Investigating the effect of early life antibiotic use on asthma and allergy risk in over 600 000 Canadian children: a protocol for a retrospective cohort study in British Columbia and Manitoba

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ABSTRACT

Introduction Allergic conditions, such as asthma, hay fever and eczema, are some of the most common conditions impacting children globally. There is a strong incentive to study their determinants to improve their prevention. Asthma, hay fever and eczema are influenced through the same immunological pathway and often coexist in children (‘the atopic march’). Increasing evidence shows a link between infant antibiotic use and the risk of childhood atopic conditions, mediated through gut microbial dysbiosis during immune system maturation, however, the potential for confounding remains. This study will investigate the relationship between infant antibiotic use and risk of allergic conditions in British Columbian and Manitoban children born over 10 years, adjusting for relevant confounders.

Methods and analysis Provincial administrative datasets will be linked to perform comparable retrospective cohort analyses, using Population Data BC and the Manitoba Population Research Data Repository. All infants born between 2001 and 2011 in BC and Manitoba will be included (approximately 460 000 and 162 500 infants, respectively), following up to age 7. Multivariable logistic regression will determine the outcome risk by the fifth birthday among children who did and did not receive antibiotics before their first birthday. Clinical, demographic and environmental covariates will be explored, and sensitivity analyses performed to reduce confounding by indication.

Ethics and dissemination The University of British Columbia Research Ethics Board (H19-03255) and University of Manitoba Ethics Board (H525156 (H2021.328)) have approved this study. Data stewardship committees for all administrative datasets have granted permissions, facilitated by Population Data BC and the Manitoba Centre for Health Policy. Permissions from the Canadian Health Infant Longitudinal Development Study and Manitoba Centre for Health Policy. Permissions from the Canadian Health Infant Longitudinal Development Study are being sought for breastfeeding data (CP185). Findings will be published in scientific journals and presented at infectious disease and respiratory health conferences. A stakeholder committee will guide and enhance sensitive and impactful communication of the findings to new parents.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Uses linked clinical, environmental and sociodemographic data for all children born in British Columbia and Manitoba and their parents over a 10-year period, with multyear follow-up from birth into childhood.

⇒ Informed by previous ecological investigations in BC while addressing individual-level confounders over a large geographical area and a long time period.

⇒ Presents a multifaceted knowledge translation and engagement strategy for ensuring that results contribute to both antimicrobial stewardship programme planning and asthma/allergy prevention strategies in BC, Manitoba and globally.

⇒ Due to the use of routine healthcare and environmental data not collected for the purposes of this cohort study, data quality and completeness will have to be evaluated.

INTRODUCTION

Early-life determinants of health and their impact on longer-term development is an important and growing area of public health and paediatric research in Canada and globally. Use of antibiotics, and their impact on the developing infant gut microbiome, is of particular interest and is believed to affect immune system development and the risk of developing chronic conditions such as asthma, wheezing, food allergies, hay fever, eczema and obesity.1-6 Antibiotic use for infants, whether it be therapeutic or prophylactic, has been shown to vary widely in practice, indicating that there is room for improvement in how these medications are used. Since 2001, there has been a 73% reduction in antibiotic use (from 868 to 236 prescriptions per 1000 population between 1999 and 2019) in British Columbian infants.7 In parallel, between 2000...
and 2018, the incidence of asthma in children aged 1–4 fell by 41% from 29 to 17 incident cases per 1000 population at risk. In Manitoba, similar downward trends have been seen in antibiotic prescribing for upper respiratory tract infections and asthma prevalence in children aged 1–4 between 2000 and 2010 (asthma incidence needs to be investigated), although this could be due to a diagnostic shift. Recent work in BC has demonstrated a correlation at the local health authority (LHA) level between early-life antibiotic use and risk of asthma later in childhood, and collaborative efforts with the Canadian Healthy Infant Longitudinal Development (CHILD) study (a Canadian prospective birth cohort) have shown a similar association, mediated through changes in the developing gut microbiome.

