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Extensive swelling of the limb and systemic symptoms after a fourth dose of acellular pertussis containing vaccines in England in children aged 3–6 years

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ABSTRACT

Extensive limb swelling (ESL) after a booster dose of acellular pertussis (aP) containing vaccine can cause concern and has the potential to be confused with cellulitis. In the United Kingdom aP-containing vaccine was introduced for primary immunisation at 2, 3 and 4 months of age in 2004, with the first cohorts eligible to receive a fourth dose in 2007 at school entry. We assessed the frequency of ESL (here defined as swelling >100 mms diameter) in 973 children receiving a fourth dose of one of four aP vaccines given combined with inactivated polio, tetanus and either low dose diphtheria (TdaP/IPV) or high dose diphtheria (DTaP/IPV) vaccine; 2 of the 3 DTaP/IPV vaccines also contained *Haemophilus influenza* b conjugate vaccine (Hib). Post-vaccination symptoms and local reactions were recorded in 7-day diaries or by a telephone follow up if no diary was returned. Local swellings >50 mm diameter were reported by 2.2% TdaP/IPV recipients compared with 6.6–11.1% of DTaP/IPV recipients; the corresponding proportions for redness >50 mms was 7.0% for TdaP/IPV and 13.3–17.7% for DTaP/IPV recipients. Among the latter, the addition of Hib did not affect the frequency or size of local reactions. Pain at the injection site and systemic symptoms did not differ between the four vaccine groups. A history of atopy was not associated with development of local swelling or redness. A total of 13 children (1.3%) experienced an ESL, three after TdaP/IPV. ESLs resolved without systemic upset within a few days and were usually painless; medical advice was only sought for two children. Parents should be informed about the possible occurrence of an ESL with the pre-school aP-containing booster vaccine but can be reassured that it is a benign and transient condition.

1. Introduction

Primary and booster vaccination with acellular pertussis (aP) vaccines generally produces fewer local and systemic reactions than vaccination with whole cell (wP) vaccines [1,2]. However, in children who have been primed with aP vaccine redness and swelling at the injection site can be increased compared with those primed with wP vaccine. In some cases this swelling can be extensive involving much of the upper limb [3–6]. While resolving quickly without treatment such local reactions can generate concern and may be confused with cellulitis which requires prompt antibiotic treatment.

In the UK aP vaccine was introduced as a pre-school booster combined with diphtheria and tetanus (DTaP) for children aged three and a half to six years in 2001. In 2004 wP was replaced by aP vaccine for the primary series at 2, 3, 4 months of age using a DTaP vaccine combined with inactivated polio and *Haemophilus* type b vaccines (DTaP/IPV/Hib). Before this, aP-containing vaccine had only been used sporadically for priming when supplies of wP vaccine were restricted. In 2007, the UK Medicines and Healthcare products Regulatory Agency (MHRA), which receives reports of suspected reactions to vaccines and other medicines, warned that the first cohorts of infants who received primary vaccination after the change to aP were now eligible for their pre-school DTaP/IPV booster and that receipt of the fourth dose of aP vaccine was likely to result in an increased incidence of extensive swelling of the limb (ESL) [7]. This warning was intended to avoid unfounded concerns that cellulitis was being caused by "contaminated" batches of booster vaccine that followed reports of ESL in children who had received aP vaccine for priming prior to 2004. However, the absolute risk of an ESL after a fourth dose of aP vaccine at school entry in the UK setting was unknown.

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At around the same time, the UK Joint Committee on Vaccines and Immunisation that advises on national vaccination policy, recommended that from September 2007 all children due their preschool DTaP booster and born between March 2003 and September 2005 should be offered a booster dose of Hib vaccine to ensure adequate protection against Hib disease [8]. Children in the cohort were too young to have been included in the national booster campaign conducted in 2003 for children aged six months to four years to combat the resurgence that occurred between 1999 and 2003. They were also were too old to have received the combined Hib/-meningitis C conjugate vaccine, introduced as routine booster in the second year of life in 2006 [9]. The only Hib-containing vaccines available for pre-school boosting were not licensed for this age group, but as there were no grounds for suspecting any adverse safety effects from their administration outside their licensed indication, JCVI recommended the temporary replacement of DTaP/IPV with DTaP/IPV/Hib for the birth cohort that had not previously been offered a Hib booster.

