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Impact of national recommendations for routine pertussis vaccination during pregnancy on infant pertussis in Ontario, Canada: a population-based time-series study

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Abstract

Background In February 2018, Canada's National Advisory Committee on Immunization (NACI) recommended antenatal tetanus–diphtheria–acellular pertussis (Tdap) immunization in every pregnancy regardless of previous Tdap immunization history. We examined the impact of the NACI recommendation on rates of infant pertussis in Ontario, Canada.

Methods We conducted a population-based time-series study of all live births in Ontario between August 1, 2011 and February 28, 2020. We used interventional autoregressive integrated moving average models to examine the impact of the NACI recommendation on monthly rates of pertussis among infants ≤ 3 months of age.

Results We observed 675 incident cases of pertussis among 1,368,024 infants 3 months of age or less between August 2011 and February 2020. The average monthly percent change in infant pertussis during the period up to and including publication of the NACI guidance and the period following publication were 0.0% (95% CI: -0.4–0.3%) and -0.8% (95% CI -2.3% to -0.1%), respectively. Following interventional ARIMA modelling, publication of the NACI guidance was not associated with a statistically significant decrease in the monthly pertussis incidence trend (-0.67 cases per 100,000 infants; $p = 0.73$).

Conclusion Publication of national recommendations for antenatal Tdap immunization in every pregnancy did not significantly reduce infant pertussis rates. This may reflect the persistently low rate of antenatal vaccination following publication of the recommendations. Expanding the scope of practice of allied health care providers to include antenatal Tdap immunization and patient education regarding antenatal pertussis immunization should be considered to further optimize uptake of vaccination.

Keywords Pertussis, Infant, Vaccine, Tdap, Time series analysis

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Introduction

Pertussis is a highly contagious respiratory tract infection associated with substantial morbidity in infants [1]. In 2019, age-specific incidence rates of pertussis reported in Canada were highest among infants less than one year of age (35.5 cases per 100,000 population) [2]. Moreover, infants under one year of age are at greatest risk of severe illness, with pertussis-related hospitalization and intensive care admission rates of 42.3 and 8.6 admissions per 100,000 population of Canadian infants, respectively, between 1999 and 2015, compared with less than one admission per 100,000 population in other age groups [3]. Importantly, the majority (76.5%) of hospitalized infants during this period were three months of age or less [3]. Similar findings have been observed in other countries, reflecting the greater vulnerability to severe pertussis among infants too young to have completed their primary three-dose immunization series against *Bordetella pertussis*. [4–8] In light of recent outbreaks, even in highly-vaccinated populations [9, 10], strategies are needed to protect young infants from pertussis and its sequelae in the period before they have initiated and/or completed their primary immunization series.

Antenatal vaccination with tetanus, diphtheria, and acellular pertussis-containing vaccine (Tdap) is an increasingly adopted strategy for preventing pertussis and its sequelae in young infants, with several countries integrating antenatal Tdap immunization into routine adult vaccination programs [11, 12]. In 2013, Canada's National Advisory Committee on Immunization (NACI) recommended antenatal Tdap immunization during pertussis outbreaks and for pregnant women who had not been previously immunized [13]. This was updated in 2018, recommending routine antenatal Tdap immunization in every pregnancy irrespective of previous Tdap immunization history [14]. Although 27 to 32 weeks of gestation was designated as the ideal gestational timing for vaccination, thereby optimizing cord blood antibody concentrations at the time of delivery [15], NACI recommended that immunization could be undertaken at any point beyond 13 weeks of gestation [14]. These recommendations are largely aligned with those of other jurisdictions, including the United States and United Kingdom [16, 17].

A recent population-based cohort study found that antenatal Tdap vaccination among Ontario residents increased from 0.4% in 2011–2012 to 29.2% in 2019–2020 following the publication of NACI recommendations [18]. Moreover, the increase in antenatal Tdap coverage was greatest immediately following the revised guidance. However, whether the NACI guidance and the resultant increase in antenatal Tdap coverage was associated with a corresponding change in the incidence of infant pertussis remains unknown. Accordingly, we

conducted a population-based time-series study to evaluate the impact of the 2018 NACI recommendations on infant pertussis incidence in Ontario, Canada.

