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Low levels of detectable pertussis antibody among a large cohort of pregnant women in Canada

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ABSTRACT

Newborns and infants less than 6 months of age continue to be at highest risk of severe outcomes from pertussis infection. Pertussis vaccination during the last trimester of pregnancy can confer protection to newborns as a result of trans-placental transfer of pertussis antibodies. In several countries, pertussis vaccination in pregnancy is recommended routinely and Canada's National Advisory Committee on Immunization issued similar routine recommendations in February 2018. Using second trimester biobanked plasma samples (n = 1752) collected between 2008 and 2011, we measured the pre-existing anti-pertussis toxin (PT) levels in a large cohort of second-trimester pregnant women using a commercial ELISA test. We found that 97.5% of these women had anti-PT IgG titres below 35 IU/mL. Women with higher incomes had slightly higher anti-PT levels but 96% still had titres <35 IU/ml. In conclusion, almost all of the pregnant women in this large cohort had anti-PT levels low enough to suggest susceptibility to pertussis infection in both the mothers and their newborn infants.

1. Introduction

Pertussis is a highly contagious respiratory infection caused by *Bordetella pertussis* and in children, it is characterized by the "whoop" that often follows the severe coughing spells and from which the infection draws its common name of "whooping cough". In the pre-vaccine era, pertussis infection contributed substantially to childhood mortality. Although periodic small outbreaks of pertussis still occur, the overall incidence of pertussis has fallen more than 98% since the introduction of pertussis vaccination programs in Canada in the 1940s [1]. While it is possible that some of this decrease is due to underreporting of pertussis, the overall trend over time would still be apparent. In Canada, the primary series of pertussis vaccine is administered to infants at 2, 4, 6 months and 18 months of age followed by a booster between 4 and 6 years of age as well as an adolescent booster at 14–16 years of age [2]. A single additional dose is recommended in adulthood (>18 years of age) [2] but coverage is generally low [3]. In Canada, the average annual incidence of pertussis in infants aged less than one year was 6.45 per 100,000 between 2011 and 2015 [4]. Pertussis continues to be a significant cause of infant morbidity in Canada. Newborns and infants <1 year of age, remain the most affected, representing almost all of the pertussis-related hospitalizations and deaths [5–8].

Strategies to prevent pertussis in children in the first year of life have included the introduction of an adolescent booster [9–11] and targeted vaccination of the mother and close contacts of the newborn: so-called cocooning [12]. These strategies offer only indirect protection to infants and require the vaccination of large numbers of people which can be programmatically and clinically challenging [13–15]. Immunization at or near birth could theoretically provide direct protection to the infant with the caveat that protection is delayed until the development of an immune response [13]. Active transport of maternal IgG across the placenta is mediated by the neonatal Fc receptor (FcRn) and accelerates during the third trimester [16]. Anti-PT-antibody levels in a full-term infant can be 118–169% higher than in the mother [17–20] through this active transport mechanism. In jurisdictions where pertussis vaccination in pregnancy is routine, this intervention has been shown to be safe for both mother and child [21–25].

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Maternal immunization is not only safe but is also successful in preventing pertussis among infants [26–28]. A large case-control study from California demonstrated that maternal vaccination prevented 85% more cases of infant pertussis than postpartum vaccination of mothers in infants less than 8 weeks of age [27]. Furthermore, in contrast to cocooning, modeling data from the US suggests that this strategy can be cost-effective in preventing infection [29]. Any consideration of a maternal pertussis immunization program presupposes that the pregnant women targeted have low baseline levels of anti- pertussis antibodies. While there is no well-defined correlate of protection for pertussis [30], low levels of anti-PT antibodies are correlated with susceptibility [31,32] and anti-PT antibody levels have shown promise for tracking pertussis outbreaks and monitoring waning immunity [33]. A number of small studies from the Netherlands, USA, and Spain [18,34,35] have demonstrated low levels of maternal anti-PT IgG among pregnant women. Similarly, a limited Canadian serological survey that tested 169 pregnant women from two provinces revealed that 59% had anti-PT levels <10 IU/mL [36]. In this study, we sought to assess pertussis serological status among pregnant women from multiple sites across Canada.

2. Methods

The Maternal-Infant Research on Environmental Chemicals (MIREC) study was undertaken to examine potential adverse health effects of prenatal exposure to specific environmental chemicals on pregnancy and infant health. The study recruited pregnant women between 2008 and 2011 in ten Canadian cities in six provinces (British Columbia, Alberta, Manitoba, Ontario, Québec, and Nova Scotia) [37]. Enrolment occurred between the 6th and 13th week of pregnancy, at which time participants completed a questionnaire focused on socio-demographic characteristics and obstetrical history. Maternal blood samples were collected in each trimester and at delivery. Plasma from the second trimester was used for the current study due to its availability from the MIREC biobank. Plasma samples were heat-inactivated (56 °C × 30 min), aliquoted and held at −20 °C until used in assays.