In order to document the risk of an ESL after a fourth dose of an aP-containing vaccine given at school entry, and to compare the safety profile of DTaP/IPV vaccines with and without a Hib component, we prospectively followed up over 1000 children receiving an aP containing vaccine as a preschool booster (PSB) in England during the period December 2007 to September 2010.

2. Methods

2.1. Study population

Children aged 3.5–6 years of age scheduled to receive a PSB were enrolled following written informed consent from their parent/ legal guardian. Participants were recruited by specialist vaccine research nurses in GP surgeries in two localities – Hertfordshire and Gloucestershire.

2.2. Vaccines

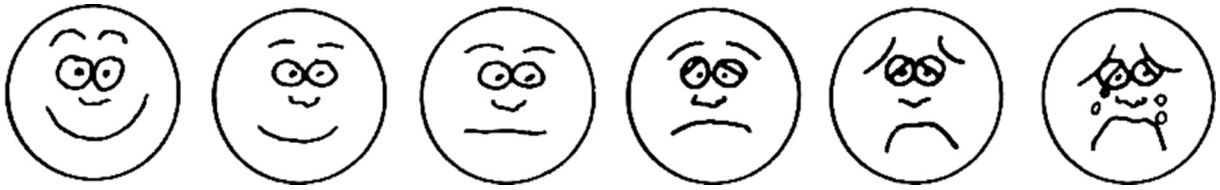
Four products were in use for the aP-containing PSB during the study period – Infanrix-IPV™, Infanrix-IPV + Hib™, Pediacel™ and Repevax™. Details of the composition of these vaccines are given in Table 1. The pertussis components of the two Infanrix products were the same; Pediacel and Repevax™ contained the same pertussis antigens but Repevax™ had a reduced amount of pertussis toxoid (PT) and filamentous haemagglutinin (FHA), and also a low dose diphtheria component (TdaP/IPV). Children were also offered MMR vaccine at the same time as the aP-containing PSB but acceptance was not a requirement for study participation. Vaccination was undertaken by routine nursing staff at the GP clinics.

2.3. Governance

Approval was gained from the Fife and Forth Valley Research ethics Committee and the local Research and Development Offices for both East & North Hertfordshire and Gloucestershire prior to commencement of the study. Local health care staff and parents were asked to report to the MHRA any serious adverse events (SAEs) suspected be related to the PSB as per routine practice.

2.4. Data collection

In this observational study, parents/ guardians completed a daily health diary for the week following their child's PSB vaccination(s). This documented local reactions at the injection site of the aP-containing vaccine and at the MMR injection site (if it was given), systemic symptoms and visits to a doctor (GP or hospital). Parents were provided with a ruler and asked to measure the maximum diameter of any redness or swelling at the injection site(s) each day. They were also telephoned at 48–72 h by the study nurse who visited the home if a large local swelling (>50 mms diameter) was reported, and photographed those considered an ESL which was defined as an extensive area of swelling involving most of the upper part of the limb with a diameter >100 mms. Pain was assessed using the Wong-Baker faces rating scale (below) which allowed the child to indicate how their arm felt when their parent/guardian touched the injection site [10]. The scales were assigned a numerical value from 0 for the happiest face, indicating no pain (left hand side of scale), to 5 for unhappiest face, indicating the site was painful (right hand side of scale).



Where the diary was not returned within two weeks of vaccination, a telephone follow-up was conducted by the vaccine research nurse to ascertain basic information on local reactions and systemic symptoms experienced, including any SAEs, by the child in the seven days following vaccination.

Details about the PSB vaccines given and primary vaccinations administered in the infant schedule including date of administration, product and batch number were obtained from immunisation records held by the GP or parent. Information on the child's medical history was obtained from GP records and parental histories.

