0	0	12	92
JE	11	9	82	4	36	3	27	1	9	10	91
BCG	6	6	100	3	50	4	67	0	0	6	100
Rabies	6	4	67	0	0	2	33	0	0	6	100
Tetanus	6	5	83	3	50	1	17	0	0	6	100
Hepatitis A	5	1	20	0	0	1	20	1	20	4	80
Men4PV	5	5	100	1	20	2	40	1	20	2	40
Typhoid	5	0	0	0	0	0	0	0	0	5	100
Hepatitis A + Typhoid	3	3	100	1	33	0	0	1	33	2	67
Anthrax	2	2	100	1	50	2	100	0	0	2	100
Yellow fever	2	1	50	0	0	0	0	0	0	2	100
Total**	1,744	1,349	77	897	51	149	9	1,009	58	696	40

* See appendix for abbreviations of vaccine names.

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

‡ Causality ratings were assigned to AEFI records using criteria described previously.[4]

§ 'Serious' outcomes are defined in the Methods section (see Table 2 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. MenCCV was listed as 'suspected' in 591 AEFI records; this was the only suspected vaccine in 79% of the 591 AEFI records, 42% had 'certain' or 'probable' causality ratings, 11% were defined as 'serious' and 47% were for children aged <7 years.

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

Table 4. Reactions of interest* listed in records of adverse events following immunisation (AEFI), ADRAC database, October 2002 to December 2003

Reaction*	AEFI records	Only reaction reported†		Certain/ probable causality rating‡		Age group§			
						< 7 years		≥ 7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Injection site reaction	870	454	52	698	80	585	67	260	30
Fever	250	21	8	64	26	149	60	99	40
Allergic reaction	194	57	29	62	32	108	56	84	43
Rash	171	54	32	49	29	109	64	60	35
Convulsions	52	12	23	14	27	27	52	23	44
Abnormal crying	45	9	20	5	11	44	98	1	2
Arthralgia	35	2	6	13	37	2	6	30	86
Lymphadenopathy/itis¶	27	5	19	9	33	11	41	15	56
HHE**	12	2	17	1	8	11	92	0	0
hypotonia/hypokinesia**	16	0	0	3	19	13	81	3	19
Anaphylactic reaction	9	3	33	2	22	3	33	6	67
Abscess	6	4	67	5	83	3	50	3	50
Thrombocytopenia	6	3	50	0	0	5	83	1	17
Arthritis	4	1	25	0	0	1	25	3	75
Death	4	3	75	0	0	2	50	2	50
Parotitis	4	3	75	0	0	2	50	1	25
Meningitis	2	0	0	0	0	2	100	0	0
Brachial neuritis	1	0	0	1	100	0	0	1	100
Encephalitis	1	1	100	0	0	1	100	0	0
Guillain-Barré syndrome	1	0	0	0	0	0	0	1	100
Orchitis	1	1	100	0	0	0	0	1	100
Acute flaccid paralysis	0	0	0	0	0	0	0	0	0
Encephalopathy	0	0	0	0	0	0	0	0	0
Osteitis	0	0	0	0	0	0	0	0	0
Osteomyelitis	0	0	0	0	0	0	0	0	0
Sepsis	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
Total	1,744	742	43	897	51	1,009	58	696	40

* Reaction term variables were created for the AEFIs of interest listed in the *Australian Immunisation Handbook*, (7th edition, p 22–23 and 271–275)[5] as described in Methods section.

† AEFI records where only one reaction was reported.

‡ Causality ratings were assigned to AEFI records using criteria described previously.[4]

§ 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 870 AEFI records listing injection site reaction, 52% listed only one type of reaction while 80 per cent had causality ratings of 'certain' or 'probable' and 67% were for children aged <7 years.

¶ Includes lymphadenitis following BCG vaccination 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.

†† Subacute sclerosing panencephalitis.

