Persistence of antibodies 3 years after booster vaccination of adults with combined acellular pertussis, diphtheria and tetanus toxoids vaccine

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ABSTRACT

The duration of protection after vaccination with reduced antigen content diphtheria, tetanus and acellular pertussis vaccines (Tdap) is not known. Long-term post-vaccination serological data will help to improve understanding of the duration of humoral immunity and guide vaccination policy for the timing of repeat dose administration. The persistence of antibodies to Tdap antigens was measured 3 years after vaccination of adults 19–64 years of age with one of 2 Tdap vaccines (Boostrix®, GlaxoSmithKline Biologicals; Tdap-B: or Adacel®, Sanofi Pasteur; Tdap-A). In both groups, geometric mean concentrations for antibodies to diphtheria, tetanus, and pertussis vaccine antigens were decreased at year 3 relative to levels observed 1 month and 1 year following vaccination, but remained higher than pre-vaccination levels. Seroprotection rates for diphtheria and tetanus remained high for both Tdap vaccines (for diphtheria, 96.9% and 97.8% for the Tdap-B and Tdap-A groups, respectively; for tetanus, 98.1% and 99.6%, respectively).

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1. Introduction

Despite relatively good vaccine coverage for children and recent recommendations for vaccination of adults and adolescents, the number of pertussis cases reported annually in the US has been increasing since the early 1990s. In 2009, the most recent year for which confirmed data are available, a total of 16,858 pertussis cases were reported in the US [1]. Pertussis is widely considered to be underreported, and estimates of actual case numbers range from 800,000 to 3.3 million per year [2]. In 2010, several US states reported pertussis epidemics: in California, 8,383 pertussis cases were reported, with 10 infant deaths [3]. The 2010 state-specific incidence rate of 21.4/100,000 population was the highest recorded since 1960 [3].

Neither disease-induced nor vaccine-induced immunity to pertussis is lifelong. Currently a single Tdap booster is recommended for US adolescents and adults. However, with few studies and relatively limited length of follow-up available to assess the persistence of antibodies to Tdap antigens after vaccination, the appropriate interval for repeat Tdap dosing is unknown.

The current study is being conducted to assess levels of antibodies to Tdap antigens in a US population up to 10 years after vaccination [4]. Levels of antibodies to vaccine antigens 1 month and 1 year following vaccination have been reported previously [5]. Antibody levels 3 years after a single dose of Tdap vaccine are reported here. Additional assessments 5 and 10 years after vaccination are planned.

2. Methods

This was an open controlled, serological follow-up study (NCT00489970, 110082) conducted in 36 centers in the United States between 18 June and 22 September 2009. In the initial vaccination study (NCT00106316, 106316) healthy adults 19–64 years of age were randomized (2:1) to receive a single dose of Boostrix® (Tdap-B; N = 1522) or Adacel® (Tdap-A; N = 762). All subjects who received study vaccination in study 106316 were invited to participate in this persistence study.

The study was conducted according to Good Clinical Practice and in accordance with the Declaration of Helsinki. The protocol and associated documents were reviewed and approved by ethics committees at each study center. Written informed consent was obtained from subjects before study entry.

Blood samples were collected from all subjects prior to and approximately 1 month after booster vaccination, and 1 and 3 years after the booster dose. Antibodies to vaccine antigens were measured using standard enzyme-linked immunosorbent assays.
(ELISA). The ELISA cut-off for seroprotection for diphtheria and tetanus was 0.1 IU/mL and the cut-off for seropositivity for pertussis antigens was 5 ELISA units/mL (EL.U/mL). Samples with anti-diphtheria concentrations <0.1 IU/mL were re-tested with a more sensitive in vitro neutralization assay on Vero cells (assay cut off for seroprotection of 0.016 IU/mL).

