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Decay of anti-*Bordetella pertussis* antibodies in women of childbearing age following COVID-19 non-pharmaceutical measures

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ABSTRACT

Background: Immunization against *Bordetella pertussis* during pregnancy reduces morbidity from severe pertussis in young infants via *trans*-placental transfer of anti-*B. pertussis* Immunoglobulin G (IgG). Studies have reported a near disappearance of respiratory pathogens including *B. pertussis* following implementation of mitigation strategies to control Coronavirus disease 2019 (COVID-19). We explored how immunity against *B. pertussis* changed in women of childbearing-age through the COVID-19 pandemic.
Methods: Paired blood samples from females of childbearing-age collected at the beginning (May-June 2020) and nearly one year into the COVID-19 pandemic (February-May 2021) in British Columbia (BC), Canada were tested for anti-*B. pertussis* IgG levels. To ascertain whether early-pandemic IgG levels in 2020 reflected levels in pregnant women early in gestation, 1st trimester sera collected from age-matched healthy pregnant women in 2018 and 2019 were tested for anti-*B. pertussis* IgG. Levels were compared by t tests. P-value of 0.05 was assigned and statistical significance was set as $p < 0.016$ using Bonferroni correction.
Results: Annual provincial *B. pertussis* incidences per 100,000 in BC in 2020 (3/100,000) and 2021 (<1/100,000) approximated the lowest levels since 1990. In 2021 vs. 2020, anti-pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (PRN) IgG levels declined in women of childbearing-age: 6.8 IU/ml (95 %CI, 4.2–10.9) vs. 8.4 IU/ml (5.1–13.9; $p = 0.004$); 18.8 IU/ml (10.9–32.2) vs. 23.6 IU/ml (13.2–42.1; $p < 0.001$); and 37.1 IU/ml (18.1–75.9) vs. 47.2 IU/ml (24.8–89.9; $p = 0.092$), respectively. Although all values were slightly higher, anti-PT, FHA and PRN IgG levels in women of childbearing age did not significantly differ in 2020 compared with early-gestation pregnant women in 2018–2019, 8.4 IU/ml (95% CI, 5.1–13.9) vs. 5.4 IU/ml (95% CI, 3.8–7.7; $p = 0.166$), 23.6 IU/ml (95% CI, 13.2–42.1) vs. 20.1 IU/ml (95% CI, 13.4–30.2; $p = 0.656$), and 47.2 IU/ml (24.8–89.9) vs. 17.3 IU/ml (95% CI, 10.5–28.7; $p = 0.021$), respectively.
Discussion: *B. pertussis* infections should be closely monitored during the relaxing of mitigation measures for COVID-19.

1. Introduction

Young infants are at risk for severe pertussis (or "whooping cough") disease caused by the respiratory pathogen *Bordetella pertussis* [1]. In order to protect young babies from pertussis in early infancy, immunization with a tetanus-diphtheria-acellular-pertussis (Tdap) vaccine is recommended during each pregnancy [2]. Two vaccines are available to protect from pertussis, the whole cell pertussis (wP) and acellular pertussis (aP) vaccines. The wP vaccine is composed of the whole inactivated *B. pertussis* organism, with all the bacteria's virulence factors and antigens, while the aP vaccines are composed of purified bacterial antigens (pertussis toxin [PT], filamentous hemagglutinin [FHA], pertactin [PRN], fimbriae). In Canada, routine pediatric immunization with aP replaced the wP vaccine in 1997.

Tdap administration during pregnancy boosts maternal pre-existing antibody levels against *B. pertussis* and increases trans-placental transfer to the newborn [3–5]. In the context of COVID-19 mitigation measures, countries have seen a profound decrease in clinical detection of *B. pertussis* infections in populations [6–9]. In Canada, data from the province of Ontario showed that only 3 cases of pertussis were reported between January-June 2021, a sig-

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nificantly lower reported number compared to 193 5-year average year-to-date count [10]. This conjuncture offers an opportunity to study the trends of *B. pertussis* infections during the COVID-19 pandemic in another of one of Canada's larger provinces, British Columbia (BC), and the stability of pre-existing antibody immunity against *B. pertussis* in the context of potential limited bacterial exposure in women of childbearing age.

2. Methods

***B. pertussis* infections in BC, Canada, 2015–2021:** *B. pertussis* confirmed cases (both laboratory-confirmed epidemiology-linked) reported to the BC Centre for Disease Control between January 1st 2015 and March 31st 2021 were included. In BC, confirmed *B. pertussis* cases are reportable to the Medical Health Officers under the BC Public Health Act.

