MAJOR ARTICLE

Decennial Administration of a Reduced Antigen Content Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine in Young Adults

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(See the editorial commentary by Cherry, on pages 663–667.)

Background. Booster vaccination against tetanus and diphtheria at 10-year intervals is commonly recommended. Reduced antigen content diphtheria and tetanus toxoids and acellular pertussis (dTpa) vaccines developed for booster vaccination of preschool children, adolescents, and adults are licensed for once-in-a-lifetime use in most countries.

Objective. To evaluate decennial administration of a dTpa vaccine.

Methods. Young adults vaccinated with dTpa or diphtheria and tetanus toxoids followed by acellular pertussis (DT+ap) 1 month later in a clinical trial 10 years previously received 1 dTpa dose. Blood samples were taken before and 1 month after vaccination. Antibody concentrations against vaccine antigens were measured by enzyme-linked immunosorbent assay. Solicited and unsolicited symptoms and serious adverse events were recorded.

Results. Eighty-two individuals were enrolled in the study. In the 75 individuals who had received the dTpa vaccine 10 years previously, prevaccination seroprotection or seropositivity rates were 98.8% (diphtheria), 97.5% (tetanus), 64.6% (pertussis toxoid), 100% (filamentous hemagglutinin), and 96.3% (pertactin). One month after the second booster, all study participants were seroprotected or seropositive against all vaccine antigens. Antibody concentrations increased by a similar magnitude as 10 years previously. During the 4-day follow-up, 9.9% of participants recorded grade 3 pain; 17.3% and 18.5% recorded redness and swelling of 50 mm or larger, respectively; and 8.6% recorded fever (temperature, $\geq$37.5°C). No serious adverse events were considered causally related to the vaccine.

Conclusions. A second dTpa booster was highly immunogenic and well tolerated in this population of young adults. This study supports the use of this vaccine as a decennial booster.

Trial registration. ClinicalTrials.gov identifier: NCT00610168.

Despite long-standing and effective infant immunization programs against the disease caused by *Bordetella pertussis*, pertussis continues to circulate, particularly among older children, adolescents, and adults in whom vaccine-induced or disease-induced immunity has waned [1–3]. Pertussis disease in adults and adolescents causes considerable morbidity [4] but is rarely life-threatening. By contrast, pertussis disease in young infants is associated with a significant rate of complications, including pneumonia, seizure, and encephalopathy, and can be fatal [1]. Because older individuals are the source of infection to unvaccinated infants [5–7], routine vaccination of preschool aged children, adolescents, and sometimes adults against pertussis has been introduced in many countries to prevent devastating pertussis disease in very young infants [8].

Immunization of older populations against pertussis is generally achieved through administration of a single dose of reduced antigen content combined diphtheria and tetanus toxoids and acellular pertussis (dTpa) vaccine. The dTpa vaccine Boostrix (GlaxoSmithKline Biologicals) was first licensed for use in Germany in 1999

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and is indicated for booster vaccination from the age of 4 years. Immunogenicity and tolerability of a single dose of Boostrix have been demonstrated in children [9–11], adolescents [12, 13], and adults [14, 15]. Immunogenicity and tolerability of 3-dose primary immunization with Boostrix in adults has also been evaluated [16]. Efficacy of the acellular pertussis component of the vaccine in preventing pertussis disease (defined as a cough illness lasting >5 days with polymerase chain reaction [PCR] or serologic confirmation) was demonstrated in a National Institutes of Health–sponsored vaccine trial (Acelluar Pertussis Vaccine Trial [APERT]) conducted in the United States at 92% (95% confidence interval [CI], 32%–99%) [17]. Effectiveness of Boostrix administered to 12- to 19-year-old Australian adolescents for laboratory-confirmed pertussis cases (diagnosed by PCR or serologic testings) was 85.4% (95% CI, 83.0%–87.5%) [18].

