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Immunogenicity and reactogenicity of a decennial booster dose of a combined reduced-antigen-content diphtheria–tetanus–acellular pertussis and inactivated poliovirus booster vaccine (dTpa–IPV) in healthy adults☆

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ABSTRACT

Background: Pertussis in adults and adolescents could be reduced by replacing traditional tetanus and diphtheria (Td) boosters with reduced-antigen-content diphtheria–tetanus–acellular pertussis (dTpa) vaccines. This study evaluated the administration of dTpa–IPV (dTpa–inactivated poliovirus) in adults ten years after they received a booster dose of either dTpa–IPV, dTpa+IPV or Td–IPV in trial NCT01277705.
Methods: Open multicentre, phase IV study (www.clinicaltrials.gov NCT01323959) in which healthy adults, who had received a previous dose of dTpa–IPV, dTpa+IPV or Td–IPV ten years earlier, received a single decennial booster dose of dTpa–IPV (*Boostrix*™-polio, GlaxoSmithKline Vaccines). Blood samples were collected before and one month after booster vaccination. Antibody concentrations against all vaccine antigens were measured and reactogenicity and safety were assessed.
Results: A total of 211 subjects (mean age 50.3 years) received vaccination of whom 201 were included in the according-to-protocol cohort for immunogenicity. Before the decennial dTpa–IPV booster, ≥71.0% subjects were seroprotected/seropositive against all vaccine antigens. One month after the booster dose, all subjects were seroprotected against tetanus and poliovirus types 2 and 3; ≥95.7% subjects were seroprotected against diphtheria and ≥98.3% against poliovirus type 1. Anti-pertussis booster responses for the various antigens were observed in ≥76.5% (pertussis toxoid; PT), ≥85.1% (filamentous haemagglutinin; FHA) and ≥63.2% (pertactin; PRN) of subjects. During the 4-day follow-up, the overall incidence of local AEs was 71.6%, 75.0% and 72.2% in dTpa–IPV, dTpa+IPV and Td–IPV groups, respectively. Pain was the most frequent solicited local adverse event (AE; ≥62.7% subjects) and fatigue the most frequent solicited general AE (≥18.5%). No serious AEs were reported during the study.
Conclusion: A booster dose of dTpa–IPV was immunogenic and well tolerated in adults who had received a booster dose of either dTpa–IPV, dTpa+IPV or Td–IPV, ten years previously and supports the repeated administration of dTpa–IPV.

Abbreviations: AE, adverse event; ATP, according to protocol; CI, confidence interval; dTpa, reduced-antigen-content diphtheria, tetanus and acellular pertussis vaccine; FHA, filamentous haemagglutinin; GMC/T, geometric mean concentration/titre; IPV, inactivated polio virus; PRN, pertactin; PT, pertussis toxin; SAE, serious adverse event; Td, adult tetanus–diphtheria vaccine; TVC, total vaccinated cohort.

☆ This study is registered at www.clinicaltrials.gov NCT01323959.

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1. Introduction

Pertussis (whooping cough), caused by *Bordetella pertussis*, is associated with substantial morbidity in adolescents and adults, but is rarely fatal [1]. However, in infants who are too young to be vaccinated, severe pertussis can lead to hospitalization, serious complications and even death [2]. In many countries, the highest rates of pertussis disease occur in children less than six months of age [3–5].

Effective immunization programmes against pertussis have been available for decades, [6] but as neither pertussis vaccination nor natural pertussis infection provide life-long immunity, pertussis remains endemic with frequent, isolated outbreaks [6,7] in age groups that are not currently targeted for vaccination. Pertussis has been classified by the Global Pertussis Initiative as the least controlled vaccine preventable disease [8,9].

Despite high vaccine coverage, the incidence of pertussis disease continues to rise in many countries [1,10,11]. Depending on the country, this can be due to a range of factors including poorly protective vaccine, recent modifications of the vaccine schedule, increased disease awareness, improved diagnostic tests, better reporting, *B. pertussis* adaptation, or waning of vaccine induced immunity [12–14]. For instance, adolescents and adults are becoming susceptible to the disease and may in turn transmit the disease to vulnerable infants [11,15]. In order to interrupt the transmission of pertussis to unvaccinated or incompletely vaccinated infants, some countries now recommend the administration of a single booster dose of a pertussis-containing vaccine at times such as adolescence [16] or during the third trimester of pregnancy [17–19]. In addition, it is likely that repeated pertussis boosters will be necessary throughout life to deliver direct protection to vaccines [20,21], although the appropriate time intervals between pertussis booster vaccination have yet to be established.

