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# Seasonal variation in rates of emergency room visits and acute admissions following recommended infant vaccinations in Ontario, Canada: A self-controlled case series analysis

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ABSTRACT

*Objectives:* To determine if birth month has an effect on the incidence of adverse events following the 2- and 12-month recommended vaccinations.
*Study design:* Using health administrative databases, we conducted a population-based retrospective cohort study and employed a self-controlled case series analysis approach. We included children born in Ontario, Canada between April 1st 2002 and March 31st 2010 who received the diphtheria, tetanus, pertussis, inactivated poliovirus and Haemophilus influenzae type b (DTaP-IPV-Hib) vaccine recommended at 2 months and/or the measles, mumps, and rubella vaccine recommended at 12 months. We calculated the relative incidence (RI) of hospitalizations and emergency room visits within a pre-specified risk period compared to a control period following vaccination. We measured the effect of birth month using relative incidence ratios (RIRs) to compare the RI for infants born in each month to that for the month having the lowest RI.
*Results:* For the 2-month vaccination, we observed the lowest and highest RIs for infants born in October and April, respectively. The RIR (95% CI) for April compared to October was 2.06 (1.59–2.67, $p < 0.0001$), consistent with a strong seasonal effect. For the 12-month vaccination, November births had the lowest RI, whereas August births had the highest. The RIR (95% CI) for August compared to November was 1.52 (1.30–1.77, $p < 0.0001$).
*Conclusions:* Our findings suggest a seasonal effect on susceptibility to adverse events following vaccination exists. Further study will be important to elucidate potential biological and/or behavioral explanations for the seasonal effect we observed.


## 1. Introduction

Adverse events following immunization (AEFI) are reactions or other events that occur after receiving a vaccine, which may or may not be causally related to the vaccination. Increased incidence of AEFIs among subgroups of individuals could help to identify vulnerable subpopulations of children and/or issues with the safety profile of a vaccine.

In previous work we reported a significant increase in ER visits and acute admissions to hospital following measles, mumps and rubella (MMR) vaccination recommended at 12 and 18 months of age [1]. For the recommended 2-, 4- and 6-month diphtheria, tetanus, acellular pertussis, inactivated poliovirus and Haemophilus influenza type b, inactivated poliovirus (DTaP-IPV-Hib) vaccinations, we found no increase in admissions and ER visits in the post-vaccination period [2]. Using methods developed in our previous work, we have identified a number of risk factors that may

*Abbreviations:* RI, relative incidence; RIR, relative incidence ratio; ICES, Institute for Clinical Evaluative Sciences; ER, emergency room; 95% CI, 95% confidence intervals; AEFI, adverse events following immunization; MMR, measles, mumps, rubella; SCCS, self-controlled case series; UV, ultraviolet.

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increase susceptibility to AEFI, including birthweight at term [3], prematurity [4], socioeconomic status [5], sex [6] and birth order [7]. Additionally, a number of studies have reported that the season of birth affects the risk of immune-mediated diseases such as multiple sclerosis, type I diabetes and inflammatory bowel disease [8–11]. Seasonal factors could act in the perinatal period, or well before this, through environmental and epigenetic influences during gestation that may affect embryonic and fetal tissue structure during development [12,13]. The seasonal influence that has been shown for immune-mediated diseases could potentially translate into an effect of month of birth on rates of AEFI during the first year of life. In this study, we addressed this question by assessing the association between month of birth and the relative incidence (RI) of AEFI, defined as hospital admissions or ER visits, following vaccination.

## 2. Methods

### 2.1. Study population

Children born in Ontario between April 1st 2002 and March 31st 2010 who were enrolled in the Ontario Health Insurance Plan (OHIP) were eligible for inclusion in the study cohort. OHIP is Ontario's universal health insurance plan which covers nearly all Ontario residents. We excluded multiple births, infants born prematurely (<37 weeks gestation) and infants in the bottom decile of birth weight for their gestational age. After these exclusions, infants who were vaccinated at 2 and/or 12 months of age were included in the study cohort. We excluded children who died, or whose follow-up was otherwise terminated before the end of the required observation period (Supplementary Fig. 1).