This work, however, needs to be built on to investigate these trends at the patient level in the wider population to improve generalisability. Other population-based studies which have examined this relationship in other jurisdictions can provide valuable lessons around study design, covariate selection, analysis and reducing biases. This question has previously been shown to be vulnerable to confounding by indication, whereby effect measures diminish when the respiratory infections that the antibiotics are being used to treat are adjusted for in analysis, making it important to determine whether the antibiotic or the underlying infection is predisposing the patient to asthma. Considerations around temporality with respect to antibiotic administration and outcome measurement need to be accounted for, along with adjusting for potential biases introduced by confounding by indication. Allergic asthma is not the only atopic disease common in children, allergic rhinitis (hay fever) and allergic dermatitis (eczema) are also immune-regulated allergic diseases mediated by IgE, which frequently present together alongside asthma, otherwise known as ‘the atopic march’. All three of these conditions related to allergic sensitisation and its association with antibiotic use in early life need to be explored. Wider environmental factors such as air quality, rurality, access to green spaces as well as modifying factors such as breast feeding and socioeconomic status need to be included. The study outlined in this protocol, therefore, aims to investigate the atopic outcomes related to reduced antibiotic use in early life in the sociodemographic, clinical and environmental factors related to the child and the parents which may play a role in this relationship. The study will be conducted in British Columbia and Manitoba to compare results across provincial jurisdictions where paediatric antibiotic use and rates of asthma have decreased in recent years.

**Objective**
Quantify the odds of developing asthma, allergic rhinitis and allergic dermatitis before the fifth birthday in children who received systemic antibiotics in their first year of life compared with children who did not, adjusting for relevant patient-level and area-level factors.

**Data sources**
Data will come from Population Data BC and the Manitoba Population Research Data Repository and data collection, variable categorisation and analysis will be aligned as closely as possible across the provinces (online supplemental appendix 1). These repositories house whole-population administrative health, social and education data for virtually all provincial residents who are registered for the provinces’ universal health insurance programmes. Subgroup analyses will use data from the CHILD study cohort and from the Manitoba Interdisciplinary Lactation Centre (MILC) to investigate breastfeeding behaviours. Details of the requested datasets are presented in online supplemental appendix table 1.

Approvals for use and linkage of these datasets have been given by the UBC Clinical Research Ethics Board (H1 09-03255) and by the data stewardship committee through Population Data BC. The CHILD study will provide data for the breastfeeding predictors subanalysis and the CHILD Study National Coordinating Centre is in the process of giving approval for the use of these data (CP185). Ethical approval from the University of Manitoba has been granted (HS25156 (H2021:328)) as well as approval from all relevant data stewards for the use of Manitoba data for this study.

**METHODS AND ANALYSIS**

**Population**
These population-based retrospective cohort studies will include (A) all singleton infants born at or after 36 weeks gestation in BC between 2001 and 2011 captured in the BC Perinatal Data Registry and (B) all singleton infants born at or after 36 weeks gestation in Manitoba over the same time period captured in the Health Insurance Registry, with follow-up to age 7 (2018) for confirmation of disease trajectory and outcome measurement by the fifth birthday. Infants placed for adoption within 28 days of birth will be excluded from the study. Infants who died or moved out of province during the follow-up period will be excluded from the study. Mothers of the included infants in BC will be captured in the BC Perinatal Data Registry and registered fathers will be captured in Vital Statistics. Mothers of the included infants in Manitoba will be identified using the Manitoba Health Insurance Registry and fathers identified through Vital Statistics and the Health Insurance Registry. Parental data will be used to determine the history of atopic disease of the parents in the 5 years prior to the infant’s birth, thereby accounting for genetic predispositions to asthma and atopic disease. The birth inclusion period will run from 2001 to 2011 and with parental history and child follow-up the full dataset will include data from 1996 to 2018.

