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Whole-cell or acellular pertussis vaccination in infancy determines IgG subclass profiles to DTaP booster vaccination

Saskia van der Lee [a,b,*], Elisabeth A.M. Sanders [a,b], Guy A.M. Berbers [a], Anne-Marie Buisman [a]

[a] Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
[b] Department of Peadiatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital, University Medical Center, Utrecht, The Netherlands

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ABSTRACT

Introduction: Duration of protection against pertussis is shorter in adolescents who have been immunized with acellular pertussis (aP) in infancy compared with adolescents who received whole-cell pertussis (wP) vaccines in infancy, which is related to immune responses elicited by these priming vaccines. To better understand differences in vaccine induced immunity, we determined pertussis, diphtheria, and tetanus (DTaP) vaccine antigen-specific IgG subclass responses in wP- and aP-primed children before and after two successive DTaP booster vaccinations.

Methods: Blood samples were collected in a cross-sectional study from wP- or aP-primed children before and 1 month after the pre-school DTaP booster vaccination at age 4 years. Blood samples were collected from two different wP- and aP-primed groups of children before, 1 month and 1 year after an additional pre-adolescent Tdap booster at age 9 years. IgG subclass levels against the antigens included in the DTaP vaccine have been determined with fluorescent-bead-based multiplex immunoassays.

Results: At 4 years of age, the IgG4 proportion and concentration for pertussis, diphtheria and tetanus vaccine antigens were significantly higher in aP-primed children compared with wP-primed children. IgG4 concentrations further increased upon the two successive booster vaccinations at 4 and 9 years of age in both wP- and aP-primed children, but remained significantly higher in aP-primed children.

Conclusions: The pertussis vaccinations administered in the primary series at infancy determine the vaccine antigen-specific IgG subclass profiles, not only against the pertussis vaccine antigens, but also against the co-administered diphtheria and tetanus vaccine antigens. These profiles did not change after DTaP booster vaccinations later in childhood. The different immune response with high proportions of specific IgG4 in some aP-primed children may contribute to a reduced protection against pertussis.

Conclusions: ISRCTN65428640; ISRCTN64117538; NTR4089.

1. Introduction

Since the 1990s, pertussis is re-emerging in many countries, despite high coverage of pertussis vaccination in national immunization programs [1–3]. Pertussis outbreaks are reported every two to three years, not only in infants, but also in children, adolescents and adults [4–7]. The replacement of whole-cell pertussis (wP) vaccines by acellular pertussis (aP) vaccines in the primary vaccination series during infancy is thought to contribute to the re-emergence of pertussis [8]. In order to reduce the pertussis burden in children, aP booster vaccinations around 4–6 years of age were implemented in many countries [9,10].

Epidemiological data indicate reduced vaccine-derived protection in aP-primed adolescents compared with adolescents who received at least one wP vaccine in the primary series in infancy [11,12]. Immunological studies comparing wP- and aP-primed children showed differences both in humoral and cellular pertussis-specific immune responses. After a pre-school DTaP booster vaccination at 4 years of age, aP-primed children showed higher pertussis-specific antibody levels and memory B- and T-cell responses compared with wP-primed children [13–17]. Comparable differences with regard to antibody and T-cell responses between wP- and aP-primed infants were observed in children shortly after the primary vaccination series at 13 months of age [18]. In contrast, an additional Tdap booster vaccination in pre-adolescents resulted in better DTaP-specific humoral and cellular

* Corresponding author at: National institute for Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA Bilthoven, The Netherlands.
E-mail addresses: Saskia.van.der.Lee@rivm.nl (S. van der Lee), Lieke.Sanders@rivm.nl (E.A.M. Sanders), Guy.Berbers@rivm.nl (G.A.M. Berbers), Annemarie.Buisman@rivm.nl (A.-M. Buisman).

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immune responses in children who had received wP vaccinations in infancy (van der Lee, submitted).

Although an internationally accepted correlate of protection for pertussis has not been established, pertussis-specific IgG antibodies are involved in protection against clinical pertussis [19,20]. The high effectiveness of preventing pertussis in the first months of life following maternal pertussis vaccination also indicates protection mediated by IgG antibodies [21,22]. Even though all four IgG subclasses are transported over the placenta, IgG4 antibodies are unable to bind complement which makes the contribution to protection against pertussis less likely [23]. Previously, Hendrikx et al. reported a higher proportion of pertussis-specific IgG4 antibodies in 4 year old children primed with DTaP, and boosted with a 5th dose of the same vaccine, compared with children primed with wP vaccines [24]. Increased levels of the IgG4 subclass are associated with a Th2-skewed immune response, which may influence the induced protection against pertussis in vaccinated children [25].

Nowadays, several countries have implemented a 6th DTaP booster vaccination in (pre-) adolescents in order to reduce the pertussis disease burden in adolescents [26]. Information about the pertussis antigen-specific IgG subclass responses in this age group after such a booster is scarce. Furthermore, IgG subclass profiles specific for diphtheria and tetanus, the other components in the DTaP vaccine, have not been studied in aP-primed children.