Booster vaccination against diphtheria and tetanus using traditional Td vaccine is widely recommended throughout life. Pertussis in adults and adolescents could therefore be reduced by replacing traditional Td boosters with reduced-antigen content acellular pertussis, diphtheria and tetanus (dTpa) vaccines. Inactivated poliovirus (IPV) vaccine can also be included for additional protection against poliovirus; for example where regular boosting against polio is recommended or before travelling [22]. *Boostrix*™*-Polio*, (GlaxoSmithKline Vaccines), a vaccine that combines dTpa–IPV in a single injection has been demonstrated to be immunogenic and well tolerated in adult and adolescent populations [4,21,23,24]. In order to study the impact of repeated booster administration, this trial was undertaken to evaluate the administration of a dose of dTpa–IPV in adults, ten years after they had received a booster of either dTpa–IPV, dTpa+IPV or Td–IPV [24].

2. Methods

2.1. Study design and subjects

This was a phase IV, open follow-up study (NCT01323959) conducted between 27 April 2011 and 01 March 2012 at 19 centres in France and Germany. Healthy males and females who received dTpa–IPV (*Boostrix*™-Polio; GSK Vaccines, Belgium), dTpa (Boostrix™; GSK Vaccines, Belgium) + IPV (*Poliorix*™; GSK Vaccines, Belgium), or Td–IPV (*Revaxis*™; Sanofi-Pasteur) in the original booster study (NCT01277705) 10 years previously, were invited to participate in the current booster study. The study criteria were the same as in the original booster study [24], except that in Germany subjects from the Td–IPV group were allowed to have received a previous dose of monovalent pertussis vaccine (PAC-Merieux® [Sanofi-Pasteur-MSD, Germany] containing 25 μg pertactin [PRN] and 25 μg filamentous haemagglutinin [FHA] per dose).

The study protocol and the associated documents were reviewed and approved by the ethics committee of the participating centres and written informed consent was obtained from all participating subjects.

2.2. Vaccines

Each subject received a single 0.5 ml dose of dTpa–IPV (GlaxoSmithKline Vaccines; Lot number: AC39B029B), which contained ≥2 IU diphtheria toxoid, ≥20 IU tetanus toxoid, 8 μg pertussis toxoid (PT), 8 μg FHA and 2.5 μg PRN and 40 D-, 8 D- and 32 D-antigen units of poliovirus types 1–3, respectively. The vaccine also contained 0.5 mg aluminium as salts.

The vaccine was injected intramuscularly into the deltoid region of the non-dominant arm using a needle ≥25 mm length and 23–25 ga.

2.3. Assessment of immunogenicity

Blood samples were collected from all subjects before and one month after booster dose administration. Anti-diphtheria (anti-D) and anti-tetanus (anti-T) antibody concentrations were measured using enzyme-linked immunosorbent assay (ELISA) with an assay cut-off of 0.1 IU/ml. Subjects who were seronegative for anti-D antibodies by ELISA were retested using the *in vitro* neutralization assay on Vero cells (the cut-off for this assay, which is more sensitive than ELISA for low antibody concentrations, is 0.016 IU/ml). However, for this study, 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).

Anti-poliovirus types 1–3 antibodies were determined using a virus micro-neutralization test with an assay cut-off of 1:8. Antibodies against the pertussis antigens were measured using ELISA (cut-off ≥5 ELISA units per millilitre [EL U/ml] for each pertussis antigen). As there is no established correlate of protection against pertussis, seropositivity and vaccine response rates were used to evaluate immunogenicity.

2.4. Assessment of reactogenicity and safety

Subjects were given diary cards to record solicited local (pain, redness and swelling) and general (fever [axillary temperature ≥37.5 °C], fatigue, gastrointestinal [nausea, vomiting, diarrhoea and/or abdominal pain] and headache) adverse events (AEs) for four days (day 0–3) after the booster dose.

A 3-point scaling system was used to grade the intensity of solicited AEs, where Grade 3 AEs were defined as: injection site diameter >50 mm (redness and swelling), temperature >39 °C (fever) and/or AEs preventing normal activities (pain, fatigue, gastrointestinal symptoms and headache).

Large swelling reactions at the injection site (diameter >100 mm with or without diffuse swelling or increased limb circumference) and unsolicited AEs, including serious adverse events (SAEs) were recorded throughout the study period.

2.5. Statistical analysis

Statistical Analysis System (SAS®) version 9.2 on windows and StatXact-8.1 procedure on SAS® were used for the analysis. The primary objectives were the immunogenicity of the decennial booster with respect to seroprotection rates against diphtheria, tetanus and poliovirus types 1, 2 and 3 and the long-term persistence of antibodies against all vaccine antigens ten years after subjects had received a booster of either dTpa–IPV, dTpa+IPV or Td–IPV

in study NCT01277705. The secondary objectives were to assess the immunogenicity of the decennial booster with respect to the pertussis antigens and the safety and reactogenicity of the vaccine.