Methods

Study design and setting

We conducted a population-based time-series study of all infants less than 3 months of age in Ontario between August 1, 2011 and February 28, 2020. We selected this time period to allow a sufficiently long observation period prior to the publication of the NACI guidance and to avoid the confounding effects of COVID on the incidence and diagnosis of other respiratory infections. Ontario residents have universal access to hospital care and physicians' services, including prenatal care. However, Ontario did not have a publicly-funded program for repeated Tdap vaccination, including during pregnancy, in place during the study period.

Data sources and study population

We used Ontario's administrative health databases, which are securely linked using unique, encoded identifiers and analyzed at ICES in Toronto, Ontario (<https://www.ices.on.ca>). We used the Canadian Institute for Health Information National Ambulatory Care Reporting System and Discharge Abstract Database to identify pertussis-related emergency department visits and hospital admissions, respectively, among infants 3 months of age or lower. These databases contain detailed clinical information regarding all emergency department visits and hospital admissions in Ontario. We used the Ontario Health Insurance Plan (OHIP) database to identify claims for physician services, including immunizations identified through fee codes, and obtained basic demographic data from the Registered Persons Database, a registry of all Ontario residents eligible for health insurance. The use of data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Study outcomes

Our primary outcome was the monthly incidence of pertussis in infants 3 months of age or less. We defined an incident case as an outpatient physician visit [International Classification of Diseases, Ninth Revision (ICD-9), code 033] or an emergency department visit or hospital admission [International Classification of Disease, 10th Revision (ICD-10), code A37] with a diagnosis of pertussis. To prevent misclassification due to outpatient visits for infant pertussis vaccination, we excluded all infant physician encounters that included OHIP fee codes associated with any pertussis-containing immunizations (G840, G841, G847).

Statistical analysis

We determined the crude average monthly percent change prior to and following the NACI guidance. Because the average monthly percent change does not account for prior trends, temporal correlation of the time series and seasonality, we used interventional autoregressive integrated moving average (ARIMA) models to estimate the association between the NACI guidance and infant pertussis rates [19, 20]. We used the Dickey Fuller test to determine the stationarity of the time series, and applied first order and seasonal differencing to arrive at a stationary series [20, 21]. We used the autocorrelation function and partial autocorrelation function to identify autoregressive and/or moving average components in the time series and correct for autocorrelation remaining after differencing, and selected the best models using goodness-of-fit tests [20, 21]. We used residual plots and the Portmanteau statistic to confirm that residuals from specified ARIMA models were a white noise process [19, 20, 22]. Finally, once the ARIMA models were specified, we used a ramp intervention function to test for a gradual slope change in antenatal Tdap immunization beginning one month following the NACI guidance (i.e., March 2018) [20].

We conducted several analyses to triangulate and test the robustness of our findings. First, we used ordinary least squares segmented regression with Newey–West standard errors to account for heteroscedasticity and with k lags to account for autocorrelation, where the value for k was determined using the Cumby–Huizinga general test for autocorrelation [23, 24]. Next, we conducted a structural break analysis of each time series by plotting the cumulative sums of ordinary least squares residuals (CUSUM-OLS) and corresponding confidence bands over the study period [25]. A structural break is identified by movement of the plotted CUSUM beyond the confidence bands and the associated test statistic. All analyses were completed using SAS Enterprise Guide, version 7.1 (SAS Institute Inc., Cary, NC, USA), R Studio, and Stata version 17.0 (Stata Corp LP, TX).

