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Surveillance of adverse events following immunisation in Australia annual report, 2016

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Surveillance of adverse events following immunisation in Australia annual report, 2016

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Abstract

This report summarises Australian passive surveillance data for adverse events following immunisation (AEFI) for 2016 reported to the Therapeutic Goods Administration and describes reporting trends over the 17-year period 1 January 2000 to 31 December 2016. There were 3,407 AEFI records for vaccines administered in 2016; an annual AEFI reporting rate of 14.1 per 100,000 population. There was a 14% increase in the overall AEFI reporting rate in 2016 compared with 2015. This increase in reported adverse events in 2016, compared to the previous year, was mainly attributable to introduction of the booster dose of the diphtheria, tetanus, and acellular pertussis-containing vaccine (DTPa)ⁱ at 18 months of age in March 2016 and the zoster vaccine for those aged 70–79 years in November 2016. AEFI reporting rates for most other individual vaccines in 2016 were similar to 2015. The most commonly reported reactions were injection site reaction (29%), pyrexia (19%), rash (17%), vomiting (8%) and headache (7%). The majority of AEFI reports (90%) were described as non-serious events and a 24% decline was observed in events classified as ‘serious’ in this reporting period compared to the previous reporting period. There were 2 deaths reported but no clear causal relationship with vaccination found.

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

Introduction

This report summarises national passive surveillance data for adverse events following immunisation (AEFI) reported to the Therapeutic Goods Administration (TGA) by 28th February 2017. The report focuses on AEFI reported for vaccines administered during 2016 and trends in AEFI reporting over the 17-year period 1 January 2000 – 31 December 2016.

An adverse event following immunisation is defined as any untoward medical occurrence which follows immunisation and which does not necessarily have a causal relationship with the usage of the vaccine.¹ The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.¹

Thus, AEFI may be caused by a vaccine(s) or may be coincidental. Adverse events may also include conditions that occur following the incorrect handling and/or administration of a vaccine(s). The post-marketing surveillance of AEFI is particularly important to detect signals of rare, late onset or unexpected events, which are difficult to detect in pre-registration vaccine trials.

Reports summarising national AEFI surveillance data have been published regularly since 2003.^{2–15} Trends in reported adverse events fol-

ⁱ Diphtheria toxoid is available in Australia only in combination with tetanus, with or without other antigens such as pertussis, inactivated poliomyelitis, hepatitis B and Haemophilus influenzae type b. The acronym DTPa, using capital letters, signifies child formulations of diphtheria, tetanus and acellular pertussis-containing vaccines. The acronym dTpa is used for formulations that contain substantially lesser amounts of diphtheria toxoid and pertussis antigens than child (DTPa-containing) formulations; dTpa vaccines are usually used in adolescents and adults. Source: The Australian Immunisation Handbook 10th Edition (<http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/Handbook10-home~handbook10part4~handbook10-4-2>)

lowing immunisation are heavily influenced by changes to vaccine funding and availability provided through the National Immunisation Program (NIP). These changes impact on the interpretation of trend data and have been described in detail in reports published since 2003.²⁻¹⁵ Table 1 shows the chronological listing of the changes.

Recent changes that impact on AEFI surveillance data presented in this 2016 report are:

November 2016 – Zoster vaccine (Zostavax[®]) provided free for people aged 70 years under the NIP with a 5 year catch-up program for people aged 71–79 years.

March 2016 – NIP-funded booster dose of the diphtheria, tetanus, and acellular pertussis-containing vaccine (DTPa) at 18 months of age. This was earlier recommended from March 2015.

April 2015 – New immunisation requirements for family assistance payments were announced by the federal government. With the ‘No Jab, No pay’ policy coming into effect as of 1 January 2016, only parents of children (aged less than 20 years) who are ‘fully immunised’ or on a recognised catch-up schedule will continue to receive the Child Care Benefit, Child Care Rebate, and/or the Family Tax Benefit Part A end-of-year supplement. Children with medical contraindications or natural immunity for certain diseases continue to be exempt from the requirements; however, conscientious objection was no longer a valid exemption from immunisation requirements.

From March to June 2015, the dTpa vaccine for women during the third trimester of pregnancy was funded by New South Wales, South Australia, Western Australia, the Australian Capital Territory, Victoria and Tasmania. The Northern Territory had funded it since September 2013 and Queensland since July 2014.

In March 2015, annual seasonal influenza vaccine was funded for Aboriginal and Torres Strait Islander children aged 6 months to less than 5 years.

To assist readers, at the end of this report there is a glossary of the abbreviations of the vaccines referred to in this report.

Methods

AEFI are notified to the TGA by state and territory health departments, health professionals, vaccine companies and members of the public.^{16,17} All reports are assessed using internationally consistent criteria¹⁸ and entered into the Australian Adverse Drug Reactions System (ADRS) database. Reports are used in data mining and signal detection activities conducted by the TGA. Where there is insufficient information in a report to determine causality for a serious adverse event the TGA will contact the reporter on up to 3 occasions to elicit further information.

AEFI data

De-identified information on all AEFI reported to the TGA from 1 January 2000 to 31 December 2016 and stored in the ADRS database, were released to the National Centre for Immunisation Research and Surveillance (NCIRS) in March 2017. Readers are referred to previous AEFI surveillance reports for description of the surveillance system.^{3,6}

Recordsⁱ contained in the ADRS database were eligible for inclusion in the analysis if a vaccine was recorded as ‘suspected’ⁱⁱ of involvement in the reported adverse event and either:

- a. the vaccination occurred between 1 January 2000 and 31 December 2016; or
- b. for records where the vaccination date was

ⁱ The term ‘AEFI record’ is used throughout this report because a single AEFI notification/report to the Office of Product review can generate more than one record in the ADRS database.

ⁱⁱ Vaccines are classified as ‘suspected’ if the report contains sufficient information to be valid and the relationship between reported reactions and the vaccine is deemed at least possible.

Table 1: Changes in immunisation policy and the National Immunisation Program (2005–2016)^{2,4,5,7,10,12,14,15,37}

Year	Intervention
2016	<p>From November 2016 – Zoster vaccine (Zostavax®) provided free for people aged 70 years under the National Immunisation Program with a 5 year catch-up program for people aged 71 – 79 years.</p> <p>From March 2016 – Free booster dose of the diphtheria, tetanus, and acellular pertussis-containing vaccine (DTPa) at 18 months of age.</p>
2015	<p>From March 2015, seasonal influenza vaccine funded for Aboriginal and Torres Strait Islander children aged 6 months to less than 5 years.</p> <p>From March to June 2015, the dTpa vaccine for women during the third trimester of pregnancy was funded by New South Wales, South Australia, Western Australia, the Australian Capital Territory, Victoria and Tasmania. The Northern Territory had funded it since September 2013 and Queensland since July 2014.</p> <p>In March 2015, a booster dose of DTPa recommended at 18 months of age (funded in March 2016).</p> <p>In April 2015, new immunisation requirements for family assistance payments were announced by the federal government (the 'No Jab, No Pay' policy), to come into effect on 1 January 2016. Only parents of children (aged less than 20 years) who are 'fully immunised' or on a recognised catch-up schedule remain eligible to receive the Child Care Benefit, Child Care Rebate, and/or the Family Tax Benefit Part A end-of-year supplement.</p>
2014	<p>4vHPV catch-up program for males aged 14–15 years ceased in December 2014.</p> <p>In July 2014, dTpa was funded by Queensland for women during the third trimester of pregnancy.</p>
2013	<p>From 1 February 2013, 4vHPV was extended to males aged 12–13 years, delivered through a school-based program, with a catch-up program for males aged 14–15 years in 2013 and 2014.</p> <p>From July 2013, the 2nd dose of MMR vaccine, previously given at 4 years, was brought forward to 18 months of age and delivered as a combination MMRV vaccine.</p> <p>From July 2013, combined <i>Haemophilus influenzae</i> type b (Hib) and meningococcal serogroup C (MenC) vaccine, Menitorix®, was funded for infants aged 12 months. This combination vaccine replaced the single dose of monovalent meningococcal C conjugate vaccine (MenCCV) and booster dose of monovalent Hib vaccine previously scheduled at 12 months of age.</p> <p>At the end of December 2013, the secondary school Year 7 hepatitis B vaccine catch-up program ceased, as all younger age cohorts were eligible for infant immunisation under the NIP (commenced 2000).</p> <p>In September 2013, dTpa funded by NT for women during the third trimester of pregnancy and for parents of infants aged <7 months under cocoon strategy</p>
2012	<p>From 1 October 2012, a fourth dose of Prevenar 13®, (13vPCV, a 13-valent pneumococcal conjugate vaccine) was listed on the National Immunisation Program (NIP) for Indigenous children, aged 12-18 months, residing in Queensland, South Australia, Western Australia and the Northern Territory. This replaced the booster dose of Pneumovax23®, (23vPPV, a 23-valent pneumococcal polysaccharide vaccine) administered between 18 and 24 months of age for Indigenous children from these jurisdictions.</p>
2011	<p>From 1 July 2011, Prevenar 13® replaced Prevenar® on the NIP for children at 2, 4 and 6 months of age in all states and territories except the Northern Territory which adopted 13vPCV from 1 October 2011.</p> <p>1 October 2011 to 30 September 2012 – all children aged between 12 - 35 months who had completed a primary pneumococcal vaccination course with 7vPCV were eligible to receive a free supplementary dose of Prevenar 13®</p> <p>On 25 March 2011, TGA issued a recall of Batch N3336 of the 23 valent pneumococcal polysaccharide vaccine 23vPPV, Pneumovax® 23. April 2011 - health professionals were advised not to administer a second or subsequent dose of Pneumovax 23 vaccine. December 2011 - Revised recommendations regarding which patients should be re-vaccinated under the NIP were provided.</p>

