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Humoral immunity 10 years after booster immunization with an adolescent and adult formulation combined tetanus, diphtheria, and 5-component acellular pertussis vaccine in the USA

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ABSTRACT

Background: In a prospective, randomized pivotal phase III clinical trial, the immunogenicity and reactogenicity of a tetanus-diphtheria-acellular pertussis vaccine (Tdap) and a tetanus-diphtheria vaccine (Td) vaccine were studied in participants aged 11–64 years. Here we report antibody persistence through 10 years after vaccination.
Methods: Participants who received Tdap or Td in the original phase III trial and provided pre- and post-vaccination serum samples were recruited to donate sera at 1, 3, 5 and 10 years post-vaccination. Antibody concentrations were measured using standard assay techniques.
Results: Initially, 1457 Tdap and 1152 Td recipients were included; of these, 175 persons from Tdap group were available at the final study bleed point. Nearly all adolescents in both groups had diphtheria antibody levels ≥0.1 IU/mL 1 month after vaccination, which were maintained in ≥95% of vaccinees at 5 and 10 years. Among adults, ≥94% had diphtheria antibody levels ≥0.1 IU/mL 1 month after vaccination, which were maintained in ≥80% at 5 and 10 years. Nearly all participants had tetanus antibodies ≥0.1 IU/mL throughout the study. PT antibodies declined to pre-vaccination levels approximately 5 years post-vaccination; FHA, PRN and FIM antibodies waned at 5 and 10 years but remained several-fold higher than pre-vaccination levels.
Conclusions: Tdap and Td provide long-lasting protective immune responses against diphtheria and tetanus. Pertussis antibodies following Tdap generally exceeded pre-vaccination levels throughout the study, but showed substantial waning. These data may inform discussion of the need for repeat Tdap booster vaccinations among adults.
Trial registration: The original phase III clinical trial, as well as the 1-, 3-, and 5-year serology follow-up studies were conducted prior to mandatory registration. The 10-year serology follow-up data collection was performed as part of a repeat Tdap administration clinical trial that was registered under clinicaltrials.gov number NCT01439165.

1. Introduction

The universal use of pediatric diphtheria, tetanus, and pertussis vaccines in the United States, as well as in many other countries, has resulted in a marked reduction in morbidity and mortality among infants and young children. Because protection afforded by these inactivated vaccines is not life-long, the risk of pertussis may increase as vaccinated children age. For example, in 2005, the year the first two Tdap vaccines were approved in the USA, following unvaccinated infants, the second highest incidence of reported pertussis was observed among persons aged 10–19 years (10.6 per 100,000 population per year). It is believed that pertussis among adults is grossly underreported and that there is substantial morbidity in this population; studies of prolonged cough illness among adolescents and adults conducted in the 1990s showed that between 12% and 32% were due to *Bordetella pertussis* [1]. More

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recent studies also confirm that pertussis infection continues to be endemic among adolescents and adults [2].

Adacel® (Sanofi Pasteur, Swiftwater, PA), a tetanus, reduced diphtheria, and 5-component acellular pertussis combination vaccine (Tdap), was designed to help provide continuous protection against three diseases as a booster in adolescents and adults. In the USA, this Tdap vaccine was licensed in 2005 based on the results of a pivotal phase III randomized clinical trial conducted in adolescents and adults [3]. As part of a post-licensure commitment with the US Food and Drug Administration (FDA), long-term serology follow-up studies have been conducted to determine diphtheria, tetanus, and pertussis antibody persistence up to 10 years after the initial Tdap dose. Such data may help inform decisions on the timing of and the need for periodic Td or Tdap booster(s).

2. Materials and methods

2.1. Study design

Participants studied in this long-term serology follow-up were those from a large pivotal phase III trial conducted in the USA in 2001–2002. Adolescents and adults aged 11 through 64 years, who received whole-cell pertussis vaccine series in their childhood, were enrolled and randomized to receive Tdap or Td (3:2 for adolescents; 3:1 for adults) [3]. A subset of participants (representing 50% of Tdap recipients, 75% of adolescent Td recipients, and 100% of adult Td recipients) were included in the immunogenicity assessment group. These participants provided pre- and 1 month post-vaccination serum samples and agreed to be contacted to provide additional blood samples at later time points. They were subsequently contacted via letter, phone, or email at approximately 1, 3, and 5 years after vaccination to donate blood for serology testing. Only those who received Tdap vaccine in the original study were contacted and recruited at the 10-year follow-up point. Participants were excluded from analysis if they received any vaccine containing tetanus, diphtheria, or pertussis antigens after the initial study vaccination, or were clinically diagnosed or laboratory confirmed to have had pertussis. Antibody responses were analyzed separately for adolescents 11–17 years of age and adults 18–64 years of age at enrollment in the original study and this was continued at each of the follow-up points.