2.5. Data analysis

Diary data were combined with information from telephone follow ups conducted by the study nurses for those with no diary. Vaccine product names were reconciled with batch information recorded in medical notes and parent held records. Textual information in the diary and the recruitment case report form (CRF) relating to medical history or symptoms was scrutinised and

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Table 1
Composition of aP-containing pre-school booster vaccines.

Product	Infanrix-IPV	Infanrix-IPV + Hib	Pediacel	Repevax
Manufacturer	GSK	GSK	Sanofi Pasteur MSD	Sanofi Pasteur MSD
Presentation	Prefilled syringe	Prefilled syringe	Prefilled syringe	Prefilled syringe
Volume per dose	0.5 ml	0.5 ml	0.5 ml	0.5 ml
Antigens				
Diphtheria toxoid[a]	Not less than 30 IU	Not less than 30 IU	Not less than 30 IU	Not less than 2 IU (2 Lf)
Tetanus toxoid[a]	Not less than 40 IU	Not less than 40 IU	Not less than 40 IU	Not less than 20 IU (5 Lf)
Pertussis toxoid[a]	25 μg	25 μg	20 μg	2.5 μg
Filamentous Haemagglutinin[a]	25 μg	25 μg	20 μg	5 μg
Pertactin[a]	8 μg	8 μg	3 μg	3 μg
Fimbriae Types 2 and 3	N/a	N/a	5 μg	5 μg
Poliovirus (inactivated) type 1	40 D antigen units	40 D antigen units	40 D antigen units	40 D antigen units
Poliovirus (inactivated) type 2	8 D antigen units	8 D antigen units	8 D antigen units	8 D antigen units
Poliovirus (inactivated) type 3	32 D antigen units	32 D antigen units	32 D antigen units	32 D antigen units
Polyribosylribitol *Haemophilus influenzae* Type b Polysaccharide: Phosphate Conjugated to	N/a	10 μg	10 μg	N/a
Tetanus Toxoid (PRP-T)	N/a	30 μg	18–30 μg	N/a

[b] All polio virus was propagated in VERO cells and the virus strains were – Type 1 Mahoney strain; Type 2 MEF-1 strain; Type 3 Saukett strain.
[a] GSK pertussis components were adsorbed on aluminium hydroxide; Sanofi Pasteur MSD pertussis components were adsorbed on aluminium phosphate.

coded. Children without documented receipt of three doses of an acellular pertussis-containing vaccine for primary immunisation were excluded from analyses, as were children who had received a non-study vaccine by the GP surgery, or whose vaccination sites were unclear due to discrepancies between the health diary and CRF.

To achieve precision in assessing the risk of a large local reaction (>50 mms diameter) after a 4th dose of an aP-containing vaccine, recruitment continued until a minimum of 300 follow-ups had been conducted in each group receiving an aP-containing vaccine with a different pertussis antigen content. This number gave 80% power at a 1% significance level to detect a 10% reaction rate in one aP group as different to 20% in another group. Given the secondary objective of comparing the reactogenicity of aP-containing vaccines with and without a Hib component, the data are presented separately for Infanrix-IPV and Infanrix-IPV + Hib in the analysis, for which differences of 10% from 27% could be detected (assuming 100 in one group, 200 in the other, 80% power, 1% significance). The significance level of 1% was chosen because four separate groups were being compared with one another.

Fisher's exact test was used to compare the rate of local reactions between the different aP-containing vaccine groups (comparing the proportions with any reaction and reaction >50 mms). Local reactions at the injection site of the aP-containing vaccine were compared with those at the MMR injection site by Fisher's exact test. The relationships between reactogenicity and parent-reported pre-existing conditions including asthma, eczema and any allergies were also assessed by Fisher's exact test.

The Wong-Baker faces ratings were compared using a Kruskall Wallis test, according to the numerical values assigned, as described above, and an average score per vaccine per day was calculated. Differences are reported at a 1% significance level.

3. Results

3.1. Demographics

A total of 1081 participants were recruited to the study (Fig. 1), of whom 108 were excluded from the analyses for a variety of reasons including withdrawal without follow up information, not providing a diary, being uncontactable, receipt of an incomplete primary course of vaccination and receipt of a vaccine outside those being studied at the PSB stage. The remaining 973 were included in the analyses presented here.

Participants were included in one of four groups for analyses, depending on which aP-containing PSB vaccine they received; Infanrix-IPV (n = 105), Infanrix-IPV + Hib (n = 196), Pediacel (n = 314) or Repevax (n = 358). Median ages at vaccination were the same in the Infanrix-IPV, Pediacel and Repevax groups and significantly lower, but only by 0.04 years, in the Infanrix-IPV + Hib group (Table 2). Male:female ratios and proportions reporting a history of asthma were similar between groups (Table 2). However, the study groups differed in history of eczema, with a significantly higher proportion in the Infanrix-IPV group.

3.2. Local reactions

Swelling at the injection site was most frequently reported in Pediacel recipients of whom 11.1% had a large swelling (>50 mm) compared with 2.2% after Repevax; the proportion with a swelling >50 mm was similar after the two Infanrix vaccines (Table 3). Swelling was reported significantly less often after MMR than any of the aP-containing vaccines; only one child (0.1%) had a swelling >50 mm after MMR compared with 6.6% after an aP-containing vaccine. Based on the daily measurements in the health diaries large swellings were maximal on day 2, had a median duration of 2 days and a median diameter of 70 mm. In 13 (1.3%) aP recipients the swelling was >100 mm diameter and encompassed almost the whole upper arm, as illustrated in Fig. 2; six had received Pediacel, four Infanrix-IPV + Hib and three Repevax. The area of swelling exhibited erythema but was not necessarily tender with nine of the 13 children with local swelling >100 mm experiencing no or only mild pain on touching the affected area. Medical advice was sought for two of the 13 children, one at the GP and the second at hospital; oral antihistamines were prescribed and also amoxicillin and ibuprofen for this child who had a fever >40 °C with enlarged tonsils and signs of otitis media. A further six children were given over the counter paracetamol or ibuprofen medication by their parents.

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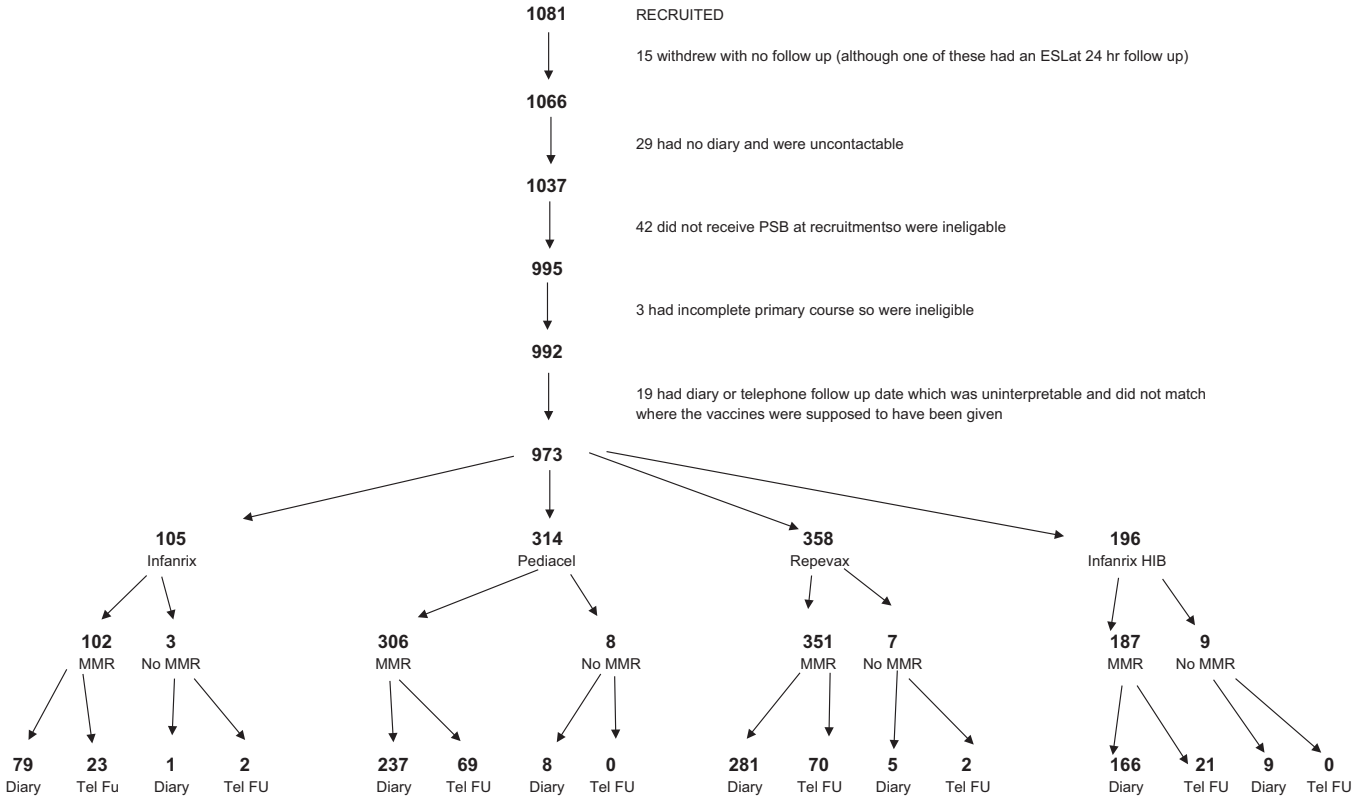

Fig. 1. Consort diagram illustrating the recruitment pathway of the study.

Table 2
Demographics of children recruited to the study according to which preschool booster vaccine they had received. n = number recruited to each group.

	Infanrix (n = 105)	Infanrix-Hib (n = 196)	Pediacel (n = 314)	Repevax (n = 358	p value for comparison between groups
Median (range) age at recruitment (years)	3.56 (3.29–4.68)	3.52 (3.36–5.44)	3.56 (3.39–6.04)	3.61 (2.70–5.88)	<0.001[a]
Male:Female (ratio)	59:46 (1.28)	89:107 (0.83)	168:146 (1.15)	174:184 (0.95)	0.40[b]
History of asthma (%)	6/99 (6.1)	9/187 (4.8)	18/296 (5.7)	22/336 (6.1)	0.83[b]
History of eczema (%)	11/94 (11.7)	41/155 (26.5)	16/298 (5.1)	38/320 (10.6)	<0.001[b]

[a] Kruskal Wallis test.
[b] Fisher's Exact test.

Table 3
Swelling at the injection site within 7 days of vaccination by size and vaccine received.

Swelling at injection site (maximum diameter)	INFANRIX n (% of total)	Infanrix-Hib n (%of total)	PEDIACEL n (% of total)	REPEVAX n (% of total)	Total aP containing PSB n (% total)	MMR n (% of total)
N	105	196	313[a]	358	972	946
NONE	76 (72.4)	145 (74.0)	205 (62.3)	273 (76.3)	699 (71.8)	874 (92.5)
SOME:	29 (27.6)	51 (26.0)	108 (34.4)	85 (23.7)	273 (28.1)	72 (7.6)
<30 mm	11 (10.5)	26 (13.3)	51 (16.2)	58 (16.2)	146 (15.0)	59 (6.2)
30–50 mm	10 (9.5)	12 (6.1)	22 (7.0)	19 (5.3)	63 (6.5)	12 (1.3)
>50 mm	8 (7.6)	13 (6.6)	35 (11.1)	8 (2.2)	64 (6.6)	1 (0.1)

Note: Significant differences ($p < 0.01$) for some swelling were observed for Pediacel vs Repevax, as well as for each aP-containing vaccine vs MMR; and for swelling >50 mm for Pediacel vs Repevax as well as for each aP-containing vaccine except Repevax vs MMR.
[a] 1 individual had swelling reported as unknown in telephone follow-up.

Redness at the injection site was most frequently reported with Infanrix-IPV + Hib (61.2%), though the highest proportion with redness >50 mm diameter was reported at the Pediacel injection site (17.5%) (Table 4). The proportions reporting redness at the injection site after the aP-containing vaccines were all significantly higher than seen at the MMR injection site with only 16.5% reporting some redness and less than 1% redness of >50 mm.

Pain at the injection site was reported in similar proportions at the four aP-containing vaccine injection sites, with significantly higher proportions reporting pain and for longer durations than at the MMR injection site (Table 5).

A history of asthma was reported by 5.7% of participants, eczema in 10.9% and other allergies in 2.8%. There were no significant differences in the proportions with any, or >50 mm redness

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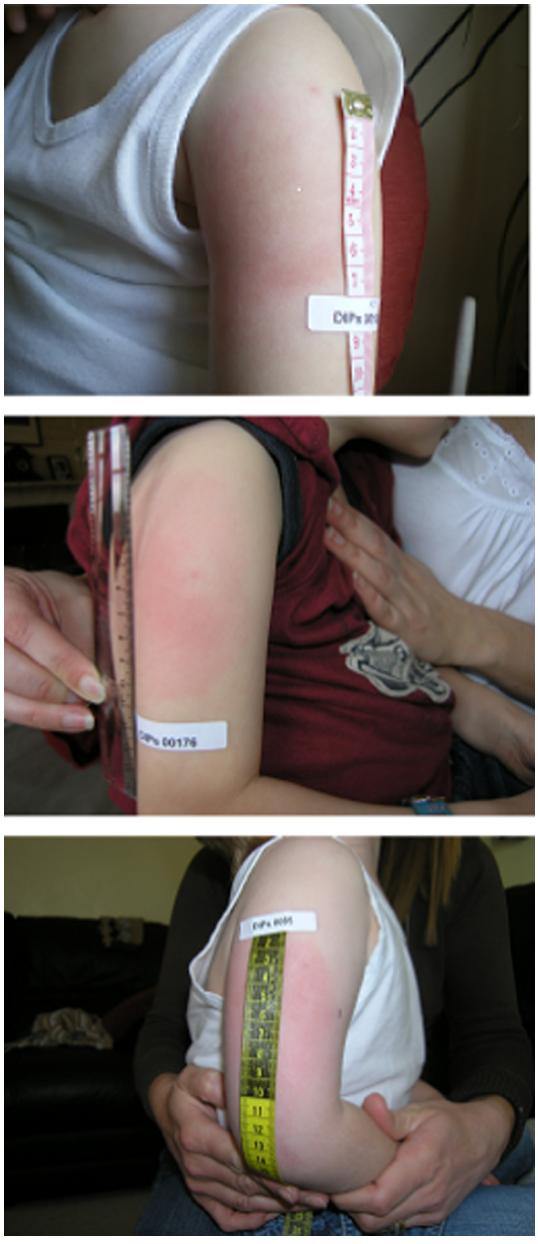

Fig. 2. Photos of ESLs in the limb where PSB was administered, followed up by VRNs during the week following vaccination.

or swelling at the aP-booster site in those with or without these pre-existing conditions (data not shown). However, three of the 13 children with swelling >100 mm diameter had a history of allergy (asthma, eczema and cows' milk intolerance).

3.3. Systemic symptoms

There were no significant differences between the aP-containing vaccines in the proportions of children reported in the health diary with the solicited symptoms of lethargy/tiredness, crying or diarrhoea and vomiting in the 7 days after vaccination (Table 6).

The distribution of Wong Baker scores and mean scores per day by the four aP-containing vaccines is illustrated in Fig. 3. A similar pattern to the daily reports of swelling was noted for the Wong Baker scores, with the Pediacel group reporting the highest scores followed by Infanrix then Repevax. Differences were significant between Pediacel and Repevax on days 0–3. Differences were not significant at a 1% level on other days or between Infanrix and Pediacel or Infanrix and Repevax.

4. Discussion

Extensive swelling involving most of the upper part of a limb after a booster dose of aP-containing vaccine is a well documented phenomenon. It was first noted in a report in 1987 from a group of US scientists who visited Japan to obtain information on the safety and efficacy of the new purified vaccines developed there. Their report noted instances of whole arm swelling in Japanese children following an aP PSB, but clinicians reassured them of their spontaneous resolution within days [11]. The first paper to document the incidence of ESL reported that 1.1% of toddlers receiving a fourth dose of an DTaP vaccine had extensive swelling involving most of the upper limb [12] an incidence similar to that in our study though potentially lower as it was unsolicited compared to our study where it was actively monitored. The incidence of ESL can increase after a fifth dose which in many aP using countries is given at around 5 years of age.

In this study we found an incidence of extensive limb swelling (defined as >100 mms in diameter) in 1.3% of children given a fourth dose of an aP containing vaccine at age 3–6 years. The ESL usually occurred without fever, tenderness or systemic upset and resolved quickly without treatment. For swellings >50 mms in diameter the risk was lowest in children receiving the low dose diphtheria vaccine. Our findings are therefore similar to those of Rennels et al. who compared reactions to 12 different DTaP vaccines given as a fourth dose in the second year of life and found an overall frequency of ESL of 2% with some evidence of an association with the diphtheria content of the vaccine [3]. As expected the addition of Hib to the DTaP/IPV vaccine did not adversely affect the local or systemic reactogenicity profile.

Before replacement of the DT PSB with a pertussis-containing vaccine in 2001 we conducted a randomised single -blind trial to evaluate the acceptability of using a DTwP vaccine [13]. The frequency of large local reactions and systemic symptoms such as prolonged crying and a disturbed night was 2–3-fold higher in

Table 4
Redness at the injection site within 7 days of vaccination by size and vaccine received.

Redness at injection site (highest level in 7 days after vaccination)	INFANRIX n (% of total)	Infanrix-Hib n (%of total)	PEDIACEL n (% of total)	REPEVAX n (% of total)	Total aP-containing PSB n (% total)	MMR n (% of total)
N	105	196	312[a]	358	971	946
NONE	59 (56.2)	120 (61.2)	156 (50.0)	216 (60.3)	551 (56.7)	789 (83.5)
SOME:	46 (43.8)	76 (38.8)	156 (50.0)	142 (39.7)	420 (43.2)	156 (16.5)
<30 mm	17 (16.2)	32 (16.3)	63 (20.1)	87 (24.3)	199 (20.5)	141 (14.9)
30–50 mm	13 (12.4)	18 (9.2)	38 (12.1)	30 (8.4)	99 (10.2)	12 (1.3)
>50 mm	16 (15.2)	26 (13.3)	55 (17.5)	25 (7.0)	122 (12.5)	3 (0.3)

Note: Significant differences ($p < 0.01$) for some redness and for redness >50 mm were observed for: Pediacel versus Repevax as well as for each aP-containing vaccine vs MMR.

[a] 2 individuals had redness reported as unknown in telephone follow-up.

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Table 5
Pain at the injection site within 7 days of vaccination by duration and vaccine received.

PAIN at injection site	INFANRIX n (% of total)	Infanrix-Hib n (%of total)	PEDIACEL n (% of total)	REPEVAX n (% of total)	Total aP-containing PSB n (% total)	MMR n (% of total)
N	80[a]	175[a]	245[a]	286[a]	786[a]	763[a]
NONE	33 (41.3)	65 (37.1)	81 (33.1)	119 (41.6)	298 (37.9)	497(65.1)
SOME	47 (58.8)	110 (62.9)	164 (66.9)	167 (58.4)	488 (62.1)	266 (34.9)
1–5 days	45 (56.3)	106 (60.6)	154 (62.9)	158 (55.2)	463 (58.9)	262 (34.3)
>5 days	2 (2.5)	4 (2.3)	10 (4.1)	9 (3.1)	25 (3.2)	4 (0.5)

Note: Significant differences ($p < 0.01$) for some pain were observed for each aP-containing vaccine vs MMR and for >5 days pain for Pediacel and Repevax vs MMR.
[a] Pain information only available for those with a diary returned as this was not assessed in the telephone follow-up.

Table 6
Proportions reporting systemic symptoms in the health diary completed following vaccination.

	INFANRIX n (%)	INFANRIX HIB n (%)	PEDIACEL n (%)	REPEVAX n (%)
N	105	196	313	358
Crying	3 (2.9)	12 (6.1)	17 (5.4)	12 (3.4)
Lethargy/tiredness	6 (5.7)	8 (4.1)	12 (3.8)	16 (4.5)
Vomiting/diarrhoea	3 (2.9)	8 (4.1)	7 (2.2)	7 (2.0)

Note: No differences significant between PSB vaccines.

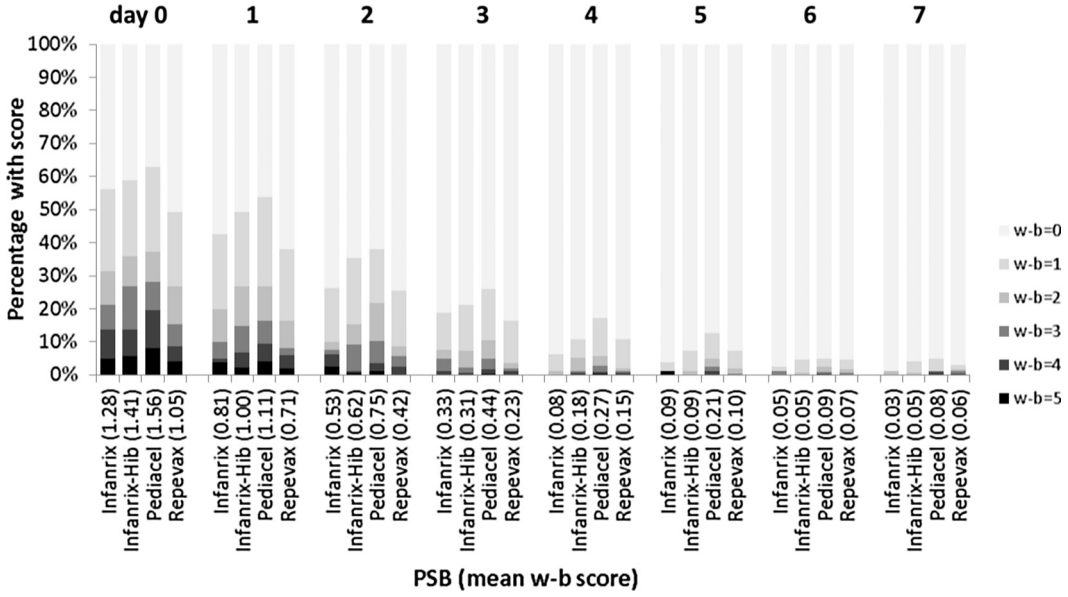

Fig. 3. Distribution of Wong Baker scores and mean scores by aP-boooster vaccine and days since vaccination.

DTwP than DT vaccinees, with 44% requiring medication compared with 23% of DT vaccinees. It was considered that this increase in reactogenicity at a time when pertussis was well controlled would be unacceptable. A randomised trial in over 1000 children was subsequently conducted to compare local reactions and systemic symptoms in DT vaccinated children with those in children given one of four DTaP vaccines as a PSB following a primary course of wP-containing vaccine. Systemic symptoms and local reactions were similar between the five groups although local reactions occurred more quickly in the DTaP vaccinated children. A small subset of 71 children primed with an aP-containing vaccine during the wP-containing vaccine shortages, were twice as likely to develop local swelling and erythema as wP-primed children.

The mechanism by which aP-containing booster vaccines predispose to extensive swelling in the injected limb is not understood. Ultrasound examination suggests that the phenomenon is similar to angioedema rather than inflammatory cellulitis [14]. Studies with the fourth and fifth doses of aP-containing vaccines in Canada have shown a positive association with body mass index and, like our findings, a history of atopy was not associated with the reaction [15]. Whatever the mechanism, parents should informed about the small risk of an ESL after the pre-school booster of an aP-containing vaccine but reassured that the condition is benign and transient. The findings of this study are useful in informing the frequency of ESL following vaccination in contrast to cellulitis, where tenderness, fever and toxicity would likely accompany the large local swelling.

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Conflicts of interest

None of the authors have any conflicts of interest to declare.

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