Year	Intervention
2010	Annual vaccination with seasonal trivalent influenza vaccine (TIV, containing 3 influenza strains: A/H1N1, A/H3N2 and B) was funded under the 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). 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 2 available brands registered for use in young children, were associated with an unacceptably high risk of febrile convulsions. 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 made in August 2010.
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 <i>Haemophilus influenzae</i> type b (Hib) (PedvaxHib [®] [monovalent] and Comvax [®] [Hib-HepB]) vaccines. Pandemic H1N1 2009 influenza vaccine (Panvax [®]) was rolled out across Australia from 30 September 2009 for people aged ≥ 10 years. From December 2009, the pandemic vaccine was made available to children aged 6 months to 10 years.
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 2 combination vaccines (quadrivalent DTPa-IPV and Hib-HepB) to the single hexavalent DTPa-IPV-HepB-Hib vaccine.
2007	From 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. From 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 [®]).
2005	From 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. From November 2005, universal funded immunisation against varicella at 18 months of age with a school-based catch-up program for children at 10–13 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 was funded to replace OPV, in combination vaccines.

not recorded, the date of onset of symptoms or signs occurred between 1 January 2000 and 31 December 2016.

Study definitions of AEFI outcomes and reactions

AEFI were defined as 'serious' or 'non-serious' based on information in the report sent to the TGA and criteria similar to those used by the World Health Organization and the US Vaccine Adverse Events Reporting System.^{18,19} In this report, an AEFI is defined as 'serious' if it meets

one or more of the following criteria: (1) results in death; (2) is life-threatening; (3) requires inpatient hospitalisation or prolongation of existing hospitalisation; (4) results in persistent or significant disability/incapacity; (5) is a congenital anomaly/birth defect or; (6) is a medically important event or reaction.

Typically, each record lists several reaction terms that are symptoms, signs and/or diagnoses that have been coded by TGA staff from the reporter's

description into standardised terms using the Medical Dictionary for Regulatory Activities (MedDRA®).^{20,21}

In reports published previously, in order to analyse the data, MedDRA® coding terms were grouped to create a set of reaction categories that were broadly analogous to the reactions listed in previous *Australian Immunisation Handbooks*.^{16,17} However, the methodological framework of reporting of adverse events was revised in 2014 and an amended format for AEFI analyses using MedDRA® preferred terms (PTs) was adopted.²² For this report, MedDRA® PTs are used for analysis. Grouping of reactions using PTs is more comparable with data from other countries and internationally accepted.²³⁻²⁵ In conjunction with the currently used national vaccine-specific reporting form,²⁶ the use of PTs allow better reflection of post-marketing surveillance data on vaccines in Australia.

Data analysis

All data analyses were performed using SAS software version 9.4.²⁷ Average annual population-based reporting rates were calculated for each state and territory and by age group using 2016 population estimates obtained from the Australian Bureau of Statistics.²⁸ All rates are presented as average annual rates per 100,000 population. Reporting rates per 100,000 administered doses were estimated where information was available on the number of doses administered. This was done for vaccines funded through the NIP for children aged <7 years. The number of administered doses of each of the vaccines given to this age group was obtained from the Australian Immunisation Register (AIR), a national population-based register.²⁹ From 30 September 2016, the Australian Childhood Immunisation Register (ACIR) became the Australian Immunisation Register (AIR), a national register that records vaccinations given to people of all ages in Australia.³⁰ In the future, as reporting in older age groups (>7 years) becomes more complete, denomina-

tor data on vaccine doses administered in older age groups will be analysed for the purposes of AEFI reporting.

Notes on interpretation

Caution is required when interpreting the 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 2016. Data published in previous reports may differ from that presented in this report for the same period because this report has been updated to include delayed notifications to the TGA that were not included in prior publications. Data can also differ because reports may be updated and recoded when follow up information is received or when vaccine-specific analyses are conducted.

The information collated in the ADRS database is intended primarily for signal detection and hypothesis generation. While reporting rates can be estimated using appropriate denominators, they cannot be interpreted as incidence rates due to under-reporting and biased reporting of suspected events, and the variable quality and completeness of information provided in individual notifications.^{3-14,31}

It is important to note that this report is based on vaccine information and MedDRA® preferred terms collated in the ADRS database and not on comprehensive clinical notes or case reviews. The reported symptoms, signs and diagnoses in each AEFI record in the ADRS database are temporally associated with vaccination but are not necessarily causally associated with a vaccine or vaccines.

Comparison with online Database of Adverse Events Notifications (DAEN)

In August 2012, the TGA made available to the public on its website a searchable database, the Database of Adverse Event Notifications (DAEN) that contains reports of all adverse event reports for medicines and vaccines.³² The data in this report have not been downloaded from DAEN.

This report uses data sent to NCIRS by the TGA and includes more detailed information than provided by the DAEN. The numbers published in this report may be different to the numbers in the DAEN database, due to different dates of data extraction and amendment to reports where further information has become available. In addition, this report provides several features that are not available from the DAEN database, including long-term trends and population and dose-based reporting rates, described in the context of changes in vaccine policy and utilisation, and reporting practices.

Results

The ADRS database included a total of 3,407 records where the date of vaccination (or onset of adverse event, if vaccination date was not reported) was between 1 January and 31 December 2016. Of these, 55% were females

