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Pertussis vaccination during pregnancy in Belgium: Results of a prospective controlled cohort study

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

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

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ABSTRACT

Vaccination during pregnancy has been recommended in some countries as a means to protect young infants from severe infection. Nevertheless, many aspects are still unknown and possible blunting of the infant's immune responses by maternal antibodies, is one of the concerns with maternal vaccination. We report the first prospective controlled cohort study in women and infants on the effects of using Boostrix®, a combined tetanus, diphtheria and acellular pertussis vaccine, during pregnancy. The primary aim was to measure the influence of this booster dose on the titer and duration of the presence of maternal antibodies in the infants and assess possible interference with infant immune responses.

In a controlled cohort study, 57 pregnant women were vaccinated with Tdap vaccine (Tetanus Diphtheria acellular Pertussis, Boostrix, GSK Biologicals), at a mean gestational age of 28.6 weeks. A control group of pregnant women ($N = 42$) received no vaccine. Antibody geometric mean concentrations (GMCs) against tetanus (TT), diphtheria (DT), pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (Prn) were measured with commercial ELISA tests in samples taken preceding maternal vaccination and one month afterwards, at delivery and from the cord blood, and in infants before and 1 month after the primary series of 3 pertussis containing hexavalent vaccines.

Infants born to vaccinated women had significantly higher GMC at birth and during the first 2 months of life for all vaccine antigens compared to the offspring of unvaccinated women, thereby closing the susceptibility gap for pertussis in infants. However, blunting was noticed for infant diphtheria and pertussis toxin vaccine responses ($p < 0.001$) in the infants from vaccinated women after the primary vaccination schedule (weeks 8,12 and 16).

Since pertussis vaccination has been recommended during pregnancy already, the results of this study support that recommendation and provide additional scientific evidence to document possible interference by maternal antibodies.

1. Introduction

Pertussis, caused by *Bordetella pertussis*, is a highly contagious respiratory illness and a major cause of infant morbidity and mortality. Global pertussis vaccination programs have been introduced with success and approximately 86% of infants worldwide have received 3 doses of the diphtheria-tetanus–pertussis (DTP3) vaccine [1].

However, a decade after the switch from the whole-cell (wP) vaccine to the acellular pertussis (aP) vaccine, a cyclic resurgence has been reported in several industrialized countries. The reason is presumed to be multifactorial, with waning immunity after the primary or booster vaccination as the primary cause. A resurgence has been observed in all age categories; however, severe morbidity and mortality occurs primarily in young infants who are not fully vaccinated [2,3]. The majority of cases are found in adolescents and adults, due to waning immunity [4], and these populations represent sources of infection for young infants.

* Corresponding author at: University of Antwerp, Centre for the Evaluation of Vaccination, Vaccine and Infectious Diseases Institute, Universiteitsplein 1, 2610 Wilrijk, Belgium. Tel.: +0032 32652944; fax: +0032 32652460.
** Corresponding author. Tel.: +0032 32652885; fax: +0032 32652460.
E-mail addresses: kirsten.maertens@uantwerp.be (K. Maertens), elke.leuridan@uantwerp.be (E. Leuridan).

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In Belgium, pertussis vaccination with a hexavalent aP-containing vaccine is offered at 8, 12, and 16 weeks and 15 months of age. Booster doses for children at 4–6 years of age (since 2004) and for adolescents at 14–16 years of age have been recommended (since 2009). Additionally, receiving a booster dose once during adulthood has been recommended since 2013 [5]. Nevertheless, the total number of confirmed cases increased in Belgium from 93 in 2005 to 843 cases in 2013 [6], of which many (25.4% in 2013) were found in infants under the age of 1 year.

Partial primary protection against infectious diseases is offered at birth by maternal immunoglobulin G (IgG) antibodies [7,8], with an estimated half-life of 6 weeks for pertussis [8]. The amount of transmitted antibodies depends on the placental function and the concentration of maternal antibodies in the pregnant woman [9]. The latter depends on the time lapse since the last vaccination or infection [10] and the titer of passively transmitted pertussis maternal antibodies is often low [11]. Thus, increasing the load of maternal antibodies by vaccination during pregnancy is, with the currently available vaccines, the only way to offer passive protection to the newborn at birth [12]. During the first weeks of life, these maternal antibodies disappear in the newborn due to natural clearance [9,13].

Vaccination during pregnancy is recommended in an increasing number of countries (e.g. UK, USA, Belgium, New Zealand, etc.). Research has been performed on the immunological and safety aspects of the strategy [14–18]; nevertheless, many aspects are still unknown, and the possible interference of maternal antibodies with the infant's immune responses is one of the concerns.

