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Decennial administration in young adults of a reduced-antigen content diphtheria, tetanus, acellular pertussis vaccine containing two different concentrations of aluminium

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ABSTRACT

Background: Regular booster vaccination might be necessary throughout life to protect against pertussis infection. Nevertheless the duration of protection after booster vaccination remains unclear. In this study, antibody persistence up to 10 years after previous vaccination of adolescents ($N = 478$) with combined reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine (dTpa, *Boostrix*™, GlaxoSmithKline Belgium) containing 0.5 mg, 0.3 mg or 0.133 mg of aluminium was assessed. The immunogenicity, reactogenicity and safety of a decennial booster dTpa dose were also investigated.

Methods: Young adults vaccinated as adolescents in the initial booster study were invited to participate in an assessment of antibody persistence at years 8.5 and 10, and to receive a dTpa booster dose at year 10 with immunogenicity assessment one month later. Those who originally received the 0.5 mg or 0.3 mg formulations received the same vaccine at year 10. Those in the 0.133 mg group received the 0.5 mg formulation. Reactogenicity and safety endpoints were captured until 30 days after booster vaccination.

Results: Prior to the decennial booster at year 8.5 and year 10, all participants had seroprotective antibodies for diphtheria (ELISA or neutralisation assay) and tetanus. At least 77.8% were seropositive for anti-pertussis toxin (PT) antibodies at year 8.5 and 82.8% at year 10. All participants were seropositive for antibodies for filamentous haemagglutinin and pertactin at both time points. The decennial booster dose induced robust increases in antibody GMCs to all antigens. The post-booster anti-PT geometric mean concentration was 82.5 EL.U/ml (95%CI 67.0–101.6) and 124.0 (103.5–148.5) in the 0.3 mg and 0.5 mg groups, respectively. The reactogenicity and safety profile of the decennial booster dose was consistent with the known safety profile of dTpa. No serious adverse events were reported.

Conclusions: Decennial booster vaccination with either of the two licensed formulations of dTpa was highly immunogenic and well tolerated in young adults. Either formulation could be confidently used as a decennial booster.

This study is registered at www.clinicaltrials.gov NCT01147900

Abbreviations: AE, adverse event; ATP, according to protocol; BR, booster response; CI, confidence interval; DT, diphtheria toxoid; dTpa, reduced antigen content diphtheria-tetanus-acellular pertussis vaccine; ELISA, enzyme-linked immunosorbent assays; FHA, filamentous haemagglutinin; GMC, geometric mean antibody concentration; PRN, pertactin; PT, pertussis toxoid; SAE, serious adverse event; TT, tetanus toxoid.

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1. Introduction

Routine infant vaccination against pertussis has decreased severe disease and death due to pertussis in children, but outbreaks with fatal cases in infants too young to be vaccinated continue to occur in countries with high pertussis vaccination coverage [1,2]. Neither whole-cell (Pw) vaccines, acellular vaccines nor pertussis infection provide life-long immunity against re-infection. As a result, *Bordetella pertussis* continues to circulate in vaccinated communities. In older children, adolescents and adults, pertussis typically causes a prolonged cough illness which may be associated with complications and a substantial economic cost [3,4]. Older age groups are the primary source of pertussis transmission to infants who are at greatest risk of severe pertussis disease and death [5–7]. Therefore, while immunization of older individuals against pertussis can prevent disease [8], immunization of adults may also prevent transmission to vulnerable infants [9]. Booster vaccination of adults is achieved using combined reduced-antigen content diphtheria-tetanus-acellular pertussis (dTpa) vaccines. While a number of countries recommend single pertussis booster vaccinations for adolescents, healthcare workers, and immunization during pregnancy and/or cocoon immunization, few recommend decennial pertussis booster doses throughout life [10].

A single serological correlate predictive of protection against pertussis has not been identified [11], hampering estimation of the duration of protection after pertussis booster vaccination. Decennial diphtheria-tetanus (dT) booster vaccination is recommended in many countries, and the Consensus on Pertussis Booster Vaccination in Europe Initiative recommends regular pertussis boosting of adults, achievable by replacing dT boosters with dTpa in national schedules [12].

Boostrix™ (GlaxoSmithKline Vaccines) is a dTpa vaccine indicated for booster vaccination from 4 years of age [13]. There are two licensed *Boostrix*™ formulations that differ only in aluminium content: the formulation licensed in the United States contains 0.3 mg aluminium whereas the formulation licensed in Europe and elsewhere contains 0.5 mg. The immunogenicity and safety of the licensed 0.3 mg and 0.5mg-aluminium dTpa vaccines have been demonstrated in clinical trials in children [14,15], adolescents [16–18], and adults [19,20], including adults aged ≥65 years [21,22].

The immunogenicity, reactogenicity and safety of each formulation was initially established in a randomised comparative study [18] in which adolescents between 10–18 years of age who had received primary vaccination against diphtheria, tetanus and Pw were randomised to receive a single dose of dTpa containing either 0.5 mg, 0.3 mg or 0.133 mg aluminium. While all of the study vaccines were immunogenic with similar reactogenicity and safety profiles, the study concluded that there was a positive effect of aluminium content on anti-pertussis toxin (PT) antibody concentrations [18]. In this extension study we investigated antibody persistence at 8.5 and 10 years after previous vaccination of adolescents with dTpa (0.5 mg, 0.3 mg or 0.133 mg formulations). We also assessed the immunogenicity, reactogenicity and safety of a decennial dTpa booster dose.

