Acellular Vaccines Containing Reduced Quantities of Pertussis Antigens as a Booster in Adolescents

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ABSTRACT. *Objective.* **To evaluate the immunogenicity and reactogenicity of an acellular pertussis vaccine (pa) either formulated with diphtheria and tetanus toxoids (dTpa) or administered consecutively with a licensed tetanus and diphtheria vaccine (Td) as a 5th dose in adolescents.**

Methods. **A total of 510 healthy children 10 to 13 years of age were assigned randomly, using a single-blind design, to receive either the dTpa vaccine or the Td vaccine with the pa vaccine 1 month later. The quantities of 3 pertussis antigens (pertussis toxin, filamentous hemagglutinin, and pertactin) in the dTpa and the pa vaccines were one third of those of the Infanrix vaccine (SmithKline Beecham Biologicals, Rixensart, Beligium) licensed for use in infants. For enzyme-linked immunosorbent assay measurement of serum immunoglobulin G antibodies and proliferation assay of peripheral blood mononuclear cells, blood samples were obtained before and 1 month after immunization. Local and systemic reactions were recorded on diary cards for 15 days after immunization.**

Results. **After immunization with dTpa or pa, significant and comparable rises in geometric mean values of antibodies (12- to 46-fold) and proliferations (8- to 18-fold) to each of the pertussis antigens were noted. After immunization with dTpa or Td, significant rises in geometric mean values of antidiphtheria and antitetanus antibodies (35- to 76-fold) were noted, and all subjects had values of these antibodies ≥.1 international units/mL. The dTpa and pa vaccines were at least as well tolerated as the licensed Td vaccine.**

Conclusions. **Booster immunization of adolescents with an acellular vaccine containing reduced quantities of pertussis antigens in addition to diphtheria and tetanus toxoids induces good responses in both arms of the immune system without an increase in adverse reactions.** ***Pediatrics*** **1999;104(6). URL: http://www.pediatrics.org/cgi/content/full/104/6/e70;** ***acellular pertussis vaccine, booster, immunization, immunogenicity, reactogenicity.***

ABBREVIATIONS. pa, monovalent acellular pertussis vaccine; dTpa, diphtheria and tetanus toxoids combined with acellular pertussis vaccine; Td, tetanus and diphtheria toxoids vaccine; PT, pertussis toxin; FHA, filamentous hemagglutinin; PRN, pertactin; Lf, limit flocculation unit; CMI, cell-mediated immunity; ELISA, enzyme-linked immunosorbent assay; EU, ELISA units; IU, international units; PBMC, peripheral blood mononuclear cells; GMV, geometric mean value; CI, confidence interval.

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Childhood immunization against pertussis has been effective in decreasing the incidence of pertussis but has not eliminated the circulation of *Bordetella pertussis*.[1] Infections and disease caused by *B pertussis* are recognized increasingly among older children and adults in immunized populations,[1–5] indicating that the vaccine-induced immunity wanes below the protective level in these age groups. Furthermore, several household studies and investigations of outbreaks have shown that older family members constitute an important reservoir for spread of infection to susceptible infants.[6–9] These findings suggest the need for booster immunizations of older children and adults, also with the goal of preventing transmission of *B pertussis* from these age groups to infants. However, the high reactogenicity of conventional whole cell pertussis vaccines has prevented their use as booster doses in individuals >6 years of age.[10] Modern acellular vaccines, which are less reactogenic than whole cell vaccines, seem to be suitable not only for primary immunization,[11,12] but also for boosting of preschool children and adults.[13–19]

This study was performed to evaluate the immunogenicity and reactogenicity of an acellular pertussis vaccine (pa) either formulated with diphtheria and tetanus toxoids (dTpa) or administered consecutively with a licensed tetanus and diphtheria vaccine (Td) as a 5th dose in children 10 to 13 years of age.