Study cohort: Paired serum samples were collected in gold-top serum separator tubes with polymer gel (BD Biosciences) from female health care workers of childbearing age enrolled at the Children's & Women's Health Centre of BC and BC Children's Hospital Research Institute, and born between January 1st, 1974 and January 1st, 1997, through an untargeted email to staff. At the beginning of the pandemic, BC implemented COVID-19 non-pharmaceutical measures including mandatory mask donning, social distancing, and limits on social gatherings. Early pandemic samples were collected early in the pandemic (May-June 2020) and nearly one year into the COVID-19 pandemic (February-May 2021). Age criteria (birth between January 1st, 1974 and January 1st, 1997) were selected to restrict the study to a homogenous population of women who received wP for their primary immunization. Blood from age-matched healthy pregnant women collected at time of first trimester prenatal screening at the BC Centre for Disease Control Public Health Laboratory in 2018 (April-May) and 2019 (April-June) served as a control group to examine whether anti-*B. pertussis* antibody levels at the beginning of the pandemic reflect levels expected early in pregnancy, prior to antenatal vaccination per policy.

Serology: Anti-*B. pertussis* IgG (PT [EI 2050–9601 G], FHA [EI 2050–9601-3 G] and PRN [EI 2050–9601-4 G]) levels were measured by a standardized enzyme-linked immunosorbent assay (ELISA) (EUROIMMUN Medizinische Labordiagnostika, Lübeck, Germany). ELISA results were calibrated using the first International WHO standard (WHO International Standard Pertussis Antiserum, human, 1st IS NIBSC Code 06/140), and reported in International Units [IU]/mL as recommended by the European Pertstrain group [11]. Lower limits of detection for IgG to PT, FHA and PRN were 0.2 IU/mL, 1 IU/mL and 0.6 IU/mL, respectively.

Statistics: Anti-*B. pertussis* IgG levels were log transformed and compared between the years 2020 vs. 2021 using a paired 2-sided student *t*-test, and the years 2018–2019 vs. 2020 using unpaired 2-sided student *t*-test. The proportions of subjects with anti-PT IgG levels $\geq$ 5 IU/mL, $\geq$15 IU/mL, $\geq$30 IU/mL or $\geq$ 40 IU/mL were also compared between 2021 and 2020, and between 2020 and 2018–2019 using chi-squared tests. Although there is no clear antibody correlate of protection against pertussis, these arbitrary cut-offs were used to define the population with quantifiable anti-*B. pertussis* antibodies (anti-PT IgG $\geq$ 5 IU/mL), and the seropositive or potentially protected population (with anti-PT IgG $\geq$ 15 IU/mL, $\geq$30 IU/mL or $\geq$ 40 IU/mL) as suggested previously [12]. P-value of 0.05 was assigned and statistical significance was set at $P < 0.016$ after adjustment for multiple comparisons (n = 3 for 3 *B. pertussis* antigen-specific IgG levels for each comparison) using Bonferroni correction. R version 3.4.0 was used for statistical analysis and GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California USA) was used to illustrate figures.

Ethics: The study was approved by the University of BC Children's and Women's Research Ethics Board. Written informed consent was obtained from all participants.

3. Results

In BC, the incidence of reported confirmed *B. pertussis* cases declined in the years 2020 and 2021 compared with pre-pandemic years (2015–2019) in all age groups (Fig. 1).

The median age of the study participants with paired samples (2020–2021 cohort: N = 18 women in total) was 37 years (Interquartile range [IQR]: 28–41) and the median interval between sample collections in 2021 and 2020 was 277 days (IQR: 256–301). None of these healthcare worker participants received Tdap vaccine after 2017. The geometric mean concentration of IgG levels against PT and FHA showed a statistically significant decline in women of childbearing age in 2021 compared with 2020, 6.8 IU/ml (95% confidence interval [CI], 4.2–10.9) vs. 8.4 IU/ml (95% CI, 5.1–13.9; p = 0.004), 18.8 IU/ml (95% CI, 10.9–32.2) vs. 23.6 IU/ml (95% CI, 13.2–42.1; $p < 0.001$), respectively. Although also lower, the geometric mean concentration of IgG levels against PRN were not statistically significantly different in 2021 compared with 2020, 37.1 IU/ml (18.1–75.9) vs. 47.2 IU/ml (24.8–89.9; p = 0.092), respectively (Fig. 2). The proportion of women with IgG levels against PT $\geq$ 5 IU/mL, $\geq$15 IU/mL, $\geq$30 IU/mL or $\geq$ 40 IU/mL in 2021 compared with 2020 was 55.5% [10/18] vs. 66.6% [12/18] (p = 0.73), 27.8% [5/18] vs. 33.3% [6/18] (p = 1), 11.1% [2/18] vs. 16.7% [3/18] (p = 1) and 5.6% [1/18] vs. 5.6% [1/18] (p = 1), respectively.

