Reactogenicity and Immunogenicity at Preschool Age of a Booster Dose of Two Three-Component Diphtheria-Tetanus-Acellular Pertussis Vaccines in Children Primed in Infancy With Acellular Vaccines

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ABSTRACT. *Objectives.* **To determine the reactogenicity and immunogenicity of a fourth dose of 2 three-component acellular pertussis vaccines combined with diphtheria-tetanus-acellular pertussis (DTaP) when administered at preschool age to children primed in infancy with 3 doses of the same DTaP and who had received a diphtheria-tetanus (DT) dose at the age of 12 months.**

Setting. **Local health units of 4 Italian regions.**

Study Design. **Three thousand five hundred twenty-two children, who had been randomized in the first year of life to be immunized with a DTaP vaccine by either SmithKline Beecham or Chiron Biocine, were offered a booster of the same vaccine or, if refusing, a DT vaccine at the age of 5 to 6 years. Families of children were aware of the vaccine administered. The occurrence of adverse events was compared between the children who received a DTaP booster and those boosted with a DT only. Antibody titers to pertussis vaccine components (pertussis toxin, filamentous hemoagglutinin, and pertactin) were determined on 558 paired sera taken before and 30 days after the DTaP booster administration.**

Results. **Four episodes of temperature ≥39.5°C, 2 in each DTaP group, were recorded. Fever ≥38°C occurred infrequently in both DTaP and DT recipients (DTaP range: 2.5%–2.8%; DT range: 0%–4.8%), as did irritability (DTaP range: 10.1%–11.7%; DT range: 7.4%–12.6%). The frequency of local reactions was significantly higher for DTaP recipients (range: 44.0%–52.8%), with respect to DT recipients (range: 29.5%–44.4%). Extensive local reactions were observed in 1.2% of DTaP recipients and in .5% of DT recipients. Both DTaP vaccines induced high antibody titers against pertussis toxin, filamentous hemoagglutinin, and pertactin, with an increase of >10 times the prebooster geometric mean titers.**

Conclusions. **A booster dose of DTaP at preschool age in children primed with the same acellular pertussis vaccine is safe and immunogenic. However, the frequency of local reactions is higher compared with that following primary immunization and with that following booster with DT only, and parents should be informed of the potential for these reactions to occur.** *Pediatrics* **2001; 107(2). URL: http://www.pediatrics.org/cgi/content/full/107/2/e25;** *pertussis vaccine, adverse effects, immunoresponse, booster dose, children.*

ABBREVIATIONS. DTaP, diphtheria-tetanus-acellular pertussis; DT, diphtheria-tetanus; SB, SmithKline Beecham; CB, Chiron Biocine; PT, pertussis toxin; FHA, filamentous hemoagglutinin; PRN, pertactin; IgG, immunoglobulin G; ELISA, enzyme-linked immunosorbent assay; EU, ELISA units; MLD, minimal level of detection; PT CHO, antibodies neutralizing pertussis toxin on Chinese hamster ovary cells; GMT, geometric mean titer; RR, relative risk; CI, confidence interval.

Recent studies, including clinical trials, have demonstrated that acellular pertussis vaccines are efficacious and have a lower reactogenicity than whole-cell vaccines.[1–5] These findings have led various countries to use acellular vaccines for primary immunization. With specific regard to Europe, clinical trials were recently conducted in Sweden, Germany, and Italy, leading to the use of acellular pertussis vaccines for primary immunization and consequently to high vaccination coverage.[5–7]

Although acellular vaccines have been thoroughly investigated with regard to their use for primary immunization, there still exist few data on their reactogenicity and immunogenicity when used as booster doses in children primed with these vaccines.[8] Previous studies have suggested that the reactogenicity of acellular pertussis vaccines, particularly for local reactions, increases with age and with the number of doses administered.[2,8–10] Because the low reactogenicity of primary immunization with these vaccines has been crucial in increasing vaccination coverage where the safety of whole-cell vaccines was a matter of concern,[11] the reactogenicity of booster doses needs to be accurately assessed, to inform parents and to prevent loss of confidence in vaccination programs. This is particularly important when considering that the first large cohorts of children primed with these vaccines are now reaching, or have already reached, the age at which they are eligible for a preschool booster dose, as for example in the United States, where the Food and Drug Administration approved the use of acellular vaccines for primary immunization in 1996.[12]

The objective of the present study was to evaluate the reactogenicity and immunogenicity of a booster dose of 2 three-component acellular pertussis vac-

cines combined with diphtheria-tetanus-acellular pertussis (DTaP) administered at preschool age to children primed with 3 doses of the same DTaP vaccine in infancy and who had received a diphtheria-tetanus (DT) dose at the age of 12 months. We also aimed to determine the reactogenicity attributable to the pertussis component of the booster dose by comparing children who received the DTaP booster with those who received a booster dose of a DT only vaccine.

METHODS

Study Design

This study was conducted as a prospective, open, nonrandomized observational study; families of vaccine recipients were aware of the product administered.

