Injection-Site Reactions to Booster Doses of Acellular Pertussis Vaccine: Rate, Severity, and Anticipated Impact

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ABSTRACT. *Background.* **Acellular pertussis (aP)-containing vaccines cause fewer adverse events than whole-cell versions for primary doses. Booster doses, however, may be followed by extensive injection-site reactions. This study compares the frequency, severity, and impact of local reactions among children receiving 5 consecutive doses of an aP combination vaccine (including inactivated polio virus, conjugated *Haemophilus influenzae* type b antigen, and diphtheria and tetanus toxoids) to children receiving a mixed series of whole-cell and aP combination vaccines.**

Methods. **Participants were parents or guardians of children 4 to 6 years old immunized at public health clinics across British Columbia, Canada. This included 398 children receiving the fifth consecutive dose of an aP combination vaccine and 402 receiving the fifth dose in a mixed series consisting of at least 1 prior dose of whole-cell pertussis combination vaccine with the remainder as aP combination vaccine. A cross-sectional telephone survey evaluated the extent of local reactions 48 to 96 hours after immunization by asking participants to compare the size of redness and swelling with familiar household items such as Oreo cookies or coins. Associated discomfort and impact on recreational activities, health care utilization, parental time off work, and attitudes toward immunization were also assessed.**

Results. **Children who received the fifth consecutive dose of an aP combination vaccine more often experienced redness (24%) or swelling (16%) the size of an Oreo cookie or larger (≥46 mm) than children given a mixed series (10% and 9%, respectively) but less often experienced tenderness or limitation of movement at the injection site. Related health care utilization was low. There was no discernible effect on participation in recreational activities or parental attitudes toward vaccine; 90% would recommend the same vaccine to others with children of the same age.**

Conclusions. **We conclude that injection-site reactions are more extensive after the fifth consecutive dose of an aP combination vaccine compared with the fifth dose in a mixed series of whole-cell and aP combination vaccines. These reactions are unlikely to affect parental acceptance of immunization recommendations or health care utilization.** *Pediatrics* **2003;112:e453–e459. URL: http://www.pediatrics.org/cgi/content/full/112/6/e453;** ***adverse reactions, local adverse reactions, acellular pertussis vaccine, whole-cell pertussis vaccine, vaccine safety, booster doses.***

ABBREVIATIONS. wP, whole-cell pertussis; IPV, inactivated polio virus; Hib, *Haemophilus influenzae* type b antigen; DT, diphtheria; T, tetanus; aP, acellular pertussis; BC, British Columbia; Lf, limits of flocculation; CI, confidence interval; OR, odds ratio.

A whole-cell pertussis (wP) combination vaccine including inactivated polio virus (IPV), conjugated *Haemophilus influenzae* type b (Hib) antigen, and diphtheria (D) and tetanus (T) toxoids was introduced in Canada in 1994. The wP combination vaccine was replaced by a 5-component acellular pertussis (aP) version beginning in July 1997. Since April 1998, all provinces and territories have been using this aP combination vaccine for universal childhood immunization. Primary doses are given at 2, 4, and 6 months and booster doses at 18 months (fourth dose) and 4 to 6 years (fifth dose).[1]

In addition to improved efficacy, the aP combination vaccine has shown improved safety over its previous whole-cell counterpart.[2–7] In clinical trials, injection-site redness or swelling were infrequent after doses of the primary series; redness >10 mm occurred in 3% to 5% of children after the second or third dose of prototype aP formulations, whereas <1% experienced redness ≥35 mm.[6] Postmarketing surveillance also confirmed reduction in severe adverse effects such as febrile convulsions and hypotonic-hyporesponsive episodes.[6]

In clinical trials involving booster doses, an increase in the size and rate of injection-site reactions was observed.[8–12] A similar trend was seen with all DTaP vaccines given to children for the primary series and booster doses compared with children primed with wP versions.[10,11] After 4 consecutive doses of an aP combination vaccine, 20% of children experienced redness or swelling ≥35 mm, and nearly 3% experienced reactions ≥50 mm.[8–10] Moreover, 1 study found that after 5 consecutive doses, 50% of immunized children experienced redness or swelling ≥50 mm compared with 17% given the preceding 4 doses as wP. In a trial in the United States, up to 3% of children given 2 or more different aP combination vaccines experienced entire limb swelling, although