To determine whether early-pandemic anti-*B. pertussis* IgG levels in the 2020 cohort reflected the levels of *B. pertussis* in the population of pregnant women early during their gestation prior to the pandemic, we compared anti-*B. pertussis* IgG levels and percentage meeting pre-specified levels in 2020 versus 2018 and 2019 prenatal cohorts. We found that the geometric mean concentration of IgG levels against PT, FHA and PRN were generally higher but not statistically significantly different in samples of women of childbearing age in 2020 compared with samples of pregnant women collected early in pregnancy in 2018–2019 (N = 26), 8.4 IU/ml (95% CI, 5.1–13.9) vs. 5.4 IU/ml (95% CI, 3.8–7.7; p = 0.166), 23.6 IU/ml (95% CI, 13.2–42.1) vs. 20.1 IU/ml (95% CI, 13.4–30.2; p = 0.656), and 47.2 IU/ml (24.8–89.9) vs. 17.3 IU/ml (95% CI, 10.5–28.7; p = 0.021), respectively. The proportion of women with IgG levels against PT $\geq$ 5 IU/mL, $\geq$15 IU/mL, $\geq$30 IU/mL or $\geq$ 40 IU/mL in 2020 compared with 2018–2019 was 66.6% [12/18] vs. 88.5% [23/26] (p = 0.431), 33.3% [6/18] vs. 76.9% [20/26] (p = 0.684), 16.7% [3/18] vs. 3.8% [1/26] (p = 0.357) and 5.5% [1/18] vs. 3.8% [1/26] (p = 1), respectively.

4. Discussion

Here, we show that *B. pertussis* IgG levels significantly decreased in a population of female healthcare workers of childbearing age during a period of low exposure throughout the pandemic, and absent recent boosting otherwise through Tdap vaccination. If our observations of reduced anti-*B. pertussis* antibody may be extrapolated to the general population of women of childbearing age, then as social distancing measures are relaxed, increased monitoring may be warranted to detect early increase in the risk of severe disease in infants. This could be potentially even more concerning in the context of reduced immunization coverage and a decline in total number of vaccines against *B. pertussis* administered during the COVID-19 pandemic [13].

We showed that the incidence of reported *B. pertussis* declined in the years 2020 and 2021 compared to pre-pandemic years in