The original phase III trial and the subsequent 1-, 3- and 5-year serology follow-up studies were conducted prior to mandatory registration with the ClinicalTrials.gov database. Participants who provided a blood sample at the 10-year serology follow-up point were also recruited to participate in a repeat Adacel vaccine administration trial (NCT01439165) [4].

The study protocols and informed consents were approved by each individual study center's Institutional Review Board in accordance with US FDA regulations. The studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP), and International Conference on Harmonization (ICH) regulatory guidelines regarding the protection of the rights and welfare of participants in biomedical research.

2.2. Vaccines

Adacel vaccine (Tdap) contains 5 limit of flocculation units (Lf) tetanus toxoid (T), 2 Lf diphtheria toxoid (d), 2.5 μg pertussis toxoid (PT), 5 μg filamentous hemagglutinin (FHA), 3 μg pertactin (PRN), and 5 μg fimbriae types 2 & 3 (FIM). The Td vaccine used as a control product (Td Adsorbed Vaccine, Sanofi Pasteur) contains 5 Lf tetanus toxoid and 2 Lf diphtheria toxoid. Both Tdap and Td vaccines contained 1.5 mg aluminum phosphate (equivalent to 0.33 mg aluminum) as adjuvant.

2.3. Serological assays

All diphtheria and tetanus testing was performed at the Global Clinical Immunology laboratory (GCI; Sanofi Pasteur, Swiftwater, Pennsylvania, USA). Pertussis testing (for PT, FHA, PRN and FIM antibodies) was performed at the Clinical Immunology Platform (CIP; Sanofi Pasteur, Toronto, Canada) for sera obtained pre-vaccination and 1 month, 1 year, and 3 years post-vaccination, and at GCI for the 5- and 10-year follow-up.

Tetanus antibody concentrations were measured by enzyme-linked immunosorbent assay (ELISA) and diphtheria antibody concentrations were measured by micrometabolic inhibition test (MIT). Tetanus and diphtheria concentrations were expressed as International Units (IU)/mL and were standardized against World Health Organization reference sera. For diphtheria and tetanus, seroprotective levels of antibodies were defined as $\geq$0.01 IU/mL and $\geq$0.1 IU/mL; these levels are generally accepted as proxies of short- and long-term protection, respectively [5,6].

Antibodies against PT, FHA, PRN, and FIM (2 and 3) were measured by ELISA on microtiter plates with diluted serum samples (test samples, reference standards, and quality controls). An in-house reference standard serum assayed on each plate was used to calculate the amount of specific pertussis antibody in the test samples in ELISA Units per mL (EU/mL) by comparison to the reference standard curves.

2.4. Statistical analyses

No hypothesis testing was undertaken in this study; descriptive statistics were used to summarize the data. Diphtheria and tetanus seroprotection rates, rates of pertussis antibodies greater than or equal to $\geq$4 times (x) the lower limit of quantification (LLOQ), and geometric mean concentrations (GMCs) for all measured antibodies were calculated using valid results from all vaccinated participants in the per-protocol immunogenicity (PPI) population. The PPI population included participants from the PPI population in the original study who provided a serum sample at 1 year, and/or 3 years, and/or 5 years, and/or 10 years, respectively, and who did not receive any diphtheria-, tetanus-, or pertussis-containing vaccine after the initial study vaccination. The results were generated separately for two age groups: those who were adolescents 11–17 years of age and those who were adults 18–64 years of age at enrollment in the original study.

To calculate rates of pertussis antibodies $\geq 4 \times$ LLOQ, the following thresholds were used: for sera obtained in the original study, and at 1 and 3 years post-vaccination, $4 \times$ LLOQ thresholds were 20 EU/mL for PT, 12 EU/mL for FHA and PRN, and 68 EU/ml for FIM; for sera obtained at 5 and 10 years post-vaccination, the $4 \times$ LLOQ thresholds were 16 EU/mL for PT, PRN and FIM, and 12 EU/mL for FHA.

3. Results

3.1. Participants

Of the 4450 participants in the original phase III trial, a sub-group of 2609 (1457 Tdap and 1152 Td recipients) provided pre-vaccination and 1-month post-vaccination blood samples. The disposition of the participants in the long-term follow-up PPI population by age group, gender, vaccine type, and study year is presented in Table 1. Among adolescents, there were approximately equal numbers of males and females participating, except at year 10 where two thirds of participants were female. Of the adult participants, 62–72% were female.

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