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there were no cases among children given 5 doses of the same aP combination vaccine.[10]

Despite their larger size, local reactions to booster doses of an aP combination vaccine have been less painful than those induced by consecutive or mixed regimens of wP combination vaccine. Among children who received 5 consecutive doses of aP, severe limb tenderness and limitation of movement were cited less frequently (2% and 0%, respectively) compared with children who received 5 consecutive doses of wP (42% and 36%, respectively) or mixed schedules of 4 wP and 1 aP vaccine (3% and 1%, respectively).[12]

Injection-site reactions to booster doses of an aP combination vaccine have not been evaluated outside the setting of a clinical trial. Their impact on vaccine acceptance has not been assessed. The first cohort of children to have received only consecutive doses of an aP combination vaccine is presenting for the fifth dose across Canada between 2002 and 2004. The province of British Columbia (BC), Canada, was among the first to introduce aP vaccines for the childhood immunization series (July 1997). The purpose of this cross-sectional survey was to assess the rate and impact of injection-site reactions in children receiving their fifth consecutive dose of aP combination vaccine under routine conditions in comparison with children receiving a mixed regimen of wP and aP vaccines.

METHODS

Recruitment

Eligible participants included children 4 to 6 years old presenting to health units across BC for their regularly scheduled fifth dose of aP combination vaccine. The population of BC is 4.1 million with a birth cohort of ~39 000. In BC, public health units deliver ~70% of childhood immunizations with the remainder provided by physicians' offices.

Staff were posted at regularly scheduled public health clinics to explain the study to families and obtain consent for a follow-up interview. Inclusion criteria required that children were up to date with immunizations, that all prior doses were received in BC, and that the parent or guardian would be accessible by phone 48 to 96 hours after immunization. In obtaining parental consent to immunize, public health nurses routinely review standard written material for DaPT/IPV booster (British Columbia Ministry of Health and Ministry Responsible for Seniors, Health File 15a, unpublished data, August 1998). This material did not describe increased local reactions with booster doses. Study staff provided no additional information. Information about prior immunization history was verified with participating health units. Consent, contact details, and immunization information were faxed to a call center. The University of British Columbia Clinical Ethics Review Board approved this survey.

Participants

Participants were parents or guardians whose children 4 to 6 years old were immunized with 0.5 mL of DaPT/IPV (Quadracel, Aventis Pasteur Canada Ltd, Toronto, Ontario, Canada) given by intramuscular injection into the deltoid at 1 of 15 participating health units across BC. Children belonged to 1 of 2 study groups.

1. Group 1, Fifth Dose aP: Children whose previous 4-dose immunization history included only consecutive intramuscular doses of 0.5 mL of DaPT/IPV + Hib (Pentacel, Aventis Pasteur Canada Ltd).
2. Group 2, Fifth Dose Mixed: Children whose previous 4-dose immunization history included at least 1 dose of DwPT/IPV + Hib (Penta, Aventis Pasteur Canada Ltd) with the remainder received as DaPT/IPV + Hib (Pentacel, Aventis Pasteur Canada Ltd).

Vaccines

A 0.5-mL dose of Quadracel (DaPT/IPV) contains 20 μg of pertussis toxoid, 20 μg of filamentous hemagglutinin, 5 μg of fimbriae (agglutinogens 2 + 3), 3 μg of pertactin, 15 (limits of flocculation [Lf]) of diphtheria toxoid, 5 Lf of tetanus toxoid, 1.5 mg of aluminum phosphate, 40, 8, and 32 D antigen units of inactivated purified poliomyelitis vaccine types 1, 2, and 3, respectively (derived from MRC-5 human diploid cell culture), and 0.6% 2-phenoxyethanol added as preservative.

Pentacel (DaPT/IPV + Hib) consists of Act-HIB (PRP/T; 10 μg of purified capsular polysaccharide Hib covalently bound to 20 μg of tetanus protein) reconstituted with Quadracel.

