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Two consecutive randomized controlled pertussis booster trials in children initially vaccinated in infancy with an acellular vaccine: The first with a five-component Tdap vaccine to 5-year olds and the second with five- or monocomponent Tdap vaccines at age 14–15 years

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ABSTRACT

Prior study children from a DTaP efficacy trial were recruited at ages 5 and 15 years to randomized booster trials addressing immunogenicity and reactogenicity; 475 preschool children received mixed or separate injections of a reduced antigen vaccine (Tdap5, Sanofi Pasteur MSD) and an inactivated polio vaccine, and 230 adolescents received the same or another booster vaccine (Tdap1, SSI, Denmark).

Pre-vaccination antibody concentrations against pertussis antigens were significantly higher at 15 than 5 years of age, probably due to natural boosting between the studies. Tdap5 induced comparable anti-PT concentrations at both ages, but antibody responses were significantly higher to filamentous haemagglutinin, pertactin and fimbriae 2/3 in adolescents. As expected, a higher amount of PT (Tdap1, 20 μg) induced a stronger anti-PT response than a lower amount (Tdap5, 2.5 μg).

The frequency of adverse events was low and there were no serious adverse reactions. All local reactions had an early onset and a short duration. A large swelling or redness of more than half of the upper arm circumference was reported in 8/475 5-year-olds and in 6/230 15-year-olds. Children vaccinated with Tdap5 reported more moderate pain in adolescence than at preschool age, whereas itching was only reported in preschool children.

Sweden introduced DTaP vaccines in 1996 after a 17-year hiatus with no general pertussis vaccination and pertussis was still endemic at the time of the studies. The frequency of adverse events was nevertheless low in both preschool children and adolescents and antibody responses were adequate. These studies document immunogenicity and reactogenicity in a trial cohort consecutively vaccinated with acellular pertussis vaccines from infancy to adolescence.

The adolescent study was registered at ClinicalTrials.gov on 26 March 2009 (NCT00870350).

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1. Background

Pertussis is a highly contagious disease that in the pre-vaccine era was a scourge of childhood, with peak incidences every 3–5 year and severe disease and deaths mainly in young children. From mid-20th century the whole cell pertussis (wP) vaccines almost eliminated this burden-of-disease in the industrialized

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world, although wP vaccines from different manufacturers were shown to vary greatly in efficacy. Also, there were some setbacks due to unproven allegations about safety. Common local reactions and/or fever were shown to increase in frequency with number of doses.

Starting in Japan, vaccines with purified antigens from *Bordetella pertussis* were developed in the 1970s and 1980s. Following large vaccine efficacy trials in Sweden and elsewhere, combinations including these acellular pertussis (aP) and diphtheria-tetanus (DT) vaccines were introduced in most western countries. In Sweden, pertussis was by then (1996) common, since wP vaccination had been discontinued 17 years earlier.

Other countries introduced the aP vaccines in a more controlled setting, by replacing preschool and later also infant wP doses. Already before aP vaccination, the number of reported pertussis cases started to rise in a number of countries [1–5], predominantly among older children, adolescents and adults, lately with a further shift of cases to children under 1 year of age. The explanation is not fully understood but many western countries have adopted one or more additional vaccination strategies to reduce infant morbidity and mortality. There are also renewed efforts to find new vaccines although safety is not a major issue this time because of far fewer adverse effects from DTaP than DTwP vaccines.

Moreover, resurgence is not universal and there is heterogeneity in incidence trends. In Sweden, there is as yet no generally resurgent pertussis in spite of relatively few doses within the childhood national program and no cocooning, maternal or other adult vaccination strategy. Three infant doses are since 1996 recommended at ages 3, 5 and 12 months. A preschool 4th dose of DTaP was introduced ten years later, and a school-leaving 5th dose with reduced antigen content (Tdap) will be introduced in 2016.

Notably, the DTaP vaccines were licensed for infant use after large controlled trials addressing both efficacy and safety, whereas the Tdap vaccines were approved after clinical studies addressing immunogenicity and safety, with clinical effects "estimated" by serologic bridging to the previous efficacy studies. One of these bridging studies is presented here; a phase II booster study (1999) in preschool children from a previous efficacy trial [6]. We also present an adolescent phase IV booster study performed ten years later (2009) with a subset of participants from the preschool study. The overall purpose was to study the antibody responses and safety of the 4th and 5th consecutive doses of acellular pertussis vaccine, when given at ages corresponding to the Swedish vaccination calendar.

