Local reactions after the fourth-dose of acellular pertussis vaccine in South Australia

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ABSTRACT

Objective: To assess the reported rate of local reactions after administration of acellular pertussis vaccine (DTPa) according to dose number and type of pertussis vaccine (whole-cell or acellular) used for the primary course, and to document the severity and outcome of fourth-dose local reactions.

Design and setting: Retrospective review. Reports of adverse events after vaccination in South Australia between 1 January 1997 and 31 December 2000 were reviewed, and a questionnaire administered to all parents who reported a local reaction after the fourth dose of DTPa.

Main outcome measures: The number, and rate per 100 000 administered doses, of local reactions following the primary and booster doses of DTPa, and of local reactions after the fourth-dose in cohorts of children whose primary vaccinations were with either DTPw or DTPa. Redness and/or swelling at the injection site as reported by parents.

Results: Of 581 reported adverse events after vaccination, 138 were local reactions after a pertussis-containing vaccine. Primary vaccinations with DTPa was a significant risk factor for a fourth-dose local reaction (relative risk, 6.7; 95% CI, 2.4–18.5). Parental questionnaires were completed for 45 of the 71 children (63%) with reported local reactions after the fourth dose of DTPa; extensive limb swelling was reported in 8 children (18%) and all except one child had recovered by the time of review.

Conclusions: Parents should be informed that children receiving booster doses of DTPa vaccine, after primary doses with DTPa, are at increased risk of local reactions (which tend to resolve spontaneously) but not of systemic effects. Studies should be initiated to investigate the pathogenesis and the risk of recurrence of local reactions to further improve vaccination schedules.

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ACELLULAR PERTUSSIS VACCINES have now replaced whole-cell pertussis vaccine in the immunisation schedules of many countries because of concerns and public perceptions about the reactogenicity of the whole-cell product. Clinical trials and passive surveillance data have shown that vaccines containing purified pertussis antigens are less reactogenic than whole-cell pertussis vaccines.[1-5]

In August 1997, an acellular combination diphtheria–tetanus–pertussis vaccine (DTPa [Infanrix, GlaxoSmithKline, Melbourne]) was introduced into South Australia to replace the previous whole-cell pertussis-containing vaccine (DTPw [Triple Antigen, CSL Limited, Melbourne]). All children receiving their primary vaccinations after August 1997 were given DTPa vaccine, as were all children presenting for booster doses at 18 months and 4–5 years of age; by April 1998 distribution of DTPw vaccine in SA had reduced markedly. The Australian Standard Vaccination Schedule changed from whole-cell to acellular pertussis vaccine from May 2000 (Box 1).

After DTPa vaccine was introduced, a significant decrease in the reported rates of both local and general adverse events was noted, but more recently there has been an increase in the number of reported local reactions after DTPa administration.[8]

We examined, firstly, the passive surveillance data to compare the rates of local reactions according to the dose number, and to compare such rates after the fourth dose between cohorts of children whose primary vaccinations were with DTPw and with DTPa. Secondly, we ascertained the severity and outcomes of these fourth-dose local reactions.

METHODS

Data collection

Since the passive surveillance scheme was established in 1996, medical practitioners and vaccination providers have been asked to report any serious and/or unexpected adverse event after vaccination to the South Australian Immunisation Coordination Unit (SAICU). Reports are received on a standard form, which asks for demographic details, the suspected vaccine, concomitant vaccines administered, and details of the event, including time to recovery and treatment required. At the SAICU all reports are reviewed by a paediatrician with an interest in vaccine safety (MG), and the adverse event is classified according to the definitions in Box 2.

If the reported adverse event meets the case definition of a serious "adverse event following immunisation" according to the *Australian immunisation handbook*,[7] details are forwarded to the national Adverse Drug Reaction Assessment Committee (ADRAC).

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1: Australian Standard Vaccination Schedule used in South Australia

Age of child	Vaccines given before May 2000[6]	Vaccines given after May 2000[7]
Birth		Hep-B
2 months	DTP, Hib, OPV	DTPa–Hep-B, Hib, OPV
4 months	DTP, Hib, OPV	DTPa–Hep-B, Hib, OPV
6 months	DTP, Hib, OPV	DTPa–Hep-B, OPV
12 months	MMR	MMR, Hib
18 months	DTP, Hib	DTPa
4 years	DTP, MMR, OPV	DTPa, MMR, OPV

Hep-B = hepatitis B vaccine; DTP = diphtheria–tetanus–pertussis vaccine (acellular or whole cell); DTPa = diphtheria–tetanus–pertussis vaccine (acellular); OPV = oral polio vaccine; Hib = *Haemophilus influenzae* type b vaccine; MMR = measles–mumps–rubella vaccine; DTPa–Hep-B = combined diphtheria–tetanus–pertussis (acellular) and hepatitis B vaccine.