A 0.5-mL dose of Penta (DwPT/IPV + Hib) consists of Act-HIB reconstituted with DwPT/IPV containing 4 to 12 mouse protective units of pertussis vaccine, 25 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 40, 8, and 32 D antigen units of poliovirus types 1, 2, and 3, respectively (derived from MRC-5 human diploid cell culture), 1.5 mg aluminum phosphate, and 0.5% 2-phenoxyethanol.

Sample Size Determination

Power calculations estimated that 380 children would permit detection of injection-site redness or swelling ≥50 mm in 50% of vaccinated children, with a 95% confidence interval (CI) between 45% and 55%. This would also enable detection of redness or swelling involving the entire limb in 3% of children with a 95% CI between 1% and 4%. Recruitment of 400 participants in each study group was sought.

Interviews

Ten nurses were trained to conduct a standard telephone interview by using a prepiloted questionnaire. Telephone interviews were conducted 48 to 96 hours after immunization.

Respondents were asked to estimate the largest extent of redness or swelling at the injection site by comparison with familiar objects such as a Canadian dime (18 mm), a Canadian quarter (25 mm), or an Oreo cookie (46 mm). Interviewers asked if reactions extended to the joint or involved the whole limb. Itchiness, tenderness, and limitation of movement were also evaluated. Tenderness was categorized as mild, moderate, or severe, and limitation of movement was categorized as mild or marked. Interviewers read descriptions corresponding to severity categories to standardize selection. A definition of "red and tender swelling" was also created based on presence of redness and swelling >46 mm plus any tenderness or limitation of movement. Additional analysis of red and tender swelling was based on experience of moderate or severe tenderness or marked limitation of movement. Systemic symptoms were assessed. History of local or systemic reaction with any previous dose of vaccine in the childhood series was also assessed.

By using an approach predicated on the health belief model,[13–16] respondents were asked their level of agreement with statements related to immunization benefits and safety using a 4-choice Likert scale plus a "don't know" option. Respondents' willingness to recommend the same vaccine to family or friends with children of the same age was ranked on a Likert scale.

Statistical Analysis

The χ^2 test was used for categorical variables. The appropriate parametric or nonparametric test was applied to numeric variables (t test or Mann–Whitney, respectively). Independent effects were assessed by logistic regression.

RESULTS

Participation Rate

Among parents/guardians approached to participate at immunization clinics, <5% declined or failed to meet inclusion criteria. Of the 821 that originally consented to be called, 800 (97%) were confirmed to meet inclusion criteria and completed a telephone interview. This included 398 in the fifth dose aP

group and 402 in the fifth dose mixed group. Participants in the fifth dose mixed group were recruited between October and December 2001 and in the fifth dose aP group between April and July 2002 (12% in this group enrolled in the summer month of July).

Baseline Characteristics

Few significant differences were found between study groups in baseline characteristics (Table 1) apart from several months' difference in age, time since last dose, or time to interview. Of children in the fifth dose mixed group, >95% had received 3 or more prior doses of wP. After any previous vaccination, more children in the fifth dose mixed group had experienced swelling that interfered with movement or prevented activities compared with the fifth dose aP group; they had also experienced more fever and irritability (Table 1).

Vaccine-Associated Adverse Events

Redness and swelling at the injection site exceeded the size of an Oreo cookie more often in the fifth dose aP group compared with the fifth dose mixed group (Table 2). Not >1% in either group experienced injection-site reactions extending beyond the joint to involve the whole limb, with the upper limit of the 95% CI not exceeding 2% in either group.

More children in the fifth dose mixed group experienced tenderness or limitation of movement with the current injection compared with children in the fifth dose aP group. Less than 10% in either group experienced tenderness described as severe. More in the fifth dose aP group experienced red and tender swelling compared with the fifth dose mixed group (11% with a 95% CI of 8–14% vs 4% with a 95% CI of 2–6%, respectively; $P < .001$). This increased frequency persisted even after the definition was modified to include only moderate to severe tenderness or marked limitation of movement (7% with a 95% CI of 5–10% vs 3% with a 95% CI of 1–5%, respectively; $P = .007$). Receipt of acetaminophen prophylaxis was not significantly associated with the likelihood of reporting redness, swelling, tenderness, limitation of movement, or red and tender swelling within either of the study groups.

