Annual reports

Annual report: surveillance of adverse events following immunisation in Australia, 2010

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Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) for 2010, and describes reporting trends over the 11-year period 2000 to 2010. There were 3,894 AEFI records for vaccines administered in 2010, the highest number reported in any year, and a 63% increase over the 2,396 in 2009. The increase was almost entirely attributable to the large number of reports following seasonal influenza (n=2,354) and pandemic H1N1 (pH1N1) influenza vaccines (n=514). In children <7 years of age, the number of reports following influenza vaccine increased almost 100-fold from 17 in 2009 to 1,693 in 2010 and, for people aged ≥18 years, from 135 to 496. For seasonal influenza vaccine, a disproportionate number of reports were from Western Australia (34%), consistent with more widespread influenza vaccination of children in that state, and 79% were identified as being associated with Fluvax® or Fluvax junior® (CSL Biotherapies). For pH1N1 vaccine, the number of reports in children <7 years of age increased from 23 in 2009 to 329 in 2010, but was available for this age group for only 1 month (December) in 2009. In those aged ≥18 years, for whom the pH1N1 vaccine was available from late September 2009, pH1N1 vaccine reports decreased from 1,209 in 2009 to 109 in 2010. For influenza vaccines, 79% of reports included fever, 45% allergic reactions and 15% malaise. In children aged <7 years, there were 169 reports of convulsions (127 febrile), compared with 19 in 2009. In contrast, for non-influenza vaccines, reporting rates in children <7 years of age increased only marginally from 14.1 per 100,000 in 2009 to 19.3 per 100,000 in 2010. Four deaths temporally associated with immunisation were reported but none were considered to have a causal association. *Commun Dis Intell* 2011;35(4):263–280.

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

Introduction

An 'adverse event following immunisation' is generally regarded as any serious or unexpected event that occurs after the administration of a vaccine(s), which may be related to the vaccine itself or to its handling or administration. An adverse events following immunisation (AEFI) can be *coincidentally* associated with the *timing* of immunisation without necessarily being caused by the vaccine or the immunisation process. This report summarises national passive surveillance data for AEFI reported to the Therapeutic Goods Administration (TGA) to 28 February 2011. The report focuses on AEFI reported for vaccines administered during 2010 and trends in AEFI reporting for the 11-year period 2000 to 2010. Reports summarising national AEFI surveillance data have been published regularly since 2003.[1–15] Several important changes to both AEFI surveillance methods and the Australian childhood vaccination schedule have occurred since then that affect the AEFI surveillance data presented in this report.

Recent changes to vaccine funding and availability that had a significant impact on the AEFI surveillance data presented in this report include:

(i) In 2010, annual vaccination with seasonal trivalent influenza vaccine (TIV, containing 3 influenza strains: A/H1N1, A/H3N2 and B) was funded under the National Immunisation Program (NIP) for people aged ≥6 months with medical risk factors (previously subsidised through the Pharmaceutical Benefits Scheme) and all Indigenous people aged ≥15 years (previously all Indigenous adults ≥50 years and 15–49 years with medical risk factors).[16]

(ii) The pandemic H1N1 (pH1N1) influenza vaccine (Panvax®), which was introduced in Australia from 30 September 2009 for people aged ≥10 years and from 4 December 2009 for children aged 6 months to 10 years,remained available throughout 2010.[17]

(iii) On 23 April 2010, the use of the 2010 seasonal TIV in children <5 years of age was suspended by Australia's Chief Medical Officer due to an increased number of reports of fever and febrile convulsions post vaccination. A subsequent investigation identified that Fluvax® and Fluvax junior®(CSL Biotherapies), but neither of the other two available brands registered for use in young children, were associated with an

unacceptably high risk of febrile convulsions.[18] The recommendation to resume the use of seasonal influenza vaccine in children aged 6 months to 5 years, using brands other than Fluvax® and Fluvax junior®, occurred in August 2010.[19]

Other important changes to vaccine funding and availability that impact on the interpretation of trend data have been described in detail in previous reports .[1–15] These changes are listed in Table 1 in chronological order.[20–26] To assist readers a glossary of the abbreviations of the vaccines referred to in this report is at the end of this report.

Methods

AEFI are notified to the TGA by state and territory health departments, health professionals, vaccine manufacturers and members of the public.[20,22] All reports are assessed using internationally consistent criteria[27] and entered into the Australian Adverse Drug Reactions System (ADRS) database. All serious reports for drugs and vaccines are reviewed by the TGA. Other reports are used in data mining and signal detection activities.

Adverse events following immunisation data

De-identified information on all AEFI reported to the TGA from 1 January 2000 to 28 February 2011 and stored in the ADRS database were released to the National Centre for Immunisation Research and Surveillance. Readers are referred to previous AEFI surveillance reports for a description of the surveillance system.[1,2]

AEFI records* contained in the ADRS database were eligible for inclusion in the analysis if a vaccine was recorded as 'suspected'† of involvement in the reported adverse event and *either*

(a) the vaccination occurred between 1 January 2000 and 31 December 2010, *or*

(b) for records where the vaccination date was not recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 31 December 2010.

* The term 'AEFI record is used throughout this report because a single AEFI notification (report to the Therapeutic Goods Administration) may generate more than one 'AEFI record' in the Adverse Drug Reactions System 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).

† Records are classified as 'suspected' if the report contains sufficient information to be valid and the relationship between reported reactions and drugs is deemed as biologically plausible.

Study definitions of adverse events following immunisation outcomes and reactions

AEFI were defined as 'serious' or 'non-serious' based on information recorded in the ADRS database and criteria similar to those used by the World Health Organization[27] and the US Vaccine Adverse Events Reporting System.[28] In this report, an AEFI is defined as 'serious' if the record indicated that the person had recovered with sequelae, was admitted to a hospital, experienced a life-threatening event, or died.

The causality ratings of 'certain', 'probable' and 'possible' are assigned to individual AEFI records by the TGA. They describe the likelihood that a suspected vaccine or vaccines was/were associated with the reported reaction at the level of the individual vaccine recipient. Factors considered in assigning causality ratings include the timing of the reaction following vaccination (temporal association), the spatial correlation of symptoms and signs in relation to vaccination (for injection site reactions) and whether one or more vaccines were administered. These factors are outlined in more detail elsewhere.[1] In many instances a causal association between vaccines administered to an individual and events that occurred subsequently cannot be clearly ruled in or out. Children, in particular, often receive several vaccines at the same time. All co-administered vaccines are usually listed as 'suspected' of involvement in a systemic adverse event as it is usually not possible to attribute the AEFI to a single vaccine.

Typically, each AEFI record lists several symptoms, signs and/or diagnoses that had been coded by TGA staff from the reporter's description into standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA®).[29] AEFI reports of suspected anaphylaxis and hypotonic-hyporesponsive episodes (HHE) were classified using the Brighton Collaboration case definitions when sufficient data were available.[30,31]

To analyse reported AEFI, MedDRA® coding terms were grouped to create a set of reaction categories. Firstly, reaction categories were created that were analogous to the AEFI listed and defined in *The Australian Immunisation Handbook* (9th edition).[22] Where MedDRA® coding terms could not be categorised into *Handbook* categories, additional categories were created for those that were listed in more than 1% of AEFI records (e.g. headache, dizziness, change in heart or respiratory rate or rhythm). Reaction terms listed in less than 1% of records were grouped into broader categories based on the organ system where the reaction was manifested (e.g. gastrointestinal, neurological).

Table 1: Changes to the Australian Standard Vaccination Schedule, 2003 to 2009[22–28]

Date	Intervention
2003	Commencement of the meningococcal C conjugate vaccine (MenCCV) immunisation program. 18-month dose of DTPa vaccine removed from the National Immunisation Program.
2004	dTpa funded at 15–17 years of age replacing the diphtheria-tetanus dose.
2005	**January 2005** Universal funded infant 7-valent pneumococcal conjugate vaccine (7vPCV) program replaced the previous targeted childhood program, with a catch-up program for children aged <2 years. Universal 23-valent pneumococcal polysaccharide vaccine (23vPPV) for adults aged ≥ 65 years replaced previous subsidy through the Pharmaceutical Benefits Scheme. **November 2005** Universal funded immunisation against varicella at 18 months of age from November 2005 with a school-based catch-up program for children at 10–12 years of age not previously vaccinated and without a history of varicella infection (no funded catch-up for children 2–10 years of age). IPV funded to replace OPV, in combination vaccines.
2007	**April 2007** Funded immunisation against human papillomavirus for all Australian girls aged 12–13 years delivered through a school-based program from April 2007, with a temporary catch-up program through schools or primary care providers for females aged 13–26 years until December 2009. **July 2007** Universal funded immunisation against rotavirus at 2 and 4 months of age (Rotarix®) or at 2, 4 and 6 months of age (Rotateq®).
2008	Western Australia commenced a seasonal influenza vaccination program for all children aged 6 months to < 5 years (born after 1 April 2003). In March 2008, Queensland, South Australia and Victoria changed from using two combination vaccines (quadrivalent DTPa-IPV and Hib-HepB) to the single hexavalent DTPa-IPV-HepB-Hib vaccine.
2009	By late 2009, all states and territories were using the single hexavalent DTPa-IPV-Hib-HepB (Infanrix hexa®) vaccine for all children at 2, 4 and 6 months of age, due to an international shortage of *Haemophilus influenzae* type b (Hib) (PedvaxHib® [monovalent] and Comvax® [Hib-HepB]) vaccines.

