



Short communication

The safety and reactogenicity of a reduced-antigen-content diphtheria-tetanus-acellular pertussis (dTpa) booster vaccine in healthy Vietnamese children



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ABSTRACT

Despite effective infant immunization against pertussis, the disease continues to circulate due to waning immunity. Booster vaccinations against pertussis beyond infancy are widely recommended. In Vietnam, however, no recommendations for pertussis boosters beyond the second year of life exist. This open-label, single-centre study was designed to assess the safety of a single booster dose of reduced-antigen-content-diphtheria-tetanus-acellular-pertussis vaccine (dTpa) in 300 healthy Vietnamese children (mean age 7.9 years), who had completed primary vaccination against diphtheria, tetanus and pertussis. Solicited symptoms were recorded for 4 days and unsolicited and serious adverse events (SAEs) for 31 days post-vaccination. Pain and fatigue were the most common solicited local and general symptoms in 35.0% and 14.0% of children, respectively. Grade 3 swelling occurred in 3 children; no large injection site reactions or SAEs were reported. The dTpa booster vaccine was well tolerated and this study supports its administration in school age Vietnamese children.

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1. Introduction

Vaccination coverage rates for infants against pertussis have increased over recent years, but the burden of disease remains high in developing countries [1–3]. Despite receiving a complete primary and booster vaccination course with combined diphtheria, tetanus and pertussis vaccines (DTP) within the first two years of life, older children and adolescents can become susceptible to pertussis or act as reservoirs of infection to younger pre-vaccinated siblings due to waning of immunity over time [1,3]. Therefore periodic booster vaccinations against pertussis might be necessary throughout life. In Vietnam, the current recommendation for pertussis vaccination comprises a three-dose primary vaccination course within the first six months of life, given in combination as

Abbreviations: AE, adverse event; CI, confidence interval; DTP, diphtheria, tetanus and pertussis vaccine; dTpa, reduced-antigen-content diphtheria, tetanus and acellular pertussis vaccine; IU, international units; SAE, serious adverse event; SD, standard deviation.

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DTP, followed by a booster before the age of two years [4]. Without further follow-up booster vaccinations, waning immunity against pertussis results in increased likelihood of infection and babies too young to be vaccinated will be at greater risk of contracting the disease [5,6]. This situation could further escalate since primary vaccination uptake rates in Vietnam have recently dipped, with a decline in vaccine coverage to 83% in 2012 compared with estimated values >93% for the previous 5 years [7].

Booster doses of the full-strength diphtheria-tetanus-acellular pertussis (DTPa) containing vaccines, used for primary vaccination, have been associated with increased reactogenicity [8]. Reduced-antigen-content dTpa vaccines have therefore been developed for boosting older children, adolescents and adults [9–11]. A three pertussis component, reduced-antigen-dose dTpa vaccine (*Boostrix*TM) manufactured by GSK Vaccines, Belgium was first licensed in Germany in 1999 and its safety and immunogenicity have been well established in children from the age of four years upwards [12–14].

This study was undertaken to evaluate the safety and reactogenicity of a single booster dose of dTpa in older Vietnamese children, to support the registration of the vaccine for use in children from four years of age.

2. Methods

2.1. Study design and participants

This was an open-label, phase III, safety and reactogenicity study conducted at a single centre in Vietnam between 22 February and 10 May 2014 (NCT01988857). Healthy children aged 6–10 years, who had completed routine DTP vaccination in early childhood (according to local recommendations) and had not received any DTP vaccination within the last two years, were enrolled. Children with a previous history of diphtheria, tetanus or pertussis disease, any history of anaphylactic reaction to vaccine components, any immunosuppressive or congenital disease, and children who were in care were excluded from the study.

2.2. Ethical considerations

The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol and associated documents were reviewed and approved by local ethics committees. Written informed consent was obtained before any study procedure could be undertaken.

2.3. Study vaccines

All children received a single dose of dTpa as an intramuscular injection into the deltoid muscle of the non-dominant arm, using a needle at least 2.54 cm length and 22–25 gauge. The vaccine was supplied as a prefilled syringe (lot number: C37B117A). Each 0.5 ml dose contained 2 IU (International units) diphtheria toxoid; 20 IU tetanus toxoid; 8 µg pertussis toxoid, 8 µg filamentous haemagglutinin and 2.5 µg pertactin with 0.5 mg aluminium salts.