METHODS

Subjects

Healthy 10- to 13-year-old children scheduled to receive their regular Td booster vaccine were recruited in the city of Turku, in southwestern Finland. All children had received an immunization course of 4 doses of diphtheria-tetanus-whole cell pertussis vaccine at 3, 4, 5, and 24 months of age, as scheduled in Finland.[20] Children were excluded if they had a history of diphtheria, tetanus, or pertussis disease, a 5th dose of pertussis vaccine, diphtheria, or tetanus immunization within the past 5 years, or allergic disease likely to be stimulated by the immunization. They also were excluded if they had any underlying conditions (such as major congenital defects, serous chronic illness, immunosuppressive therapy, immune disorder, and acute febrile illness) that could affect the expected responses to immunization.

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Vaccines

Each .5-mL dose of the dTpa and pa vaccines (SmithKline Beecham Biologicals, Rixensart, Belgium) contained 3 *B pertussis* antigens: 8 μg of pertussis toxin (PT) inactivated with formalin and glutaraldehyde, 8 μg of filamentous hemagglutinin (FHA), and 2.5 μg of pertactin (PRN). These quantities were approximately one third of those of the pediatric DTPa vaccine, Infanrix (SmithKline Beecham Biologicals), licensed for use in primary immunization. Each dose of dTpa also contained 2.5 limit flocculation units (Lf) of diphtheria toxoid and 5 Lf of tetanus toxoid. The antigens were absorbed onto .5 mg of aluminum salts, and 2.5 mg of 2-phenoxylethanol was used as a preservative. Each .5-mL dose of the licensed Td vaccine, Lederject (Lederle Laboratories, Pearl River, NY), contained 5 Lf of tetanus toxoid and 2 Lf of diphtheria toxoid.

Study Design

The study protocol was approved by the joint commission on ethics of the Turku University and the Turku University Central Hospital and conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines current at the time of the study initiation. Written, informed consent was obtained from the parents or guardian of all children before their enrollment.

After a physical examination and recording of the axillary temperature, subjects were assigned randomly in a 8:1 ratio, using a single-blind design, to receive either the dTpa vaccine (the dTpa group) or the Td vaccine first (in a blinded fashion); and then 1 month later the Td group received the pa vaccine (in an open fashion). The dTpa and Td vaccines were administered by a deep intramuscular injection into the left deltoid region, whereas the pa vaccine was administered into the right deltoid region. For the dTpa group, blood samples were drawn before and 1 month after the immunization. For the Td + pa group, blood samples were drawn before the first immunization and 1 month after each of the 2 immunizations. For measurement of cell-mediated immunity (CMI) by proliferation assays, every 4th subject was selected to form 2 vaccine subgroups (the dTpa and Td + pa subgroups).

Reaction Assessment

The subjects were observed closely for immediate adverse reactions for at least 15 minutes after immunization. Parents completed a diary card soliciting local (pain on digital pressure, redness, and swelling) and systemic reactions (fatigue, headache, and fever) from days 0 to 14 after immunization. The diary cards had space to record unsolicited adverse events that occurred up to 30 days after immunization. For redness and swelling (measured systematically using a study gauge), the intensity was defined as severe when it was ≥50 mm in diameter. An axillary temperature (measured daily using an electronic thermometer) ≥39.1°C was defined as severe fever. For other adverse events, the intensity was defined as severe when it prevented normal daily activities and needed medical advise. All solicited local reactions were considered related to immunization. The relationship between other adverse events and immunization was evaluated by the investigator according to the criteria of the study protocol. The outcome of all adverse events was recorded.

Laboratory Tests

Serologic Assays

Sera prepared from preimmunization and postimmunization blood samples were stored at −70°C until serologic analysis at SmithKline Beecham Biologicals. Serum immunoglobulin G (IgG; antibodies to PT, FHA, and PRN were determined by an enzyme-linked immunosorbent assay (ELISA),[13,15] which has a cutoff of 5 ELISA units(EU)/mL. Serum IgG antibodies to diphtheria and tetanus toxoids also were determined using ELISA,[21,22] which has a cutoff of .1 international units per milliliter (IU/mL). All samples with antidiphtheria antibody values <.1 IU/mL were retested using the VERO cell neutralization test,[21] which has a lower cutoff of .016 IU/mL. A positive antibody response to pertussis antigens was defined as seroconversion for initially seronegative subjects or a minimum of twofold increase in antibody values for initially seropositive subjects.