Data analysis

All data analyses were performed using SAS software version 9.2.[32] 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.

AEFI reporting rates per 100,000 administered doses were estimated where reliable information was available on the number of doses administered. This was done for 10 vaccines funded through the NIP for children aged <7 years, for influenza and pH1N1 vaccines in adults aged ≥18 years, and for 23vPPV in the ≥65-years age group.

Denominator data to estimate influenza and 23vPPV AEFI reporting rates were obtained from a national adult coverage survey conducted in 2009.[33] For 23vPPV, the number of people vaccinated in 2010 was derived from the number of people who reported receipt of the vaccine divided by 5. The number of administered doses of each of the 10 childhood vaccines was obtained from the Australian Childhood Immunisation Register (ACIR), a national population-based register of approximately 99% of children aged <7 years.[34]

Notes on interpretation

Caution is required when interpreting the AEFI data presented in this report. Due to reporting delays and late onset of some AEFI, the data are considered preliminary, particularly for the fourth quarter of 2010. Data published in previous reports for 2000–2009[1–15] may differ from that presented in this report for the same period because this report has been updated to include delayed notifications of AEFI to the TGA that were not included in prior publications.

The information collated in the ADRS database is intended primarily for signal detection and hypothesis generation. While AEFI reporting rates can be estimated using appropriate denominators, they cannot be interpreted as incidence rates due to underreporting and biased reporting of suspected AEFI, and the variable quality and completeness of information provided in individual AEFI notifications.[1–15,35]

It is important to note that this report is based on vaccine and reaction term information collated in the ADRS database and not on comprehensive clinical notes or case reviews. The reaction terms are created from available information and are similar, but not identical, to *The Australian Immunisation Handbook*[22] AEFI case definitions.

The reported symptoms, signs and diagnoses in most of the AEFI records, where possible, in the ADRS database are temporally associated with vaccination but are not necessarily causally associated with a vaccine or vaccines.

For reports where the date of vaccination was not recorded, the date of onset or date event reported to Therapeutic Goods Administration was used as a proxy for the vaccination date.

Results

The ADRS database included a total of 3,894 AEFI records where the date of vaccination (or onset of adverse event, if vaccination date was not reported) was between 1 January and 31 December 2010. Of these, 2,868 records (74%) related to influenza vaccines (seasonal influenza, 61%; pH1N1, 13%), accounting for an increase of 63% over the total records for 2009.

In 2010, 68% of AEFI (n=2,661) were reported to the TGA via states and territories, while the rest were reported directly to the TGA; 13% (n=502) were reported by members of the public, 16% (n=606) by doctors or health care providers, 2% (n=89) by hospitals, and 1% (n=36) by drug companies. The proportion reported by members of the public was less than in 2009 (n=664; 28%) but much higher than in 2008 (n=51; 3%), with 95% of the reports by members of the public following influenza vaccines.

Reporting trends

The overall AEFI reporting rate for 2010 was 17.4 per 100,000 population, compared with 11.0 per 100,000 population in 2009—the highest rate in the 11-year period from 2000 to 2010.

Figure 1 shows the increase in reporting by the general public direct to the TGA in 2009 and 2010, and that the vast majority of reported events (from all reporter types) were of a non-serious nature. Figures 2a, 2b and 2c show that the rise in the reporting rate in 2009 and in 2010 was due to reports following the receipt of pH1N1 and seasonal influenza vaccines, and that in 2010 this was predominantly in children (Table 2). Figures 2a, 2b and 2c also demonstrate marked variations of reporting levels in association with previous changes to the National Immunisation Program from 2000

Figure 1: Adverse events following immunisation, ADRS database, 2000 to 2010, by quarter

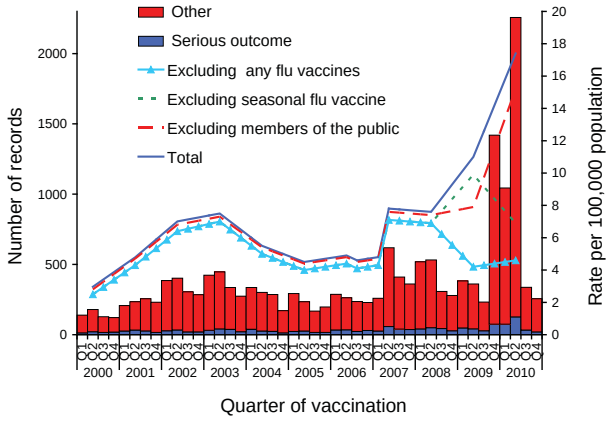


Figure 2a: Adverse events following immunisation for individuals aged > 7 years, ADRS database, 2000 to 2010, by quarter and vaccine type

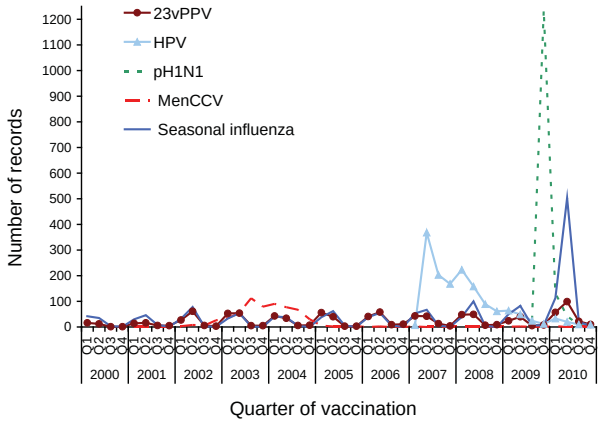


Figure 2b: Adverse events following immunisation for children aged 1 to < 7 years, ADRS database, 2000 to 2010, by quarter and vaccine type

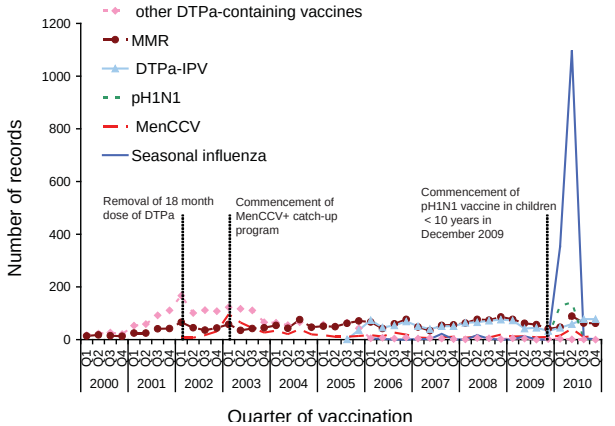
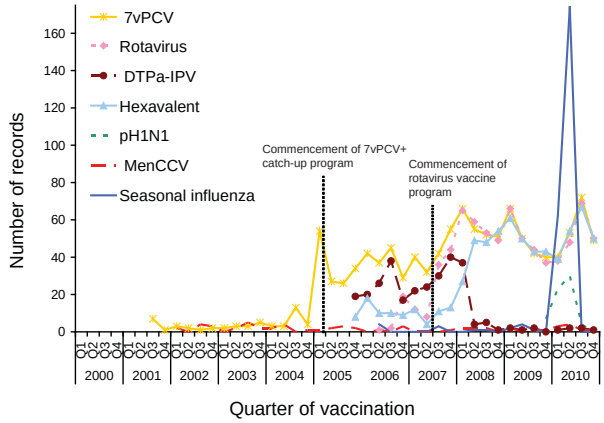


Figure 2c: Adverse events following immunisation for children aged < 1 year, ADRS database, 2000 to 2010, by quarter and vaccine type



* Meningococcal C conjugate vaccine (MenCCV) was introduced into the National Immunisation Program schedule on 1 January 2003; 7-valent pneumococcal conjugate vaccine (7vPCV) on 1 January 2005; DTPa-IPV and DTPa-IPV-HepB-Hib (hexavalent) vaccines in November 2005; rotavirus (RotaTeq® and Rotarix®) vaccines on 1 July 2007; pH1N1 influenza vaccine for children 6 months to 10 years on December 2009; and seasonal trivalent influenza vaccine in 2010 (Table 1).

onwards. Reporting rates usually increased with the commencement of a new vaccination program and then stabilised at lower rates.[2,5,7,8,14]

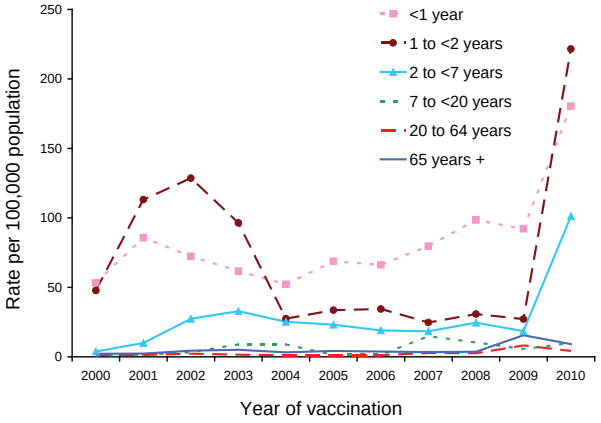
The usual seasonal pattern of AEFI reporting in adults, with peaks in the first half of the year, was also apparent in 2010 (Figure 2a), corresponding to the months when older Australians receive 23vPPV and influenza vaccine (March to June).