Results

There were 675 incident cases of pertussis among 1,368,024 infants 3 months of age or less between August 2011 and February 2020, with 121 (17.9%), 288 (42.7%) and 266 (39.4%) being diagnosed between the ages of 0 to 1 months, 1 to 2 months and 2 to 3 months, respectively. Most infants ($n=475$; 70.4%) were diagnosed as outpatients, while 76 (11.3%) and 124 (18.4%) cases were diagnosed in the emergency department and during an inpatient hospitalization, respectively. In total, 189 infants were hospitalized with pertussis, of whom 49 (25.9%) required admission to an intensive care unit (ICU). Monthly rates of infant pertussis were 53.2 cases

per 100,000 population and 18.8 cases per 100,000 population in August 2011 and February 2020, respectively (Fig. 1). The average monthly percent change (AMPC) in incident pertussis over the entire study period was -0.2% (95% CI -0.7 – 0.1%). The AMPCs during the period up to and including publication of the NACI guidance and the period following publication were 0.0% (95% CI: -0.4 – 0.3%) and -0.8% (95% CI -2.3 to -0.1%), respectively.

In interventional ARIMA modelling, publication of the NACI guidance was not associated with a statistically significant decrease in the monthly pertussis incidence trend (-0.67 cases per 100,000 infants; $p=0.73$). We also observed similar findings in sensitivity analyses, with no structural breaks identified using the OLS-CUSUM test (Supplemental Appendix 1) and a non-significant decrease in the monthly pertussis incidence trend of -1.2 cases per 100,000 infants (95% CI: -2.5 to 0.2 cases per 100,000 infants) following NACI guidance publication using segmented regression.

Discussion

In our population-based time-series study, we found a crude reduction in pertussis incidence among young infants over time. However, in interrupted time series models that accounted for trend and seasonality, the publication of the NACI guidance did not specifically influence these trends. Our findings likely reflect persisting low antenatal Tdap coverage in Ontario during the study period, with past research finding that immunization was undertaken in approximately one in four pregnancies in the 12 months following publication of the NACI guidance [18].

Our study has several implications for public health. Antenatal pertussis immunization is an effective intervention for mitigating the burden of severe pertussis illness in young infants, with estimates of vaccine effectiveness ranging from 36 to 90% in several studies [26–34]. Further, antenatal Tdap immunization is safe, with multiple studies finding no association between vaccination and adverse fetal or neonatal outcomes [12, 34–37]. Yet, despite supportive evidence, several studies have documented suboptimal uptake of maternal pertussis immunization [38–42]. Because healthcare provider recommendation is a key determinant of antenatal Tdap immunization [43, 44], reluctance of maternity care providers to administer vaccines during pregnancy in the absence of local recommendations or endorsement of a professional body is a potentially important reason for suboptimal uptake. This assertion is supported by prior research demonstrating that only 35% of surveyed Canadian maternity care providers routinely recommended pertussis vaccination during pregnancy in the period predating the publication of the updated NACI recommendations [45]. Insufficient training and concerns