Population

The study population consisted of healthy children previously enrolled in the Italian Trial on Acellular Pertussis Vaccines.[2] In the trial, 15 601 infants born in 1992 and 1993 were randomly assigned to receive 1 of 2 DTaP vaccines manufactured by SmithKline Beecham (SB; Rixensart, Belgium) or Chiron Biocine (CB; Siena, Italy), a whole-cell diphtheria-tetanus-pertussis vaccine manufactured by Connaught (Swiftwater, PA) or a DT vaccine manufactured by CB (Fig 1); all vaccines were administered in 3 doses at 2, 4, and 6 months of age. At 12 months of age, all children also received a dose of a DT vaccine (single lot, manufactured by CB), as mandated by Italian regulations. Children primed with DTaP remained blinded to the vaccine received until October 1995.[13] Active surveillance for the occurrence of pertussis was continued until October 1998, and children who developed a laboratory-confirmed pertussis infection or who received additional doses of pertussis vaccine outside of the study protocol were excluded from additional analyses.
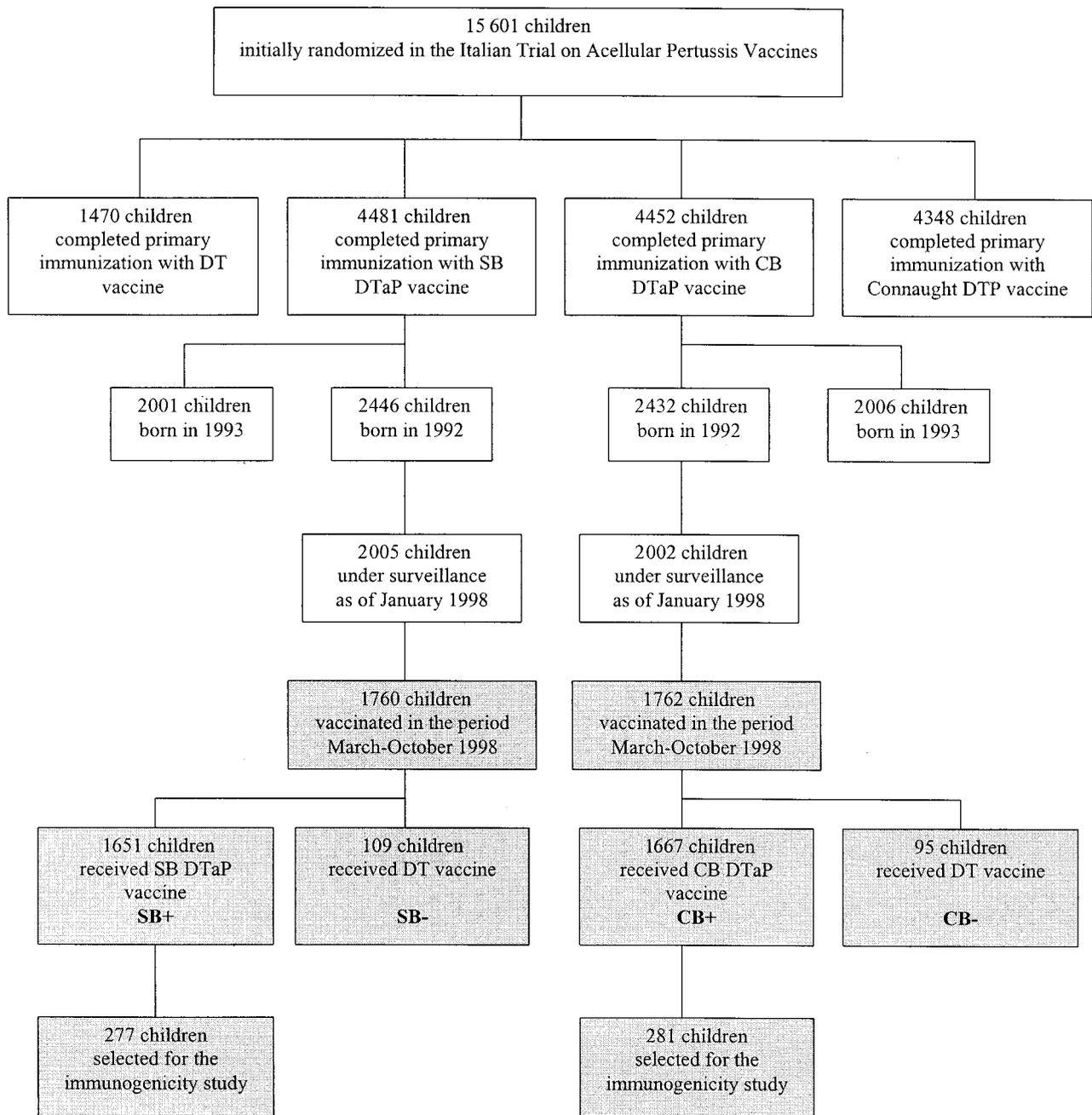

Fig 1. Study profile. Shaded boxes indicate the population included in the present study.