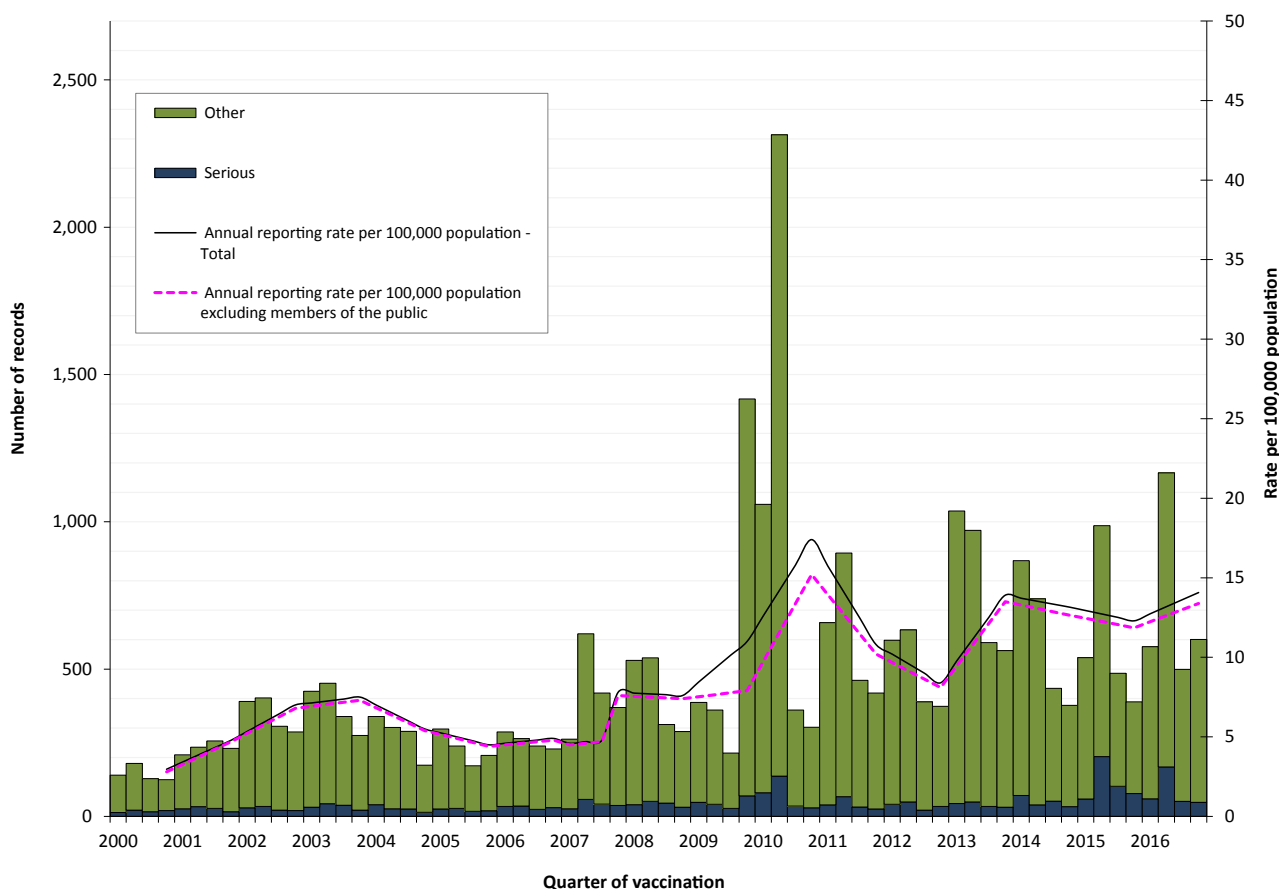
(n=1,869), 44% (n=1,495) males and 1% (n=43) missing data. Also, 2% (n=73) were reported in Aboriginal and Torres Strait Islander people.

In 2016, approximately 80% of AEFI (n=2,737) were reported to the TGA via states and territories, while the rest were reported directly to the TGA by healthcare professionals (11% n=361), members of the public (5% n=166), vaccine companies (3% n=98) and hospitals (1% n=45).

Reporting trends

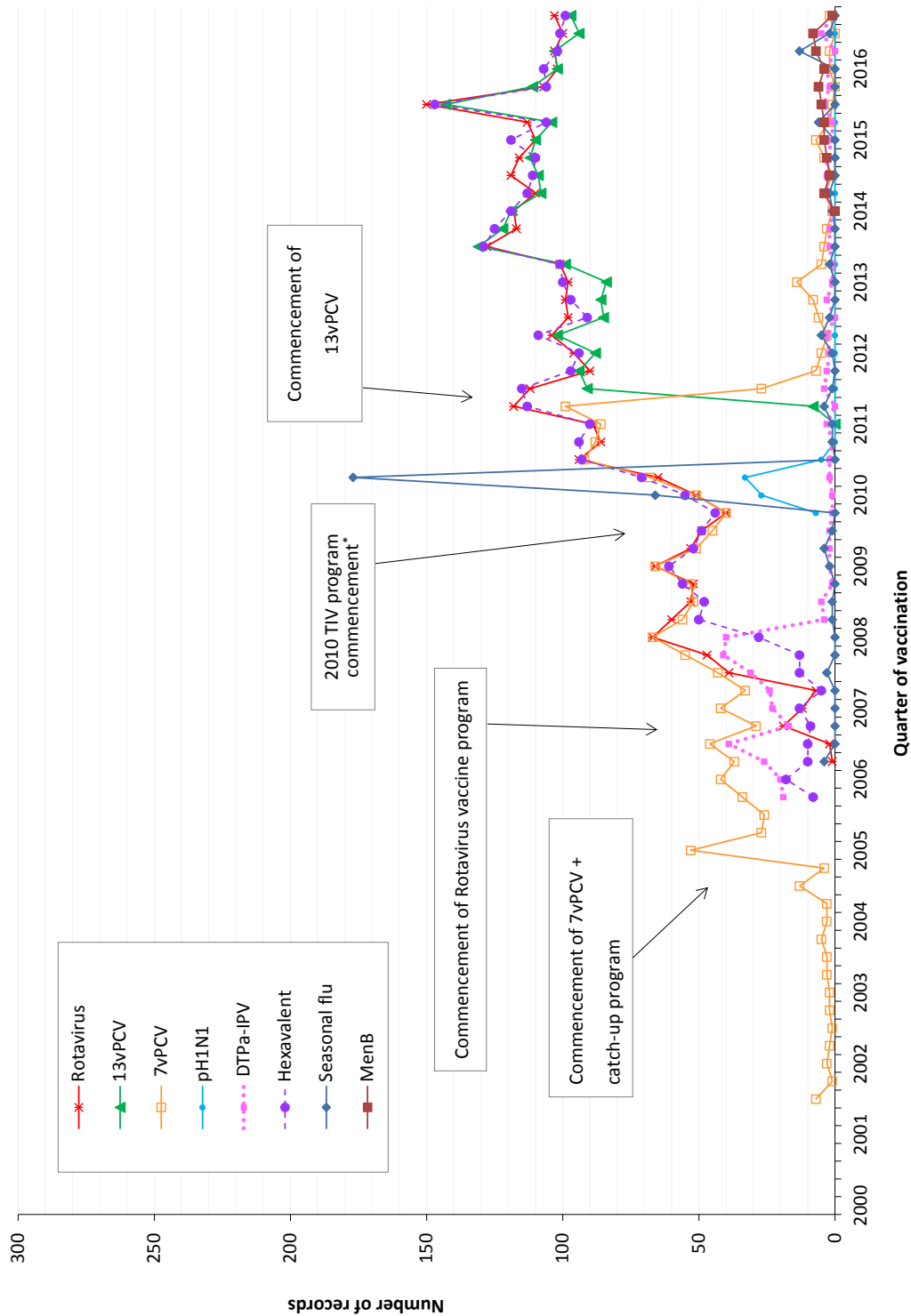
The overall reporting rate for 2016 was per 14.1 per 100,000 population compared with 12.3 per 100,000 in 2015. The highest peak was observed in 2010 (17.4 per 100,000) predominantly due to reports in children following vaccination with the pandemic and 2010 seasonal trivalent influenza vaccines.¹²

Figure 1: Adverse events following immunisation, ADRS database, 2000 to 2016, by quarter of vaccination, by date of vaccination



Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA was used as a proxy for vaccination date.

