Original Article

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Low *Bordetella pertussis* Antibody Seroprevalence Among Mothers and Infants

Annelerde ve Bebeklerde Düşük Bordetella pertussis Antikor Seroprevalansı

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ABSTRACT

Objective: *The greatest risk of morbidity and mortality from pertussis infection is observed among infants who are 6 months and younger. Therefore protection from pertussis infection is very important during the first 6 months of life. The aim of the study is to assess Bordetella pertussis antibody titers among infants after two doses of pertussis vaccination at 6 months of age.*
Method: *This was a prospective, multicentered cohort study. Paired maternal and infant serum samples were obtained during the first month after delivery and only infant serum samples were again taken at 6 months of age. Serum samples were tested for Bordetella pertussis-IgG by the enzyme-linked immunosorbent assay (ELISA).*
Results: *The study enrolled 209 mother-infant pairs. At one month after delivery 49.7% of mothers and 32.1% of infants had detectable Bordetella pertussis-IgG antibodies. After two doses of DTaP-IPV-Hib vaccine, at 6th months of age, Bordetella pertussis-IgG seroprevalence among infants increased to 43.3%.*
Conclusion: *After 2 doses of DTaP-IPV-Hib, more than half of the infants at 6 months of age had undetectable Bordetella pertussis-IgG and presumed unprotected against pertussis disease. A new strategy of protecting infants from pertussis must be implemented.*

Keywords: *pertussis, maternal antibody, infant antibody, seroconversion*

ÖZ

Amaç: *Altı aylık ve daha küçük bebekler boğmaca enfeksiyonundan en yüksek morbidite ve mortalite riskine sahiptirler. Bu nedenle boğmaca enfeksiyonundan korunma, yaşamın ilk 6 ayında çok önemlidir. Bu çalışmanın amacı, bebeklerde Bordetella pertussis antikor titrelerini 6 aylıkken iki doz boğmaca aşılamasından sonra değerlendirmektir.*
Yöntem: *Bu bir prospektif, çok merkezli kohort çalışmasıdır. Doğumdan sonraki ilk ayda anne ve bebek çiftlerinden serum örnekleri alındı ve yine sadece bebek serum örnekleri 6 aylıkken alındı. Serum numuneleri, enzime bağlı immünosorban analizi (ELISA) ile Bordetella pertussis-IgG için test edildi.*
Bulgular: *Çalışmaya 209 anne-bebek çifti alındı. Doğumdan bir ay sonra annelerin % 49,7'si ve bebeklerin % 32,1'i saptanabilir Bordetella pertussis-IgG antikorlarına sahipti. İki doz DTaP-IPV-Hib aşısından sonra, 6. aylıkken, bebeklerde Bordetella pertussis-IgG seroprevalansı % 43,3'e yükseldi.*
Sonuç: *İki doz DTaP-IPV-Hib aşısı sonrasında, 6 aylık bebeklerin yarısından fazlasında Bordetella pertussis-IgG saptanmadı ve bunların boğmaca hastalığına karşı korumasız olduğu varsayıldı. Bebekleri boğmacadan korumak için yeni bir strateji uygulanmalıdır.*

Anahtar kelimeler: *boğmaca, anneye ait antikor, bebeğe ait antikor, serokonversiyon*

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INTRODUCTION

Pertussis is especially most hazardous for infants under 6 months of age, which account for nearly all pertussis-related hospitalizations and deaths. On the other hand it was recognized that pertussis is grossly underreported. Global vaccination coverage with 3 doses of pertussis-containing vaccine was estimated to be 86% in 2016 [1,2]. In Turkey this rate of coverage was 96% in 2017 [3]. Infants whose vaccination schedule is not completed, contract the infection from their mothers and other family members [4]. In Turkey, whole cell vaccine was introduced in 1968 whereas acellular pertussis vaccine in 2008 to the Expanded Programme for Immunisation. Infants are vaccinated at 2, 4, and 6 months of age. Booster acellular pertussis vaccine is administered at the age of 18 months and 6 years [5]. The routine pertussis vaccination programme is not yet implemented for pregnant women and adults. The Global Pertussis Initiative emphasized the importance and effectiveness of maternal immunization [6]. Some countries have introduced maternal vaccination programs [7,8]. Studies are needed about the pertussis serologic status of newly delivered mothers and their infants under 6 months of age in developing countries [9].