2. Methods

2.1. Study design and participants

This open, phase IV antibody persistence and vaccination study (113055, www.clinicaltrials.gov NCT01147900) was conducted in three centres in Belgium between 15 June 2010 and 8 May 2012. Study participants who had been vaccinated with dTpa (0.5 mg, 0.3 mg or 0.133 mg aluminium formulations) in the previous booster study [18], were invited to take part in the persistence and booster phases of this follow-up study. Antibody persistence was assessed 8.5 years and 10 years after the first dTpa booster dose. Participants found to be seronegative for anti-diphtheria or anti-tetanus antibodies at year 8.5 were to be offered a booster dose of dTpa vaccine at that time.

A second dTpa booster dose was administered at year 10. Participants in the 0.5 mg and 0.3 mg aluminium groups received a booster dose of the same vaccine formulation they had received 10 years earlier. Participants who had previously received the investigational 0.133 mg formulation received a booster dose of dTpa containing 0.5 mg aluminium.

The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was reviewed and approved by the ethics committees at all participating sites. Written informed consent was given by all participants at enrolment.

Adults were excluded from participating if they had received booster vaccination or had experienced disease due to diphtheria, tetanus, or pertussis since participation in the earlier study. Because the majority of individuals had been vaccinated against meningococcal disease using conjugated meningococcal vaccines, the study protocol was amended to allow the inclusion of subjects who had received protein-conjugate vaccines that contained diphtheria toxoid (DT) or tetanus toxoid (TT) as carrier proteins. Exclusion criteria for the booster phase are provided in the Supplementary material.

2.2. Study vaccines

The dTpa vaccines were manufactured by GlaxoSmithKline Vaccines. Each 0.5 ml dose contained ≥2 international units (IU) of DT and ≥20 IU of TT, 8 μg of PT, 8 μg of filamentous haemagglutinin (FHA), 2.5 μg of pertactin (PRN) and either 0.5 mg or 0.3 mg aluminium as salts, and was preservative-free. dTpa was administered intramuscularly into the non-dominant deltoid muscle, using a needle at least 2.54 cm in length and 22–25 gauge.

2.3. Immunogenicity assessment

Blood samples were collected from all subjects available at years 8.5 and/or 10 for the assessment of antibody persistence. A third blood sample was collected one month after the booster dose. Samples were stored at −20 °C until shipment to GlaxoSmithKline's laboratories in Belgium and Quebec for testing.

Anti-diphtheria and anti-tetanus IgG antibody concentrations were measured by ELISA with an assay cut-off of 0.1 IU/ml [23,24]. Samples seronegative for anti-diphtheria antibodies by ELISA were re-tested using the more sensitive in vitro neutralisation assay on Vero cells. The cut-off for the Vero-cell assay was previously validated at 0.016 IU/ml and applied from year 8.5 onwards. After optimization and re-validation of the assay, the cut-off was decreased to 0.004 IU/ml, i.e., below the minimal protective threshold of 0.01 IU/ml.

For diphtheria and tetanus, concentrations equal to or above the ELISA assay cut-off were considered to be indicative of seroprotection. Using the optimised neutralisation assay for diphtheria, antibody concentrations of ≥0.01 IU/ml were considered to be protective [24].

Anti-PT, anti-FHA and anti-PRN IgG antibody concentrations were measured by ELISA. The assay cut-off was 5 EL.U/ml defining seropositivity [25,26].

2.4. Assessment of reactogenicity and safety

The occurrence of redness, swelling and pain at the injection site, and fatigue, fever (temperature ≥37.5 °C, oral or axillary routes),

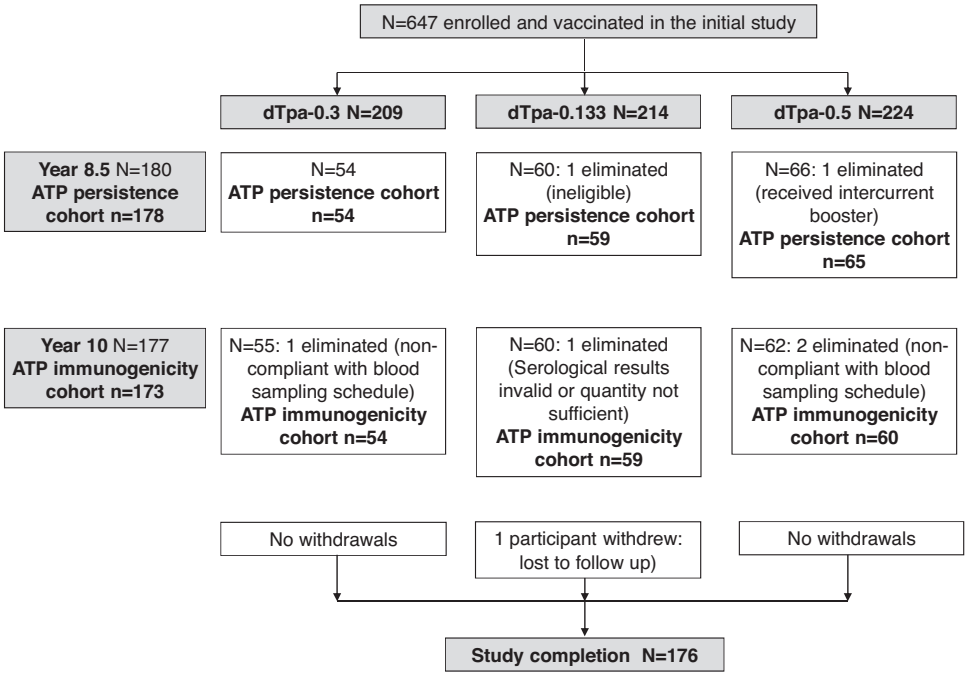

Fig. 1. Subject flow.

gastrointestinal symptoms and headache, was recorded on the day of vaccination and for three subsequent days (4-day follow-up).

