

Perinatal Health Inequities And System Resilience:
Perinatal Outcomes, Prenatal Care Access, and Antibiotic
Utilization In Manitoba Before And During the
COVID-19 Pandemic

by

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Abstract

Background: Persistent inequities in prenatal care that worsen during global pandemics continue to contribute to adverse perinatal outcomes. Pregnant women are at increased risk of infections which require antibiotic treatment, yet safe and appropriate use remains a challenge. In this thesis, I investigated adverse perinatal outcomes, prenatal care utilization, and antibiotic utilization during pregnancy and assessed the influence of the COVID-19 measures on these outcomes.

Methods: Three population-based studies were conducted using Manitoba's administrative health databases, including all women giving birth. The first study examined the immediate and lagged effect of COVID-19 measures and the influence of different durations of exposure on seven perinatal outcomes using interrupted time series analysis. The second investigated trends and determinants of prenatal care frequency and adequacy, using multivariable logistic and multinomial regression models. The third study examined the annual trends in antibiotic utilization during pregnancy using generalized linear models.

Results: Pregnancies fully exposed to the pandemic experienced higher rates of preterm birth by 16.2% in year 1 ($\beta_{100\%year1}=0.14, p=0.01$) and 11.3% in year 2 ($\beta_{100\%year2}=0.11, p<0.01$), and cesarean deliveries by 25.4% ($p=0.01$). No significant changes in neonatal intensive care unit (NICU), stillbirth, and low birthweight were observed during the pandemic. Prenatal care frequency and adequacy were stable; however, there was a relative increase in <5 visits by 38.2% ($\beta_{100\%year1}=0.29, p=0.02$), and inadequate care by 2.3% ($\beta_{100\%year1}=0.2, p<0.01$) during the first year of the pandemic. Rural residence (adjusted relative risk (aRR)=1.42, 95% confidence interval (CI):1.40-1.45), low income (aRR=1.41, 95% CI: 1.39- 1.43), and multiparity

(aRR=2.46,95%CI:2.42-2.50) were associated with higher risk of inadequate care. Among 474,054 pregnancies, 33.1% filled at least 1 antibiotic prescription during pregnancy, with a slight annual increase of 0.19% (95% CI 0.02–0.35); however, there was a temporary immediate decline by 4.6% ($\beta_{\text{immediate_change}}=-0.17, p<0.01$). While β -lactam penicillins remained the most prescribed class, their use gradually decreased over time.

Conclusions: The COVID-19 measures were associated with disruptions in perinatal outcomes and care. Significant inequities persist, with rural residence, low income, and multiparity being barriers to adequate care. Antibiotic utilization during pregnancy remained stable, with approximately one-third of pregnancies receiving at least one prescription. Overall, these findings highlight the need to strengthen prenatal care systems and address inequities.

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List of Abbreviations

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme
AMR	Antimicrobial Resistance
aOR	Adjusted Odds Ratio
APC	Annual Percentage Change
APNCUI	Adequacy of Prenatal Care Utilization Index
ARBs	Angiotensin Receptor Blockers
aRR	Adjusted Relative Risk
ATC	Anatomical Therapeutic Chemical
BFI	Breastfeeding Initiation
BIC	Bayesian Information Criterion
BMI	Body Mass Index
CAMCCO	Canadian Mother-Child Cohort Active Surveillance Initiative
CCI	Canadian Classification of Health Interventions
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
DPIN	Drug Program Information Network
FDA	Food and Drug Administration
GBS	Group B streptococcus
GINDEX	Graduated Prenatal Care Utilization Index
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ITS	Interrupted Time Series
LBW	Low birth weight
MCHP	Manitoba Centre for Health Policy
MES	Maternity Experiences Survey
MHSC	Manitoba Health Services Coverage

NICU	Neonatal Intensive Care Units
OR	Odds Ratio
PTB	Preterm Births
R-GINDEX	Revised GINDEX
RHA	Regional Health Authorities
RR	Relative Risk
RTIs	Respiratory tract infections
SD	Standard Deviations
SGA	Small for Gestational Age
SOGC	Society of Obstetricians and Gynecologists of Canada
uOR	Unadjusted Odds Ratio
UTIs	Urinary Tract Infections
VLBW	Very Low Birth Weight
WHO	World Health Organization

Preface

Each chapter of this thesis has been formatted in manuscript style, with chapters 2 to 4 connected by an overview statement at the beginning of each chapter describing how each manuscript is related to the overall thesis objectives. Chapters which have been accepted or submitted for publication also include the citation. Each chapter presents original research that has been submitted or prepared for publication in peer-reviewed journals. All studies were conceptualized by Laila Aboulatta, with contributions from her thesis advisors and advisory committee: Dr. Sherif Eltonsy (primary advisor), Dr. Kaarina Kowalec (co-advisor), Dr. Lisa Lix (committee member), Dr. Mina Tadrous (committee member), and Dr. Joseph Delaney (committee member). All studies were executed by Laila Aboulatta, who is the guarantor and fully responsible for the integrity of the manuscripts, accuracy of analysis and interpretation. All co-authors contributed to study conceptualization, review of results and interpretation of study findings. Manuscripts have been revised according to feedback from all authors, and final approval from co-authors was obtained prior to publication.

Chapter 1: Background and Objectives

Maternal health refers to the overall well-being of women during pregnancy, childbirth, and the postnatal period, a period marked by major physiological, psychological, and immunological changes(1). Each year, about 140 million births take place globally, yet in 2020, an estimated 287,000 women died during pregnancy or childbirth, largely from preventable causes such as infection and excessive blood loss(1). Limited access to timely, high-quality prenatal care remains a key factor for adverse perinatal outcomes, revealing persistent inequalities within and across countries. Key determinants of late initiation or inadequate prenatal care include younger maternal age, lower education and income, rural residence, higher parity, and minority or immigrant status(2). While progress has been made over the past two decades, it remains critical to expand efforts that address social and structural inequities influencing maternal and neonatal health outcomes. The World Health Organization (WHO) has identified maternal and newborn health as a global priority, highlighting the need to improve access to high-quality perinatal services and prevent maternal and neonatal complications. Investing in maternal and newborn health is crucial because it invests in stronger families and healthier societies(1).

Pregnant women face a higher risk of severe infections due to their unique physiologic and immunological characteristics(3). According to the WHO, approximately 11.9 million cases of maternal infections were reported in 2017, of which 5.7 million women experienced sepsis during or after pregnancy or during childbirth(4). Common infections during pregnancy are urinary tract infections (UTIs) (28%), respiratory tract infections (RTIs) (9%), sexually transmitted infections, and group B streptococcus (GBS) infections(5,6). If untreated, these infections can lead to severe

maternal and neonatal morbidity and mortality(7). These complications can be prevented through the rational use of antibiotics and improved adherence to the antimicrobial stewardship framework. The optimal use of antibiotics, particularly macrolides, is challenging because it requires balancing maternal benefits with maximal fetal safety(3,8).

Due to ethical and safety concerns, pregnant women have historically been excluded from randomized drug trials. As a result, there are significant evidence gaps in pregnancy-specific dosing, pharmacokinetics/pharmacodynamics, and risk–benefit assessment needed to balance maternal benefit against potential fetal risk. Recent guidance by the U.S. FDA recommends ethically including pregnant women when suitable and developing pregnancy-specific evidence to guide care(9). Medication use is common in pregnancy, and treatment decisions should balance maternal benefit with fetal safety. A Canadian study showed that approximately one-third of pregnancies have at least one prescription throughout pregnancy, and antibiotics were the most frequently prescribed class(10).

The COVID-19 pandemic has affected perinatal health directly through infection with the novel coronavirus and indirectly by the implemented public health measures(11,12). Studies indicated that maternal infection with SARS-CoV-2 has been consistently associated with higher risks of preterm birth, neonatal intensive care unit admission, maternal morbidity, and mortality(13,14). The implementation of these measures has disrupted how individuals seek and receive medical care. Evidence indicates that changes in health care delivery, such as limiting in-person visits and increasing barriers to timely assessments, disproportionately impacted the health of pregnant women and their infants(11,12).

Understanding the broader context of maternal health provides the foundation for examining key aspects that directly influence maternal and neonatal outcomes. The following sections focus on four domains: (1) perinatal outcomes, (2) prenatal care utilization, (3) drug utilization during pregnancy, with a focus on antibiotic use, and (4) the implemented COVID-19 pandemic measures and their impact on perinatal care, perinatal outcomes, and antibiotic utilization.

1.1. Perinatal Outcomes

Perinatal outcomes, including preterm birth, low birth weight, small for gestational age, stillbirth, NICU admissions, and breastfeeding initiation, are considered key indicators of maternal and infant health(15). These outcomes are strongly associated with short-term infant survival, long-term child development, maternal well-being, and healthcare costs.

1.1.1. Preterm Birth

Definition

Preterm births (PTB), defined by the WHO as delivery before 37 weeks of gestation, generally constitute around 10% of all live births(16).

Epidemiology

In Canada, recent reports estimate PTB rates at approximately 8% (17,18), which is comparable to WHO estimates for high-income countries(16). In contrast, rates in low- and middle-income countries are higher, ranging from 10.3% to 11%(16).

Health Impact

Despite representing around 10% of births, more than 80% of neonatal deaths occur among those born prematurely(19–21). The risk of infant mortality increases with decreasing gestational age; where infants born at 28 weeks have a 45-fold higher risk of death, while those born at 32 weeks of gestation had a 7-fold higher risk compared with infants born at 36 weeks(22). Beyond mortality, PTB is associated with short-term neonatal and infant morbidities and long-term complications among the survived infants. These include respiratory problems, intraventricular hemorrhage, infection, developmental delays, impairment, and disability, all occurring at higher rates compared to term infants(23–25). PTB also heavily burdens health systems, especially neonatal intensive care units.

1.1.2. Low Birth Weight

Definition

Low birth weight (LBW) refers to newborn infants with a birth weight of less than 2500 grams at delivery and is a critical indicator of general neonatal health(26).

Epidemiology

According to the WHO, it is estimated that 15-20% of all births worldwide, equivalent to more than 20 million births annually, are affected by LBW(26). The majority of LBW occur in low- and middle-income countries, which could be attributed to the fact that maternal health, nutrition, and access to prenatal care remain significant challenges(26). Over the last decade, Canada has reported LBW rates of approximately 6.5% among all live births, which is slightly lower than the 8.2% reported in the United States(27).

Health Impact

LBW presents a major public health challenge as its associated with increased fetal and neonatal mortality and morbidity, inhibited growth, impaired neurodevelopment, and elevated risks of chronic diseases later in adulthood(28). Infants born with LBW face a markedly higher risk of adverse outcomes, including a 20-fold greater risk of neonatal death compared to infants born at higher birth weights(28).

1.1.3. Small for Gestational Age

Definition

Small for gestational age (SGA) is widely used in both clinical and public health practice as a measure of fetal growth(29,30). SGA is defined as any live birth with a birth weight below the 10th percentile for gestational age and sex. This classification was first introduced by the WHO 1995 expert committee and is based on comparing infants' birthweight for gestational age measure to sex-specific reference population(31).

Epidemiology

While SGA rates increased from 7.2% in 2000 to 8.0% in 2016(32), the rates in low- and middle-income were relatively high, ranging between 8.6% and 27%(33).

Health Impact

SGA could be associated with neurodevelopmental disorders, a higher risk of obesity, and a higher risk of chronic diseases such as type 2 diabetes and cardiovascular diseases in adulthood(34,35).

1.1.4. Stillbirth

Definition

Stillbirth, one of the leading causes of perinatal death worldwide, is defined as fetal death at ≥ 20 weeks of gestation(36).

Epidemiology

The WHO estimates that approximately two million stillbirths occur globally each year, with approximately 40% occurring during childbirth(37). The stillbirth rate in Canada is reported to be around 8.9 per 1,000 births(38). Although this rate is consistent with rates observed in other high-income countries, direct comparison is limited by inconsistent definitions of stillbirth.

Health Impact

While Stillbirth rates are influenced by many factors, such as maternal age, comorbidities, and access to timely prenatal care(36), its impact extends beyond the loss of life. Stillbirth has profound psychological, emotional, and social impacts on families and places a significant emotional burden on healthcare providers and health systems(39).

1.1.5. Cesarean Delivery

Definiton

Cesarean delivery is the surgical procedure to deliver the baby by incisions in the abdomen and uterus when vaginal delivery is contraindicated or poses a significant risk to the mother or fetus. Although cesarean delivery can be lifesaving when medically indicated, the steady rise in its use has raised concerns about the potential overuse(40–42).

Epidemiology

In Canada, cesarean deliveries are the most common surgical procedure, with rates exceeding recommended levels(40–42). According to the Public Health Agency of Canada, the cesarean delivery rate increased to 33.9% in 2022(43,44). The rate depends on multiple factors, including health status, sociodemographic characteristics, clinical and health system-level factors(45).

Health Impact

The rise in cesarean delivery rates reflects complex interactions between clinical practice patterns, patient preferences, and healthcare system factors. While cesarean delivery can be lifesaving when medically indicated, non-medically indicated cesarean deliveries contribute to maternal morbidity through increased infection risk, hemorrhage, venous thromboembolism, and complications in subsequent pregnancies, including placenta accreta spectrum disorders. Understanding trends in cesarean delivery rates, therefore, serves as a proxy for healthcare system medicalization(46).

1.1.6. Neonatal Intensive Care Unit Admission

Definition

Neonatal intensive care units (NICU) are specialized facilities designed to provide critical care for newborns born preterm (before 37 weeks of gestation) or with serious medical complications (47).

Epidemiology

The rates of infants admitted to NICUs in Canada were stable between 2015 and 2019 at around 12%(48). In the United States, the percentage of infants admitted to a NICU increased among all gestational age and birthweight categories from 8.7% in 2016 to 9.8% in 2023(47).

Health Impact

Evidence consistently shows that high-risk infants have improved survival when managed in NICUs, compared to non-specialized care settings(47). However, NICU has been linked to longer-term implications, including increased risk of neurodevelopmental conditions, parental psychological distress, and significant burdens on families and health-care systems(49,50).

1.1.7. Breastfeeding Initiation

Definition

Breastfeeding initiation refers to the practice of beginning breastfeeding or providing breast milk to the infant shortly after birth(51). Early breastfeeding, defined as breastfeeding within one hour after birth, supports the infants and mothers, including reduced infection risk and improved maternal recovery(52).

Epidemiology

In Canada, more than 9 in 10 women (91%) initiate breastfeeding or provide breast milk to their infant shortly after birth, but this varies by region and socioeconomic status. Breastfeeding initiation is influenced by several factors such as maternal education, age, comorbidities, mode of delivery and access to breastfeeding education and support(53). Breastfeeding initiation rates are lower in the United States (84%) and the United Kingdom (81%) than Canada, while Australia reports higher rates at around 96%(52) .

Health Impact

The benefits of breastfeeding during the first six months of infant life are well established in terms of infants' mortality and morbidity. For mothers, breastfeeding is also associated with reduced risk of obesity, diabetes, and breast and ovarian cancer(54). Delayed or lower rates of breastfeeding initiation may lead to higher risks of infant morbidity and may reflect underlying inequities in maternal education, support, or access to lactation services(54).

1.2. Prenatal Care Utilization

1.2.1. Importance of Prenatal Care for Maternal and Neonatal Health

Prenatal care refers to the health care provided to a woman during pregnancy to promote healthy pregnancy and delivery(55). Prenatal care is a cornerstone of mother and infant health as it offers opportunities for early detection and management of pregnancy-related complications, timely interventions, and continuity of care throughout gestation. Prenatal care is multidisciplinary and requires coordination among a wide range of healthcare professionals, including physicians, midwives, nurses, dietitians, social workers, mental health providers, and community-based workers. Therefore, effective communication and thorough documentation are essential when multiple providers are involved, which adds complexity to prenatal care delivery(55). Ideally, pregnant women should be informed of their choices since access to different types of prenatal care depends on the geographic location, community size, and available resources. The Maternity Experiences Survey (MES) indicate that in Canada, most women (58%) receive care from obstetricians, followed by family physicians (34%) and midwives

(6%)(56). However, evidence suggests that women at low obstetrical risk can be managed by primary care providers such as family physicians or midwives, thereby reserving the specialist services for high-risk pregnancies. Studies show that maternal and infant outcomes are similar across these models of care providers(57,58).

The WHO issued recommendations to improve the quality of prenatal care to reduce stillbirths and pregnancy complications in 2016(59). These guidelines serve to promote a healthy pregnancy for both mother and infant and ensure a smooth transition to labour and delivery. Despite these recommendations, pregnancy-related deaths and illnesses are still high worldwide, with an estimated 303,000 women dying from pregnancy-related causes in 2015. Additionally, 2.7 million newborns died within the first 28 days of birth, and 2.6 million infants were stillborn. These high rates are partly attributed to inadequate prenatal care access, as evidence shows that only 64% of pregnant women worldwide receive at least four prenatal care visits throughout their pregnancy(59). Over the past two decades, the WHO has aimed to increase access and utilization of high-quality perinatal care to prevent many deaths and complications. Currently, only 64% of women worldwide receive at least four prenatal care visits during pregnancy(59). Studies have shown that adequate prenatal care was associated with reduced adverse maternal and neonatal outcomes and preventable hospitalization(60–62).