The aim of this study was to assess pertussis seroprevalence in mothers and their infants at 1 month after delivery and in 6-month-old infants before they received the third dose of pertussis-containing vaccine.

MATERIAL and METHODS

This prospective, multi-centered clinical study was carried out at Well Child Outpatient Clinics of 4 hospitals between October 2013 and October 2014. Infants brought for routine well child visits were consecutively enrolled. Paired maternal and infant blood samples were obtained at the first well child visit during the first month after delivery. All women reported that they had been vaccinated against pertussis during childhood but this was not confirmed by any documentation.

The qualitative immunoenzymatic determination of Ig G-class antibodies against *Bordetella pertussis* was carried out by the Enzyme-Linked Immunosorbent Assay (ELISA) technique according to the instructions of the manufacturer (GenWay Biotech, Inc, San Diego, CA, USA). The investigation covered the determination of Ig G-Class antibodies against *Bordetella pertussis* and *Bordetella pertussis* toxin. The samples were tested in duplicate. Diagnostic specificity was reported as 93.02% (95% CI: 80.94%-98.54%), and sensitivity as 98.31% (95% CI: 90.91%-99.96%). Inclusion criteria for the study were maternal age between 18 and 45 years and infant gestational age of 37 to 42 weeks. The exclusion criteria included history of premature or low birth weight, acute or chronic illness, transfusion of blood and/or blood product(s). Demographic characteristics such as maternal age, infant gestational age, birth weight, mode of delivery, gender of the study participants were recorded.

Blood was drawn from 209 mother-infant pairs during the first month after delivery and from 164 infants at 6 months of age before the administration of the third dose of DTaP-IPV-Hib vaccine (Figure 1). The vaccines were all administered at the Well Child Clinic. The samples were centrifuged and stored at -20 C until analyzed at Istanbul University Virology and Immunology Department Laboratory. The results were classified as negative and positive based on the cut-off values of the manufacturer's kit. *Bordetella pertussis*-IgG titers of positive serum samples were recorded. Mother-infant pairs were categorized into seronegative versus seropositive groups based on their antibody titers. Vaccine-associated seroconversion was defined as the change from seronegative to seropositive.

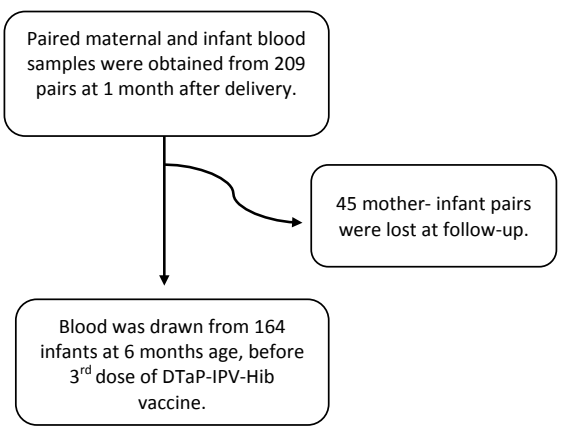

Figure 1. Flowchart of the study population.

Ethical approval and necessary institutional permissions were obtained for the study (05/24/2013 No:10). All mothers provided written informed consent prior to enrollment.

Statistical analyses were performed using the SPSS software version 21. The univariate analyses to identify variables associated with immune response were performed using Chi-square, Fisher exact, Student's t and Mann-Whitney U tests, where appropriate. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analyses to determine independent predictors of immune response. Continuous variables were presented as means with standard deviations or confidence intervals where applicable. Categorical variables were presented as numbers with corresponding percentages. Pearson correlation coefficient was used to assess the relationship between maternal and infant serum Bordetella pertussis-IgG concentrations.