Proliferation Assay

Preparation of peripheral blood mononuclear cells (PBMC) and culture conditions for the proliferation assay were as reported earlier.[23] Briefly, all blood samples were processed within 3 hours, and triplicate cultures (.2 mL) of PBMC suspension (5×10^5 cells/mL) were incubated with 1 μg of heat-inactivated PT/mL, 1 μg of FHA/mL, or 2.5 μg of PRN/mL (SmithKline Beecham Biologicals). Controls were cultures without stimulus or with pokeweed mitogen. After a 5-day incubation at 37°C in an atmosphere with 5% CO_2, ^{3}H-thymidine (.5 μCi/well) was added and, 16 hours later, incorporated radioactivity was measured by scintillation counting. The results were expressed as mean counts per minute from triplicate cultures. A CMI response was defined to be positive when the antigen-induced proliferation was at least fourfold higher than the spontaneous proliferation (stimulation index ≥4).[23,24]

Statistical Analysis

Serologic results lower than the assay cutoff were assigned an arbitrary value of one half the assay cutoff. Calculations of geometric mean values (GMVs) of antibodies and proliferations were performed on $\log_{10}$ transformed data, reporting the antilogarithm. For each group, GMVs and 95% confidence intervals (CIs) were calculated. GMVs were compared using the Student's *t* test. Frequencies of reaction, seropositivity, and positive antibody and proliferative responses were compared using the Fisher's exact test. Analysis of correlations was performed using the Spearman rank correlation coefficient. Comparisons manifesting a two-tailed *P* value of <.05 were considered statistically significant.

RESULTS

Demographics

Of the 510 subjects enrolled (450 in the dTpa group and 60 in the Td + pa group), 3 were excluded because of randomization failure (1), consent withdrawal (1), or additional immunization during the study (1), resulting in 507 subjects (99%) eligible for the analysis of reactogenicity. Three additional subjects were noncompliant with blood sampling, leaving 504 subjects (98%) eligible for the analysis of immunogenicity. All subjects were white and between 10 and 13 years of age at the beginning of the study (mean age ± standard deviation; 10.8 ± .43). The overall ratio of male to female subjects was 1.00:1.21, with no difference between the 2 study groups.

Reactogenicity

The incidences of solicited local and systemic adverse reactions that occurred during the 15-day follow-up after immunization are presented in Table 1. Pain was the most frequently reported adverse reaction in all groups; however, severe pain was reported only in 3.8% and 10.0% of subjects receiving dTpa and Td, respectively. Redness was reported with a significantly lower incidence in the dTpa (33.0%) than in the Td group (53.3%). The incidences of severe local reactions were low in all groups. The median (range) diameter and duration of severe redness and swelling were 65 (50–180) mm and 2 (1–11) days, and 70 (50–170) mm and 3 (1–12) days, respectively. Entire arm swelling was not noted. The incidences of severe systemic reactions were also low in all groups; only 2 cases of fever ≥39.1°C were reported. The majority of solicited adverse reactions were mild and transient, and all resolved spontaneously without sequelae.

Of all local reactions, 94.6% appeared ≤2 days after immunization, whereas the majority of cases of

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TABLE 1. Percentage of Subjects With Solicited Adverse Reactions During the 15-Day Follow-Up Period After Immunization

Adverse Reaction	Grade	Vaccine Group		
		dTpa (n = 448) (95% CI)	Td (n = 60) (95% CI)	pa (n = 59) (95% CI)
Local reactions				
Pain	Any	79.0 (75.0–82.7)	83.3 (71.5–91.7)	67.8 (54.4–79.4)
	Severe*	3.8 (2.2–6.0)	10.0 (3.8–20.5)	8.5 (2.8–18.7)
Redness	Any	33.0 (28.7–37.6)†	53.3 (40.0–66.3)†	8.5 (2.8–18.7)
	≥50 mm	5.8 (3.8–8.4)	16.7 (8.3–28.5)	.0 (.0–6.1)
Swelling	Any	35.0 (30.6–39.7)	46.7 (33.7–60.0)	15.3 (7.2–27.0)
	≥50 mm	7.8 (5.5–10.7)	10.0 (3.8–20.5)	1.7 (.0–9.1)
Systemic reactions				
Fatigue	Any	56.2 (51.5–60.9)	50.0 (36.8–63.2)	40.7 (28.1–54.3)
	Severe	2.9 (1.6–4.9)	1.7 (.0–8.9)	.0 (.0–6.1)
Headache	Any	51.3 (46.6–56.1)	51.7 (38.4–64.8)	35.6 (23.6–49.1)
	Severe	3.6 (2.1–5.7)	1.7 (.0–8.9)	5.1 (1.1–14.2)
Fever	≥37.5°C	8.9 (6.5–12.0)	8.3 (2.8–18.4)	5.1 (1.1–14.2)
	≥39.1°C	.4 (.1–1.6)	.0 (.0–.6)	.0 (.0–6.1)