Although current recommendations only provide for a single vaccination with dTpa in targeted populations, the need for continued boosting against pertussis is lifelong and administration of subsequent dTpa doses has not been evaluated. In this study, we assess the immunogenicity and safety of a second booster dose of dTpa vaccine administered to young adults 10 years after they were originally vaccinated with dTpa at 10–14 years of age [12]. Antibody concentrations before the decennial booster were also assessed.

METHODS

Study design and study participants. In a previous study conducted in Turku, Finland, 510 adolescents 10–14 years of age were randomized to receive a single dose of dTpa vaccine ($n = 450$) or adult diphtheria and tetanus toxoids followed by acellular pertussis (DT+aP) 1 month later ($n = 60$) [19]. Serologic follow-up of this cohort was conducted at 3 and 5 years after vaccination and the results have been published previously [19].

At year 10, the same cohort was invited to return for additional blood sampling and administration of a dTpa booster dose (clinical trial registration no. NCT00610168). This open study was conducted at a single center in Turku, Finland. The study protocol was approved by the Joint Commission on Ethics of the Turku University and the Turku University Central Hospital, and written informed consent was obtained from the study participants before enrollment. The study was conducted in accordance with Good Clinical Practice Guidelines and the Somerset West, 1996 version of the Declaration of Helsinki.

Healthy individuals were enrolled providing they had not experienced illness due to or received any booster vaccination against diphtheria, tetanus, or pertussis since the previous dTpa dose administered at the age of 10–14 years. Pregnant and lactating women were excluded from participation. Women planning to become pregnant or planning to discontinue contraceptive precautions were not enrolled.

Vaccine. Each 0.5-mL dose of dTpa vaccine contained ⩾2 IU of diphtheria toxoid, ⩾20 IU of tetanus toxoid, 8 μg of pertussis toxin, 8 μg of filamentous hemagglutinin, and 2.5 μg of pertactin. The vaccine was administered as a deep intramuscular injection into the deltoid muscle of the nondominant arm.

Assessment of immunogenicity. Blood samples were collected before and 1 month after the booster dose. Antibody concentrations were measured by standardized enzyme-linked immunosorbent assay (ELISA). An antibody concentration of ⩾0.1 IU/mL was defined as evidence of seroprotection against diphtheria and tetanus. Individuals seronegative for diphtheria antibodies by ELISA were retested using the more sensitive in vitro neutralization assay on Vero cells (cutoff for seroprotection, 0.016 IU/mL). Seropositivity against pertussis toxin, filamentous hemagglutinin, and pertactin was defined as an antibody concentration of 5 EL.U/mL or higher.

Assessment of safety. Diary cards were provided to study participants on which to record the presence of pain, redness, and swelling, as well as fever (measured via the axillary route), headache, fatigue, and gastrointestinal symptoms for 4 days (days 0–3) after the booster dose. Study participants were given a measuring tool to assess the magnitude of local reactions. Symptoms of grade 3 intensity were considered severe and were defined as follows: redness and swelling of ⩾50 mm in diameter, temperature higher than 39.0°C, and as preventing normal activity for all other symptoms. Large injection site reactions defined as swelling with a diameter >100 mm, noticeable diffuse swelling, or noticeable increase of limb circumference were evaluated by the investigator. All adverse events, including serious adverse events, occurring within a minimum of 30 days after the booster dose were also recorded. With the exception of solicited symptoms at the injection site that were considered to be related to vaccination, the investigator made an assessment of possible causal relationships between the adverse event and the study vaccine.

Statistical analyses. The primary objective of the study was to demonstrate that a booster dose of dTpa vaccine administered to young adults 10 years after a previous dose of dTpa elicited seroprotective antibody concentrations in 80% or more of individuals against diphtheria and in 90% or more of the individuals against tetanus. With 141 study participants and assuming a seroprotection rate of 98% for both antigens, the study had 98% power to meet both objectives.