In this study we determined the IgG subclass profiles for the pertussis, diphtheria and tetanus vaccine antigens in children around 4 and 9 years of age, before and after a pre-school DTaP and a pre-adolescent Tdap booster vaccination. We compared groups vaccinated with either wP- or aP-combination vaccines in the first year of life.

2. Methods

2.1. Study design and participants

The participants were primed according to the Dutch national immunization program: DTwP or DTaP at 2, 3, 4, and 11 months of age and received a DTaP booster vaccination at 4 years of age (Fig. 1). Blood samples were collected from children 4 years of age before and 1 month after the pre-school DTaP booster vaccination (cross-sectional study ISRCTN65428640) [27]. Two groups of children 9 years of age were included in longitudinal intervention studies and received an additional Tdap booster vaccination. Blood samples were collected before, 1 month and 1 year after the Tdap vaccination and plasma's were stored at −20 °C until analysis. These children were primed with either DTwP-combination vaccines in infancy (ISRCTN64117538) [28,29], or with DTaP-combination vaccines (NTR4089) (van der Lee, manuscript submitted for publication). The numbers of participants vary between 40 and 83 participants per time point.

2.2. Vaccines

At 2, 3, 4, and 11 months of age, the participants received either a DTwP-IPV-Hib combination vaccine (Netherlands vaccine institute, Bilthoven, the Netherlands), or a DTaP-IPV-Hib (Infanrix-IPV-Hib™, GlaxoSmithKline (GSK), Rixensart, Belgium) combination vaccine. The children received a pre-school DTaP booster vaccination at 4 years of age (Infanrix-IPV™, GSK), and a pre-adolescent Tdap booster vaccination at 9 years of age (Boostrix-IPV™, GSK).

2.3. Serological analysis

Pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn) (the 3 aP vaccine antigens), diphtheria toxoid and tetanus toxin specific total IgG (IgGt) antibody concentrations were measured with the multiplex immunoassay as described earlier [30,31]. IgG subclass levels for the DTaP antigens were also determined with the fluorescent-bead-based multiplex immunoassay as described separately for PT, FHA and Prn [24] and for diphtheria toxoid and tetanus toxin [32]. Since no IgG subclass reference sample is available for these vaccine antigens, each IgG subclass was expressed in mean fluorescent intensity (MFI) values. The sum of MFI values of all four IgG-subclasses together was set at 100% and than each subclass was expressed as a proportion (in %) of the total. Using the IgGt concentration and the IgG subclass percentages, arbitrary IgG subclass concentrations were calculated. For the pertussis antigens, 5 arbitrary units (AU) per mL was used as cut-off for a seropositive response for each IgG subclass, in line with Hendrikx et al. [24], and the lower limit of quantitation was set at 0.1 AU/mL. For diphtheria and tetanus, an IgG concentration >0.01 IU/mL was used as a cut-off for protection, using the international standard for diphtheria and tetanus [33,34]. In line with this, we applied 0.01 AU/mL as a cut-off for the diphtheria and tetanus IgG subclasses as well. The lower limit of quantitation for diphtheria and tetanus was set at 0.001 AU/mL.

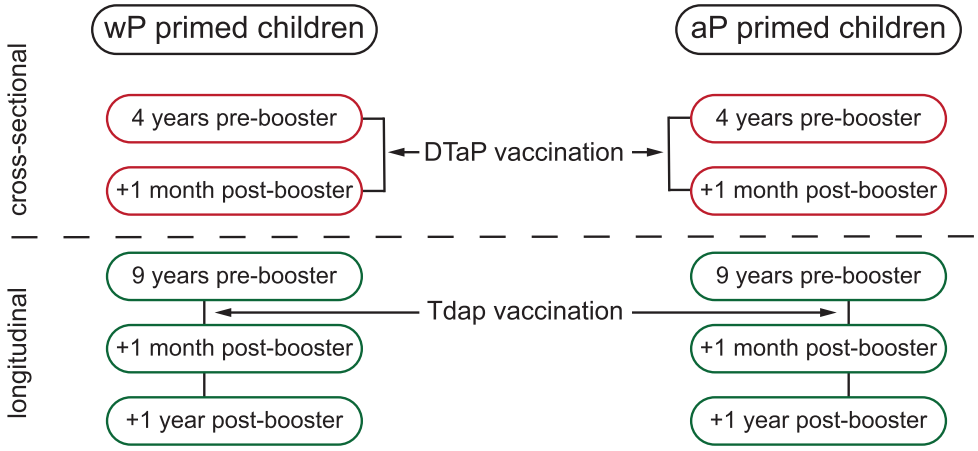

Fig. 1. Overview of the study groups of the participants 4–9 years of age. Children were primed at the age of 2, 3, 4, and 11 months with either whole-cell pertussis (wP) (left panels) or acellular pertussis (aP) (right panels) combination vaccines according to the Dutch national immunization program (NIP). Before and 1 month after the pre-school DTaP booster at age 4 years (received according to the Dutch NIP), blood samples were collected cross-sectionally (red circles) [14]. Children 9 years of age, primed with wP vaccines [27,28] or aP vaccines (NTR4089) received an additional Tdap booster vaccination and were sampled longitudinally before, 1 month and 1 year after the booster (green circles). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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