Age distribution

Compared with 2009, AEFI reporting rates in children increased substantially in all age groups but the magnitude differed: among the <1 year age group, it increased approximately 2-fold from 92.1 to 180.4 per 100,000 population, but in the 1 to <2 year age group it increased by a factor of almost 10 from 27.2 to 221.6, and in the 2 to <7 year age group the increase was just over 5-fold from 18.5 to 101.2 (Figure 3). These differences were almost entirely related to the increase in reports following influenza vaccines; primarily seasonal influenza vaccines.

In those over the age of 7 years, there were also increases in the reporting rates of most other individual vaccines given to these age groups in 2010, compared with 2009. However, AEFI reporting rates decreased for the 20–64 year age group (from 8.2 to 4.3 per 100,000 population) and the >65 year age group (from 15.5 to 9.2), mainly associated with the decline in reports following pH1N1 influenza vaccine in these age groups (Figures 2a and 3).

Figure 3: Rates of adverse events following immunisation per 100,000 population, ADRS database, 2000 to 2010, by age group and year of vaccination



Geographical distribution

AEFI reporting patterns varied between states and territories for vaccines received during 2010 (Table 3) as reported previously.[1,2,6–9,13,14] Western Australia, South Australia and the Australian Capital Territory had the highest reporting rates (42.1, 34.9 and 32.6 per 100,000 population, respectively) while New South Wales had the lowest rate (5.9 per 100,000 population). AEFI reporting rates increased in all jurisdictions in 2010 compared with 2009, except in Victoria and New South Wales.[14] After excluding influenza vaccines, there was a decrease in reporting rates in all jurisdictions and in all age groups (Figure 1).

Vaccines

Thirty-three different vaccines were included in the 3,894 AEFI records received in 2010 (Table 2). The percentage of records where only one vaccine was reported differed by vaccine, typically varying according to whether multiple vaccines were routinely co-administered for the patient's age. The percentage of AEFI records assigned causality ratings of 'certain' or 'probable' also varied, in accordance with the frequency of injection site reactions, for which the attribution of causality is more straightforward. There were also variations in the proportions with outcomes defined as 'serious'.

The most frequently reported individual vaccine was seasonal influenza vaccine with 2,354 records (61% of total) followed by pH1N1 (n=514; 13%) (Table 2).

Table 2: Vaccine types listed as 'suspected' in records of adverse events following immunisation, ADRS database, 2010

Suspected vaccine type*	AEFI records	One suspected vaccine or drug only†		'Certain'/ 'probable' causality rating		'Serious' outcome‡		Age group§			
								<7 years		≥7 years	
	n	n	%‖	n	%‖	n	%‖	n	%‖	n	%‖
Influenza	2,354	2,124	90	41	2	134	6	1,693	72	640	27
pH1N1	514	471	92	28	5	41	8	329	64	181	35
MMR	288	27	9	13	5	17	6	274	95	13	5
DTPa-IPV	269	101	38	52	19	8	3	266	99	3	1
DTPa-IPV-HepB-Hib	221	9	4	7	3	29	13	221	100	0	0
7vPCV	216	7	3	8	4	29	13	216	100	0	0
Rotavirus	210	29	14	7	3	37	18	209	100	1	0
23vPPV	201	122	61	38	19	15	7	11	5	188	94
dTpa	133	108	81	34	26	6	5	1	1	130	98
Varicella	118	40	34	2	2	16	14	97	82	18	15
Hib	91	5	5	0	0	7	8	89	98	2	2
Hepatitis B	90	30	33	1	1	4	4	10	11	79	88
MenCCV	86	4	5	3	3	6	7	84	98	2	2
HPV	72	37	51	6	8	2	3	0	0	72	100
DTPa	20	12	60	6	30	2	10	9	45	10	50
Hepatitis A	18	3	17	0	0	1	6	13	72	4	22
dT	14	8	57	2	14	0	0	2	14	12	86
Hepatitis A + B	10	5	50	0	0	2	20	0	0	10	100
10vPCV	10	4	40	2	20	2	20	9	90	1	10
BCG	9	8	89	4	44	1	11	5	56	4	44
Hepatitis A-Typhoid	8	3	38	0	0	0	0	0	0	8	100
Typhoid	7	1	14	0	0	2	29	3	43	3	43
Cholera	5	3	60	2	40	1	20	0	0	4	80
Men4PV	5	1	20	0	0	1	20	4	80	1	20
Rabies	5	4	80	1	20	0	0	1	20	4	80
Yellow fever	5	2	40	0	0	2	40	0	0	5	100
DTPa-IPV-HepB	4	1	25	0	0	0	0	4	100	0	0
Q fever	4	4	100	2	50	0	0	0	0	4	100
IPV	3	1	33	0	0	0	0	2	67	1	33
dTpa-IPV	2	0	0	0	0	0	0	0	0	2	100
Japanese encephalitis	1	0	0	0	0	0	0	0	0	1	100
Hib-Hepatitis B	1	0	0	0	0	0	0	1	100	0	0
Tetanus	1	1	100	0	0	0	0	0	0	1	100
Total¶	3,894	3,169	81	245	6	255	7	2,629	68	1,230	32

* See appendix for abbreviations of vaccine names.

† Adverse events following immunisation (AEFI) records where only one vaccine was suspected of involvement in a reported adverse event.

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

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

‖ Percentages are calculated for the number of AEFI records where the vaccine was suspected of involvement in the AEFI, e.g. HPV was 'suspected' in 72 AEFI records; this was the only suspected vaccine in 51% of the 72 AEFI records, 8% had 'certain' or 'probable' causality ratings, 3% were defined as 'serious' and 100% were for those aged ≥7 years.

¶ Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and an AEFI record may list more than one vaccine.

Table 3: Adverse events following immunisation, ADRS database, 2010, by state or territory

State or territory	AEFI records n	AEFI records %	Annual reporting rate per 100,000 population* Overall	'Certain'/ 'probable' causality rating	'Serious' outcome†	Aged <7 years
Australian Capital Territory	117	3	32.6	2.0	1.4	216.6
New South Wales	424	11	5.9	0.4	0.5	38.0
Northern Territory	61	1	26.6	3.9	2.2	144.8
Queensland	1,048	27	23.2	2.0	1.5	164.8
South Australia	574	15	34.9	2.1	0.9	228.9
Tasmania	79	2	15.6	1.2	1.2	95.9
Victoria	575	15	10.4	0.6	0.7	81.9
Western Australia	966	25	42.1	1.2	3.2	376.4
Other‡	50	1	na	na	na	na
Total	3,894	100	17.4	1.1	1.1	130.9

* Average annual rates per 100,000 population calculated using mid-2010 population estimates (Australian Bureau of Statistics).

† Adverse events following immunisation (AEFI) records defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening or death).

‡ Records where the jurisdiction in which the AEFI occurred was not reported or was unclear. AEFI records in this category were notified mainly by pharmaceutical companies (n = 36), members of the public (n = 9), states and territories (n = 3), and health care providers (n = 2).

Reactions

The distribution and frequency of reactions listed in AEFI records for vaccines received in 2010 are shown in Tables 4a and 4b. In Table 4a, only the reaction terms analogous to those listed in *The Australian Immunisation Handbook*[22] are shown. In Table 4b, other reaction categories are listed in descending order of frequency.

The most frequently reported adverse events were fever (61%), allergic reaction (39%), injection site reaction (ISR) (19%), malaise (13%), neurological/ psychological and headache (10% each), nausea (6%), and respiratory, myalgia, rash and convulsions (5% each) (Table 4a, Table 4b and Figure 4).

The number of reports in each reaction category has changed over time. In previous years, reports of allergic reactions peaked in 2003 and 2007, coinciding with the national school-based MenCCV immunisation program and the HPV school program.[2,7,8] Much of the variation in reporting of ISR related to specific changes in the immunisation schedules for vaccines that are known to have higher rates of ISR, including DTPa-containing vaccines, MenCCV, 23vPPV and HPV vaccine.[5–19,36,37] Increases in reports of fever were largely associated with the new vaccines added to the NIP in the reporting period, including rotavirus and HPV in 2007. However, by far the largest peaks in reports since 2000 have been associated with the pH1N1 and seasonal influenza 2010 vaccines (Figure 4). In particular, there were large peaks of reports of fever and allergic reactions in 2009 associated with the pH1N1 vaccine, and in 2010 associated with both pH1N1 and seasonal influenza vaccines. Reports of convulsions peaked in 2010, mainly associated with seasonal influenza but also to a lesser extent with pH1N1. The peaks in neurological or psychological conditions in both years is mainly related to pH1N1 and seasonal influenza vaccine, while the increase in ISR was particularly associated with non-influenza vaccines, particularly 23vPPV.