The primary analysis of immunogenicity was the according to protocol cohort comprising individuals who complied with protocol procedures and for whom immunogenicity data were available. Seroprotection and seropositivity rates with exact

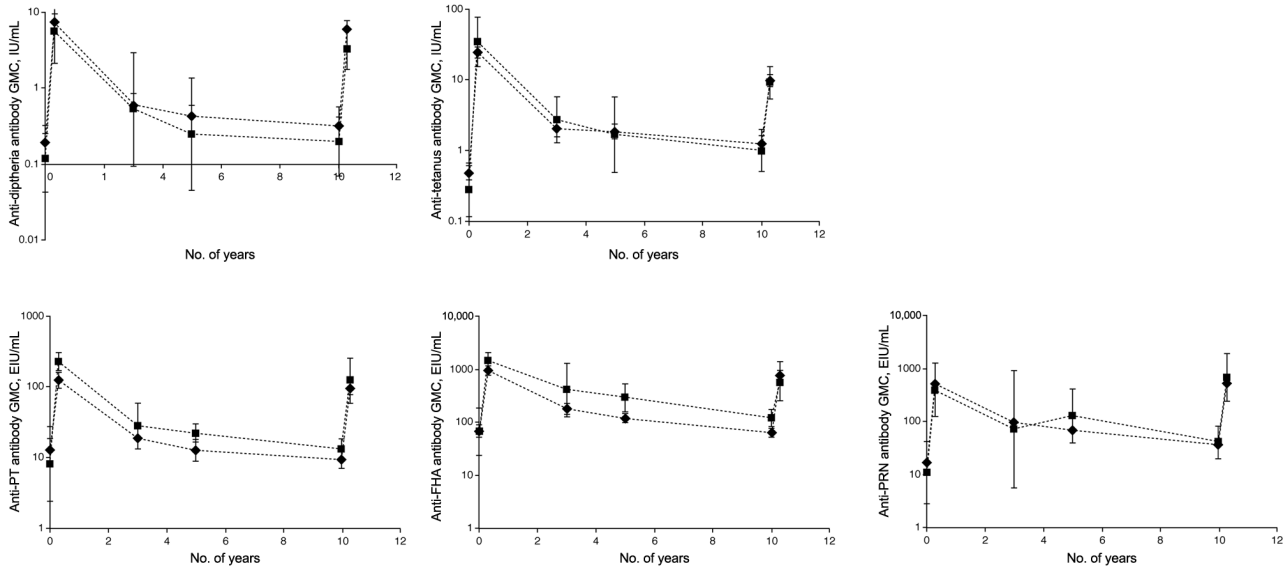

Figure 1. Antibody geometric mean antibody concentrations (GMCs) up to 10 years after initial vaccination and 1 month after the booster dose (according to protocol immunogenicity cohort). *Diamonds,* diphtheria and tetanus toxoids and acellular pertussis group; *squares,* diphtheria and tetanus toxoids followed by acellular pertussis 1 month later group; *vertical lines,* 95% confidence intervals. FHA, filamentous hemagglutinin; PRN, pertactin; PT, pertussis toxin.

95% CIs were calculated for each antigen, along with the geometric mean antibody concentration (GMC).

Booster response rates to pertussis antigens were calculated with 95% CIs. A booster response was defined as the appearance of antibodies in initially seronegative individuals (concentration <5 IU/mL) or a ⩾2-fold increase in prevaccination antibody concentration in initially seropositive study participants. The analysis of safety was performed on the total vaccinated cohort, which comprised all study participants for whom safety data were available.

RESULTS

The study was conducted from 23 January to 30 April 2008. Of 510 individuals enrolled in the original vaccination study 10 years previously, 82 were enrolled to receive the 10-year booster dose. Of these, 75 had received dTpa and 7 had received DT+aP 10 years previously. Reasons for nonparticipation were noneligibility (132 individuals, most of whom were males who had received diphtheria and tetanus or dTpa vaccination during military service), lost to follow-up (140 individuals), and unwillingness to participate (154 individuals). Two individuals had died. Two individuals did not complete the booster study after withdrawing consent. No study participant had been diagnosed as having pertussis illness during the 10-year follow-up.