Serum IgG specific for PT were measured using the Sekisui/Virotech EIA (#EC215G00: Sekisui/Virotech Gmbh, Russelsheim, Germany) according to the manufacturer's instructions using the company's IgG Quanti-kit. This kit was one of two commercial assays that performed most consistently for the diagnosis of pertussis in a recent review [38]. In our hands, the variance from the 216 samples run in duplicate on the same plates was <2% and variance for the 178 samples run in duplicate on different plates and days was <10%. The assay is supplied with 2 internal controls: 'equivocal' and 'positive' and only assay runs in which these controls fell within the manufacturer's specified ranges were accepted. Assignment of 'negative', 'equivocal' or 'positive' was unambiguous for the 394 samples run in duplicate. Results were reported as both arbitrary Virotech units (VE) and international units (IU) based on the WHO Standard Pertussis Antiserum (NIBSC (National Institute for Biological Standards and Control) code: 06/140). This IgG assay was designed to identify clinical *Bordetella pertussis* infections and has a lower limit of detection (LLD) of 5 IU/mL. VE values <9/mL (≤35 IU/mL) were considered to be 'negative', VE values 9–11/mL (36–44 IU/mL) were considered to be 'indeterminate' and VE values >11/mL (>45 IU/mL) were considered to be consistent with recent Bordetella exposure through infection or vaccination. *Bordetella* reference centres in several countries have suggested that the WHO standard serum should be used for a two-part cut-off system for *Bordetella* infection, with a lower limit of 40/50 IU/mL and an upper limit of 100/120 IU/mL [39]. In preliminary studies, variance between duplicate wells on the same EIA plate was <15%. Ten percent of the MIREC samples (n = 178) were run in duplicate with 10% of specimens run twice in separate assay runs. Inter-assay variance was less than 20%.

The proportion of participants with anti PT levels less than 5 IU/mL (LLD) and 36 IU/ml, along with 95% binomial confidence intervals, were calculated for the entire sample across select sociodemographic and household factors. Variables of interest included age at first prenatal visit, highest level of education attained, household income, birthplace, and number of previous live births. Associations between the selected variables and anti- PT level cut-offs were investigated using unadjusted Cochran-Armitage test for trends. The geometric mean of anti-PT IgG titres with their 95% confidence intervals were calculated using all participants, assigning those with values under the LLD a titre of '2.5 IU/mL'. All data were analyzed using SAS Enterprise Guide 5.1 (SAS, Cary, NC, USA).

The MIREC study was originally reviewed and approved by the REBs of the Centre Hospitalier Universitaire Sainte-Justine, all recruitment sites and Health Canada and Public Health Agency of Canada. The informed consent form provided by participants allowed for the use of anonymized data and bio-banked biological samples for further research related to maternal and neonatal health.

3. Results

1928 participants were enrolled in the MIREC study of which 1752 (90.9%) had a second-trimester plasma sample available for testing. A single result with a matched specimen was excluded from the analysis due to an error in the ELISA assay. Age at enrolment ranged between 18 and 48 years with most women (55.4%) reporting at least one previous live birth (Table 1). Slightly more than half of the women were enrolled in the province of Ontario (52.6%). Nearly two-thirds of the cohort was university educated and had incomes higher than the median income reported in a

Table 1
Socio-demographic characteristics and birth history of MIREC study participants with a second-trimester plasma sample available for testing (n = 1752).

Characteristic	n	%
Province of residence		
Nova Scotia	263	15.0
Quebec	334	19.1
Ontario	922	52.6
Manitoba	77	4.4
Alberta	17	1.0
British Columbia	139	7.9
Age at first visit		
18–24 years	109	6.2
25–29 years	412	23.5
30–34 years	640	36.5
35–48 years	591	33.7
Highest education level attained		
High School or less	232	13.3
College or Trade Diploma	403	23.0
University Degree	1115	63.6
Not stated	2	0.1
Household income		
$1 – $60,000	371	21.2
$60,001 – $100,000	620	35.4
$100,001 or more	689	39.3
Not stated	72	4.1
Born outside Canada		
No	1425	81.3
Yes	327	18.7
Number of previous live births		
0	781	44.6
1	704	40.2
≥2	267	15.2