Pneumococcal immune response in infants whose mothers received Tdap vaccination during pregnancy

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Short title: Tdap in pregnancy affects infant pneumococcal responses

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Abbreviations

Tdap: Vaccine containing tetanus, diphtheria and acellular pertussis components

aP: Acellular pertussis

PT: Pertussis Toxin

FHA: Filamentous Haemagluttinin

Prn: Pertactin

GMC: Geometric Mean Concentration

PCV: Pneumococcal Conjugate Vaccine

Table of Contents summary:

After maternal Tdap vaccination, blunting of infant pneumococcal antibody response is confirmed after a primary series of vaccines, but disappears after a booster dose.

What this study adds: Blunting of primary pneumococcal antibody responses after maternal Tdap vaccination in pregnancy has been described in the UK and is confirmed in the present study. A booster dose can overcome the blunting effect.

Contributors's statement

Drs. Kirsten Maertens assisted in data collection, performed the statistical analysis, drafted the initial manuscript and approved the final manuscript as submitted.

Polly Burbidge performed the laboratory analysis and approved the final manuscript as submitted.

Prof. Dr. Pierre Van Damme critically reviewed the manuscript and approved the final manuscript as submitted.

Prof. Dr. David Goldblatt critically reviewed the raw data, critically reviewed the manuscript and approved the final manuscript as submitted.

Prof. Dr. Elke Leuridan conceptualized and designed the study, drafted the initial manuscript and approved the final manuscript as submitted.

Abstract 250

Background: Maternal immunization with a tetanus, diphtheria and acellular pertussis (Tdap) vaccine, has been shown to possibly blunt infant pneumococcal immune responses after a primary series of vaccines.

Methods: As part of a prospective controlled cohort trial (Belgium) on Boostrix® vaccination in pregnancy (52 infants of Tdap vaccinated women and 25 of control unvaccinated women), infant sera were tested for pneumococcal antibody titers against all serotypes included in the Prevenar 13® vaccine. Infants were vaccinated according to the schedule 8, 16 weeks and 12 months and serum was available from ages 20 weeks and 15 months.

Results: Seroprotection rates were high after 2 doses of Prevenar 13® in both study groups and, for serotypes 3, 5, 6B, 9V and 23F further increased after a booster dose. Geometric mean concentration of antibodies to serotype 1, 3, 4, 5, 6A, 7F, 9V, 14 and 19A were significantly lower after 2 doses of Prevenar 13® vaccine in the offspring of the vaccine group. This blunting effect disappeared after a booster dose at the age of 12 months, except for serotype 1 and 4.

Conclusions: The clinical effect of blunting by maternal immunization on protection from pneumococcal disease will be low in the Belgian setting, since seroprotection remains high for almost all serotypes and circulation of vaccine serotypes is almost inexistent. In view of global recommendations for maternal Tdap immunization to protect infants from disease, the effect on infant pneumococcal immune responses regarding both seroprotection rate and clinical effectiveness is of importance.

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Introduction

Pertussis, caused by the gram negative bacteria *Bordetella pertussis*, is a global endemic respiratory disease and an important cause of morbidity and mortality among infants [1]. Worldwide, pertussis is estimated to cause 63,000 deaths in <5 year old children (2013), although there is considerable uncertainty around these estimates due to the paucity of reliable surveillance data, particularly from developing countries [1]. In industrialized countries, outbreaks of pertussis have been reported during the last decade and the overall incidence is increasing, with most severe cases and fatalities among young, not fully vaccinated infants [2].

The only way to offer protection against pertussis disease from birth is, with the currently available vaccines and vaccination schedules, to immunize during pregnancy. High titers of maternal antibodies, elicited by maternal vaccination, are transported transplacentally to the fetus, offering possibly protection until the start of the primary infant vaccination schedule and thereby closing the susceptibility gap for infection [3-7]. Several industrialized countries have already put in place a recommendation for this strategy although some safety and immunological aspects were still unknown at implementation. Blunting of infant immune responses to pertussis antigens included in the infant vaccination, has been described after a primary series of infant vaccination in the presence of maternal antibodies [4,7]. Currently, one of the most important remaining knowledge gaps is whether maternal Tdap (tetanus, diphtheria, acellular pertussis (aP)) vaccination also causes blunting of the infant immune response to other antigens, included in the regular infant vaccination schedule, but not in the Tdap vaccine.

