SAFETY 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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Objective The safety of a booster dose of a reduced-antigen-content tetanus–diphtheria–acellular pertussis (Tdap) vaccine was evaluated in adolescents previously vaccinated with five doses of acellular pertussis–containing vaccine.

Study design Adolescents (n = 319) previously vaccinated with either 5 doses of diphtheria–tetanus–acellular pertussis (DTaP) (n = 193) or 4 doses of DTaP plus another acellular pertussis–containing vaccine received one dose each of Tdap and hepatitis A vaccine in a double-blinded, randomized, crossover trial. Rates of adverse events (AEs) after vaccination with Tdap versus hepatitis A and rates of local AEs among adolescents vaccinated with Tdap (sixth acellular pertussis–containing vaccine dose) versus rates in these same individuals after vaccination with their fifth DTaP dose were assessed.

Results After Tdap, pain (63.6%), redness (51.7%), and swelling (41.4%) were the most frequently reported AEs. Large injection site swelling (swelling >100 mm, arm circumference increase >50 mm or diffuse swelling interfering with daily activities) occurred in three adolescents and resolved without sequelae. After the sixth dose of acellular pertussis–containing vaccine, adolescents reported more pain and less redness and swelling compared with incidences of these AEs reported when these same individuals received their fifth DTaP dose.

Conclusions These results suggest that Tdap is well tolerated as a sixth consecutive dose of acellular pertussis–containing vaccine. *(J Pediatr 2006;149:603-10)*

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Diphtheria, tetanus, and acellular pertussis combined vaccines have been available for more than a decade and are included in national childhood immunization programs in developed countries throughout the world. Despite good control of pertussis in young children, the overall number of reported pertussis cases has risen over the past few decades.[1,2] This increase has been due largely to the substantial increase of reported cases in persons 10 years or older, of which the greatest number of cases is reported in adolescents. In 2004, 10- to 19-year-olds accounted for 38% of cases reported to the US Centers for Disease Control and Prevention (CDC).[3,4]

Before the widespread use of acellular pertussis (aP and ap, depending on antigen content) vaccines, vaccination against pertussis was not recommended for individuals older than 6 years of age because of concerns of increased reactogenicity of the whole-cell diphtheria-tetanus-pertussis vaccines (DTwP). The advent of reduced-antigen-content acellular pertussis vaccines offers the opportunity to extend pertussis prevention to older age groups. In 2005, two reduced-antigen-content tetanus–diphtheria–acellular pertussis (Tdap) vaccines were licensed by the Food of Drug Administration for single-dose use in

AE	Adverse event	DTP	Diphtheria, tetanus, and pertussis
aP	Pediatric formulation of acellular pertussis vaccine	DTwP	Diphtheria, tetanus, and whole-cell pertussis vaccine
ap	Adolescent formulation of acellular pertussis vaccine	IPV	Inactivated polio virus
CDC	Centers for Disease Control and Prevention	Lf	Limit of flocculation unit
DTaP	Diphtheria, tetanus, and acellular pertussis vaccine	PT	Pertussis toxin
		Tdap	Reduced-antigen-content tetanus, diphtheria, and acellular pertussis vaccine

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adolescents in the United States.[5] One of these Tdap vaccines also was licensed for single-dose use in adults.[5] Outside of the United States, Tdap vaccine is licensed worldwide for use as a booster dose in individuals from 4 years of age or from 10 years of age.

Pediatric diphtheria–tetanus–acellular pertussis (DTaP) vaccines have only been recommended in the United States for use as the five-dose childhood series since 1997. Therefore, with infrequent exceptions for individuals who participated in infant DTaP vaccine research studies, the adolescents who enrolled in the US Tdap prelicensure studies had not received an all-acellular pertussis vaccine schedule. Previous studies have shown that rates of local reactions increase with successive doses of acellular pertussis vaccine.[6] This study evaluated the safety and reactogenicity of a booster dose of a US-licensed Tdap vaccine (Boostrix®, GlaxoSmithKline Biologicals, Rixensart, Belgium) when administered to adolescents previously vaccinated with five consecutive doses of acellular pertussis–containing vaccine. The cohort for this study is unique; to our knowledge, this is the first cohort of individuals specifically enrolled in a clinical trial to be vaccinated with a sixth consecutive dose of acellular pertussis–containing vaccine (the majority of these individuals received five doses of DTaP). The objectives of this study were to assess the overall safety profile of Tdap among adolescents previously vaccinated with five consecutive doses of acellular pertussis–containing vaccine and to compare the rates of local adverse events (AEs) among adolescents vaccinated with Tdap (sixth acellular pertussis–containing vaccine dose) with rates of local AEs in these same individuals after vaccination with their fifth DTaP dose at age 4 to 6 years.