TABLE 1. Baseline Characteristics of Vaccinated Children by Study Group

	Fifth Dose aP ($N = 398$), *n* (%)	Fifth Dose Mixed ($N = 402$), *n* (%)	*P* Value
Female sex of child	184 (46)	193 (48)	.6
Mother as respondent	355 (89)	349 (87)	.1
Caucasian child	335 (84)	323 (80)	.3
Median age of child (y)	4.8	5.3	<.0001
Number of prior whole-cell vaccine doses:			NA
0	398	0	
1	0	4 (1)	
2	0	7 (2)	
3	0	378 (94)	
4	0	6 (2)	
Unknown (but at least 1)	0	7 (2)	
Time since last pertussis combination dose (y)			
≤2	6 (2)	4 (1)	
>2–2.5	9 (2)	9 (2)	
>2.5–3	117 (30)	12 (3)	
>3–3.5	249 (63)	104 (26)	
>3.5–4	12 (3)	192 (48)	
>4–4.5	5 (1)	80 (20)	
Median time since last dose (y)*	3.1	3.7	<.0001
Adverse event experience with any prior doses of vaccine†			
Any redness	89 (22)	102 (25)	
Redness beyond the joint	0	0	
Any swelling	67 (17)	81 (20)	
Swelling beyond the joint	1 (0.2)	3 (0.7)	
Swelling that interfered with limb movement	1 (0.2)	13 (3)	.001
Swelling that stopped child from normal activities	1 (0.2)	12 (3)	.002
Any fever	170 (43)	224 (56)	<.001
Fever that was incapacitating, stopped normal activities, or required medical care	1 (0.2)	33 (8)	<.0001
Any irritability	137 (34)	171 (42)	.02
Irritability that was incapacitating, stopped normal activities, or required medical care	1 (0.2)	23 (6)	<.0001
Prophylactic medication given before or at this injection	32 (8)	34 (8)	.8
Site of current injection			.8
Left arm	336 (84)	342 (85)	
Right arm	62 (16)	60 (15)	
Median delay to first interview in hours (range)‡	71 (46–96)	64 (48–96)	<.001

* Information on interval since last dose is not available for one participant in the fifth dose mixed group.
† Recalled by the guardian during the current interview. For both groups, childhood series also includes measles/mumps/rubella immunization at 12 and 18 months.
‡ Information on delay to first interview is not available for 2 participants in the fifth dose aP group.

TABLE 2. Injection-Site Reactions and Severity by Study Group

	Fifth Dose aP (N = 398), n (%); (95% CI)	Fifth Dose Mixed (N = 402), n (%); (95% CI)	P Value
Any redness	140 (35); (31–40)	86 (21); (18–26)	<.001
Extent of redness			<.001*
<Oreo cookie	43 (11)	46 (12)	
≥Oreo cookie (46 mm)			
To the joint	97 (24); (20–29)	40 (10); (7–13)	
Beyond the joint	11 (3)	3 (1)	
Whole limb	1 (0.2)	1 (0.2)	
	2 (0.5)	2 (0.5)	
Any swelling	87 (22); (18–26)	63 (16); (12–20)	.02
Extent of swelling			.003*
<Oreo cookie	25 (7)	28 (7)	
≥Oreo cookie (46 mm)			
To the joint	62 (16); (12–19)	35 (9); (6–12)	
Beyond the joint	8 (2)	3 (1)	
Whole limb	0	1 (0.2)	
	0	0	
Median time to onset of redness or swelling (hours)†	18	6	.02
Any injection site itchiness‡	18 (5); (3–7)	11 (3); (1–5)	.2
Median time to onset of itchiness	24	4	.7
Any tenderness§	287 (72); (68–76)	338 (84); (80–87)	<.001
Median time to onset of tenderness (hours)¶	2	3	.7
Tenderness ranked as§			.1
Mild (complains with hard pressure as with bump or bang)	159 (40)	160 (40)	
Moderate (complains with light pressure as with parent touch)	100 (25)	145 (36)	
Severe (complains with light touch as with clothing rubbing)	26 (7)	33 (8)	
Any limitation of movement	113 (28); (24–33)	146 (36); (32–41)	.02
Limitation of movement ranked as			.3
Mild (noticeable but did not interfere with activities)	83 (21)	99 (25)	
Marked (refuses to move shoulder, holds arm immobile, unable to perform usual activities)	30 (7)	47 (12)	

* P value refers to comparison on extent ≥ Oreo cookie (46 mm).
† Time to onset of redness is not available for 6 participants in fifth dose mixed group; time to onset of swelling is not available for 1 participant in fifth dose aP and 4 participants in fifth dose mixed groups.
‡ Time to onset of itchiness is not available for 1 participant in fifth dose aP group.
§ Experience with tenderness is not available for 2 participants in fifth dose aP group.
¶ Time to onset of tenderness is not available for 2 participants in fifth dose aP and 8 participants in fifth dose mixed groups.