A UK study [7] showed a blunting effect on some serotypes of the primary pneumococcal infant humoral immune response, whenever the mother had received a Tdap vaccine (Repevax®, Sanofi Pasteur, Lyon, France) during pregnancy. The proposed explanation is that the diphtheria vaccination during pregnancy interferes with the immune response of the infants to the CRM 197 carrier protein included in the infant pneumococcal vaccine. Any additional data of controlled clinical trials on the beneficial and possible unknown side effects of maternal Tdap vaccination is therefore welcomed to support the evidence of maternal vaccination as a global strategy to protect young infants.

We report on the effect of maternal Tdap vaccination (Boostrix®, GSK Biologicals, Rixensart, Belgium) on all vaccine included serotypes of the infant pneumococcal immune responses 1 month after 2 dose pneumococcal priming (at 2 and 4 months of age) and three months after the pneumococcal booster dose (given at 12 months of age). This output adds to the body of knowledge on potential blunting of infant immune responses to childhood vaccination following maternal Tdap vaccination. The study will ultimately contribute to inform decision-making bodies on implementing maternal immunization, both in industrialized and low and middle income (LMIC) countries.

Patients and Methods

A prospective controlled cohort study was conducted in Belgium in 2011-2015, in accordance with the Declaration of Helsinki, ICH-GCP, and procedures established by Belgian law (clinicaltrials.gov identifier: NCT01698346). The study, including the present analysis, was approved by the ethics committee of the University of Antwerp, Belgium. Written informed consent was obtained from both parents of the participating infants, and details on the study procedures can be consulted in previous publications [4,8].

Participating women were included in either a vaccine group: women vaccinated with Tdap (Boostrix®, GSK Biologicals, Rixensart, Belgium) between 18 and 34 weeks of gestation (as per protocol), or a control group of pregnant women not vaccinated with a pertussis containing vaccine for at least 10 years. The offspring was included in 2 groups according to the vaccination status of their mother. Infant pneumococcal vaccines were administered within the regular health care system at the well-baby clinics, by a general pediatrician or general practitioner at the age of 8 and 16 weeks and 12 months, simultaneously with other recommended infant vaccines (rotavirus and hexavalent vaccine at week 8 and 16 – and measles, mumps and rubella vaccine at month 12).

Study vaccines

Licensed Tdap vaccine (Boostrix®, GSK Biologicals) was used to vaccinate pregnant women. Boostrix® contains 5Lf of tetanus toxoid (TT), 2.5 Lf of diphtheria toxoid (DT), 8 mcg inactivated PT, 8 mcg filamentous hemagglutinin (FHA) and 2.5 mcg Prn.
Infants were vaccinated with the 13-valent pneumococcal vaccine Prevenar 13® (Pfizer, United Kingdom). Prevenar 13® contains 2.2 mcg serotype 1, 2.2 mcg serotype 3, 2.2 mcg serotype 4,

2.2 mcg serotype 5, 2.2 mcg serotype 6A, 4.4 mcg serotype 6B, 2.2 mcg serotype 7F, 2.2 mcg serotype 9V, 2.2 mcg serotype 14, 2.2 mcg serotype 18C, 2.2 mcg serotype 19A, 2.2 mcg serotype 19F and 2.2 mcg serotype 23F.

Study procedures

Blood samples were collected from the infants at month 5 (28-35 days after the second pneumococcal vaccine dose) and at month 15 (2.5 months after the pneumococcal booster dose / related to the hexavalent booster vaccine administered at 15 months of age). Blood samples were centrifuged at 2000 rpm within 24 hours after blood collection and stored at -20°C.

Laboratory

Sera were tested for antibodies to the 13 vaccine-type capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F) at the University College London, Institute of Child Health. Immunoglobulin G (IgG) antibody levels were measured by the World Health Organization (WHO) reference enzyme-linked immunosorbent assay (ELISA) after adsorption with cell wall and 22F polysaccharide [9]. The lower limit of quantification (LLOQ) has been set at 0.15 mcg/mL. The protective threshold for all 13 pneumococcal serotypes is set at 0.35 mcg/mL [10].

Laboratory procedures used to test the samples were exactly the same as in the Ladhani et al.[7] study which was also analyzed in the WHO Reference laboratory. Results of both studies are therefore comparable.