1.2.2. Frequency of Prenatal Care

Regular prenatal care can help manage risk factors associated with pregnancy complications by enabling timely diagnosis and management of maternal health conditions such as gestational diabetes and hypertension, as well as screening and support for mental health issues(63–66). Prenatal care should be tailored to the mother and infant's physical and

psychosocial needs and to each country's healthcare system. Recommended prenatal care should be initiated early, during the first trimester, and continue regularly to offer opportunities for timely assessment and intervention throughout pregnancy(67). Early initiation is recommended because the first trimester, which is a critical period of fetal organ development, allows for screening of congenital anomalies, prevention of neural tube defects and early detection of maternal conditions. Delayed initiation of care may miss this optimal window for prevention, increase the risk of undiagnosed complications, and lead to adverse maternal and neonatal outcomes(67).

The Society of Obstetricians and Gynecologists of Canada (SOGC) recommend visits every 4–6 weeks in early pregnancy, every 2–3 weeks after 30 weeks, and weekly or biweekly after 36 weeks of pregnancy(68). However, there is no universal or Canadian consensus on the ideal number of prenatal visits required to achieve optimal maternal and fetal outcomes(69). The frequency and timing of these visits should be tailored to the physical and psychosocial health needs of the pregnant woman and her newborn. In high-income countries, women typically receive seven to eleven prenatal care visits at regular intervals(70). The WHO defines insufficient prenatal care as receiving only four visits based on its 2002 Focused Antenatal Care model, which considered five visits adequate for low-risk pregnancies in low-resource settings(71). In 2016, the WHO recommended a minimum of eight visits as women receiving fewer than four visits may limit early detection, prevention, and management of complications(71). Furthermore, if a pregnant woman receives less than 50% of the recommended care visits, this is also considered insufficient(72). This criterion captures women who have significantly fewer visits and are least likely to benefit from early detection of complications, ongoing risk monitoring, or timely

interventions. On this basis, researchers from Canada and Finland defined insufficient care as fewer than five prenatal visits throughout pregnancy or initiating care late in pregnancy (≥ 28 weeks of gestation)(73–75) .

1.2.3. Adequacy of Prenatal Care and Utilization Indices

Prenatal care influences the pregnant woman and newborn's health in multifactorial ways, and timely, regular care is associated with better maternal and infant health(68). Several indices have been used in past research to quantify the adequacy of prenatal care use among low-risk pregnancies. Different scoring systems with each index applying different algorithms have been developed over the last few decades. Early measures of prenatal care adequacy included the Kessner Index(76) and the Graduated Prenatal Care Utilization Index (GINDEX)(77), while recent indices include the Kotelchuk (also known as the Adequacy of Prenatal Care Utilization Index (APNCUI)) and the Revised GINDEX (R-GINDEX)(78,79).

Kessner index

The Kessner Index, developed in 1973 and represents one of the earliest measures of prenatal care adequacy(76). The index classifies prenatal care based on two components: the trimester when care began and the total number of visits adjusted for gestational age. Pregnancies are then assigned to one of three categories: adequate, intermediate, or inadequate. While the Kessner Index is simple and has been used for historical comparisons, it has several methodological limitations. The index does not adequately adjust for gestational age at delivery, which leads to misclassification. For instance, PTB are classified as inadequate care simply because there were fewer opportunities for visits. In addition, the index cannot identify pregnancies with excessive visits since it lacks an intensive care category(76).

Adequacy of Prenatal Care Utilization Index (APNCUI)/ Kotelchuk Index

The APNCUI, commonly called the Kotelchuk Index after its developer Milton Kotelchuck, was introduced in 1994 to address the limitations of the Kessner Index (78,80). This index uses two main domains for low-risk pregnancies: the time when prenatal care began and the ratio of observed visits to expected visits. The ratio is calculated by dividing the observed visits by the expected number (based on ACOG recommended schedule) and adjusted for both gestational age at delivery and when the care was initiated. The APNCUI classifies pregnancies into four categories: Inadequate (less than 50% of expected visits), Intermediate (50-79% of expected), Adequate (80-109% of expected), and Adequate Plus or intensive (110% or more of expected visits). The APNCUI includes an extra category of intensive care that the Kessner Index does not. In addition, the observed/expected ratio eliminates the bias against PTB, and using ACOG guidelines provides a nationally recognized clinical standard (78,80). Despite these strengths, the APNCUI has limitations as the adequate-plus category combines medically necessary intensive care for high-risk pregnancies with potential over utilization in low-risk cases, making interpretation challenging without clinical context. The index treats all prenatal visits equally, regardless of who provided the care or the kind of care provided during the visit, thus does not focus on content or quality of care.

Revised Graduated Prenatal Care Utilization Index (R-GINDEX)

Alexander and Kotelchuck developed the R-GINDEX in 1996, which is a revised version of the GINDEX and based on recommended schedules from the ACOG guidelines for prenatal visits (78–80). The index is based on: gestational age of the newborn, the trimester that prenatal care began, and the total number of prenatal care visits during pregnancy. Each pregnancy is classified

into one of six categories: no care, inadequate, intermediate, adequate, intensive, or missing care.(78,80) Within each category, the index has subcategories based on the trimester prenatal care is initiated. For example, a pregnant woman (around 40 weeks of gestation) would have received adequate care if she started prenatal care in the first trimester with 13–16 visits. However, pregnant women who initiated care in the second trimester or later and had fewer than eight visits would be classified as inadequate. The intensive care category captures high-risk pregnancies, with a significantly higher-than-expected number of visits(78,80). Prenatal care is classified as missing if there is Insufficient data to classify adequacy due to missing information on the number of visits, gestational age, or timing of care initiation. A key strength of R-GINDEX is that it adjusts the expected number of visits for gestational age. So, preterm deliveries are not penalized for having fewer visits, late care initiators are evaluated based on what they could reasonably have attended, and pregnancies extending beyond 41 weeks have a higher expected number of visits. R-GINDEX uses six mutually exclusive categories, which are more granular than other indices. However, this index has not undergone rigorous validation, and it does not clearly define what constitutes adequate care for women with high-risk pregnancies.

Comparability and Choice of Index

Although these indices are widely used, they are not interchangeable, and their comparability in assessing the adequacy of care for low-risk pregnancies remains unexamined. The classification of prenatal care adequacy depends on the index applied, which may introduce misclassification and affect the observed associations between prenatal care utilization and perinatal outcomes(78,79). Moreover, these indices only measure the quantity and timing of visits, disregarding the quality or content of the care provided(78,79). A recent systematic review

of various indices reported that the commonly used indices have only moderate to limited evidence supporting their validity(78). Therefore, there is insufficient evidence to determine the best index, as the choice can vary depending on which measurement properties are most important to the users. The choice of index is guided by the local clinical practice and specific research or policy question being addressed(78).

A study examined the association between adequate prenatal care and neighborhood risk and demonstrated how index choice significantly influenced the results(79). When adequacy was measured using the APNCUI, 80.9% of pregnant women received adequate care compared to 55.6% using the R-GINDEX(79). These discrepancies may be attributed to differences between the two measurement methods. The APNCUI emphasizes starting early care within the first four months of pregnancy and at least 11 visits during pregnancy to be considered adequate. In contrast, R-GINDEX uses a gestational-age-specific framework and counts only visits with a health professional, excluding other types such as non-physician services and supportive visits. This more restricted definition probably explains its more conservative classification of adequacy(79).

While the indices described above quantify the frequency and timing of care, they do not capture the effectiveness of care delivered during those visits. Evidence suggests that the “what” of prenatal care, including screening comprehensiveness, patient-centered communication, cultural competency, provider continuity, and integration of social services, may be as important as the “when” and “how many” of visits(2,81,82). This limitation becomes relevant when interpreting trends during the COVID-19 pandemic. During this time, virtual care

partially replaced in-person visits, which changed both the content and experience of prenatal care without necessarily changing visit counts(83).

1.2.4. Rates of inadequate care

In developed countries the prevalence of inadequate prenatal care is substantially lower than in developing countries, with an average range of 17%(84,85). Data from ten European countries showed that approximately 11% of women received inadequate prenatal care, with 11% both initiated care late and attended fewer than three visits(86). In the United States, Kotelchuck found that 6.7% of women attended fewer than 50% of the recommended prenatal visits(84). Notably, comparison inadequacy rates across studies should be interpreted with caution, as definitions of adequate care and the thresholds for recommended visits vary considerably. These methodological differences limit the validity of direct comparisons between countries and regions.

In Canada, the Maternity Experiences Survey (MES) was conducted in 2006-2007 with the participation of over 6,400 women across the country(56). According to the MES, 94.9% of women initiated prenatal care in the first trimester, while 31.7% (95% CI: 30.4–32.9) had between five and ten visits. Around 1.1% (95% CI: 0.8–1.3) reported receiving inadequate care, defined as having four or fewer prenatal care visits(56).

Inadequate care in Manitoba

Several studies have examined the adequacy of prenatal care within the province across different population subgroups. Heaman *et al.* (2005–2009) reported that 11.5% of women received either no care or inadequate prenatal care, while 33.3% adequate and 4.1%

intensive prenatal care(80). Another Manitoba-based study focused on women whose first child was placed in out-of-home care and assessed the adequacy of prenatal care using the R-GINDEX. Findings showed that these mothers had more than four times higher odds of receiving inadequate care than mothers whose first child was not placed in care (OR 4.29, 95% CI: 3.68–5.01)(87). Moreover, a study by Heaman *et al.* reported that 15.7% of Aboriginal women received inadequate care compared to 3.6% of non-Aboriginal women(88).

1.2.5. Disparities in Prenatal Care Utilization

Prenatal care affects maternal and neonatal health through complex and multifaceted factors(68). Women from socioeconomically disadvantaged backgrounds, racialized communities, and those residing in rural or remote areas face persistent barriers to adequate care. These barriers may be psychosocial, attitudinal, economic or structural factors which are more pronounced among low-income groups(2). Importantly, these determinants do not operate in isolation but intersect to create compounded disadvantages. For example, a young, low-income, multiparous woman living in a rural area faces compounded barriers to care. Understanding maternal health inequities, globally and in Canada, requires examining how multiple marginalized identities intersect with structural barriers to shape prenatal care access and outcomes.

Global Inequities in Prenatal Care

Studies have identified several factors associated with differences in prenatal care utilization such as young maternal age, multiparity, low educational attainment, low socio-economic status, lack of health insurance, maternal ethnicity and marital status. Using the Demographic and Health

Surveys data from 32 low-income countries across Asia, Sub-Saharan Africa, and Latin America, Gulliani *et al.* found that several sociodemographic factors strongly influenced both the likelihood of attending prenatal care and the total number of visits. Predictors include maternal age, educational attainment, desirability of pregnancy, household income, area of residence, and regional poverty levels(89). A case-control study conducted across ten European countries involving 1,283 women with inadequate prenatal care found that lack of health insurance (OR=30.1, 95% CI 20.1-47.1) and stable income (OR=3.6, 95% CI 3.0–4.3) are significant risk factors for inadequate prenatal care(86). Women with inadequate care were also more likely to face issues related to health services organization (OR=1.8, 95% CI 1.4–2.3), cultural barriers (OR=2.9, 95% CI 2.1–3.9), and lack of childcare (OR=1.8, 95% CI 1.1–2.9) compared to controls(86). A recent study by Habtemariam *et al.* examined the association between neighborhood-level disadvantage and inadequate prenatal care in Rhode Island using a neighborhood risk index that captures multiple dimensions of socioeconomic and environmental vulnerability(90). The study found that individuals living in high-risk neighborhoods were significantly less likely to receive adequate care, as measured by both the APNCU Index (aOR=0.91, 95% CI 0.87–0.95) and the R-GINDEX (aOR=0.88, 95% CI 0.85–0.91), compared with those living in low-risk neighborhoods(90).

A systematic review of eight studies investigated factors affecting prenatal healthcare utilization in high-income countries(91). Several individual-level characteristics were consistently associated with lower use of prenatal services, such as being a young mother (under 20 years), unmarried, or having less than nine years of education. Ethnicity was found to be a significant determinant, with racialized women more likely to experience delayed initiation of care.

Additionally, uninsured women and those with Medicaid or private prepaid insurance were more likely to initiate care late and experience inadequate care compared to women with private fee-for-service insurance(91). Findings regarding medical or obstetric risk factors were inconsistent: one study(92) indicated that primiparous women with at least one risk factor were 13.4% more likely to start prenatal care late than the low-risk group (aOR 1.134, 95% CI 1.011, 1.272). In contrast, Perloff and Jaffee(93) found no significant association between late initiation and medical risk factors. Multiparous women, defined as those with three or more previous live births, were more likely to initiate care after the third month of pregnancy and experienced higher rates of inadequate care(91). The review also identified geographic disparities, with women living in remote areas or neighbourhoods with limited access to primary care physicians being more likely to start prenatal care late and consequently receive inadequate care(91). Although all studies included in the review examined the determinants of prenatal healthcare utilization, there was substantial methodological heterogeneity. Across the studies, 12 different definitions were used to describe both the determinants and the measurement of prenatal care utilization, making direct comparison and synthesis of findings challenging(91).

Inequities in Canada and Manitoba

Canada Context

Although Canada provides universal access to health care, challenges in the consistent use and retention of prenatal care exist. The specific barriers contributing to these gaps are not fully understood, and universal uptake of prenatal services has yet to be achieved(94). In a large community-based randomized controlled trial of prenatal care in Alberta, researchers examined the characteristics of 1561 pregnant women who were not retained in prenatal care(94). The

study involved three intervention groups: the current standard of care, and two additional groups receiving either support from nursing staff or home visits(94). Researchers noted that women of non-Caucasian ethnicity, young maternal age, low education, single marital status, and low levels of social support were associated with dropping out of any intervention and receiving inadequate care(94).

The Maternity Experiences Survey, a nationwide cross-sectional study, examined peri- and post-natal experiences of mothers across Canadian provinces and territories(56). This study found that women from Prairie (OR = 1.62; 95% CI: 1.27–2.08) or Central Provinces (OR = 1.36; 95% CI: 1.08–1.70) were more likely to receive inadequate care compared with mothers from the Atlantic Provinces. The authors attributed these differences to variations in healthcare system resources and population characteristics within each province(56).

Additionally, a study by Jarvis *et al.* conducted at two family practice centres in Montreal, Quebec, revealed that over 60% of uninsured women, who were more likely to be immigrants, received inadequate prenatal care compared to insured pregnant women(95). In Ontario, women in the inadequate care group were more likely to be unemployed, uninsured or receiving social assistance compared to the control group(96). Ng *et al.* conducted a population-based study of over 1.1 million pregnancies in Ontario between 2002 and 2011 and found disparities in prenatal care utilization among women living with HIV(97). Compared with women without HIV, those living with HIV were significantly less likely to receive adequate prenatal care (aOR 0.74, 95% CI 0.62–0.88) or to initiate care in the first trimester (aOR 0.51, 95% CI 0.43–0.60). Within the HIV-positive population, recent immigrants (≤ 5 years) from Africa and the Caribbean

had even lower adequacy of care (aOR 0.51, 95% CI 0.32–0.81) compared with Canadian-born women(97).

Manitoba Context

Similar patterns of persistent inequities were observed within Manitoba across different geography and socioeconomic conditions. A population-based study examining disparities in prenatal care utilization among women in Manitoba found substantial geographic variation in rates of inadequate care, ranging from 1.1% to 21.5%. The highest rates were observed in northern and remote regions, socioeconomically deprived areas, and within rural regions (98).

In addition to geographic differences, it was found that both individual and neighbourhood-level characteristics significantly influenced inadequate prenatal care in Manitoba. After adjusting for individual factors, single-parent families, Indigenous populations, immigrants, and smokers exhibited two to three times higher rates of inadequate care than those in more advantaged communities(98). Evidence shows that women in Manitoba who received inadequate prenatal care, defined based on both the timing of the first visit and total number of visits, were more likely to live in poverty, face high levels of life stress, and be Aboriginal(88).

A recent study examined the individual-level factors associated with inadequate prenatal care among 64,166 Manitoban women(69). Pregnant women with medical conditions such as hypertensive disorders (aOR 0.76, 95% CI 0.66–0.85), diabetes (aOR 0.47, 95% CI 0.41–0.53), and prenatal psychological distress (aOR 0.80, 95% CI 0.79–0.85) were less likely to receive inadequate prenatal care. In contrast, women receiving income assistance (aOR 2.15, 95% CI 2.00–2.30), multiparous women (aOR 2.29, 95% CI 2.09–2.50), or with a short inter-pregnancy

interval of less than 180 days (aOR 3.11, 95% CI 2.79–3.48) were more likely to receive inadequate care utilization(80).