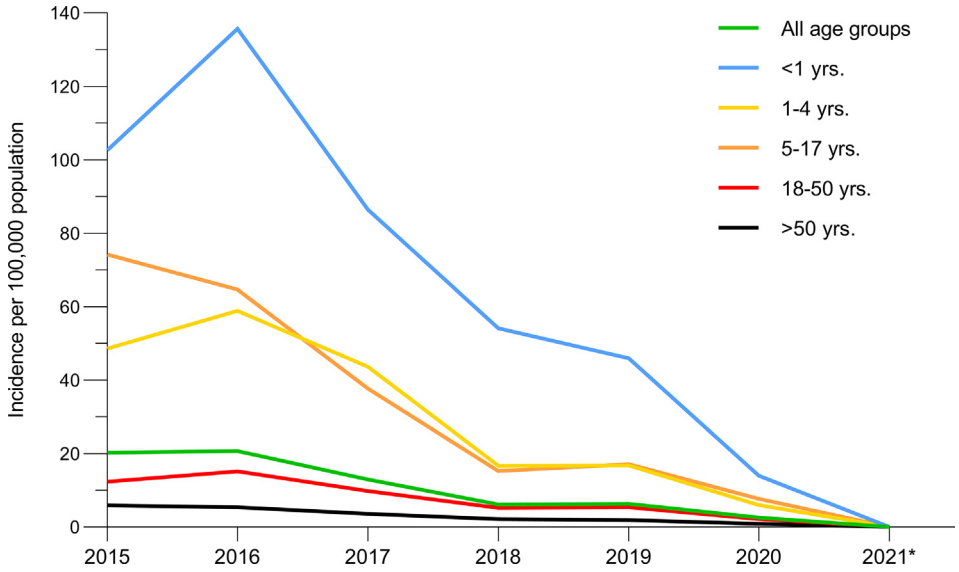

Fig. 1. Incidence of laboratory-confirmed and epidemiology-linked *Bordetella pertussis* cases reported to the British Columbia Centre for Disease Control during the years 2015–2021. *Incidence in 2021 was < 1/100,000 overall, as well as stratified by age among infants < 1 year as well as adults 18–50 and > 50 years. Case definition of a laboratory-confirmed case was isolation of *B. pertussis* from nasopharyngeal swab or nasopharyngeal wash or detection of *B. pertussis* DNA using a polymerase chain reaction assay from an appropriate clinical specimen, and one or more of the following: Cough lasting 2 weeks or longer; Paroxysmal cough of any duration; Cough with inspiratory "whoop"; Cough ending in vomiting or gagging, or associated with apnea. Epidemiology-linked case was defined as epidemiological link to a laboratory-confirmed case and one or more of the following for which there is no other etiology: Paroxysmal cough of any duration; Cough with inspiratory "whoop"; Cough ending in vomiting or gagging, or associated with apnea (Source: British Columbia Centre for Disease Control [28]).

all age groups. This is consistent with recent literature that showed a decrease in identification of *B. pertussis* infections in the population during the COVID-19 pandemic [6–9]. Most recently, data from Public Health England showed that the incidence of pertussis decreased significantly in the years 2020 and 2021, compared to pre-pandemic years (2014–2019) in all age groups [14]. Of note, surveillance trends in BC related to pertussis incidence apply not only to the population as a whole but also to infants in whom severe outcomes are more likely and under-reporting is less likely on that basis.

The findings of low levels of anti-*B. pertussis* antibodies measured in 2020 are consistent with a previous study in Canada, which showed that 97% of pregnant women between 2008 and 2011 had anti-PT IgG levels < 35 IU/ml, and 44% had levels < 5 IU/ml [15]. Similar to our findings, the GMC of anti-PT IgG was 5.5 IU/mL in pregnant women in Canada [15], and similar to findings from the Netherlands (10.1 IU/mL) [16] and the USA (6.0 IU/mL) [17]. However, these studies were conducted in settings of potential exposure to *B. pertussis* during the study period.

In this study we report a further decline in anti-*B. pertussis* IgG levels in the setting of low *B. pertussis* exposure in females of childbearing age. To our knowledge, this is the first to study the impact of COVID-19 restrictions on anti-*B. pertussis* antibody levels. Multiple observations in the literature support that decay in anti-*B. pertussis* antibodies is due to loss of exposure to *B.* pertussis circulation endemically or during cyclical peak activity. The APERT study evaluated the kinetics of anti-*B. pertussis* antibodies during an 18-month period following aP vaccination, showing a decay in anti-*B. pertussis* IgG levels beginning 1 month after vaccination. After 12 months, anti-*B. pertussis* IgG levels reached equilibrium (IgG to PT 8.84 EU/ml at 12 months vs. IgG PT 8.67 EU/ml after 18 months) [18]. Other studies showed that anti-*B. pertussis* antibody levels either stabilize or increase during follow up observations, supporting that some level of immunity against *B. pertussis* may be maintained in the context of exposure to the bacterium. A study performed in Germany with samples collected in 1994 showed stable anti-*B. pertussis* antibodies over a 2–5-year observation period. This latter finding suggests that exposure to *B. pertussis* happened within the population prior to the pandemic, and were able to maintain stable antibody levels [19]. Based on a longitudinal study in the USA, 90% of adults showed serological evidence of exposure to *B. pertussis* in the era of the wP vaccine (1984–1989), with an increase in one or two antigen-specific anti- *B. pertussis* antibodies between 2 consecutive years (during 5-year period). These data suggest that *B. pertussis* infections in adults may be more common than clinically recognized [20]. Finally, a most recent study from Sweden showed a near disappearance of *B. pertussis* among young infants < 1 year of age following non-strict mitigation strategies to limit the spread of COVID-19, where schools were still open and no lockdown or mandatory face masking mandates were issued [9]. Overall, these data support a more widespread transmission of *B. pertussis* than what is reported by routine surveillance systems and that this transmission can be interrupted by soft physical distancing measures. In this study, anti-PRN IgG levels were also lower in 2021 compared with 2020 but this did not reach statistical significance. Given significant decline in antibody to other *B. pertussis* proteins, we think lack of statistical power due to limited sample size is the most likely explanation. We are not aware otherwise of evidence to indicate that anti-PRN IgG levels are more stable than other *B. pertussis* antigen-specific antibodies.