The mean age (± standard deviation) of the study participants at the time of the decennial booster was 21.1 ± 0.31 years, and 97.6% of participants were white. Because of the ineligibility of many males who had taken part in national military service, most participants (87.8%) were female. The mean time between the previous vaccine dose and the 10-year booster (± standard deviation) was 10.0 ± 0.0 years. No study participants were excluded from the according to protocol immunogenicity analysis.

Immunogenicity

Antibody concentrations 10 years after initial dTpa vaccination. By year 10, antibody GMCs to all antigens had returned to levels close to those observed before the first booster dose 10 years previously (Figure 1). The percentage of study participants with seroprotective antidiphtheria and antitetanus antibody levels remained high (Table 1). In participants previously vaccinated with dTpa, 98.6% had antidiphtheria antibody concentrations consistent with seroprotection (⩾0.016 IU/mL by Vero cell assay or ⩾0.1 IU/mL by ELISA); 97.3% of participants maintained antitetanus antibody concentrations of ⩾0.1 IU/mL.

By year 10, the percentage of dTpa vaccinees with detectable antibody against pertussis toxin had reduced to prevaccination levels (Table 2), whereas all study participants remained seropositive for filamentous hemagglutinin and 96% for pertactin.

Response to the decennial booster dose. One month after the dTpa booster dose, all participants, regardless of initial vaccination group, had seroprotective (⩾0.1 IU/mL by ELISA) antibody levels against diphtheria and tetanus and were seropositive against all pertussis vaccine antigens. The percentage of participants in the dTpa group who reached the higher 1.0-IU/mL cutoff was 93.2% (95% CI, 84.7%–97.7%) for diphtheria and 97.3% (95% CI, 90.5%–99.7%) for tetanus.

Table 1. Longitudinal Antibody Seroprotection Rates and Geometric Mean Antibody Concentrations (GMCs) against Diphtheria and Tetanus for 10 Years after Vaccination and 1 Month after Receipt of a Booster Dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis (dTpa) Vaccine

		dTpa group	
Timing	No. of subjects[a]	Seroprotection rate, % (95% CI)	GMC (95% CI)
Diphtheria (ELISA)			
Before initial dTpa vaccination 10 years ago	74	70.3 (58.5–80.3)	0.2 (0.1–0.2)
Month 1	75	100 (95.2–100)	7.4 (5.8–9.4)
Year 3	46	93.5 (82.1–98.6)	0.6 (0.4–0.8)
Year 5	52	90.4 (79.0–96.8)	0.4 (0.3–0.6)
Year 10 prebooster	74	82.4 (71.8–90.3)	0.3 (0.2–0.4)
Year 10 postbooster ELISA and Vero	74	98.6 (92.7–100)	
Year 10 postbooster	73	100 (95.1–100)	6.0 (4.7–7.7)
Tetanus (ELISA)			
Before initial dTpa vaccination 10 years ago	75	96.0 (88.8–99.2)	0.5 (0.4–0.6)
Month 1	75	100 (95.2–100)	24.2 (20.2–29.1)
Year 3	46	100 (92.3–100)	2.0 (1.6–2.6)
Year 5	52	100 (93.2–100)	1.8 (1.4–2.3)
Year 10 prebooster	74	97.3 (90.6–99.7)	1.2 (1.0–1.6)
Year 10 postbooster	73	100 (95.1–100)	9.6 (8.0–11.5)

NOTE. Seroprotection is defined as an antibody concentration of 0.1 IU/mL or higher. Enzyme-linked immunosorbent assay (ELISA) and Vero refers to the percentage of study participants with seroprotective diphtheria antibody levels by either ELISA or Vero cell neutralization assay (antibody concentration ⩾0.1 IU/mL or ⩾0.016 IU/mL, respectively). Year 10 prebooster and postbooster indicate before and 1 month after vaccination at year 10. CI, confidence interval.