1.3. Medication Use in Pregnancy

Medication use in pregnancy is common, yet for many drugs the evidence on fetal safety is limited. Despite the need for improved understanding of drug use in pregnancy, clinical trials involving pregnant women are rare(99,100). Since the thalidomide disaster more than sixty years ago, precaution and fear have influenced clinical research and prescribing practices in pregnancy. Thalidomide was widely used in the late 1950s and early 1960s for the treatment of nausea in pregnant women, causing severe birth defects in thousands of children and leading to major regulatory reforms and strict requirements for fetal-safety testing to prevent a similar catastrophe(99,100). Thus, prescribing medications for pregnant women requires a careful balance between the risks of untreated conditions and the potential complications of medication use(101). While some medications are generally considered safe, others, like tetracyclines and phenytoin, should be avoided due to their associated risks(102,103). Traditionally, the FDA used a five-category system to assess the risk of medication use during pregnancy, but this method was often misleading and did not accurately reflect the severity of the risk(104). To address these issues, the FDA introduced the Pregnancy and Lactation Labelling Rule in 2015, which provides a more detailed and structured approach to guide medication use during pregnancy(103). The labelling in Canada follows Health Canada's product monograph framework with narrative, evidence-based pregnancy and lactation statements that are evaluated and updated on a case-by-case basis instead of applying a uniform letter category system(105).

In Canada, nearly two-thirds of pregnant women (61%) are prescribed medications during pregnancy, and among these, with most (89%) prescribed during the first trimester, the critical period of organogenesis(10). This pattern is consistent with the literature and is likely influenced by the high proportion of unplanned pregnancies which increases the likelihood of inadvertent drug exposure(10). The most prescribed medication classes, in Canada, included antibiotics (26%), antiemetics (14%), asthma therapies (8%), high-dose folic acid (7%), and antidepressants (4%) (10). Similarly, in the province of Manitoba, the proportion of pregnancies with at least one prescribed medication increased slightly from 62.3% in 2001 to 68.8% in 2013 ($p<0.01$)(106).

1.3.1. Antibiotic Use During Pregnancy

Risk of Infections during pregnancy

Common infections during pregnancy are urinary tract infections (UTIs), respiratory tract infections (RTIs), sexually transmitted infections, and group B streptococcus (GBS) infections(5). Untreated infections during pregnancy have been associated with adverse perinatal outcomes such as spontaneous abortion, LBW and PTB(107). Antibiotics are commonly prescribed to treat these infections, with about one in four pregnant women receiving at least one antibiotic, which accounts for nearly 80% of all prescription medications used during pregnancy(107). Penicillins, other beta-lactams, and macrolides are commonly prescribed during pregnancy(107).

Potential Risks Associated with Prenatal Antibiotic Exposure

Antibiotic use in pregnancy is frequent and clinically important during pregnancy; however, it has been associated with both short- and long-term effects on the infant's health. Conflicting

evidence is growing on the potential link between prenatal antibiotic exposure and congenital malformations(108,109), neurological development such as cerebral palsy and epilepsy(108), childhood obesity(110,111), and asthma(112,113). Thus, the optimal use of antibiotics is challenging as it requires balancing maternal benefits with maximal fetal safety.

Antimicrobial Stewardship during Pregnancy

Antimicrobial stewardship during pregnancy presents additional challenges in risk–benefit assessment. Infections require timely treatment to prevent progression to maternal sepsis and adverse fetal outcomes. At the same time, it is essential to minimize fetal exposure to potentially teratogenic or developmentally disruptive medications. The microbiome hypothesis adds further complexity as evidence suggests that prenatal antibiotic exposure may alter infant’s gut colonization, potentially affecting immune development, metabolic programming, and long-term risks of allergic or autoimmune conditions. These considerations highlight the importance of evidence-based prescribing that optimizes maternal treatment while minimizing unnecessary fetal exposure(114,115).

Global Trends in Antibiotic Utilization

A large population-based Danish study by Broe *et al.* analyzed nearly one million pregnancies over a ten-year period and reported a steady increase in antibiotic use during pregnancy(116). More than 38% of all deliveries filled one or more prescriptions for antibiotics during pregnancy, with considerable variation across maternal sociodemographic characteristics. The use of systemic antibiotics showed a similar upward trend, increasing from 28.4% of deliveries in 2000 to 37% in 2010(116). Servadio *et al.* conducted a population-based study including 449,012

women who gave birth between 2016 and 2018 across eight Italian regions. Researchers found that the overall prevalence of antibiotic use was 33.9% (95% CI 33.8–34.0) before pregnancy, 31.8% during pregnancy, and 29.3% (95% CI 29.2–29.4) after pregnancy(117). A U.S. study showed that antibiotics were among the most frequently prescribed medications during pregnancy(118). Among women with private insurance, amoxicillin (13.5%) and azithromycin (12.4%) were the most common medications prescribed, while nitrofurantoin (22.2%) was most often dispensed to those with public insurance(118). A large French population-based study reported a decreasing trend in antibiotic use during pregnancy, dropping from 38.0% in 2010 to 32.1% in 2019(119). In a meta-analysis of 116 studies, the pooled prevalence of antibiotic use during pregnancy was 23.6% (95% CI: 20.1%–27.5%)(120). The prevalence varied by region, with the highest at 34.4% (95% CI: 13.4–64.1) in the Western Pacific and the lowest at 8.2% (95% CI: 3.4–18.3) in South-East Asia(120). These findings indicate that healthcare management varied across regions and does not align with national recommendations. Penicillins were the most frequently prescribed antibiotic throughout pregnancy, with use peaking in the second trimester at 7.9% (95% CI 7.8–8.0). Macrolide prescriptions also peaked during the second trimester, reaching 5.1% (95% CI 5.0–5.1) (117).

Canadian Trends in Antibiotic Utilization

Data from the Canadian Mother-Child Cohort Active Surveillance Initiative (CAMCCO) indicate that antibiotics were among the most prescribed medications during pregnancy, accounting for 26% of all prenatal medications across four provinces(10). Within Manitoba, a study examined all prescribed medications during pregnancy and reported that amoxicillin, nitrofurantoin, and cefalexin were listed among the five most prescribed prenatal medications(121). Loewen *et al.*

further reported that 36.8% of mothers had at least one antibiotic prescription during pregnancy; 16.2% occurred in the first trimester, 18.4% in the second, and 14.7% in the third trimester(113). β -lactam penicillins were the most frequently prescribed antibiotic class during pregnancy(113).

1.3.2. Determinants of Antibiotic Use

Several sociodemographic and clinical factors were associated with higher prenatal antibiotic prescriptions. Younger women (<20 years) had higher odds of antibiotic exposure (OR 1.35, 95% CI 1.30–1.39) than those of age 20-29 years(116). Additionally, obesity was a strong predictor of antibiotic use, possibly due to the higher prevalence of diabetes and related infections. Women with BMI 30–34 kg/m² had 1.3 times higher odds of receiving antibiotics than those with BMI 18-24 kg/m² (95% CI 1.27–1.33)(116). Similarly, women with higher parity (OR 1.28, 95% CI 1.27–1.30) and those who smoked during pregnancy (OR 1.22, 95% CI 1.20–1.23) were more likely to receive antibiotics(116). In contrast, a Finnish study reported greater antibiotic use among older-aged women (≥ 35 years) and those of higher socioeconomic status(122). Evidence suggests that social deprivation, area of residence, lower education levels, and chronic diseases(119,123). Recent meta-analysis found that the most examined and significant determinants of antibiotic use were maternal age, socioeconomic status, and the presence of chronic diseases(120). Additionally, researchers observed structural and behavioural disparities in antibiotic use based on region, country income level, ethnicity, and whether antibiotics were prescribed by healthcare providers or obtained through self-medication(120).

1.4. COVID-19 pandemic and public health measures

The WHO declared coronavirus disease 2019 (COVID-19) a pandemic in March 2020(124,125). Public health measures are collectively the set of measures implemented in an individual country or city to limit the spread of the novel Severe Acute Respiratory Syndrome (SARS-CoV-2) virus. These measures were highly variable between and within countries over the course of the pandemic(126–130). The local and provincial Canadian governments-imposed measures, such as wearing masks and physical distancing between individuals, as policies to reduce the spread of the novel coronavirus(131–133). The implemented measures may have differentially affected vulnerable individuals' health and access to routine health services in numerous pathways, including a reduction in services offered, a change to virtual visits, a limited health workforce, and a shortage in drug supply(134–138). In addition, the financial and economic repercussions of the pandemic, fear of contracting the viral infection, and gathering and transportation restrictions may have constrained access to healthcare and impeded the quality of healthcare services(137,139–142).

1.4.1. COVID-19 pandemic public health measures implemented in Manitoba

On March 12, 2020, Manitoba reported the first confirmed COVID-19 case, and the Premier of Manitoba declared a state of emergency for 30 days on March 20, 2020(143–145). A Pandemic Response System called “RestartMB” was introduced in Manitoba to provide a clear and responsive overview of the current risk of COVID-19 and the measures implemented(146). Several public health measures were applied, including physical distancing, closure of several facilities, and changes to health-care services, such as a shift to virtual care, postponement of non-urgent elective surgeries, and restriction to a one-month supply for all prescribed

medications(138,143,145,147–150). During the first wave, the daily number of COVID-19 cases declined after the widespread mitigation measures, including physical distancing, gathering restrictions, and closure of several facilities and businesses. Whereas during the second wave, upon lifting some of the measures, the numbers increased exponentially, which required more strict strategies, such as mandated mask wearing, limiting visits to household members, and closure of many public commercial spaces (144). Thus, all of Manitoba was declared to be at the highest Pandemic Response System level (“critical”) in November 2020. The number of positive cases stabilized during December and continued declining until January 2021. While some measures were lifted during January and February 2021, strict measures were reintroduced during the third wave of COVID-19 (April 2021). In April–May 2021, the gamma variant was reported in Manitoba, and the infection rate peaked on May 12 at 42.5 per 100,000 (144). Thus, further measures were applied, limiting gatherings to household members only and reducing retail capacity to 10%. As critically ill patients in ICU surged, Manitoba sent ICU patients to hospitals in Ontario and Saskatchewan (144). Between June and September 2021, reported cases stabilized, some measures were relaxed, and Manitoba launched a three-stage reopening plan on June 26. As of October 1, 2021, over 70% of eligible Manitobans were fully vaccinated, but there has been an increase in Delta variant cases and hospitalizations(144). The province moved to the “restricted” level and issued new public health measures limiting many activities for unvaccinated, vaccine-eligible residents. The province reported its first Omicron variant on December 7, 2021, and cases peaked on January 7, 2022, at 202.2 infections per 100,000. Public measures were extended through January, and by February 15, 2022, the infection rate had fallen to 21.8 per 100,000, and Manitoba moved to a lower restriction level; however, proof of

vaccination was still required for most activities(144). **Figures 1.1 and 1.2** demonstrate the daily reported cases and measures applied in Manitoba during the pandemic.

These changes were abrupt, population-wide, and disproportionately affected vulnerable populations. The onset of the pandemic and the implementation of public health measures created a unique opportunity for research, as the implemented measures beginning in March 2020 can be a form of a “*natural experiment*” in epidemiology.

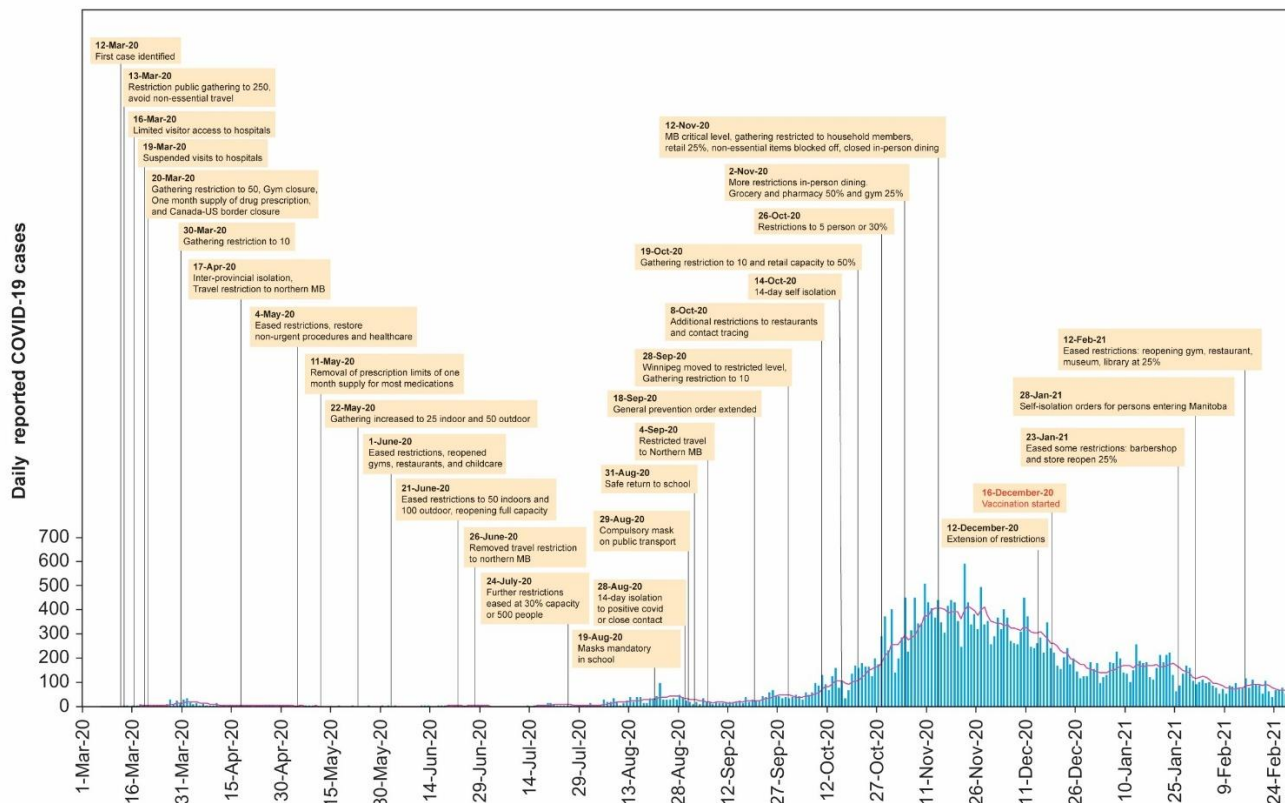


Figure 1.1 Measures applied and reported COVID-19 cases in Manitoba (MB) from March 1, 2020 to February 28, 2021. (Red line represents the 7-day moving average of reported cases).

Adapted from: Aboulatta, L., Kowalec, K., Delaney, J. et al. Trends of COVID-19 incidence in Manitoba and public health measures: March 2020 to February 2022. BMC Res Notes 15, 162 (2022). <https://doi.org/10.1186/s13104-022-06049-5> (144)

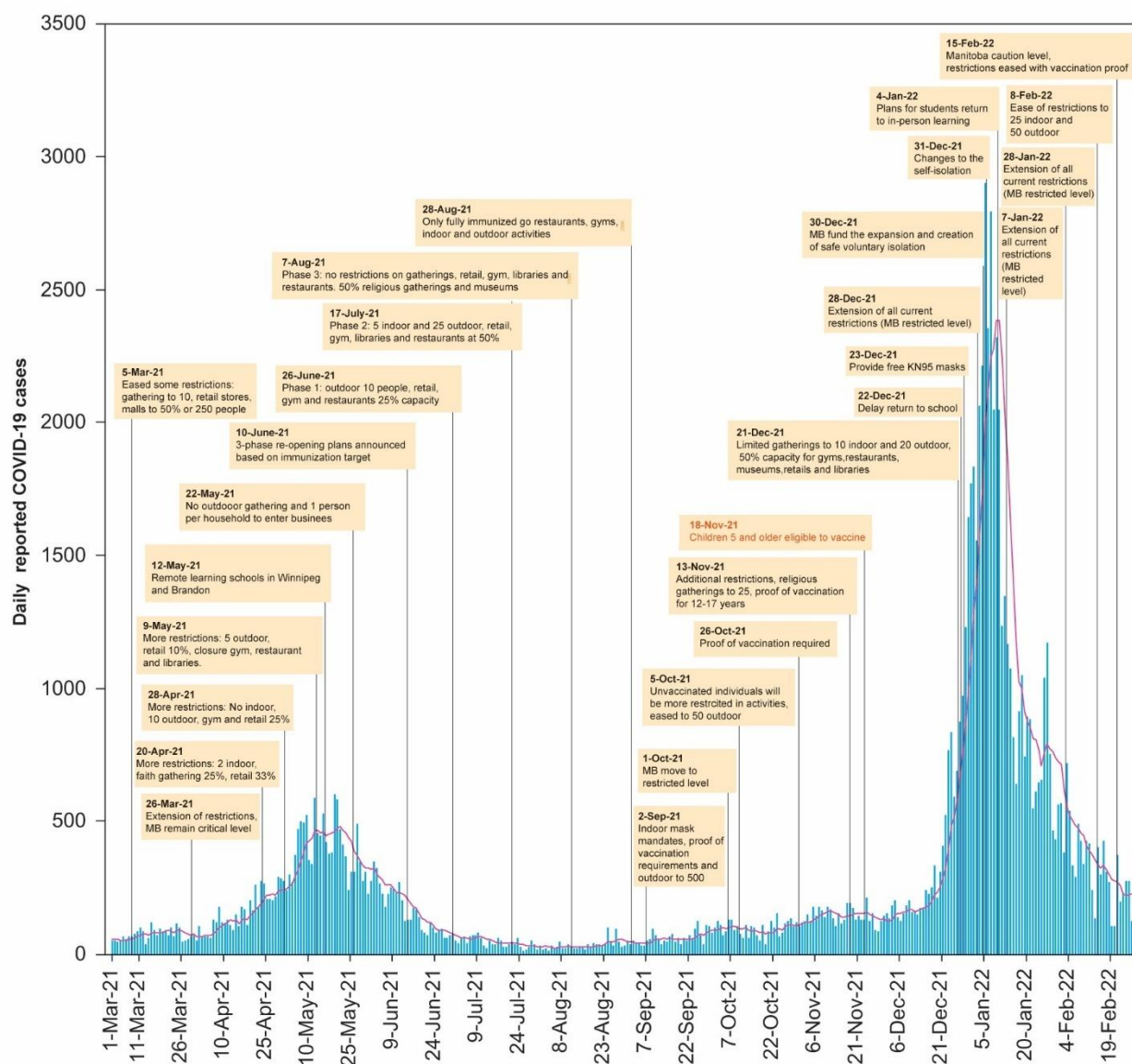


Figure 1.2 Measures applied and reported COVID-19 cases in Manitoba (MB) from March 1, 2021 to February 28, 2022. (Red line represents the 7-day moving average of reported cases).