The analysis of immunogenicity was conducted on the Year 3 according to protocol (ATP) immunogenicity cohort, which included all vaccinated subjects who attended the Year 3 visit, who met all protocol-defined eligibility criteria, who complied with protocol-defined procedures, and for whom assay results were available. Subjects were excluded from the ATP cohort if they reported tetanus toxoid or diphtheria toxoid-containing vaccinations other than study vaccines since enrollment in study 106316, or, had been diagnosed with diphtheria, tetanus or pertussis disease, or if they were immunosuppressed (defined as >14 days of immunosuppressants or other immune-modifying drugs within 90 days prior to blood sampling; or any confirmed or suspected immunosuppressive or immunodeficient condition based on medical history and physical examination).

Potential differences between groups in terms of D and T responses were assessed by exploratory comparisons: a statistically significant difference between groups was considered when the 2-sided standardized asymptotic 95% CI on the group difference in seroprotection rate excluded the value ‘0’, or, if the 95% CI on the geometric mean antibody concentration (GMC) ratio excluded the value ‘1’. GMC ratios were obtained using an ANCOVA model on the log10-transformed concentrations with study group as fixed effect and age at Year 3 and pre-vaccine antibody concentration as regressors. No adjustment for multiplicity of endpoints was made.

3. Results

A total of 2284 individuals were vaccinated with one of the Tdap vaccines in study 106316. Of these, 1505 subjects provided a blood sample at Year 3. A total of 119 subjects (82 in the Tdap-B group and 37 in the Tdap-A group) were eliminated from the According-to-Protocol (ATP) cohorts (39 for prohibited vaccinations, 7 for use of immunosuppressive medications, 73 due to inadequate or missing serological specimens). All elimination conditions occurred after the original vaccination phase. The remaining 1386 subjects were included in the ATP analyses of immunogenicity for the Year 3 cohort. Demographic characteristics of the subjects in each group were similar and representative of the ATP immunogenicity cohort in study 106316 in terms of age distribution and gender (Table 1).

Three years after vaccination, seroprotection rates for diphtheria and tetanus had decreased minimally since the immediate post-vaccination period. The percentage of subjects with antibody concentrations ≥0.1 IU/mL was 93.8% in the Tdap-B group and 96.2% in the Tdap-A group for diphtheria, and 98.1% and 99.6%, respectively, for tetanus (Fig. 1). Subject sera with anti-diphtheria antibody concentrations below the ELISA assay cutoff of 0.1 IU/mL were retested using the more sensitive Vero cell neutralization assay. The overall diphtheria seroprotection rate (given by the percentage of subjects with anti-diphtheria antibody concentrations ≥0.1 IU/mL by ELISA or ≥0.016 IU/mL by the Vero cell neutralization assay) was 96.9% in the Tdap-B group and 97.8% in the Tdap-A group. In both groups, antibody GMCs for diphtheria and tetanus decreased at each follow-up time point yet remained higher than pre-vaccination levels (Fig. 2). Exploratory comparisons showed that the percentage of subjects with anti-tetanus antibody concentrations ≥0.1 IU/mL and the anti-tetanus antibody GMC were statistically significantly higher in the Tdap-A group than the Tdap-B group at year 3. Reverse cumulative curves (RCCs) for anti-D and anti-T antibodies at year 3 are given as supplemental material (Fig. 2).

The percentage of subjects with detectable antibodies against PT, FHA and PRN at each sampling time point is provided in Supplemental Table 2. For both vaccines, seropositivity rates at year 3 were not notably decreased relative to year 1 for anti-FHA and anti-PRN, while the seropositivity rates for anti-PT appeared to have decreased from the values observed 1 month and 1 year
after vaccination. However, the seropositivity rates for all 3 pertussis antibodies remained higher than pre-vaccination levels in both vaccine groups.

