Supplementary report: surveillance of adverse events following immunisation among children aged <7 years in Australia, 1 January to 30 June 2006

Glenda Lawrence,[1] Ian Boyd[2]

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

This report summarises national passive surveillance data collated in the Adverse Drug Reactions Advisory Committee (ADRAC) database at 30 September 2006 for adverse events following immunisation (AEFI) reported for children aged less than 7 years who received vaccines between 1 January and 30 June 2006.[1–3] It is the first full reporting period for AEFI data following the introduction of a new National Immunisation Program (NIP) schedule, which commenced on 1 November 2005. From that date, varicella vaccine was introduced for children at 18 months of age and inactivated poliovirus vaccines (IPV) replaced oral poliovirus vaccine (OPV) for children at 2, 4 and 6 months and 4 years of age. All children in Australia receive IPV in combined vaccines containing diphtheria-tetanus-acellular pertussis (DTPa) antigens (i.e DTPa-IPV; quadrivalent). In some states and territories, combined vaccines also include hepatitis B (HepB) (i.e. DTPa-IPV-HepB; pentavalent) or both HepB and *Haemophilus* influenzae type b (Hib) (i.e. DTPa-IPV-HepB-Hib; hexavalent).[4] As a result of these changes, DTPa and DTPa-HepB vaccines are no longer included in the NIP schedule.

Average annual population-based AEFI reporting rates were calculated using mid-2005 population estimates. Reporting rates per 100,000 doses were calculated for vaccines that are funded by the NIP using denominator data from the Australian Childhood Immunisation Register (ACIR).

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

Corresponding author: Dr Glenda Lawrence, NCIRS, Locked Bag 4001, Westmead 2145. Telephone: +61 2 9845 1433. Facsimile: +61 2 9845 1418. Email: glendal@chw.edu.au

The data reported here are provisional only. It is important to note that an AEFI is defined as a medical event that is temporally associated with immunisation but not necessarily causally associated with immunisation. Readers are referred to previous reports for a description of the national AEFI passive surveillance system[1] methods used to analyse the data[1–3] and information regarding limitations and interpretation of the data.[2] Often several vaccines and reaction codes are listed in an AEFI record so the number of both vaccines and reaction codes will exceed the total number of AEFI records. When several vaccines are administered at the same time, the reported AEFI is usually assigned a causality rating of 'possible' unless the AEFI is an injection site reaction and the vaccine name and site are known. In that situation, a causality rating of 'certain' will be assigned to the report.

1 January to 30 June 2006

There were a total of 240 AEFI records (28.9 per 100,000 population) for children aged <7 years for vaccines administered in the first six months of 2006. This was a nine per cent decrease on the 265 records (29.7 per 100,000 population) for the corresponding six month period in 2005. Thirty-three per cent (n=79) of records were for children aged <1 year, 14 per cent (n=33) for children aged 1 to < 2 years and 53 per cent (n=128) for children aged 2 to <7 years, similar to 2005. The male to female ratio was 1.2:1.

Of the 240 records analysed, 32 (13%) had outcomes defined as 'serious' (i.e. recovery with sequelae, hospitalisation, life-threatening event or death), and was higher than previously reported for children aged <7 years (average of 8% for 2000–2005; range 7–13%). Serious or potentially life-threatening AEFIs reported included apnoea or respiratory depression (n=11), bradycardia (n=10), seizure (n=7) and hypotonic-hyporesponsive episode (HHE; n=10). There were no reports of anaphylaxis or death. The most common reaction categories were injection site reaction (n=140; 58%), fever (n=38; 16%) and allergic reaction (n=31; 13%).

One or more of the vaccines on the current NIP schedule, shown in the Table, was recorded as suspected of involvement in the reported adverse event for 232 of the 240 records analysed. Eight records listed only non-NIP vaccines as suspected of involvement in the reported AEFI. The nine vaccines listed in these AEFI records were influenza (n=5), BCG (n=1), hepatitis A (n=1), combined hepatitis A and B (n=1) and pneumococcal polysaccharide (n=1) vaccines.