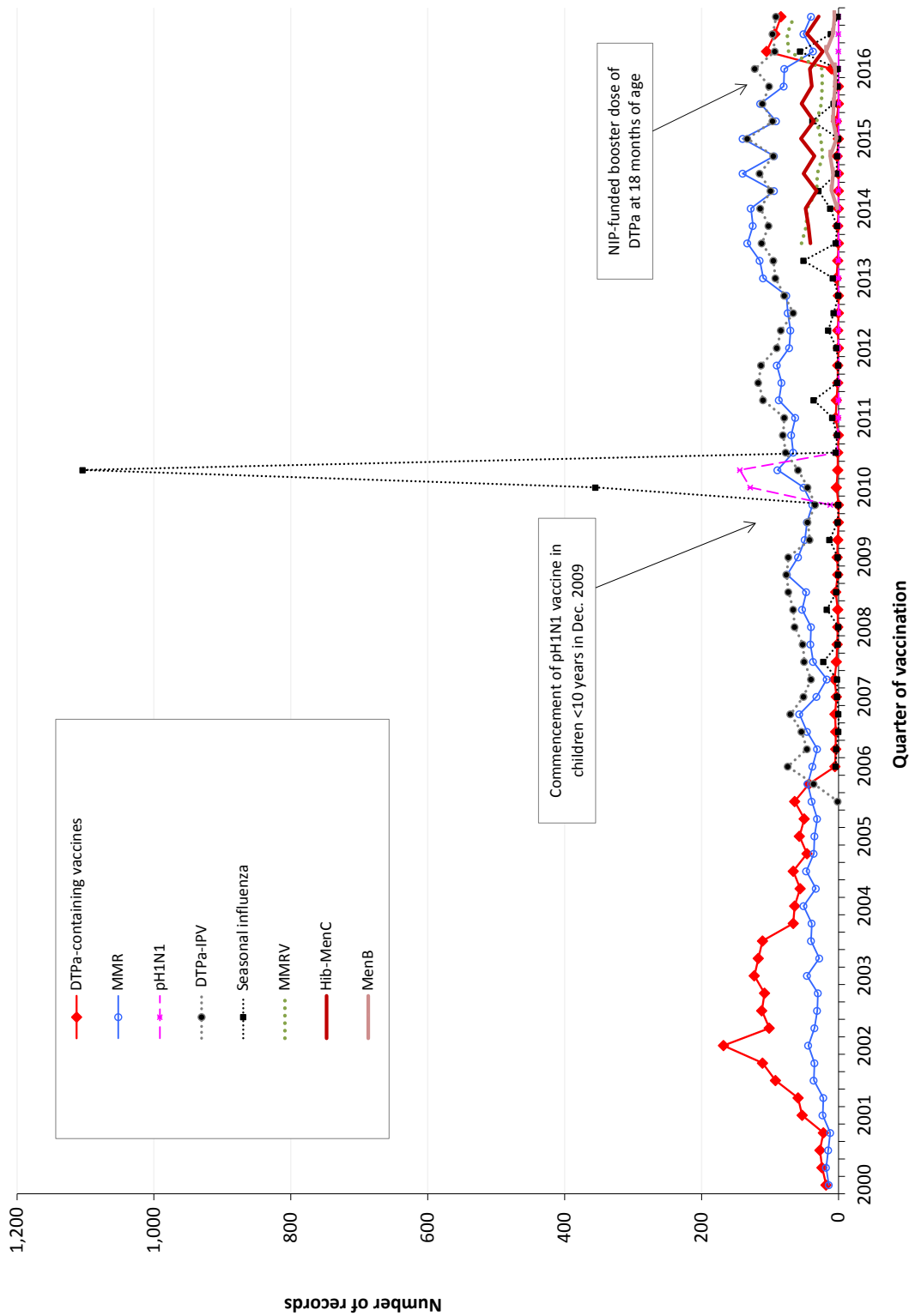
Figure 2a: Adverse events following immunisation for children aged <1 year, ADRS database, 2000 to 2016, by quarter of vaccination, by date of vaccination



* safety signal for fever and febrile convulsion found to be due to Seqirus (formerly bioCSL) Fluvox 2010 TIV in children
 DTPa-IPV and DTPa-IPV-HepB-Hib (hexavalent) vaccines were introduced into the NIP schedule 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; seasonal trivalent influenza vaccine in 2010 which was an extension of existing adult and indigenous programs to at risk populations; and the

13-valent pneumococcal conjugate vaccine (13vPCV) on 1 July 2011. Also, MenB vaccine is recommended for use in those with increased risk of invasive meningococcal disease and is not currently funded under the NIP.
Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA was used as a proxy for vaccination date.

Figure 2b: Adverse events following immunisation for children aged 1 to <7 years in frequently reported vaccines, ADRS database, 2000 to 2016, by quarter of vaccination, by date of vaccination

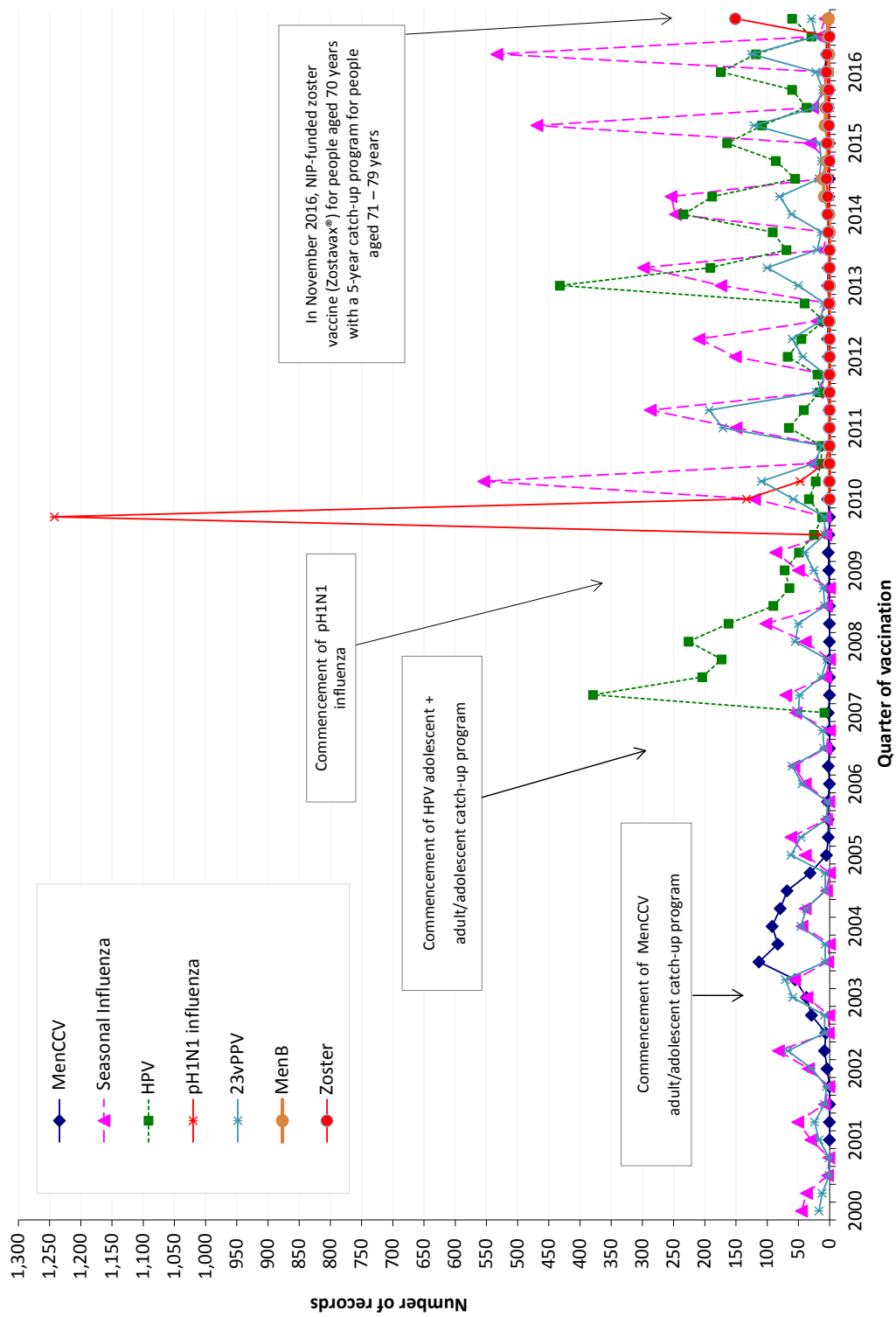


DTPa-IPV was introduced into the NIP schedule in November 2005 replacing DTPa and OPV; seasonal trivalent influenza vaccine in 2010 which was an extension of existing adult and Indigenous programs to at risk populations; MMRV and Hib-MenC vaccines on July 2013, and HPV program extended to

boys in February 2013. Also, MenB vaccine is recommended for use in those with increased risk of invasive meningococcal disease and is not currently funded under the NIP. In April 2016 – NIP-funded booster dose of DTPa at 18 months of age.

Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA was used as a proxy for vaccination date.

Figure 2c. Adverse events following immunisation for people aged ≥ 7 years in frequently reported vaccines, ADRS database, 2000–2016, by quarter of vaccination.



MenCCV was introduced into the NIP schedule on 1 January 2003; pH1N1 influenza vaccine for children 6 months to 10 years on December 2009; pH1N1 vaccination for those ≥ 10 years commenced on 30 Sep 2009; seasonal trivalent influenza vaccine in 2010 which was an extension of existing adult and indigenous programs to at risk populations; and HPV program extended to boys in February 2013. Also, MenB vaccine is recommended for use in those with increased risk of invasive meningococcal disease and is not currently funded under the NIP.

In November 2016, zoster vaccine (Zostavax®) was NIP-funded for people aged 70 years with a 5-year catch-up program for people aged 71 – 79 years.

Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA was used as a proxy for vaccination date.