Adapted from: Aboulatta, L., Kowalec, K., Delaney, J. et al. Trends of COVID-19 incidence in Manitoba and public health measures: March 2020 to February 2022. BMC Res Notes 15, 162 (2022). <https://doi.org/10.1186/s13104-022-06049-5> (144)

1.4.2. Impact Of the COVID-19 Pandemic Measures on Prenatal Care and Maternal and Neonatal Outcomes

In addition to changes and challenges in drug utilization, the pandemic measures led to enormous changes in perinatal care and neonatal health. Zonarado *et al.* noted that changes adopted due to the pandemic were associated with reduced rates of breastfeeding initiation and increased psychological distress among women who delivered in an Italian hospital (151). The reduced access to prenatal services created an obstacle for pregnant women to receive optimal care, thus potentially increasing the risk of adverse pregnancy outcomes(152–158). In fact, evidence indicates that the pandemic and the implemented measures exacerbated the existing social inequalities(159–162). While telehealth improved access for some women, women with limited internet access or lower digital literacy faced additional barriers to virtual care(163–165). This technological inequity could likely contribute to the increase in inadequate care during the pandemic. A scoping review of 95 studies reported a decline in the number of prenatal visits and the quality of care during the pandemic(11). Studies conducted across Canada and Ontario province have shown a disruption in prenatal care access during the COVID-19 pandemic, largely due to changes in how prenatal care was delivered and healthcare restrictions(166–168).

In developing countries, as Nepal, a nationwide study of nine hospitals found that hospital births decreased by more than 50% during the pandemic lockdown (March-May 2020), with a reduced quality of care(161). Ashish *et al.* stated a rise in the rates of PTB (aRR=1.3, 95% CI 1.2, 1.4), cesarean deliveries (p=0.01), neonatal mortality (p<0.01), and stillbirth (aRR=1.46, 95% CI 1.13, 1.89) during the lockdown(161). The pandemic was also associated with a significant 3.5% (95%CI -4.6,-2.6) reduction in breastfeeding initiation within 1 hour of birth(161). These

results contrast with a prospective population-based study in 6 low- and middle-income countries, which examined pregnancy and neonatal outcomes before (March 2019-February 2020) and during (March 2020-February 2021) the pandemic lockdown(169). The risk of cesarean deliveries increased (aRR=1.11, 95% CI 1.03, 1.19) during the pandemic, while there was a decrease in LBW (aRR=0.94, 95% CI 0.89, 0.99). However, no change in rates of stillbirth, PTB, and 28-day neonatal death was observed(169). Moreover, based on an observational study at eight government wards in Botswana with 68,448 women, Caniglia *et al.*, reported a 7% relative reduction in SGA during the post-lockdown period (95% CI 2.26%, 0.12%) while a 0.47% reduction (95% CI -1.35%, 2.29%) during lockdown (April to May 2020) compared to pre-lockdown(170). PTB rates decreased significantly in the post-lockdown period, underscoring that pandemic-related measures may have delayed effects(170).

In contrast, in developed countries, a quasi-experimental study by Been *et al.* examined over 1.5 million singleton births in the Netherlands(171). The first wave lockdown measures were associated with a decrease in PTB rates (OR=0.84, p=0.023)(171). The study also showed no association between the implemented measures and adverse pregnancy outcomes while accounting for maternal socioeconomic status as an effect modifier(171). These findings were consistent with a Danish study conducted, which reported a significant reduction of 86.8% (OR=0.09, p<0.01) in premature babies born at a gestational age of 27 weeks or less(172). Non-significant differences were detected in other gestational age categories, such as 28-31 weeks (p=0.589) and 32-36 weeks (p=0.742)(172). During the first year of the pandemic in Denmark, PTB rates were slightly lower with RR of 0.96 (95% CI 0.93, 0.99), however, non-significant changes in the rates of stillbirth (RR=1.04, 95% CI 0.86, 1.26) and SGA (RR=0.90, 95% CI 0.79, 1.03)

were detected(173). A study that included data on stillbirths and live births in Sweden, Norway, and Denmark between January 2014 and December 2020 reported no decline in PTB and stillbirth rates(174). Similarly, evidence from UK national cohort studies showed that pandemic measures were not associated with significant changes in PTB, stillbirths, caesarean deliveries, and neonatal intensive care unit (NICU) admissions(175–177). In contrast, a study from 3 maternity hospitals in Melbourne, Australia, reported a significant drop in PTB during lockdown (OR=0.81, 95% CI 0.67, 0.98)(178). Gallo *et al.* examined stillbirth rate in 10,044 singleton pregnancies in Queensland between 16 March and 1 May 2020 and found that the rate did not change from previous years ($p=0.70$)(179). A recent single-centre study in Queensland examining a longer duration of the pandemic (April-July 2020) found a 40% decline in rates of PTB ($p=0.02$) and a significant drop in emergency caesarean deliveries ($p<0.01$)(180).

In Canada, Alshaikh *et al.* conducted a cohort study in Calgary between January 2015 and June 2020(181). During the pandemic (March to June 2020), stillbirth and PTB rates remained unchanged; however, a significant drop in very PTB (<32 weeks of gestation) and VLBW was observed(181). There was also no change in the rates of NICU admissions during the examined pandemic period compared to the corresponding period before the pandemic ($p=0.40$)(181). Three retrospective cohort studies, in the Canadian province of Ontario, examined the influence of the pandemic first wave lockdown measures on perinatal health outcomes and reported non-significant changes in PTB and stillbirth rates(182–184). Moreover, other adverse perinatal outcomes, including NICU admission and 28-day neonatal death, did not change significantly during the pandemic(182,184). A Canadian study, using the Discharge Abstract Database (excluding Quebec), examined 136,445 singleton births during the pandemic and found no

change in PTB rates, while caesarean deliveries declined(185). Although stillbirth rates remained unchanged in Canada, Ontario had higher rates during March ($p<0.001$) and May ($p=0.005$) 2020(185). Furthermore, studies conducted in Argentina(186), France(187), Turkey(188), Israel(189,190), US(191–195), China(196–198), India(199), Pakistan(200), Spain(201), Switzerland(202), and Austria(203) have shown conflicting results regarding the influence of the pandemic-related measures on adverse neonatal and maternal outcomes.

In a meta-analysis of 36 studies, Yang *et al.* observed a significant reduction in single-center studies ($uOR=0.99$, 95% CI 0.86, 0.94); however, a non-significant decline in the odds of PTB during the pandemic period in national studies ($uOR=0.99$, 95% CI 0.94, 1.03)(204). Furthermore, there was no difference in stillbirths in both national and single-centre studies between before and during the pandemic periods(204). Although an increase in mean birthweight was observed during the pandemic (mean difference=17, 95% CI 7, 28), there was no difference in the odds of LBW and VLBW compared with the pre-pandemic period(204). Six studies assessed neonatal mortality, and no significant difference was reported before and during the pandemic ($uOR=1.34$, 95% CI 0.71, 2.55)(204). A meta-analysis of 17 studies noted an association between the pandemic-related measures and stillbirths ($RR=1.33$, 95% CI 1.04, 1.69) but not PTB ($RR=0.93$, 95% CI 0.84, 1.03).(205) Also, no significant risks of VLBW and LBW during the pandemic were observed(205).

1.4.3. Impact of the Pandemic Measures on Antibiotic Utilization

Antibiotic Utilization in General Population

Challenges in healthcare access may have led to a disruption in the utilization of medications to treat chronic and acute diseases. Evidence shows a drop in the prescribed antibiotics during the pandemic period, as in Italy, the overall consumption of antibiotics decreased; however, there was a rise in azithromycin, possibly due to theories of its role in the treatment of COVID-19(206). A similar pattern was observed among children; Barbieri et al. noted a sudden 80% decline in the monthly prescribed antibiotics in an Italian primary care setting(207). Likewise, studies conducted in the US(208–210), Australia(211), Finland(212), and Canada(213,214) reported a drop in the antibiotic use once the pandemic started. However, in Australia(211), a 20% rebound increase was observed when the restrictions were lifted. The authors hypothesized that the observed trends are attributable to the fact that the pandemic measures may have potentially affected the development of microbial infections that are commonly treated with outpatient antibiotics(206,208,209,215,217).

Antibiotic Utilization in Pregnant Women

Despite the increasing evidence on the impact of pandemic measures on medication use in the general population, few studies have assessed the trends of medication use among pregnant women. Across five European countries, Ceulemans et al. conducted a survey study to assess medication use in breastfeeding and pregnant women during the first wave(218). Of the 8,378 women examined, 60% were prescribed at least one medication in the three months before the survey, with nervous system and respiratory medications being the most prevalent(218). A cohort study by Esposito et al. noted an immediate decline of 0.54% in

antibiotic dispensing after the onset of the pandemic, followed by a significant increase in the subsequent months in Lombardy, Italy(219).

1.5. Knowledge gaps

During the COVID-19 pandemic, pregnant women faced risk of infection with the novel coronavirus and limited access to maternal and neonatal healthcare. The effect of the COVID-19 pandemic measures on perinatal outcomes has shown conflicting results in Canada. Few studies showed no significant changes in NICU admissions, stillbirths, and preterm birth during the examined pandemic period compared to the pre-pandemic period(220), while other studies reported changes in stillbirths, preterm birth, and caesarean deliveries(221,222). These differences across studies highlight that pandemic's impact on pregnant women was inconsistent by different regions. While several studies examined pandemic effects on perinatal outcomes, most treated the pandemic as a binary exposure (pre- vs. during pandemic). Studies did not examine dose-response relationships based on the proportion of pregnancy spent under pandemic measures, limiting understanding of critical exposure windows and cumulative effects of prolonged healthcare disruption.

Canadian prenatal care utilization studies cover short time periods and long-term trend examining whether universal insurance translates to equitable prenatal care utilization, particularly across socioeconomic and geographic subgroups, remain limited. In Manitoba, pregnant women experienced a significant increase in inadequate prenatal care between 2004 and 2009, which was associated with underlying social inequalities(80). Given these changes and

the time elapsed since the last estimates, there is a need to examine the current trends and determinants to understand whether access and quality of health services have improved or further declined in recent years, and whether existing inequalities have widened or narrowed. Furthermore, the pandemic's impact on pre-existing inequities requires examination to understand whether the pandemic exacerbated or mitigated existing disparities. Yet, no studies in Manitoba have examined how the pandemic influenced prenatal care use, the number of visits, or the adequacy of care.

Medication use during pregnancy remains a complex and challenging issue for both pregnant women and clinicians. As pregnant women are more susceptible to infections, antibiotics are among the most used medications during pregnancy. However, the use of antibiotics should be weighed against the benefits to the mother and the potential risks to the fetus. Existing studies in Manitoba have focused primarily on the overall medication use during pregnancy, thus provided limited evidence on how antibiotic prescribing patterns have shifted in response to changes in clinical practice and rising antimicrobial resistance. Over the past two decades, there have been shifts in antimicrobial resistance, updates to clinical practice, and the introduction of national and provincial antimicrobial stewardship frameworks. While previous research in Manitoba has examined outpatient antibiotic prescribing in the general population, there is limited population-based evidence describing antibiotic prescribing patterns during pregnancy. A Comprehensive, long-term study of prescribing patterns, class-specific trends, and trimester-specific utilization is therefore needed. Such evidence is imperative to establish baselines for antibiotic safety research, antimicrobial stewardship initiatives and to evaluate whether national and provincial stewardship frameworks have influenced obstetric prescribing.

1.6. Thesis Framework

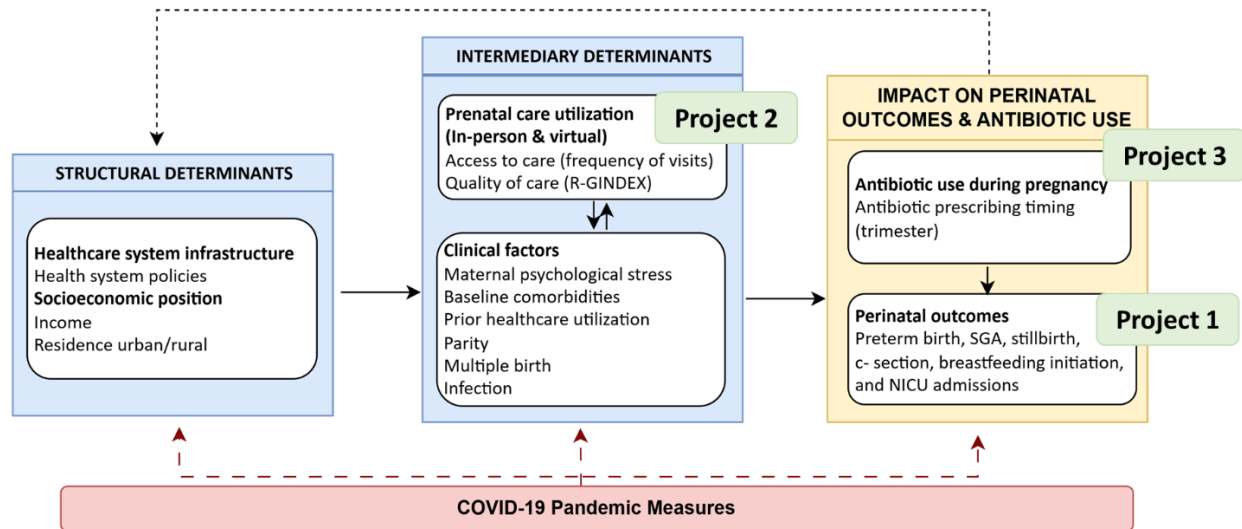


Figure 1.3. Thesis framework and projects based on the WHO Commission on Social Determinants of Health (CSDH) framework

Based on the knowledge gaps identified, my thesis is organized around the WHO Commission on Social Determinants of Health (CSDH) framework (223). The CSDH framework is well suited to this thesis because it conceptualizes how structural determinants, such as health system organization, policy responses, and socioeconomic position, shape intermediary determinants including access to and quality of prenatal care, maternal comorbidities, psychological stress, and infection, which in turn influence perinatal outcomes and patterns of antibiotic use. Within this thesis, Manitoba's universal healthcare system, provincial prenatal care models, and evolving antimicrobial stewardship policies are treated as key structural determinants, while prenatal care trajectories and maternal clinical characteristics constitute intermediary pathways through which these factors affect antibiotic utilization and perinatal health. The COVID-19 pandemic, and the associated public health measures, are conceptualized as an exogenous structural shock that disrupted these pathways, providing a natural experiment to observe whether and how existing

inequities in access to care and maternal–infant outcomes were amplified or mitigated. Framing the research within the WHO CSDH model thus offers a coherent, theory-driven rationale for the thesis. This framework provides a clear way to connect the three thesis objectives to how pregnancy outcomes are produced in real-world settings, because it places health equity and the health system at the center of interpretation rather than treating them as secondary considerations. Using this framework, the three studies provide Manitoba evidence that aligns with WHO priorities for ending preventable maternal mortality, including the need for strong measurement and surveillance and for reducing inequities in access to quality maternal care.

1.7. Objectives

Overall objective: I aim to investigate maternal and neonatal health outcomes, prenatal care utilization, and antibiotic utilization during pregnancy in Manitoba, and to assess the influence of the COVID-19 measures on these outcomes.

Chapter 2 Objective: To test the impact of the COVID-19 measures on rates of seven perinatal outcomes: preterm birth, stillbirth, mode of delivery, small for gestational age, and low birth weight, Neonatal Intensive Care Unit (NICU) admissions, and breastfeeding initiation, from January 2008 to March 2022.