Those children not excluded as of January 1998 were included in the present study. Specifically, the study population consisted of the 4007 children primed with a DTaP vaccine and who were born in 1992, that is, those children who in 1998 would turn 6 years old, the age at which a booster dose of DT is required by Italian regulations (ie, before enrollment in school; Fig 1). From March 1, 1998 to October 31, 1998, we offered these children a booster dose of the same DTaP product used for primary immunization (ie, SB or CB). Children whose parents declined this offer were offered the commercial DT only vaccine, available at the local vaccination clinic. Children born in 1993 were not included in this analysis, although they later received a dose of either DTaP or DT. The recommendations of the American Academy of Pediatrics regarding contraindications and precautions for the administration of DTaP vaccines were followed.[14]

Informed written consent was obtained from the parents of all children included in this study. Separate informed written consent was obtained for taking a blood sample for the immunogenicity study.

Vaccines and Vaccinations

The pertussis component of the SB DTaP vaccine includes 25 μg of pertussis toxin (PT), 25 μg of filamentous hemagglutinin (FHA), and 8 μg of pertactin (PRN), whereas the CB DTaP vaccine includes 5 μg of genetically inactivated PT, 2.5 μg of FHA, and 2.5 μg of PRN. Children who received a DT booster only were injected with 1 of 5 different commercial products, according to local availability. The DTaP and DT vaccines include 25 to 30 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, a maximum of 0.05 mg of thimerosal, or 2.5 mg of 2-phenoxyethanol (SB DTaP), as preservative, and aluminum salts, as adjuvant.

Vaccinations were performed in 62 vaccination clinics in the 4 regions participating in the Pertussis Trial, within the Italian National Health Service. Vaccines were injected intramuscularly (in the buttock, arm, or thigh) with a syringe with a 22- to 24-gauge, 2.5-cm long needle, by the local staff. Information on immunization and reactogenicity was recorded on individual case report forms.

Reactogenicity

Adverse events were surveyed by 72 study nurses specifically hired and trained for the Pertussis Trial, using the same methods used during primary immunization.[2] At the time of booster administration, the study nurses instructed parents in monitoring reactogenicity, asking them to record observed events on a standardized daily diary for 8 days after administration. Parents were also asked to notify the study nurse of the occurrence of any severe event or symptoms not listed in the diary with onset within 8 days. Systemic events such as body temperature (axillary or inguinal), vomiting, loss of appetite, and irritability, as well as local reactions at the site of injection (redness, swelling, and tenderness) were listed in the daily diary. Body temperature was not requested after the third day of vaccination if the child was afebrile. Fever was defined as an external temperature of ≥38°C; irritability was defined as being more irritable than usual, as perceived by parents. Regarding the severity of events, parents were asked to describe irritability and local tenderness as either moderate or severe (moderate tenderness: pain on digital pressure; severe tenderness: spontaneously reported pain); for local redness and swelling at the injection site, severity was based on the size of the affected area (ie, <5 cm, ≥5 cm), as measured by parents.

Five solicited symptoms (ie, fever, irritability, and local redness, swelling, and tenderness) were considered key symptoms, as defined in the literature,[15,16] and their frequency of occurrence within 3 days of booster administration was analyzed. The frequency of 2 unsolicited symptoms occurring within 3 days of booster administration was also analyzed (ie, local itching and extensive local reactions) was also analyzed. Extensive local reactions were defined as swelling and redness, regardless of the presence of tenderness, involving the whole buttock, arm, or thigh where the injection had been given. The study nurses were instructed to immediately notify the study coordinators of severe adverse events (ie, anaphylaxis within 24 hours of receiving the booster, fever ≥39.5°C within 48 hours, hypotonic-hyporesponsive episodes within 48 hours, seizures within 72 hours, generalized cyanosis within 48 hours, and encephalitis/encephalopathy within 7 days).

Immunogenicity

The immunogenicity of the 2 DTaP vaccines was evaluated for a subsample of the study population, using the same methods used in the previous trial.[2] Capillary blood samples were taken by study nurses immediately before booster administration and 30 days later.

Antibodies to PT, FHA, and PRN (immunoglobulin G [IgG] PT, IgG FHA, and IgG PRN) were measured at the University of Palermo by enzyme-linked immunosorbent assay (ELISA), as described elsewhere.[17,18] The reference-line method was used to calculate ELISA units (EUs) with a standardized software (Unitcalc, Biosys INOVA, Stockholm, Sweden), and results were expressed as EU per milliliter. The following minimum levels of detection (MLD) were established: 2 EU/mL for PT, 2 EU/mL for FHA, and 3 EU/mL for PRN. The assay for antibodies neutralizing PT on Chinese hamster ovary cells (PT CHO) was performed when the amount of collected serum was sufficient (assay performed at the Istituto Superiore di Sanità). All assays were performed in a blind manner. The results were expressed as reciprocal dilutions causing complete inhibition of the clustering activity induced by the native toxin. The MLD for PT CHO was set at 1:40. In the statistical analyses, serologic results lower than the MLD were assigned a default value of one half the MLD; calculations were performed on logarithmically transformed data.