RESULTS

Two hundred and nine mother-infant pairs were eligible for the study. None of the mothers were vaccinated against pertussis either during pregnancy or within the previous 5 years. No participants reported a recent history of pertussis disease, or known pertussis exposure at the beginning or during the follow-up period. Of all deliveries, 44.5 % were normal vaginal delivery and 50.2% of infants were female. Mean (± SD) birth weight of infants were 3337±375 grams. The mean (± SD) gestational age of infants was 38.7±1 weeks and maternal age was 29.6±6.2 years.

Seroprevalence rates of *Bordetella pertussis*-IgG up to 1 month postpartum were 49.7% (104/209) in mothers and 32.1% (67/209) in infants. Of babies born to seropositive mothers, 46.2% (48/104) were Bordetella pertussis-IgG seronegative. A significant positive correlation was observed between maternal and infant Bordetella pertussis-IgG status at 1 month postpartum (p<0.001, r=0.600).

Forty-five infants were lost at follow-up and serum samples of 164 infants were evaluated at 6 months of age (Figure 1). At Table 1, the distribution of seropositivity rates of mother-infant pairs at one month after delivery is given in Table 1.

After receiving 2 documented doses of pertussis-containing-vaccines at 2 and 4 months of age, 56.7% (71/164) of the infants were seropositive for Bordetella pertussis-IgG (Table 1). Out of total seropositive 71 infants, twenty-two (13.4 %) continued their prevaccination immunity. When we exclude the cases that were lost at follow-up; seronegative infants showed seroconversion after the vaccination. This difference between seronegative and seropositive infants was statistically significant (p<0.001). Of 113 seronegative infants at one month 49 became seropositive after two doses of pertussis-containing vaccine. According to the definition used in this study, vaccine-associated response after two doses of pertussis vaccine was 43.4%. This figure could be slightly underestimated because we could not identify the seroconverted babies among 22 infants who were seropositive at the beginning and also at the end of the study after administration of two doses of vaccine. Some of these infants might also be converters after the vaccination.

Table 1. Serology of mother-infant pairs followed until 6 months (n=164).

		Seronegative (%)	Seropositive n (%)	Total n (%)
One month after delivery	Mother	77 (47)	87 (53)	164 (100)
	Infant	113 (68.9)	51 (31.1)	164 (100)
At 6 months	Infant	93 (56.7)	71 (43.3)	164 (100)

When we compared the vaccine-associated seropositivity in babies at 6 months according to maternal serology, seroconversion was observed in 48.3% (42/87) of babies who were born to seropositive mothers and this rate was 37.7% (29/77) in babies born to seronegative mothers. The difference was not statistically significant (p=0.170).

At 6 months, vaccine-associated seroprevalence was 2 times higher in boys (OR 2.1, 95% CI: 1.09-4.12). This difference was statistically significant (p<0.026). Gender was entered into logistic regression for vaccine-associated response at 6 months and remained statistically significant (p=0.019; RR:2.2 with 95% CI: 1.07-4.55).

DISCUSSION

In our study, *Bordetella pertussis*-IgG seroprevalence rates were 49.7% in mothers and 32.1% in infants up to one month after delivery. After two doses of pertussis vaccine, 56.7% of the infants were still seronegative at 6 months. When vaccine-associated seroprevalence was considered, only 43.4% of infants had seropositivity after two doses of TDaP-IPV-Hib vaccination. The study demonstrated a low level of seropositivity against *B. pertussis* in mothers, which may increase the risk of pertussis in very young infants. Thus the greatest risk of morbidity and mortality from pertussis infection is among infants who are below 6 months of age and yet more than half of the babies in our study were susceptible to pertussis [1]. It is suggested that maternal pertussis antibodies protect the infants from pertussis by passive immunity. In a study of Turkish mothers where maternal and cord blood levels of anti-pertussis toxin were detected, only 34,6 % of infants had protective levels of antigens against pertussis [10]. Similarly, our results showed that only 32% of the infants have been protected, leaving the majority of infants unprotected to pertussis infection.