Severity of outcomes

Summary data on outcomes are presented in Table 5. Sixty-seven per cent of reported AEFI in 2010 were defined as 'non-serious' while 7% were defined as 'serious' (i.e. recovery with sequelae, requiring hospitalisation, experiencing a life-threatening event or death). This is similar to the proportions of serious AEFI observed in previous

Figure 4: Selected frequently reported adverse events following immunisation, ADRS database, 2000 to 2010, by event type and quarter

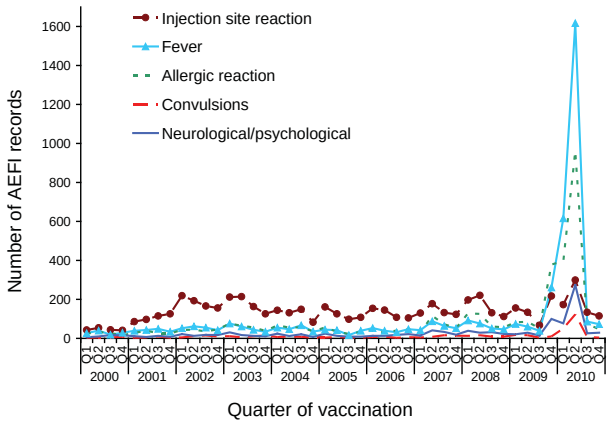


Table 4a: Reaction categories of interest* mentioned in records of adverse events following immunisation, 2010

Reaction category*	AEFI records	Only reaction reported†		'Certain'/'probable' causality rating		Age group‡ <7 years		≥7 years	
	n	n	%§	n	%§	n	%§	n	%§
Fever	2,392	261	11	40	2	1,989	83	381	16
Allergic reaction‖	1,534	82	5	27	2	1,197	78	322	21
Injection site reaction	721	126	17	185	26	312	43	404	56
Rash¶	196	53	27	6	3	149	76	45	23
Convulsions	185	54	29	0	–	174	94	11	6
Abnormal crying	161	3	2	2	1	157	98	4	2
Syncope	84	44	52	13	15	19	23	65	77
Arthralgia	66	2	3	1	2	5	8	58	88
Lymphadenopathy/itis**	48	4	8	4	8	5	10	42	88
Hypotonic-hyporesponsive episodes	39	22	56	2	5	38	97	1	3
Arthritis	22	4	18	1	5	5	23	16	73
Anaphylactic reaction	16	14	88	1	6	4	25	12	75
Guillain-Barré syndrome	10	10	100	0	–	0	–	10	100
Intussusception	10	7	70	1	10	10	100	0	–
Death††	3	1	33	0	–	2	67	1	33
Abscess	3	1	33	2	67	2	67	1	33
Sepsis	2	0	–	0	–	2	100	0	–
Thrombocytopenia	2	1	50	0	–	1	50	1	50
Brachial neuritis	1	1	100	0	–	0	–	1	100
Parotitis	1	0	–	0	–	1	100	0	–
Orchitis	0	0	–	0	–	0	–	0	–
Encephalitis	0	0	–	0	–	0	–	0	–
Osteitis	0	0	–	0	–	0	–	0	–
Encephalopathy	0	0	–	0	–	0	–	0	–
Total‡‡	3,894	3,169	81	245	6	2,629	68	1,230	32

* Reaction categories were created for the adverse events following immunisation (AEFI) of interest listed and defined in *The Australian Immunisation Handbook*, (9th edition, p 58–65 and 360–3)[22] as described in the Methods section.

† AEFI records where only one reaction was reported.

‡ Not shown if neither age nor date of birth were recorded.

§ Percentages relate to the number of AEFI records in which the specific reaction term was listed, e.g. of 721 AEFI records listing injection site reaction, 17% listed only one type of reaction while 26% had a causality rating of 'certain' or 'probable' and 43% were for children aged <7 years.

‖ Allergic reaction includes skin reactions including pruritus, urticaria, periorbital oedema, facial oedema, erythema multiforme etc. (excludes skin reactions presented elsewhere in this table); and/or gastrointestinal (e.g. diarrhoea, vomiting) symptoms and signs but does not include other abdominal symptoms like abdominal pain, nausea, flatulence, abnormal faeces, haematochesia, etc. Does not include anaphylaxis.

¶ Includes general terms of rash but does not include pruritic rash.

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

†† A fourth case of intra-uterine foetal death at 22 weeks gestation not included as the child was not born and does not fit in the age group categories.

‡‡ Total number of AEFI records analysed, not the total in each column as categories are not mutually exclusive and an AEFI record may list more than one reaction term.

Table 4b: 'Other'* reaction terms listed in records of adverse events following immunisation, 2010

Reaction term*	AEFI records	Only reaction reported†		'Certain'/'probable' causality rating		Age group‡			
						<7 years		≥7 years	
	n	n	%§	n	%§	n	%§	n	%§
Malaise	505	1	0.2	11	2	334	66	166	33
Neurological/psychological	406	0	–	7	2	337	83	67	17
Headache	388	2	1	7	2	162	42	225	58
Nausea	220	0	–	2	1	59	27	161	73
Respiratory	201	12	6	3	1	140	70	61	30
Myalgia	199	4	2	4	2	6	3	130	65
Pain	153	3	2	4	3	53	35	98	64
Tremor	148	0	–	0	–	121	82	27	18
Dizziness	119	3	3	4	3	17	14	101	85
Somnolence	113	2	2	3	3	97	86	15	13
Pallor	107	5	5	3	3	82	77	24	22
Abdominal pain	105	2	2	3	3	63	60	41	39
Circulatory	86	3	3	2	2	48	56	38	44
Increased sweating	75	2	3	1	1	28	37	47	63
Gastrointestinal – RVV‖	71	12	17	3	4	70	99	1	1
Reduced sensation	54	6	11	0	–	3	6	50	93
ENT	49	3	6	1	2	6	12	42	86
Erythema	47	7	15	1	2	28	60	19	40
Oedema	47	1	2	1	2	22	47	25	53
Flushing	25	0	–	0	–	11	44	13	52
Vision impaired	24	1	4	0	–	8	33	16	67
Weakness	21	0	–	1	5	5	24	16	76
Other	409	34	8	15	4	230	56	173	42
eye or ear	65	1	2	1	2	42	65	23	35
cardiovascular	57	2	4	2	4	38	67	18	32
general non-specific	37	9	24	2	5	17	46	19	51
infection	32	4	13	1	3	17	53	14	44
respiratory	28	1	4	–	–	17	61	11	39
psychological	26	0	–	1	4	20	77	6	23
neurological	28	6	21	1	4	13	46	15	54
skin¶	17	2	12	1	6	11	65	6	35
renal/urogenital	16	1	6	0	–	7	44	9	56
gastrointestinal**	15	1	7	2	13	7	47	6	40
musculoskeletal	12	1	8	1	8	3	25	9	75
metabolic/endocrine	12	0	–	0	–	9	75	3	25
pregnancy/congenital	9	5	56	0	–	0	–	9	100
miscellaneous	8	1	13	0	–	2	25	5	63
haematological	9	0	–	0	–	4	44	5	56

* Reaction terms not listed in *The Australian Immunisation Handbook*[22] but included in adverse events following immunisation (AEFI) records in the Adverse Drug Reactions System database. The top part of the table shows reaction terms included in 1% or more of AEFI records; the bottom part of the table shows reaction terms, grouped by organ system, that were included in less than 1% of AEFI records.

† AEFI records where only one reaction was reported.

‡ Not shown if neither age nor date of birth were recorded.

§ Percentages relate to the number of AEFI records in which the specific reaction term was listed, e.g. of 721 AEFI records listing injection site reaction, 17% listed only one type of reaction while 26% had a causality rating of 'certain' or 'probable' and 43% were for children aged <7 years.

‖ Gastrointestinal – RVV includes GI reactions following rotavirus vaccination only.

¶ Other, skin includes purpura, petechie, blister, burning, dermatitis, dry skin etc. but does not include skin reactions.

** Other, gastrointestinal does not include reaction categories coded as GI reactions or gastrointestinal – RVV signs and symptoms.

years.[13,14] A further 11% were recorded as not fully recovered at the time of reporting and 56% of these were following receipt of pH1N1 and seasonal influenza vaccine. Eighty-eight per cent of cases recorded as 'not fully recovered' had missing information on hospitalisation; 57% were reported by states and territories, 27% by health care providers and 12% by members of the public. Information on severity could not be determined for 15% (n=597) of records due to insufficient data. Of these, 79% were following receipt of influenza vaccines and the majority of these reports came from either states and territories (46%) or members of public (34%), with little specific information provided. Thirty-three per cent of these reports were reported by Western Australia and 68% were for children <7 years of age. Of those without information describing severity, the most commonly reported adverse reactions were: fever (63%); allergic reactions (41%); injection site reaction (14%); malaise (11%); headache (10%); rash (6%); convulsion and myalgia (5% each); and nausea (4%).

A total of 245 (6%) AEFI records were assigned causality ratings of either 'certain' (n=175; 4%) or 'probable' (n=70; 2%) and the rest (94%) were rated as 'possible'. A similar number of 'serious' AEFI were assigned certain or probable causality ratings compared with 'non-serious' AEFI (5% versus 6%) (Table 5).