In both groups antibodies to pertussis antigens (PT, FHA and PRN) were decreased relative to the levels observed at 1 month and 1 year following vaccination. For anti-FHA and anti-PRN, antibody GMCs remained elevated relative to baseline; for anti-PT, antibody GMCs 3 years after vaccination approached those observed prior to vaccination (Fig. 2). At year 3, anti-PT and anti-FHA antibody GMCs remained numerically higher in Tdap-B recipients than in Tdap-A recipients (Fig. 2), reflecting observations made 1 month post-vaccination [5].

4. Discussion

The Tdap vaccine (Boostrix®) is licensed in the United States for use as a single booster dose in adolescents and adults 10 years of age and older. Booster vaccination against diphtheria and tetanus is recommended every 10 years in adults [6]. By contrast, Tdap vaccine is recommended as a single dose in adolescents and adults, and currently there is no provision for administration of booster doses. No data on long-term immunogenicity following Tdap vaccination, or of the safety and immunogenicity of repeated Tdap booster vaccination in US populations, are currently available. Such data are needed to guide vaccination policy for the timing of repeat doses.

This study shows that 3 years after vaccination with Tdap the percentage of subjects with seroprotective levels of antibodies against diphtheria and tetanus remained high (>96.9%) in both groups of vaccinees. Consistent with observations 1 month and 1 year after vaccination, anti-tetanus antibody GMCs were higher at year 3 in the Tdap-A group than in the Tdap-B group [5]. Exploratory analysis at year 3 indicated tetanus seroprotection rates were higher for Tdap-A than for Tdap-B; this was not observed at earlier time points. Whether this represents a clinically important difference in tetanus protection is not clear [7,8].

Antibody levels against PT, FHA and PRN decreased over time and remained higher at Year 3 than prior to booster vaccination, although anti-PT levels approached pre-vaccination levels. Since there are no established serological correlates of protection for pertussis vaccination, no conclusions can be made with regard to differences in antibody levels and protective potential of these vaccines. Studies of Tdap-B (using a formulation marketed outside of the US) showed persisting cell-mediated immune responses up to

Fig. 2. Antibody GMCs before and up to 3 years after vaccination with Tdap-B or Tdap-A (Year 3 ATP immunogenicity cohort). ◆ Tdap-B group; □, Tdap-A group. *Statistically significant difference between groups: the 95% CI for the between-group anti-tetanus GMC ratio (adjusted) excluded 1.
5 years after vaccination, even in subjects who were seronegative for antibodies against vaccine antigens [9]. Therefore, the duration of protection against disease may be longer than that predicted by the duration of antibodies alone.

To date, few studies have been conducted to assess long-term persistence of antibody levels following Tdap vaccination. Antibody persistence following Tdap-B vaccination has been investigated in 2 studies conducted in Europe and Australia, using a Tdap-B formulation containing 0.5 mg Al per dose, in which levels of antibodies to Tdap-B antigens were measured at intervals of up to 10 years following vaccination [7,10]. In these studies, antibodies against FHA and PRN decreased over time, and levels of anti-diphtheria, anti-tetanus and anti-PT antibody concentrations approached pre-booster levels 10 years following vaccination [7,10]. In the US, Tdap-B contains 0.3 mg Al per dose; results from the present study using the US vaccine formulation are consistent with those using the higher Al formulation.

This study supports the immunogenicity of Tdap in US adolescents and adults and demonstrates persistence of antibodies against vaccine antigens through the first 3 years after vaccination. Additional assessment at year 5 and year 10 are planned and will contribute to a better understanding of the kinetics of antibody decay after vaccination, and the potential timing of additional doses.

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Conflict of interest statement

Wayde Weston, Leonard Friedland, Xiangfeng Wu, and Barbara Howe are employees of GlaxoSmithKline. At the time of writing this manuscript, Marc Messier was contracted to work for GSK via CHILTERN, an independent Contract Research Organization. WW, LF, MM and BH, declare ownership of GSK stock/stock options.

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BOOSTRIX is a trademark of the GlaxoSmithKline group of companies. ADACEL is a registered trademark of Sanofi Pasteur.

Appendix A. Supplementary data


References