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Pertussis vaccination during pregnancy in Belgium: Follow-up of infants until 1 month after the fourth infant pertussis vaccination at 15 months of age

Q1 Kirsten Maertens[a,*], Raïssa Nadège Caboré[b], Kris Huygen[b], Sandra Vermeiren[a], Niel Hens[c,d], Pierre Van Damme[a], Elke Leuridan[a]

[a] Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, University of Antwerp, Belgium
[b] National Reference Centre Bordetella, National Reference Centre Toxigenic Corynebacteria, Service Immunology, Scientific Institute of Public Health (WIV-ISP), Brussels, Belgium
Q2 [c] Interuniversity Institute for Biostatistics and Statistical Bioinformatics (I-BIOSTAT), Hasselt University, Hasselt, Belgium
[d] Centre for Health Economics Research and Modeling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Belgium

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ABSTRACT

Vaccination of pregnant women with a pertussis containing vaccine is a recommended strategy in some industrialized countries, to protect young infants from severe disease. One of the effects of the presence of high titers of passively acquired maternal antibodies in young infants is blunting of immune responses to infant vaccination. We present infant immune responses to a fourth pertussis containing vaccine dose at 15 months of age, as a follow-up of previously presented data.

In a prospective cohort study, women were either vaccinated with an acellular pertussis vaccine (Boostrix®) during pregnancy (vaccine group) or received no vaccine (control group).

All infants were vaccinated with Infanrix Hexa® according to the standard Belgian vaccination schedule (8/12/16 weeks, 15 months). We report results from blood samples collected before and 1 month after the fourth vaccine dose. Immunoglobulin G (IgG) antibodies against pertussis toxin (PT), filamentous hemagglutinin (FHA), pertactin (Prn), tetanus toxoid (TT) and diphtheria toxoid (DT) were measured using commercially available ELISA tests. Antibody levels were expressed in International Units per milliliter.

Demographic characteristics were similar in the vaccine and control group. Before the fourth vaccine dose, significantly lower antibody titers were measured in the vaccine group compared to the control group for anti-Prn IgG ($p = 0.003$) and anti-DT IgG ($p = 0.023$), with a steep decay of antibody titers since post-primary vaccination. One month after the fourth dose, antibody titers were only significantly lower in the vaccine group for anti-PT IgG ($p = 0.006$). For all antigens, there was a rise in antibody titer after the fourth vaccine dose.

The present results indicate still a minor blunting effect 1 month after a fourth vaccine dose for anti-PT antibodies. However, a good humoral immune response on all measured antigens was elicited in both groups of children. The clinical significance of such blunting effect is yet unknown.

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1. Introduction

Q3 Pertussis, primarily caused by the gram negative bacteria *Bordetella pertussis*, is a worldwide endemic and epidemic respiratory disease. Despite the successful introduction of global vaccination programs with high immunization rates, pertussis remains an important public health issue [1]. Mainly young infants, too young to be protected by the currently available vaccination schedules, are prone to severe pertussis disease with the highest hospitalization and complication rates among the population [2].

In Belgium, pertussis vaccination with an acellular pertussis containing vaccine (aP) is recommended by the National Immunization Technical Advisory Group (NITAG) at 8, 12 and 16 weeks (primary vaccination). A fourth vaccine dose of an aP containing vaccine is recommended at 15 months of age. Additional booster doses for children and adolescents are equally put in place.

* Corresponding author at: University of Antwerp, Centre for the Evaluation of Vaccination, Vaccine and Infectious Disease Institute, Universiteitsplein 1, 2610 Wilrijk, Belgium. Tel.: +32 32652862.
E-mail address: kirsten.maertens@uantwerpen.be (K. Maertens).

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Furthermore, maternal pertussis vaccination is recommended since August 2013 for pregnant women during every pregnancy between 24 and 32 weeks of gestation. Finally, adults in close contact with young infants are also advised to receive a booster aP vaccine [3]. Despite these national recommendations, the total number of confirmed pertussis cases increased significantly in Belgium from 243 cases in 2011 [4] to 1501 cases in 2014 [5]. The increase in pertussis cases was most prominent in adults between 40 and 60 years. However, the absolute (total) number of pertussis cases remained the highest in infants below one year of age [5].

As a consequence of the presence of high titers of maternal antibodies after maternal vaccination, a blunting effect of infant immune responses has been observed after the first three doses of an aP containing vaccine [6–9]. In a recent clinical study, this blunting effect disappeared after a fourth dose of a pertussis containing vaccine administered at the age of 12 months [6]. However, only limited data are available concerning the effect of a fourth infant dose of an aP containing vaccine [6,10] and data after the administration of a fourth vaccine dose at the age of 15 months are, to our knowledge, lacking. Therefore, the vaccination schedule in Belgium offers the unique opportunity to investigate the effect of high titers of maternal antibodies on the humoral immune responses in infants after a fourth dose of a pertussis containing vaccine at 15 months of age.