Participants with large swelling reactions (diameter >100 mm, diffuse swelling or noticeable increase in limb circumference) at the injection site were asked to contact study personnel and return to the study centre for assessment. All other adverse events (AEs) were recorded for 30 days after vaccination (31-day follow up). Serious adverse events (SAEs) related to study participation or to any GlaxoSmithKline medication, and all fatal SAEs were recorded during the entire study period. All local symptoms were considered to be vaccine related. The investigator assessed the relationship of all other symptoms to vaccination.

2.5. Statistical analyses

Analyses were performed using SAS® software version 9.2 (SAS Institute Inc., Cary, NC, United States) and StatXact-8.1 procedure on SAS®.

The primary analysis of antibody persistence at year 8.5 was done on the according-to-protocol (ATP) persistence cohort, which included eligible participants with serological results available at year 8.5. The analysis of persistence and booster immunogenicity at year 10 was conducted on the year 10 ATP immunogenicity cohort, which included eligible participants with serological results available at the one-month post-booster time point.

Seroprotection/seropositivity rates were calculated for each treatment group with exact 95% confidence intervals (CI). Booster response (BR) rates to pertussis antigens were calculated using two pre-defined definitions (see Table 3 footnote) used in previous studies of dTpa (note that different definitions of a booster response are accepted in the United States as compared to other countries). Results according to both definitions are provided for ease of comparison with other studies. Additional longitudinal analyses were conducted using repeated measurement technique on immunogenicity data obtained between the two booster vaccinations in order to evaluate potential bias related to missing data.

3. Results

3.1. Study subjects

Of 478 adolescents who participated in the booster study 10 years previously, 180 returned at year 8.5, and 177 returned and were vaccinated at year 10 (Fig. 1). Treatment groups were similar in age at each follow-up time point (Table 1).

By year 10, 77.4% ($n = 137$) of participants had received vaccination with a CRM (modified diphtheria toxoid)-conjugated meningococcal vaccine and 7.9% ($n = 14$) had received a TT-conjugated meningococcal vaccine since the initial dTpa booster dose. Most meningococcal vaccines were given 1 month after the initial dTpa study vaccination (at the time of blood sampling).

The most common reasons for non-participation in this extension study were: lost to follow-up ($n = 92$), unwilling to participate (not due to an AE, $n = 88$) or ineligible ($n = 30$). No participant required a booster dose of dTpa at year 8.5.

3.2. IgG antibody persistence at year 8.5 and year 10

Except for one participant in the dTpa-0.3 group, all other study participants had anti-diphtheria concentrations ≥0.1 IU/ml by ELISA at year 8.5, with no change observed at year 10. The single participant with ELISA concentrations ≤0.1 IU/ml was seroprotected at each time point as assessed using the in vitro neutralisation assay (Table 2).

The percentage of participants with anti-diphtheria concentrations ≥1.0 IU/ml decreased between year 8.5 and year 10 in each treatment group, and was 59.3% in the dTpa-0.133 group, 44.4% in the dTpa-0.3 group, and 33.3% in the dTpa-0.5 group at year 10 (Table 2). Anti-diphtheria GMCs also decreased over time but remained higher than levels prior to the first dTpa dose (Fig. 2).

All participants maintained anti-tetanus concentrations of ≥0.1 IU/ml until year 10. The percentage with anti-tetanus concentrations ≥1.0 IU/ml ranged between 84.7% and 88.9% in each group at years 8.5 and 10. Anti-tetanus antibody GMCs were similar at

Table 1
Demographic characteristics (ATP cohort for persistence at year 8.5 and ATP immunogenicity cohort at year 10).

		Year 8.5			Year 10		
		dTpa-0.3 *N* = 54	dTpa-0.133 *N* = 59	dTpa-0.5 *N* = 65	dTpa-0.3 *N* = 54	dTpa-0.133 *N* = 59	dTpa-0.5 *N* = 60
Age (years)	Mean (SD)	22.4 (1.46)	22.3 (1.21)	22.3 (1.18)	23.5 (1.45)	23.4 (1.21)	23.4 (1.15)
	Range	20–27	19–27	19–25	20–28	20–28	20–26
Gender	Female n (%)	29 (53.7)	33 (55.9)	39 (60.0)	28 (51.9)	30 (50.8)	35 (58.3)
	Male n (%)	25 (46.3)	26 (44.1)	26 (40.0)	26 (48.1)	29 (49.2)	25 (41.7)

SD = standard deviation.

years 8.5 and 10, but were lower than levels observed after the first booster dose (Fig. 2).