The AEFI reporting rates per 100,000 vaccine doses recorded on the ACIR were similar to those in 2005 for most of the vaccines that have been included in the NIP schedule for some time, including meningococcal C conjugate vaccine (MenCCV), seven-valent pneumococcal conjugate vaccine (7vPCV) and Hib vaccine (Table). The apparent increase in the reporting rate for Hib-HepB vaccine may be related to reporting of AEFIs for the newer quadrivalent DTP-IPV vaccine among children aged <1 year as the two vaccines are both given at 2 and 4 months of age.[4]

Reporting rates for the different DTPa-IPV combination vaccines varied by vaccine type (Table). The reporting rate for pentavalent vaccine is likely to be inaccurate due to the small number of reports and some under-reporting to the ACIR of doses administered. The reporting rate for quadrivalent DTPa-IPV includes reports for children aged <1 year who were scheduled to receive the vaccine at 2, 4, and 6 months of age (reporting rate of 20.3 per 100,000 doses) and reports for children aged 4 years (reporting rate of 88 per 100,000 doses).

While the number of AEFI reports for children aged <1 year and 2 to <7 years was similar in 2006 and 2005, AEFI reporting rates per 100,000 vaccine doses increased for children in these two age groups (Table). The reporting rate for AEFIs defined as serious also increased from 0.6 in 2005 to 1.8 in 2006. Reasons for these changes are discussed below and relate mainly to a reduction in the denominator following the introduction of multivalent vaccines in November 2005.

DTPa-IPV combination vaccines

There were a total of 69 AEFI records for children aged <1 year where a DTPa-IPV quadrivalent, pentavalent or hexavalent combination vaccine was listed as suspected of involvement in the reported AEFI and the vaccine was administered during January to June 2006 (hexavalent = 32; pentavalent = 4; quadrivalent = 33). The overall reporting rate for these three vaccines was 18.9 AEFI records per 100,000 doses for children aged <1 year. This is slightly higher than the reporting rates in 2005 for DTPa and DTPa-HepB vaccines among children aged <1 year in 2005 (12.7 and 14.0 per 100,000 doses, respectively).

Of the 69 records, DTPa-IPV combination vaccines were listed as the only suspected vaccine for 9 (13%) while 62 (90%) had causality ratings of 'possible' and 20 (29%) records listed outcomes defined as 'serious'. The most frequently reported adverse events following DTPa-IPV combination vaccines, administered alone or with other vaccines, were injection site reaction (n=14), fever (n=13) and allergic reac-

Table. Reporting rates of adverse events following immunisation (AEFI) per 100,000 vaccine doses,* children aged less than 7 years, ADRAC database, January to June 2006

Vaccine†	AEFI records* (n)	Vaccine doses‡ (n)	Reporting rate per 100,000 doses§	
			Jan–June 2006	Jan–June 2005
Haemophilus influenzae type b	10	51,768	19.3	18.1
Haemophilus influenzae type b-hepatitis B	45	203,482	22.1	15.4
Measles-mumps-rubella	54	253,134	21.3	23.2
Meningococcal C conjugate	23	138,626	16.6	17.9
Pneumococcal conjugate	62	390,975	15.9	15.6
Diphtheria-tetanus-pertussis-IPV	126	311,608	46.9	–
Pentavalent (DTPa-IPV-HepB)	4	8,643	46.3	–
Hexavalent (DTPa-IPV-HepB-Hib)	32	174,596	18.3	–
Varicella	15	109,093	13.7	–
Age group				
<1 year	76	907,593	8.4	6.4
1 to <2 years	32	444,313	7.2	7.5
2 to <7 years	124	290,019	42.8	26.3
AEFI category†				
Total	232	1,641,925	14.1	10.5
‘Certain’ or ‘probable’ causality rating	100	1,641,925	6.1	4.6
‘Serious’ outcome	29	1,641,925	1.8	0.6

* 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 30 June 2006. More than one vaccine may be coded as ‘suspected’ if several were administered at the same time.

† Records where at least one of the nine vaccines shown in the table was suspected of involvement in the reported adverse event. AEFI category includes all records (i.e. total), those assigned ‘certain’ or ‘probable’ causality ratings, and those with outcomes defined as ‘serious’. Causality ratings were assigned using the criteria described previously.[1,2] A ‘serious’ outcome is defined as recovery with sequelae, hospitalisation, life-threatening event or death.[1,2]

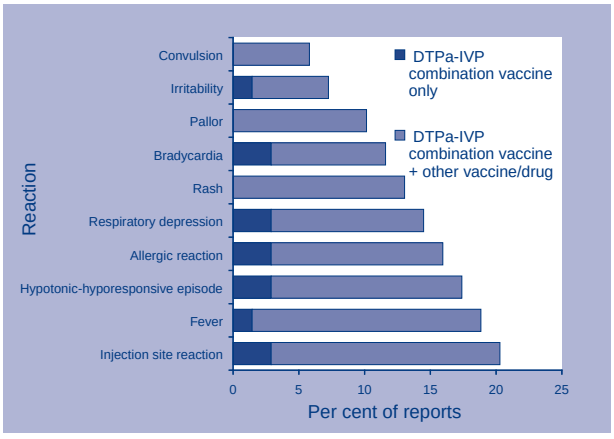
‡ Number of vaccine doses recorded on the Australian Childhood Immunisation Register (ACIR) and administered between 1 January and 30 June 2006.