**Antibiotic exposure**
Antibiotics will be defined using the Anatomical Therapeutic Chemical (ATC) code J01 ‘Antibacterials for
systemic use’ (https://www.whocc.no/atc_ddd_index/?code=J01&showdescription=no). Infants will be classified into two groups: ‘exposed’ (infants dispensed systemic antibiotics in their first year) and ‘unexposed’ (infants not dispensed systemic antibiotics in their first year). The primary analysis will investigate whether the infants received antibiotics (Y/N). Subgroup analyses will stratify the exposure variable by (1) whether the antibiotics received were broad spectrum versus narrow spectrum, (2) the antibiotic class, (3) the number of antibiotic courses in the first year and (4) the cumulative days of antibiotic exposure. Antibiotic exposure will only be measured as antibiotics dispensed for the infant, however, prenatal and intrapartum antibiotic use in the mothers will be adjusted for.

**Atopic outcomes**

All infants will be followed up to measure allergic outcomes (asthma, allergic rhinitis or allergic dermatitis) between their first birthday and their fifth birthday. Estimates will be reported for ‘any of the three allergic outcomes’ as well as for each allergic outcome separately.

To allow comparison between the two provinces, the clinical case definition for asthma will be informed by the Canadian Chronic Disease Surveillance System prevalent asthma case definition. Based on previous work by Sbihi et al., transient and chronic phenotypes of asthma will be defined in the cohort (transient asthma defined as the case definition being met by age 1 with peak prevalence by age 2, and no asthma activity after age 6) and transient asthma cases will not be included in the ‘case’ group. Group-based trajectory modelling, similar to the Sbihi et al paper, will be used to characterise transient and chronic cases of allergic rhinitis and allergic dermatitis by quantifying the distribution of outcome trajectories over time. Transient phenotypes of allergic rhinitis and allergic dermatitis will not be included in the ‘case’ groups.

**Potential confounders**

All analyses will be adjusted for clinical, sociodemographic and environmental factors related to the infant and the parents. Candidate covariates have been informed by a scoping review of the literature and will include: parental factors (ie, maternal age, prenatal smoking/alcohol/drug use, antibiotic use in pregnancy and childbirth, diabetes, group B Streptococcal screening, parental history of atopic disease (clinical consultations for asthma, hay fever or eczema within 5 years prior to each included birth), maternal education, ethnicity, material and Social Deprivation Indices), infant factors (ie, mode of delivery, sex, birth weight, gestational age at delivery, season of birth, number of older siblings, immunisation completeness at age 1 according to the provincial immunisation schedule, number of healthcare contacts, respiratory infections in the first year) and environmental factors (ie, urban/rural residence, greenness and the area-level air quality indicators nitrogen dioxide (NO2) and fine particulate matter (PM2.5)).

**Modelling breastfeeding behaviour**

Breastfeeding has been shown to be an important modifying factor when examining early-life determinants of asthma, reducing the risk of asthma in infants who had prenatal exposure to antibiotics and reducing the risk of wheezing in infants born to mothers with a history of asthma. Data related to exposure to breastmilk and duration of breast feeding, however, are only captured in BC (through Perinatal Services BC) as ‘initiation of breast feeding’ during the hospital stay for the birth. Longer-term follow-up of infant feeding behaviours is not captured through administrative data. Therefore, the CHILD study dataset, which includes data on maternal lifestyle factors, the birth event and infant feeding, will be used to identify trajectories of breastfeeding behaviours among a sample of Canadian mothers over the first year of each infant’s life using latent class analysis. Candidate indicator variables will be selected from the literature and expert opinion to categorise each mother/infant dyad into different breastfeeding trajectories, determining the probability of membership to each breastfeeding trajectory for each dyad, the percentages of dyads falling into each trajectory and the indicator profile for dyads most likely to follow each trajectory based on multinomial logistic regression modelling. Candidate indicators will be available in both CHILD and the administrative cohort and will include: maternal education, maternal age, gestational age, birth mode, sex of the infant, initiation of breast feeding in hospital, maternal prepregnancy body mass index, smoking during pregnancy, parity, birth order, maternal history of mental illness during pregnancy and postpartum, home crowdedness, area-level socioeconomic status (Canadian Marginalisation Index, which includes ‘area-level % visible minority’), household income, province, region/LHA and year. The probability of membership in each feeding trajectory (latent class) will then be used as a proxy for breast feeding in the cohort study based on the indicator profiles characterising each feeding trajectory. Data from the MILC will be used to validate the proxy breastfeeding indicator derived for Manitoba mothers using the CHILD cohort, giving an indication of model performance.