In each treatment group, seropositivity rates for anti-PT antibodies before the decennial booster dose were between 82.8% and 86.2%, while all participants remained seropositive for antibodies for FHA and PRN (Table 2). GMCs for PT, FHA and PRN all decreased over time after the initial booster dose (Fig. 2). Consistent with findings after the first dTpa dose 10 years earlier, the persisting anti-PT

Table 2
Antibody persistence (ELISA) to year 10 and immunogenicity of the booster dose (ATP cohort for persistence at year 8.5 and ATP immunogenicity cohort at year 10).

Antibody	Group	Timing	*N*[a]	≥0.1 IU/ml		≥1.0 IU/ml	
				N[b]	% (95% CI)[c]	*N*[b]	% (95% CI)
Anti-diphtheria	dTpa-0.3	Year 8.5	54	53[d]	98.1 (90.1; 100)	29	53.7 (39.6; 67.4)
		Year 10 pre	54	53[d]	98.1 (90.1; 100)	24	44.4 (30.9; 58.6)
		Year 10 post	54	54	100 (93.4; 100)	54	100 (93.4; 100)
	dTpa-0.133	Year 8.5	59	59	100 (93.9; 100)	41	69.5 (56.1; 80.8)
		Year 10 Pre	59	59	100 (93.9; 100)	35	59.3 (45.7; 71.9)
		Year 10 post	59	59	100 (93.9; 100)	58	98.3 (90.9; 100)
	dTpa-0.5	Year 8.5	65	65	100 (94.5; 100)	26	40.0 (28.0; 52.9)
		Year 10 pre	60	60	100 (94.0; 100)	20	33.3 (21.7; 46.7)
		Year 10 post	60	60	100 (94.0; 100)	60	100 (94.0; 100)
Anti-Tetanus	dTpa-0.3	Year 8.5	54	54	100 (93.4; 100)	48	88.9 (77.4; 95.8)
		Year 10 pre	54	54	100 (93.4; 100)	47	87.0 (75.1; 94.6)
		Year 10 post	54	54	100 (93.4; 100)	54	100 (93.4; 100)
	dTpa-0.133	Year 8.5	59	59	100 (93.9; 100)	50	84.7 (73.0; 92.8)
		Year 10 Pre	59	59	100 (93.9; 100)	51	86.4 (75.0; 94.0)
		Year 10 post	59	59	100 (93.9; 100)	58	98.3 (90.9; 100)
	dTpa-0.5	Year 8.5	65	65	100 (94.5; 100)	57	87.7 (77.2; 94.5)
		Year 10 pre	60	60	100 (94.0; 100)	52	86.7 (75.4; 94.1)
		Year 10 post	60	60	100 (94.0; 100)	60	100 (94.0; 100)
≥5 EL.U/ml					**≥20 EL.U/ml**		
Anti-PT	dTpa-0.3	Year 8.5	54	42	77.8 (64.4; 88.0)		–
		Year 10 pre	52	44	84.6 (71.9; 93.1)	17	32.7 (20.3; 47.1)
		Year 10 post	54	54	100 (93.4; 100)	54	100 (93.4; 100)
	dTpa-0.133	Year 8.5	59	48	81.4 (69.1; 90.3)		–
		Year 10 pre	58	48	82.8 (70.6; 91.4)	24	41.4 (28.6; 55.1)
		Year 10 post	59	59	100 (93.9; 100)	58	98.3 (90.9; 100)
	dTpa-0.5	Year 8.5	65	60	92.3 (83.0; 97.5)		–
		Year 10 pre	58	50	86.2 (74.6; 93.9)	25	43.1 (30.2; 56.8)
		Year 10 post	60	60	100 (94.0; 100)	60	100 (94.0; 100)
Anti-FHA	dTpa-0.3	Year 8.5	54	54	100 (93.4; 100)		–
		Year 10 pre	54	54	100 (93.4; 100)	53	98.1 (90.1; 100)
		Year 10 post	53	53	100 (93.3; 100)	53	100 (93.3; 100)
	dTpa-0.133	Year 8.5	59	59	100 (93.9; 100)		–
		Year 10 pre	59	59	100 (93.9; 100)	58	98.3 (90.9; 100)
		Year 10 post	59	59	100 (93.9; 100)	59	100 (93.9; 100)
	dTpa-0.5	Year 8.5	62	62	100 (94.2; 100)		–
		Year 10 pre	59	59	100 (93.9; 100)	59	100 (93.9; 100)
		Year 10 post	60	60	100 (94.0; 100)	60	100 (94.0; 100)
Anti-PRN	dTpa-0.3	Year 8.5	54	54	100 (93.4; 100)		–
		Year 10 pre	54	54	100 (93.4; 100)	52	96.3 (87.3; 99.5)
		Year 10 post	53	53	100 (93.3; 100)	53	100 (93.3; 100)
	dTpa-0.133	Year 8.5	59	59	100 (93.9; 100)		–
		Year 10 pre	59	59	100 (93.9; 100)	58	98.3 (90.9; 100)
		Year 10 post	59	59	100 (93.9; 100)	59	100 (93.9; 100)
	dTpa-0.5	Year 8.5	65	65	100 (94.5; 100)		–
		Year 10 pre	59	59	100 (93.9; 100)	57	96.6 (88.3; 99.6)
		Year 10 post	60	60	100 (94.0; 100)	60	100 (94.0; 100)

[a] *N* = number of subjects with both pre- and post-vaccination results available.
[b] *n*/% = number/percentage of subjects which reached cut-off level.
[c] 95% CI = Exact 95% confidence interval.
[d] one subject seronegative for anti-diphtheria antibodies by ELISA had antibodies ≥0.016 IU/ml at year 8.5 and ≥0.01 IU/ml at year 10 when re-tested using the in vitro neutralisation assay.