[a] No. of study participants with data available at that time point.

The primary objective of the study was achieved: the lower limit of the 95% CIs of the percentage of participants who reached the 0.1-IU/mL cutoff was above the prespecified limit for both diphtheria and tetanus.

In the dTpa group, a booster response was observed in 98.6% of participants against pertussis toxin, 97.3% against filamentous hemagglutinin, and 93.2% against pertactin. One nonresponder to pertussis toxin had a prevaccination antipertussis toxin antibody concentration of 19 IU/mL. Two nonresponders to filamentous hemagglutinin had prevaccination anti–filamentous hemagglutinin antibody concentrations of at least 243 IU/mL, and 5 nonresponders to pertactin had a prevaccination concentration of at least 118 IU/mL. With the exception of 1 study participant, all nonresponders had fold increases of 1.2–1.9 after the booster dose. Antibody GMCs increased by 18-fold for diphtheria antibodies, 7-fold for tetanus, and 10-, 12-, and 15-fold for pertussis toxin, filamentous hemagglutinin, and pertactin, respectively. The responses in the DT+aP group were within the same range as the dTpa group. The magnitude of the postvaccination GMC against each vaccine antigen was within the same range as observed after the first booster dose 10 years previously (Figure 1).

Reactogenicity of the Decennial Booster Dose

Symptoms at the injection site were reported by most study participants (Figure 2). In total, 93.8% of participants reported pain after vaccination. However, grade 3 pain was reported by only 9.9% of study participants. Redness and swelling were reported by >50% of participants and grade 3 redness and swelling (⩾50 mm) by 17.3% and 18.5% of participants, respectively. Two participants reported a large local swelling reaction: one was localized to the injection site and the other was a diffuse swelling of the injected limb. Neither affected an adjacent joint.

Fatigue was the most commonly reported general symptom considered to be related to vaccination, reported by 44.4% of participants. Fever after vaccination was uncommon (8.6% of participants). Grade 3 fatigue was reported by 2.5% of participants. One participant recorded a grade 3 gastrointestinal symptom.

Within 30 days of the booster dose, 26 study participants (31.7%) reported other symptoms, of whom 13 reported 21 symptoms considered by the investigator to be related to vaccination. Two-thirds of these related symptoms (14 of 21 cases) were injection site reactions, including injection site hema-

Table 2. Longitudinal Antibody Seropositivity Rates against Pertussis Antigens for 10 Years after Vaccination and 1 Month after Receipt of a Booster Dose of Diphtheria and Tetanus Toxoids and Acellular Pertussis (dTpa) Vaccine

Timing	No. of subjects[a]	dTpa group	
		Seropositivity rate, % (95% CI)	GMC (95% CI)
Pertussis toxin			
Before initial dTpa vaccination 10 years ago	74	62.2 (50.1–73.2)	12.3 (8.5–17.7)
Month 1	75	97.3 (90.7–99.7)	118.5 (89.9–156.2)
Year 3	45	84.4 (70.5–93.5)	18.3 (12.8–26.3)
Year 5	48	72.9 (58.2–84.7)	12.3 (8.7–17.3)
Year 10 prebooster	75	61.3 (49.4–72.4)	9.1 (6.9–11.9)
Year 10 postbooster	73	100 (95.1–100)	90.3 (73.9–110.5)
Filamentous hemagglutinin			
Before initial dTpa vaccination 10 years ago	74	98.6 (92.7–100)	67.7 (52.0–88.2)
Month 1	75	100 (95.2–100)	945.3 (782.7–1141.7)
Year 3	46	100 (92.3–100)	177.5 (142.1–221.8)
Year 5	52	100 (93.2–100)	121.4 (100.0–147.4)
Year 10 prebooster	75	100 (95.2–100)	63.8 (53.1–76.8)
Year 10 postbooster	73	100 (95.1–100)	793.4 (670.3–939.2)
Pertactin			
Before initial dTpa vaccination 10 years ago	75	82.7 (72.2–90.4)	17.1 (12.2–24.1)
Month 1	75	100 (95.2–100)	513.4 (370.0–712.2)
Year 3	46	100 (92.3–100)	99.3 (67.9–145.3)
Year 5	52	98.1 (89.7–100)	72.6 (48.7–108.3)
Year 10 prebooster	75	96.0 (88.8–99.2)	36.9 (27.7–49.2)
Year 10 postbooster	73	100 (95.1–100)	548.1 (456.9–657.5)