For each antigen, 2 definitions were used to classify children as "responders": 1) postbooster titer at least 4 times greater than both the MLD and the prebooster titer; and 2) postbooster titer at least 4 times greater than the MLD, irrespective of the prebooster titer. Taking into consideration only the first definition, responders and nonresponders were compared for prebooster geometric mean titers (GMTs). For all children, postbooster GMTs for all antigens were compared by site of injection (buttock vs arm or thigh).

Sample Size

The minimum number of observations necessary for allowing for statistical comparisons of reactogenicity was computed based on the frequency of common events reported after primary immunization with DTaP in the same study population. During primary immunization, the lowest frequency of occurrence for common events was the 5% reported for tenderness among DTaP recipients after the third dose. A total of 1500 children for each DTaP group would have provided an 80% power to detect a relative risk (RR) of 1.5 at the α = .05 level. To compare the DTaP groups with the DT group, a total of 100 DT vaccinees would have provided an 80% power to detect an RR of 2.6 at the α = .05 level. Therefore, it was decided to include all of the consecutive DTaP and DT booster recipients, at least until acquiring the necessary number of observations.

The size of the sample for the immunogenicity study was arbitrarily set at 200 children for each DTaP group and was balanced across the 4 geographical regions, because any geographical differences in pertussis circulation could have led to differences in prebooster titers. To recruit children for the immunogenicity study, the study nurses asked the parents of children who received a DTaP booster if they wanted to participate; the nurses were asked to provide a minimum of 3 paired sera for each of the 2 DTaP study groups. The necessary sample size was reached in March to April 1998.

Statistical Analysis

Children were divided into study groups based on the specific product used for primary immunization and on whether they received a booster of DTaP or DT only: SB+ and CB+ designate children primed and boosted with the SB vaccine and with the CB DTaP vaccine, respectively, and SB− and CB− designate those primed with the DTaP vaccines but who only received a DT booster (Fig 1).

The information included in case report forms (ie, type of vaccine used for primary immunization, type of vaccine used for boosting, adverse events, immunogenicity results) was entered in a database and analyzed using SPSS for Windows (SPSS Inc, Chicago, IL).

To evaluate the possibility of a selection bias, the frequency of adverse events observed after primary immunization was compared between children included in this study and those not participating. Moreover, to explore whether the refusal of the

DTaP booster was related to previous experience with adverse events after primary immunization, the frequency of reported adverse events after primary immunization was compared between children receiving a DTaP booster and those receiving the DT booster only.

The association between the site of injection and the occurrence of local reactions was also investigated, comparing reactogenicity after injection in the buttock with that in the arm or thigh.

The proportions of children experiencing any adverse event, whether common or severe, in the first 3 days after booster administration were compared among the 4 vaccine groups, using the χ^2 test or Fisher's exact test, when appropriate. The same tests were used for the analysis of the effect of site of injection on local reactions.

For the immunogenicity analysis, the χ^2 or Fisher's exact test was used to compare the proportions of responders, whereas the GMTs were compared using the Mann-Whitney U test.

RESULTS

A total of 3522 children were included in the present analysis. Of the 1760 children who had undergone primary immunization with the SB DTaP vaccine, 1651 received a fourth dose of the same vaccine (group SB^+) and 109 a dose of DT only (group SB^-). Of the 1762 who had undergone primary immunization with the CB DTaP vaccine, 1667 received a fourth dose of the same vaccine (group CB^+) and 95 a dose of DT only (group CB^-; Fig 1). The DT vaccines administered to the SB^- and CB^- groups were produced by 5 manufacturers, and the brands were similarly distributed between the 2 study groups.

The distribution of children by age, gender, site of injection, and vaccine group is illustrated in Table 1. No important differences were observed among study groups in terms of age, gender, or site of injection. Vaccines were rarely administered in the thigh (5%), regardless of the study group.

Children participating in the present study were more likely to have reported irritability after primary immunization than children not included in the present study (60.7% vs 57.8%; $P = .007$). When comparing DTaP booster recipients with those who received only DT, again, only irritability after primary immunization had been more frequently reported in children who received a DT booster compared with those who received a DTaP booster (66.7% vs 57.3%; $P = .008$).

Reactogenicity

The only severe event reported was fever $\geq39.5°C$ within 48 hours of booster administration, which occurred in 2 children of the CB^+ group and 2 children of the SB^+ group. No other severe events were reported during the study.