2: Classification of adverse events after vaccination, used by the South Australian Immunisation Coordination Unit

Local reaction: redness and/or swelling (without abscess formation) occurring within 7 days at the vaccine site.

Serious local reaction: redness and/or swelling at the injection site AND at least one of: (i) pain, redness and swelling lasting more than 3 days, (ii) hospitalisation, (iii) redness and/or swelling extending from the injection site beyond one or both joints, or (iv) redness of the entire proximal limb from joint to joint.

Extensive limb swelling: swelling extending from the injection site beyond one or both joints or swelling of the entire proximal limb from joint to joint.

Skin rash: any skin eruption (erythema, urticaria, or angioedema).

Seizure: sudden loss of consciousness with motor or sensory symptoms or signs, both occurring within 7 days of vaccination.

Hypotonic hyporesponsive episode: an event of sudden onset occurring within 48 hours of immunisation and presenting with hypotonia, hyporesponsiveness and pallor or cyanosis or failure of the observer to recall any change in skin colouration.[9]

For this study, all reports of a local reaction, skin rash, hypotonic hyporesponsive episode or seizure associated with the administration of a pertussis-containing vaccine, received between 1 January 1997 and 31 December 2000, were included.

Before August 1997, only DTPw was distributed. This was replaced with DTPa between August 1997 and December 1998.

For the purpose of analysing the effect of having had primary vaccinations with DTPw or DTPa, the reported rates of adverse events after the fourth dose of DTPa were compared in two groups as follows:

DTPw primary vaccination group: children whose reactions to the fourth dose occurred before January 1999 were assumed to have received DTPw for their first, second and third doses. This group of children would have received their third dose of DTP vaccine before June 1997, when DTPw was the only DTP vaccine available.

DTPa primary vaccination group: children whose reactions to the fourth dose occurred from June 1999 were assumed to have received DTPa for their first, second and third doses. These children would have received their third dose of DTP vaccine after June 1998, 10 months after DTPa was introduced.

The Australian Childhood Immunisation Register (ACIR), which was established in January 1996 to record all vaccines administered to Australian children under 7 years of age from data provided by vaccine providers, was used to estimate the number of administered doses of DTPa.[10]

From 1 January 1998 to 31 December 2000, reports of any fourth-dose local reaction after DTPa vaccine administration were identified. At the time of submitting the report of an adverse event after vaccination to SAICU, all parents routinely provide written consent to be contacted. Three attempts were made to contact the parents of affected children at different times of the day. Those successfully contacted were invited to complete a telephone questionnaire, which aimed to ascertain a description of the reaction, effect on the child's behaviour, time to recovery, other concurrent adverse events, and the site of the DTPa injection.

Statistical analysis

The rates of reports for local reactions, skin rash and convulsions were compared between the first dose and subsequent doses, and the χ^2 test was used to calculate the significance of these differences. To assess the effect of primary vaccinations with DTPw, the number of reported events in children whose primary vaccinations were with DTPw was compared with the number whose primary vaccinations were with DTPa by means of χ^2 analysis.

RESULTS

Surveillance

In the study period, 581 reports of adverse events after vaccination were received. The annual rate of reports received varied (ranging from 20 reports per 100 000 distributed vaccines in 1999 to 44 per 100 000 in 1997), but did not increase. Of the 209 local reactions reported, 28 (13%) met the criteria for reporting to ADRAC, and 138 were associated with the administration of a pertussis-containing vaccine. Of these, 100 (73%) were associated with DTPa, 82 of which occurred after a fourth dose (Box 3).

Box 4 documents adverse events after receiving DTPa as the fourth dose, for cohorts whose primary vaccinations were with DTPw or DTPa.

Severity and outcomes

Between 1 January 1998 and 31 December 2000, 71 reports were received of local reactions after the fourth dose of DTPa. Parents were contacted and completed the telephone interview in 45 of these cases (63%); in 26 cases parents could not be contacted either because details were incorrect or contact attempts failed.