The reactions recorded as 'serious' (n=255) were fever (n=119; 47%); allergic reactions (n=71; 27%); convulsions (n=65; 25%), including 52 febrile convulsions; injection site reactions (n=28; 11%); diarrhoea/vomiting (n=17; 7%); HHE (n=9; 4%); anaphylaxis (n=8; 3%); Guillain-Barré syndrome (GBS) (n=7; 3%); intussusception (n=7; 3%); 5 cases of syncope (2%); 4 reports of death (2%); and 1 case of idiopathic thrombocytopenic purpura (ITP). Other relatively severe reactions that were not classified as 'serious', either because they did not satisfy the criteria, or due to a lack of information about their outcome and/or hospitalisation status, included: convulsion (n=120; 120/185=65%), including 75 febrile convulsions; HHE (n=30; 30/39=77%); anaphylaxis (n=8; 8/16=50%); GBS (n=3; 3/10=30%); and intussusception (n=3; 3/10=30%).

Of the total 185 cases of convulsion, 169 (91%) were children aged <5 years and 66% were reported in the second quarter of 2010. Thirty-eight per cent of reports (n=71) were from Western Australia followed by Queensland (19%; n=35) and New South Wales (16%; n=29). The most commonly suspected vaccines were seasonal influenza vaccine (n=119) and pH1N1 (n=44), either given alone or co-administered with other vaccines. There were 127 cases classified as febrile convulsions across Australia in all age groups during 2010, of which 73% (n=124) were reported in children <5 years of age.

Table 5: Outcomes of adverse events following immunisation, ADRS database, 2010

Outcome	AEFI records		'Certain'/ 'probable' causality rating†		Age group‡ <7 years		≥7 years	
	n	%	n	%	n	%	n	%
Non-serious	2,624	67	147	6	1,865	71	742	28
Not recovered at time of report	418	11	53	13	183	44	231	55
Not known (missing data) – total	597	15	32	5	403	68	180	30
Not known (missing data)‖	394	10	25	6	252	64	129	33
Serious:	255	7	13	5	178	70	77	30
recovered with sequelae	3		–		2		1	
hospital treatment – admission	227		13		158		69	
life-threatening event	20		–		15		5	
Death¶	3		–		2		1	
Total	3,894	100	245	6	2,629	68	1,230	32

* Percentages relate to the total number of adverse events following immunisation (AEFI) records (n=3,894).

† Causality ratings were assigned to AEFI records using criteria described previously.[1]

‡ AEFI records where both age and date of birth were not recorded are not shown (35 missing).

§ Percentages relate to the number of AEFI records with the specific outcome, e.g. of 2,624 AEFI records with a 'non-serious' outcome, 6% had causality ratings of 'certain' or 'probable' and 71% were for children aged <7 years.

‖ AEFI records with missing data reported by health care providers and states or territories only (excluding reports from members of the public).

¶ A fourth case of intra-uterine foetal death at 22 weeks gestation is not included as the child was not born and does not fit in the age group categories.

Of the 39 reported HHE, 38 (97%) were from children aged <7 years. Thirty reports (77%) were following administration of hexavalent/pneumococcal and rotavirus vaccines while only 3 reports were following influenza vaccines administered alone. The only case of HHE aged >7 years was aged 49 years and followed administration of the adult formulation dTpa vaccine. All the 10 cases of GBS were in people aged ≥35 years. Eight reports followed seasonal flu vaccine (6 following vaccination with Fluvax®, and one each with Influvac® and Vaxigrip®); one followed pH1N1 and another one followed adult dTpa. The timing in relation to administration of vaccine and onset of symptoms varied from 11 days to >4 months.

All 10 reports of intussusception were from infants (<1 year of age) following rotavirus vaccine administered alone or in combination with other vaccines.

Twelve of the 16 reports of anaphylaxis in 2010 occurred following receipt of one of the influenza vaccines administered alone or in combination with other vaccines (seasonal influenza vaccine n=8; pH1N1 n=4), while others occurred following the receipt of MMR (n=3), varicella (n=2), and one each following DTPa-IPV, HPV, HepA, HepB, DT, and adult dTpa.

Four deaths were recorded as being temporally associated with the receipt of vaccines; two following receipt of seasonal influenza vaccine.

- One case was a 2-year-old child who was found deceased on the morning following receipt of seasonal influenza vaccine (Fluvax Junior®, CSL Biotherapies). A post-mortem determined that a causal relationship between vaccination and death was not established.[15]
- The second case was an infant with a history of prematurity and apnoea, who had an apnoeic episode and died 5 days post vaccination with hexavalent, 7vPCV and rotavirus vaccines.
- The third death was a very elderly person 4 days following receipt of 23vPPV vaccine. He had pneumonia and was bacteraemic with *Streptococcus pneumoniae* (serotype 11A).

The fourth case was an intra-uterine foetal death at 22 weeks gestation following vaccination of a 20-year-old pregnant female who received the seasonal influenza vaccine (Influvac®, Solvay Biosciences) 16 days prior to the event. The cause of death was reported to be most likely because of intra-uterine infection. This case was not included in both the Tables 4 and 5 because of the nature of the death (see footnote of the Table 4 and 5). All deaths were investigated by the TGA and classified as not causally related to vaccination.

Adverse events following immunisation reports not including influenza vaccines

There were 1,316 reports in 2010 that related to non-influenza vaccines, of which 290 (22%) were co-administered with pH1N1 or seasonal influenza vaccine. Of those not co-administered with influenza vaccines (n=1,026), only 23 cases (2%) were reported by members of the public.

The most commonly reported vaccines in this category were those containing diphtheria, tetanus and acellular pertussis antigens (including combination DTPa-containing vaccines and dTpa [adult/adolescent formulation]) (649; 17% of the total 3,894 AEFI records) (Table 2). DTPa-IPV (269 records; 7%) and hexavalent DTPa-IPV-HepB-Hib (221 records; 6%) were the most frequently reported vaccines in this group. In the <1 year age group, reports that included DTPa-IPV decreased and reports of DTPa-IPV-HepB-Hib increased, in line with the changes in usage of those vaccines as outlined in the Introduction (Figure 2c). The other frequently reported vaccines were MMR (288 records; 7%), 7vPCV (216 records; 6%), and rotavirus (210 records; 5%).

In comparison to the number reported in 2009, AEFI reports were substantially reduced for HPV vaccine (153 in 2009 vs 72 in 2010) following the peak during the catch-up program in 2008–2009, and for Hib-HepB (10 in 2009 vs 1 in 2010) following the reduction in its use.[14] The number of reports for all other vaccines increased in 2010 (Figures 2a and 2b), which appears related to these vaccines being either co-administered with the influenza vaccines, and/or stimulated reporting associated with general heightened awareness of vaccine safety issues (associated with the childhood influenza vaccine suspension) that may have resulted in increased reporting of milder AEFI for other vaccines.

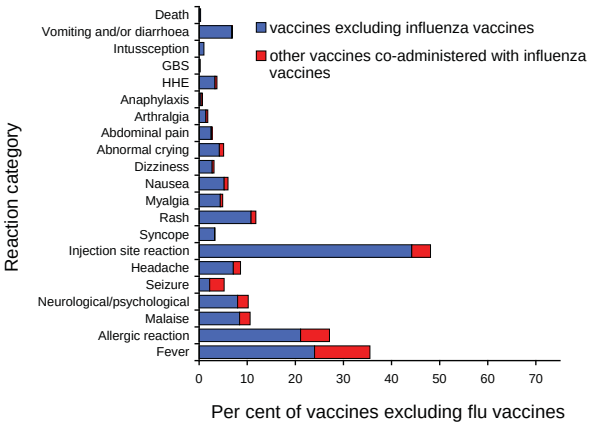
Eight per cent (n=80) of the non-influenza (n=1,026) AEFI records had outcomes defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening event or death) and 74% (n=59) were for children <7 years of age. There were no reports of life-threatening events; 77 people (96%) were admitted to hospital and there were 2 reports of death (described previously).

Serious AEFI included injection site reactions (44%), diarrhoea (21%), fever (24%), allergic reactions (21%), HHE (3%), and seizure (2%). There were 10 reports of intussusception, 4 reports of anaphylaxis and 1 report each of GBS and ITP.

The only case of ITP classified as serious was 17 days following administration of varicella vaccine. However, due to an alternate cause (febrile

intercurrent viral infection), the causality rating of 'unlikely' to be related to the vaccine was assigned. The distribution of more commonly reported AEFI is listed in Figure 5a.

Figure 5a: Frequently reported adverse events following immunisation with non-influenza vaccines, ADRS database, 2010



Pneumococcal vaccine and adults aged ≥65 years

There were 155 AEFI reports for older adults that included 23vPPV, of which 14 (9%) were coded as serious. Of the 14 serious cases, 6 cases were following receipt of 23vPPV vaccine administered alone while 8 cases were following receipt of one of the influenza vaccines co-administered with 23vPPV vaccine. The reports included 126 (81%) ISR, 33 (21%) fever, and 1 each of GBS, anaphylaxis and death. Forty-two per cent of reports in 2010 were following 23vPPV vaccine conjointly administered with one of the influenza vaccines, compared with 24% in 2009. Using the 2009 estimate of the number of doses of 23vPPV administered to people aged ≥65 years (n=317,400), the AEFI reporting rate was 48.8 per 100,000 doses, with rates of 4.4 per 100,000 for events classified as serious and 39.7 per 100,000 for ISR. This is substantially higher than the rates reported for 2009 and 2008 (13.3 and 18.9 respectively) (Table 6). The reporting rates for ISR for 23vPPV not co-administered with influenza vaccines was 22.1 per 100,000 doses for 2010 compared with 11.3 in 2009 and 14.8 in 2008.