The frequency of fever, irritability, and local redness, swelling, and tenderness experienced in the first 3 days after booster administration is shown in Fig 2. Fever and irritability were infrequent (fever: SB^+, 2.5%; SB^-, 4.8%; CB^+, 2.8%; CB^-, 0%; irritability: SB^+, 10.1%; SB^-, 7.4%; CB^+, 11.7%; CB^-, 12.6%), and none of the differences among the 4 groups were statistically significant. By contrast, local redness and swelling were significantly more frequent in children who received a DTaP booster (redness: SB^+, 44.0%; CB^+, 48.1%; swelling: SB^+, 48.2%; CB^+, 52.8%) compared with those who received only a DT booster (redness: SB^-, 30.6%; CB^-, 29.5%; swelling: SB^-, 36.1%; CB^-, 32.6%). For local tenderness, a significant difference in frequency was detected only when the CB^+ group was compared with the CB^- group (SB^+, 47.7%; SB^-, 44.4%; CB^+, 52.2%; CB^-, 35.8%). Redness ≥5 cm was observed more frequently in the SB^+ group than in the SB^- group (SB^+, 15.2%; SB^-, 6.5%; $P = .01$); swelling ≥5 cm was more frequent in DTaP compared with DT recipients (SB^+, 16.0%; SB^-, 5.6%; $P = .003$; CB^+, 18.9%; CB^-, 9.5%; $P = .02$), as was severe tenderness (SB^+, 12.9%; SB^-, 5.6%, $P = .02$; CB^+, 13.8%; CB^-, 2.1%; $P = .001$). Moreover, all local reactions were reported more frequently in the CB^+ than in the SB^+ vaccine group.

The frequency of extensive local reactions (ie, swelling and redness involving the whole buttock, arm, or thigh) was as follows: 1.0% for SB^+, 1.4% for CB^+, 0.9% for SB^-, and 0% for CB^-. Local itching was reported more frequently in DTaP recipients (SB^+, 20.6%; CB^+, 20.1%) than in DT recipients (SB^-, 4.6%; CB^-, 5.3%; $P < .001$). All of the above mentioned events subsided in a few days without sequelae.

Regarding the frequency of local reactions by site of injection, the frequency of local redness was similar by site of injection in each of the study groups, whereas that of local swelling was higher at the

TABLE 1. Characteristics of the Study Population by Demographic Variables and Site of Booster Injection

	Primed With SB DTaP Vaccine $n = 1760$		Primed With CB DTaP Vaccine $n = 1762$	
	Boosted With SB DTaP Vaccine (SB^+) $n = 1651$	Received a DT Vaccine Only (SB^-) $n = 109$	Boosted With CB DTaP Vaccine (CB^+) $n = 1667$	Received a DT Vaccine Only (CB^-) $n = 95$
Mean age at booster, years (range)	5.8 (5.2–6.3)	5.7 (5.0–6.2)	5.8 (5.2–6.3)	5.7 (4.9–6.1)
Females, no. (percent)	852 (51.6)	59 (54.1)	840 (50.4)	46 (48.4)
Injection site, no. (percent)				
Buttock	681 (41.2)	42 (38.5)	660 (39.6)	44 (46.3)
Thigh	93 (5.6)	—	89 (5.3)	—
Arm	877 (53.1)	67 (61.5)	918 (55.1)	51 (53.7)
Total	1651 (100)	109 (100)	1667 (100)	95 (100)

