Epidemiology of pertussis in the Netherlands and implications for future vaccination strategies


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Seroprevalence of *Bordetella pertussis* infection during pregnancy measured by IgG antibodies against pertussis toxin

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Abstract

_Bordetella pertussis_ infection may cause severe illness in newborns. Mothers with _B. pertussis_ infection during delivery can infect newborns. The seroprevalence of _B. pertussis_ infection in pregnancy was measured in pregnant women by detection of immunoglobulin G against pertussis toxin; 6.3% had serological evidence of infection. Maternal vaccination should be considered to prevent pertussis in newborns.
Introduction
Whooping cough, caused by *Bordetella pertussis*, may cause severe illness and substantial mortality, especially among neonates [1]. Despite nationwide vaccination programmes with high coverage, the incidence of pertussis is rising in many developed countries during recent decades, with infection frequency assumed to be highest among adolescents and young adults [2]. In the Netherlands, pertussis vaccination is given to infants at the ages of 2, 3, 4, and 11 months. Before 2005, a whole-cell vaccine was used, which was replaced by an acellular vaccine [2]. Since 2001, a booster vaccination with acellular pertussis vaccine at the age of 4 years has been included in the National Immunization Programme. A booster vaccination during adolescence is not recommended.

Infants, who are too young to be (completely) vaccinated, account for the majority of hospital admissions for pertussis [1, 2]. Although adolescents and adults usually are thought to have mild pertussis symptoms, they can be an important source of infection for newborns. Household contacts, especially mothers and siblings, are thought to be responsible for up to 75% of *B. pertussis* infections in infants [3, 4]. Mothers with pertussis at time of delivery have a high chance to infect newborns. Depending on the time of onset of infection of the mother, the neonate may not be protected by maternal antibodies acquired through placental transfer [5].

The aim of this study was to determine the seroprevalence of *B. pertussis* infection in women during and shortly after pregnancy. Knowledge on the infection frequency of *B. pertussis* infection among expectant mothers may support further research to explore the possibilities of vaccination during pregnancy to protect neonates who are still at high risk of severe pertussis.

Methods
All pregnant women who were about to deliver from January 2004 through January 2006 in a general hospital in the Netherlands were asked to participate in the study. After obtaining informed consent, an umbilical cord blood sample was taken and maternal blood samples were taken at delivery and 2 months after delivery. If available, a routinely obtained maternal blood sample at 12 weeks of gestational age was retrospectively analysed.

All samples were frozen at -20°C until analysis. Individual samples were analysed by the National Institute for Public Health and the Environment (RIVM) in the Netherlands. Pertussis specific antibodies against pertussis toxin (IgG-Ptx) were measured with an in-house enzyme-linked immunosorbent assay [6]. A 4-fold increase or decrease of IgG-Ptx to a level of at least 20 U/ml, or IgG-Ptx >100 U/ml in a single sample was indicative of recent *B. pertussis* infection [6]. The IgG-Ptx assay has a lower detection limit of 3 U/ml.
A standardised questionnaire was used to collect information on demographics, vaccination history, coughing complaints, coughing complaints in the household, and general practitioner visits.

This study was approved by the Medical Ethical Committee of the Groene Hart Ziekenhuis. Data were analysed using SPSS, version 12.0.1 (SPSS) and SAS, version 9.1.3 (SAS Institute). Pertussis specific IgG-Ptx levels at different sampling points are reported as geometric mean value with 95% confidence interval (95%CI). To study placental transfer, comparisons of log-transformed levels in maternal delivery serum and in cord serum were tested with a paired Student’s t-test. A P-value <.05 was considered to be statistically significant.

**Results**

During the period of study, 315 mothers were included. The median maternal age at time of delivery was 30 years (range, 15-44 years). The median gestational age was 39.4 weeks (range, 33-43 weeks). Two hundred forty-two women (76%) reported that they were vaccinated against pertussis during childhood, 27 (8.5%) reported that they were unvaccinated, and 46 mothers (15%) had unknown vaccination status.

![Figure 1](image-url)  
*Figure 1.* Immunoglobulin G antibodies against pertussis toxin (IgG-Ptx) at 12 weeks of gestational age (1), around the time of delivery (2), and 2 months after delivery (3).
A distribution of IgG-Ptx levels in the serum of mothers during different sampling times is presented in Figure 1. The majority of women had antibody levels of 3-20 U/ml measured at 12 weeks gestation, at delivery, and at 2 months after birth. Twelve (3.8%) women had antibody levels of 50-100 U/ml in at least one sample. IgG-Ptx concentration below the level of detection (i.e., <3 U/ml) at all measurements occurred in 48 (15.7%) women. IgG-Ptx levels >100 U/ml in at least one sample or a 4-fold increase between 2 consecutive serum samples were detected in 2 (1.8%) of 109 women for whom all samples were available and in 5 (3.4%) of 145 women with 2 samples available. In women with only 1 sample available, 1 (1.6%) of 61 had serological confirmed pertussis. All together, 8 (2.5%) of 315 women had serologically confirmed B. pertussis infection in an 8-month period of follow-up. Therefore, the incidence rate of B. pertussis infection was 3.8 per person-year.