3: Adverse events after acellular diphtheria–tetanus–pertussis (DTPa) and combined acellular diphtheria–tetanus–pertussis and hepatitis B vaccine (DTPa–Hep-B) administration, according to dose number, 1 January 1997 to 31 December 2000

	Dose number				
	1	2	3	4	Total
No. of doses of DTPa and DTPa–Hep-B administered	41 807	41 529	41 585	41 459	166 380
No. (rate)* of local reactions	2 (5)	3 (7)	5 (12)	71 (171)	81 (47)
Relative risk† (95% CI)		1.51 (0.25–9.04)	2.51 (0.49–12.95)	36‡ (8.78–146)	
No. (rate) of skin rash reports	8 (19)	5 (12)	5 (12)	8 (19)	26 (16)
Relative risk† (95% CI)		0.63 (0.21–1.92)	0.63 (0.21–1.92)	1.01 (0.38–2.69)	
No. (rate) of convulsions and HHE	7 (17)	1 (2)	0	3 (7)	11 (7)
Relative risk† (95% CI)		0.14 (0.02–1.17)		0.43 (0.11–1.67)	

*Rate per 100 000 administered doses. †Compared with 1st dose. ‡ $P < 0.001$. HHE = hypotonic hyporesponsive episode.

4: Adverse events after receiving DTPa as a fourth dose in cohorts whose primary vaccinations were with DTPw (1 January 1997 to 31 December 1998) or DTPa (1 June 1999 to 31 December 2000)

		Number (rate per 100 000 administered doses)		
	No. DTPa 4th doses administered	Local reactions	Skin rash	Convulsions and HHE
Primary vaccinations at 2, 4, and 6 months				
DTPw	11 071	4 (36)	1 (10)	1 (10)
DTPa	24 719	60 (243)	4 (16)	0
Relative risk (95% CI) of reaction after DTPa versus DTPw primary vaccinations		6.7 (2.4–18.5)*	1.61 (0.18–14.2)	—

* $P < 0.001$ Fisher exact test. HHE = hypotonic hyporesponsive episode.

The median age of these 71 children at the time of the fourth dose was 19.5 months (range, 18–48 months) and their median age at the time of the interview was 32 months (range, 19–93 months). There were no significant differences with regard to sex or age at the time of the fourth vaccination between children whose parents could and could not be contacted.

Of the 45 children whose parents were contacted, 27 (60%) had the site of administration of the DTP vaccine documented, and this was the same site as the reported local reaction. One child received the DTP vaccine in the buttock (not recommended in Australia), 36 in the arm (the preferred site) and eight in the anterolateral thigh. Forty-two of the 45 children had the administered vaccine recorded as DTPa, three had no brand documented, and none had DTPw documented.

All parents reported that swelling occurred with the local reaction, and all but one reported redness with it. The median time to symptom onset was 19.3 hours (range, immediate to 72 hours). The median durations of redness and swelling were 75 hours (range, 24–168 hours) and 77 hours (range, 24–168 hours), respectively. All but one reported complete recovery by the time of review. In 10 of the 45 children (22%), the local reaction met the case definition for a report to ADRAC, and eight of these (18%) had extensive limb swelling.

DISCUSSION

Our surveillance data show that, after the introduction of DTPa in South Australia, the reported rates of a local reaction following the fourth dose of DTPa are 34 times higher than after the first dose. This increased rate of local reaction may reflect a true increase, or a selective increase in reporting of adverse events after the fourth dose. However, we did not find the same trend for reported skin rash, convulsions or hypotonic hyporesponsive episodes after the fourth dose of the same vaccine. In addition, the number of reports of adverse events per 100 000 distributed vaccines received by SAICU was higher in 1997 than in 2000. Therefore, ascertainment bias is unlikely. Local reactions are being reported in children who have had primary vaccinations with DTPa rather than DTPw. This might explain why the initial surveillance data indicated a lower rate of local reactions following the fourth dose of DTPa. As the surveillance database and ACIR register were established in 1996, it was not possible to compare the rates of local reactions following the fourth and fifth dose of DTPw with DTPa.

An increase in the frequency of local reactions is recognised to occur with booster doses of acellular pertussis vaccines.[11,12] In a multicentre trial evaluating 1293 children who received a fourth dose of DTPa vaccine at 15–20 months of age, local reactions were less common with DTPa than with DTPw, but more common with an increasing number of DTPa doses and after DTPa primary vaccinations (as compared with DTPw primary vaccinations).[11] No consistent pattern was revealed for different DTPa vaccines.

Extensive limb swelling after booster doses of DTPa appears to occur in up to one in 36 vacinees.[5,12-15] Our surveillance data indicate that there is still an underreporting of extensive limb swelling in South Australia.