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

tion (n=11) (Figure 1). More severe AEFIs included apnoea/respiratory depression (n=8), bradycardia (n=10), convulsion (n=4) and HHE (n=10). Reporting rates for these AEFIs were similar for both quadrivalent and hexavalent vaccines, except for HHE (4.8 per 100,000 doses of quadrivalent vaccine *cf* 0.6 per 100,000 doses of hexavalent vaccine, including reports where other vaccines were co-administered with either quadrivalent or hexavalent vaccine).

For children aged 2 to <7 years, there were 107 AEFI records that listed quadrivalent DTPa-IPV as a suspected vaccine (88 records per 100,000 doses). Of these, 73 records (68%) listed the vaccine as the only suspected vaccine while 67 (63%) had causality ratings of ‘certain’ or ‘probable’ and 7 (7%) listed outcomes defined as serious. Ninety-per cent (n=97) of records listed injection site reaction. This is a reporting rate of 80 injection site reactions per 100,000 doses, the same as seen over the past

Figure 1. Frequently reported adverse events following immunisation with DTPa-IVP quadrivalent, pentavalent and hexavalent combination vaccines, children aged <1 year, ADRAC database, 1 January to 30 June 2006 (n=69 records)



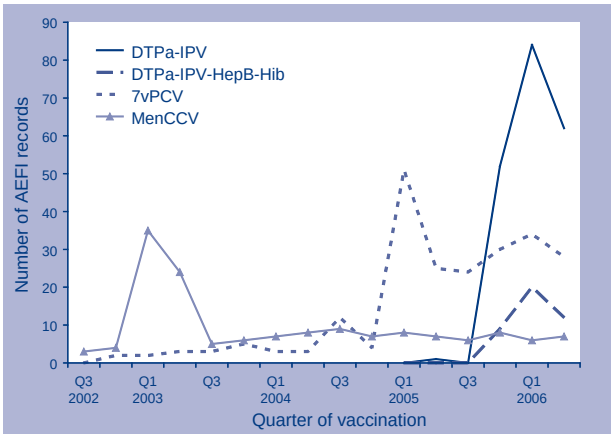
three years for children receiving a fifth dose of a DTPa-containing vaccine.[3]

Discussion

The total number of AEFI records and population-based reporting rates were slightly lower (by 9%) for January to June 2006 compared with the same period in 2005. The increase in summary and age group reporting rates per 100,000 vaccine doses (Table) is largely related to two factors. First, there has been a reduction in the total number of vaccine doses administered to children aged <1 year and 2 to <7 years following removal of OPV from the NIP schedule and the introduction of IPV-containing multi-antigen vaccines from 1 November 2005. This reduced the total number of doses administered by approximately one third (i.e. approximately 800,000 doses) compared with the first six months of 2005, while there has been little change in the number of AEFI reports to ADRAC. Second, there appears to have been increased reporting by providers following the introduction of new vaccines into the NIP in November 2005, as has been observed following the introduction of other vaccines in recent years (Figure 2). It is expected that reporting of AEFIs for DTPa-IPV combination vaccines will decline from the peaks seen in the first quarter of 2006 and stabilise over time, as has occurred with both MenCCV and 7vPCV.

The largest change in this reporting period has been the increase in the proportion of AEFI records with outcomes defined as serious. This increased from seven per cent of records in 2005 (a period following the introduction of 7vPCV) to 13 per cent for the first six months of 2006 after the introduction of the DTPa-IPV combination vaccines. Serious AEFIs reported for these vaccines were predominantly in children aged <1 year and included HHE, apnoea or respiratory depression and bradycardia. Importantly, there were no reports of anaphylaxis or death. The total number of serious reports is low and may represent increased awareness among providers following published reports from Germany that suggested an increased risk of sudden unexpected death in children aged <2 years after receipt of a hexavalent vaccine marketed in Germany.[5,6] It is important to note that (i) a large case-control epidemiological study conducted in Germany found no link between the use of hexavalent vaccines and sudden unexpected death in children;[7] (ii) the Global Advisory Committee on Vaccine Safety, convened by the World Health Organization, concluded that hexavalent vaccines are safe[8] and (iii) the specific vaccine in question is not used in Australia.