Table 1 presents characteristics of women with serologically confirmed B. pertussis infection. Patients 1, 6, and 8 were likely to be infected during pregnancy, because they had very low antibody levels detected in their first sample. Subjects 2, 5, and 7 already showed a high response in their first sample and were likely to have been infected shortly before or in the first weeks of their pregnancy. Only 2 (25%) of these 8 women reported coughing during pregnancy, 1 of whom visited her general practitioner. Pertussis, accompanied with coughing, was noted in both families.

Mean IgG-Ptx levels at 12 weeks, at delivery, at 2 months postpartum and in cord serum were 11.9 (95%CI: 9.6-14.2), 10.1 (95%CI: 7.8-12.4), 13.6 (95%CI: 11.3-15.9), and 14.4 (95%CI: 11.8-17.0) U/ml, respectively. The geometric mean level of IgG-Ptx in cord serum in subjects without pertussis was higher than the mean IgG-Ptx levels around the time of delivery (15.7 U/ml [95%CI: 13.5-17.9 U/ml] versus 9.2 U/ml [95%CI: 7.2-11.2 U/ml], P<.01), suggesting some active placental transfer. Active placental transfer is also suggested to occur in subjects with B. pertussis infection (Table 1).

**Discussion**

Despite high levels of vaccination in childhood, we found serological evidence of B. pertussis infection in 8 (2.5%) of 315 mothers during pregnancy. Another 12 (3.8%) of 315 women had antibody levels of 50-100 U/ml. Although these values do not correspond with active or recent infection, it is indicative of B. pertussis infection in the past year [7]. In total, 20 (6.3%) of 315 pregnant women in our study had serological evidence of B. pertussis infection during or shortly before pregnancy, which is much higher than the incidence of reported cases in this
Table 1. Demographic and clinical characteristics of women with *Bordetella pertussis* infection.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Specific immunoglobulin against pertussis toxin, U/mL</th>
<th>Age</th>
<th>Vaccination</th>
<th>Coughing</th>
<th>Pertussis in family</th>
<th>General practitioner visit</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>At 12 weeks of gestation</td>
<td>At time of delivery</td>
<td>In umbilical cord</td>
<td>At 2 months after birth</td>
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<tr>
<td>1</td>
<td>4 183 399 35 Unknown No No</td>
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Our findings emphasize once more that *B. pertussis* infection often remains unreported, possibly because of a subclinical course of infection or the failure to recognize or report the disease by a general practitioner.

The incidence we observed is in line with the incidence of 6.6% of *B. pertussis* infection estimated in another study on the seroprevalence of pertussis in the general population in the Netherlands [7]. Likewise, seroprevalence studies in other countries have demonstrated incidences of 3.3%-8% per year in cohorts of adults [8-10]. A recent study conducted in pregnant women [11] found a lower seroprevalence of 1.8%. However, in this study, antibody levels were measured in cord serum. In our study, maternal samples were collected at 3 time points, which increased the diagnostic yield.

Our data suggests efficient placental transfer of maternal IgG-Ptx in pregnant women, which corresponds with findings in other studies [12]. There is evidence that maternal antibodies can offer protection against pertussis in neonates [5]. The majority of women in our study had antibody levels <20 U/ml around the time of delivery (Table 1), and 15.7% had an antibody level below the limit of detection. Although protective levels for antibodies against pertussis have not been established, low IgG-PT levels correlate with increased susceptibility to pertussis [13].

Our study had some limitations. Selection bias may have occurred, because 30% of Dutch pregnant women with uncomplicated pregnancies deliver at home. Women in our study all underwent a hospital delivery. Because obstetrical reasons were responsible for the hospital deliveries we think that our results are still representative. Unfortunately, for logistical reasons, some maternal samples obtained at 2 months after delivery were unavailable. Therefore, we may have underestimated the true number of infections that occurred in mothers shortly after delivery.

The relatively high seroprevalence of *B. pertussis* infection in mothers who are about to deliver illustrates that the bacterium likely circulates within the family and that there is a risk of transmission to the unprotected newborn [14, 15]. Infants can be protected from infection when frequent transmission routes are interrupted by vaccinating all close contacts of newborns, the “cocooning strategy”. In some countries, this strategy has been implemented or recommended. However, the extent to which infant morbidity will be reduced depends on the willingness of contacts to be vaccinated.

A more direct way to protect young infants would be to induce protecting antibodies in these infants by starting to vaccinate directly after birth [16]. However, the type of vaccine and timing will be important for the success of neonatal vaccination; Halasa et al. [17] observed lower antibody responses to acellular pertussis vaccine administered shortly after birth, possibly because of interference [17, 18].
Our results contribute more to the arguments that favour the idea of vaccinating women during the third trimester of pregnancy with an aim to passively protect neonates by elevating maternal antibody levels. The possibilities, advantages, and disadvantages of maternal vaccination have been reviewed elsewhere [5]. Currently, the feasibility of maternal vaccination is hampered by concerns regarding adverse effects of the vaccine in the mother and/or newborn. Thus, further research on safety and effectiveness of maternal vaccination would be very valuable.

References