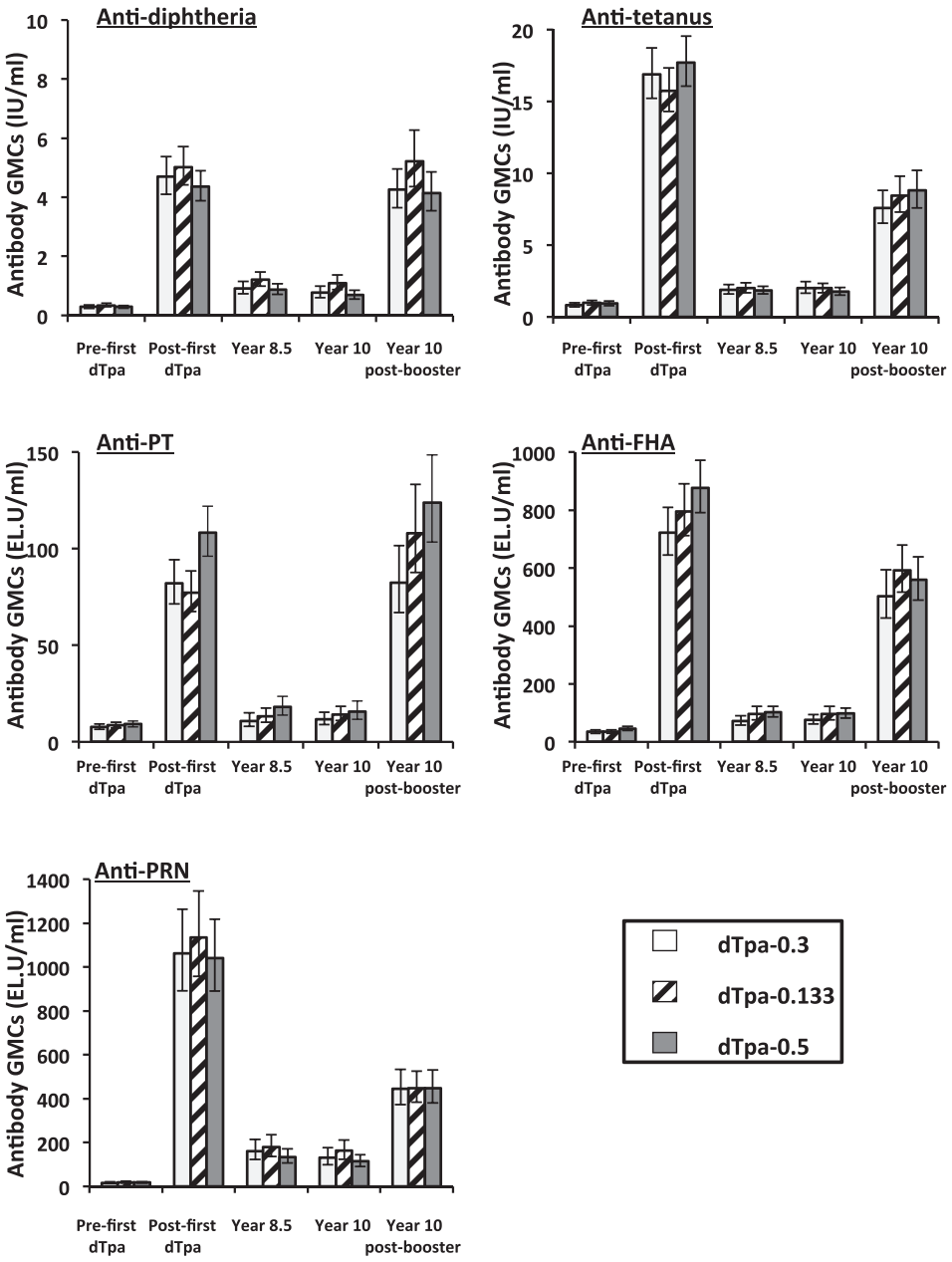

Fig. 2. Antibody geometric mean concentrations (GMCs) over time: all subjects who participated in the initial booster vaccination study (study 029 ATP immunogenicity cohort) and those who received the decennial booster dose (year 10 ATP immunogenicity cohort).
Footnote: vertical lines indicate 95% CIs.

GMCs at years 8.5 and 10 were observed to be numerically higher in the dTpa-0.5 group.

3.2.1. *Sensitivity analysis*

GMCs estimated at years 8.5 and 10 using the repeated measurements model were close to observed values in each treatment group (data not shown). This indicates that the analyses of antibody persistence performed at years 8.5 and 10 were not unduly affected by subjects who dropped out.

3.3. *Response to booster vaccination*

One month after the decennial dTpa booster dose all participants had anti-diphtheria and anti-tetanus concentrations ≥0.1 IU/ml, and between 98.3% and 100% had concentrations ≥1.0 IU/ml (Table 2). In each group, anti-diphtheria and anti-tetanus GMCs increased between 3.8- and 6.0-fold.