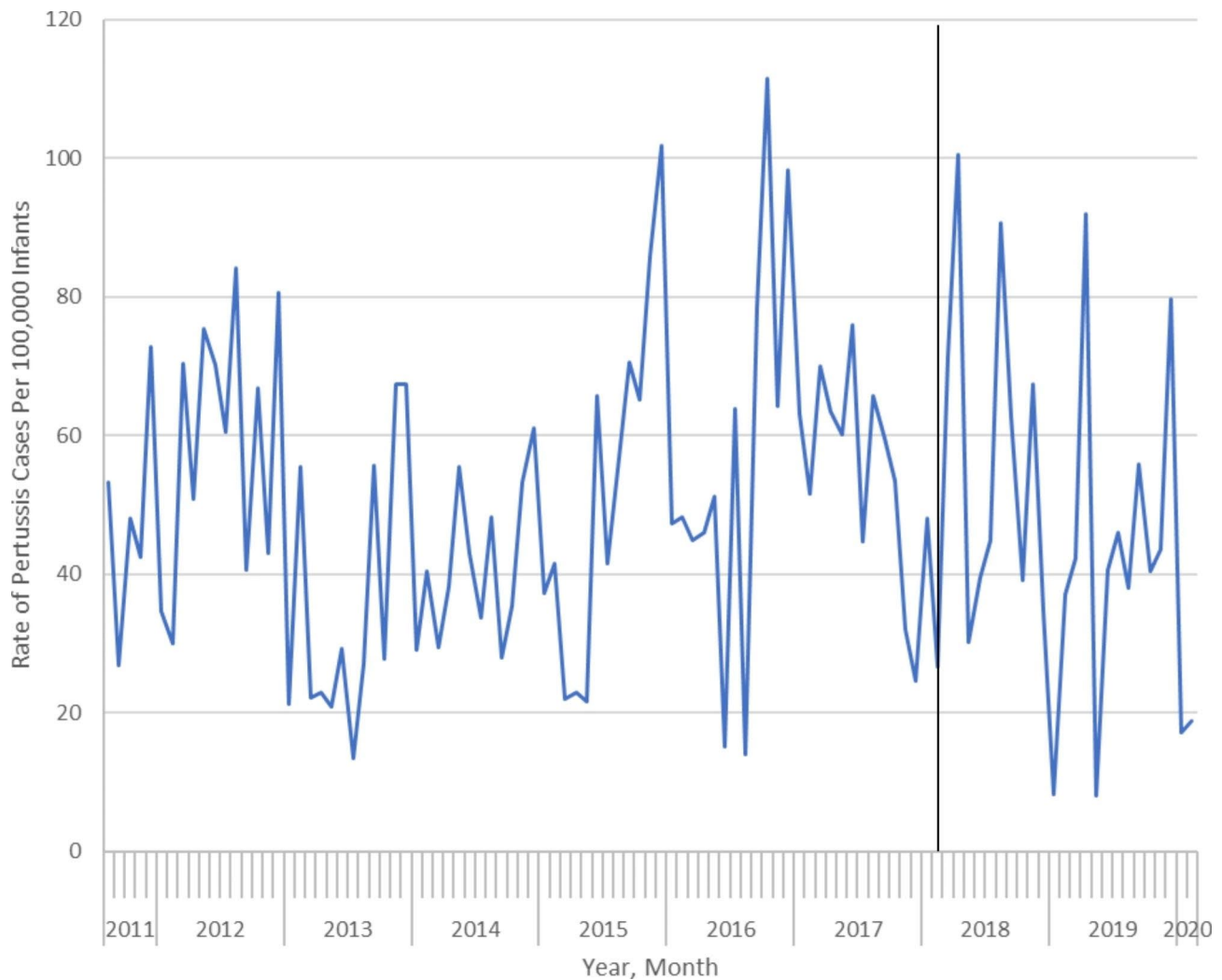


Fig. 1 Monthly rate of incident infant pertussis per 100,000 infants ≤ 3 months of age in Ontario, Canada between August 2011 and February 2020

about vaccine safety are among the principal reasons provided by healthcare providers for not recommending antenatal Tdap immunization [45, 46]. Specifically, a cross-sectional web-based survey of Canadian maternity providers found that relative to physicians and nurses, a lower proportion of midwives and pharmacists considered Tdap to be an effective means for protecting infants [45]. Moreover, midwives had greater reservations about the safety of Tdap during pregnancy, whereas pharmacists were more likely to report that other maternity care providers discuss vaccination with their pregnant patients [45]. Although inferences from this study are limited by its non-representative sample and the possibility that perspectives have changed since its publication in 2020, these findings suggest that greater training and education regarding vaccine safety and efficacy, as well as expanding the scope of pharmacy practice to include Tdap, may increase maternity provider endorsement of this measure.

In addition, funding for repeated Tdap vaccination varies across Canada, and the lack of a publicly funded program for repeated Tdap immunization in Ontario during the study period may have limited uptake of vaccination during pregnancy. However, a national survey of 4,607 mothers conducted following the publication of NACI guidance found that cost was cited as the reason for non-vaccination by less than 1% of unvaccinated mothers, with lack of awareness about pertussis immunization being the main reason for not having been vaccinated [47]. Although the province of Ontario expanded its publicly funded Tdap immunization program in April 2022 to include a routine dose in every pregnancy [48], additional strategies may be needed to increase awareness and maximize coverage of Tdap immunization among pregnant women. Example interventions that have been demonstrated to be effective include providing education to increase provider awareness of vaccine recommendations during pregnancy and expanding the scope

of midwives and pharmacists to include antenatal Tdap immunization [49, 50]. Although evidence-based, these strategies require policy change and the involvement of professional regulatory bodies for implementation.