We have previously reported on the effect of high titers of maternal antibodies on infant immune responses on the primary infant vaccination schedule at 8, 12 and 16 weeks, after maternal vaccination during pregnancy with the combined tetanus, diphtheria and acellular pertussis (Tdap) vaccine Boostrix® (GSK Biologicals, Rixensart, Belgium). Here we have analyzed possible remaining interference of maternal antibodies with the infant humoral immune responses after a fourth aP containing vaccine dose administered at 15 months of age.

2. Material and methods

A prospective controlled cohort study was conducted in accordance with the Declaration of Helsinki, ICH-GCP and the procedures established by Belgian law. The study was approved by the ethics committee of the University of Antwerp, Belgium (Clinicaltrials.gov identifier: NCT01698346). Informed consent was obtained from both parents of the participating infants. Extended information on material and methods can be found in a previous publication [7].

Children born from healthy women in 5 different hospitals in the province of Antwerp, Belgium, were included in the study and were followed until 1 month after their fourth pertussis containing vaccine dose, administered at 15 months of age. Participating children were included in either a vaccine group, i.e. children born from women vaccinated with an aP containing vaccine (Boostrix®) between 18 and 34 weeks of gestation or a control group, i.e. children born from women not vaccinated with a pertussis containing vaccine for at least 10 years. Women in both study groups did not differ in any underlying characteristics, but randomization was incomplete as explained in the previous publication [7].

For all children, an extended questionnaire on demographics, growth parameters, breastfeeding and immunization data and day-care attendance was completed at every visit.

2.1. Study vaccines

All infants were vaccinated with the licensed hexavalent vaccine (Infanrix hexa®, GSK Biologicals, Rixensart, Belgium). Infanrix hexa® contains 25 Lf of diphtheria toxoid (DT), 10 Lf of tetanus toxoid (TT), 25 μg pertussis toxoid (PT), 25 μg filamentous hemagglutinin (FHA) and 8 μg pertactin (Prn), inactivated poliovirus, hepatitis B surface antigens and *Haemophilus influenzae* type B polysaccharide.

2.2. Study procedures

Blood samples were collected from the infants before (1–14 days) and 1 month after the fourth vaccine dose (28–49 days). Infant vaccines were administered in the regular health system at the well-baby clinics, by a general practitioner or by a pediatrician at the age of 15 months. The samples were centrifuged at 2000 rpm within 24 h after blood collection and stored at −20 °C.

2.3. Safety assessments

At each study visit, medical history of diseases in the household, mainly respiratory diseases, was assessed. All serious adverse events in the infants occurring during the study period were recorded. All infants were examined by a medical doctor at 15 or 16 months of age using the "Van Wiechen developmental test" [11]. This is a Dutch screening test for neurodevelopment used in the general practice to monitor the development of children from birth up to four years of age [12] in a few categories: fine motor activity, adaptive and personal social behavior, communication and gross motor activity (Annex 1).

2.4. Laboratory

All samples were tested with commercially available ELISA kits at the National Institute of Public Health in Brussels, Belgium. The Virion/Serion® kit (ANL, Copenhagen) was used to detect anti-PT IgG antibodies and the Euroimmune® ELISA kit was used to detect anti-FHA and anti-Prn IgG antibodies. Anti-TT and anti-DT IgG antibodies were detected using the Virotech/Sekisui® ELISA kit. Serum samples were tested at a dilution of 1:100. ELISA results were expressed in International Units per millilitre (IU/mL), using respective WHO standards (NIBSC code 06/140 for pertussis, NIBSC code TE-3 for tetanus and NIBSC code 00/496 for diphtheria). For pertussis, these international units are equivalent to the CBER EU units of FDA [13]. The lower limit of detection of the assays was 0.7 IU/mL for PT, 1 IU/mL for FHA, 3 IU/mL for Prn, 0.01 IU/mL for TT and 0.03 IU/mL for DT.

An international independent validation was performed to guarantee the reliability of the results at the Canadian Center for Vaccinology in Halifax, Canada [7].

For pertussis, an actual protective antibody threshold (correlate of protection) is not known [14]. For tetanus and diphtheria, the protective antibody level is defined as 0.1 IU/mL for tetanus and 0.01–0.1 IU/mL for diphtheria.

Blunting of the immune response on the fourth vaccine dose among infants was defined by the authors as a lower geometric mean concentration (GMC) of antigen specific IgG antibodies 1 month after the fourth vaccine dose in the vaccine group compared to the control group.

2.5. Statistics

The initial sample size calculation was performed, based on previous results [15]: a population of 50 subjects in each study arm would be sufficient to detect significant differences in antibody titers at several time points. However, during the conduct of the study, we were confronted with substantial drop-out rates resulting in a smaller sample size before and 1 month after the fourth vaccine dose, mainly in the control group.

Antigen specific antibody GMCs and 95% confidence interval (CI) were calculated at each time point in both study groups.

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