<u>Statistics</u>

Statistical tests included parametric tests: (paired) t-tests and chi-square tests, and their non-parametric alternatives: (paired) Wilcoxon tests and Fisher exact tests whenever the underlying normality and sparseness assumptions of the parametric tests were violated. Linear regression models were used to identify characteristics that could potentially impact infant antibody titers. The analysis was performed using SPSS statistical software 23.0. Two-sided p-value <0.05 was considered as statistical significant. Pneumococcal antibody titers below the LLOQ (0.15 mcg/mL) were all replaced by a value of 0.075 mcg/mL to perform the analysis.

Blunting of the infant immune response is defined as a statistically significant lower GMC of serotype-specific antibodies in infants from one group compared to the other group.

Results

General characteristics of the study population

All women were naïve to pneumococcal vaccine. All infants were vaccinated with Prevenar-13®
at any point in time. Fifty-two mother-infant pairs were included in the vaccine group and 25
pairs in the control group. Women in the vaccine group were vaccinated with a Tdap vaccine
(Boostrix®) between 22 and 32 weeks of gestation. Children were born between April 2nd, 2012
and April 16th, 2014. Blood samples were taken between August 27th, 2012 and July 27th, 2015.
The mean interval between Tdap vaccination and delivery was 77.7 days (range: 39-117 days).
The mean gestational age at vaccination was 28.8 weeks (range: 22-33 weeks).
Table 1 summarizes the characteristics of all mother-infant pairs, the vaccination data and the
interval between vaccination and blood sampling in the infants. All women in the control group
had additional education after secondary school resulting in a significant difference in education
(p=0.008) between both groups. Significantly lower mean age at hexavalent vaccine dose 1
(p=0.026) and dose 2 (p=0.015) were calculated in the vaccine compared to the control group.

Seroprotection results

Table 2 provides an overview of the percentage of infants with an antibody titer above the
correlate of protection (0.35 µg/mL [10]) 1 month after the second Prevenar 13® dose and 2.5
months after the third Prevenar 13® dose. After priming, a significantly lower seroprotection rate
was seen in the vaccine group compared to the control group for serotype 3 (p=0.045). Low
levels of seroprotection are described in both study groups for serotype 6B and 23F after priming,
but there is a significant rise after the third vaccine dose for both serotypes. After the booster
dose, comparable seroprotection rates are found in both study groups for all serotypes.

Table 3 provides an overview of the GMCs per serotype in both study groups at all time points. One month after the priming, significantly lower GMC's are seen in the vaccine group for serotype 1, 3, 4, 5, 6A, 7F, 9V, 14, and 19A. For serotypes 6B, 18C, 19F and 23F, comparable but lower antibody titers were found in the vaccine group. After the administration of the third pneumococcal vaccine dose, significantly lower GMC's were only seen in the vaccine group for serotypes 1 and 4, with a slight increase in antibody titer after the booster for serotype 1. In general, the increase in antibody titer between both time points is higher in the vaccine group, except for serotype 4, 6B, 18C and 23F. Figure 1 shows the reverse distribution curve (RDC) of the data for serotype 1, as an example.

Overall, following primary vaccination, the vaccine was immunogenic in both groups with similar proportions achieving protective concentrations. For most infants in the vaccine group, immune responses following the booster vaccination were higher than immune responses after primary immunization despite the fact that post-primary immune responses were measured one month, but booster responses 2.5 months after vaccination.

<u>Results from the regression analysis</u>

A few variables do not influence the serotype specific GMC's at all: gestational age of the mother at vaccination, the age for receipt of the hexavalent vaccines and the interval between Prevenar 13® dose 2 and 3. Some variables randomly influence serotype specific antibody titers at one single time point: gender influences serotype 7F titer at 5 months of age in the Tdap group, lactation influences serotype 5 titer at the age of 15 months in the Tdap group, gestational age at delivery influences the serotype 4 titer at 5 months of age in the Tdap group, weight influences serotype 6B titer at the age of 5 months in both study groups and serotype 14 is influenced by the interval between pneumococcal vaccine dose 1 and 2 at the age of 5 months. There is no consistency in these effects, and they are hard to explain.