METHODS

Study Design

The study was conducted according to good clinical practice and in accordance with the Declaration of Helsinki. The ethics committees at each center reviewed the protocol. Written informed assent was obtained from the children/adolescents, with consent from their parents/guardians before study entry.

This was a prospective, comparative, double-blinded, randomized, multicenter study. Adolescents were randomly assigned into two groups (1:1); one group received Tdap vaccine at day 0 and a hepatitis A vaccine (Havrix®) at day 30; the other group received the hepatitis A vaccine at day 0 and Tdap vaccine at day 30 in a crossover design. Prevaccination temperature and mid–upper arm circumference of the injection arm were recorded before each injection. Rates of AEs were compared after vaccination with Tdap (sixth acellular pertussis–containing vaccine dose) versus hepatitis A vaccine, and rates of local AEs were compared among the adolescents vaccinated with Tdap (sixth acellular pertussis–containing vaccine dose) versus rates in these same individuals after vaccination with their fifth DTaP dose at age 4 to 6 years.

Study Subjects

This cohort derives from a series of DTaP vaccine studies of subjects receiving primary and booster doses in trials conducted in Germany throughout the 1990s. All of the individuals received four doses of the DTaP vaccine Infanrix®. Local adverse events that are commonly reported to occur after vaccination with this vaccine are injection site pain, swelling, and redness.[7] The last of these trials included 835 individuals who were 4 to 6 years old and was conducted to evaluate a fifth dose of acellular pertussis–containing vaccine either as DTaP (n = 520), Tdap (n = 211), or aP/ap (n = 104). Approximately 40% of the 835 enrolled in the previous studies were anticipated to enroll in this study to receive their sixth consecutive acellular pertussis–containing vaccine. A total of 321 adolescents (38.4%) were enrolled.

The study was conducted at 16 different study centers in Germany. Protocol criteria were checked before enrollment. Adolescents must have participated in the previous fifth consecutive dose trials of acellular pertussis–containing vaccine. Furthermore, individuals were included if they were 9 to 13 years of age at study entry and were healthy (established by medical history and physical examination). Exclusion criteria included receipt of any investigational or nonregistered drug or any vaccine other than the study vaccines within 30 days of study entry, any diphtheria–tetanus–pertussis antigen–containing vaccine since completion of the fifth acellular pertussis–dose studies, a history of hypersensitivity to any components of the vaccines, history of previous hepatitis A vaccination or infection, or DTP contraindication or precaution.[8] Concomitant protein conjugate vaccines (such as meningococcal conjugate vaccine) were not administered because these vaccines were not recommended for adolescents in Germany at the time of this study.

Vaccines

The Tdap and hepatitis A vaccines used in this study were developed and manufactured by GlaxoSmithKline Biologicals in Rixensart, Belgium. The Tdap vaccine Boostrix® contains tetanus toxoid (5 limit of flocculation unit [Lf]), diphtheria toxoid (2.5 Lf), 8 μg each of pertussis toxoid (PT) and filamentous hemagglutinin, 2.5 μg of pertactin, aluminum adjuvant (not more than 0.39 mg aluminum by assay) per 0.5 mL dose, and is free of thimerosal and other preservatives. The hepatitis A vaccine used in this study, Havrix®, contains 720 enzyme-linked immunosorbent assay (ELISA) units of inactivated hepatitis A viral antigen grown in human diploid cell culture, adsorbed onto 0.25 mg aluminum as aluminum hydroxide, per 0.5 mL dose. The DTaP vaccine given to these children in the previous primary and booster studies contained tetanus toxoid (10 Lf), diphtheria toxoid (25 Lf), 25 μg each of PT and filamentous hemagglutinin, 8 μg of pertactin, and aluminum adjuvant (not more than 0.65 mg aluminum by assay) per 0.5 mL dose. The Tdap vaccine given to these children when they were 4 to 6 years old contained the identical tetanus, diphtheria, and pertussis antigens and antigen quantities as contained in the Tdap vaccine