2.4. Assessment of reactogenicity and safety

Solicited local reactions (pain, redness and swelling) and general symptoms (fatigue, fever, headache and gastrointestinal [GI] symptoms) were recorded on diary cards on the day of vaccination and for three subsequent days (4-day follow-up). Unsolicited adverse events (AEs) and serious adverse events (SAEs) were recorded by children's parents or legally acceptable representatives for 31 days after booster vaccination, using diary cards which were returned at the last visit. All AEs were proactively followed by the investigator after the initial report.

Symptom intensity was graded on a 3-point scale. Grade 1 symptoms were defined as easily tolerated, and Grade 2 symptoms as interfering with normal every-day activities. Grade 3 redness and swelling were defined as having a surface diameter >50 mm, and Grade 3 fever as axillary temperature >39.0 °C. For all other symptoms "Grade 3" was defined as preventing normal activities.

The causality of systemic adverse events was assessed by the investigator; all local adverse events were considered as being related to study vaccine.

Children with large injection site swellings (diameter >100 mm, noticeable diffuse swelling or increase in arm circumference) were evaluated as soon as possible by the investigator.

2.5. Statistical analyses

A sample size of approximately 300 study participants was required for the analysis of safety according to Vietnamese regulatory requirements. The analyses to ascertain the percentage of children reporting adverse events with 95% confidence intervals (CI) were performed on all vaccinated study participants (Total Vaccinated Cohort; TVC).

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

3. Results

3.1. Study participants

302 children were screened of whom 300 received the dTpa vaccine and completed the study; there were no protocol deviations. The mean age (SD) of the enrolled children was 7.9 (±1.38) years; 151 study participants were male and all were of South East Asian ethnicity.

3.2. Safety and reactogenicity

Solicited local and general adverse events occurring during the 4-day follow-up post-vaccination period are shown in Fig. 1. Pain was the most common solicited local symptom in 105 (35.0%) children. Redness and swelling occurred in 55 (18.3%) and 40 (13.3%) children, respectively. Grade 3 swelling occurred in only 3 children (1.0%) and no large injection site swelling was reported. No local symptom requiring medical attention was reported.

Fatigue was the most common general symptom in 42 (14.0%) children. There was a single case of grade 3 fatigue, but no other grade 3 general adverse events. Medical advice was required for 1 child, for whom fatigue, headache and fever, were reported.

Unsolicited AEs were reported in 19 (6.3%) children during the 31-day follow-up (Table 1). Pharyngitis was the most common unsolicited symptom in 7 (2.3%) children. No SAEs were recorded during the study.

4. Discussion

In this reactogenicity study, a booster dose of reduced-antigen content dTpa vaccine was well tolerated in Vietnamese children; the safety profile was consistent with previous studies undertaken in Asian children in Thailand, India, China and Taiwan [15,16]. In a study conducted in 60 healthy Taiwanese children aged 6–8 years,

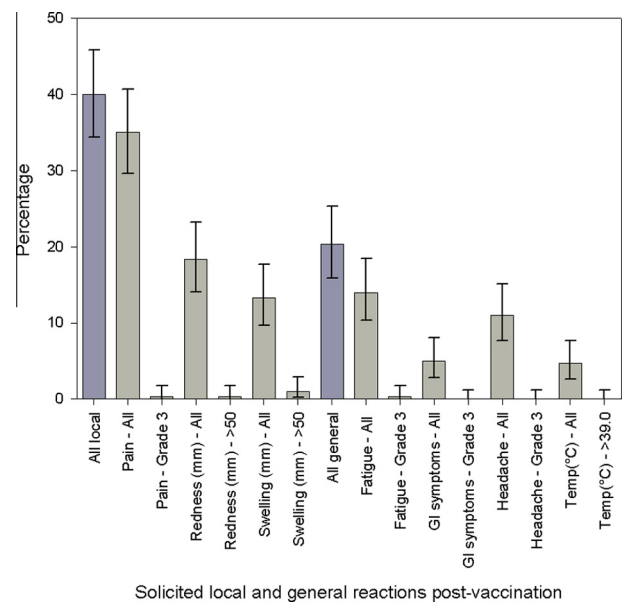


Fig. 1. Solicited local and general adverse events during the 4-day post-vaccination follow-up period (Total Vaccinated Cohort). Footnote: GI, gastrointestinal; temp, temperature.

Table 1
Percentage of children reporting unsolicited adverse events within the 31-day post-vaccination period (Total Vaccinated Cohort; N = 300).