* Severe indicates an adverse event that prevents normal daily activities and needs medical advice.
† $P < .001$ between dTpa and Td groups.

fever had an onset ≥3 days after immunization (ie, late-onset reaction). The total incidences of late-onset reactions (pain, redness, swelling, and fever) were low in all groups: dTpa (14.5%), Td (8.3%), and pa (6.7%). The nature of late-onset reactions were similar in all groups: median time of onset was day 5 (range: 3–14 days), duration was mostly 1 day (range: 1–11 days), and the majority of these reactions were mild in intensity.

Of the 198 unsolicited signs and symptoms, only 28 (14.1%) were assessed as probably or suspected to be related to immunization. Five mild local injection site symptoms (all sterile abscesses, according to the World Health Organization preferred terms) were ongoing at the end of the study period (30 days after immunization), all other events resolved within the study period. No severe unsolicited event was probably or suspected to be related to the immunization.

Immunogenicity

Antibody Responses

GMVs of serum IgG antibodies and antibody response rates of groups receiving dTpa or Td + pa are presented in Table 2. Before immunization, 97%, 74%, and 54% of the total 504 subjects tested had detectable antibodies to FHA, PRN, and PT, respectively, whereas nearly all subjects had protective values of antibodies to diphtheria (97%) and tetanus toxoids (95%). After immunization with dTpa or pa, significant rises in GMVs of antibodies to each of the pertussis antigens (12- to 33-fold for dTpa and 20- to

TABLE 2. Preimmunization and Postimmunization Geometric Mean Antibodies (95% CI) and Antibody Response Rates of Groups Receiving dTpa or Td + pa*

Variable	Vaccine Group		
	dTpa (n = 447)	Td (n = 57)	pa (n = 57)
Pertussis toxin			
Pre-GMV† (EU/mL)	10 (8–11)	10 (6–14)	8 (6–12)
Post-GMV	118 (105–131)	8 (6–12)	158 (121–206)
Response‡ (%)	92	0	96
Filamentous hemagglutinin			
Pre-GMV (EU/mL)	58 (52–66)	60 (41–86)	53 (36–77)
Post-GMV	923 (852–1000)	53 (36–77)	1106 (857–1427)
Response (%)	97	0	98
Pertactin			
Pre-GMV (EU/mL)	18 (15–20)	17 (11–28)	18 (11–30)
Post-GMV	595 (520–680)	18 (11–30)	823 (570–1188)
Response (%)	99	0	100
Diphtheria toxoid			
Pre-GMV (IU/mL)	.2 (.2–.2)	.2 (.1–.2)	8 (6–10)
Post-GMV	7 (6–8)	8 (6–10)	6 (5–8)
≥.1 IU/mL (%)	100	100	0
Tetanus toxoid			
Pre-GMV (IU/mL)	.5 (.5–.6)	.5 (.4–.7)	38 (31–46)
Post-GMV	24 (23–26)§	38 (31–46)§	28 (23–33)
≥.1 IU/mL (%)	100	100	0

* The pa vaccine was given 1 month after the Td vaccine to the same subjects.
† Pre-GMV indicates preimmunization geometric mean antibody value.
‡ A positive antibody response to pertussis antigens was defined as seroconversion for initially seronegative subjects or a minimum of twofold increase in antibody values for initially seropositive subjects.
§ $P < .001$ between dTpa and Td groups.