All participants were seropositive for anti-PT antibodies one month after the booster dose (Table 2). In each group GMCs increased by 5.7- and 7.9-fold for anti-PT and anti-FHA, respectively, and between 2.8- and 3.9-fold for anti-PRN antibodies. The post-booster anti-PT geometric mean concentration was 82.5 EL.U/ml (95% CI 67.0–101.6) in the 0.3 mg group 108.1 (95% CI 87.7–133.2) in the 0.133 mg group and 124.0 (95% CI 103.5–148.5) in the 0.5 mg group, reaching numerically higher GMC levels compared to the first booster dose in the 0.133 mg and 0.5 mg groups (Fig. 2).

Using definition 1, a BR for PT or FHA was observed in at least 90.4% of participants in each group, including all participants who were initially seronegative for anti-PT antibodies (Table 3). For PRN, a BR was observed in 51.1% of participants in the dTpa-0.3

Table 3
Pertussis booster response rates after dTpa booster vaccination at year 10 (ATP immunogenicity cohort).

Antibody	Group	N[a]	N[b]	% (95% CI)
Definition 1[c]				
Anti-PT	dTpa-0.3	44	44	100 (92.0; 100)
	dTpa-0.133	51	51	100 (93.0; 100)
	dTpa-0.5	51	48	94.1 (83.8; 98.8)
Anti-FHA	dTpa-0.3	46	43	93.5 (82.1; 98.6)
	dTpa-0.133	52	47	90.4 (79.0; 96.8)
	dTpa-0.5	50	48	96.0 (86.3; 99.5)
Anti-PRN	dTpa-0.3	45	23	51.1 (35.8; 66.3)
	dTpa-0.133	52	29	55.8 (41.3; 69.5)
	dTpa-0.5	52	35	67.3 (52.9; 79.7)
Definition 2[d]				
Anti-PT	dTpa-0.3	44	40	90.9 (78.3; 97.5)
	dTpa-0.133	51	47	92.2 (81.1; 97.8)
	dTpa-0.5	51	48	94.1 (83.8; 98.8)
Anti-FHA	dTpa-0.3	46	43	93.5 (82.1; 98.6)
	dTpa-0.133	52	47	90.4 (79.0; 96.8)
	dTpa-0.5	50	48	96.0 (86.3; 99.5)
Anti-PRN	dTpa-0.3	45	23	51.1 (35.8; 66.3)
	dTpa-0.133	52	29	55.8 (41.3; 69.5)
	dTpa-0.5	52	35	67.3 (52.9; 79.7)

[a] *N* = number of subjects with both pre- and post-vaccination results available.
[b] *N*/% = number/percentage of subjects with a booster response
[c] Definition 1: the appearance of antibodies in participants who were seronegative prior to the booster dose, or a ≥2-fold increase in concentration in initially seropositive participants.
[d] Definition 2: a ≥4-fold increase (post-booster antibody concentration ≥20 EL.U/ml) in initially seronegative participants, a ≥4-fold increase in initially seropositive participants with a pre-booster antibody concentration ≥5 EL.U/ml and <20 EL.U/ml, and a ≥2-fold increase in initially seropositive participants with a pre-booster antibody concentration ≥20 EL.U/ml.

group 55.8%, in the dTpa-0.133 group and 67.3% in the dTpa-0.5 group.

Similar trends were observed using definition 2 (Table 3), with BRs for PT or FHA observed in at least 90.4% of participants (including all initially seronegative subjects), and in 51.1%–67.3% of participants for PRN.

3.4. Safety

Pain at the injection site was the most frequently reported local symptom, reported by 87.1%–93.2% of vaccinees in each group (Table 4). Grade 3 local symptoms (see Table 4 footnote for grade 3 definitions) were reported by not more than five participants in any group. One participant (dTpa-0.133 group) reported a large swelling reaction with onset 3 days after the booster dose. The swelling was confined to the injection site and resolved after 2 days.

The most frequently reported systemic symptoms in each group were fatigue (31.5%–35.5% of vaccinees) and headache (21.0%–32.2%) (Table 4). Fever (all <39 °C) was reported by one participant (<2.0%) in each treatment group. Grade 3 solicited systemic symptoms considered to be related to vaccination were reported by not more than three vaccinees in each group (Table 4). No solicited local or general symptoms resulted in a medically attended visit.

At least one AE occurring within 31 days after vaccination considered by the investigator to be related to vaccination was reported by 12.7% (95% CI 5.3;24.5) of participants in the dTpa-0.3 group, 11.7% (4.8;22.6) in the dTpa-0.133 group and 14.5% (6.9;25.8) in the dTpa-0.5 group. Vaccine-related AEs reported at least twice in any group were injection site induration, injection site pruritus, arthralgia and myalgia. No related AEs were reported by more than two participants in any group. No SAEs were reported during the entire study period.

Reactogenicity and safety in this and the previous booster study were assessed using identical methods. The incidence of local and solicited symptoms after the decennial booster dose was similar or lower to that observed in the same subjects after the first booster dose 10 years previously (Table 4).