Primary System Organ Class	Preferred term	n	%	95% CI
At least one symptom		19	6.3	3.9–9.7
General disorders	Pyrexia	2	0.7	0.1–2.4
Infections and infestations	Bronchitis	2	0.7	0.1–2.4
	Nasopharyngitis	2	0.7	0.1–2.4
	Pharyngitis	7	2.3	0.9–4.7
	Respiratory tract infection	3	1.0	0.2–2.9
	Tonsillitis	1	0.3	0.0–1.8
Respiratory, thoracic and mediastinal disorders	Cough	3	1.0	0.2–2.9
	Rhinorrhoea	1	0.3	0.0–1.8
Skin and subcutaneous tissue disorders	Pruritus allergic	1	0.3	0.0–1.8

Footnote: N, total number of participants; n, number of participants in a given category; CI, confidence interval.

local symptoms following a booster dose of dTpa vaccine were reported with a higher incidence than in the current study. Pain was also the most frequently reported local symptom (in 66.7% of children) within the 15-day period following vaccination [16]. Redness and swelling occurred in 35% and 40% of children. Local symptoms seemed to be approximately 3 times more frequent than general symptoms, an observation which was not apparent during our study. Incidence of fatigue (14.0% vs 16.7%), gastrointestinal symptoms (5.0% vs 6.7%) and headache (11.0% vs 10.0%) were comparable between the present study and the one conducted in Taiwanese children. A potential limitation of this comparison is that symptoms were reported over a longer period in the Taiwanese trial. However, the majority of solicited symptoms had an onset within 48 hours after vaccination. In general, consistent patterns of AEs were described in a very broad range of age groups following administration of a dTpa booster dose [17], and no notable exceptions were observed in the present study.

A review of data on dTpa administered as a single booster dose showed that although lower incidences of local and general solicited reactions were reported following vaccination with dTpa compared with DTPa, no significant differences between the vaccines in terms of reactogenicity in children aged 4–8 years were evident [18]. However, repeated booster vaccination with full strength DTPa (4th and 5th doses in toddlers and pre-school age children, respectively) has been associated with large injection site reactions [8]. The reduced-antigen content dTpa vaccine has been previously shown to induce fewer extensive swelling reactions than full-strength DTPa [19] and in this study, no large injection site reactions were observed.

Using a booster dose beyond infancy is a prophylactic strategy to prevent pertussis in older children and also to minimize the risk of transmission to infants too young to be vaccinated, in whom the disease is most severe [1]. Although this study was not designed to evaluate immunogenicity, many previous studies from around the world have demonstrated high immunogenicity in a similar aged population [12,13,15,16,20] as well as in adolescents and adults [17].

This was a reactogenicity study, limited in being open-label and conducted at a single centre. In addition, no detailed information on previous DTP vaccination (full or reduced doses) was collected, which might impact the interpretation of the study results. A strength of the study was that all 300 vaccinated children were followed for the duration of the study; there were no withdrawals or protocol violations.

In Vietnam, the current recommendation is for a three-dose primary vaccination series against diphtheria, tetanus and pertussis within the first six months of age followed by a booster dose at 18 months of age [4]. Our results, which evaluated the safety and reactogenicity of the vaccine are consistent with previous results

and support the use of dTpa booster vaccination in school age Vietnamese children.

5. Financial disclosure

GlaxoSmithKline Biologicals SA was the funding source and was involved in all stages of the study conduct and analysis. GlaxoSmithKline Biologicals SA also paid all costs associated with the development and publication of this manuscript.

6. Conflict of interest

HHH, SK and GJ are employees of GSK group of companies and HHH and GJ declare having GSK stocks. DDA has no conflicts to declare.

Boostrix is a trademark of the GSK group of companies.