In addition to persistently low rates of antenatal Tdap vaccination, our findings may reflect a preponderance of milder illness among infants during our study period, with only 28.0% of cases requiring hospitalization. Because antenatal Tdap vaccination appears less effective at preventing mild illness (i.e., illness not leading to hospital admission) [31], the large number of infants diagnosed as outpatients may have obfuscated the clinical impact of increased maternal vaccination rates following the NACI guidance.

Our study has some limitations. First, the validity of the diagnostic codes used to define cases of infant pertussis is unknown. However, rates of infant pertussis derived in our study approximated published estimates of laboratory-confirmed cases [2]. Second, the very low rate of infant pertussis and inherent variability in the occurrence of this outcome may have resulted in a lack of power for detecting a significant change following the publication of NACI guidance and also precluded our ability to evaluate just severe pertussis (i.e., illness leading to hospital admission) [51]. For similar reasons, we could not replicate our analyses stratified by age group. Third, as with all interrupted time series studies, temporal confounding related to discrete events occurring in close proximity to the interventions of interest or changes in the source population is a potential source of bias. However, we are unaware of any co-occurring interventions, and there were no other interventions implemented during this period that could confound our findings.

In summary, we found no appreciable change in infant pertussis rates in Ontario following the publication of the NACI immunization standard recommending antenatal Tdap immunization in all pregnancies. This finding most likely reflects persistently suboptimal antenatal Tdap coverage. Further research is needed to understand how health care providers interpret and promote NACI guidance to their patients. In addition, expanding the scope of allied health professionals such as midwives and pharmacists to include Tdap immunization and programs to promote awareness of the updated guidance among clinicians and patients should be considered to further increase uptake of antenatal Tdap immunization. Moreover, research exploring uptake of evidence regarding the effectiveness of vaccination during pregnancy and expanding the pool of health care professionals able to provide vaccines to pregnancy is also relevant to other vaccines recommended during the antenatal period, including influenza and COVID-19 [52]. The latter recommendation is especially important in light of recent evidence confirming a reduced risk of severe illness and

death among women with complete or boosted vaccine doses during the Omicron phase of the COVID-19 pandemic [53].

List of abbreviations

AMPC	Average Monthly Percent Change
ARIMA	Autoregressive Integrated Moving average
CUSUM-OLS	Cumulative sums of ordinary least squares
ICD-10	International Classification of Disease, 10th Revision
ICD-9	International Classification of Diseases, Ninth Revision
NACI	National Advisory Committee on Immunization
OHIP	Ontario Health Insurance Plan
Tdap	Tetanus, Diphtheria, and Acellular Pertussis-containing vaccine

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12884-023-05938-2>.

Supplementary Material 1

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Not applicable.

Authors' contributions

TA, DM, DBF, JCK and TG conceptualized and designed the study, and were involved in the interpretation of the data. DM and TA conducted the analyses. TA drafted the initial manuscript. All authors critically reviewed the manuscript for intellectual content and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data Availability

The data set from this study is not available publicly and is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request (tony.antoniou@unityhealth.to), understanding that the programs may rely upon coding templates or macros that are unique to ICES.

Declarations

Ethics approval and consent to participate

ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. ICES is a prescribed entity under Sect. 45 of Ontario's Personal Health Information Protection Act. Section 45 authorizes ICES to collect personal health information, without consent, for the purpose of

analysis or compiling statistical information with respect to the management of, evaluation or monitoring of, the allocation of resources to or planning for all or part of the health system. Projects conducted under Sect. 45, by definition, are exempt from and do not require review by a Research Ethics Board. This is confirmed in a letter from the REB of Sunnybrook Health Sciences Centre, ICES' Research Ethics Board of Record (See Appendix A). This project was conducted under Sect. 45, and approved by ICES' Privacy and Compliance Office. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

Tony Antoniou has no conflicts of interest. Daniel McCormack has no conflicts of interest. Deshayne Fell has no conflicts of interest. Jeff Kwong has no conflicts of interest. Tara Gomes has received grant funding from the Ontario Ministry of Health and Long-Term Care.

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