Table 5. 'Other'* reactions listed in records of adverse events following immunisation (AEFI), ADRAC database, October 2002 to December 2003

Reaction*	AEFI records	Only reaction reported†		Certain/probable causality rating‡		Age group§			
						< 7 years		≥ 7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖
Oedema	225	6	3	154	68	151	67	70	31
Headache	164	25	15	59	36	15	9	145	88
Vomiting	109	11	10	28	26	60	55	46	42
Malaise	100	5	5	23	23	33	33	66	66
Pain	81	0	0	38	47	16	20	64	79
Dizziness	56	1	2	26	46	2	4	53	95
Nausea	52	1	2	12	23	4	8	48	92
Pallor	51	0	0	16	31	29	57	21	41
Irritability	48	1	2	10	21	42	88	6	13
Erythema	45	3	7	14	31	30	67	15	33
Respiratory rate/rhythm change	43	4	9	13	30	17	40	25	58
Syncope	38	3	8	22	58	8	21	30	79
Fatigue	35	1	3	10	29	11	31	21	60
Myalgia	35	0	0	16	46	3	9	29	83
Reduced sensation	33	2	6	17	52	1	3	32	97
Increased sweating	32	0	0	14	44	12	38	20	63
Anorexia	30	0	0	6	20	22	73	7	23
Diarrhoea	29	2	7	6	21	20	69	8	28
Abdominal pain	28	0	0	8	29	5	18	23	82
Loss of consciousness	27	0	0	10	37	8	30	19	70
Pharyngitis	24	1	4	6	25	5	21	18	75
Heart rate/rhythm change	23	0	0	11	48	5	22	18	78
Somnolence	20	3	15	7	35	11	55	9	45
Other									
general non-specific	108	6	6	53	49	53	49	54	50
neurological	74	10	14	28	38	25	34	47	64
respiratory	49	5	10	9	18	26	53	20	41
cardiovascular	47	5	11	21	45	14	30	32	68
musculoskeletal	46	1	2	22	48	5	11	41	89
skin	44	8	18	18	41	31	70	13	30
psychological	42	0	0	15	36	18	43	22	52
eye or ear	23	0	0	7	30	10	43	13	57
gastrointestinal	18	1	6	6	33	7	39	10	56
metabolic/endocrine	18	1	6	4	22	12	67	6	33
renal/urogenital	9	1	11	4	44	1	11	8	89
haematological	7	0	0	2	29	1	14	6	86
infection	5	1	20	0	0	5	100	0	0
miscellaneous	2	0	0	0	0	1	50	1	50
pregnancy/congenital	1	1	100	0	0	0	0	0	0

* Reaction terms not listed in the *Australian Immunisation Handbook*[5] but included in AEFI records in the ADRAC database. The top part of the table shows reaction terms included in 1% or more of AEFI records; the bottom part of the table shows reaction terms grouped by organ system that were included in <1% of AEFI records.

NOS Not otherwise specified.

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

Reactions mentioned in fewer than one per cent of AEFI records for October 2002 to December 2003 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'. This included broad terms that could not be assigned to an organ system (e.g. 'influenza-like illness'; 'discomfort not otherwise specified').

The trends in the most frequently reported types of reactions changed over time (Figure 3). There were fewer reports of injection site reactions and more of headache in 2003 compared to 2002. Reports of fever and allergic reaction were less variable over time.

Dose-based AEFI reporting rates

Scheduled vaccines for children aged <7 years

Dose-based AEFI reporting rates are shown in Table 6 for seven funded ASVS vaccines received by children aged <7 years between 1 October 2002 and 31 December 2003. The overall reporting rate increased to 19.8 per 100,000 doses from 14.6 per 100,000 doses for the period January 2000 to September 2002, while rates for 'certain/probable' causality or 'serious' outcomes were more stable (10.0 and 1.2 per 100,000 doses, respectively). The reporting rates for most vaccines did not differ markedly to those estimated for the January 2000 to September 2002 period. The highest AEFI reporting rates and largest changes in reporting rates for individual vaccines were for DTPa vaccine and MenCCV (Table 6).

Dose-based reporting rates of the most commonly reported reactions differed by vaccine type (Figure 5). Injection site reactions following DTPa vaccine were reported at a rate of 47.9 per 100,000 doses of DTPa vaccine, up from 27.9 per 100,000 doses for the January 2000 to September 2002 period.[4] This increase occurred among children aged 1 to <2 years and 2 to <7 years, the ages where a fourth or fifth dose of the vaccine were due (Figure 6). The reporting rates of injection site reactions for the <1 year, 1 to <2 years and 2 to <7 years age groups were 4, 65 and 80 per 100,000 doses of DTPa vaccine, respectively, for the October 2002 to December 2003 period while reporting rates of all other reactions were approximately 18 per 100,000 doses (Figure 6).