The vast majority of reported events in 2016 (from all reporter types) were of a non-serious nature similar to the previous years (Figure 1)^{10,11} Figures 2a, 2b and 2c demonstrate marked variations in reporting levels in association with previous changes to the NIP from 2000 onwards. The increase in reports in 2016 was predominantly associated with the booster dose of DTPa at 18 months of age (Figures 2a and 2b) and also an increase in reports of adverse events following immunisation with zoster vaccine in the elderly (Figure 2c).

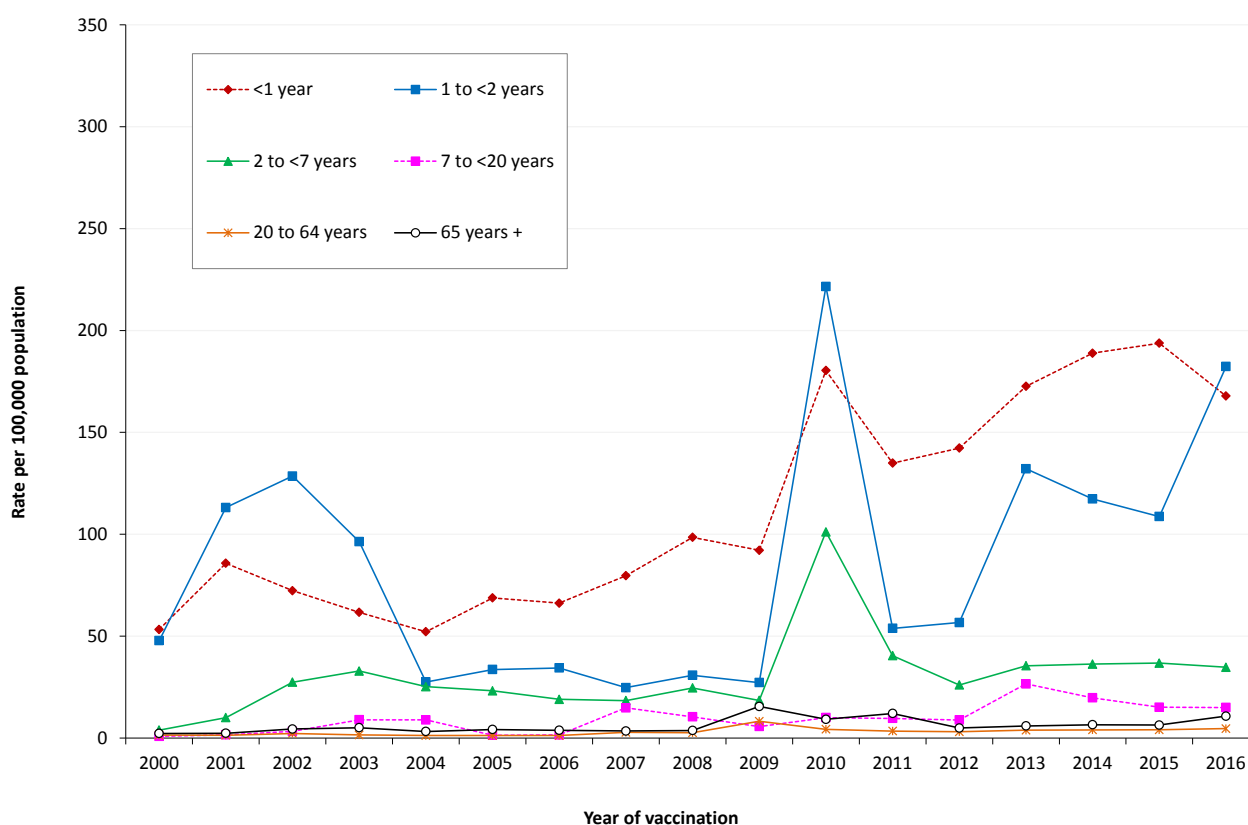
A seasonal pattern of AEFI reporting was apparent in 2016 as in previous years, with the highest number of AEFI notifications for vaccinations administered in the first half of the year (Figure 1). This corresponds to the months when influenza vaccine is given and older Australians receive 23vPPV (March to June). However, more AEFI reports following influenza vaccine were received in each of the last 5 years than years prior to 2009 (pre-pandemic era) (Figure 2c).

Age distribution

The highest population-based AEFI reporting rate per 100,000 population occurred in children aged 1-<2 years, the age group that received the booster dose of DTPa at 18 months of age (Figure 3). Compared with 2015, AEFI reporting rates in children decreased in the <1 year age group from 193.8 to 167.8. A decline was also observed in the 2 to <7 years and 7 to <20 year age groups, however, there were increases observed in children aged 1 to <2 years and adults aged 65 years and older (Figure 3).

There were no significant differences in reporting rates per 100,000 doses for most individual vaccines in 2016 compared to 2015, and noting new additions to the NIP schedule namely DTPa & zoster (Table 2).

Figure 3: Reporting rates of adverse events following immunisation per 100,000 population, ADRS database, 2000 to 2016, by age group and year of vaccination, by date of vaccination



Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA was used as a proxy for vaccination date.

Table 2: Vaccine types listed as ‘suspected’ in records of adverse events following immunisation by age groups (<7, 7–17, 18–64 and ≥65 years), ADRS database, 2016

Vaccines*	AEFI records† (n)	Vaccine Doses 2016 ‡	Reporting rate per 100,000 doses§ (95% CI)	
			2016	2015
<7 years				
Rate (95% Confidence Interval)				
DTPa-containing vaccines	1,165	1,427,824	81.6 (77.0–86.4)	80.7 (75.7–86.0)
• Hexavalent (DTPa-IPV-HepB-Hib)	455	884,158	51.5 (46.8–56.4)	58.6 (53.6–63.9)
• DTPa-IPV	411	310,854	132.2 (119.7–145.6)	142.5 (129.5–156.4)
• DTPa	296	232,812	127.1 (113.1–142.5)	–
Pneumococcal conjugate -13PCV	424	896,728	47.3 (42.9–52.0)	54.8 (50.0–59.9)
Rotavirus vaccine	414	736,605	56.2 (50.9–61.9)	65.2 (59.4–71.4)
Measles-mumps-rubella-varicella	243	304,329	79.8 (70.1–90.5)	77.0 (70.0–84.5)
Measles-mumps-rubella	218	343,792	63.4 (55.3–72.4)	64.7 (56.0–74.3)
Hib-MenC	152	307,332	49.5 (41.9–58.0)	33.3 (27.1–40.5)
Seasonal influenza	84	77,042	109.0 (87.0–135.0)	64.5 (48.0–84.8)
Meningococcal B	57	32,396	175.9 (133.3–228.0)	210.6 (150.4–286.8)
Varicella	14	11,573	121.0 (66.1–203.0)	76.2 (30.6–157.0)
Hepatitis B	11	45,229	24.3 (12.1–43.5)	–
Meningococcal C conjugate	8	8,336	96.0 (41.4–189.1)	140.1 (56.3–288.7)
Haemophilus influenzae type b	5	9,478	52.8 (17.1–123.1)	62.1 (20.2–144.9)
7–17 years				
HPV	373	n/a	–	–
dTpa	212	n/a	–	–
Varicella	116	n/a	–	–
Seasonal influenza	30	n/a	–	–
Hepatitis B	23	n/a	–	–
Measles-mumps-rubella	22	n/a	–	–
dTpa_ipv	17	n/a	–	–

Vaccines*	AEFI records [†] (n)	Vaccine Doses 2016 [‡]	Reporting rate per 100,000 doses [§] (95% CI)	
			2016	2015
23vPPV	17	n/a	–	–
Measles-mumps-rubella-varicella	16	n/a	–	–
Meningococcal C conjugate	8	n/a	–	–
Meningococcal B	4	n/a	–	–
18–64 years				
Seasonal influenza	412	n/a	–	–
dTpa	106	n/a	–	–
23vPPV	59	n/a	–	–
Hepatitis B	33	n/a	–	–
MMR	31	n/a	–	–
Varicella	13	n/a	–	–
Q fever	8	n/a	–	–
dTpa_ipv	4	n/a	–	–
Meningococcal B	4	n/a	–	–
≥65 years				
Zoster	154	n/a	–	–
23vPPV	132	n/a	–	–
Seasonal influenza	129	n/a	–	–
dTpa	14	n/a	–	–

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

† Number of AEFI records in which the vaccine was coded as 'suspected' of involvement in the reported adverse event and the vaccination was administered between 1 January and 31 December 2016. More than one vaccine may be coded as 'suspected' if several were administered at the same time.