To the best of our knowledge, no other data have been published on the effects of using the combined tetanus, diphtheria and acellular pertussis vaccine Boostrix® (GSK, Rixensart, Belgium) during pregnancy. The primary aim was to measure the influence of this booster vaccination on the titer and the duration of maternal antibodies in infants and to assess possible interference.

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 and was approved by the ethics committee of the University of Antwerp, Belgium (Clinicaltrials.gov identifier: NCT01698346). Written informed consent was obtained from all participants and from both parents of the participating infants (in accordance with the Belgian law and IRB regulations).

Healthy pregnant women and their healthy offspring from 5 different hospitals in the province of Antwerp, Belgium, were included in the study, and follow-up remains ongoing. Pregnant women were included in either a vaccine group, receiving an acellular pertussis vaccine, or a control group, if they had not received any pertussis-containing vaccine for at least 10 years. Strict randomization was not possible because some women were advised positively or negatively by their treating physician on the pertussis vaccination in pregnancy and were included accordingly. The recommendation for receiving the pertussis vaccination during pregnancy by the Belgian National Immunization Technical Advisory Group (NITAG, since August 2013) was not yet in place during the recruitment phase of this study, only a recommendation for cocoon vaccination. However, by 2012, the VVOG (Association of Flemish Obstetricians and Gynecologists) had recommended the ACIP as a valuable alternative for cocoon vaccination on its website. This recommendation was followed by some Belgian clinicians. Strict inclusion and exclusion criteria were used (Annex 1)

An extended questionnaire collected information on obstetrical risk factors, demographics, a general vaccination and pertussis-specific history, and a general medical history. Growth parameters, breastfeeding data, day-care attendance, immunization data, and medical histories for all household members were collected at each visit.

2.1. Study vaccines

Licensed Tdap vaccine (Boostrix®, GSK Biologicals, Rixensart, Belgium) was used to immunize pregnant women. Boostrix® contains 5 Lf of tetanus toxoid (TT), 2.5 Lf of diphtheria toxoid (DT), 8 mcg of inactivated pertussis toxoid (PT), 8 mcg of filamentous haemaglutinin (FHA), and 2.5 mcg of pertactin (Prn). Infants were vaccinated with a hexavalent vaccine (Infanrix hexa®, GSK Biologicals, Rixensart, Belgium). Infanrix hexa® contains 25 Lf of DT, 10 Lf of TT, 25 mcg PT, 25 mcg FHA and 8 mcg Prn, inactivated poliovirus, hepatitis B surface antigens and *Haemophilus influenzae* type B polysaccharide.

2.2. Study procedures

Venous blood (10 cc) was collected from all participating women immediately preceding the vaccination, at 1 month (28–31 days) after vaccination, and at delivery. The maternal vaccination was performed by the study physician or study nurse under supervision. Cord blood was collected at delivery (10 cc). Blood samples (2 cc) were collected from the infants before starting the primary schedule (week 8 ± 4 days) and at month 5 (28–35 days after the third vaccine dose). Infant vaccines were administered in the regular health care system at the well-baby clinics or a pediatrician. Further follow-up is ongoing, with blood samples being collected before and after an Infanrix hexa® booster dose is given at month 15 (data not shown). The samples were centrifuged at 2000 rpm within 24 h and stored at $-20\,^{\circ}C$.

2.3. Safety assessments

Systemic reactions were monitored by a medical doctor in all women for 30 min post-vaccination. Adverse events were monitored for 30 days post-vaccination and included: injection site pain, swelling, erythema, and general symptoms such as myalgia and fever. Serious adverse events during the pregnancy and follow-up period were documented. Whether an adverse reaction was caused by the immunization was judged by the investigators who considered temporality, biologic plausibility, as well as the identification of alternative etiologies for each event. Possible congenital abnormalities were also monitored in the offspring.

2.4. Laboratory

All samples were tested with commercially available ELISA kits at the National Reference Centre for Bordetella. 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. Serum samples were tested in duplicate at a dilution of 1:100 (PT, TT and DT), 1:400 (FHA) and 1:800 (Prn). All OD results were converted into international units per milliliter (IU/mL). For tetanus and diphtheria, the limits of detection were 0.01 IU/mL and 0.03 IU/mL, respectively. All titers are expressed in International Units IU/ml, using respective WHO standards (NIBSC 06/140 for pertussis, NIBSC code TE-3 for tetanus and NIBSC 00/496 for diphtheria). For Pertussis these international units are equivalent to the CBER EU units of FDA [19].

An international independent validation was performed to guarantee the reliability of the results. A random selection of samples ($N = 177$) was reanalyzed at the Canadian Center for Vaccinology in Halifax, where CBER equivalent sera based on the WHO standard