The finding of non-statistically significant higher anti-*B. pertussis* antibody levels in women of childbearing age in 2020 compared with women in early pregnancy in 2018–2019 may stem from different reasons. The cohort of females of childbearing age consisted of health care workers at BC Children's Hospital and staff at the BC Children's Hospital Research Institute. Notwithstanding our age and sex matching, a health care workers population may have greater cumulative risk of exposure to respiratory pathogens more generally, including *B. pertussis*, and may also be more likely boosted through vaccination at some point compared to a general population of young women early in pregnancy. Additional opportunity for *B. pertussis* exposure in the intervening years between 2018–2019 and 2020 is possible but unlikely to explain the higher

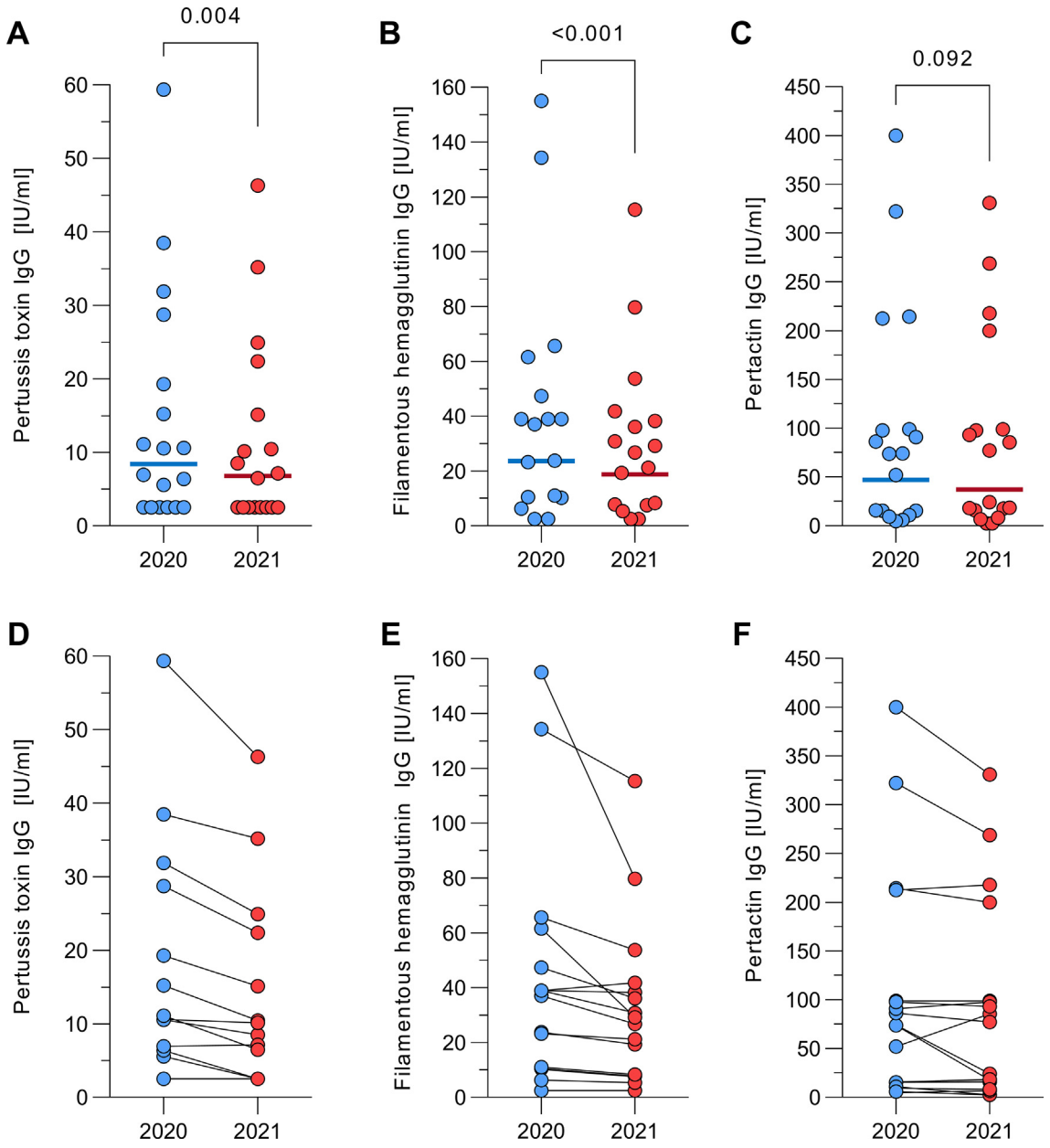

Fig. 2. Geometric mean concentration of serum immunoglobulin (Ig) G to pertussis toxin (A), filamentous hemagglutinin (B), and pertactin (C) in paired samples of women of childbearing age early in the COVID-19 pandemic (2020 in blue dots; n = 18 [for filamentous hemagglutinin n = 17]) and one year after non-pharmaceutical measures (2021 in red dots; n = 18 [for filamentous hemagglutinin n = 17]). Dot-line plot of serum IgG to pertussis toxin (D), filamentous hemagglutinin (E), and pertactin (F) in paired samples of women of childbearing age early in the COVID-19 pandemic (2020 in blue dots; n = 18 [for filamentous hemagglutinin n = 17]) and one year after non-pharmaceutical measures (2021 in red dots; n = 18 [for filamentous hemagglutinin n = 17])).

2020 sero-prevalence in our comparator group because, as shown in our Fig. 1, provincial incidence roughly plateaued in 2018 and 2019 (~6/100,000), and then declined in 2020 (~3/100,000) and 2021 (<1/100,000) to the lowest levels in the past decade since 2010 (3/100,000) and 2011 (~1/100,000), the latter incidence considered the lowest observed provincially since 1990 [21]. Although decreased testing for *B. pertussis* may have led to under-ascertainment and under-reporting of cases in 2020 and 2021 (i.e. lower owing to SARS-CoV-2 pandemic-related prioritization of laboratory and public health resources), dramatically-decreased *B. pertussis* incidence is also evident in infants < 1 year of age in 2020 (14/100,000) and 2021 (nil) compared to 2018 and 2019 (~50 per 100,000), comparable to or lower also than the trough years of 2010 (18/100,000) and 2011 (16/100,000) [21]. This temporal comparison among infants in particular is relevant because severe B. *pertussis* outcomes are more likely in that very young age group and less likely to be missed (i.e. under-reporting typically less of an issue among infants < 1 year of age). If our observations of reduced anti-*B. pertussis* antibody in healthcare workers may be extrapolated to the general population of women of childbearing age, then as social distancing measures are relaxed, increased monitoring may be warranted to detect early increase in the risk of severe disease in infants.