‡ Number of vaccine doses recorded on the AIR/ACIR and administered between 1 January and 31 December 2016.

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

n/a Not applicable

Table 3: Adverse events following immunisation (AEFI) records, ADRS database, January to December 2016, by jurisdiction

State or territory	AEFI records n	AEFI records (%)	Annual reporting rate per 100,000 population*			
			'Serious' [†]	Aged <7 years	Overall Rate	(95% Confidence Interval)
Australian Capital Territory	87	(2.6)	2.7	61.5	21.6	(17.3 – 26.6)
New South Wales	632	(18.6)	1.0	32.0	8.2	(7.5 – 8.8)
Northern Territory	57	(1.7)	2.4	100.5	23.2	(17.6 – 30.1)
Queensland	647	(19.0)	1.3	67.2	13.3	(12.3 – 14.4)
South Australia	279	(8.2)	1.1	83.6	16.3	(14.4 – 18.3)
Tasmania	40	(1.2)	0.8	39.7	7.7	(5.5 – 10.5)
Victoria	1,303	(38.2)	1.8	129.1	21.1	(20.0 – 22.3)
Western Australia	362	(10.6)	1.8	87.3	14.1	(12.7 – 15.7)
Total	3,407		1.4	74.7	14.1	(13.6 – 14.6)

*Average annual rates per 100,000 population calculated using mid-2016 population estimates (Australian Bureau of Statistics).

[†] AEFI records defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening or death).

For children <7 years of age, rates for varicella, Hib and MenC should be interpreted with caution since these monovalent vaccines were replaced by combination vaccines in July 2013 and hence very few doses were recorded in 2016.

Geographical distribution

Population-based reporting patterns varied between states and territories during 2016 (Table 3). Reporting rates were not significantly different (with overlapping confidence intervals) across most jurisdictions in 2016 compared with 2015.³³

Vaccines

There were 3,407 AEFI records received in 2016 (Table 4). The percentage of records where only one vaccine was reported as being the suspected vaccine differed by vaccine administered, typically varying according to whether multiple vaccines were routinely co-administered for the patient's age. There were slight variations in the numbers with outcomes defined as 'serious', which have remained low as in previous years.

The most frequently reported individual vaccine was seasonal influenza vaccine with 700 records (21%) followed by hexavalent DTPa-IPV-HepB-Hib (n=474; 14%), 13vPCV (n=436; 13%), DTPa-IPV (n= 433; n=13%), rotavirus vaccine (n=426; 13%) and HPV (n=396; 12%) (Table 4).

For the newly funded DTPa vaccine in March 2016, there were 310 reports and 5% of these were coded as serious (Table 4). Of the total reports of DTPa (n=310), 90% of these were in children aged between 1 to 2 years of age in 2016.

Similarly, for the newly funded zoster vaccine in November 2016, there were 165 reports and only 4% of these were coded as serious in 2016.

For seasonal influenza vaccine in 2016, there were 3 reports of Aboriginal and Torres Strait Islander children aged 6 months to 5 years who had an adverse event following an influenza vaccine and these were reported as 'not serious'.

Table 4: Vaccine types listed as 'suspected' in records of adverse events following immunisation (AEFI), ADRS database, 2016

Suspected vaccine type*	AEFI records		One suspected vaccine only†		'Serious' §		Age group <7 years		Age group ≥7 years	
	n	(%)	n	(%)¶	n	(%)¶	n	(%)¶	n	(%)¶
Influenza	700	(20.5)	599	(85.6)	73	(10.4)	84	(12.0)	567	(81.0)
DTPa-IPV-HepB-Hib	474	(13.9)	41	(8.6)	86	(18.1)	455	(96.0)	13	(2.7)
13vPCV	436	(12.8)	12	(2.8)	85	(19.5)	424	(97.2)	7	(1.6)
DTPa-IPV	433	(12.7)	376	(86.8)	32	(7.4)	441	(101.8)	8	(1.8)
Rotavirus	426	(12.5)	48	(11.3)	98	(23.0)	465	(109.2)	0	–
HPV	396	(11.6)	151	(38.1)	34	(8.6)	2	(0.5)	381	(96.2)
dTpa	346	(10.2)	136	(39.3)	24	(6.9)	3	(0.9)	332	(96.0)
DTPa	310	(9.1)	130	(41.9)	16	(5.2)	296	(95.5)	10	(3.2)
MMR	276	(8.1)	78	(28.3)	26	(9.4)	443	(160.5)	32	(11.6)
MMRV	261	(7.7)	54	(20.7)	24	(9.2)	243	(93.1)	16	(6.1)
23vPPV	217	(6.4)	142	(62.7)	13	(6.0)	12	(3.8)	198	(96.2)
Zoster	165	(4.8)	160	(97.0)	7	(4.2)	0	–	160	(97.0)
Hib-MenC	160	(4.7)	6	(3.8)	14	(8.8)	152	(95.0)	6	(3.8)
Varicella	148	(4.3)	41	(27.7)	16	(10.8)	14	(9.5)	129	(87.2)
Hepatitis B	71	(2.1)	36	(50.7)	5	(7.0)	11	(15.5)	58	(81.7)
Meningococcal B	67	(2.0)	55	(82.1)	6	(9.0)	57	(85.1)	9	(13.4)
MenCCV	28	(0.8)	5	(17.9)	3	(10.7)	8	(28.6)	20	(71.4)

Suspected vaccine type*	AEFI records		One suspected vaccine only†		'Serious'‡		Age group§ <7 years		Age group ≥7 years	
	n	(%)	n	(%)¶	n	(%)¶	n	(%)¶	n	(%)¶
Hepatitis A-Typhoid	21	(0.6)	10	(47.6)	1	(4.8)	0	–	19	(90.5)
Hepatitis A	20	(0.6)	8	(40.0)	1	(5.0)	11	(55.0)	9	(45.0)
dT	19	(0.6)	8	(42.1)	1	(5.3)	0	–	19	(100.0)
Typhoid	16	(0.5)	7	(43.8)	4	(25.0)	0	–	16	(100.0)
Rabies	16	(0.5)	13	(81.3)	2	(12.5)	1	(6.3)	15	(93.8)
Yellow fever	14	(0.4)	10	(71.4)	2	(14.3)	0	–	13	(92.9)
Q fever	10	(0.3)	10	(100.0)	1	(10.0)	0	–	9	(90.0)
Hib	7	(0.2)	2	(28.6)	1	(14.3)	5	(71.4)	2	(28.6)
Hepatitis A + B	4	(0.1)	2	(50.0)	0	–	0	–	4	(100.0)
Cholera	2	(0.1)	1	(50.0)	1	(50.0)	0	–	1	(50.0)
Japanese encephalitis	1	(0.0)	0	–	0	–	0	–	1	(100.0)
Total**	3407	(100.0)	2158	(63.3)	334	(9.8)	1648	(48.4)	1642	(48.2)

* See appendix for abbreviations of vaccine names.

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

‡ 'Serious' is defined in the Methods section.

§ Includes only AEFI records where an age or date of birth has been reported.