Denominator data from the ACIR allowed us to estimate reporting rates of more severe known adverse events for children aged <7 years. The reporting rate

Table 6. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* children aged less than 7 years, ADRAC database, October 2002 to December 2003

Suspected vaccine type† or AEFI category‡	AEFI records n	Vaccine doses n	Rate per 100,000 doses§	Difference‖
DTPa	564	876,853	64.3	+22.0
DTPa-hepB	106	560,627	18.9	-6.3
Hib	125	572,858	21.8	-1.3
Hib-hebB	36	319,626	11.3	-0.8
Polio	176	1,191,496	14.8	+2.2
MMR	189	605,611	31.2	+4.6
MenCCV	277	715,873	38.7	na
Total‡	958	4,842,917	19.8	+5.2
'Certain' or 'probable' causality rating‡	486	4,842,917	10.0	+3.6
'Serious' outcome‡	60	4,842,917	1.2	0

* Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 October 2000 and 31 December 2003.

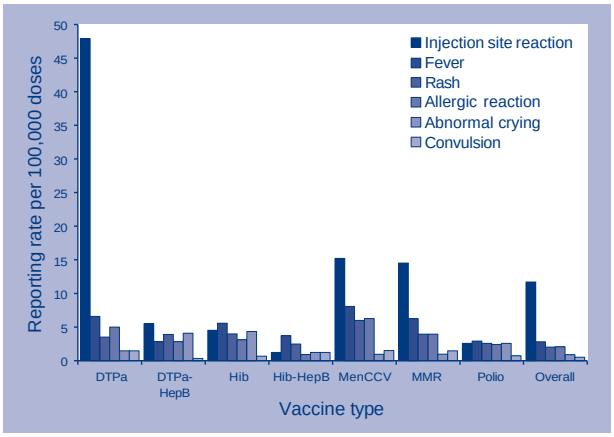
† AEFI records where the vaccine was one of those listed as 'suspected' of involvement in the reported adverse event. See appendix for abbreviations of vaccine names.

‡ 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.

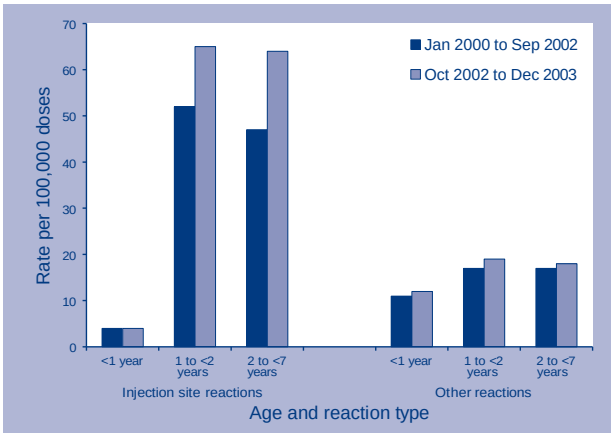
‖ Difference in reporting rate per 100,000 doses for vaccinations administered during October 2002 to December 2003 and January 2000 to September 2002.

Figure 5. Rates of frequently reported reactions per 100,000 vaccine doses administered to children aged <7 years for recommended vaccines, ADRAC database, October 2002 to December 2003



Note: see appendix for abbreviations of vaccine names.

Figure 6 Rates of injection site and other reported reactions per 100,000 vaccine doses of DTPa vaccine, ADRAC database, 2000 to 2003, by age group and year of vaccination



of HHE and convulsion following DTPa vaccination (either alone or in combination with other vaccines) was 1.14 and 1.37 per 100,000 doses respectively. The reporting rate of thrombocytopenia following MMR vaccine was 0.66 per 100,000 doses of MMR vaccine.

Influenza vaccine and adults aged ≥40 years

Influenza vaccine was suspected of involvement in 94 AEFI records for people aged ≥40 years. The dose-based AEFI reporting rates are shown in Table 7. As seen previously,[4] the AEFI reporting rates were higher among influenza vaccinees aged 40–64 years than those aged >65 years (2.8 and 1.6 per 100,000 doses, respectively). The most frequently reported adverse events were injection site reactions, fever and allergic reactions (0.6, 0.3 and 0.3 per 100, 000 doses, respectively). There was one report of Guillain-Barré syndrome following influenza vaccination (Table 4). This corresponds to a reporting rate of <0.03 per 100,000 doses and is unchanged from the previous report.[4]

Meningococcal C conjugate vaccine

A more comprehensive analysis of adverse events following MenCCV will be reported elsewhere. In summary, between licensure of the vaccine in Australia in 2000 and 31 December 2003, a total of 647 AEFI records were entered into the ADRAC database where MenCCV was suspected of involvement in the reported adverse event. The majority of reports for MenCCV were received for children aged 2 to <7 years (n=217, 34%) and those aged 7 to <20 years (n=308, 47%). There were more reports for females than males (male to female ratio of 0.8:1.0).