Children in the fifth dose mixed group experienced significantly more drowsiness than the fifth dose aP group (26% vs 15%; $P < .001$). There were otherwise no differences in the overall rate of systemic symptoms after immunization including irritability (30%), fever (28%), headache (7%), loss of appetite (18%), vomiting (3%), or diarrhea (2%). Among children who experienced irritability, this more often interfered with activities within the fifth dose mixed (57/121) compared with the fifth dose aP (43 of 125) group (47% vs 34%, respectively; $P = .04$). There was no difference between the fifth dose aP or the fifth dose mixed groups in time to onset of fever (median: 7 and 5 hours, respectively; $P = .2$) or irritability (median: 5 and 4 hours, respectively; $P = .5$).

On logistic regression ($n = 792$), the likelihood of redness or swelling exceeding 46 mm at the injection site was independently associated with the number of prior doses of aP combination vaccine received (odds ratio [OR] of 1.4 and 95% CI of 1.2–1.6 and OR of 1.2 and 95% CI of 1.1–1.4, respectively). Red and tender swelling was also independently associated with the number of prior doses of aP vaccine received (OR: 1.4; 95% CI: 1.2–1.7). Tenderness, limitation of movement at the injection site, and drowsiness were independently but inversely associated with the number of prior doses of aP vaccine received (OR of 0.8 and 95% CI of 0.7–0.9; OR of 0.9 and 95% CI of 0.8–1.0; and OR of 0.8 and 95% CI of 0.7–0.9, respectively). Neither age nor the interval since last dose of vaccine was associated with these reactions. Girls were more likely than boys to manifest limitation of movement at the injection site after adjusting for number of doses of aP, age, and interval since last dose (OR: 1.4; 95% CI: 1.0–1.9). Gender was not otherwise independently associated with adverse effects.

Social and Health Care Impact

Few children experienced disruption of recreation activities as a result of symptoms after immunization (Table 3). Parents of children in the fifth dose mixed group more often required time off work after their child's immunization (3%) than parents of children in the fifth dose aP group (0.2%; $P = .004$). There was no difference between study groups in the requirement for medical attention or medication prescriptions (≤2%). No children were hospitalized after immunization.

Impact on Perception of Vaccine Safety and Willingness to Recommend Vaccine

Respondents did not differ significantly by study group in their attitudes toward vaccine benefits or safety (Table 4). More than 95% felt their child could

TABLE 3. Impact of Vaccine-Associated Adverse Event by Study Group

	Fifth Dose aP (N = 398) n (%)	Fifth Dose Mixed (N = 402) n (%)	P Value
Interference with recreation activities	19 (5)	28 (7)	.2
Interference with recreation activities related to injection site reactions	9 (2)	12 (3)	.5
Parental time off work required	1 (0.2)	11 (3)	.004
Health care contacts	8 (2)	8 (2)	.9
Health care contacts for local reaction	4 (1)	7 (2)	.4
Location where health care sought			
Emergency department	0	1	
Walk-in clinic	0	1	
Family physician	1	1	
Health unit	3	3	
911	0	1	
Medication prescribed	2 (1)	2 (1)	.7
Hospitalized overnight	0	0	

cope with the discomfort of injections. Fewer than 10% of respondents in either group considered that vaccines have too many "bad" side effects. The experience of red and tender swelling in children did not alter these parental perceptions except within the fifth dose mixed group. Among this group, more with this type of reaction considered vaccines to have too many "bad" side effects (25%) compared with those without (7%; $P = .04$).