¶ Percentages are calculated for the number of AEFI records where the vaccine was suspected of involvement in the AEFI

** 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 5: Selected reported adverse events and reactions of interest* classified by MedDRA Preferred Terms in records of adverse events following immunisation (AEFI), ADRS database, 2016^x

MedDRA Preferred Terms (Adverse events)	AEFI records		Only reaction reported†		'Serious'		Age group* <7 years		Age group* ≥7 years		
	N	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Injection site reaction**	1001	517	(51.6)	42	(4.2)	512	(51.1)	467	(46.7)		
Pyrexia	649	27	(4.2)	76	(11.7)	415	(63.9)	221	(34.1)		
Rash***	585	203	(34.7)	54	(9.2)	378	(64.6)	191	(32.6)		
Vomiting	281	15	(5.3)	32	(11.4)	156	(55.5)	119	(42.3)		
Extensive limb swelling	257	170	(66.1)	9	(3.5)	166	(64.6)	90	(35.0)		
Headache	240	3	(1.3)	18	(7.5)	19	(7.9)	207	(86.3)		
Pain	188	16	(8.5)	12	(6.4)	29	(15.4)	151	(80.3)		
Diarrhoea	168	14	(8.3)	24	(14.3)	119	(70.8)	48	(28.6)		
Nausea	163	0	(0.0)	16	(9.8)	6	(3.7)	152	(93.3)		
Urticaria	158	64	(40.5)	10	(6.3)	79	(50.0)	74	(46.8)		
Irritability	143	4	(2.8)	18	(12.6)	136	(95.1)	6	(4.2)		
Lethargy	134	0	(0.0)	15	(11.2)	36	(26.9)	72	(53.7)		
Syncope	131	82	(62.6)	14	(10.7)	12	(9.2)	115	(87.8)		
Dizziness	114	3	(2.6)	11	(9.6)	0	(0.0)	111	(97.4)		
Myalgia	104	1	(1.0)	5	(4.8)	1	(1.0)	95	(91.3)		
Injected limb mobility decreased	76	0	(0.0)	1	(1.3)	11	(14.5)	63	(82.9)		
Chills	73	1	(1.4)	7	(9.6)	12	(16.4)	59	(80.8)		
Erythema	66	9	(13.6)	5	(7.6)	30	(45.5)	34	(51.5)		
Fatigue	65	1	(1.5)	5	(7.7)	12	(18.5)	53	(81.5)		
Malaise	64	1	(1.6)	8	(12.5)	7	(10.9)	53	(82.8)		
Paraesthesia	64	3	(4.7)	7	(10.9)	0	(0.0)	61	(95.3)		
Pruritus	63	2	(3.2)	2	(3.2)	14	(22.2)	46	(73.0)		
Abdominal pain	56	4	(7.1)	10	(17.9)	16	(28.6)	39	(69.6)		
Presyncope	47	27	(57.4)	3	(6.4)	11	(23.4)	34	(72.3)		
Cough	47	2	(4.3)	8	(17.0)	15	(31.9)	28	(59.6)		
Hypotonic-hyporesponsive episode	46	36	(78.3)	15	(32.6)	46	(100.0)	0	(0.0)		

MedDRA Preferred Terms (Adverse events)	AEFI records		Only reaction reported [†]		'Serious'		Age group* <7 years		Age group* ≥7 years		
	N	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Decreased appetite	46	0	(0.0)	2	(4.3)	31	(67.4)	14	(30.4)		
Arthralgia	46	3	(6.5)	4	(8.7)	2	(4.3)	43	(93.5)		
Convulsions****	45	29	(64.4)	17	(37.8)	40	(88.9)	3	(6.7)		
Dyspnoea	42	2	(4.8)	10	(23.8)	5	(11.9)	36	(85.7)		
Pallor	36	3	(8.3)	7	(19.4)	21	(58.3)	14	(38.9)		
Rhinorrhoea	29	1	(3.4)	3	(10.3)	18	(62.1)	10	(34.5)		
Hyperhidrosis	28	1	(3.6)	4	(14.3)	0	(0.0)	28	(100.0)		
Chest discomfort	24	0	(0.0)	5	(20.8)	1	(4.2)	22	(91.7)		
Tachycardia	23	0	(0.0)	11	(47.8)	8	(34.8)	13	(56.5)		
Oropharyngeal pain	21	0	(0.0)	1	(4.8)	3	(14.3)	15	(71.4)		
Hypoaesthesia	19	3	(15.8)	3	(15.8)	0	(0.0)	19	(100.0)		
Haematochezia	18	6	(33.3)	3	(16.7)	17	(94.4)	1	(5.6)		
Intussusception	16	14	(87.5)	15	(93.8)	16	(100.0)	0	(0.0)		
Somnolence	14	0	(0.0)	3	(21.4)	9	(64.3)	5	(35.7)		
Throat irritation	12	2	(16.7)	4	(33.3)	0	(0.0)	12	(100.0)		
Blister	9	0	(0.0)	2	(22.2)	4	(44.4)	5	(55.6)		
Anaphylactic reaction	8	5	(62.5)	4	(50.0)	1	(12.5)	3	(37.5)		
Gait disturbance	7	0	(0.0)	3	(42.9)	1	(14.3)	5	(71.4)		
Guillain-Barre Syndrome	6	4	(66.7)	2	(33.3)	0	(0.0)	5	(83.3)		
Tremor	5	2	(40.0)	0	(0.0)	0	(0.0)	4	(80.0)		
Lymphadenitis	1	0	(0.0)	0	(0.0)	1	(100.0)	0	(0.0)		

[†] A complete list of adverse reactions as classified by individual Preferred Terms is available on request.

* Selected reported adverse events reported during Jan-Dec 2016. Note: for injection site reaction, rash and convulsions, PT's were grouped as described below.

** Injection site reaction includes the following MedDRA PTs: injection site reaction, injection site swelling, injection site pain, injection site erythema, injection site cellulitis, injection site rash, injection site induration, injection site abscess, injection site pruritus, injection site nodule, injection site mobility decreased, injection site urticaria, injection site inflammation, injection site bruising, injection site infection, and injection site warmth.

*** Rash includes the following MedDRA PTs: rash, rash generalised, rash erythematous, rash pruritic, rash maculo-papular, rash macular, rash vesicular, rash papular, rash morbilliform, and rash pustular.

**** Convulsion includes the following MedDRA PTs: febrile convulsion, and convulsion, grand mal convulsion, and partial seizures.

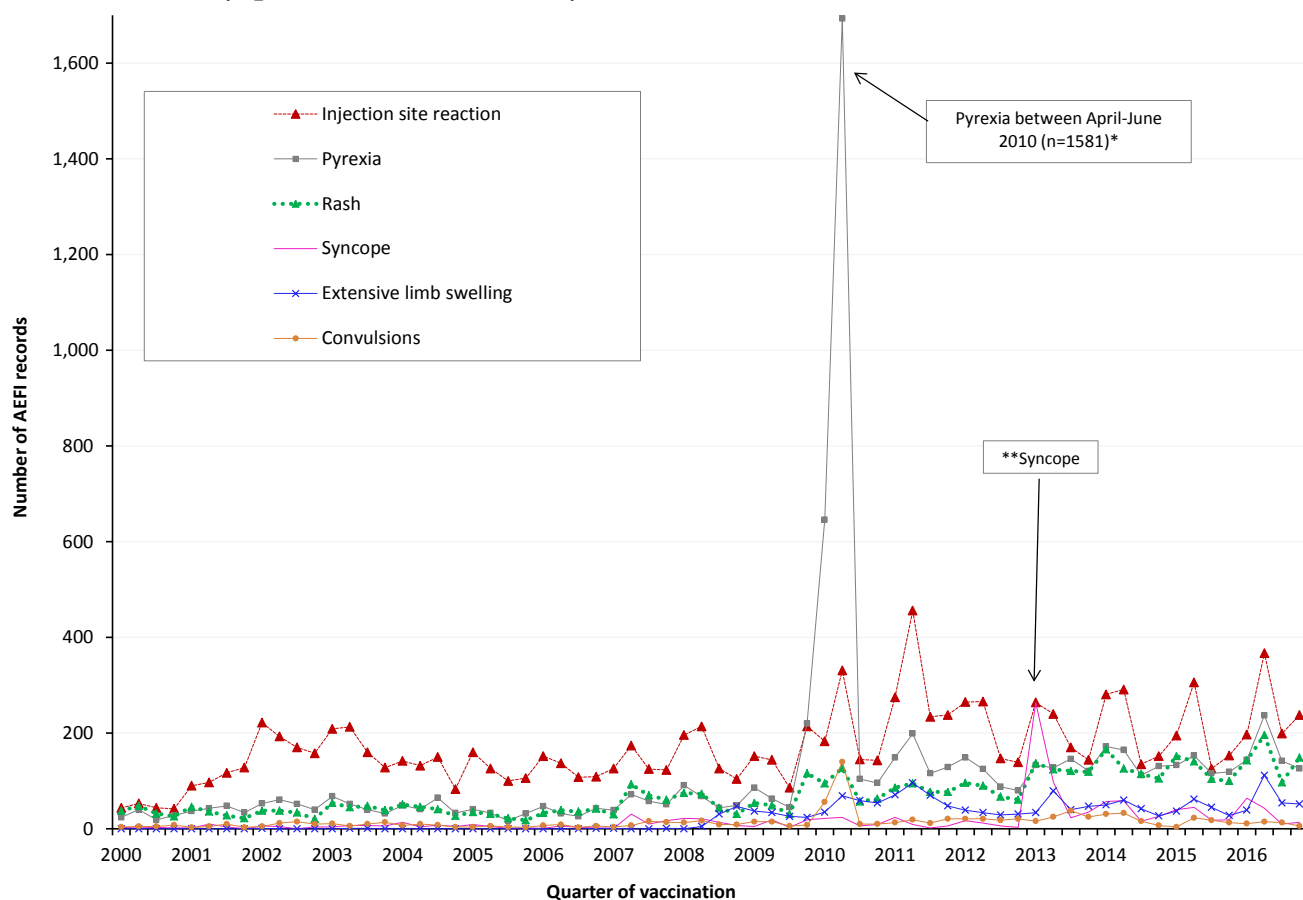
† AEFI records where only one reaction was reported.