Figure 2. Reports of adverse events following immunisation, ADRAC database, 1 July 2002 to 30 June 2006, for vaccines recently introduced into the National Immunisation Program*



* Meningococcal C conjugate vaccine (MenCCV) was introduced into the NIP on 1 January 2003, 7-valent pneumococcal conjugate vaccine (7vPCV) on 1 January 2005, and both DTPa-IPV and DTPa-IPV-HepB-Hib combination vaccines on 1 November 2005.

Observed differences in reporting rates of HHE following receipt of quadrivalent DTPa-IPV compared with hexavalent vaccine may be due to different AEFI surveillance practices in the states where the quadrivalent vaccine is used (i.e. South Australia, Victoria and Queensland) compared with other jurisdictions.[2]

A number of the reports to ADRAC of apnoea and bradycardia following quadrivalent and hexavalent vaccines occurred in very pre-term infants who received vaccines at eight weeks of age whilst in a hospital setting, as recommended in the *Australian Immunisation Handbook*.[9] Cardio-respiratory events including apnoea and bradycardia are known AEFIs in hospitalised pre-term infants and are managed appropriately in a hospital setting.[10,11] The benefits of immunisation in pre-term infants continues to outweigh the small risk of these manageable adverse events.

Conclusion

This report further demonstrates that changes to the NIP are reflected in the national passive AEFI surveillance data.[2,3] Changes in AEFI reporting rates for vaccines administered in the first six months of 2006, compared with same period for 2005, correspond in time with the replacement of OPV and DTPa vaccines with DTPa-IPV combination vaccines from 1 November 2005. Although serious AEFIs increased as a proportion of total reports compared with the previous reporting period, the majority of AEFIs reported to ADRAC were mild transient events. Close monitoring of passive AEFI surveillance data for DTPa-IPV combination and other

vaccines administered to children continues through ADRAC, the Therapeutic Goods Administration and state and territory health departments.

Acknowledgements

We thank Mike Gold, Peter McIntyre and Nick Wood for their contribution to the report. The National Centre for Immunisation Research and Surveillance is supported by the Australian Government Department of Health and Ageing, the New South Wales Health Department and the Children's Hospital at Westmead.

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;27:307–323.

2. Lawrence G, Boyd I, McIntyre P, Isaacs D. Annual report: surveillance of adverse events following immunisation in Australia, 2005. *Commun Dis Intell* 2006;30:319–333.

3. Lawrence G, Boyd I. Adverse events following immunisation for children aged less than 7 years, 1 January to 30 June 2005. *Commun Dis Intell* 2005;29:413–416.

4. Australian Government Department of Health and Ageing. Immunise Australia Program–immunisation programs and initiatives. Available from: http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/programs Accessed December 2006.

5. Von Kries R, Toschle AM, Strassburger K, Kundi M, Kalies H, Nennsteil U, *et al.* Sudden and unexpected deaths after the administration of hexavalent vaccines (diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, *Haemophilius influenzae* type b): is there a signal? *Eur J Pediatr* 2005;164:61-69.

6. Zinka B, Rauch E, Buettner A, Penning R, Rueff F. Unexplained cases of sudden infant death shortly after hexavalent vaccination. *Vaccine* 2006;24:5779–5780.

7. Vennemann MMT, Butterfass-Bahloul T, Jorch G, Brinkmann B, Findeisen M, Sauerland C, *et al.* Sudden infant death syndrome: no increased risk after immunisation. *Vaccine* 2007;25:336–340. E-pub ahead of print.

8. Global Advisory Committee on Vaccine Safety. Safety of hexavalent vaccines. *Wkly Epidemiol Rec* 2005;28:245–246. Available from: http://www.who.int/vaccine_safety/reports/June_2005/en/index.html Accessed in December 2006.

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

10. Botham SJ, Isaacs D, Henderson-Smart DJ. Incidence of apnoea and bradycardia in preterm infants following DTPw and Hib immunization: a prospective study. *J Paediatr Child Health* 1997;33:418–421.

11. Schulzke S, Heininger U, Lucking-Famira M, Fahenstich H. Apnoea and bradycardia in preterm infants following immunisation with pentavalent and hexavalent vaccines. *Eur J Pediatr* 2005;164:432–435.