Temperature ≥ 38° C

A

Irritability

B

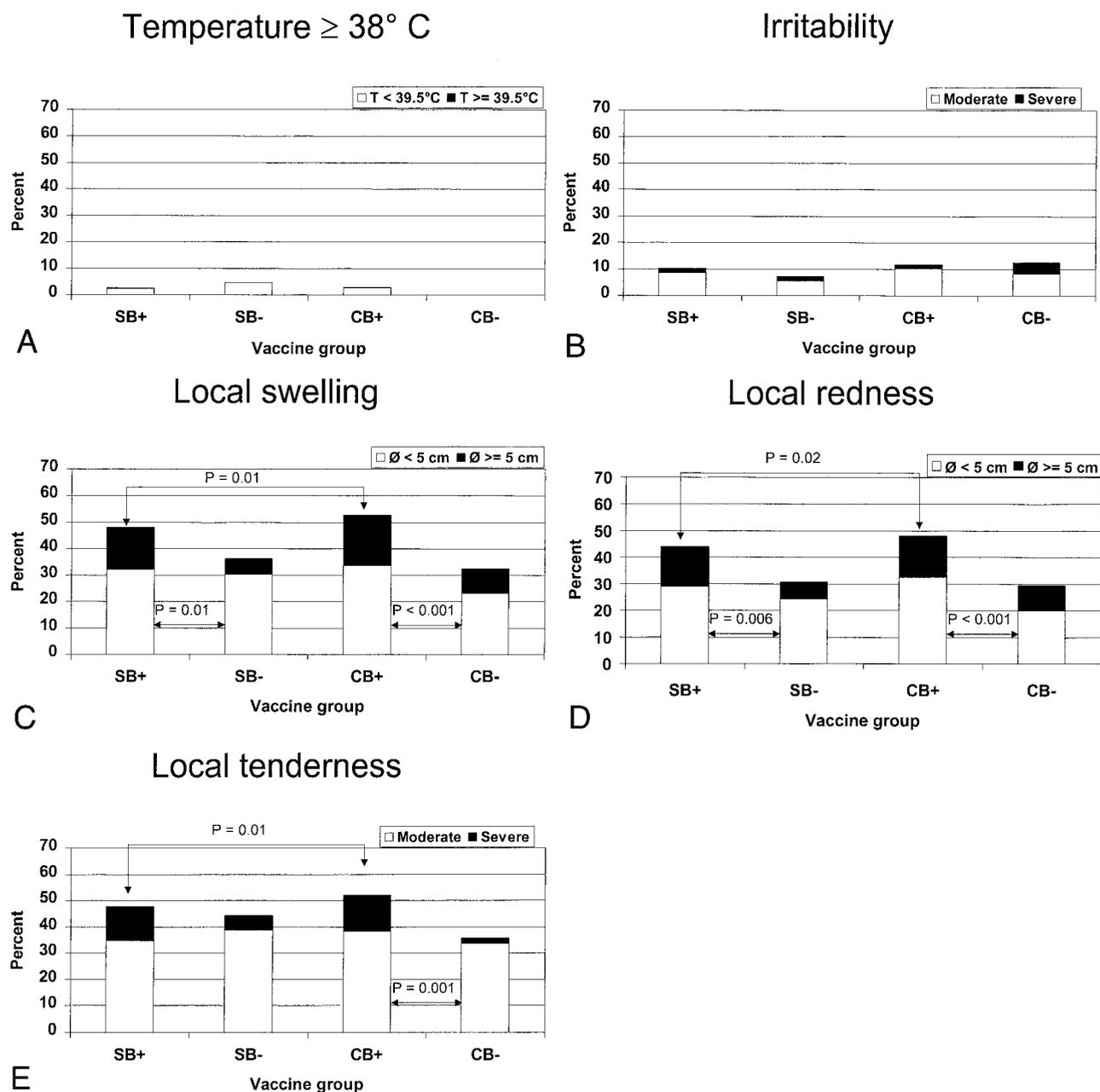## Local swelling

C

Local redness

D

Local tenderness

E

Fig 2. Frequency of temperature ≥38°C, irritability, and local redness, swelling, and tenderness in the first 3 days after booster administration, by vaccine group.

arm/thigh both in the SB+ group (arm/thigh, 56.0%; buttock, 37.3%; $P < .001$) and the CB+ group (arm/thigh, 59.8%; buttock, 42.3%; $P < .001$). Similarly, local tenderness was significantly more frequent when the booster was administered in the arm or thigh, in all groups (SB+: arm/thigh, 55.3%; buttock, 36.9%; $P < .001$; SB−: arm/thigh, 53.0%; buttock, 31.0%; $P = .02$; CB+: arm/thigh, 58.6%, buttock, 42.6%; $P < .001$; CB−: arm/thigh, 45.1%; buttock, 25.0%; $P = .04$).

Extensive local reactions were observed with a similar frequency when stratifying by site of injection, whereas local itching was reported more frequently when the injection was administered in the arm or thigh in the SB+ group (arm/thigh, 27.3%; buttock, 19.8%; $P = .001$).

Immunogenicity

A total of 558 paired sera from DTaP booster recipients were collected for the immunogenicity study (277 SB+ and 281 CB+; Fig 1). The amount of available serum was sufficient for performing PT CHO assay on 317 paired samples (164 SB+ and 153 CB+).

Table 2 shows the prebooster and postbooster GMTs with 95% confidence intervals (CIs) for IgG PT, IgG FHA, IgG PRN, and PT CHO, by vaccine group. Prebooster GMTs were low in both groups, with values close to the MLD, especially for IgG PT (percent of cases below the MLD: IgG PT, 48.7%; IgG FHA, 6.0%; IgG PRN, 13.5%). In both DTaP groups, postbooster GMTs were at least 10 times higher than prebooster GMTs. When considering the response to

TABLE 2. Comparison of Pre- and Postbooster GMTs in EUs of IgG PT, IgG FHA, IgG PRN, and PT CHO Neutralization Antibodies by Vaccine Group

	Prebooster GMT (95% CI)		Postbooster GMT (95% CI)	
	SB DTaP	CB DTaP	SB DTaP	CB DTaP
IgG PT	2.03	2.67*	68.88	120.65*
	(1.79–2.31)	(2.32–3.07)	(61.00–77.78)	(108.32–134.38)
IgG FHA	29.69	22.75	621.48*	216.31
	(25.80–35.04)	(18.74–27.63)	(570.13–677.45)	(191.18–244.74)
IgG PRN	17.44*	12.08	712.16*	256.75
	(14.94–20.36)	(10.15–14.39)	(620.86–816.89)	(220.35–299.16)
PT CHO	113.14	247.18*	3412.50	5504.93*
	(83.33–153.60)	(182.06–335.58)	(2843.87–4094.83)	(4569.69–6631.59)

* $P < .01$ SB DTaP versus CB DTaP.

specific antigens, postbooster IgG PT titers were higher for the CB DTaP recipients, with respect to the SB DTaP recipients, whereas IgG FHA and IgG PRN titers were higher for the SB DTaP vaccine. Both vaccines induced high titers of PT CHO, although titer levels were higher among the CB DTaP vaccine recipients.