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46-fold for pa) were noted, and all subjects showed a positive antibody response to at least 1 of the pertussis antigens. GMVs of antipertussis antibodies were similar after dTpa and pa immunization. After immunization with dTpa or Td, significant rises in GMVs of antidiphtheria and antitetanus antibodies (35- to 48-fold for dTpa and 40- to 76-fold for Td) were noted. GMVs of antidiphtheria antibodies were similar after dTpa and Td immunization, and all subjects had antidiphtheria antibody value ≥.1 IU/mL. GMVs of antitetanus antibodies were higher after Td than dTpa immunization. However, this difference is unlikely to be of clinical significance, because all subjects had antitetanus antibody value ≥1.0 IU/mL, which is a 100-fold higher than a generally accepted protective value against tetanus.[25]

CMI Responses

GMVs of PBMC proliferations and CMI response rates of subgroups receiving dTpa ($n = 110$) or Td + pa ($n = 12$) are presented in Table 3. After immunization with dTpa or pa, significant rises in GMVs of proliferation to each of the pertussis antigens (8- to 10-fold for dTpa and 16- to 18-fold for pa) were noted; all but 1 subject showed a positive CMI response to at least 1 of the pertussis antigens. CMI response rates to each of the pertussis antigens were similar following dTpa and pa immunization. The 2 subgroups had similar proliferations induced by pokeweed mitogen (control antigen) before and after immunization (data not shown).

Differences in the Immune Responses

To evaluate the outcome of the immune responses between the subjects in relation to their preimmunization immune status, postimmunization antipertussis antibody and CMI values were compared between subgroups with or without positive antibodies and/or CMI before immunization (Fig 1). Subjects with both positive antipertussis antibodies and CMI before immunization obtained higher values of postimmunization antibodies and CMI compared with those with either negative antibodies or CMI or both before immunization. Strong positive correlations were found between preimmunization and postimmunization anti-PT antibodies ($\gamma = .598$; $P < .001$), anti-PRN antibodies ($\gamma = .748$; $P < .001$), PT-induced CMI ($\gamma = .414$; $P < .001$), and FHA-induced CMI ($\gamma = .556$; $P < .001$), respectively.

DISCUSSION

Earlier studies[13–19] have demonstrated safety, good tolerability, and immunogenicity of acellular pertussis vaccines as booster doses in preschool children and adults. It is well known that adverse reactions to diphtheria-tetanus-pertussis immunization increase with age, additional doses, or both. This is seen not only after boosting with whole cell vaccines but also with acellular vaccines. Schmitt et al[19] have reported recently that local reaction rates after boosting with the Infanrix vaccine exceeded those seen after primary immunization with the same vaccine. Therefore, the quantities of pertussis antigens in the dTpa vaccine used in this study had been reduced to one third of those of the Infanrix. Our results show that the dTpa vaccine is safe and at least as well tolerated as the control-licensed Td vaccine when administered as a 5th-dose booster in 10- to 13-year-old children. Although the percentages of subjects experiencing any adverse reactions were high, the frequencies of all severe adverse reactions were low. Furthermore, the frequencies of severe local reactions were lower in the dTpa group than in the control Td group, which suggests that the perceived clinical relevance of these reactions is low.

We found the dTpa vaccine to be highly immuno-

TABLE 3. Preimmunization and Postimmunization Geometric Mean Proliferation (95% CI) and CMI Response Rates of Groups Receiving dTpa or Td + pa*

Variable	Vaccine Group		
	dTpa ($n = 110$)	Td ($n = 12$)	pa ($n = 12$)
Pertussis toxin			
Pre-GMP† (cpm)	840 (665–1061)	644 (246–1687)	503 (240–1053)
Post-GMP	7969 (6984–9092)	503 (240–1053)	8950 (6087–13161)
Pre-CMI+‡ (%)	46	42	42
Post-CMI+	98	42	100
Filamentous hemagglutinin			
Pre-GMP (cpm)	590 (461–755)	637 (250–1627)	473 (220–1015)
Post-GMP	5903 (5117–6808)	473 (220–1015)	7601 (5144–11232)
Pre-CMI+ (%)	35	33	33
Post-CMI+	96	33	100
Pertactin			
Pre-GMP (cpm)	402 (328–494)	404 (192–851)	324 (163–643)
Post-GMP	3333 (2852–3895)§	324 (163–643)	5578 (4196–7414)§
Pre-CMI+ (%)	24	25	25
Post-CMI+	88	25	100
Spontaneous proliferation			
Pre-GMP (cpm)	223 (189–263)	221 (129–381)	207 (121–352)
Post-GMP	228 (199–261)	207 (121–352)	202 (129–317)