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References

- [1] Tan T, Trindade E, Skowronski D. Epidemiology of pertussis. *Pediatr Infect Dis J* 2005;24:S10–8.
- [2] Jackson DW, Rohani P. Perplexities of pertussis: recent global epidemiological trends and their potential causes. *Epidemiol Infect* 2014;142:672–84.
- [3] WHO. Pertussis vaccines: WHO position paper. *Wkly Epidemiol Rec* 2010;85:385–400.
- [4] Centers for Disease Control and Prevention: Pertussis: Summary of Vaccine Recommendations; 2013. Available from: <<http://www.cdc.gov/vaccines/vpd-vac/pertussis/recs-summary.htm>> [accessed 11th August 2015].
- [5] de Greeff SC, Mooi FR, Westerhof A, Verbakel JM, Peeters MF, Heuvelman CJ, et al. Pertussis disease burden in the household: how to protect young infants. *Clin Infect Dis* 2010;50:1339–45.
- [6] Safadi MA. Control of pertussis in infants: time has finally come? *Expert Rev Vaccines* 2015;14:781–3.
- [7] WHO. Viet Nam: WHO and UNICEF estimates of immunization coverage. Available from: <http://www.who.int/immunization/monitoring_surveillance/data/vnm.pdf> [accessed 11th August 2015].
- [8] Rennels MB. Extensive swelling reactions occurring after booster doses of diphtheria-tetanus-acellular pertussis vaccines. *Semin Pediatr Infect Dis* 2003;14:196–8.
- [9] Booy R, Van der Meeren O, Ng SP, Celzo F, Ramakrishnan G, Jacquet JM. A decennial booster dose of reduced antigen content diphtheria, tetanus, acellular pertussis vaccine (Boostrix™) is immunogenic and well tolerated in adults. *Vaccine* 2010;29:45–50.
- [10] Broder KR, Cortese MM, Iskander JK, Kretsinger K, Slade BA, Brown KH, et al. Preventing tetanus, diphtheria, and pertussis among adolescents: use of

- tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006;55:1–34.
- [11] Abarca K, Valdivieso F, Potin M, Ibanez I, Vial P. Immunogenicity and reactogenicity of a reduced antigen content diphtheria, tetanus and acellular pertussis vaccine (dTpa) in 10 to 11 years old children and in adults. *Rev Med Chil* 2002;130:502–10.
- [12] Bose A, Dubey AP, Gandhi D, Pandit A, Raghu MB, Raghupathy P, et al. Safety and reactogenicity of a low dose diphtheria tetanus acellular pertussis vaccine (Boostrix™) in pre-school Indian children. *Indian Pediatr* 2007;44:421–4.
- [13] Kosuwon P, Warachit B, Hutagalung Y, Borkird T, Kosalaraksa P, Bock HL, et al. Reactogenicity and immunogenicity of reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (dTpa) administered as a booster to 4–6 year-old children primed with four doses of whole-cell pertussis vaccine. *Vaccine* 2003;21:4194–200.
- [14] Zhu F, Zhang S, Hou Q, Zhang Y, Xu Y, Ma X, et al. Booster vaccination against pertussis in Chinese children at six years of age using reduced antigen content diphtheria-tetanus-acellular pertussis vaccine (Boostrix™). *Hum Vaccin* 2010;6.
- [15] Lin TY, Wang YH, Huang YC, Chiu CH, Lin PY, Tang H, et al. Booster vaccination at 6–8 years of age with a reduced antigen content dTpa-IPV vaccine is immunogenic and safe after priming with whole-cell pertussis vaccine. *Hum Vaccin* 2008;4:50–3.
- [16] Huang LM, Chang LY, Tang H, Bock HL, Lu CY, Huang FY, et al. Immunogenicity and reactogenicity of a reduced-antigen-content diphtheria-tetanus-acellular pertussis vaccine in healthy Taiwanese children and adolescents. *J Adolesc Health* 2005;37:517.
- [17] Scott LJ, McCormack PL. Reduced-antigen, combined diphtheria, tetanus, and acellular pertussis vaccine, adsorbed (Boostrix®): a guide to its use as a single-dose booster immunization against pertussis. *BioDrugs* 2013;27:75–81.
- [18] McCormack PL. Reduced-antigen, combined diphtheria, tetanus and acellular pertussis vaccine, adsorbed (Boostrix®): a review of its properties and use as a single-dose booster immunization. *Drugs* 2012;72:1765–91.
- [19] Quinn P, Gold M, Royle J, Buttery J, Richmond P, McIntyre P, et al. Recurrence of extensive injection site reactions following DTPa or dTpa vaccine in children 4–6 years old. *Vaccine* 2011;29:4230–7.
- [20] Ferrera G, Cuccia M, Mereu G, Icardi G, Bona G, Esposito S, et al. Booster vaccination of pre-school children with reduced-antigen-content diphtheria-tetanus-acellular pertussis-inactivated poliovirus vaccine co-administered with measles-mumps-rubella-varicella vaccine: a randomized, controlled trial in children primed according to a 2 + 1 schedule in infancy. *Hum Vaccin Immunother* 2012;8:355–62.