Our study has strengths and limitations. Strengths include that the kinetics of anti-*B. pertussis* antibodies was assessed in paired samples at the beginning and one year into the pandemic, in a homogenous population in terms of priming with a wP vaccine and results were reported using a standardized assay. Among lim-

itations in the interpretation of our findings is that the clinical significance of anti-*B. pertussis* antibody levels is unclear in the absence of well-established correlates of protection. Although an absolute correlation cannot be claimed, higher anti-PT, anti-FHA, and anti-PRN IgG levels are generally associated with greater likelihood of clinical protection from pertussis [22,23]. The potential significance of these low antibody levels may also vary as PT, FHA and PRN as virulence factors contribution to the development of pertussis disease in humans at different stages. PT is an important virulence factor that induces lymphocytosis, which can lead to pulmonary hypertension, respiratory failure and death [24]. FHA is implicated in the initiation of the disease by the attachment of the bacteria to the respiratory epithelium[25]. PRN is a surface-associated protein [26], and also contributes to adherence of *B. pertussis* to ciliated respiratory epithelium [27]. It should be noted that due to pandemic related pressures across all health authorities in BC and prioritization of COVID-19 notifications, the standard surveillance data verification processes for non-COVID notifiable diseases were scaled back. We acknowledge, that surveillance data are subject to change as the usual audits and verifications of notifiable diseases, including retrospectively, resume post-pandemic. Our 2019–2021 surveillance summaries in particular need to be interpreted with caution. Our study is also limited by a small sample size of the 2020–2021 paired subjects and the small number of subjects in 2018–2019 cohort.

In conclusion, this study provides evidence for reduction in anti- *B. pertussis* IgG levels in women of childbearing age during a period of low pathogen exposure. Although the clinical implications are uncertain, careful surveillance monitoring for potential increase in *B. pertussis* among infants at highest risk of severe outcomes seems prudent during the post-pandemic period.

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CRediT authorship contribution statement

Frederic Reicherz: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Liam Golding:** Conceptualization, Writing – review & editing. **Pascal M. Lavoie:** Conceptualization, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – review & editing. **Bahaa Abu-Raya:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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