The site of injection affected postbooster GMTs to some antigens: higher titers to FHA were found when the vaccine was administered in the thigh or arm, compared with the buttock, for both DTaP vaccines (SB: arm/thigh GMT, 674.8; buttock GMT, 521.8; $P = .003$; CB: arm/thigh GMT, 251.4; buttock GMT, 163.9; $P = .001$). Higher titers to PT were also found when the vaccine was administered in the arm or thigh (SB: arm/thigh GMT, 74.5; buttock GMT, 58.3; $P = .03$; CB: arm/thigh GMT, 130.9; buttock GMT, 103.9; $P = .02$).

The proportion of responders by definition and vaccine group is shown in Table 3. Although the proportion of responders was high under both definitions, when using the first definition (ie, postbooster titers at least 4 times greater than both the MLD and prebooster titers), there was a significantly higher proportion of responders to FHA and PRN among the SB DTaP booster recipients, compared

TABLE 3. Percentage of Responders to Single Antigens by Vaccine and by Specific Definition

Postbooster Titer ≥ Fourfold MLD and ≥ Fourfold Prebooster Titer		
Antigen	SB DTaP Responders (%)	CB DTaP Responders (%)
PT	95.6	95.7
FHA	89.5**	70.3
PRN	97.1**	89.9
PT CHO	86.7	85.1

Postbooster Titer ≥ Fourfold MLD and ≥ Fourfold Prebooster Titer		
Antigen	SB DTaP Responders (%)	CB DTaP Responders (%)
PT	98.2	100*
FHA	100	99.6
PRN	99.6	98.2
PT CHO	99.4	98.7

* $P = .02$, SB DTaP versus CB DTaP.
** $P < .001$, SB DTaP versus CB DTaP.

with the CB DTaP booster recipients. When using the second definition (ie, postbooster titers at least 4 times greater than the MLD), the proportion of responders was close to 100% for all antigens. To ascertain whether the lack of response under the first definition was attributable to high prebooster titers, these titers were broken down by responder status under the first definition. The results of this analysis (Table 4) clearly show that nonresponders under the first definition had much higher antibody titers than did responders and that for this reason they did not meet the fourfold increase in titers.

DISCUSSION

The necessity of providing a booster dose of acellular pertussis vaccines and the age at which this dose should be administered have yet to be determined. In many countries, child immunization consists of 4 or 5 doses of a pertussis vaccine, 1 of which is administered at preschool age, and the first cohorts of children primed with acellular products have now reached this age. Because the low reactogenicity at primary immunization has been crucial for the acceptance of the new vaccines, the results of the present study are relevant in that they provide data on the reactogenicity of a fourth dose of DTaP administered 4 years after primary immunization with the same acellular vaccine. Moreover, this study estimated the net effect in terms of reactogenicity of the pertussis component of the booster by comparing DTaP and DT recipients. The effect of site of injection on local reactogenicity was also estimated.

The results of this study indicate that the reactogenicity of both the SB and CB DTaP vaccines is satisfactory when used as booster doses at preschool age in children primed with the same DTaP vaccine. In fact, the only severe events observed were 4 episodes of fever ≥39.5°C (.1% of DTaP recipients). Regarding common adverse events, the frequency of fever ≥38°C and that of irritability were both negligible. By contrast, the frequency of local symptoms was notable in all groups and higher among children receiving a DTaP booster, compared with DT recipients. The frequency of these local reactions was also much higher than the maximum frequency of 15% reported in the same group of children after the third dose of primary immunization[2,19] and the 24% maximum frequency reported in children undergoing catch-up primary immunization at 21 to 40 months

TABLE 4. Prebooster GMTs to Single Antigens by Vaccine Group in Responders and Nonresponders According to the First Definition

Vaccine	Antigen	GMTs in Nonresponders (95% CI)	GMTs in Responders (95% CI)
SB DTaP	IgG PT	15.94* (3.60–70.53)	1.86 (1.68–2.06)
	IgG FHA	197.02** (143.12–271.22)	23.81 (20.25–27.99)
	IgG PRN	132.87** (28.80–613.04)	16.55 (14.27–19.19)
	PT CHO	4961.19** (2645.64–9303.37)	64.32 (51.77–79.92)
CB DTaP	IgG PT	60.55** (37.32–98.22)	2.31 (2.05–2.60)
	IgG FHA	90.14** (69.89–116.27)	12.90 (10.50–15.85)
	IgG PRN	48.19** (23.43–99.09)	10.25 (8.67–12.11)
	PT CHO	4146.42** (1808.03–9509.10)	147.79 (115.79–188.63)

* $P < .05$, nonresponders versus responders.
** $P < .01$, nonresponders versus responders.

with 3 doses of a monovalent acellular pertussis vaccine.[9]