Adverse events following immunisation reports including influenza vaccines

Of 3,894 total AEFI records reported in 2010, 74% (n=2,868) of records were related to influenza vaccines (seasonal influenza – 61% (n=2,354); pH1N1 – 13% (n=514)). This was a sharp contrast to 2009 (seasonal influenza vaccine – 162; pH1N1 – 1,312).[14]

The large number of reports following pH1N1 vaccination in 2009 was mainly attributed to more pH1N1 vaccine being used in 2009 than in 2010.

2010 seasonal influenza vaccine

The majority of the reports for seasonal influenza vaccine were for either Fluvax® or Fluvax junior® (CSL Biotherapies) (n=1,855; 79%) while another 15% did not specify the vaccine brand and were coded only as influenza vaccine. There were 86 adverse event reports following vaccination with Influvac® (Solvay Biosciences), 66 with Vaxigrip® (Sanofi Pasteur) and 1 with Fluarix® (GlaxoSmithKline); 82 (3%) were co-administered with 23vPPV.

A large proportion of the AEFI following seasonal influenza vaccine was reported to TGA via states and territories (70%). Of the remaining AEFI reports, 18% were provided by doctors and other health care providers and 12% were reported by members of the public. A large proportion of the total number of reports for seasonal influenza vaccine was from Western Australia (34%), compared with only 11% of reports for other vaccine types from that state. The increased proportion of reports from Western Australia is consistent with the greater use of seasonal influenza vaccine in that state due to their vaccine program for children <5 years of age.[38] Seventy-five per cent of the reports following seasonal influenza vaccine were defined as 'non-serious', 6% (n=134) were defined as 'serious' and an additional 11% were not categorised because of the non-availability of data on hospitalisation and outcome.

In 2010, there were 1,693 reported adverse events following seasonal influenza vaccination in children <7 years of age and 496 in people aged ≥18 years. The AEFI reporting rate in those aged ≥18 years was 10.4 per 100,000 administered doses, which was more than 3-fold higher than in 2009. As seen in previous years, the overall AEFI reporting rates were higher for vaccinees aged 18–64 years than among older people. However, there was an increase in the reporting rate of serious AEFI in all age groups and particularly among older people (aged ≥65 years). The most frequently reported adverse events were ISR (3.4 per 100,000 doses), fever (3.1), allergic reaction (2.4), headache (1.9), malaise (1.6), myalgia (1.4), nausea (1.4) and dizziness (0.9). The rate for each of these reactions was higher in the 18–64 year age group. There were 8 reports of GBS following seasonal influenza vaccination in 2010; 6 reports of anaphylaxis and 1 case of ITP. There were two reported deaths following seasonal vaccination as described previously.

The distribution of reaction types for seasonal influenza vaccine is presented in Figure 5b. The spectrum of reactions for seasonal influenza vac-

Table 6: Vaccine types listed as 'suspected' in records of adverse events following immunisation for four age groups (< 7, 7–17, 18–64 and ≥ 65 years), ADRS database, 2010

Vaccines*	AEFI records† (n)	Vaccine doses‡ (n)	Reporting rate per 100,000 doses§ 2010	2009	2008
<7 years					
DTPa-containing vaccines	491	1,115,696	44.0	37.4	46.3
DTPa-IPV	266	282,567	94.1	72.1	92.1
Pentavalent (DTPa-IPV-HepB)	4	387	1,033.6	28.4	22.5
Hexavalent (DTPa-IPV-HepB-Hib)	221	832,742	26.5	25.0	25.0
Haemophilus influenzae type b	89	279,263	31.9	16.3	19.4
Haemophilus influenzae type b-hepatitis B	1	829	120.6	163.6	39.6
Measles-mumps-rubella	274	568,799	48.2	34.0	38.5
Meningococcal C conjugate	84	293,499	28.6	16.4	17.5
Pneumococcal conjugate	216	822,514	26.3	25.4	27.0
Rotavirus vaccine	209	525,383	39.8	38.2	43.1
Varicella	97	275,893	35.2	8.3	14.9
Seasonal influenza	1,693	na	na	na	na
pH1N1	329	na	na	na	na
Total (<7 years)‖	750	3,881,876	19.3	14.1	17.8
7–17 years					
HPV	71	na	na	na	na
Hepatitis B	62	na	na	na	na
dTpa	52	na	na	na	na
Varicella	11	na	na	na	na
Seasonal influenza	144	na	na	na	na
pH1N1	72	na	na	na	na
Total (7–17 years)	412	na	na	na	na
18–64 years					
Seasonal influenza¶	343	3,170,300	10.8	3.8	3.4
pH1N1	90	na	na	na	na
dTpa	72	na	na	na	na
23vPPV¶	30	132,520	22.6	9.2	15.9
Total (18–64 years)	535	3,302,820	11.3	4.3	4.5
≥65 years					
23vPPV¶	155	317,400	48.8	13.3	18.9
Seasonal influenza¶	153	2,176,000	7.0	1.6	1.7
pH1N1	19	na	na	na	na
dTpa	6	na	na	na	na
Total ≥65 years	333	2,493,400	12.4	3.6	4.6

* Records where at least one of the vaccines shown in the table was suspected of involvement in the reported adverse event.

† Number of adverse events following immunisation (AEFI) records in which the vaccine was coded as 'suspected' of involvement in the reported adverse event and the vaccination was administered between 1 January and 31 December 2010. More than one vaccine may be coded as 'suspected' if several were administered at the same time.

‡ Number of vaccine doses recorded on the Australian Childhood Immunisation Register and administered between 1 January and 31 December 2010.

§ The estimated AEFI reporting rate per 100,000 vaccine doses recorded.

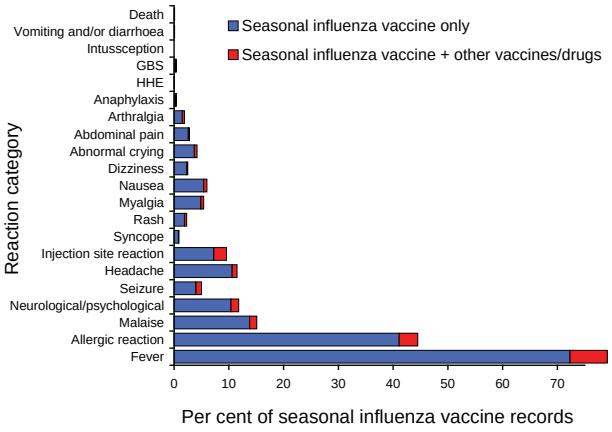
‖ Number of AEFI records excluding influenza vaccines administered alone. Most reports include more than one vaccine.

¶ Number of administered doses of 23vPPV and seasonal influenza vaccine estimated from the 2009 Australian Institute of Health and Welfare national adult vaccination survey.[35]

na Not applicable

cine was different to that for non-influenza vaccines with a substantially higher proportion of fever (79% compared with 24% for non-influenza vaccines) and allergic reaction (45% vs 21%) and a lower proportion of ISR (7% vs 44%). There were 119 (5%) reports of convulsions, including 88 febrile convulsions; 20 (1%) syncope; 8 (0.3%) each of anaphylaxis and GBS; and 2 (0.1%) reports of death following seasonal influenza vaccine. A higher proportion of reports following seasonal influenza vaccine came from members of the public (12% compared with 2% for non-influenza vaccines).

Figure 5b: Frequently reported adverse events following seasonal influenza immunisation administered alone as well as in combination with other vaccines,* ADRS database, 2010



* pH1N1 (% of 514 adverse events following immunisation (AEFI) records); seasonal influenza vaccine (% of 2,354 AEFI records); and vaccines excluding influenza vaccines (% of 1,030 AEFI records), where the corresponding vaccines were listed as suspected of involvement in the reported adverse event following immunisation.

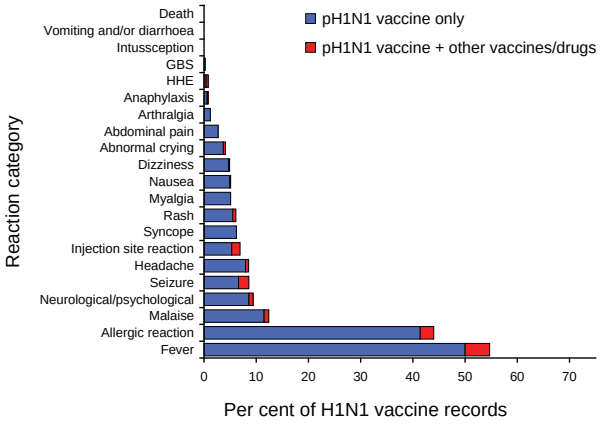
Monovalent pH1N1 influenza vaccine

There was a total of 514 AEFI reports received for 2010 where pH1N1 influenza vaccine was listed as a suspected vaccine (Table 3). It was the only suspected vaccine in 471 (92%) reports. Twenty-eight reports (5%) had causality classified as 'certain' or 'probable' while the other 486 cases (95%) were classified as 'possible'. Forty-one cases (8%) were defined as 'serious' (Table 3). Thirty-three per cent of reports (n=171) came from Queensland, 25% (n=126) from New South Wales, 10% (n=50) from Victoria, 9% each from Western Australia (n=47) and the Australian Capital Territory (n=44), 5% each from South Australia (n=28) and Tasmania (n=25), and 3% (n=13) from the Northern Territory.

