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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

Q1 Corinne Vandermeulen[a,*], Heidi Theeten[b], Niraj Rathi[c,d], Sherine Kuriyakose[d], Htay Htay Han[d], Etienne Sokal[e], Karel Hoppenbrouwers[a], Pierre Van Damme[b]

[a] KU Leuven, University of Leuven, Centre for Environment and Health, Youth Health Care Leuven, Belgium
[b] Centre for the Evaluation of Vaccinations, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium
[c] PATH. New Delhi, India
[d] GlaxoSmithKline Vaccines, India and United States
[e] Universite Catholique de Louvain, Cliniques St Luc, Pediatric Clinical Research Unit, Brussels, Belgium

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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.

* Corresponding author. Tel.:+32 16 34 20 20; fax: +32 16 34 20 50.
E-mail addresses: corinne.vandermeulen@uzleuven.be (C. Vandermeulen), heidi.theeten@uantwerpen.be (H. Theeten), drnirajrathi@yahoo.com (N. Rathi), sherine.o.kuriyakose@gsk.com (S. Kuriyakose), Htay.H.Han@gsk.com (H.H. Han), Etienne.Sokal@uclouvain.be (E. Sokal), karel.hoppenbrouwers@med.kuleuven.be (K. Hoppenbrouwers), pierre.vandamme@uantwerpen.be (P. Van Damme).

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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 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], immunisation 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 immunisation 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. 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),

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