4. Discussion

We previously reported that a booster dose of dTpa containing 0.133 mg, 0.3 mg or 0.5 mg aluminium administered to healthy adolescents primed in infancy with DTPw, induced robust BRs to all vaccine antigens [18]. In the present study conducted 10 years later, all returning participants continued to have seroprotective antibodies for diphtheria and tetanus (using ELISA or in vitro neutralisation assay), at least 82.8% were seropositive for anti-PT antibodies and all participants were seropositive for anti-FHA and anti-PRN antibodies. In our cohort, anti-pertussis antibodies appeared to persist longer after the first dTpa dose than after Pw-primary vaccination. Furthermore, antibodies to PT, FHA and PRN appeared to be higher 10 years after the first dTpa booster than observed in children after infant vaccination with acellular pertussis vaccines [27,28].

A positive association between aluminium content of the dTpa vaccine and the anti-PT antibody response observed after the initial booster vaccination continued to be observed up to 10 years later, with a numerically higher anti-PT antibody seropositivity rate and GMC in the dTpa-0.5 group. In view of the robust response to PT at both time points, these results are unlikely to be of clinical importance.

A decennial booster dose induced robust increases in antibody GMCs for all antigens. Post-booster anti-diphtheria and anti-PT GMCs were similar to levels achieved after the first booster dose 10 years previously, whereas GMCs for tetanus, FHA and PRN were lower than after the previous booster, possibly reflecting the higher pre-vaccination concentrations at the time of the second booster dose compared to the first. Indeed, similar trends have been observed in other studies that assessed a decennial dTpa booster vaccination [29,30]. In these studies, high pre-booster concentrations were associated with lower booster rates and post-booster GMCs.

The reactogenicity and safety profile of the decennial booster dose was in line with the known safety profile of *Boostrix*™, which is characterised by early onset of short-lived symptoms at the

Table 4
Incidence of solicited general symptoms reported within 4 days after the first dTpa booster dose, and after the decennial dTpa booster dose in subjects who received the decennial booster dose (Total vaccinated cohorts).

		First dTpa booster dose 10 years earlier						Decennial dTpa booster dose (present study)					
		dTpa-0.3 *N* = 55[a]		dTpa-0.133 *N* = 59		dTpa-0.5 *N* = 62		dTpa-0.3 *N* = 54–55[a]		dTpa-0.133 *N* = 59		dTpa-0.5 *N* = 62	
		n[b]	**% (95% CI)** [c]	***n***	**% (95% CI)**	***n***	**% (95% CI)**	***n***[b]	**% (95% CI)** [c]	***n***	**% (95% CI)**	***n***	**% (95% CI)**
Pain	Any	52	94.5 (84.9; 98.9)	54	91.5 (81.3; 97.2)	59	95.2 (86.5; 99.0)	50	90.9 (80.0; 97.0)	55	93.2 (83.5; 98.1)	54	87.1 (76.1; 94.3)
	Grade 3	7	12.7 (5.3; 24.5)	7	11.9 (4.9; 22.9)	6	9.7 (3.6; 19.9)	2	3.6 (0.4; 12.5)	5	8.5 (2.8; 18.7)	3	4.8 (1.0; 13.5)
Redness (mm)	Any	22	40.0 (27.0; 54.1)	15	25.4 (15.0; 38.4)	17	27.4 (16.9; 40.2)	23	41.8 (28.7; 55.9)	23	39.0 (26.5; 52.6)	21	33.9 (22.3; 47.0)
	≥50 mm	10	18.2 (9.1; 30.9)	6	10.2 (3.8; 20.8)	2	3.2 (0.4; 11.2)	2	3.6 (0.4; 12.5)	0	0.0 (0.0; 6.1)	2	3.2 (0.4; 11.2)
Swelling (mm)	Any	18	32.7 (20.7; 46.7)	16	27.1 (16.4; 40.3)	23	37.1 (25.2; 50.3)	21	38.2 (25.4; 52.3)	20	33.9 (22.1; 47.4)	19	30.6 (19.6; 43.7)
	≥50 mm	7	12.7 (5.3; 24.5)	4	6.8 (1.9; 16.5)	8	12.9 (5.7; 23.9)	3	5.5 (1.1; 15.1)	3	5.1 (1.1; 14.1)	1	1.6 (0.0; 8.7)
Fatigue	Any	20	37.0 (24.3; 51.3)	23	39.0 (26.5; 52.6)	24	38.7 (26.6; 51.9)	17	31.5 (19.5; 45.6)	20	33.9 (22.1; 47.4)	22	35.5 (23.7; 48.7)
	Grade 3[d] Related[e]	3	5.6 (1.2; 15.4)	2	3.4 (0.4; 11.7)	3	4.8 (1.0; 13.5)	0	0.0 (0.0; 6.6)	0	0.0 (0.0; 6.1)	2	3.2 (0.4; 11.2)
Gastrointestinal	Any	7	13.0 (5.4; 24.9)	9	15.3 (7.2; 27.0)	11	17.7 (9.2; 29.5)	10	18.5 (9.3; 31.4)	9	15.3 (7.2; 27.0)	13	21.0 (11.7; 33.2)
	Grade 3[d] Related[e]	1	1.9 (0.0; 9.9)	1	1.7 (0.0; 9.1)	1	1.6 (0.0; 8.7)	1	1.9 (0.0; 9.9)	1	1.7 (0.0; 9.1)	3	4.8 (1.0; 13.5)
Headache	Any	23	42.6 (29.2; 56.8)	25	42.4 (29.6; 55.9)	30	48.4 (35.5; 61.4)	13	24.1 (13.5; 37.6)	19	32.2 (20.6; 45.6)	13	21.0 (11.7; 33.2)
	Grade 3[d] Related[e]	0	0.0 (0.0; 6.6)	2	3.4 (0.4; 11.7)	2	3.2 (0.4; 11.2)	1	1.9 (0.0; 9.9)	0	0.0 (0.0; 6.1)	1	1.6 (0.0; 8.7)
Temperature	Any	5	9.3 (3.1; 20.3)	4	6.8 (1.9; 16.5)	9	14.5 (6.9; 25.8)	1	1.9 (0.0; 9.9)	1	1.7 (0.0; 9.1)	1	1.6 (0.0; 8.7)
	>39.0 °C Related[e]	0	0.0 (0.0; 6.6)	0	0.0 (0.0; 6.1)	0	0.0 (0.0; 5.8)	0	0.0 (0.0; 6.6)	0	0.0 (0.0; 6.1)	0	0.0 (0.0; 5.8)