* The pa vaccine was given 1 month after the Td vaccine to the same subjects.
† Pre-GMP indicates preimmunization geometric mean proliferation value.
‡ CMI+ indicates a CMI response was defined positive when antigen-induced proliferation was at least fourfold higher than spontaneous proliferation.
§ $P < .003$ between dTpa and pa groups.

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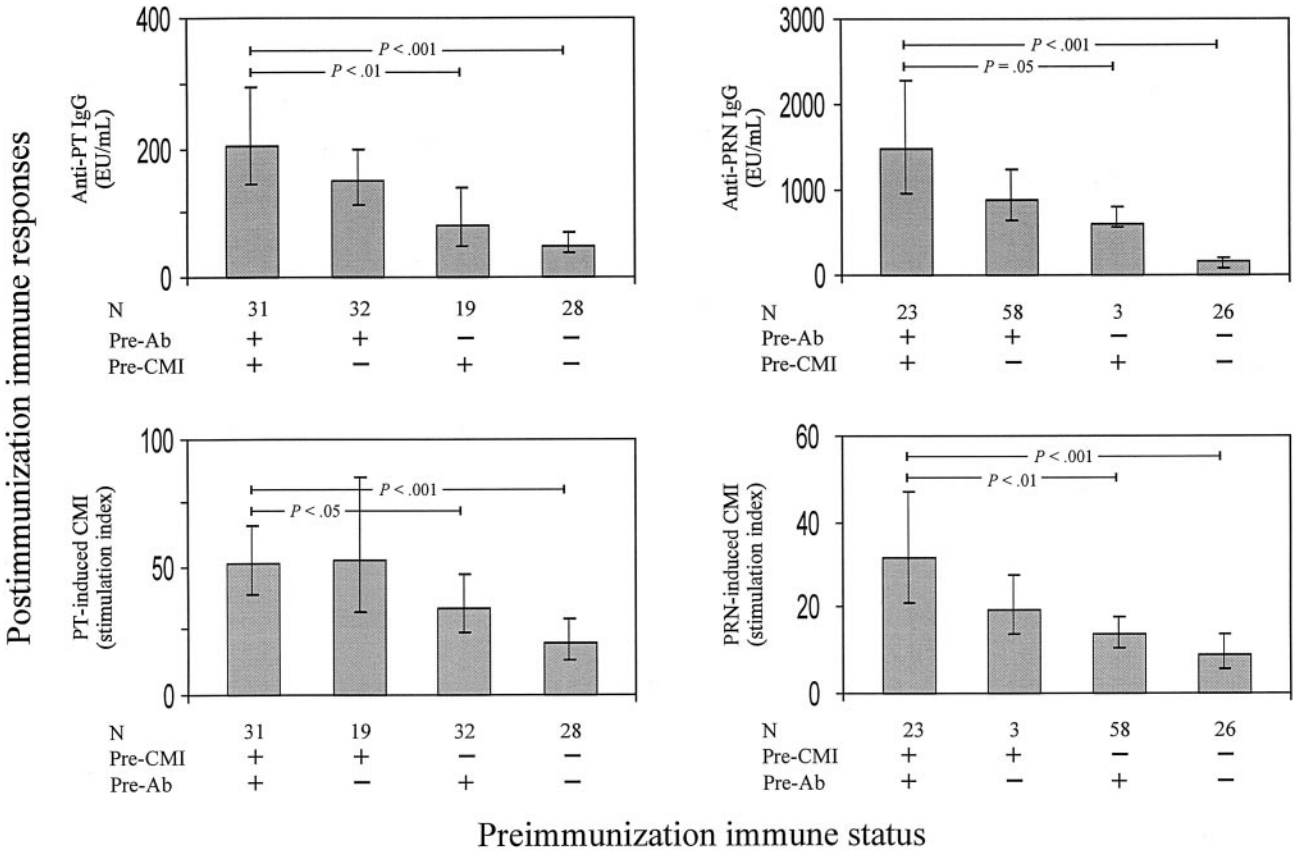