There was no difference between groups in the likelihood of recommending the same vaccine to friends or family with children of the same age (91%; see Table 4) Among children who experienced red and tender swelling, parental willingness to recommend the vaccine to others remained high in the fifth dose aP group (98%) but was significantly diminished within the fifth dose mixed group (69%) compared with those who had not experienced this type of reaction (91%; $P = .001$).

DISCUSSION

This simple survey used community-based clinics to recruit participants. We invited parents to characterize the frequency, extent, and severity of injection-site reactions by using familiar household items as descriptors (cookies and coins). Our observations are consistent with trends identified in clinical trials using more precise measurements. This survey additionally characterizes these reactions and offers population-based assessment of their likely impact on childhood immunization uptake.

Children immunized with 5 consecutive doses of an aP combination vaccine more often experienced extensive redness and swelling at the injection site compared with children given a mixed schedule of wP and aP combination vaccines. Approximately 25% (upper limit: 29%) of children given 5 consecutive doses of an aP combination vaccine experienced redness larger than an Oreo cookie. Despite the imprecise nature of the estimation method, the observed rate closely resembles that found in a clinical trial by Halperin et al[17]; in that trial 33% of 317 children experienced redness ≥50 mm. In another Canadian trial, 17% of children who received 4 prior doses of wP vaccine followed by 1 dose of aP experienced redness ≥50 mm; the corresponding rate in our survey for children receiving a mixed schedule (typically in the ratio of 3 wP:2 aP) was 10% (upper limit: 13%).[12] As in clinical trials, few children in our survey experienced effects involving the whole limb; within the fifth dose aP group, 3% had redness extending to the joint.[10]

Although subject to recall bias, history of previous redness and swelling was consistent with a higher rate of local reaction after the fifth dose compared with any or all previous doses combined among the fifth dose aP group (35% vs 22% for redness and 22% vs 17% for swelling; $P < .0001$ and $P = .07$, respectively) but not the fifth dose mixed (21% vs 25% for redness and 16% vs 20% for swelling; $P = .2$ and .1, respectively). We conducted a simultaneous telephone survey among 400 parents of children after their fourth consecutive dose of aP vaccine (primary series and booster dose of Pentacel). That survey found rates of redness (15%; 95% CI: 12–19%) or swelling (10%; 95% CI: 8–14%) exceeding the size of an Oreo cookie that were intermediate between those of the fifth dose aP and the fifth dose mixed groups and significantly different from the former ($P < .001$ and $P = .03$, respectively) but not the latter (University of British Columbia Centre for Disease Control, unpublished data, January 2003). These findings provide additional evidence for a dose-response relationship between receipt of aP combination vaccine and extensive injection-site reactions.

Increased injection-site reactions were not associated with severe tenderness or reduced mobility. Halperin et al[17] found that up to 10% of children experienced severe injection-site tenderness and 4% experienced moderate to severe limitation of movement. These rates closely resemble our own findings in the community setting. We found a higher rate of red and tender swelling among recipients of 5 consecutive doses of aP compared with those who received a mixed schedule. This difference might be attributed to simple increase in redness and swelling superimposed on a background of commonly noted tenderness in both groups. When the definition was revised to include redness and swelling and only severe manifestations of pain, children in the fifth dose aP group still marginally exceeded the fifth dose mixed group. Avoiding unnecessary treatment

TABLE 4. Caretaker Perception of Vaccine Benefits and Safety and Willingness to Recommend Vaccine to Others

Strongly Agree or Agree That	Fifth Dose aP (N = 398) n (%)	Fifth Dose Mixed (N = 402) n (%)	P Value
Vaccine benefits			
Vaccines protect my child from serious disease	388 (98)	395 (98)	.5
There is a good chance that my child will get sick if he/she does not get his/her injections	312 (78)	322 (80)	.2
My child could get very sick if he/she did not get his/her injection	323 (81)	339 (84)	.1
It is important that my child get his/her injections on time	377 (95)	381 (95)	.7
Vaccine safety			
Vaccines have too many bad side effects	24 (6)	31 (8)	.2
Vaccines are safe	349 (88)	358 (89)	.8
If a child has any type of reaction to an injection, he/she should not get it again	52 (13)	64 (16)	.5
My child can cope with the discomfort of injections	383 (96)	389 (97)	.9
Willingness to recommend vaccine			
Very likely or likely to recommend that friends or family with children of the same age as this child get this injection	368 (93)	362 (90)	.2

for erroneously diagnosed cellulitis is an important reason to notify parents about expected local reactions after booster doses.

Of 800 parents in our survey, 16 sought medical care for their children after immunization. Despite the elevated rate of injection-site reactions, only 1% of children receiving 5 consecutive doses of aP required health care contact for this, and in only 1 case was this with a physician. None required hospitalization, and few children had to interrupt recreational activities after immunization. Twelve parents required time away from work; this included only 1 within the fifth dose aP group.

Parental attitudes toward vaccine safety seem largely unaffected by differences in the injection-site effects experienced by their children. The vast majority of respondents in both study groups indicated their continuing belief in vaccine safety, considered that their child could cope with the discomfort of injections, and would recommend the same vaccine to others. The experience of red and tender swelling did not alter parental perception of vaccine safety or willingness to recommend vaccine except within the fifth dose mixed group. This latter finding supports the notion of more benign symptoms among 5-dose aP recipients.

Parental attitudes may not reflect the concerns of immunized children; we did not ask children about their experience related to these reactions. In addition, parents voluntarily presenting to immunization clinics may be different in their sensitivity to minor adverse events compared with parents who require some coaxing to attend. The attitudes of respondents to our survey may not reflect the view of all parents, but they likely represent the majority. We do not anticipate that immunization rates will decrease as a result of these reactions. Reducing the overall rate of adverse events nevertheless remains an important goal of childhood vaccine programs.

The material prepared for public health nurses in eliciting informed consent did not include reference to increased local reactions after a fifth consecutive dose. It is possible, however, that some nurses were aware of this information and discussed it with their clients. Such information may have eased parental concern. The current product monograph for Quadracel (and thus Pentacel) refers to "a trend toward increasing local reaction rates at the fourth and fifth doses. . . "[18] It is important that this information is routinely provided to parents. As familiarity with the seriousness of target diseases decreases, objection to even minor adverse effects is likely to increase; full disclosure can offset this negative response. Information about these reactions should be provided in the context of overall improvement in vaccine safety. Historic rates of redness and swelling exceeding 50 mm were higher after 5 consecutive doses of wP combination vaccine (66% and 60%, respectively), as were pain and discomfort.[12]

The cause of increased redness and swelling at the injection site with booster doses of aP-based vaccines is unknown. Skin-test evaluation has shown a correlation between extensive injection-site redness and positive skin tests for DT and aP, both measured 48 hours after injection.[19] Correlation between diphtheria toxoid content and injection-site effects has been found with both whole-cell and aP combination vaccines.[10,20] Although Arthus or type III reaction is possible, levels of antibodies have not correlated with injection-site reactions.[20–23] The absence of concomitant increase in pain is also curious. In our survey, average time to onset of injection-site redness and swelling as well as itchiness was significantly delayed in the fifth dose aP group (18 and 24 hours, respectively) relative to the fifth dose mixed (6 and 4 hours, respectively). Difference in time to onset of systemic symptoms was not observed. This may suggest separate triggers or immunologic pathways for injection-site symptoms after consecutive doses of aP combination vaccine. Delayed hypersensitivity with a Th2-bias, immunoglobulin E production and inflammation characterized by predominance of eosinophils, is consistent with local features of delayed redness, swelling, and itchiness in the fifth dose aP group. The role of immunoglobulin E is unresolved, but in other studies, prophylaxis with antihistamines has offered no redress.[24] Histologic examination from the injection site and immunohistochemistry

might offer the most direct evidence for pathogenesis.

CONCLUSIONS

We have confirmed more extensive but less painful injection-site reactions in children receiving cumulative doses of an aP combination vaccine relative to those who received a mixed schedule of wP and aP combination vaccines. Such effects are unlikely to cause a measurable change in vaccine acceptance. Parents should be informed of the increase in local reactions to minimize unnecessary concern or consultation. We confirm that the frequency of these reactions increases with the number of consecutive doses of aP combination vaccine received. If a sixth dose of aP is contemplated for a teen or adult booster, these injection-site effects should be evaluated further before this first cohort of children reaches adolescence.

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