Either vaccination of the mothers during pregnancy or accelerated immunization of the infants for pertussis is a proposed strategy in preventing infant pertussis. Pertussis vaccination during pregnancy has already been shown to be effective in achieving higher pertussis antibody concentrations in infants and it has been introduced in several countries. However due to economic costs; universal vaccination of mothers during pregnancy cannot be covered at the moment. So, accelerated vaccination of infants for pertussis may be beneficial. One possible strategy to address this might be revisiting the current infant TDaP-IPV-Hib primary immunization schedule in Turkey. In the United Kingdom, pertussis vaccine is given when infants are 8, 12 and 16 weeks old [11]. In Netherlands, TDaP-IPV-Hib vaccine is administered at 3,5 and 11 months of age. If the mother was not vaccinated against pertussis during pregnancy then her infant receives an extra vaccination at the age of 2 months [12]. Current TDaP-IPV-Hib vaccine administrations are at 2,4,6 months in Turkey and may be that regimen needs to be changed to 2,3,4 or 2,3,5 months in order to immunize against pertussis at an earlier age. If one assumes that acceptable level of immunity is reached 1 month after the third injection, then infants younger than 5–7 months become at least partly susceptible to pertussis [7].

It is suggested that the effectiveness of the first dose of vaccine varies between 62% to 68% in infants under 6 months of age, and effectiveness increases with subsequent doses [13-15]. However, our study results showed that seropositivity is achieved in only 43.3% of the infants after two doses of the vaccine. The lower efficacy of the vaccine observed in our study should be explored in future studies.

Maternal passive immunity may affect infants' immune response to vaccination. Maternal antibodies can interfere with the immune response to vaccination, a phenomenon known as "blunting" [16]. In this study, seroconversion rate among babies at 6 months of age was not statistically significant according to maternal serology. Yet, we can assume that maternal immunity did not affect immune response to vaccination in our study.

Conflicting findings are reported about gender difference for pertussis seropositivity [17,18]. In the current study, we found out that vaccine immune response positivity was seen 2 times more in boys in univariate analysis. In a study conducted in Turkey, geometric mean titers were also statistically higher in boys [19]. Underlying immunological differences between gender may also result in differential immune responses to vaccination. In a Dutch study, pertussis vaccine immunity did not reportedly differ between genders [20]. Fischinger et al. stated that sex differences have been noted in quality of vaccine-induced immune response to MMR and DTP across the sexes [21]. This finding should be explored in future studies.

Limitations of the study

There are some limitations of our study. Cord blood samples of infants were not available. The pertussis serology was measured by the determination of Ig G-Class antibodies against *Bordetella pertussis* and *Bordetella pertussis* toxin. Antibodies for filamentous hemagglutinin, pertactin, and fimbriae were not measured. On the other hand, our findings shed light for future studies and changes in immunization schedule of infants.

CONCLUSION

Maternal pertussis seropositivity and infant protection by passive immunity was low suggesting maternal pertussis immunization should be considered in addition to the existing tetanus maternal immunization programme in Turkey [12,22]. Cocooning strategy may be suggested to parents who cannot receive pertussis vaccine during pregnancy [23].

After 2 doses of DTaP-IPV-Hib more than half of the infants at 6 months of age were found to be *Bordetella pertussis*-Ig G seronegative. An alternative accelerated vaccine strategy, changing the immunization timeline for DTaP-IPV-Hib vaccination may be an option for protection of infants against pertussis.

Ethics Committee Approval: Approval was obtained from the Istanbul Medical Faculty Clinical Research Ethics Committee (05/24/2013 No: 10).

Conflict of Interest: The authors declared no conflict of interest.

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Informed Consent: All mothers provided written informed consent prior to enrollment.

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