The primary analysis of immunogenicity was performed on the according-to-protocol (ATP) cohort which consisted of subjects meeting all eligibility criteria, complying with study procedures and having all immunogenicity data. Antibody seroprotection/seropositivity rates and booster response rates were calculated with exact 95% confidence intervals (CI). Geometric mean concentrations/titres (GMC/GMTs) with 95% CI were calculated from the anti-log of the mean of log-transformed values. Antibody concentrations below the assay cut-off were given an arbitrary value of half the cut-off for the purpose of GMC/GMT calculation.

A booster response was defined as post-booster antibody concentrations: ≥20 EL U/ml for initially seronegative subjects; ≥4 times the pre-vaccination antibody concentrations for initially seropositive subjects with pre-vaccination antibody concentrations <20 EL U/ml; ≥2 times the pre-vaccination antibody concentration for initially seropositive subjects with pre-vaccination antibody concentrations ≥20 EL U/ml.

The analysis of safety was performed on the Total Vaccinated Cohort (TVC), which consisted of all subjects who received the decennial booster dose.

The primary study had a sample size of 270 in each group [24]. Considering the subjects who would drop out or be lost to follow-up after 10 years, the booster study was planned with at least 100 subjects in each group. Thus, the sample size of the current booster study was contingent on the number of subjects in the primary study. This sample size allowed for the inference on immunogenicity: the lower limit of 95% CI for seroprotection rate was ≥80% for diphtheria, ≥90% for tetanus and ≥80% for poliovirus with 99% power. Finally, after accounting for a 10% drop out rate, ≥110 subjects were included in each group (330 in total).

3. Results

3.1. Study population

A total of 211 subjects received the dTpa–IPV decennial booster, of whom 201 (dTpa–IPV, $N = 63$; dTpa+IPV, $N = 69$ and Td–IPV, $N = 69$) were included in the ATP cohort for immunogenicity (Fig. 1). Thus, approximately 25.6% of the subjects that formed ATP cohort in the original study received the dTpa–IPV decennial booster [24]. The mean age (SD) of the subjects in the current ATP cohort was 50.2 years (±12.75); 58.2% were female and 98.5% were White/Caucasian (Table 1).

3.2. Ten-year antibody persistence

Long-term persistence before the decennial dTpa–IPV booster dose is shown in Table 2. Seroprotective concentrations of anti-D and anti-T antibodies were detected in at least 73.5% and 94.2% of the subjects across the treatment groups, respectively. After re-testing samples found to be seronegative by ELISA, using Vero cells neutralization assay, 92.1% (95% CI: 82.4–97.4) subjects in the dTpa–IPV group, 79.4% (95% CI: 67.9–88.3) subjects in the dTpa+IPV and 84.1% (95% CI: 73.3–91.8) subjects in the Td–IPV group were found to be seroprotected against diphtheria (data not shown).

Seroprotective concentrations of anti-poliovirus 1 and 2 antibodies were observed in all subjects in the dTpa–IPV and dTpa+IPV groups and at least 98.3% subjects in the Td–IPV group. Seroprotective concentrations of anti-poliovirus type 3 antibodies were observed in at least 98.3% of subjects across the groups.

The percentage of subjects who remained seropositive for pertussis antigens was 78.7% and 84.1% for PT in the dTpa–IPV and dTpa+IPV group, respectively. All subjects in both groups had persisting antibodies against FHA and 88.7% (dTpa–IPV group) and 94.1% (dTpa+IPV group) had persisting antibodies against PRN. In the subjects who received the Td–IPV booster ten years previously, 19.4% subjects in the TVC had in the meantime received monovalent pertussis vaccination; before the decennial booster 71.0, 98.5 and 85.5% were seropositive for PT, FHA and PRN, respectively.

Ten years after the original dTpa–IPV or dTpa+IPV booster vaccinations, the observed seroprotection rates against diphtheria, tetanus and poliovirus and seropositivity rates against pertussis antigens had reduced, but remained higher than before the previous booster vaccination (data not shown). In the subjects who received Td–IPV vaccination ten years previously, the pre-decennial booster seroprotection rates against diphtheria, tetanus and poliovirus types 2 and 3 and seropositivity rates against PT and PRN had decreased, but remained higher than before the previous booster vaccination; the rates for poliovirus type 1 and FHA were, however, lower than before the previous booster dose (data not shown). GMC/GMTs also decreased progressively after the booster dose ten years previously, but for all antigens remained higher than before the initial booster dose (data not shown).

3.3. Booster immunogenicity

One month after the decennial booster dose of dTpa–IPV, seroprotective concentrations of anti-D antibodies and anti-T antibodies (≥0.1 IU/ml by ELISA) were observed in at least 95.7% and 100% of subjects, respectively, across the groups. Seroprotective concentrations of anti-poliovirus 1, 2 and 3 antibodies were observed in at least 98.3% of subjects across the groups (Table 2). Anti-PT, anti-FHA and anti-PRN seropositivity was observed in at least 98.5% subjects across the three groups (Table 2).