Hypothesis: COVID-19 measures were associated with an increase in preterm birth, stillbirth, cesarean delivery, small for gestational age, low birth weight, and a decrease in NICU admissions, and breastfeeding initiation.

Chapter 3 Objective: To test temporal trends in the frequency of prenatal visits and prenatal care adequacy, categorized using R-GINDEX. In addition, to investigate determinants of inadequate care and fewer than five visits, as well as to assess the impact of COVID-19 measures on prenatal care utilization in Manitoba from January 2010 to March 2022.

Hypothesis: The pre-pandemic trends in prenatal visit frequency and prenatal care adequacy were stable. Maternal clinical and sociodemographic characteristics were key determinants of prenatal care utilization. COVID-19 measures were associated with higher rates of inadequate care and fewer than 5 visits.

Chapter 4 Objective: To examine the trend of antibiotic use among pregnant women and the impact of the COVID-19 public health measures on antibiotic utilization during pregnancy in Manitoba from January 2000 to March 2023.

Hypothesis: Percentage of pregnancies with antibiotic use did not change during the study period. COVID-19 measures were associated with a decrease in rates of antibiotic utilization during pregnancy.

1.8. Research questions

This thesis aims to answer three key questions:

Research question 1: What is the effect of COVID-19 measures on preterm birth, stillbirth, mode of delivery, small for gestational age, low birth weight, NICU admissions, and breastfeeding initiation in Manitoba?

Research question 2: What are the trends in the frequency and adequacy of prenatal care among women who gave birth in Manitoba, and what is the effect of COVID-19 measures on prenatal care utilization, including inadequate care and fewer than five visits?

Research question 3: What are the trends of antibiotic use among pregnant women, and what is the impact of the COVID-19 measures on antibiotic utilization during pregnancy in Manitoba?

Chapter 2: Disruptions in Perinatal Outcomes Across Manitoba, Canada: Before and Over Two Years of the COVID-19 Pandemic

Aboulatta, L.; Kowalec, K.; Lix, L. M.; Tadrous, M.; Delaney, J. A.; Leong, C.; Falk, J.; Alessi-Severini, S.; Raimondi, C.; Kearns, K.; Haidar, L.; Peymani, P.; Tan, Q. & Eltonsy, S. Disruptions in perinatal outcomes across Manitoba, Canada: before and over two years of the COVID-19 pandemic. *Scientific Reports* (submitted BMJ Pediatrics Open, February 2026).

2.1. Overview

Studies from Canada on the effects of COVID-19 pandemic measures on perinatal outcomes have been conflicting. The observed changes in adverse pregnancy and neonatal outcomes across different pandemic periods highlight the varying impact of the pandemic on pregnant women. There is limited evidence regarding the proportion of pregnancy spent under pandemic measures and how this relates to prenatal outcomes. Pandemic measures such as restrictions on healthcare access, reduced social support, changes in hospital policies, and shifts to virtual care may have differentially influenced outcomes across regional and socioeconomic contexts. This project presents the results of perinatal outcomes during the COVID-19 pandemic in the Manitoba population using interrupted time series (ITS) analysis. ITS uses longitudinal data collected before and after the COVID-19 pandemic and is considered one of the strongest quasi-experimental designs for evaluating population-level interventions when randomized controlled trials are not feasible. This approach was therefore appropriate for examining to assess whether COVID-19 pandemic measures were associated with changes in the level or slope of perinatal outcomes. We fit two ITS models to assess both the impact of immediate and lagged effects of pandemic measures, as well as the varying duration of exposure to these measures on adverse perinatal outcomes. This rigorous design enabled a comprehensive examination of perinatal outcomes,

including preterm birth, low birth weight, cesarean delivery, stillbirth, small for gestational age, neonatal intensive care unit (NICU) admissions, and breastfeeding initiation (BFI).

2.2. Abstract

Background

The COVID-19 pandemic disrupted healthcare service utilization, but evidence on its impact on perinatal outcomes is conflicting. We investigated the pandemic impact on preterm birth (PTB), stillbirth, low birthweight (LBW), small for gestational age (SGA), caesarean delivery, breastfeeding initiation (BFI) and neonatal ICU (NICU) admissions.

Methods

Using linked administrative health databases, we conducted a population-based study of pregnancies before (January 2008-February 2020) or during (March 2020-March 2022) the pandemic; for the latter period, they were categorized by exposure duration. We conducted interrupted time series analyses using season-adjusted generalized linear models, and analyses were stratified by income.

Results

Among 221,255 pregnancies, PTB rates are higher during the pandemic than pre-pandemic period, with a 19.9% relative increase overall ($p<0.01$), a 31% rise in the lower income group ($p=0.01$) and a 9.6% rise in the higher income group ($p=0.02$). Pregnancies with 100% exposure experience higher rates of PTB by 16.2% in year 1 ($\beta_{100Y1}=0.14, p=0.01$) and 11.3% in year 2 ($\beta_{100Y2}=0.11, p<0.01$). The pandemic measures are associated with no changes in stillbirth or NICU admissions; a 12% relative decrease in LBW ($\beta_{\text{immediate effect}}=0.13, p=0.05$) is observed. Pregnancies

spanning the entire first year of the pandemic experience higher rates of cesarean deliveries by 25.4% ($p=0.01$). BFI showed a 1.6% relative decrease ($p<0.01$) followed by a slight increase ($\beta_{\text{lagged effect}}=0.002, p=0.01$).

Conclusions

The COVID-19 pandemic is associated with increased PTB and cesarean delivery rates, particularly among pregnancies fully exposed to pandemic measures. Over the 2-year pandemic period, stillbirth, NICU admissions and BFI rates are stable.

2.3. Plain language summary

The COVID-19 pandemic disrupted healthcare, and pregnant women were especially affected. We examined how these disruptions influenced pregnancy outcomes in Manitoba, Canada. We found more premature births and cesarean deliveries, particularly when the entire pregnancy occurred during the pandemic. Overall, stillbirth rates did not increase, but they were higher when pregnancies lasted longer under pandemic conditions. Breastfeeding initiation and newborn admissions to intensive care remained stable. These results suggest that reduced access to prenatal care and differences in income may have played a role. Protecting routine prenatal services and ensuring fair support for all women will be important in future health emergencies.

2.4. Introduction

Perinatal outcomes, including preterm birth, stillbirth, low birth weight, and NICU admissions, are considered key indicators of maternal and infant health(1). Recent reports from Canada has described rates of preterm birth (PTB) at approximately 8%(2,3) and stillbirth rates around 8.9 per 1,000 total births(4). The rate of cesarean deliveries, Canada's most common surgical procedure, has steadily risen, exceeding the World Health Organization's recommended level(5–7). COVID-19 public health measures exacerbated social inequalities and impacted the health of vulnerable individuals and their access to routine care(8–11). Reduced access to prenatal services, fear of contracting the novel coronavirus infection, and gathering and transportation restrictions may have created an obstacle for pregnant women to receive optimal care, thus potentially increasing the risk of adverse pregnancy outcomes(12–25).

While the effects of COVID-19 pandemic measures on rates of adverse perinatal outcomes have been widely documented across countries,(26–34) the precise impact remains less certain. A study based in a hospital in Northeastern Italy reported that changes in hospital policies and prenatal care adopted due to the pandemic were associated with reduced rates of breastfeeding initiation and increased psychological distress among women who delivered there(35). Public health measures in the Netherlands and Denmark were associated with a decrease in PTB rates during the early months of the pandemic(30,31). However, pandemic measures in the United Kingdom were not associated with significant changes in PTB, stillbirths, cesarean deliveries, and neonatal intensive care unit (NICU) admissions(32–34). A meta-analysis of 36 studies found no difference in PTB, stillbirths and low birth weight in both national and single-center studies before

and during the pandemic(36). A meta-analysis of 17 studies found an association between the pandemic-related measures and stillbirths, but not PTB and low birth weight(37).

Reports from Canada on the effects of COVID-19 pandemic measures on perinatal outcomes have been conflicting. While some studies showed no significant changes in NICU admissions, stillbirths, and PTB during the examined pandemic period compared to pre-pandemic period,(26–29) other studies reported an increase in stillbirths and PTB and a decline in cesarean deliveries(38,39). The observed changes in adverse pregnancy and neonatal outcomes across different periods highlight the varying impact of the pandemic on pregnant women. However, there is limited evidence with respect to the length of exposure to pandemic measures, i.e. during how much of their pregnancy were pandemic measures in place, and how this relates to prenatal care and associated outcomes. Pandemic measures—such as restrictions on healthcare access, reduced social support, changes in hospital policies, shifts in hygiene practices, and physical distancing—may have differentially impacted perinatal outcomes across different regional and socio-economic settings.

In this province-wide study, we observe that the COVID-19 pandemic measures are linked to higher rates of preterm birth (PTB) and cesarean deliveries, which vary across different income groups and exposure periods. The duration of exposure to the pandemic measures emerges as a crucial factor influencing perinatal health, with heightened risks of PTB, cesarean deliveries, and LBW among pregnancies that occur entirely during the pandemic. Our findings suggest that the short- and long-term pandemic measures have a minimal influence on stillbirths, breastfeeding initiation (BFI), neonatal intensive care unit (NICU) admissions, and small for gestational age (SGA), during the study period that extended till 2022. Addressing regional and socioeconomic

disparities is critical to advancing the understanding of maternal and neonatal outcomes and to guiding evidence-based healthcare policies for vulnerable populations in future public health crises.

2.5. Methods

2.5.1. Study Design and Period

This population-based cohort study used data from 1 January 2008 to 31 March 2022. We examined the monthly rate of each outcome over two periods: (1) pre-COVID-19, from 01 January 2008 to 29 February 2020, and (2) during COVID-19, from 01 March 2020 to 31 March 2022. More than ten years of data from 2008 to 2019 allowed us to account for the underlying trends in the perinatal outcomes of interest during the pre-pandemic period.

2.5.2. Data source

We used the Population Research Data Repository hosted at the Manitoba Centre for Health Policy (MCHP), a secure provincial health and administrative database containing de-identified individual health information for the entire province's population eligible to receive health services. The reliability and validity of the MCHP Repository for epidemiological research have been documented in prior studies(40–45). Our study included multiple databases to capture demographic, clinical, and socioeconomic information. The hospital discharge abstract database captured perinatal outcomes, age, and comorbidities, with diagnoses coded using the International Classification of Diseases (ICD) system, Tenth Revision, with Canadian enhancements (ICD-10-CA)(46). Medical claims and services databases provided physician records to identify comorbidities, with diagnoses reported using ICD-9-CM codes(46). The

Manitoba Health Insurance Registry provided information on age and area of residence, while the Drug Program Information Network (DPIN) was used to capture prescription drug dispensations. Statistics Canada census data provided information on household income.

2.5.3. Study Population

An established mother-infant linked data cohort from Manitoba was used to create pregnancy cohorts pre- and during the pandemic. We included all pregnant women giving birth, either live birth or stillbirth, in hospitals in Manitoba during the study period. The delivery date was defined as the date associated with procedure code of delivery as recorded in the hospital discharge abstract database(47,48). We excluded out-of-hospital deliveries, pregnancies ending in miscarriage (pregnancy loss prior to 20 weeks gestation), and ectopic pregnancies. The following variables were examined: maternal age at delivery, income quintile,(49) parity (primipara or multipara),(50) pre-existing comorbid diseases (validated definitions of diabetes(51) and hypertension(52) as well as maternal psychological distress(53), and area of residence (urban or rural)(54). Maternal psychological distress in our population before and during the pandemic which is defined as mood and anxiety disorders with a broad spectrum of conditions that range from anxiety state to anxiety disorders, phobic disorders, obsessive-compulsive disorders, depressive disorders, affective psychoses, and neurotic depression. In this study, maternal psychological distress was identified if diagnosed within the eight months before birth using ICD Codes from hospital abstracts and medical claims databases and Prescription Drug Data (DPIN)(53).

Within Manitoba, there are five regional health authorities (RHA) responsible for organizing and delivering healthcare services within specific geographic regions to which individuals are assigned

based on address of residence: Winnipeg (includes the city of Winnipeg and the town of Churchill), Interlake-Eastern (Interlake, North Eastman), Prairie Mountain (Assiniboine, Brandon, Parkland), Southern (Central, South Eastman), and Northern (Burntwood, NOR-MAN)(55,56). Variations in healthcare services and access exist across Manitoba's RHAs, which might contribute to disparities in maternal and neonatal care and an increased risk of adverse outcomes. As a proxy for maternal socioeconomic status, we used the classification based on the median neighborhood income quintile: lower income (lowest (1st) and 2nd median quintile), higher income (3rd) to highest (5th) median neighborhood income quintiles), and Income unknown (individuals who cannot be assigned a neighbourhood income)(57). Race and ethnicity are not available in our database; thus, we could not examine differences across racial and ethnic groups.

2.5.4. Pandemic Measures and Exposure Levels

Pregnancies exposed to pandemic measures between March 2020 and March 2022 were compared to those occurring in the decade prior to the pandemic. Manitoba's first COVID-19 case was reported on March 12, 2020, and public health measures began to influence clinical practices by the end of that month(58,59). In March 2020, the provincial government implemented strict measures, including lockdown, physical distancing, limiting the numbers at gatherings, changes to health-care services, non-urgent medical care restrictions, and limiting supply of drug prescriptions, followed by a temporary relaxation of some restrictions between June and July 2020. Additional restrictions were reinstated in August 2020, and Manitoba reached its peak levels of restriction measures in November 2020 and May 2021(58,59).

We examined the impact of the duration of exposure to COVID-19 public health measures on perinatal outcomes. To reflect this, delivery dates were categorized into groups based on the approximate fraction of time that each pregnancy was under COVID-19 measures. Categories include unexposed (birth between January 2008 to March 2020); 25% exposed (birth in April or May 2020); 50% exposed (birth between June and August 2020); 75% exposed (September to November 2020); and fully exposed (December 2020 to March 2022). However, there were differences between the first and second years of the fully exposed period; COVID-19 vaccination for pregnant women began in Manitoba in 2021, and in the second year, gathering and healthcare restrictions were eased as the province announced phase re-opening plans based on immunization targets(58,59). Therefore, pregnancies occurring entirely during the pandemic were divided into 100% exposed year 1 (December 2020 to March 2021) and 100% exposed year 2 (April 2021 to March 2022).

2.5.5. Perinatal Outcomes

We examined seven perinatal outcomes. The primary outcomes were preterm birth (PTB)(60) and stillbirth(61). Secondary outcomes included low birth weight (LBW)(62), small for gestational age (SGA)(63,64), neonatal intensive care unit (NICU) admission(65), cesarean delivery(66), and breastfeeding initiation (BFI)(67). The definitions and corresponding codes used are summarized in Supplementary **Table S2.1**.

2.5.6. Analyses

The demographic and clinical characteristics of pregnant women were described before and during the pandemic using percentages and their 95% confidence intervals (CI) for categorical

variables and means and standard deviations (SD) for continuous variables. Monthly incidence rates of perinatal outcomes were estimated and the crude relative risk (RR) and 95% CI for each outcome were calculated. The denominator for PTB, LBW, SGA, NICU admissions, and BFI outcomes included the total number of live births in Manitoba for each month. For cesarean delivery and stillbirth, the denominator included the total number of pregnancies, such as live births, stillbirths, multiple births, and singletons, in each month.

The effect of the pandemic measures on the outcomes was examined using interrupted time series (ITS) analysis through generalized linear models, with March 2020 chosen as the intervention point for the pandemic measures. We used the monthly rates in our analyses when the number of reported cases in each month was ≥ 80 events, while bimonthly or quarterly rates were used otherwise. This recommended cut-off was chosen as a sufficient number of outcome events per time point to achieve desired efficiency for ITS models(68–70). Relative percentage change was calculated as the relative change in the percentage between March 2020 and April 2020.

We fit two models for each outcome: Model 1 (immediate and lagged changes) was used to estimate the abrupt change in the outcomes of interest following the onset of pandemic measures and the changes during the 2-year pandemic period. Model 1 included an indicator variable for the pandemic measures (COVID-19: 1/0), a continuous variable for the COVID-19 period (24-time points, April 2020=1 to March 2022=24), and season (fall/winter/spring/summer) to account for seasonality. Model 1 provided estimates for the abrupt effect using immediate change in level ($\beta_{\text{immediate effect}}$) from pre- to post-COVID-19(71–73). The change during the pandemic was estimated using the change in slope ($\beta_{\text{lagged effect}}$) from pre- to post-interruption in

the monthly outcomes rates while accounting for any secular trend in the pre-pandemic period(74–80). Model 2 (change by exposure) was used to estimate the outcome change according to varying lengths of exposure to pandemic measures. Model 2 included a variable for exposure: 0%, 25%, 50%, 75% and 100%year 1, 100% year 2 and season (fall/winter/spring/summer) to account for the seasonality. In this model, $\beta_{25\%exposed}$, $\beta_{50\%exposed}$, and $\beta_{75\%exposed}$ represent the estimated differences in the outcomes at 25%, 50%, and 75% exposure compared with 0%, respectively. $\beta_{100\%Y1}$ represents the estimated difference in the outcome for 100% exposure during the first year of the pandemic, while $\beta_{100\%Y2}$ represents the difference for 100% exposure during the second year. The models fit were evaluated using the scaled deviance(81). Model fit for ITS analyses using GLM was evaluated using the scaled deviance (deviance divided by the degrees of freedom). However, relying on a single statistic has limitations because scaled deviance primarily reflects overall dispersion and does not assess residual patterns, model misspecification, or the presence of autocorrelation. To further evaluate model assumptions, residual plots and autocorrelation diagnostics were examined to assess whether systematic patterns or autocorrelation were present. The full model equations are provided in *supplementary*.