The reporting rate for people aged ≥18 years was 3.1 per 100,000 doses, which was a substantial decline from 2009 (34.2). However, the overall rates were higher for vaccinees aged 18–64 years than among older people. The majority (41%; n=211) were reported by states and territories, 38% (n=196) by members of the public, 18% (n=90) by doctors and health care providers, 2% (n=12) by hospitals and 1% (n=5) by drug companies.

The spectrum of reactions for the pH1N1 influenza vaccine was similar to that for seasonal influenza vaccine, showing higher rates for fever (55%), allergic reaction (44%), malaise (13%), and convulsion (9%), including 28 reports of febrile convulsions (27 of which were in children <5 years of age). There was a total of 4 reports each of anaphylactic reaction and HHE, and 1 case reported as GBS following pH1N1 influenza vaccine (Figure 5c).

Figure 5c: Frequently reported adverse events following pH1N1 administered alone as well as in combination with other vaccines, ADRS database, 2010



Discussion

There has been a substantial increase in both the number of AEFI reports and population-based reporting rates in both 2009 and 2010, predominantly due to the substantial increase in reports in children following vaccination with two influenza vaccines: the 2010 seasonal trivalent influenza vaccine and the pandemic (pH1N1) influenza vaccine.

The pH1N1 vaccine program for adults that commenced in September 2009 resulted in a large peak in reports for that age group in the last quarter of that year, followed by lower levels of AEFI reported in adults in 2010. Reports in children peaked in early 2010 following the roll-out to children aged 6 months to 10 years from 4 December 2009. The safety of the pH1N1 vaccine has been examined closely both nationally and internationally. The World Health

Organization reports that approximately 30 different pH1N1 vaccines have been developed using a range of methods.[39] All progressed successfully through vaccine trials to licensure, showing satisfactory safety profiles. In general, the safety profile, including that for the Australian pH1N1 vaccine, has been similar to those of other vaccines, with predominantly mild transient events and a small number of serious reactions reported.[40] In Australia, reports of febrile convulsions in children aged ≤4 years of age following Panvax® administration were found to be between 7 and 18 per 100,000 doses using denominator data from a number of sources, and based on estimated doses administered up to 31 May 2010.[41] Febrile convulsions have been identified as a rare AEFI in children based on post-marketing surveillance data.[42] Rare side effects are generally regarded as those that occur at a rate between 1 per 1,000 and 1 per 10,000 doses. This rate is substantially less (at least 25-fold lower) than the estimated rate of 700 per 100,000 febrile convulsions seen with Fluvax®/Fluvax junior® following the extensive epidemiologic investigation of the safety profile of that vaccine, which occurred following the vaccine suspension in 2010.[41] Active surveillance for GBS following pH1N1 vaccine has resulted in no evidence of an increased incidence, and reports of anaphylaxis are also rare and within expectations.[43]

The very large number of reports following pH1N1 can be attributed, in part, to the active promotion to both health professionals and consumers of reporting to the TGA. They also reflect the fact that immunisation providers are more likely to report milder, less serious AEFI for vaccines they are not familiar with. This tendency to report an AEFI for newer vaccines increases the sensitivity of the system to detect signals of serious, rare or previously unknown events, but also complicates the interpretation of trends.

The trends in AEFI rates in 2010 were also greatly influenced by the emergence of a new vaccine safety concern regarding the use of seasonal influenza vaccines in children. Epidemiological studies determined that the 2010 seasonal influenza vaccine produced by CSL Biotherapies (Fluvax® and Fluvax junior®) was associated with an increased number of febrile adverse events in young children,[44] and particularly with an unacceptably high rate of febrile convulsions within 24 hours of administration (500–700 per 100,000 doses).[45] This rate was between 5 and 20 times higher than for other seasonal influenza vaccines (Influvac® [Solvay Biosciences] and Vaxigrip® [Sanofi Pasteur]) and pH1N1 vaccine (Panvax®, CSL Biotherapies), which were also in use in this age group throughout 2010. These epidemiologic data were supported by two retrospective cohort studies of children given influenza vaccines, including Fluvax®/Fluvax junior® in Australia and in New Zealand.[45] The use of the 2010 seasonal TIV in children <5 years of age was suspended in April 2010,[3] after which reporting of AEFI from seasonal influenza vaccine declined. The recommendation to resume the use of seasonal influenza vaccine in children aged 6 months to 5 years, using brands other than Fluvax® and Fluvax junior®, was subsequently made in August 2010.[4] This issue was initially detected in Western Australia, where a funded influenza vaccine was provided for all children aged 6 months to 5 years via a state-based program. In other jurisdictions, NIP-funded influenza vaccine is only provided to children with medical risk factors. While dose-based reporting rates were difficult to estimate due to lack of consistent reporting of influenza vaccines to the ACIR, subsequent analyses found a similar rate of febrile convulsions following Fluvax® in other jurisdictions to that in Western Australia.[45] A biologic cause for the increased rate of fever and febrile convulsions in young children following the 2010 Fluvax®/Fluvax junior® vaccine has not yet been determined; however, investigations are ongoing.

Stimulated reporting associated with a new vaccine (pH1N1) and a vaccine safety issue (Fluvax®) is likely to have resulted in increased reporting of milder AEFI and for other vaccines. AEFI reporting rates for non-influenza vaccines in children were higher in 2010 compared with 2009. However, after excluding reports of influenza vaccines, the population-based AEFI reporting rate in children aged <7 years (31.1 per 100,000 population) was approximately one-quarter that of the overall rate for 2010 in that age group (134.1). This is consistent with AEFI reporting rates in 2004–2008.

The recent increase in reports from members of the public (13% in 2010 compared with 3% in 2008) indicates a high level of public interest in both the pH1N1 and seasonal influenza vaccines. This is likely to be due at least in part to the active promotion of the reporting of events following pH1N1 vaccination directly to TGA,[40] as well as the issues mentioned above.

Conclusion

There was a 58% higher rate of AEFIs per 100,000 population in 2010 compared with 2009. The high rate in 2010 was attributable to a large number of reports following receipt of the pH1N1 vaccines across all age groups, and seasonal influenza vaccines, particularly in children. A higher proportion of these events were reported directly to the TGA by members of the public following promotion of this for pH1N1. The majority of reports were of mild transient events. Increases in reporting following introduction of a new vaccine (pH1N1) are

expected. However, high rates of febrile convulsions and fever following seasonal influenza vaccine, predominantly in Western Australia where the vaccine was offered to all children aged 6 months to <5 years, ultimately resulted in the removal of the indication for the use of Fluvax® and Fluvax junior® in children of that age, nationally.[3] A joint working party of the Australian Technical Advisory Group on Immunisation and the TGA was established to consider the reports of febrile convulsion in children and to provide advice around the possible resumption of the program. The working party returned its findings in July 2010, with the result that the Chief Medical Officer recommended Fluvax Junior® not be used in children <5 years of age, and that the other seasonal influenza vaccines available in Australia and registered for use in young children (Vaxigrip® and Influvac®) be used instead.[4] Subsequent advice was provided in March 2011 stating that Fluvax® can only be used in children aged 5 to <10 years if other brands are unavailable. The regular analysis of AEFI surveillance data is very important in examining trends in AEFI and stimulating investigations into potential safety signals.