**Statistical methods**

As this study is collecting data for all infants born in BC and Manitoba, this amounts to study populations of approximately 460000 and 162500 infants, respectively.
(estimates gathered from Vital Statistics Births\textsuperscript{24}). Under a two-sided test with a type I error rate of 0.05, with the probability of the outcome being 0.214 in children exposed to antibiotics and 0.146 in children not exposed to antibiotics,\textsuperscript{11} and a study population of 230,000 in each group for BC and 81,250 in each group for Manitoba, these studies will be 100\% powered to detect a 7\% difference in the outcome.

With the use of administrative data certain challenges such as the possibility for missing data may arise. The approach for augmenting the administrative data with a variable indicating the ‘probability of breast feeding’ derived from the CHILD study data and how this predictive model for breast feeding will be externally validated using the Manitoba MILC dataset has been outlined above. However, for completeness in other variables, we will first seek to understand whether data are missing completely at random, missing at random or missing not at random. We will run the models on a complete case basis for variables essential to the analysis (those related to defining the exposure and the outcome) and will perform sensitivity analyses running the models with and without the covariates containing higher levels of missingness to determine how this effects the relationship between exposure and outcome.

Univariate and multivariable logistic regression models will be used to determine the odds of the outcomes in the exposed versus unexposed individuals, adjusting for relevant covariates. The models will include a cluster function, clustering on maternal ID, to account for the possibility of multiple (singleton) live births for each mother being included over the study period and in recognition that children raised in the same family will be more similar to each other than to other children.

Nitrogen dioxide (a marker of traffic-related pollution) is provided as a land use regression-based annual concentration estimate at the small-area level\textsuperscript{25–27}. Fine PM2.5 (produced by natural or anthropogenic sources, with a particularly harmful effect on the lungs due to small particle size) is provided as a 3-year annual average satellite-based concentration estimate at the small-area level\textsuperscript{26–29}. Greenness (a measure of vegetation and canopy cover) is provided as annual mean normalised difference vegetation indices at the small-area level\textsuperscript{26–34}.\textsuperscript{4}

\textbf{Sensitivity analyses}

To address confounding by indication and explore the relationship further, several sensitivity analyses will be performed. For all analyses, the outcome (atopic conditions by the fifth birthday) will remain the same. The analyses will include:

- Restricting the ‘exposed’ group to only those who received antibiotics for non-respiratory tract infections (ie, urinary tract infections and gastrointestinal infections).
- Excluding children with diagnoses of ‘viral wheeze’, ‘recurrent wheeze’ and ‘bronchiolitis’ occurring before antibiotic exposure in the first year.
- Categorising the antibiotic exposure into four time windows (0–3 months, 4–6 months, 7–9 months and 10–12 months) to determine whether there is a differential effect over time when looking at antibiotic exposure during earlier stages of immune system development compared with later.
- Analysing the outcome risk in a subgroup of children with upper respiratory tract infections (otitis media, pharyngitis, bronchitis, bronchiolitis, sinusitis), comparing those treated with and without antibiotics.