Subgroup analyses were conducted by income group (higher vs. lower); however, we did not examine differences between income groups. We conducted the primary ITS analyses (Models 1 and 2) to investigate the effect of the pandemic measures among income groups. To examine regional differences, we calculated the relative change in the outcomes of interest between the average rates two years before the pandemic and the average rates during the pandemic. A

nominal $\alpha=0.05$ was used to assess statistical significance. Analyses were conducted using SAS version 9.4 (SAS Institute, Inc).

2.6. Results

2.6.1. Population Characteristics

Table 2.1 shows the characteristics of pregnant women who gave birth during the study period from January 2008 to March 2022. We identified pregnant women who gave birth before ($n=190,694$) and during ($n=31,942$) the COVID-19 pandemic. Among those, there were 189,538 live births before the pandemic and 31,717 live births during the pandemic. The average age of women was 28.6 years ($SD=5.8$) before the pandemic and 29.9 years ($SD=5.6$) during the pandemic. Around half of the pregnant women lived in urban areas and were in the higher-income group in both periods.

2.6.2. Perinatal Outcomes

Preterm birth (PTB)

Monthly rates of PTB across all pregnancies and by income group over the study period are shown in **Figure 2.1(A)**. In the pre-pandemic period, 8% of live births were PTB compared to 9.1% during the pandemic period, with a relative increase of 14% (crude $RR=1.14$, 95% CI, 1.1-1.18, **Figure 2.2**). PTB rates differed by region during the pandemic period, with the Southern region experiencing the highest relative increase (9.9%), followed by the Northern region (6.7%, **Supplementary Table S2.2 and Figure S2.1**).

Pandemic measures were associated with an immediate relative increase of 19.9% ($\beta_{\text{immediate effect}}=0.2$, $p<0.01$) in PTB monthly rates among all pregnancies, 9.6% ($\beta_{\text{immediate effect}}=0.18$, $p=0.02$)

in the higher income group, and 31% ($\beta_{\text{immediate effect}}=0.24$, $p=0.01$) in the lower-income group (**Table 2.2**). During the pandemic period, there was a decrease in PTB monthly rates in the lower-income group ($\beta_{\text{lagged effect}}= -0.02$, $p=0.03$). Analysis by exposure duration indicated the pandemic was associated with a statistically significant relative increase in PTB rates among those exposed to pandemic measures for 50% of their pregnancies compared to the pre-pandemic period, with a peak increase of 31.8% ($\beta_{50\%\text{exposed}}=0.25$, $p<0.01$) among all pregnancies, 26.8% ($\beta_{50\%\text{exposed}}=0.27$, $p=0.01$) and 37.1% ($\beta_{50\%\text{exposed}}=0.24$, $p=0.01$) for higher and lower income groups, respectively. Pregnancies that occurred entirely within the first or second year of the pandemic period experienced higher rates of PTB by 16.2% ($\beta_{100\%Y1}=0.14$, $p=0.01$) and 11.3% ($\beta_{100\%Y2}=0.11$, $p<0.01$), respectively, compared to the pre-pandemic period (**Table 2.2 and Figure 2.1(A)**).

Low birth weight (LBW)

During the pandemic period, the percentage of live births with low weight increased compared to the pre-pandemic period, with a relative increase of 15% (crude RR=1.15, 95% CI, 1.01-1.21, **Figure 2**). A similar pattern was observed across all regions in Manitoba. During the pandemic period, the Northern region showed a relative increase of 16.1%, while Winnipeg showed a smaller relative increase of 5.8% (*Supplementary: Table S2.2 and Figure S2.1*).

The pandemic measures were associated with an immediate relative drop in LBW occurrence of 12% ($\beta_{\text{immediate effect}}=0.13$, $p=0.05$) among all live births, although there was a relative increase of 7.9% ($\beta_{\text{immediate effect}}=0.22$, $p=0.01$) in the lower income group (**Table 2.2**). Rates of LBW peaked for pregnancies with 50% pandemic exposure compared to pre-pandemic, with a relative increase of 32.6% ($\beta_{50\%\text{exposed}}=0.26$, $p=0.01$) among all pregnancies and 38.9% ($\beta_{50\%\text{exposed}}=0.33$, $p=0.01$) in the

lower-income group. Although LBW rates for pregnancies that spanned the full term during the second year of the pandemic showed a reduction compared to those during the first year, the rates remained elevated and did not return to the pre-pandemic level (**Table 2.2 and Figure 2.1(B)**).

Small for gestational age (SGA)

During the pandemic period, the percentage of SGA infants among live births increased by 4% relative to pre-pandemic period levels (crude RR=1.04, 95% CI, 1.01-1.09, **Figure 2.2**). During the pandemic period, average SGA rates differed by region, with Winnipeg having the highest average SGA rate before and during the pandemic period (10.02% and 10.49%, respectively, *Supplementary: Table S2.2 and Figure S2.1*). Among all pregnancies, the pandemic was not associated with significant changes in SGA monthly rates (**Table 2.2**). We found an increase in the incidence of SGA rate among the higher income group for pregnancies exposed 100% during the second year ($\beta_{100\%Y1}=0.14$, $p<0.01$) (**Table 2.2 and Figure 2.1(C)**).

NICU admissions

NICU admissions among live births remained stable at 8.2% before and during the pandemic period, with no change in the relative risk (RR:1.00, 95% CI, 0.96-1.04, **Figure 2.2**). However, across regions of Manitoba, the Prairie Mountain region showed an 11.5% relative increase, while the other regions showed reductions (*Supplementary: Table S2.2 and Figure S2.1*). NICU admission rates by region, income groups, and exposure groups did not differ significantly from the pre-pandemic period. For pregnancies that were fully exposed during the second year of the pandemic period, NICU admission rates returned to pre-pandemic period levels among all pregnancies and different income groups (**Table 2.2 and Figure 2.1(D)**).

Breastfeeding initiation (BFI)

During the pandemic period, rates of BFI in hospital were similar with a relative risk of 0.98 (95% CI, 0.98-0.99) (**Figure 2.2**) and with the largest reduction in the Northern region (6.9%, *Supplementary Table S2.2 and Figure S2.1*). Pandemic measures were associated with an immediate relative decline in BFI by 1.6% among all pregnancies ($\beta_{\text{immediate effect}}=-0.04$, $p=0.01$), followed by a minor increase in breastfeeding monthly rates during the 2-year pandemic period ($\beta_{\text{lagged effect}}<0.01$, $p=0.02$, **Table 2.2**). The ITS analyses of BFI rates by exposure duration showed no statistically significant changes (**Table 2.2 and Figure 2.3(A)**).

Cesarean delivery

During the pandemic period, 28% of all pregnancies were cesarean deliveries compared to 23% pre-pandemic, representing a relative increase of 22% (crude RR=1.22, 95% CI, 1.19-1.25) (**Figure 2.2**). Cesarean delivery rates were notably higher in higher income groups compared to lower income groups (**Figure 2.3(B)**). The increase occurred across most regions in Manitoba during the pandemic, with the exception of Prairie Mountain (*Supplementary: Table S2.2 and Figure S2.1*). Following the onset of pandemic measures, an immediate relative increase of 11.7% in cesarean delivery rates was observed among all pregnancies ($\beta_{\text{immediate effect}}=0.20$, $p<0.01$), 16.2% ($\beta_{\text{immediate effect}}=0.19$, $p<0.01$) in the higher-income group, and 7.4% ($\beta_{\text{immediate effect}}=0.22$, $p<0.01$) in the lower income group (**Table 2.2**). The pandemic period was associated with a significant relative increase in monthly rates among those exposed to restrictions for 50% of their pregnancy, with a peak increase of 26.5% ($\beta_{50\%\text{exposed}}=0.24$, $p<0.01$) among all pregnancies, 27.9% ($\beta_{50\%\text{exposed}}=0.24$, $p<0.01$) in higher income, and 25.3% ($\beta_{50\%\text{exposed}}=0.24$, $p<0.01$) in the lower income group. Pregnancies occurring entirely within the first or second year of the pandemic period experienced

higher rates of cesarean deliveries by 25.4% ($\beta_{100\%Y1}=0.22$, $p<0.01$) and 21.3% ($\beta_{100\%Y2}=0.19$, $p<0.01$), respectively (**Table 2.2 and Figure 2.3(B)**).

Stillbirth

The average pre-pandemic period stillbirth rate among all pregnancies was 0.6% and rose to 0.7% during the pandemic period (**Figure 2.3(C)**). The relative risk of stillbirth increased to 1.16 (95% CI, 1.01-1.34) during the pandemic period (**Figure 2.2**). Stratified by income, these results became non-significant but in a similar direction. We observed no change in the stillbirth quarterly rates following the onset of the pandemic period ($p=0.1$) or over the 2-year pandemic period ($p=0.37$, **Table 2.2**). Given the relatively low rate of stillbirths in Manitoba, it was not feasible to conduct monthly rate analyses and ITS analyses by exposure duration (**Figure 2.3(C)**).

2.7. Discussion

In this study of 222,636 pregnancies, we observed significant effects for the pandemic measures on perinatal outcomes, including PTB and LBW, which varied across income groups and certain rural regions. The exposure duration under the pandemic measure was also a significant determinant for perinatal health, where increased risks of PTB, cesarean delivery, and LBW were observed among pregnancies that spanned in its entirety during the pandemic. Our analyses suggest that the short- and long-term measures had minimal effect on breastfeeding initiation, NICU admissions and SGA rates during the study period.

Previous studies have not included the influence of duration of exposure to pandemic measures on prenatal care and the associated perinatal and delivery outcomes. A US study categorized pregnancies based on exposure to multimodal prenatal healthcare (combined in-person and virtual visits) between July 2018 and October 2021(82). Their findings showed a decrease in NICU

admissions among the partially exposed group (change/4-week: -0.91%; 95%CI: -1.77% to -0.03%), but an increased risk in fully exposed pregnancies (change/4-week: 1.75%; 95%CI: 0.49% to 3.02%), with no significant changes in PTB, cesarean delivery, or SGA rates(82). In contrast, our study found that NICU admission rates by exposure did not differ from the pre-pandemic period, whereas we found a significant increase in PTB and cesarean delivery rates among those exposed to 50% of their pregnancy during the pandemic. The COVID-19 pandemic has strained the healthcare system across the province. Factors such as staff shortages, the redeployment of nurses, the return of retired nurses to the workforce, and challenges in maintaining continuity of care while supporting the staff well-being could explain the observed changes in perinatal outcomes. Previous studies have defined exposed cohort of pregnancies based on any period during the pandemic(27–29,82–84). In our view, this carries the risk of inaccurate exposure assignments and potentially biased and conflicting results. For instance, women who gave birth shortly after the onset of pandemic measures likely had different pregnancy experiences compared to those who spent a longer time under the pandemic measures, experiencing altered prenatal care due to changes in healthcare access. When categorized as a dichotomous measure, this difference could account for the conflicting results seen across studies.

Meta-analyses of early-pandemic studies have reported mixed findings. A meta-analysis of 31 studies suggested pandemic measures were associated with an increase in stillbirths and a reduction in PTB (<37 weeks of gestation), particularly in high-income European countries(85). However, no significant differences were found in LBW, NICU admissions, or cesarean delivery rates(85). A larger meta-analysis examined the first nine months of the pandemic and found a reduction in PTB (<34 weeks) in countries with stringent implemented measures (OR=0.71, 95%

CI 0.58–0.88), while no changes were observed for PTB (<37 weeks of gestation), NICU admissions, stillbirths, or LBW(86). Studies covering 12 months or more during the pandemic found either no change or an increase in adverse perinatal outcomes compared to pre-pandemic periods(87–92). However, these studies did not address the differential impact of the duration of pregnancy that was spent under pandemic measures. Our results suggest that the duration of exposure to the implemented COVID-19 pandemic measures was a strong determinant of adverse perinatal outcomes, with a dose-response relationship observed in stillbirth, PTB and cesarean deliveries.

Socio-economic disparities, including fears of contracting COVID-19 at healthcare facilities, transportation restrictions, reduced social support, exacerbated financial insecurity, stress, and mental health challenges, could have negatively impacted maternal health and contributed to higher rates of PTB and stillbirths(93). In addition, more strict pandemic measures, such as travel restrictions and 14-day isolation requirements, in northern and remote communities may have disproportionately affected pregnant women by limiting their access to timely prenatal care in Manitoba. The shift to virtual prenatal care during the pandemic may have added further challenges for these communities. However, a recent study in the Canadian province of Ontario that examined the first 21 months of the pandemic found a 15% reduction in PTB (adjusted OR=0.85, 95%CI; 0.82 to 0.87) compared to the pre-pandemic period(87). Differences in findings between Ontario study and the current study may be due to differences in the pandemic measures implemented across provinces, or differences in the analytical methods applied. Specifically, the Ontario study did not account for the pre-pandemic trend nor the exposure duration to pandemic measures, which may explain their reported reduction in PTB.

Several previous studies noted higher rates of cesarean deliveries during the pandemic period compared to the pre-pandemic period, which is consistent with the findings of the current study(87,94,95). A cohort study conducted in the Canadian province of Ontario reported increased odds of cesarean deliveries during the pandemic period compared to the pre-pandemic period (adjusted OR of 1.09, 95% CI; 1.08 to 1.11)(87). The observed increase in rates may reflect the efforts of obstetricians to provide the optimal care, and “best services” adapting to changes in guidelines aimed at better neonatal outcomes during the pandemic(95,96). Additionally, the rise in cesarean deliveries may have been driven by concerns over adverse events such as respiratory complications, placental infections, potential vertical transmission and neonatal death associated with vaginal delivery(97). The increase might also be attributed to the rise in maternal requests for cesarean deliveries, which might have been influenced by anxiety over restrictive hospital policies and limited support networks during the pandemic(93,96). These factors may also explain the increased rates associated with longer exposure durations.

Our study found no changes in NICU admissions and SGA rates, consistent with evidence from Denmark, Botswana, and other Canadian studies(27,28,98–100). Other studies have shown either an increase(101) or a decrease in NICU admissions(87,102) during the COVID-19 pandemic. The current study found that the breastfeeding initiation rate was largely unchanged over time, which may be attributed to the short follow-up period as we only captured the initiation recorded after delivery in hospitals and not after discharge. The slight initial decline during the early pandemic, especially among lower income and rural populations, highlights the need for targeted support to address these disparities. Varying access levels to breastfeeding support, reduced face-to-face professional support, or differences in maternal preferences across different regions

during the pandemic could have led to minor changes in breastfeeding rates in Manitoba(103–105). Studies from Spain and the UK reported increased breastfeeding rates at discharge for term infants, while others from Italy and Canada observed decline or no change in breastfeeding rates during the pandemic(106–110). A UK survey conducted during early pandemic, between May and June 2020, found two contrasting experiences: around 41% of mothers felt that breastfeeding was supported, while 27% struggled with support and subsequently stopped breastfeeding(111). The current study has several strengths. First, our province-wide database captures all births in the province of Manitoba over 2 years during the pandemic and 12 years prior. Second, the use of interrupted time series analysis by exposure level provided the temporal detail to distinguish the immediate effect of the pandemic from its cumulative long-term effects. Third, we examined the pandemic differential effect across income groups and different regions within Manitoba. Limitations of this study should be acknowledged. A causal interpretation of the impact of pandemic measures cannot be inferred, as pregnant women were also exposed to the novel coronavirus and restrictions to healthcare access; thus, the results should be interpreted cautiously. While breastfeeding initiation was defined as any exclusive or partial breastfeeding within the first 3 days postpartum, we did not capture breastfeeding initiation after hospital discharge. Although this is unlikely to significantly affect the reported initiation rates, assessing the continuation of breastfeeding after discharge would be important for understanding longer-term breastfeeding patterns. Administrative data does not include variables such as race and ethnicity, limiting our ability to fully investigate disparities and inequities in perinatal outcomes. In addition, we did not examine the effect of COVID-19 infection on perinatal outcomes, though the small number of COVID-19-positive pregnancies (n=225) in our cohort during the first wave

makes it unlikely that this would strongly influence the results of our immediate effect models. Despite the increase in stillbirth rates with more prolonged exposure, rates were relatively low, and our interrupted time series analysis was therefore underpowered. We examined the effect of the measures across different income groups; however, we did not investigate the effect modification through interaction terms or examine differences between income groups. Additionally, while we did not investigate variations in prenatal care, the changes to maternal healthcare were implemented consistently across the provincial healthcare system, reducing differential variability. However, rural regions and lower-income areas may have experienced a disproportionate impact compared to urban centers. Our study did not capture out-of-hospital births, including those attended by midwives or at nursing stations, as these are not included in medical services or hospital abstract databases. We therefore cannot determine whether out-of-hospital birth rates changed during the COVID-19 pandemic. Moreover, we could not account for vaccination rates among pregnant women. We also did not examine other maternal outcomes such as morbidity, death, and hospital admissions. We could not distinguish between spontaneous and medically indicated preterm births, nor between planned and emergency cesarean sections, which may reflect different underlying mechanisms.