Fig 1. Postimmunization GMVs of antibodies and CMI to PT and PRN in 4 subgroups of vaccinees (immunized with dTpa; $N = 110$) with different immune status before immunization. Bars indicate 95% CI; pre-Ab+, positive preimmunization antibodies (≥5 EU/mL); pre-CMI+, positive preimmunization CMI response (stimulation index ≥4).

genic, indicating that vigorous booster responses can be elicited by reduced quantities of vaccine antigens in previously primed subjects. GMVs achieved for antibodies to pertussis antigens were shown to be twofold to sixfold higher than those after primary immunization with the Infanrix.[11] Moreover, pertussis-specific CMI responses, another important immune parameter, had similar trends compared with those observed after primary immunization with acellular vaccines.[24,26] Similar results have been found in our previous study,[27] using an earlier formulation of the dTpa vaccine, with regard to the pertussis components. However in this previous study, the postimmunization antidiphtheria and antitetanus antibody values were lower than those in the control Td group. The reformulated dTpa used in this study not only has a higher diphtheria toxoid content but both the diphtheria and tetanus toxoids are now from the same source as the Infanrix. With the present data, however, we cannot conclude which of these factors is responsible for the improved immune response.

Preimmunization immune status has been suggested to influence the immunogenicity of a vaccine. With this regard, the correlations between preimmunization and postimmunization antibody and CMI values are interesting. Our results show that the magnitudes of antibody and CMI responses induced by immunization correlate with preimmunization humoral and cellular immune status: subjects with both positive preimmunization antipertussis antibodies and CMI obtained the most vigorous antibody and CMI responses to a dose of the dTpa vaccine.

Given that the dTpa vaccine demonstrated immunogenicity comparable to the licensed Td vaccine, it can be anticipated that protection against diphtheria and tetanus after the dTpa immunization will be at least equivalent to that obtained by the current Td. With regard to protection against pertussis, it is important to note that there is presently no generally accepted laboratory measure of immunity. Because the pertussis components in the dTpa are identical to those in the Infanrix that has been shown to be efficacious against pertussis in efficacy trials,[11,12] demonstration of comparable immune responses induced by the dTpa in adolescents and the Infanrix in infants supports the concept that the dTpa will be efficacious in adolescents.

Because the degree and duration of protection are undetermined, the most appropriate timing for a pertussis vaccine booster in terms of protection is not known. In the absence of such knowledge, it is plausible to recommend pertussis booster immunization in accordance with current recommendations for Td booster immunization. In this regard, it is interesting to note that diphtheria-tetanus-whole cell pertussis vaccine-induced immunity has been shown to wane[28,29] with vaccinees becoming fully susceptible to pertussis 10 to 12 years after immunization. As-

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suming that the persistence of protection provided by acellular pertussis vaccines is in the same range, such an interval may be appropriate for maintenance of immunity against pertussis. A recent study[30] from Sweden, where pertussis has been highly endemic, indicated that an acellular vaccine provided good protection against pertussis for up to 10 years after booster immunization.

One remaining question is whether to introduce the combined dTpa or the pa alone into routine medical practices. With regard to comfort, convenience, and compliance with immunization, the dTpa is very useful, because it provides a well-tolerated and immunogenic alternative to Td vaccine, while offering the additional benefit of protection against pertussis. However, in countries with high immunization coverage, the pa vaccine might be particularly appropriate for populations with a higher risk for exposure to, or transmission of, pertussis, such as parents of young children, child care workers, and health care personnel who already have the Td immunization up to date but who are still lacking immune protection against pertussis.

We conclude that booster immunization of adolescents with an acellular vaccine containing reduced quantities of pertussis antigens in addition to diphtheria and tetanus toxoids induces good responses in both arms of the immune system without an increase in adverse reactions, indicating that the use of acellular pertussis vaccines as a booster for adolescents is feasible. When introducing booster doses in individual countries, factors such as differences in epidemiology of pertussis and immunization programs should be considered.

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