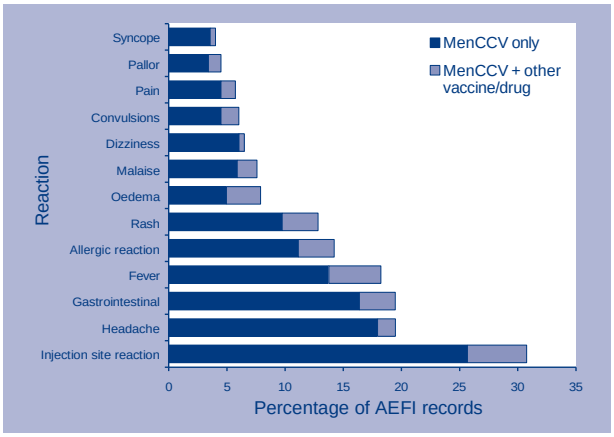
Of the 647 records, MenCCV was the only suspected vaccine in 523 (81%) records, 271 (42%) had causality ratings of 'certain' or 'probable' and 70 (11%) were defined as 'serious'. No deaths were reported. There were a total of three reports of anaphylactic reaction (one involving other vaccines in addition to MenCCV), and 39 (6%) reports of convulsion. The most frequently reported categories of reactions associated with MenCCV administration were injection site reactions (31%), headache (20%), gastrointestinal symptoms (vomiting, nausea, abdominal pain or diarrhoea, 20%), fever (18%) and allergic reactions (14%) (Figure 7).

Approximately 3.5 million doses of MenCCV had been distributed in Australia until 31 December 2003. The reporting rate of anaphylactic reactions was approximately one per one million distributed doses, convulsions at one in 90,000 distributed doses while the overall AEFI reporting rate to ADRAC, across all ages, was one in 5,400 distributed doses.

Discussion

The data presented in this report demonstrate the continued high levels of safety of the most frequently administered vaccines in Australia. In the 15 months to December 2003, over three million doses of influenza vaccine were administered to adults aged ≥40 years while more than 4.8 million

Figure 7. Frequently reported reactions following MenCCV (percentage of 647 records), ADRAC database, 2000 to 2003, by the number of vaccines suspected of involvement in reported adverse event



doses of scheduled vaccines were administered to children aged <7 years. The corresponding AEFI reporting rates were 2.1 per 100,000 doses of influenza vaccine and 19.8 per 100,000 scheduled doses for children <7 years. The majority of AEFIs notified were for injection site reactions and non-serious systemic events. Estimated reporting rates of known potentially life-threatening AEFIs such as HHE and convulsions following DTPa vaccination, and thrombocytopenia following MMR vaccination, were very low and comparable to reporting rates in other passive surveillance systems.[9,13,14]

The number of AEFIs reported to ADRAC has risen each year between 2000 and 2003 while the percentage of serious AEFIs remained stable at 9–10 per cent. The trends in age-specific and vaccine-specific reporting rates demonstrate that the annual increase in overall AEFI reporting rates is mainly due to increased reporting of injection site reactions among children aged 1 to <7 years following a fourth or fifth dose of acellular pertussis-containing vaccines, and to reporting of AEFIs following the introduction of the MenCCV immunisation program for those aged 1–19 years from January 2003. Both of these factors were expected to impact on AEFI reporting rates in 2003.

Extensive injection site swelling is a known adverse event associated with the fourth and fifth doses of acellular pertussis containing vaccines.[4,9,15,16] The higher reporting rates of injection site reactions per 100,000 doses of DTPa vaccine for children aged 1 to <2 and 2 to <7 years for October 2002–December 2003, compared with January 2000–October 2002, was expected as more children became eligible to receive their fourth or fifth consecutive dose of the vaccine in 2003. This birth cohort effect is related to changes in public funding for DTPa across Australia in 1999.[4,17] Rates of injection site reactions should decrease among children aged 1 to <2 years, and to a lesser extent among children aged 2 to <7 years, following the removal of the DTPa dose due at 18 months from the ASVS in September 2003. The impact on the younger age group is already evident with only two reports of injection site reactions following DTPa administered in the fourth quarter of 2003 compared with 33–36 per quarter for the previous quarters of 2003 (data not shown).