These sensitivity analyses will allow for the effect measures to be thoroughly interrogated among different patient subgroups to fully understand the individual effects of treatment and infection diagnosis on subsequent atopic risk and whether biases such as confounding by indication are present. Additionally, effect modifiers will be explored by stratifying on the variable of interest to determine whether the exposure effect is heterogeneous across different subgroups. Effect modifiers to investigate will be guided by the outcomes of the analysis, but potential candidates may include infant sex, likelihood of breast feeding (defined above), material deprivation, area-level air quality measures, etc. The presence of interaction will also be explored, particularly interactions between birth mode (caesarean section vs vaginal delivery) and formula exposure in hospital, to test whether antibiotic exposure in infants already at risk of microbial dysbiosis are more at risk of atopic outcomes than other infants. Lastly, associations will be tested for infants who have not met the inclusion criteria for the study to determine whether they differ significantly from the analytical population with respect to risk of atopic disease following antibiotic exposure.

\textbf{Limitations}

As this study makes use of administrative data, not all potential confounders that may have an effect on atopic disease risk in children will be able to be adjusted for. Namely, day care attendance, pet ownership and the quality of housing cannot be accounted for in this study and may be a source of residual confounding.

The BabyFirst/Families First Screening programme in Manitoba has coverage of approximately 83\% of births in the province, with women living in First Nations reserve communities and women who are vulnerable and challenging to follow up not being covered by the screening programme. The potential implications on representativeness of the findings in Manitoba will, therefore, have to be assessed.

\textbf{Patient and public involvement}

Patient and public involvement in this study will be integral to the reporting and dissemination of this work. A stakeholder committee will be formed comprising relevant scientific, clinical and policy experts alongside parent and public representatives to help guide the interpretation, reporting and knowledge translation of the findings. Additionally, one or more public engagement events will
be held where we will invite a diverse group of soon-to-be and new parents to inform and guide our communication strategy to our target audience of parents of young children. We hope that by seeking public guidance we will be better able to communicate our findings in a way that is informative, impactful, relevant and sensitive. This is of particular importance when discussing issues around infant feeding practices.

ETHICS AND DISSEMINATION

Ethics approval for this study has been granted by the UBC Research Ethics Board (H19-03255). Permissions have been granted from the data stewardship committee for all datasets provided through the Population Data BC platform. Ethics approval for the Manitoba component of the study has been granted by the University of Manitoba Ethics Board (HS23156 (H2021:328)) and permissions from the data stewardship committee for all datasets being used have been granted. Permissions from the CHILD Study National Coordinating Centre are being sought for the use of breastfeeding data for the breastfeeding predictors analysis (concept proposal CP185).

Results of the study will be disseminated with a focus on four main audiences: professionals, academic researchers, policy-makers and affected publics. The findings of this work will be disseminated through publications in peer-reviewed journals, presentations at scientific conferences, op-eds in newspapers and through social media at BCDC, UBC and University of Manitoba. They will also be disseminated through our paediatric clinical networks at BC Children’s Hospital and MCHP’s Need to Know Team. We will establish a stakeholder committee of clinicians, researchers and policy-makers to consult with them on our communication plans and the future knowledge translation of our work in professional healthcare settings and governmental bodies. For our affected publics, we will establish an additional stakeholder committee to consult on the progress and dissemination of our research. We will design an engagement event to explore how our results are best understood and communicated to parents as well as subgroups like mothers who are or are not considering breast feeding.

CONCLUSIONS

Findings from the study will shed light on whether an association exists between antibiotic exposure within the first year of life and the risk of developing asthma, hay fever and eczema in children. The outcomes of this work could influence clinical guidance and policy by informing on whether accelerating prudent antibiotic stewardship efforts in infants can be used as a means of reducing the risk of some of the most commonly diagnosed chronic atopic conditions in childhood.

REFERENCES


26 CanMap postal code suite v2015.3. [computer file]. Markham DMTI Spatial Inc; 2015.