Some other factors do seem to influence more consistently serotype specific antibody responses. For serotype 6A, 14 and 18C, a higher age at blood sampling correlates with a higher antibody titer in the Tdap group. For serotypes 14, 5, 6B and 18C on the other hand, a higher age at blood sampling correlates with a lower antibody titer in the control group. A higher age at pneumococcal vaccine dose 2 correlates with a higher antibody titer for serotype 18C in the Tdap group and with a lower antibody titer for serotype 14 in the control group. A higher age at pneumococcal booster vaccination correlates with higher antibody titers for serotypes 6A and 14 in the Tdap group and for serotypes 5, 6B and 18C in the control group. In both study groups, a significant influence of the interval between pneumococcal vaccine dose 3 and blood sampling was found for some serotypes (18C, 6A, 14, 5, 6B) where a higher interval between vaccination and blood sampling results in a significantly lower antibody titer.

Discussion

This study of pneumococcal vaccine responses in infants born to mothers who received Tdap vaccine (Boostrix®, GSK Biologicals) during pregnancy, shows that while infant responses to PCV are blunted, proportions of infants achieving protective concentrations of serotype specific IgG are similar in 2 study groups, irrespective of maternal vaccination status. These results support those previously published for British mothers and their infants by Ladhani et al. [7] . Our findings are important as it confirms that the impact of maternal Tdap vaccination on pneumococcal humoral responses is not an isolated result in the UK and needs to be considered whenever recommending the maternal pertussis vaccination strategy with the available combination vaccines.

In comparison with the UK data, we confirm low levels of seroprotection for serotype 3 (significantly lower in the Tdap group), 6B and 23F post priminary but otherwise good levels of seroprotection (>65%) in both study groups for most other serotypes. In contrast to the UK data, we cannot confirm lower proportions achieving the threshold for serotypes 5 and 9V. In addition, the effect of a pneumococcal booster dose is described for the first time in this study. All serotype specific titers reached a high percentage of seroprotection after the booster dose, with lowest rate for serotype 4 and 23F (87.78%) and no significant differences in seroprotection rate between the vaccine and the control group. This finding is reassuring that the blunting effect is transitional. Belgian and British population are expected to be quite similar in characteristics and both countries have a vaccination program in place with high coverages. Circulation of vaccine serotypes is therefore very limited and the protective relevance of blunting needs to be interpreted carefully. This is certainly different in countries where other schedules and coverages of pneumococcal vaccination are reported, e.g. LMIC, where no booster doses are foreseen or

coverage of pneumococcal vaccination might be lower resulting in ongoing circulation of vaccine included serotypes.

Looking at seroprevalence levels, we report a significant blunting effect 1 month after the administration of 2 doses of Prevenar 13® for serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14 and 19A. In the UK, blunting of the immune response is described for the same serotypes except for serotype 14 and 19A. One suggestion to explain this, as put forward by Ladhani et al. [7], is that carriage reduction due to exposure to the vaccine could be a confounder since their control group was a historical control, recruited a few years ahead of the study group. In our setting however, both groups were recruited in the same time period, yet blunting was quite similar.

Within this study, the second blood sample is taken relatively late after the third pneumococcal vaccination and the titers measured at that time point might be on the wane. We assume that waning of titers is similar in both groups of infants, thus allowing us to compare these results between both study groups. Post priming and post booster GMC results were similar for both groups, perhaps due to the waning effect. A blunting effect only persisted for serotype 1 and 4. For serotypes 6A, 6B, 7F, 14, 19A and 19F, the third pneumococcal vaccine dose is beneficial in boosting the immune response adequately. This high response for these specific serotypes has already been reported previously [11] [12].

Unusually, booster responses in the control group were lower for some serotypes 2.5 months after boosting compared to primary responses. This may be due to rapid decay following boosting and the delayed time point for bleeding the infants which may have missed the peak of the response, although this phenomenon was only seen for two serotypes (4 and 18C) in the infants born to vaccinated mothers.

Comparison of GMC to post-vaccination data after regular vaccination with distinct vaccination schedules is useful to interpret the present results. Spijkerman et al [12] compared several PCV13 vaccination schedules. Children receiving a 3+1 schedule, reached higher levels of antibodies after the primary vaccination compared to our study, yet all schedules had similar high seroprotection levels after completion. Nevertheless, we report similar antibody titers after a short primary schedule as do Rodgers et al [13] in their comparative overview on different priming schedules with PCV 13. Higher response rates are reported for serotype 4 but similar lower rates for serotype 23F.