Whenever a new vaccine is licensed or added to an immunisation program for a large section of the population, as was the case for MenCCV in 2003, there is an appropriate and expected increase in

Table 7. Dose-based reporting rates of adverse events following immunisation (AEFI) with influenza vaccine,* 40 years and over, ADRAC database, October 2002 to December 2003

Suspected vaccine type† or AEFI category‡	AEFI records n	Rate per 100,000 doses§	Difference‖
Total‡	68	2.1	-0.1
'Certain' or 'probable' causality rating‡	27	0.8	0
'Serious' outcome‡	5	0.2	-0.1

* Number of administered influenza vaccine doses (n=3,286,400) estimated from the 2003 national influenza survey.[11]

† 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 described previously.[4] 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 September 2002 and 31 December 2003.

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

‖ Difference in reporting rate per 100,000 doses for vaccinations administered during October 2002 to December 2003 and January 2000 to September 2002

awareness and vigilance about vaccine safety and reporting of AEFIs. Examples of the impact this has on passive AEFI surveillance data include the introduction of varicella vaccine in the United States of America (USA)[18] in the mid-1990s and the MenCCV program in the United Kingdom (UK) in 1999.[19] The profile and rates of adverse events reported to ADRAC following MenCCV are broadly similar to those reported in the UK[19,20] and South Australia[21] with injection site reactions, headaches and gastrointestinal symptoms the most commonly reported reactions. The low reporting rates of serious adverse events show that the MenCCV vaccines used in Australia have high safety levels.

The pattern in AEFI reporting rates for the states and territories for October 2002 to December 2003 is similar to that observed for the period January 2000 to September 2002.[4] The differences in reporting rates between the states and territories reflect differences in populations and, more importantly, different AEFI surveillance practices. As seen in the USA and Canada,[9,22] the less populous jurisdictions (Australian Capital Territory, Northern Territory, South Australia) generally had higher AEFI reporting rates than more populous jurisdictions (New South Wales, Queensland, Victoria).

The impact of different surveillance practices on AEFI reporting rates is highlighted by the observation that Tasmania and Victoria, which have similar reporting requirements, had the lowest population-based AEFI reporting rates (3.9 and 4.5 per 100,000 population, respectively) while the Australian Capital Territory and South Australia were among the highest (23.0 and 16.1 per 100,000 population, respectively), particularly for children aged <7 years (approximately 150 per 100,000 population). Both these jurisdictions have similar surveillance systems where AEFIs are not notifiable but direct parent reporting to the respective state or territory health department is strongly encouraged. While reporting is not mandatory in Tasmania or Victoria, both require AEFIs to be notified directly to the ADRU in Canberra and not to the state health department. In contrast, medical practitioners in New South Wales, Queensland, Western Australia and the Northern Territory are required to notify AEFIs to the local health department with other health professionals, parents and members of the public also encouraged to report AEFIs to the health department. Reporting rates were similar for the three states, both overall and for children aged <7 years (range 5.2–6.4 and 33.1–43.6 per 100,000 population, respectively) (Table 1). The higher AEFI reporting rates in the Northern Territory could be due to a number of factors including local AEFI surveillance practices and a smaller population with different characteristics, compared with other jurisdictions.

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 clearly demonstrate the impact of DTPa booster doses on lowering the incidence of pertussis among primary school-aged children[17] while deaths due to *Haemophilus influenzae* type b have declined dramatically following the introduction of Hib vaccination for all children in 1993.[17,23] The most recent example of the benefits of immunisation is the reduction in cases of meningococcal group C disease, particularly in Victoria, following the introduction of the MenCCV program in January 2003.[24] The UK has also seen a significant reduction in meningococcal type C disease among adolescents following the introduction of this vaccine in 1999.[19]

This second report of AEFIs in Australia detected through passive surveillance provides reassurance to immunisation providers, program managers and the public about the safety of vaccines in Australia. The data demonstrate that the system is sufficiently sensitive to detect both expected changes in AEFIs, such as those related to DTPa and MenCCV vaccines, and known rarer and more severe adverse events such as anaphylaxis, HHE, and thrombocytopenia. The 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. Annual AEFI surveillance reports are planned for the future.