[§] 'Serious' outcomes are defined in the Methods section.

* Includes only AEFI records where an age or date of birth has been reported

|| Percentages relate to the number of AEFI records in which the specific reaction term was listed

Figure 4: Selected frequently reported adverse events following immunisation, ADRS database, 2000 to 2016, by quarter of vaccination, by date of vaccination



* Associated with administration of Seqirus (formerly bioCSL) Fluvax 2010 TIV and associated stimulated reporting.

** The peak in syncope coincided with the enhanced HPV surveillance program in which there was stimulated reporting of syncope for the first 6 months of 2013.

Note: For reports where the date of vaccination was not recorded, the date of onset or date event was reported to TGA was used as a proxy for vaccination date. Also, grouping for reactions are different for this report though these reactions have been mapped back to 2000 as mentioned in the Methods section.

Reactions

In 2016, out of the 3,407 records, the most frequently reported adverse events were injection site reactions (ISRs) (n=1,001; 29%), pyrexia (n=649; 19%), rash (n=585; 17%), vomiting (n=281; 8%), extensive swelling of vaccinated limb (n=257; 8%) and headache (n=240; 7%) (Table 5, Figure 4). Some of the other reactions of interest were hypotonic-hyporesponsive episode (n=46; 1.4%), convulsions (n=45; 1.3%), intussusception (n=16; 0.5%) and Guillain-Barré

Syndrome (n=6; 0.2%) (Table 5). Anaphylaxis (n=8) was reported for 0.2 per cent of AEFI records in 2016.

The number of reports for each reaction has changed over time (Figure 4). The variation in reporting of ISRs is related to changes in the immunisation schedule for vaccines that are known to have higher rates of ISR, including DTPa-containing vaccines, 23vPPV and HPV vaccine.^{3-14,34,35} Increases in reports of fever were largely associated with time periods when new vaccines were added to the NIP in the reporting period, such as 7vPCV and HPV; the extension of seasonal influenza vaccine on the NIP to

include persons <65 years at high risk of influenza in 2010; 13vPCV replacing 7vPCV in July 2011; and the extension of HPV to males in 2013.

Severity of outcomes

The majority of reported events in 2016 were defined as 'non-serious' (n=3,073; 90.2%). There is a 24% decline in 'serious' events in this reporting period compared to the previous reporting period (Figure 1).

Two deaths were reported from NSW as temporally associated with receipt of vaccines in 2016.

A 40 year old male died 2 weeks after receiving a dose of hepatitis A vaccine and a dose of the typhoid vaccine. These vaccines are not included in the NIP. The cause of death was acute disseminated encephalomyelitis (ADEM).

A one year old male died a day after receiving the first dose of the MMR vaccine and a dose of the combined Hib-MenC vaccine. The child presented at hospital with prolonged seizures. There was a history of seizures in the family. The cause of death was noted as status epilepticus. The post mortem findings showed the effects of status epilepticus and cardiopulmonary arrest. After a thorough investigation by the TGA the cause was determined to be coincidental to vaccination.

In addition to the above 2 deaths, 2 fetal deaths in utero were reported in this period:

- A 23 year old female at 35 weeks gestation who presented to the emergency department 5 days post administration of the dTpa vaccine. The patient presented with decreased fetal movement and subsequent fetal death in utero. Third trimester ultrasound demonstrated small for gestational age fetus with declining asymmetric growth, which indicates an underlying problem was affecting the fetus prior to the vaccination.
- A 32 year old female at 36 weeks gestation was given the dTpa vaccine at the antenatal clinic a day before she presented at hospital

with lack of fetal movements. Fetal death was confirmed at hospital.

Stillbirth affects around 1 in 200 pregnancies that reach at least 20 weeks gestation in NSW.³⁶ It is likely that these late fetal deaths were coincidental to vaccination; however, there was not sufficient information available to conduct a causality assessment.

In summary, all deaths following immunisation reported to the TGA were investigated by the TGA and based on the information received from reporters, no clear causal relationship with vaccination was found. In some cases this was because no further information was provided by the reporter to allow an assessment of causality. The TGA encourages all reporters to provide sufficient information to allow the TGA to assess any causal relationship between the administration of a vaccine and the adverse event reported.

Discussion

This report uses a similar methodology of analysis used in the previous 3 annual reports.^{2,15,33} As per the previous report, this method allows for clearer reporting of adverse events using MedDRA® PTs, as used in the DAEN. This change in methodology needs to be taken into account when comparing with data on specific reaction terms and categories from annual reports prior to 2013.

In 2016, there appeared to be a 14% increase in the AEFI reporting rate compared with the previous year. This increase in reported adverse events in 2016, compared to the previous year, was mainly attributable to introduction of the booster dose of the DTPa at 18 months of age in April 2016 and the zoster vaccine for those aged 70- 79 years in November 2016. There is usually an increase in reporting of adverse events when a program is newly rolled out. Previous data have shown early increase in AEFI reporting occur each time a new vaccine is introduced, as immunisation providers are more likely to report milder, less serious AEFIs for vaccines they are not as familiar with. A reduction and

stabilisation of reporting rates over time occurs thereafter.^{2,4,5,7,10,12-15,33,37} During this first year of implementation of the DTPa at 18 months national program, there were 310 AEFI reports though majority (95%) of the reactions were mild reactions and not serious. Also, for those adults who had received the zoster vaccine, there were 165 AEFI reports though majority (96%) of the reactions were mild reactions and not serious.

Also in 2016, the second year of implementation of the season influenza vaccine program for all Aboriginal and Torres Strait Islander children aged 6 months to 5 years, an adverse event following seasonal influenza vaccine was reported in 3 Aboriginal and Torres Strait Islander child aged 6 months to 5 years and was reported as not serious.

These findings are similar to national vaccine safety data from AusVaxSafety, that currently monitors the safety of pertussis, zoster and influenza vaccines via participants recruited in 156 sentinel surveillance sites nationwide where there was no safety signals observed for these vaccines during this reporting period.³⁸

Overall, in Australia, injection site reaction, pyrexia, rash, vomiting and headache were the most commonly reported reactions in 2016. AEFI reporting rates for most individual vaccines in 2016 were similar to 2015.

The majority of AEFI reports (90%) were described as non-serious events. There were 2 deaths reported with causal relationship unable to be determined.

Conclusion

The reported AEFIs increased in 2016 compared with 2015 though the majority of AEFIs reported to the TGA were mild transient events. The data reported here are consistent with an overall high level of safety for vaccines included in the NIP schedule.

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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 diphtheria-tetanus-pertussis (acellular) and inactivated poliovirus (quadrivalent)
DTPa-IPV-HepB-Hib	combined diphtheria-tetanus-pertussis (acellular), inactivated poliovirus, hepatitis B and <i>Haemophilus influenzae</i> type b vaccine (hexavalent)
HepB	hepatitis B
Hib	<i>Haemophilus influenzae</i> type b
Hib-HepB	combined <i>Haemophilus influenzae</i> type b and hepatitis B
Hib-MenC	combined <i>Haemophilus influenzae</i> type b and meningococcal C conjugate vaccine
HPV	human papillomavirus
MenB	meningococcal B vaccine
MenCCV	meningococcal C conjugate vaccine
MMR	measles-mumps-rubella
MMRV	measles-mumps-rubella-varicella
pH1N1	pandemic H1N1 influenza 2009
7vPCV	7-valent pneumococcal conjugate vaccine
13vPCV	13-valent pneumococcal conjugate vaccine
23vPPV	23-valent pneumococcal polysaccharide vaccine