In subjects receiving their second dose of dTpa–IPV, a booster response was observed in 98.4% for PT, 85.5% for FHA and 74.2% for PRN (Table 3). For subjects in the dTpa+IPV group boosted with dTpa–IPV, 87.0% had a booster response against PT, 89.9% against FHA and 63.2% against PRN. In subjects who received Td–IPV for their first booster followed by dTpa–IPV ten years later, the booster responses were 76.5% (anti-PT), 85.1% (anti-FHA) and 91.3% (anti-PRN).

Immune boosting, as evidenced by many-fold increases in GMC/T was observed for all the vaccine antigens after the booster dose of dTpa–IPV (Table 2).

3.4. Reactogenicity and safety

The overall incidence of local AEs (solicited and unsolicited) was 71.6% (dTpa–IPV group), 75.0% (dTpa+IPV group) and 72.2% (Td–IPV group) during the 4 day post-vaccination period. Pain was the most frequently reported solicited local AE which was reported in at least 62.7% of the subjects across the groups (Fig. 2). Injection site redness (>50 mm) was the most frequently reported Grade 3 AE, affecting 1.5% (dTpa–IPV group), 5.6% (dTpa+IPV group) and 4.2% (Td–IPV group) of the study subjects.

Solicited general AEs were reported by no more than 22.5% subjects and no more than 1.5% were of grade 3 intensity (Fig. 2). Fatigue was most frequently reported solicited general AE, reported by at least 18.5% of the subjects overall. No cases of fever >39.0 °C were recorded during the study.

During the 31-day post-booster follow-up period, at least 6.9% subjects reported at least one unsolicited AE in each group. Injection site pruritus, reported by 2.8% subjects in the dTpa+IPV and Td–IPV groups, was the most commonly reported unsolicited AE. The percentage of subjects reporting Grade 3 unsolicited AEs ranged

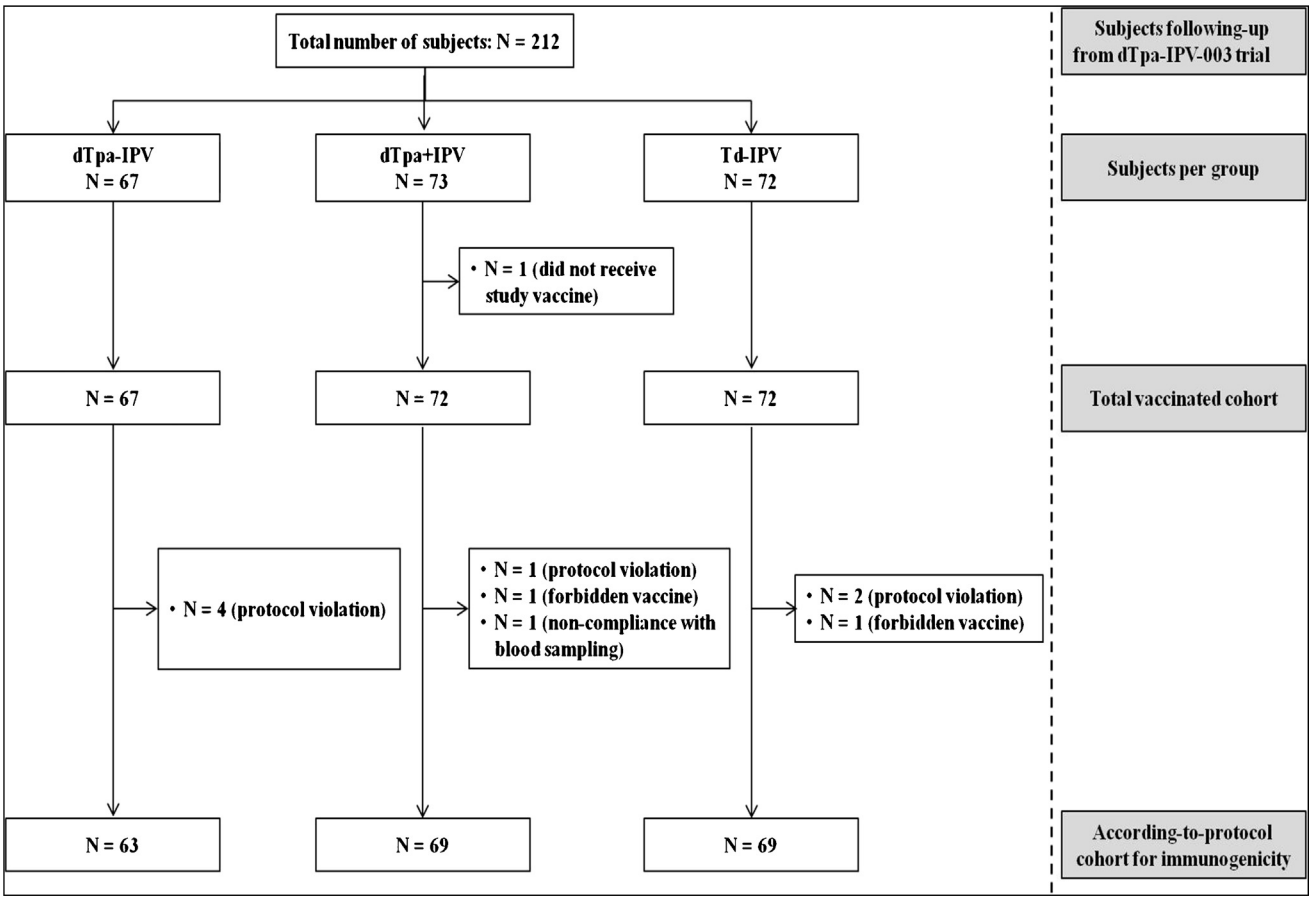

Fig. 1. Subject disposition.

Table 1
Baseline characteristics (ATP cohort for immunogenicity).

	dTpa–IPV *N* = 63	dTpa+IPV *N* = 69	Td–IPV *N* = 69	Total *N* = 201
Age (years)				
Mean (SD)	50.1 (12.87)	49.4 (12.48)	51.2 (13.04)	50.2 (12.75)
Median (range)	51.0 (24–83)	50.0 (25–76)	51.0 (24–78)	51.0 (24–83)
Gender				
Female (%)	35 (55.6)	46 (66.7)	36 (52.2)	117 (58.2)
Male (%)	28 (44.4)	23 (33.3)	33 (47.8)	84 (41.8)
Ethnicity				
Black (%)	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.5)
White/Caucasian (%)	62 (98.4)	69 (100)	67 (97.1)	198 (98.5)
Oriental (%)	1 (1.6)	0 (0.0)	1 (1.4)	2 (1.0)

dTpa–IPV Group: subjects received dTpa–IPV vaccine in study NCT01277705; dTpa+IPV Group: subjects received dTpa+IPV vaccines in study NCT01277705; Td–IPV Group: subjects received Td–IPV vaccine in study NCT01277705; N: number of subjects with available results.

between 0% and 1.5%. At least one unsolicited AE related to the vaccination was reported in each group: neuralgia (one dTpa–IPV subject); injection site induration (one dTpa+IPV subject); injection site pruritus (2 dTpa+IPV subjects; 2 Td–IPV subjects) and injection site warmth (one Td–IPV subject).

No SAEs occurred during the study period and no subjects withdrew due to an AE.

4. Discussion

The administration of dTpa combination booster doses throughout life may prove to be an efficient way to reduce the susceptibility of adolescents and adults to pertussis [20]. As found in previous studies [4,16,21], we also demonstrated that a decennial booster dose of combined dTpa–IPV vaccine was immunogenic and well tolerated across three groups who had previously received dTpa–IPV, dTpa+IPV or Td–IPV. The current study demonstrated persistent seroprotection against the vaccine antigens (D, T, poliovirus types 1, 2, 3) in at least 79.4% subjects 10 years after an initial booster dose of dTpa–IPV, dTpa+IPV or Td–IPV vaccines. These results are comparable with those of Booy et al. [4], who showed that at least 62.9% of the subjects who received a booster dose of dTpa 10 years previously attained seroprotection/seropositive levels against diphtheria, tetanus and pertussis antigens. Also, as reported by Booy et al. [4], we too observed high levels of antibody GMC/Ts against diphtheria, tetanus and pertussis antigens. Moreover, a robust increase in GMTs was also observed against the three poliovirus types (1, 2 and 3). The majority of subjects

Table 2
Seroprotection/seropositivity rates and GMCs before and one month post-booster (ATP cohort for immunogenicity).

Antibody	Group	Pre-booster								Post-booster							
		Seroprotection/Seropositive					GMC/T			Seroprotection/Seropositive					GMC/T		
		N	*n*	%	LL	UL	Value	LL	UL	*N*	*n*	%	LL	UL	Value	LL	UL
Anti-Diphtheria (ELISA)	dTpa–IPV	63	51	81.0	69.1	89.8	0.416	0.293	0.592	63	61	96.8	89.0	99.6	2.159	1.579	2.952
	dTpa+IPV	68	50	73.5	61.4	83.5	0.360	0.249	0.519	69	66	95.7	87.8	99.1	1.821	1.312	2.528
Cut-off ≥ 0.1 IU/ml	Td–IPV	69	55	79.7	68.3	88.4	0.501	0.348	0.721	69	68	98.6	92.2	100	2.649	1.948	3.603
Anti-Tetanus	dTpa–IPV	63	62	98.4	91.5	100	1.371	1.019	1.844	63	63	100	94.3	100	8.568	7.361	9.972
Cut-off ≥ 0.1 IU/ml	dTpa+IPV	69	68	98.6	92.2	100	1.578	1.227	2.028	69	69	100	94.8	100	9.692	8.217	11.431
	Td–IPV	69	65	94.2	85.8	98.4	1.491	1.096	2.028	69	69	100	94.8	100	9.390	7.946	11.096
Anti-Poliovirus 1	dTpa–IPV	52	52	100	93.2	100	341.0	233.5	497.9	58	58	100	93.8	100	1519.0	1156.9	1994.4
Cut-off ≥ 8 ED50	dTpa+IPV	58	58	100	93.8	100	567.0	392.3	819.4	62	62	100	94.2	100	1665.4	1263.5	2195.2
	Td–IPV	60	59	98.3	91.1	100	332.0	239.0	461.2	59	58	98.3	90.9	100	1526.7	1106.8	2105.9
Anti-Poliovirus 2	dTpa–IPV	56	56	100	93.6	100	308.3	218.9	434.3	46	46	100	92.3	100	1071.3	806.2	1423.5
Cut-off ≥ 8 ED50	dTpa+IPV	60	60	100	94.0	100	322.6	234.3	444.2	58	58	100	93.8	100	1269.8	954.5	1689.4
	Td–IPV	63	62	98.4	91.5	100	331.5	246.3	446.0	56	56	100	93.6	100	1550.1	1202.8	1997.7
Anti-Poliovirus 3	dTpa–IPV	58	57	98.3	90.8	100	388.9	271.2	557.7	58	58	100	93.8	100	2035.7	1653.4	2506.4
Cut-off ≥ 8 ED50	dTpa+IPV	66	65	98.5	91.8	100	648.5	476.7	882.2	60	60	100	94.0	100	2047.9	1604.6	2613.7
	Td–IPV	67	67	100	94.6	100	542.1	397.1	740.1	60	60	100	94.0	100	2024.6	1513.3	2708.6
Anti-PT	dTpa–IPV	61	48	78.7	66.3	88.1	10.3	8.2	13.0	63	63	100	94.3	100	97.5	81.4	116.9
Cut-off ≥ 5 EL U/ml	dTpa+IPV	69	58	84.1	73.3	91.8	13.4	10.4	17.2	69	69	100	94.8	100	100.1	80.3	124.8
	Td–IPV	69	49	71.0	58.8	81.3	14.7	10.1	21.5	68	67	98.5	92.1	100	92.9	68.7	125.6
Anti-FHA	dTpa–IPV	62	62	100	94.2	100	93.7	72.9	120.6	63	63	100	94.3	100	485.8	413.8	570.4
Cut-off ≥ 5 EL U/ml	dTpa+IPV	69	69	100	94.8	100	124.0	102.5	150.1	69	69	100	94.8	100	553.5	465.9	657.6
	Td–IPV	67	66	98.5	92.0	100	68.6	49.2	95.9	69	69	100	94.8	100	854.9	714.9	1022.3
Anti-PRN	dTpa–IPV	62	55	88.7	78.1	95.3	66.1	41.9	104.1	63	63	100	94.3	100	365.9	281.5	475.6
Cut-off ≥ 5 EL U/ml	dTpa+IPV	68	64	94.1	85.6	98.4	93.9	62.7	140.7	69	69	100	94.8	100	404.2	324.2	504.0
	Td–IPV	69	59	85.5	75.0	92.8	19.4	14.2	26.5	69	69	100	94.8	100	581.0	401.6	840.7

dTpa–IPV Group: subjects received dTpa–IPV vaccine in study NCT01277705; dTpa+IPV Group: subjects received dTpa+IPV vaccines in study NCT01277705; Td–IPV Group: subjects received Td–IPV vaccine in study NCT01277705.
GMC/T: geometric mean antibody concentration/titre; *N*: number of subjects with available results; 95% CI: 95% confidence interval; LL: lower limit, UL: upper limit.

Table 3
Booster response rates to pertussis antibodies one month after the decennial booster dose (ATP cohort for immunogenicity).

Antibody	Group	Pre-vaccination status	*N*	*n*	%	Booster response 95% CI	
						LL	UL
Anti-PT	dTpa–IPV	S–	13	13	100	75.3	100
		S+ (<20 EL U/ml)	29	28	96.6	82.2	99.9
		S+ (≥20 EL U/ml)	19	19	100	82.4	100
		Total	61	60	98.4	91.2	100
	dTpa+IPV	S–	11	9	81.8	48.2	97.7
		S+ (<20 EL U/ml)	37	32	86.5	71.2	95.5
		S+ (≥20 EL U/ml)	21	19	90.5	69.6	98.8
		Total	69	60	87.0	76.7	93.9
	Td–IPV	S–	20	14	70.0	45.7	88.1
		S+ (<20 EL U/ml)	26	23	88.5	69.8	97.6
		S+ (≥20 EL U/ml)	22	15	68.2	45.1	86.1
		Total	68	52	76.5	64.6	85.9
Anti-FHA	dTpa–IPV	S–	0	0	–	–	–
		S+ (<20 EL U/ml)	3	3	100	29.2	100
		S+ (≥20 EL U/ml)	59	50	84.7	73.0	92.8
		Total	62	53	85.5	74.2	93.1
	dTpa+IPV	S–	0	0	–	–	–
		S+ (<20 EL U/ml)	0	0	–	–	–
		S+ (≥20 EL U/ml)	69	62	89.9	80.2	95.8
		Total	69	62	89.9	80.2	95.8
	Td–IPV	S–	1	1	100	2.5	100
		S+ (<20 EL U/ml)	10	10	100	69.2	100
		S+ (≥20 EL U/ml)	56	46	82.1	69.6	91.1
		Total	67	57	85.1	74.3	92.6
Anti-PRN	dTpa–IPV	S–	7	7	100	59.0	100
		S+ (<20 EL U/ml)	7	7	100	59.0	100
		S+ (≥20 EL U/ml)	48	32	66.7	51.6	79.6
		Total	62	46	74.2	61.5	84.5
	dTpa+IPV	S–	4	3	75.0	19.4	99.4
		S+ (<20 EL U/ml)	9	8	88.9	51.8	99.7
		S+ (≥20 EL U/ml)	55	32	58.2	44.1	71.3
		Total	68	43	63.2	50.7	74.6
	Td–IPV	S–	10	7	70.0	34.8	93.3
		S+ (<20 EL U/ml)	27	26	96.3	81.0	99.9
		S+ (≥20 EL U/ml)	32	30	93.8	79.2	99.2
		Total	69	63	91.3	82.0	96.7

dTpa–IPV Group: subjects received dTpa–IPV vaccine in study NCT01277705; dTpa+IPV Group: subjects received dTpa+IPV vaccines in study NCT01277705; Td–IPV Group: subjects received Td–IPV vaccine in study NCT01277705. S–: seronegative subjects (antibody concentration <5 EL U/ml) before vaccination; S+: seropositive subjects (antibody concentration ≥5 EL U/ml) before vaccination. Total = subjects either seropositive or seronegative before vaccination. Booster response defined as: (a) For initially seronegative subjects, antibody concentration ≥20 EL U/ml post-booster. (b) For initially seropositive subjects with pre-vaccination antibody concentration <20 EL U/ml: antibody concentration at post ≥4 fold the pre-vaccination antibody concentration. (c) For initially seropositive subjects with pre-vaccination antibody concentration ≥20 EL U/ml: antibody concentration at post ≥2 fold the pre-vaccination antibody concentration. *N*: Number of subjects with pre- and post-vaccination results available; *n*/%: Number/percentage of subjects with a booster response; 95% CI: Exact 95% confidence interval, LL: lower limit, UL: upper limit.

still had pre-antibody titres at the time of the booster and a good booster response was observed. Given the age of these subjects, it is likely that they had already received one dose of oral polio vaccine in their childhood. For such adults, a single IPV booster is sufficient (as in the primary study [24]) and this additional booster dose was not needed for this trial population. Nevertheless, the safety of this additional booster dose was demonstrated and the anamnestic response was strong.

19.4% subjects in the Td–IPV group (TVC) received an additional dose of acellular pertussis vaccine (containing PRN and FHA) before this study. As expected, a lower booster response to PT antigen was observed in the Td–IPV group, compared to the other groups, but the booster response to PRN antigen was higher in the Td–IPV group. No differences in the booster response for FHA antigens between the three groups were observed. However, after the decennial booster, at least 98.5% subjects in each group were seropositive against the pertussis antigens and booster response rates against all three pertussis antigens were attained in 63.2–98.4% of subjects. Comparably, 69.7–100% of subjects in the study conducted by Booy et al. attained a booster response against the three pertussis antigens [4]. In our present study, the number of non-responders was low and they did not belong to the group of non–responders in the original booster study (data not shown).

In the current study, the decennial booster dose of dTpa–IPV was shown to have an acceptable overall safety profile and was well tolerated, which is in line with existing safety data [25]. The reactogenicity results are in accordance with the known safety profile of the licensed dTpa vaccine and also in line with reactogenicity of dTpa–IPV and dTpa+IPV boosters given 10 years earlier [24]. In comparison with the safety results from Knuf et al. [21], swelling and redness (>50 mm) among adults was low across the treatment groups in the current study. None of the participating subjects required medical attention for local symptoms.

The inclusion of an acellular pertussis component for the booster vaccination of adolescents and adults, by replacing Td vaccines with dTpa combined vaccines, has been recommended across Europe due to their equivalent protection against diphtheria and tetanus. Additional protection against poliovirus can be achieved using dTpa–IPV [20]. Currently, pertussis vaccination schedules in adults vary widely, but decennial boosting with dTpa combined vaccine could help deliver protection against waning pertussis immunity [21] and reduce further transmission of pertussis to susceptible young infants. In 2011, the Consensus on Pertussis Booster Vaccine in Europe initiative recommended regular adult boosting by replacing Td boosters with dTpa-containing vaccines in national schedules [20].

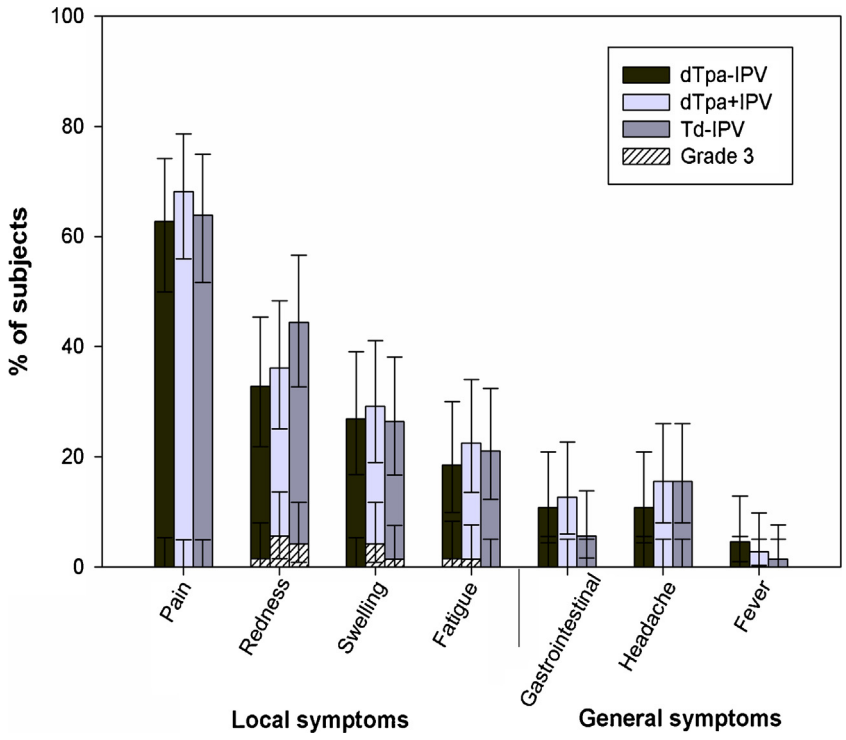

Fig. 2. Incidence of solicited local/general adverse events during 4-day follow-up after decennial booster dose administration (Total Vaccinated Cohort).

One of the major challenges in giving dTpa booster dose to adults is the incidence of increased reactogenicity (particularly injection site pain) after repeated doses [21,26]. However, in the current study, the observed reactogenicity rates were as expected and in line with existing data [27]. Another challenge would be to deliver decennial booster doses to an adult population who are often difficult to reach [24]; indeed, coverage of the traditional decennial Td boosters is already suboptimal in most countries [27]. In the developed world, Td boosters are often given as part of a wound management strategy to patients who are not up-to-date with their vaccination recommendations, rather than booster dosing *per se* [28]. Administration of dTpa–IPV instead of Td in this setting would provide one option for additional vaccination against pertussis and polio in adults.

Although limited by the open design, the restricted number of subjects returning to participate in this trial and not analysing the effect of age on immune response as undertaken in the original study [24], we demonstrated that a decennial booster dose of dTpa–IPV vaccine was both immunogenic and well tolerated in adults who had received either dTpa–IPV, dTpa+IPV or Td boosters 10 years previously. Based on medical need, our findings support the replacement of Td with dTpa–IPV booster dose as a way of reducing pertussis circulation among adolescents and adults in developed countries, as well as providing additional protection against poliovirus.

Contributors

TFS was the principal investigator and together with MK, NR and KH contributed to the conception, design, analysis and interpretation of the study. SK undertook the statistical analysis. All authors participated in the development of this manuscript.

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Conflict of interest statement

SK, KH and MK are employees of GSK and KH and MK declare having GSK stocks. NR was previously employed by GSK group of Companies. TFS has received honoraria from GSK as consultant, lecturer, member of advisory boards and for conducting clinical trials on behalf of his institution.

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