Acknowledgements

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

References

1. Mansoor O, Shin S, Maher C, the Immunization Focus of WPRO. Immunization safety surveillance: guidelines for managers of immunization programmes on reporting and investigating adverse events following immunization. Manila: World Health Organization

Regional Office for the Western Pacific; 1999. Available from: http://www.wpro.who.int/pdf/ISS.pdf Accessed 11 August 2004.

2. Duclos P. A global perspective on vaccine safety. *Vaccine* 2004;22:2059–2063.

3. Chen RT, DeStefano F, Pless R, Mootrey G, Kramarz P, Hibbs B. Challenges and controversies in immunization safety. *Infect Dis Clin North Am* 2001;15:21–39.

4. Lawrence GL, Menzies R, Burgess M, McIntyre P, Wood N, Boyd I, et al. Adverse events following immunisation: Australia 2000–2002. *Commun Dis Intell* 2003;27:307–323.

5. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 7th edn. Canberra: Australian Government Publishing Service; 2000.

6. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 8th edn. Canberra: Australian Government Publishing Service; 2003.

7. Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. Available from: http://www.who-umc.org/index2.html Accessed 11 August 2004.

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

9. Zhou W, Pool V, Iskander JK, English-Bullard R, Ball R, Wise RP, et al. Surveillance for safety after immunization: Vaccine Adverse Event Reporting System (VAERS)—United States, 1991–2001. *MMWR Morb Mortal Wkly Rep* 2003;52 Suppl1:1–28.

10. The SAS system for Windows [computer program]. Version 8.02. Cary (NC): SAS Institute Inc.; 1999.

11. Australian Institute of Health and Welfare. *2003 Influenza Vaccine Survey: Summary Results.* Canberra: Australian Institute of Health and Welfare; 2004.

12. Varricchio F, Iskander J, DeStefano F, Ball R, Pless R, Braun MM, et al. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis* J 2004;23:287–294.

13. DuVernoy TS, Braun MM. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996–1998. *Pediatrics* 2000;106:E52.

14. Jonville-Bera AP, Autret E, Galy-Eyraud C, Hessel L. Thrombocytopenic purpura after measles, mumps and rubella vaccination: a retrospective survey by the French regional Pharmacovigilance centres and Pasteur-Merieux Serums et Vaccins. *Pediatr Infect Dis* J 1996;15:44–48.

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

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

17. McIntyre PB, Gidding HF, Gilmore R, Lawrence G, Hull B, Horby P, et al. Vaccine preventable diseases and vaccination coverage in Australia, 1999–2000. *Commun Dis Intell* 2002; Suppl:S1–S111. Available from: http://www.health.gov.au/pubhlth/cdi/pubs/pdf/vpd9900.pdf

18. Wise RP, Salive ME, Braun MM, Mootrey GT, Seward JF, Rider LG, *et al*. Postlicensure safety surveillance for varicella vaccine. [Published erratum appears in *JAMA*; 2000 Dec 27;284:3129]. *JAMA* 2000;284:1271–1279.

19. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine* 2002;20 Suppl 1: S58–S67.

20. Report of the Committee on Safety of Medicines Expert Working Group on Meningococcal Group C Conjugate Vaccines. May 2002. Available from: http://www.mca.gov.uk/ourwork/monitorsafequalmed/safetymessages/mencwgreport.pdf Accessed 19 July 2004.

21. South Australia Department of Human Services. Meningococcal C vaccination program. CDC *Bulletin* 2003;55:1–2.

22. Health Canada. Adverse events temporally associated with vaccines — 1992 report. *Can Commun Dis Rep* 1995;21:F1–F9.

23. Horby P, Gilmour R, Wang H, McIntyre P. Progress towards eliminating Hib in Australia: An evaluation of *Haemophilus influenzae* type b prevention in Australia, 1 July 1993 to 30 June 2000. *Commun Dis Intell* 2003;27:324–341.

24. Victorian Department of Human Services. Notifications of infectious diseases: Victorian Summary – 1 January to 12 July 2004. State Government of Victoria. Available from: http://www.health.vic.gov.au/ideas/downloads/daily_reports/rptVictorianSummary.pdf Accessed 19 July 2004 – report updated daily.

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
Hep B	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)