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References

1. Lawrence G, Menzies R, Burgess M, McIntyre P, Wood N, Boyd I, et al. Surveillance of adverse events following immunisation: Australia, 2000–2002. *Commun Dis Intell* 2003;27(3):307–323.
2. Lawrence G, Boyd I, McIntyre P, Isaacs D. Surveillance of adverse events following immunisation: Australia 2002 to 2003. *Commun Dis Intell* 2004;28(3):324–338.
3. Lawrence G, Boyd I. Surveillance of adverse events following immunisation for children aged less than 7 years, 1 January to 30 June 2004. *Commun Dis Intell* 2004;28(4):490–492.
4. Lawrence G, Boyd I. Supplementary report: surveillance of adverse events following immunisation among children aged less than 7 years in Australia, 1 January to 30 June 2005. *Commun Dis Intell* 2005;29(4):413–416.
5. Lawrence G, Boyd I, McIntyre P, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2005. *Commun Dis Intell* 2006;30(3):319–333.
6. Lawrence G, Boyd I. Supplementary report: surveillance of adverse events following immunisation among children aged <7 years in Australia, 1 January to 30 June 2006. *Commun Dis Intell* 2006;30(4):438–442.
7. Lawrence G, Gold MS, Hill R, Deeks S, Glasswell A, McIntyre PB. Annual report: surveillance of adverse events following immunisation in Australia, 2007. *Commun Dis Intell* 2008;32(4):371–387.
8. Lawrence GL, Boyd I, McIntyre PB, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2004. [erratum appears in *Commun Dis Intell* 2005;29(4):416]. *Commun Dis Intell* 2005;29(3):248–262.
9. Lawrence GL, Aratchige PE, Boyd I, McIntyre PB, Gold MS. Annual report on surveillance of adverse events following immunisation in Australia, 2006. *Commun Dis Intell* 2007;31(3):269–282.
10. Lawrence GL, Aratchige PE, Hill R. Supplementary report: surveillance of adverse events following immunisation among children aged less than 7 years in Australia, 1 January to 30 June 2007. *Commun Dis Intell* 2007;31(4):379–382.
11. Lawrence GL, Mahajan D, Roomiani I. Supplementary report: surveillance of adverse events following immunisation among children aged <7 years in Australia, 1 January to 30 June 2008. *Commun Dis Intell* 2009;33(1):27–31.
12. Mahajan D, Menzies R, Roomiani I, Lawrence GL. Supplementary report: surveillance of adverse events following immunisation among children aged <7 years in Australia, 1 January to 30 June 2009. *Commun Dis Intell* 2010;34(1):49–53.
13. Menzies R, Mahajan D, Gold MS, Roomiani I, McIntyre P, Lawrence G. Annual report: surveillance of adverse events following immunisation in Australia, 2008. *Commun Dis Intell* 2009;33(4):365–381.
14. Mahajan D, Roomiani I, Gold M, Lawrence G, McIntyre P, Menzies R. Annual report: surveillance of adverse events following immunisation in Australia, 2009. *Commun Dis Intell* 2010;34(3):259–276.
15. Mahajan D, Menzies R, Cook J, Macartney K, McIntyre P. Supplementary report: surveillance of adverse events following immunisation among children aged <7 years in Australia, 1 January to 30 June 2010. *Commun Dis Intell* 2011;35(1):18–25.
16. Victorian State Government, Department of Health. National immunisation program schedule. Accessed on 1 December 2010. Available from: http://health.vic.gov.au/immunisation/fact-sheets/factsheets/schedule_victoria

17. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. TGA approves vaccine against pandemic (H1N1) 2009 influenza. 18 September 2009. Accessed on 2 December 2010. Available from: http://www.tga.gov.au/media/mr2009.htm

18. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Departmental media releases 23 April 2010: Seasonal Flu Vaccine and young children. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept230410.htm

19. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Departmental media releases 30 July 2010: Seasonal flu vaccination for young children can be resumed – Updated advice from the Chief Medical Officer. Available from: http://www.health.gov.au/internet/main/publishing.nsf/Content/mr-yr10-dept-dept300710.htm

20. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 8th edn. Canberra: Australian Government Department of Health and Ageing, 2003.

21. Australian Government Department of Health and Ageing. Timeline of mass immunisation programs and initiatives. 2009. Accessed on 30 August 2010. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/past-immu-prog

22. National Health and Medical Research Council. *The Australian Immunisation Handbook*. 9th edn. Canberra: Australian Government Department of Health and Ageing, 2008.

23. SA Health. New vaccine schedule from 1st March 2008. Sharp and to the point. Quarterly newsletter produced by the Immunisation Section, Communicable Diseases Control Branch. March 2008 Issue 23. Accessed on 30 August 2010. Available from: http://www.dh.sa.gov.au/pehs/Immunisation/0803-sharp-point-news.pdf

24. Queensland Health. National Immunisation Program Queensland schedule commencing 1 March 2008. Accessed on 1 September 2010. Available from: http://www.health.sa.gov.au/immunisationcalculator/QldMar2008.pdf

25. Immunisation Program, Department of Human Services. Changed immunisation schedule from 1 March 2008. Immunisation newsletter. Issue 32, January 2008. Accessed on 1 September 2010. Available from: http://www.health.vic.gov.au/__data/assets/pdf_file/0015/130083/Immunisation-newsletter-issue-32.pdf

26. Centers for Disease Control and Prevention. Continued shortage of *Haemophilus influenzae* type b (Hib) conjugate vaccines and potential implications for Hib surveillance—United States, 2008. *MMWR Morb Mortal Wkly Rep* 2008;57(46):1252–1255.

27. Uppsala Monitoring Centre. WHO Collaborating Centre for International Drug Monitoring. Accessed on 30 August 2010. Available from: http://www.who-umc.org/

28. 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. [erratum appears in *MMWR Morb Mortal Wkly Rep* 2003;52(06):113]. *MMWR Surveill Summ* 2003;52(1):1–24.

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

30. Bonhoeffer J, Gold MS, Heijbel H, Vermeer P, Blumberg D, Braun M, et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. *Vaccine* 2004;22(5–6):563–568.

31. Ruggeberg JU, Gold MS, Bayas JM, Blum MD, Bonhoeffer J, Friedlander S, et al. Anaphylaxis: case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine* 2007;25(31):5675–5684.

32. The SAS system for Windows [computer program]. Version 9.2. Cary, N.C.: SAS Institute Inc, 2005.

33. Australian Institute of Health and Welfare. 2009 Adult Vaccination Survey: summary results. Cat. No. PHE 135 Canberra: AIHW, 2011.

34. Additional reports: Childhood immunisation coverage. *Commun Dis Intell* 2008;32:288–289.

35. 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.

36. Joura EA, Leodolter S, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, et al. Efficacy of a quadrivalent prophylactic human papillomavirus (types 6, 11, 16, and 18) L1 virus-like-particle vaccine against high-grade vulval and vaginal lesions: a combined analysis of three randomised clinical trials. *Lancet* 2007;369:1693–1702.

37. Reisinger KS, Block SL, Lazcano-Ponce E, Samakoses R, Esser MT, Erick J, et al. Safety and persistent immunogenicity of a quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. *Pediatr Infect Dis J* 2007;26:201–209.

38. Government of Western Australia, Department of Health. WA vaccination schedule. Accessed on 1 December 2010. Available from: http://www.public.health.wa.gov.au/3/470/3/schedule__immunisation.pm

39. World Health Organization. Safety of pandemic A (H1N1) influenza vaccines. *Wkly Epidemiol Rec* 2010;85(5):29–36.

40. Australian Government Department of Health and Ageing, Therapeutic Goods Administration, Cook J. Australian experience with non-adjuvant H1N1 vaccine (Panvax and Panvax Junior). Medicines Safety Update No.4, 2010. Accessed on 30 August 2010. Available from: http://www.tga.gov.au/adr/msu/msu1008.htm#austexper

41. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Australian Technical Advisory Group on Immunisation (ATAGI) and Therapeutic Goods Administration (TGA) Joint Working Group. Analysis of febrile convulsions following immunisation in children following monovalent pandemic H1N1 vaccine (Panvax/Panvax Junior, CSL). Accessed on 30 May 2011. Available from: http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-100928.htm

42. US Food and Drug Administration. Update on the H1N1 flu vaccine and antiviral medications. Accessed on 15 August 2011. Available from: http://www.fda.gov/downloads/NewsEvents/PublicHealthFocus/UCM217009.pdf

43. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Suspected adverse reactions to Panvax® reported to the TGA. 30 September 2009 to 17 September 2010. Accessed on 30 May 2011. Available from: http://www.tga.gov.au/safety/alerts-medicine-panvax-091120.htm

44. Blyth CC, Currie AJ, Wiertsema SP, Conway N, Kirkham LA, Fuery A, et al. Trivalent influenza vaccine and febrile adverse events in Australia, 2010: clinical features and potential mechanisms. *Vaccine* 2011;29(32):5107–5113.

45. Australian Government Department of Health and Ageing, Therapeutic Goods Administration. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. Status report as at 2 July 2010 (updated 24 September 2010). Accessed on 30 May 2011. Available from: http://www.tga.gov.au/safety/alerts-medicine-seasonal-flu-100702.htm

Abbreviations of vaccine types

BCG	Bacille Calmette-Guérin (i.e. tuberculosis)
dT	diphtheria-tetanus – adolescent and adult formulation
DTPa	diphtheria-tetanus-pertussis (acellular) – paediatric formulation
dTpa	diphtheria-tetanus-pertussis (acellular) – adolescent and adult formulation
dTpa-IPV	combined dTpa and inactivated poliovirus
DTPa-HepB	combined diphtheria-tetanus-pertussis (acellular) and hepatitis B
DTPa-IPV	combined diphtheria-tetanus-pertussis (acellular) and inactivated poliovirus (quadrivalent)
DTPa-IPV-HepB	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus and hepatitis B (pentavalent)
DTPa-IPV-HepB-Hib	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus, hepatitis B and *Haemophilus influenzae* type b vaccine (hexavalent)
HepB	hepatitis B
Hib	*Haemophilus influenzae* type b
Hib-HepB	combined *Haemophilus influenzae* type b and hepatitis B
HPV	human papillomavirus
IPV	inactivated poliovirus vaccine
Men4PV	meningococcal polysaccharide tetravalent vaccine
MenCCV	meningococcal C conjugate vaccine
MMR	measles-mumps-rubella
OPV	oral poliovirus vaccine
pH1N1	pandemic H1N1 influenza 2009
7vPCV	7-valent pneumococcal conjugate vaccine
10vPCV	10-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine