

Short communication

Immunogenicity of reduced antigen content tetanus–diphtheria–acellular pertussis vaccine in adolescents as a sixth consecutive dose of acellular pertussis-containing vaccine

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Abstract

Three hundred and nineteen adolescents aged 10–12 years who had been previously vaccinated with five doses of acellular pertussis-containing vaccines received single doses of Tdap (reduced-antigen-content tetanus, diphtheria, acellular pertussis) and hepatitis A vaccines in a double-blind crossover trial. Long-term antibody persistence following vaccination with Tdap at pre-school age was similar to that following vaccination with DTaP (diphtheria–tetanus–acellular pertussis). After the sixth dose booster, Tdap induced a vigorous immune response, consistent with protection against diphtheria, tetanus and pertussis diseases.

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1. Introduction

The tolerability of booster vaccination with a reduced-antigen-content tetanus–diphtheria–acellular pertussis (Tdap) vaccine when administered to adolescents as a sixth consecutive dose of acellular pertussis-containing vaccine (aP) has been recently reported [1]. Following vaccination with Tdap, subjects reported more pain, but less redness and swelling compared with the incidences when these same individuals received their fifth diphtheria–tetanus–acellular pertussis (DTaP) dose at pre-school age. Here we report the immunogenicity of Tdap booster in this cohort, together with antibody persistence since the fifth aP-containing vaccine dose.

2. Materials and methods

2.1. Study design

This was a double-blind, crossover study conducted across Germany [1]. Adolescents (aged 10–12 years) who had previously been vaccinated with five doses of aP-containing vaccines were randomized to vaccination with either: Tdap (Boostrix[®]) [2] at day 0 and hepatitis A (Havrix[®]) [3] at day 30 (Group Tdap → HAV), or hepatitis A at day 0 and Tdap at day 30 (Group HAV → Tdap).

2.2. Assessment of immunogenicity

Blood samples for Tdap antigens were collected before the first vaccination and 1 month after the second (i.e. 1 and 2 months after Tdap vaccination in Group HAV → Tdap and Group Tdap → HAV, respectively) and were analysed at GlaxoSmithKline Biologicals (Belgium) using standard analytical techniques and cut-offs [4].

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2.3. Statistical analysis

Analysis of immunogenicity after the booster dose was based on the according to protocol (ATP) immunogenicity cohort. Antibody persistence was assessed on the ATP persistence cohort. The ATP cohorts included all enrolled and vaccinated adolescents who met eligibility criteria, complied with protocol-defined procedures and for whom immunogenicity data were available. For each antigen seroprotection/seropositivity/booster response rates with exact 95% confidence intervals (CIs) were calculated. For diphtheria and tetanus the proportion of subjects with antibody concentrations ≥ 1.0 IU/mL was also calculated. Geometric mean antibody concentrations (GMCs) with 95% CIs were tabulated, assuming log-transformed titers were normally distributed. Immunogenicity was an exploratory secondary study objective, therefore all analyses were descriptive.

3. Results

Of 321 enrolled subjects 284 participated in ATP persistence [1] and 281 in the ATP immunogenicity cohorts. Within the total cohort: 195 subjects had previously received five doses of DTaP; 83 had received four doses of DTaP + one dose of Tdap at 4–6 years; 43 had received four doses of DTaP + another aP-containing vaccine at 4–6 years (the results from these 43 remaining subjects were analysed, but are not presented given the small cohort size and the heterogeneous nature of their last aP vaccination) [1]. The enrolled

population was entirely Caucasian of mean age 10.9 years; 51.1% were male. The mean time since the subjects received their last aP-containing vaccine was 5.8 years (range 5.4–6.3) in the group that previously received five doses of DTaP, and 5.8 years (range 5.7–6.1) in the group that previously received four doses of DTaP + one dose of Tdap.

3.1. Antibody persistence

Before vaccination, >94% subjects who previously received either five DTaP or four DTaP + Tdap remained seroprotected (≥ 0.1 IU/mL) against both anti-tetanus and anti-diphtheria antibodies (Table 1). Similarly, >99% subjects in both groups remained seropositive (≥ 5 EL U/mL) for both anti-FHA (filamentous hemagglutinin) and anti-PRN (pertactin) antibodies. Seropositive rates against anti-PT (pertussis toxin) antibodies were lower (>44%). For all DTaP antigens, antibody persistence results after either five DTaP or four DTaP + Tdap doses were similar (95% CI overlap) except for anti-tetanus antibodies ≥ 1.0 IU/ml, where the incidence was higher for the four DTaP + Tdap group (clinical relevance not known).