### 2.2. Vaccinations

As part of the publicly funded immunization schedule in Ontario, Canada, vaccinations given at 2, 4 and 6 months of age included those against pertussis, diphtheria, tetanus and polio and *Haemophilus influenzae* type b (cPDT Polio + Hib until January 2005; DTaP-IPV-Hib thereafter). As of January 2005, a pneumococcal vaccine was also administered at 2, 4, and 6 months of age (Pneu-C-7 until October 2009; Pneu-C-10 thereafter). The first dose of the measles, mumps and rubella vaccine (MMR) was given at 12 months of age throughout the entire study period, and as of September 2004, a vaccine against meningococcal disease (type C) was added to the schedule [14].

### 2.3. Data sources

All study data were linked using unique, encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES). We identified vaccinations from the OHIP database using general vaccination billing codes and methods described previously [1,2]. To identify the 2-month vaccinations, we selected those occurring on the exact recommended date (60 days) and up to two weeks before or up to one month after. For the 12-month vaccination, we selected those occurring at 365 days of age, as well as up to 60 days past that date. We ascertained hospital admissions using the Canadian Institute for Health Information's (CIHI's) Discharge Abstract Database (DAD), and ER visits using CIHI's National Ambulatory Care Reporting System (NACRS). The Registered Persons Database was used to ascertain eligibility for OHIP coverage and deaths. We defined our composite primary outcome as all-cause ER visits and admissions, with the *a priori* exclusion of events having diagnoses that could not reasonably be causally associated with vaccination (Supplementary Table 1). Ethical approval for this study was obtained from The Ottawa Hospital Research Ethics Board.

### 2.4. Design and analysis

The analysis was conducted using the self-controlled case series (SCCS) design [15,16] and the Vaccine and Immunization Surveillance in Ontario (VISION) analytic architecture [17]. Our general analytical strategy has been described in detail elsewhere [1,2]. We were primarily interested in adverse events following first vaccine exposure at two months (cPDT Polio + Hib or DTaP-IPV-Hib), and first exposure to MMR vaccine at 12 months of age. Therefore, we selected observation periods that biologically relate to these exposures. For the 2-month vaccination, we designated the 48 h post-vaccination (days 0–1) as the risk period and days 9–18 as the control period. At 12 months, the risk period included days 8–12 post-vaccination and the control period included days 20–28. These risk periods were modified *a priori* from our previous studies to include only the time of most intense excess event incidence.

In many instances, acute admissions immediately follow an ER visit (*i.e.* a patient presents to the ER and requires admission). We counted only the first event to occur in a risk or control period, thus avoiding the need to decide whether events close together in occurrence truly were distinct, or part of the same 'episode' of care.

We calculated the RI of the primary endpoint in the risk period compared to the control period using a conditional Poisson regression model, which included terms for exposure period and for identifying each individual child, thereby accounting for intra-individual correlation and allowing each individual to serve as his/her own control. To illustrate the magnitude of the effect of birth month on the RI of our endpoint, we computed relative incidence ratios (RIRs) by comparing the RI of events in infants born in each month to that for the month having the lowest RI. This was identified *post hoc*. A test for interaction between risk period and month of birth was used to establish statistical significance of differences in RIs between birth month subgroups [16].

To test for the presence of a cyclical seasonal pattern in RIs, we repeated the SCCS analysis at both the 2- and 12-month vaccination with the season effect parameterized using a cosinor modeling approach [18]. Details of the cosinor model implementation are provided in the Supplemental Methods.

All *p*-values were two-sided, and all analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

### 2.5. Sensitivity analyses

#### 2.5.1. Analysis of individual years

In order to determine whether the effect of season was similar across individual calendar years, we repeated our analysis for each year separately from 2002 to 2010.

#### 2.5.2. Original versus restricted risk periods

To determine the impact of using risk periods restricted to days 0 and 1 for 2-month vaccinations and days 8–12 for 12-month vaccinations as compared to risk periods from past studies (days 0–2 and days 4–12, respectively), we conducted our analysis by birth month using both risk period definitions.

#### 2.5.3. Event incidences in risk and control periods

In order to investigate whether effects of birth month were primarily driven by differences in (a) the risk periods or (b) the control periods, we computed ratios comparing the incidences of events in risk periods between each birth month and the reference month (relative risk incidence) and similarly, the incidences of events in