It is not known if extensive limb swelling represents a distinct pathological entity or an extreme form of a local reaction. Its rates may be correlated with the diphtheria content of individual vaccines,[14] or possibly to the pertussis[13] and aluminium content.[14] DTPa for primary vaccinations is the only identified risk factor for local reactions and extensive limb swelling with booster doses.[14] A recent study has documented a direct association between pre-booster antibody titres to diphtheria and pertussis toxin, and large local reactions in 4–6-year-old children receiving a two component DTPa vaccine.[15]

Thus, parents and caregivers of children receiving a booster dose of a DTPa vaccine following DTPa primary vaccinations should be informed that there is an increased risk of local reactions, including extensive limb swelling. However, they should also be informed that no significant sequelae have been reported following these reactions. Indeed, ADRAC recommends that children who have had extensive limb swelling with a fourth dose of DTPa should be offered a fifth dose.[16] Surveillance for local reactions after vaccination should continue to be widely promoted in order to document the frequency of fourth and fifth dose reactions. These findings may have implications for the number, timing and antigen content of DTP booster vaccines included in the vaccination schedule. A recent study reporting that protection against pertussis after a primary course may persist until six years of age, may indicate that the fourth dose of DTPa at 18 months is no longer required.[17]

Finally, prospective studies should be initiated to investigate the pathogenesis of local reactions. This should compare the frequencies of local reactions to different DTPa vaccines, identify possible risk factors, and establish the risk of recurrence in those children who have experienced a local reaction. Such measures are vital to ensure that vaccines are safe, and that public confidence in pertussis vaccination remains high.

COMPETING INTERESTS

None identified.

REFERENCES

1. Decker MD, Edwards KM, Steinhoff MC, et al. Comparison of 13 acellular pertussis vaccines: adverse reactions. *Pediatrics* 1995; 96: 557-566.
2. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *N Engl J Med* 1996; 334: 345-348.
3. Olin P, Rasmussen F, Gustafsson L, et al. Randomised trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Lancet* 1997; 350: 1569-1577.
4. Pichichero M, Deloria MA, Rennels MB, et al. Safety and immunogenicity comparison of 12 acellular pertussis vaccines and one whole cell pertussis vaccine given as a fourth dose in 15 to 20 month old children. *Pediatrics* 1997; 100: 772-788.
5. Schmitt HJ, Beutel K, Schuid A, et al. Reactogenicity and immunogenicity of a booster dose of a combined diphtheria, tetanus and tricomponent acellular pertussis vaccine at fourteen to twenty-eight months of age. *J Pediatr* 1997; 130: 616-623.
6. National Health and Medical Research Council. The Australian immunisation handbook. 6th ed. Canberra: AGPS, 1997.
7. National Health and Medical Research Council. The Australian immunisation handbook. 7th ed. Canberra: AGPS, 2000.
8. Gold M, Kempe A, Osbourn M. A comparison of serious adverse reactions to whole cell and acellular pertussis vaccines in South Australia. *Med J Aust* 1999; 171: 331-332.
9. Braun M, Terracciano G, Marcel S, et al. Report of a US public health service workshop on hypotonic-hyporesponsive episode (HHE) after pertussis immunisation. *Pediatrics* 1998; 102: 1201-1202.
10. Torvaldsen S, Hull B, McIntyre P. Using the Australian Childhood Immunisation Register to track the transition from whole cell to acellular pertussis vaccine. *Commun Dis Intell* 2002; 26: 581-583.
11. Miller E, Rush M, Ashworth LA, et al. Antibody response and reactions to the whole cell pertussis component of a combined diphtheria/tetanus/pertussis vaccine given at school entry age. *Vaccine* 1995; 13: 1183-1186.
12. Tozzi AE, Anemona A, Stefanelli P, et al. Reactogenicity and immunogenicity of a booster dose of two three-component diphtheria-tetanus-acellular pertussis vaccines in children primed in infancy with acellular vaccines. *Pediatrics* 2001; 107: e25.
13. Rennels M, Deloria M, Pichichero M, et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. *Pediatrics* 2000; 105: e12.
14. Halperin SA, Mills E, Barreto L, et al. Acellular pertussis vaccine as a booster dose for seventeen- to nineteen-month-old children immunized with either whole cell or acellular pertussis vaccine at two, four and six months of age. *Pediatr Infect Dis J* 1995; 14: 792-797.
15. Liese LG, Stojanov S, Zink TH, et al. Safety and immunogenicity of Biken acellular pertussis vaccine in combination with diphtheria and tetanus toxoid as a fifth dose at four to six years of age. *Pediatr Infect Dis J* 2001; 20: 981-988.
16. Extensive limb swelling after DTPa vaccine. *Aust Adv Drug React Bull* 2001; 20: 10.
17. Salmaso S, Mastrantonio P, Tozzi AE, et al. Sustained efficacy during the first 6 years of life of 3-component acellular pertussis vaccines administered in infancy: the Italian experience. *Pediatrics* 2001; 108: e81.

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