3.2. Booster immunogenicity

After booster vaccination all subjects in the five DTaP or four DTaP + Tdap groups had seroprotective (≥ 0.1 IU/mL) antibody concentrations against diphtheria, tetanus, and had seropositive (≥ 5 EL U/mL) anti-PT, anti-FHA and anti-PRN antibody concentrations (Table 2). Booster responses and

Table 1
Antibody persistence in 10–12-year old subjects after the last aP-containing vaccine dose at 4–6 years of age (ATP persistence cohort)

Antibody persistence	Vaccination history			
	5 DTaP		4 DTaP + 1 Tdap	
	N	% or value (95% CI)	N	% or value (95% CI)
Anti-diphtheria				
≥ 0.1 IU/mL	180	96.7 (92.9; 98.8)	69	94.2 (85.8; 98.4)
≥ 1.0 IU/mL	180	29.4 (22.9; 36.7)	69	21.7 (12.7; 33.3)
GMC (IU/mL)	180	0.57 (0.49; 0.65)	69	0.53 (0.42; 0.66)
Anti-tetanus				
≥ 0.1 IU/mL	179	98.3 (95.2; 99.7)	68	98.5 (92.1; 100)
≥ 1.0 IU/mL	179	21.8 (16.0; 28.6)	68	42.6 (30.7; 55.2)
GMC (IU/mL)	179	0.57 (0.51; 0.64)	68	0.76 (0.61; 0.95)
Anti-PT				
≥ 5 EL U/mL	173	44.5 (37.0; 52.2)	68	51.5 (39.0; 63.8)
GMC (EL U/mL)	173	5.0 (4.3; 5.7)	68	5.8 (4.6; 7.3)
Anti-FHA				
≥ 5 EL U/mL	180	99.4 (96.9; 100)	69	100 (94.8; 100)
GMC (EL U/mL)	180	62.4 (54.6; 71.3)	69	64.7 (53.0; 79.0)
Anti-PRN				
≥ 5 EL U/mL	180	99.4 (96.9; 100)	70	100 (94.9; 100)
GMC (EL U/mL)	180	61.5 (54.0; 70.0)	70	66.1 (55.0; 79.3)

N: number of subjects with available results; anti-PT: anti-pertussis toxin; anti-FHA: anti-filamentous hemagglutinin; anti-PRN: anti-pertactin; vaccination history: subjects primed and boosted with four previous doses of DTaP and a further booster dose at 4–6 years of either DTaP (group 5 DTaP) or Tdap (group 4 DTaP + 1 Tdap); 95% CI: 95% confidence interval.

Table 2
Antibody responses to diphtheria and tetanus toxoids and pertussis antigens after booster vaccination with Tdap and according to vaccine history (ATP cohort for immunogenicity)

Antibody response	Vaccination history							
	5 DTaP				4 DTaP + 1 Tdap			
	HAV → Tdap (day 30 post-Tdap)		Tdap → HAV (day 60 post-Tdap)		HAV → Tdap (day 30 post-Tdap)		Tdap → HAV (day 60 post-Tdap)	
	<i>N</i>	% or value (95% CI)	<i>N</i>	% or value (95% CI)	<i>N</i>	% or value (95% CI)	<i>N</i>	% or value (95% CI)
Anti-diphtheria								
≥0.1 IU/mL	93	100 (96.1; 100)	86	100 (95.8; 100)	34	100 (89.7; 100)	36	100 (90.3; 100)
≥1.0 IU/mL	93	98.9 (94.2; 100)	86	93.0 (85.4; 97.4)	34	97.1 (84.7; 99.9)	36	97.2 (85.5; 99.9)
GMC (IU/mL)	93	7.4 (6.3; 8.7)	86	4.3 (3.5; 5.1)	34	8.1 (6.0; 11.0)	36	6.0 (4.6; 7.7)
Booster response	92	87.0 (78.3; 93.1)	86	76.7 (66.4; 85.2)	34	97.1 (84.7; 99.9)	35	94.3 (80.8; 99.3)
Anti-tetanus								
≥0.1 IU/mL	93	100 (96.1; 100)	86	100 (95.8; 100)	34	100 (89.7; 100)	36	100 (90.3; 100)
≥1.0 IU/mL	93	100 (96.1; 100)	86	100 (95.8; 100)	34	100 (89.7; 100)	36	100 (90.3; 100)
GMC (IU/mL)	93	8.8 (7.7; 10.2)	86	5.0 (4.4; 5.8)	34	8.6 (7.1; 10.3)	36	5.7 (4.8; 6.8)
Booster response	92	90.2 (82.2; 95.4)	85	89.4 (80.8; 95.0)	33	84.8 (68.1; 94.9)	35	74.3 (56.7; 87.5)
Anti-PT								
≥5 EL U/mL	93	100 (96.1; 100)	86	100 (95.8; 100)	34	100 (89.7; 100)	36	100 (90.3; 100)
GMC (EL U/mL)	93	52.0 (45.3; 59.8)	86	33.5 (28.8; 38.9)	34	51.8 (41.6; 64.7)	36	38.1 (28.8; 50.4)
Booster response	88	81.8 (72.2; 89.2)	83	67.5 (56.3; 77.4)	32	75.0 (56.6; 88.5)	36	75.0 (57.8; 87.9)
Anti-FHA								
≥5 EL U/mL	93	100 (96.1; 100)	86	100 (95.8; 100)	34	100 (89.7; 100)	36	100 (90.3; 100)
GMC (EL U/mL)	93	656.3 (580.0; 742.8)	86	499.8 (433.7; 576.1)	34	674.4 (533.5; 852.4)	36	432.6 (349.0; 536.2)
Booster response	92	97.8 (92.4; 99.7)	86	93.0 (85.4; 97.4)	33	97.0 (84.2; 99.9)	36	100.0 (90.3; 100)
Anti-PRN								
≥5 ELU/mL	93	100 (96.1; 100)	86	100 (95.8; 100)	34	100 (89.7; 100)	36	100 (90.3; 100)
GMC (EL U/mL)	93	694.2 (593.1; 812.6)	86	384.9 (327.1; 452.8)	34	651.0 (530.0; 799.7)	36	467.4 (391.2; 558.3)
Booster response	92	95.7 (89.2; 98.8)	86	96.5 (90.1; 99.3)	34	94.1 (80.3; 99.3)	36	91.7 (77.5; 98.2)

N: number of subjects with available results; vaccination history: subjects primed and boosted with four previous doses of DTaP and a further booster dose at 4–6 years of either DTaP (group 5 DTaP) or Tdap (group 4 DTaP + 1 Tdap); anti-PT: anti-pertussis toxin; anti-FHA: anti-filamentous hemagglutinin; anti-PRN: anti-pertactin; booster responses defined as follows: for diphtheria and tetanus, post-vaccination antibody concentration ≥0.4 IU/mL in initially seronegative subjects (antibody concentrations <0.1 IU/mL) or a ≥4-fold increase in initially seropositive subjects; for PT, FHA, and PRN, antibody concentration ≥20 EL U/mL in initially seronegative subjects (antibody concentrations <5.0 EL U/mL) or ≥4-fold increase in subjects with pre-vaccination antibody concentrations ≥5.0 EL U/mL and <20 EL U/mL, or ≥2-fold increase in subjects with pre-vaccination antibody concentrations ≥20 EL U/mL; 95% CI: 95% confidence interval.

GMCs for all vaccine antigens were similar (95% CI overlapped) in both groups after Tdap vaccination. Timing of the blood sample after vaccination influenced the antibody response to vaccination towards lower immune response at 60 days post-Tdap vaccination.

3.3. Post hoc analysis for vaccine efficacy

A post hoc analysis to assess efficacy of the pertussis components of the Tdap vaccine was performed by comparing anti-pertussis antibody GMCs in the HAV → Tdap group to those observed in infants after a three-dose primary vaccination series with DTaP (Infanrix®) administered at 3, 4, and 5 months [5]. The 95% CIs of the antibody GMC ratio between the DTaP and Tdap vaccine recipients in both studies 1 month after vaccination were computed. Whereas the observed GMC before Tdap vaccination was below those observed in the DTaP study 1-month post-vaccination (48.6, 89.1 and 124.2 for PT, FHA and PRN, respectively), the upper limit of the 95% CI of the ratio of antibody GMCs (DTaP/Tdap 1 month after vaccination) was 1.06 (PT), 0.16 (FHA), and 0.21 (PRN) which was below the post hoc non-inferiority criteria (1.5).

4. Discussion

The immunogenicity of the Tdap vaccine has been demonstrated in children, adolescent and adult populations previously primed with whole-cell pertussis vaccines (DTPw), DTaP or by natural infection [4,6–9]. Many adolescents previously vaccinated with five aP doses may soon receive Tdap as their sixth aP dose [10]. Recently, Pichichero et al. reported that a sixth sequential dose of Tdap induced comparable tetanus, diphtheria and pertussis antibody responses irrespective of the prior DTaP/DTwP vaccine history [11]. In our study, a single booster dose of Tdap induced high levels of seroprotection against diphtheria and tetanus, substantial rises in antibody GMCs and anti-pertussis antibody concentrations at least as high as those observed in infants 1 month after vaccination with three doses of DTaP (Infanrix®) in whom efficacy against pertussis disease has been previously demonstrated [12].

Although most subjects had received prior vaccination with five doses of DTaP, a small number had received the Tdap vaccine for their fifth aP dose at 4–6 years of age. Within this latter group there was no evidence that Tdap at 4–6 years of age resulted in reduced antibody concentrations against any vaccine antigen compared to DTaP at 4–6 years of age. Outside of the United States, Boostrix® Tdap vaccine is licensed in more than 45 countries for use as a booster dose in individuals from 4 years of age or from 10 years of age.

It is interesting to note that for all antigens, antibody concentrations were lower when sampled 2 months after Tdap as compared to 1 month after vaccination. This is consistent with previous findings, for example for diphtheria and tetanus

where antibody decay characteristically follows a biphasic profile with a rapid non-linear phase followed by a slower linear phase [13]. Antibodies against pertussis antigens also decrease rapidly after vaccination [14,15].

This study suggests that long-term antibody persistence following vaccination with Tdap at pre-school age is similar to that following vaccination with DTaP. Furthermore, as a sixth dose booster, Tdap induces a vigorous immune response.

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