[a] *N* = with at least one documented dose, respectively.
[b] *n*/% = number/percentage of subjects who reported the symptom at least once.
[c] 95% CI = exact 95% confidence interval.
[d] Grade 3: symptoms that prevent normal activity.
[e] Related = symptoms considered by the investigator to be vaccine-related

injection site and few severe systemic reactions. The reactogenicity profile of the decennial dose resembled that of the booster administered 10 years previously.

While this study was not designed or powered to compare the immunogenicity and safety of the 0.5 mg and 0.3 mg formulations, we observed no marked differences in the immunogenicity or reactogenicity profiles when either vaccine was administered 10 years apart. While the observed post-booster GMC for PT was highest in the dTpa-0.5 group (124.0 EL.U/ml) and lowest in the dTpa-0.3 group (82.5 EL.U/ml), BR rates and seropositivity rates were similar. Interestingly, while the lowest anti-PT antibody GMCs were observed in the dTpa-0.133 group after the initial vaccination, decennial boosting with the dTpa-0.5 formulation 'corrected' the response to a level between the dTpa-0.3 and dTpa-0.5 groups. At each time point anti-diphtheria GMCs appeared to be negatively associated with aluminium content, although the small sample size precludes firm conclusions and this is likely of little clinical importance in view of the high levels of seroprotection to diphtheria in all groups over time.

The data suggest a small but consistent negative effect of lower aluminium content on anti-PT GMCs that appears to have minimal clinical consequences if a booster is given, in view of the robust responses observed. Within the limits of the study, use of dTpa containing either 0.5 mg or 0.3 mg aluminium does not appear to be associated with any clinically important difference in clinical protection, reactogenicity or safety.

Our study was limited by around 63% drop out of the originally vaccinated cohort and the sample size was thus too small to perform statistical comparisons between groups. Our study was also limited in that around 85% participants had received a conjugated meningococcal vaccine. Immune responses to the carrier protein may have elevated anti-diphtheria and anti-tetanus antibodies in the analysis of persistence. However, since most meningococcal vaccination occurred shortly after the first dTpa dose (a meningococcal C vaccination campaign in Flanders during the study period targeted the age group invited for the booster study [31,32]), any effect on the decennial booster is likely to be minimal.

Our results compare favourably with earlier evaluations of a decennial dTpa booster dose after initial vaccination in 10–14 year olds [30] and in adults ≥18 years of age [29]. Pertussis will ultimately be controlled or potentially eliminated if improved vaccines that induce a more potent immune response are developed and widely used. Until this time, regular, decennial booster vaccination of adults appears to be a feasible means by which to reduce pertussis circulation and disease in highly vaccinated populations.

Decennial vaccination using two formulations of dTpa vaccine was highly immunogenic and well tolerated in young adults. Either formulation could be confidently used as a decennial booster.

BOOSTRIX is a trademark of the GlaxoSmithKline group of companies.

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Conflicting interests

CV: acts as sub- and principal investigator for clinical trials for which the university obtained a research grant from GlaxoSmithKline Biologicals SA for this study, and research grants from other companies including Merck, Sanofi Pasteur MSD, Janssen Research and Development, Amgen, UCB and Genticel outside the submitted work.

HT: acts as sub-investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from GlaxoSmithKline Biologicals SA and other companies including Merck &Co., Novartis Vaccines, Genticel, SP-MSD, Pfizer. The University also received reimbursement for travel costs and meeting expenses from these companies.

NR: Was an employee of GlaxoSmithKline Biologicals SA during conduct of the study.

SK and HHH: are employees of GlaxoSmithKline Biologicals SA.

KH: acts as sub- and principal investigator for clinical trials for which the university obtained a research grant from GlaxoSmithKline Biologicals SA for this study, and research grants from other companies including Merck, Sanofi Pasteur MSD outside the submitted work.

ES reports no conflict of interest

PVD: acts as chief and principal investigator for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from GlaxoSmithKline Biologicals SA and other companies including Merck &Co., Novartis Vaccines, Genticel, SP-MSD, Pfizer. The University also received reimbursement for travel costs and meeting expenses from these companies.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2014.10.049

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