Moreover, whereas the frequency of common adverse events did not differ between the 2 DT groups (CB⁻ and SB⁻), a higher frequency of local redness, swelling, and tenderness was observed in the CB⁺ group, compared with the SB⁺ group. However, assuming that some reactions can be attributed to multiple exposure to the same antigens, it should be noted that all children participating in this study had received a DT vaccine manufactured by Biocine at the age of 12 months and that this vaccine includes the same DT components and excipients of the CB DTaP vaccine. Therefore, because the children participating in this study received 5 doses of diphtheria and tetanus toxoids and 4 doses of the acellular pertussis component, the observed reactogenicity in our study may be overestimated. Nonetheless, our findings are consistent with those of other studies of limited size, where local reactions were found more frequently after booster doses than after primary immunization if the same vaccine product was used.[8,10,20–22]

Extensive local reactions were observed in 1.2% of DTaP booster recipients and in .5% of DT recipients. Although the sample size of DT recipients was too small for detecting formal statistical differences for such infrequent events (only 1 extensive local reaction was observed in this group), this result is consistent with that obtained from a recent study performed on children who received a fifth dose of DTaP vaccine.[23] An additional finding was that ~20% of the DTaP booster recipients and 5% of the DT recipients experienced local itching after booster administration. The higher occurrence of extensive local reactions and local itching among DTaP booster recipients suggests that these reactions may have an immunologic component linked to the pertussis antigens included in DTaP vaccines.

Because the DTaP and DT vaccines included in this study have a comparable content of diphtheria and tetanus toxoids, our results also suggest that local reactogenicity is likely to be associated with the effect of the pertussis component rather than with the amount of diphtheria toxoid, as suggested by other authors.[23] Moreover, in our opinion, it is unlikely that the variability in the content and purity of preservatives and adjuvants across different vaccines accounts for an important part of the differences observed in the occurrence of local reactions.

The finding that injection in the buttock was associated with a lower frequency of local reactions than injection in the arm or thigh is consistent with observations made during primary immunization in the first year of life and during catch-up primary immunization at 21 and 40 months of age.[9,16]

Potential selection bias for children enrolled in the present study was assessed by comparing rates of adverse events during primary immunization in children observed in this study versus those who were not, and in children who received a DTaP vaccine versus those who received DT. The results do not support the presence of a selection bias.

Although the study was conducted among the children who, in 1992, had been randomized to receive in a double-blind manner 1 of 2 acellular DTaP vaccines, the present observations were made in open conditions, because participating families had been informed of the vaccine received at the end of stage II of the trial in October 1995. Given the open conditions, observer bias could have occurred, with a consequent overestimation of the frequency of local reactions.

Although the subpopulation for immunogenicity was selected in a nonrandomized manner based on voluntary participation, it is unlikely that those agreeing to participate in the immunogenicity study biologically differed from those who did not.

The 2 DTaP vaccines included in this study induced a strong antibody response after booster administration. Prebooster titers were in line with a previous study performed in the same trial population, showing a rapid decrease of antibody titers within 1 month of completing the primary series,[24] despite the persisting clinical efficacy. Postbooster GMTs to all antigens were higher than those ob-

served after primary immunization.[2] In the present study, the small differences found when comparing prebooster titers by DTaP group, however, reflect those found in seroresponse after primary immunization.[2]

Given the very high postbooster GMTs and the presence of children who had high preimmunization titers and failed to meet a fourfold increase after immunization, the use of postbooster titer ≥4 times the MLD seems to be sufficient criterion for defining responders in this setting. However, the differences observed in GMTs and in the proportion of responders (using either definition) between the 2 DTaP vaccines are probably negligible in terms of clinical efficacy. In fact, the 2 vaccines exhibited the same differences in immunogenicity after primary immunization, but they induced the same protective efficacy.[2] Because the antibody response elicited by the 2 DTaP vaccines is higher after booster administration compared with that following primary immunization, the clinical efficacy is expected to be at least similar to that observed after primary immunization.

Although a straightforward correlate of protection has not yet been identified, antibodies to PT and PRN seem to represent reasonable candidates.[25,26] The assessment of serologic response induced by the booster and its comparison with the response observed after primary immunization could be used to evaluate the expected efficacy of the booster dose.

The finding that injection in the arm or thigh is associated with higher postbooster titers against FHA and PT compared with the buttock should be considered in light of the potentially higher frequency of local reactions suggested by our study when using the arm or thigh as site of injection, and the very high postbooster titers obtained whatever site of injection was used.

CONCLUSION

A fourth dose of DTaP vaccine at preschool age in children primed with the same acellular vaccine in infancy is safe and immunogenic. However, the rate of local reactions after booster administration is higher than that after primary immunization. Because the pertussis component seems to increase local reactions by nearly 15% compared with DT only and given that these reactions increase with age and number of doses, this finding should be taken into account if future strategies are to target adolescents and adults. It remains to be confirmed whether new formulations of DTaP vaccines with a reduced antigenic content could be a suitable alternative for booster doses in older age groups, as already suggested.[27] Although these local reactions are modest from the clinical point of view and subside without sequelae, vaccinees' parents should be appropriately informed to avoid unnecessary concern and to maintain a high level of vaccination coverage.

ACKNOWLEDGMENTS

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