The specific aim of the first trial was to compare immunogenicity and reactogenicity from mixed or separate injections of a Tdap and an inactivated polio vaccine (IPV) in pre-school children. The aim of the second was to describe the antibody responses and tolerability in adolescents vaccinated with the same or another Tdap vaccine.

T and B cell immune responses were measured in subpopulations. These results will be or are presented elsewhere.

2. Materials and methods

2.1. Study design

Children born in 1994, previously vaccinated in an efficacy trial with three infant doses of a five acellular components vaccine DTaP5 [6], were invited to participate in booster studies of immunogenicity and reactogenicity on two separate occasions: a booster study of the corresponding five-component Tdap5 vaccine in 1999 at age 5 years, and a booster study of the same Tdap5 and a monocomponent (Tdap1) vaccine in 2009 at age 14–15 years.

Both studies used an open randomized parallel group multicenter study design (one study center each in six cities throughout Sweden) with blinded seroanalyses. Vaccines were allocated to unique study numbers by computerized blocked randomization procedures in respectively 3:1 and 1:1 ratios.

2.1.1. Booster study 1999, preschool children

Assuming a true response rate of at least 98% for all antigens, 235 participants in a study group was sufficient for the lower 95% confidence interval (CI) limit to exceed 95% with a probability of 90%. The width of the 95% CI will approximately be 3.6% [7].

Of 1682 invited subjects, 486 did not respond, 338 declined and 146 were already vaccinated with IPV. The remaining 712 were randomly allocated to receive Tdap5 and IPV vaccines separately (235 children), the combined Tdap5-IPV vaccine (240 children), or control vaccines (DT and IPV, 237 children).

Results for the control group [7], are not presented in the tables but commented in text.

2.1.2. Booster study 2009, adolescents

The sample size of the adolescent study was limited by the numbers of participants in the previous study [8].

The 475 children vaccinated in 1999 with Tdap5 were considered eligible, but 20 were lost to follow-up and 138 were already vaccinated within school health care. The remaining 322 were invited to participate, whereof 230 accepted and were randomized to receive either the Tdap5 vaccine again, or a Tdap1 vaccine.

2.1.3. Study vaccines

The dose contents of the two Tdap vaccines and the investigational DTaP5 that was administered in infancy [6] are found in Table 1. The investigational Tdap5 vaccine used in 1999 was later licensed under the names of Adacel®, Triaxis® or Covaxis®, produced by Sanofi Pasteur Limited. It is an adsorbed combination vaccine containing purified diphtheria and tetanus toxoids and five purified components of *B. Pertussis*. Covaxis® lot C2695AB was used in the 2009 study. The Tdap1 is a combined adsorbed tetanus, low dose diphtheria and monocomponent ap vaccine, produced by SSI and licensed under the name of diTeKiBooster®. Lot 832301 was used.

The Tdap vaccines were administered in the left (1999) or right (2009) deltoid muscle, using a muscle grasp between the thumb and fingers, with needle size 25 mm 23–25 Gauge at an angle of 90°.

2.2. Serological analyses

Sera obtained pre- and 28–42 days post-vaccination were analyzed by a previously described accredited indirect ELISA method [9–11] for IgG antibodies against pertussis toxin (anti-PT), filamentous haemagglutinin (anti-FHA), pertactin (anti-PRN), fimbriae 2 and 3 (anti-FIM). Antibodies against diphtheria toxin (anti-D) and tetanus toxoid (anti-T) were analyzed in 1999 by a DELFIA method [12] and in 2009 by ELISA [11].

Antigens and coating doses used for ELISA were PT (SmithKline Beecham, TOH15) 1 μg/ml, FHA (SmithKline Beecham, TOH15) 1.5 μg/ml, PRN (Aventis Pasteur Canada, SKA-QCDSCO4420) 2.5 μg/ml, FIM (Connaught Laboratories Ltd, Ontario Canada, CAG9/14-PDS) 1 μg/ml, diphtheria (SBL, Sweden, lot no 2072) and tetanus toxoids (Statens Serum Institut, Denmark, batch 59–5) 1 Lf/ml. DELFIA antigens were the same and coating doses were 2.5 and 1.5 μg/ml respectively.

The calibrators used and their antibody contents were a FDA reference human antiserum for the pertussis assays (HRP 4, 90 EU/ml for PRN, HRP 3 for PT and FHA, 200 EU/ml and FIM, 100 EU/ml, a reference human antiserum from Swiss Serum and Vaccine Institute Berne for diphtheria (183 280 105, 170 IU/ml) and a pool of

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