Gestational age of the mother at vaccination, did not influence the antibody titers at all. Our cohort was not powered to detect differences in GMC when vaccinating at different gestational ages, as has been recently suggested [14,15]. Nevertheless, some variables do seem to have influence on several serotype antibody responses. In the Tdap group, older age at blood sampling correlates with higher GMC's for some serotypes. In contrary in the control group, older age at blood sampling correlates with lower GMC's for some serotypes. In both groups, older age at vaccination with the booster dose correlates with higher GMC's for several serotypes. And lower titers are encountered after the booster dose in both groups whenever there is an increasing interval between dose 3 and the blood sampling at 15 months, obviously due to waning antibodies. However, we have to be careful drawing conclusions on influencing factors on antibody titers taking into account the relatively small sample size of the study.

In Belgium, the circulating strains causing invasive pneumococcal disease in children below 2 years of age in 2014 [16] were 3, 7F, 19A and non PCV-13 types. In the same year, 186 invasive pneumococcal infections were diagnosed in children below 16 years of age (N=283 in 2013 and N=334 in 2012). The overall incidence of IPD below 2 years of age was 53.2/10000 (compared to

156/10000 before the start of the vaccination recommendation). Coverage for the third dose of pneumococcal vaccine among infants in Flanders is > 96.5% (dose 3). The present results show interference, that is resolved after the current booster dose. Since there is low circulation of the vaccine serotypes, the blunting effect will probably not have clinical significance at all.

The study has a few limitations. The present project builds on an existing serumbank of leftovers and is therefore a convenience sample that was used for this analysis, without having a power calculation on beforehand to answer this research question. Therefore, our cohort was not powered to detect differences in GMC when vaccinating at different gestational ages for example. In addition, the main research aim was initially not to identify blunting of pneumococcal immune responses, and the moments for blood sampling are therefore not adapted to the pneumococcal vaccine schedule. And the interval between vaccination and blood sampling after the primary series (1 month) differs from the interval between the booster dose and blood sampling (2.5 months). Despite this limitation, the samples were all taken at the same time point, allowing us to compare the results post-booster vaccination between both groups, taking into consideration the possible waning of antibodies.

Conclusion

The blunting effect of maternal Tdap vaccination on pneumococcal immune responses in young infants, is confirmed in the present project. The clinical effect on protection from pneumococcal disease will be low in the Belgian setting, since seroprotection remains for almost all serotypes high and circulation of vaccine included serotypes is almost not existent anymore.

In view of global recommendations for maternal immunization to protect infants from disease, the effect of maternal vaccination strategy on infant immune responses regarding both seroprotection rate and clinical efficacy is of importance. Especially when considering also recommending the maternal vaccination strategy in LMIC with changing and different regional epidemiology as well as infant immunization schedules (without booster doses) as used in the EPI (Expanded Program on Immunization), precaution should be taken. Whenever no infant booster dose is administered, the antibody level reached after the priming schedule will indicate the protection of the infant at that moment.

Interpretation of booster responses to pneumococcal vaccines is to be interpreted correctly. In case of presence of pneumococcal antibodies, maternal pneumococcal antibodies always interfere with the infant immune responses to pneumococcal vaccines, this is the natural influence of maternal antibodies, affecting the plasma cells responses. On the long term, the booster dose helps, yet is not necessary to develop protection against disease.

In addition, when new vaccines will be developed, for example monovalent pertussis vaccines with low doses of PT to be used for maternal immunization (as a goal set by the foundation), regulatory questions are to be expected. Thorough review of the possible blunting effect of maternal immunization is therefore needed.

Acknowledgments

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Legend tables and figures

Table 1: Demographic characteristics of mother-infant pairs and vaccination and blood sampling data from infants in both study groups. * significant difference.

Table 2: Percentage of children with pneumococcal antibody titer above the correlate of protection (0.35 mcg/mL) in both study groups 1 month after the second pneumococcal vaccine dose and 2.5 months after the third pneumococcal vaccine dose. * significant difference.

Table 3: Geometric mean concentrations (GMCs) with 95% confidence interval (CI) for antibodies to serotype 1, 3, 4, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F post primary and post-booster vaccination in both groups of infants. *significant difference.

Figure 1: Reverse Cumulative Distribution of serotype 1, as an example.