2.8. Conclusions

Our findings indicate that changes around the COVID-19 pandemic, including both mitigation measures, policy changes, and direction effect of the pandemic, were associated with increased rates of preterm births and cesarean deliveries, particularly amongst pregnancies in which the full term occurred during the pandemic. These observations can be attributed to changes in access and adequacy of care, greater socioeconomic vulnerability among certain groups, or an

unknown mechanism. While the pandemic measures were not associated with significant effects on stillbirths, the rates increased with greater pandemic exposure, followed by a drop to pre-pandemic levels in the second year. Over the 2-year pandemic period, we observed no change in NICU admissions and breastfeeding initiation. Further investigation into regional and socioeconomic disparities is warranted to better understand the underlying mechanisms and to guide evidence-based maternal and neonatal healthcare policies for vulnerable populations in future public health crises.

2.9. Acknowledgement

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project (HIPC#2020/2021 - 33). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health. This study was supported by the Canadian Institutes of Health Research (CIHR).

2.10. Data availability

Data cannot be shared publicly because of privacy restrictions. Data are available from the University of Manitoba and MCHP Institutional Data Access/Ethics Committee (contact via <https://umanitoba.ca/manitoba-centre-for-health-policy/>) for researchers who meet the criteria for access to confidential data.

2.11. Author contributions

LA, SE, KK conceptualized and designed the study, drafted the manuscript, carried out the initial analyses and interpretation, reviewed and revised the manuscript. LL, MT, JD, CL, JF, SAS, KK, CR contributed to study conception and design, reviewed and critically revised the manuscript. QT assisted in data acquisition, data analyses, and critically revised the manuscript. PP and LH contributed to the study design, reviewed and critically revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. This work was supported by a research grant from Research Manitoba and funding from the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship.

2.12. Competing interests

The authors declare no competing interests.

2.13. Ethical Approval

The study was approved by the University of Manitoba Health Research Ethics Board (HREB #: H2021:063), and access to data was approved by the Provincial Health Research Privacy Committee of Manitoba Health (HIPC #: 2020/2021-33). Informed consent was not required as data are de-identified.

2.14. Tables

Table 2.1. Demographic characteristics of the included population during the study period (January 2008 to March 2022).

Characteristics	Pre-pandemic	During pandemic
	(January 2008- February 2020)	(March 2020 – March 2022)
N	190,694	31,942
Age (mean, SD)	28.6 (SD=5.8)	29.9 (SD=5.6)
Residence (n,%)		
Rural	84,456 (44.3%)	14,316 (44.8%)
Urban	106,122 (55.7%)	17,615 (55.2%)
Regional Health Authority (n,%)		
Interlake Eastern	16,356 (8.6%)	2,834 (8.9%)
Northern Health Region	19,969 (10.5%)	3,097 (9.7%)
Southern Health-Sante	33,3506 (17.6%)	5,851 (18.3%)
Prairie Mountain	23,731 (12.5%)	3,958 (12.4%)
Winnipeg	97,016 (50.2%)	16,191 (50.7%)
Income quintile group (n,%)		
Lower	90,711 (47.6%)	14,614 (45.8%)
Higher	99,304 (52.0%)	17,262 (54.0%)
Unknown	679 (0.4%)	66 (0.2%)
Parity (n,%)		
Primipara	131,881 (69.2%)	21,856 (68.4%)
Multipara	58,720 (30.8%)	10,082 (31.6%)
Comorbidities (n,%)		
Hypertension	29,454 (15.5%)	3,484 (10.9%)
Diabetes	17,290 (9.1%)	2,428 (7.6%)
Psychological distress	24941 (13.1%)	6400 (20.0%)

Table 2.2. Interrupted time series analyses for perinatal outcomes before and during the pandemic periods in the Canadian province of Manitoba.

Outcomes	Model 1: Immediate and lagged changes					Model 2: Changes by exposure percentage ⁺														
	Immediate change ^a			Change during pandemic ^b		25%			50%			75%			100% Year 1			100% Year2		
	% change	Estimate (β)	p-value	Estimate (β)	p-value	% change	Estimate (β)	p-value	% change	Estimate (β)	p-value	% change	Estimate (β)	p-value	% change	Estimate (β)	p-value	% change	Estimate (β)	p-value
1. Preterm birth																				
All pregnant	19.9%	0.2	<0.01	-0.01	0.09	16.9%	0.16	0.03	31.8%	0.25	<0.01	-0.3%	0.02	0.72	16.2%	0.14	0.01	11.3%	0.11	<0.01
Higher income ^{e*}	9.6%	0.18	0.02	<-0.01	0.66	14.7%	0.14	0.08	26.8%	0.27	0.01	14.2%	0.09	0.27	9.5%	0.07	0.57	16.6%	0.16	<0.01
Lower income ^{d*}	31.0%	0.24	0.01	-0.02	0.03	18.6%	0.1	0.15	37.1%	0.24	0.01	-15%	-0.04	0.55	23.2%	0.13	0.17	6.3%	-0.02	0.67
2. Low birthweight																				
All pregnant*	-12.0%	0.13	0.05	<0.01	0.82	6%	0.06	0.41	32.6%	0.26	0.01	12%	0.13	0.09	22.4%	0.19	0.07	14.9%	0.14	<0.01
Higher income ^{e*}	-27.5%	0.03	0.71	0.02	0.13	-3.7%	-0.0001	0.99	26.7%	0.19	0.15	10%	0.09	0.39	8.9%	0.08	0.59	22.2%	0.21	<0.01
Lower income ^{d*}	7.9%	0.22	0.01	-0.01	0.22	15.5%	0.13	0.17	38.9%	0.33	0.01	11.9%	0.15	0.11	36.5%	0.29	0.02	6.9%	0.07	0.20
3. Small for gestational age																				
All pregnant	-3.0%	<0.01	0.94	0.00	0.28	-3.2%	0.06	0.37	6.9%	-0.03	0.65	-11.5%	-0.01	0.89	-1.2%	0.09	0.07	5.2%	0.05	0.07
Higher income*	-12.3%	-0.06	0.32	0.02	0.01	9.4%	0.14	0.84	-5.8%	-0.05	0.49	1.7%	0.01	0.99	6.7%	0.11	0.27	14.9%	0.14	<0.01
Lower income ^{d*}	2.6%	0.06	0.35	0.00	0.26	4.2%	0.05	0.64	3.7%	0.02	0.85	-4.5%	-0.03	0.74	11.1%	0.11	0.13	-4.5%	-0.05	0.28
4. NICU admissions																				
All pregnant	17.3%	0.02	0.71	<-0.01	0.69	-9.1%	-0.09	0.28	5.5%	0.05	0.44	-5.3%	-0.06	0.40	8.6%	0.08	0.11	-1.1%	-0.01	0.74
Higher income ^e	-0.8%	<-0.01	0.96	<0.01	0.70	-14.7%	-0.11	0.24	5.6%	0.08	0.48	0.8%	0.01	0.97	7.1%	0.12	0.29	4.6%	0.04	0.44
Lower income ^d	37.8%	0.06	0.35	<-0.01	0.26	-4.9%	-0.03	0.67	6.3%	0.12	0.21	-10.6%	-0.04	0.64	11.0%	0.10	0.30	-5.9%	-0.05	0.22
5. Breastfeeding initiation																				
All pregnant	-1.6%	-0.04	0.01	<0.01	0.02	-2.1%	-0.02	0.41	-1.6%	-0.02	0.34	-1.7%	-0.02	0.22	0%	-0.03	0.12	0.5%	0.01	0.62
Higher income ^e	4.5%	-0.03	0.06	<0.01	0.01	-1.5%	-0.01	0.83	0.7%	-0.01	0.80	0.4%	<0.01	0.87	-3.9%	-0.05	<0.01	5.3%	<0.01	0.62
Lower income ^d	-5.5%	-0.03	0.11	<-0.01	0.66	-2.8%	-0.01	0.82	-4.2%	<-0.01	0.80	-4.2%	<0.01	0.87	-1.4%	-0.01	0.66	-5.3%	0.05	<0.01

6. Cesarean delivery																				
All pregnant	11.7%	0.20	<0.01	<-0.01	0.99	17.9%	0.16	0.01	26.5%	0.24	<0.01	20.6%	0.19	<0.01	25.4%	0.22	<0.01	21.3%	0.19	<0.01
Higher income^e	16.2%	0.19	<0.01	<0.01	0.14	19.3%	0.18	0.01	27.9%	0.24	<0.01	20.1%	0.19	<0.01	26%	0.22	<0.01	30.6%	0.27	<0.01
Lower income^d	7.4%	0.22	<0.01	-0.01	0.10	16.4%	0.14	0.07	25.3%	0.24	<0.01	21.4%	0.19	<0.01	24.5%	0.22	<0.01	11.4%	0.11	<0.01
7. Stillbirth**																				
All pregnant	18.6%	0.26	0.10	-0.02	0.37	NA			NA			NA			NA			NA		

*Change by exposure to pandemic measures: Exposure 25%: April 2020-May2020, Exposure 50%: June 2020 to August 2020, Exposure 75%: Sep 2020 to Nov 2020, Exposure Year 1 100%:Dec 2020 to March 2021, and Exposure Year 2 100%: April 2021 to March 2022.

^aImmediate change examines the change in level immediately after the onset of the pandemic in outcomes rates compared to pre-pandemic period.

^bChange during pandemic examines the change in slope during the pandemic in outcomes rates compared to pre-pandemic period.

^cPercentage change= (Percentage in April2020 – Percentage in March2020)/ Percentage in March2020 * 100.

^dLower income: pregnant women in the lowest and second lowest median neighbourhood income quintile.

^eHigher income: pregnant women residing in the neighbourhoods with the three highest median neighbourhood income quintiles.

* Analysis every 2 months

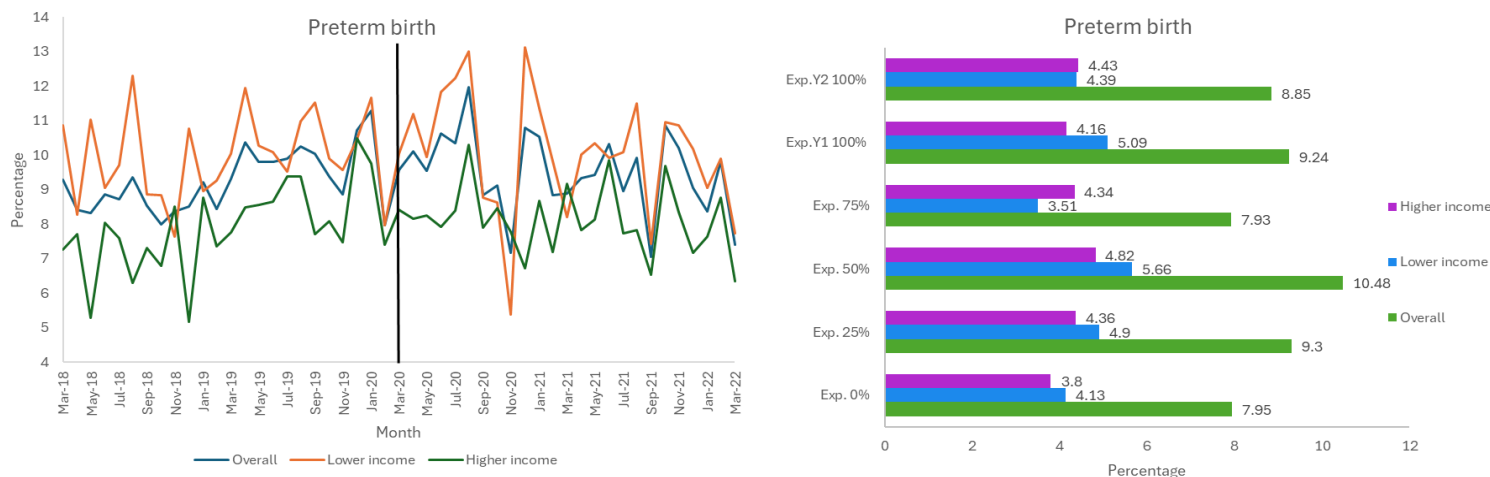
**ITS analysis for Quarterly stillbirth rates. Analysis among lower and higher income groups was not feasible due to low rates.

Two-sided p-values are reported; p<0.05 was considered statistically significant

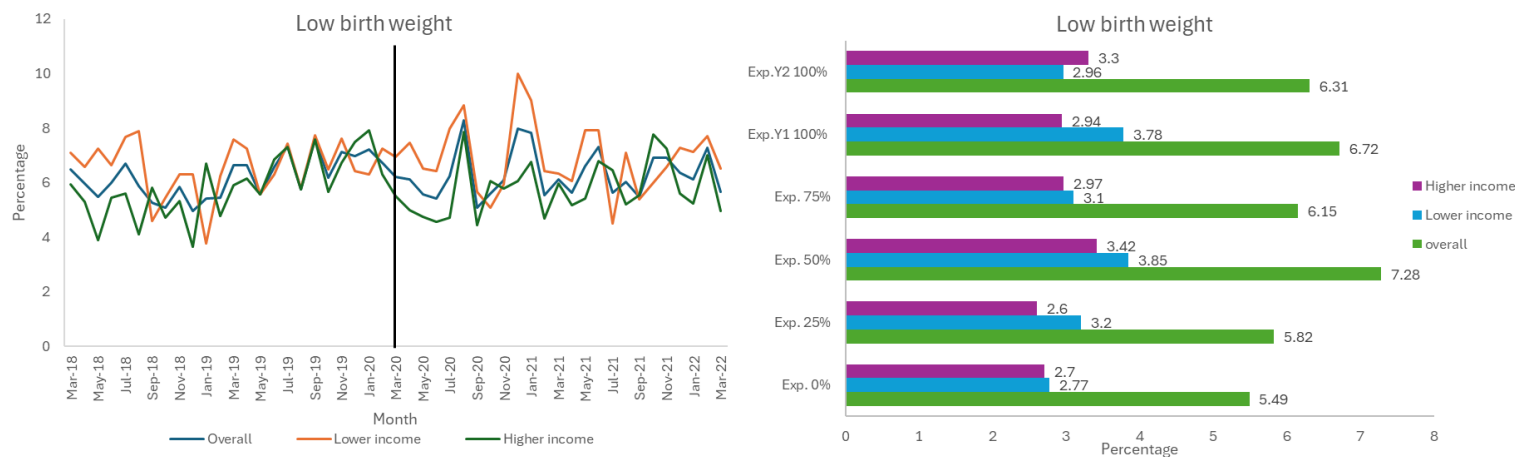
2.15. Figures

Figure 2.1. Trend and percentage of A) preterm birth, B) low birthweight, C) small for gestational age, D) NICU admissions among all pregnancies, lower and higher income groups according to exposure duration percentage during the study period.