NOTE. Seropositivity against pertussis antigens is defined as an antibody concentration of ⩾5 EL.U/mL. CI, confidence interval; GMC, geometric mean antibody concentration.

[a] No. of study subjects with data available at that time point.

toma, induration, pruritus, warmth, and rash. One serious adverse event was reported during the study (hyperventilation) that was considered unrelated to vaccination. During the study, 3 individuals (3.7%) received medical attention for an adverse event after vaccination. All 3 occurrences were caused by influenza infection, which was assessed as unrelated to vaccination.

DISCUSSION

A booster dose of dTpa was immunogenic in young adults boosted with the same vaccine 10 years earlier. To our knowledge, this is the first study of a cohort assessed periodically for 10 years after vaccination with dTpa and given a second dose 10 years after the first dose. We showed that 10 years after vaccination with dTpa during adolescence pertussis antibody levels had decreased to or approached prevaccination levels. The presence of antibodies against pertussis toxin, pertactin, and fimbriae has been linked to protection against pertussis disease in children [20, 21]. A household contact study of monovalent pertussis toxin vaccine demonstrated a relationship between anti–pertussis toxin antibody concentrations and disease severity in children [22]. We observed detectable anti–pertussis toxin antibodies in only 64.6% of study participants overall. Although anti–pertussis toxin antibodies are not the only factor contributing to protection against pertussis, these results suggest increasing susceptibility to pertussis disease over time as vaccine-induced immunity wanes, warranting administration of additional booster doses.

Although most individuals had seroprotective antibody concentrations against diphtheria and tetanus before vaccination, booster responses to vaccination were evident, with increases in antibody GMCs against diphtheria and tetanus after the decennial dose.

Acellular pertussis vaccines have a safety profile that is characterized by somewhat higher rates of local symptoms and lower rates of systemic symptoms after a booster dose, compared with primary vaccination doses [23]. In line with these characteristics, we observed that most individuals reported local

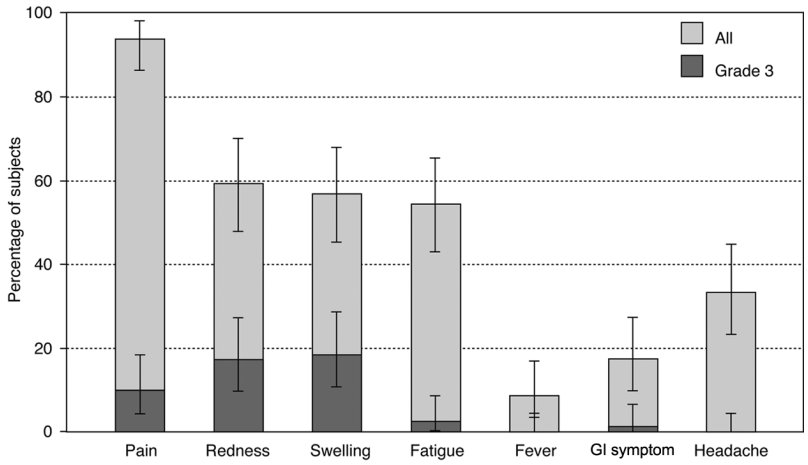

Figure 2. Incidence of solicited local and general symptoms within 4 days after the diphtheria and tetanus toxoids and acellular pertussis (dTpa) booster dose (total vaccinated cohort, 81 subjects). Data from all study participants (dTpa and diphtheria and tetanus toxoids groups). GI, gastrointestinal.

symptoms at the injection site after the decennial booster dose and 29.3% of individuals experienced a local adverse event of grade 3 intensity. Local reactions, but not general reactions, were reported somewhat more frequently after the decennial booster compared with the dose administered 10 years previously [12]. Grade 3 pain was reported as frequently (in 9.9% of all individuals) as after diphtheria and tetanus vaccine in adolescents (10%) [12]. Notably, no study participants required medical attention for local adverse events occurring after vaccination, suggesting that these adverse events were of minor clinical importance. The incidence of local reactions was within the range reported for acellular pertussis booster doses across different age groups [24, 25].

Systemic symptoms were less commonly reported, with grade 3 general symptoms (fatigue) reported by only 2 participants. Overall, the reactogenicity and safety profile of the decennial booster dose resembled that of the dTpa or diphtheria and tetanus vaccine administered 10 years previously [12] and the dTpa vaccine administered as a booster dose to adults [26].

One limitation of the study is the disproportionate representation of female participants. This was a result of the ineligibility of most males who had previously participated because of receipt of diphtheria and tetanus vaccination during national military service. Sex differences in immune responses and reactogenicity reporting have been previously described in adults after dTpa vaccination, with females characterized by lower immune responses and higher reactogenicity reporting than males [14]. An exploratory post hoc analysis according to sex in our study tended to support these previous observations (data not shown), although the number of males was too small to draw firm conclusions.

Booster doses of many vaccines, including acellular pertussis vaccines, may be followed by entire limb swelling, sometimes referred to as extensive swelling reactions. Two large local reactions were observed in this study, only one of which was a diffuse swelling reaction. Neither swelling reaction involved an adjacent joint. The observed incidence of proximal limb swelling of 1.2% (1 of 82) is below the reported range for booster doses of acellular pertussis–based vaccines in children of 2%–6% [27]. The tolerability of repeated dTpa doses was also demonstrated in a study of adults aged ⩾40 years with no history of diphtheria or tetanus vaccination for at least 20 years. In these study participants, 3 priming doses of dTpa (Boostrix) or diphtheria and tetanus toxoids administered at 0, 1, and 6 months were not associated with increasing local reactogenicity or systemic symptoms, and large swelling reactions were uncommon and comparable in dTpa and diphtheria and tetanus vaccine recipients [16].

Finland and other countries that have implemented pertussis booster schedules for adolescents and adults currently recommend a single dTpa booster dose, followed by regular diphtheria and tetanus boosters, commonly at intervals of 10 years. To date, there are no recommendations for recurrent, lifelong booster vaccinations against pertussis. Linking a regular pertussis booster with current recommendations for decennial vaccination against diphtheria and tetanus requires no additional injection when dTpa vaccines are used. Implementation of dTpa at the decennial booster dose would, over time, improve coverage against pertussis in adults and contribute to preventing serious pertussis disease in susceptible infants. Predictions of antibody decay from adults vaccinated with an investigational standalone acellular pertussis vaccine also support a 10-year interval between pertussis booster doses [28, 29].

Booster vaccination against pertussis throughout life may substantially reduce or even eliminate pertussis circulation [3, 30]. Prevention of disease in adults and adolescents will halt

transmission of pertussis to vulnerable populations. We have shown that 10 years after vaccination with dTpa, antibodies against pertussis approach levels observed before vaccination, suggesting that 10 years represents an appropriate interval for a pertussis booster dose. A decennial dTpa booster dose was highly immunogenic, with an acceptable safety profile in this population of young adults. This study supports the replacement of the decennial diphtheria and tetanus booster with a decennial dose of dTpa.

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