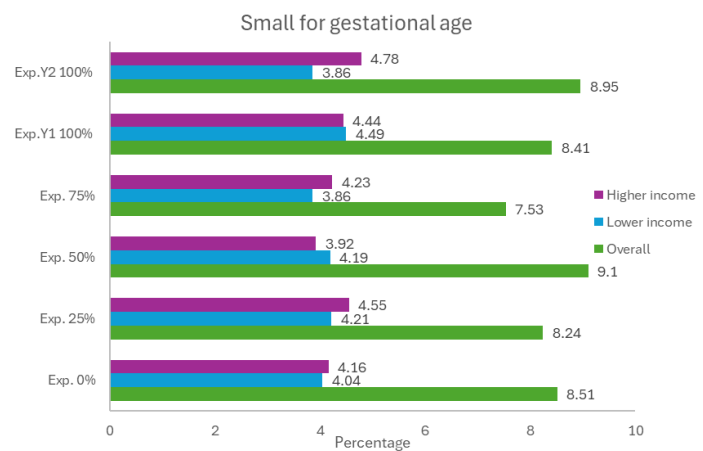
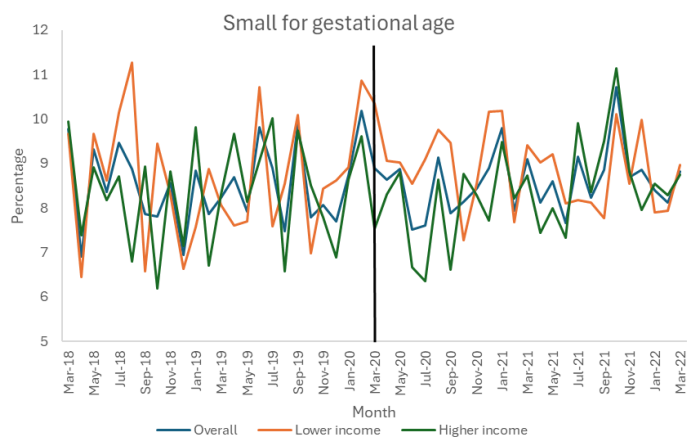
A)



B)



c)



D)

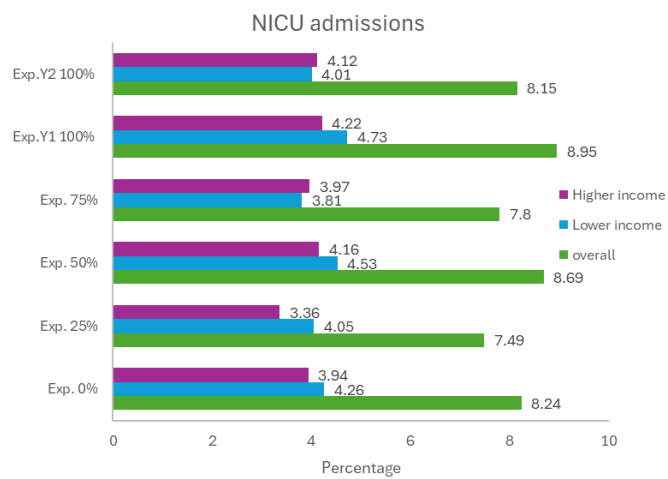
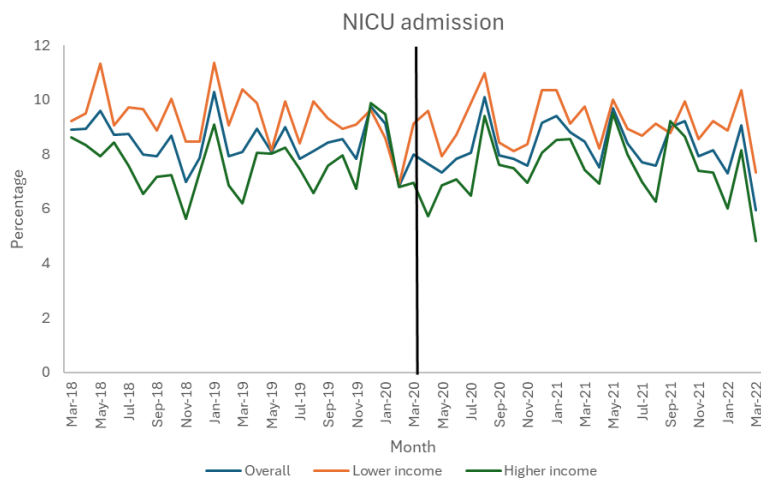


Figure 2.2.Crude Relative Risk and 95% CI of adverse perinatal outcomes during the pandemic vs. before the pandemic.

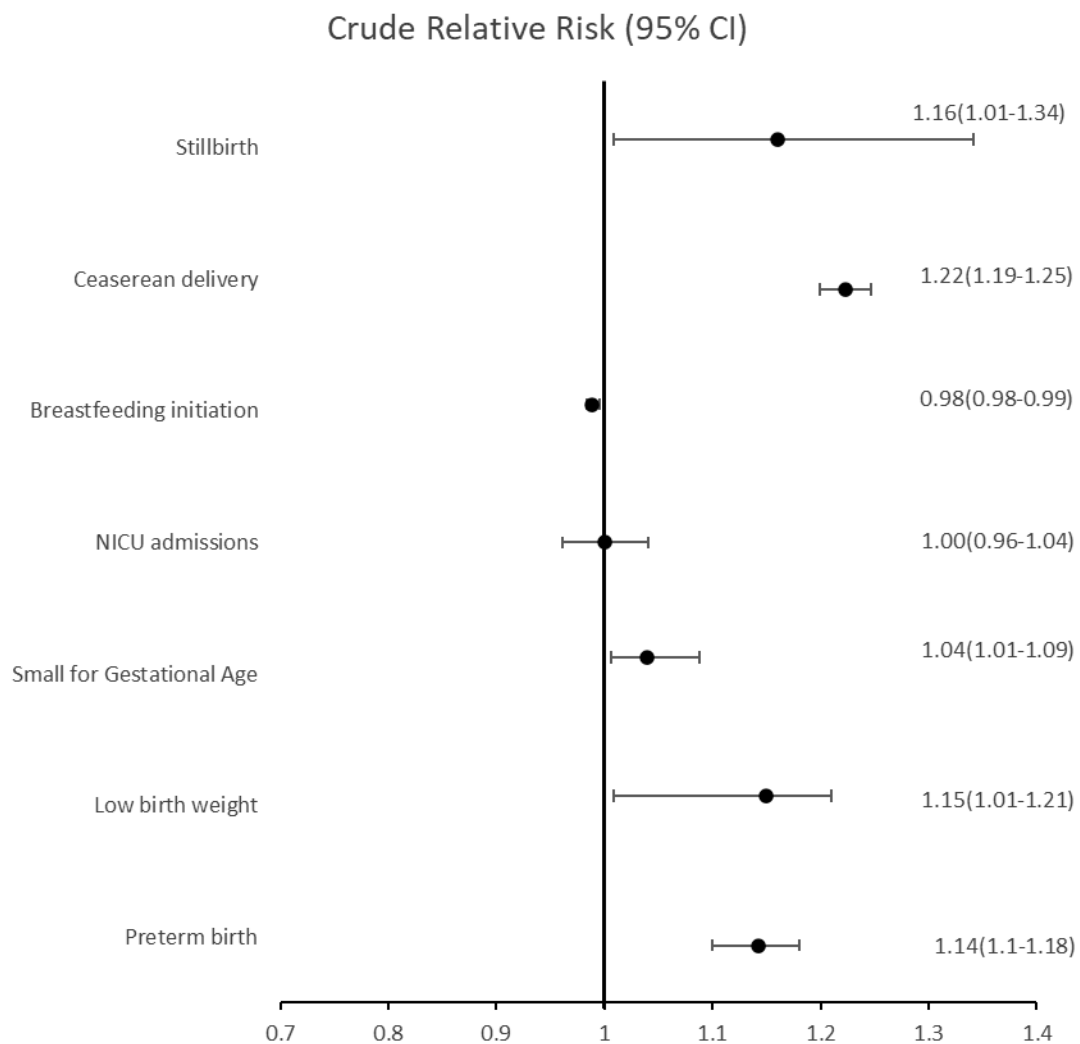
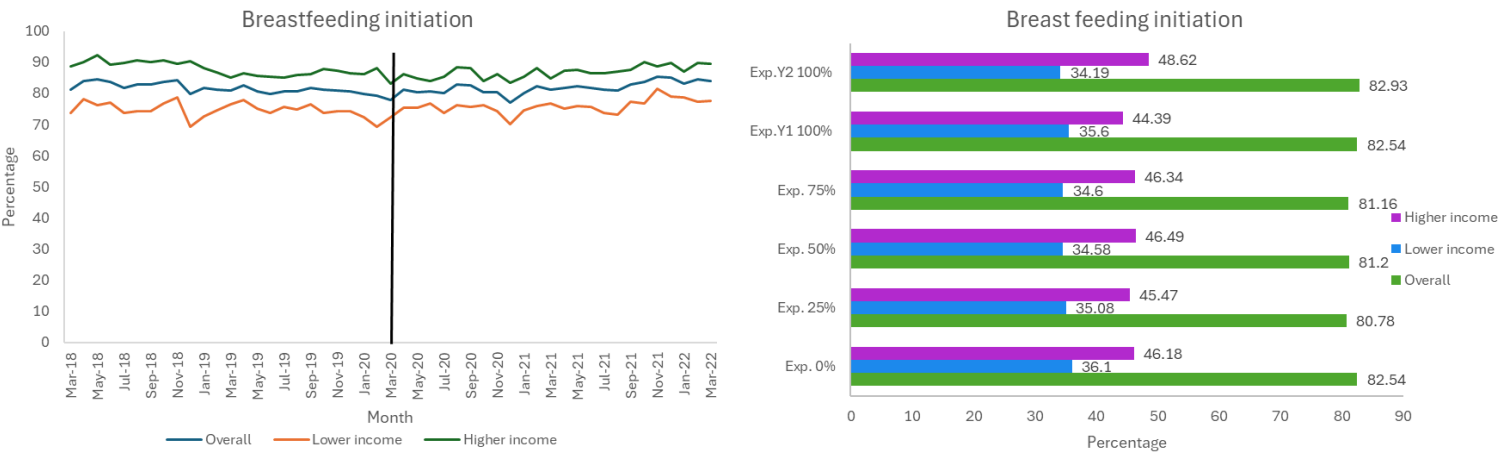
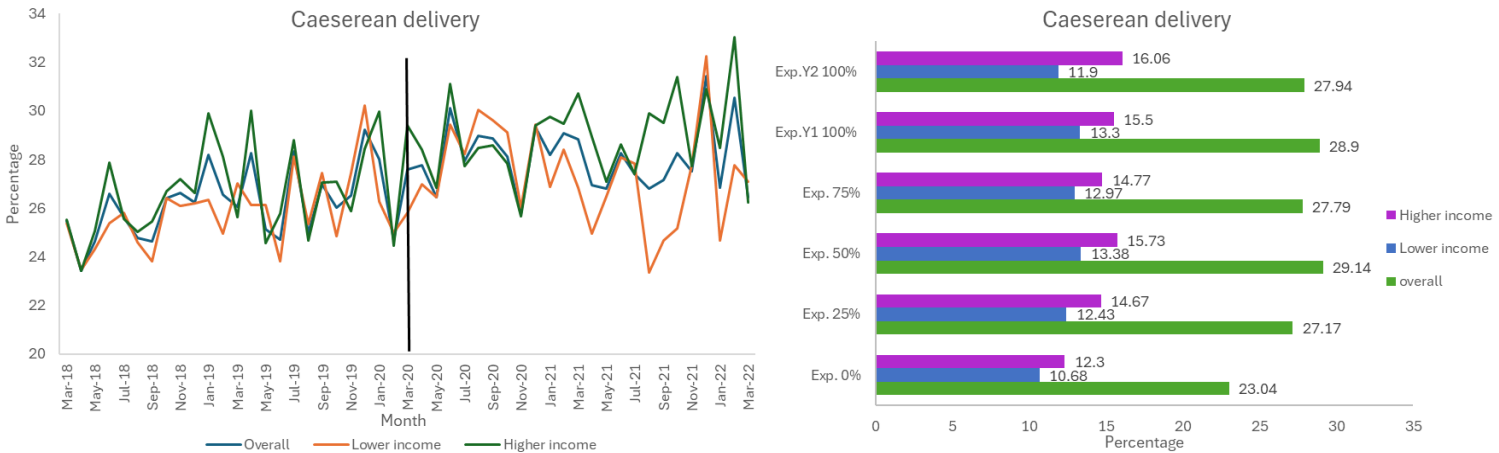


Figure 2.3. Trend and percentage of A) breastfeeding initiation, B) cesarean delivery, C) stillbirth among all pregnancies, lower and higher income groups according to exposure duration percentage during the study period.

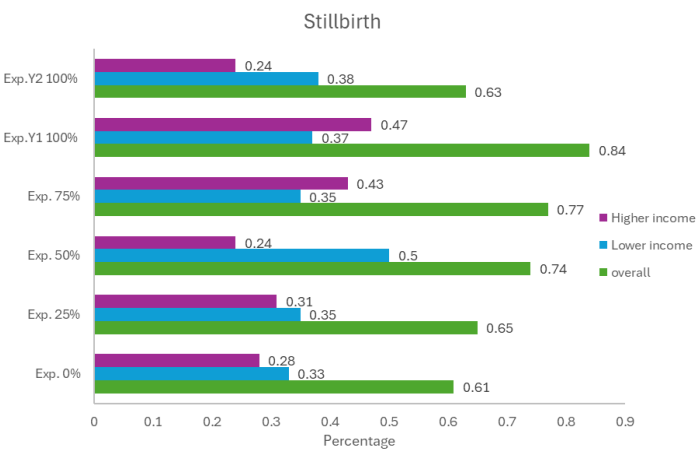
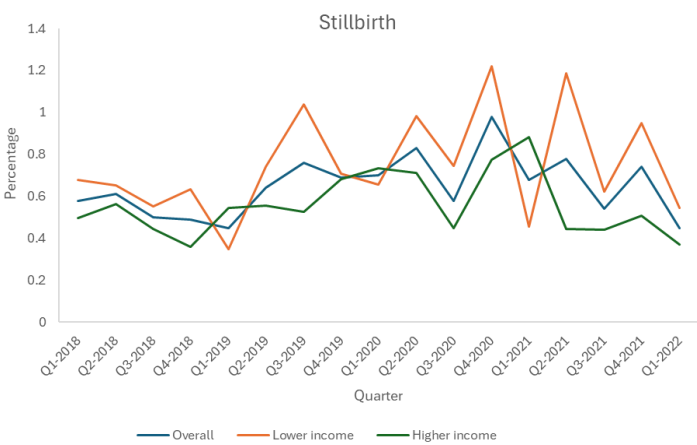
A)



B)



c)



2.16. Supplementary

Supplementary Table S2.1. Perinatal outcomes definitions and diagnosis and procedure/intervention codes.

Outcome	Definition	Diagnosis Codes and procedure/intervention codes
Preterm Birth (PTB)	Live birth at <37 weeks of gestation	ICD-9-CM: V271, V273, V274, V276, V277; ICD-10-CA: Z371, Z373, Z374, Z376, Z377
Stillbirth	Fetal death at or after 20 weeks of gestation	ICD-9-CM: V271, V273, V274, V276, V277; ICD-10-CA: Z371, Z373, Z374, Z376, Z377
Low Birth Weight (LBW)	Infant weight <2500 grams at birth	N/A
Small for Gestational Age (SGA)	Live birth weight at or below the 10th percentile for their gestational age and sex (Canadian standard)	N/A
Neonatal Intensive Care Unit (NICU)	Any live birth with admission to a special care unit or NICU during the birth hospitalization	N/A
Cesarean Delivery	Surgical extraction from the uterus (i.e., not a vaginal delivery) provided from hospital abstract database	Canadian Classification of Health Interventions (CCI) code 5MD60
Breastfeeding Initiation (BFI)	Any live birth with partial or exclusive breastfeeding initiation during newborn hospitalization	ICD-10-CA: Z38

N/A: Not available

Supplementary Table S2.2. Average of perinatal outcomes before and during the pandemic by the Manitoba 5 Regional Health Authority (RHA).

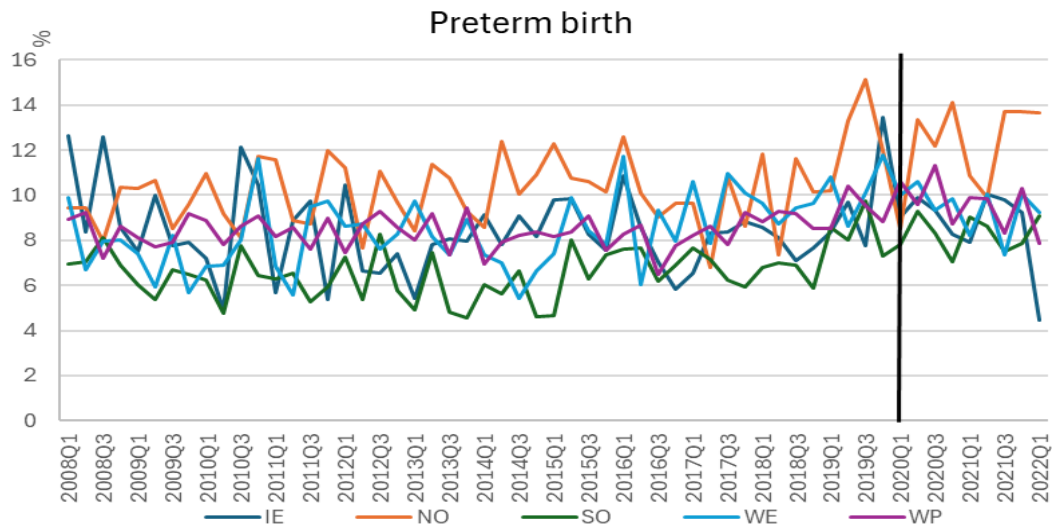
Outcome	Region	Average pre-pandemic (%)	Average during pandemic (%)	Relative percentage change
Preterm Birth (PTB)	Interlake-Eastern	8.84	8.66	-2.01%
	Northern	11.46	12.22	6.69%
	Southern	7.53	8.28	9.98%
	Prairie Mountain	9.88	9.41	-4.76%
	Winnipeg	9.14	9.61	-0.99%
Low Birth Weight (LBW)	Interlake-Eastern	5.75	5.86	1.94%
	Northern	6.73	7.81	16.05%
	Southern	5.40	5.78	7.31%
	Prairie Mountain	6.49	6.88	6.02%
	Winnipeg	6.78	7.17	5.80%
Small for Gestational Age (SGA)	Interlake-Eastern	6.71	7.20	7.23%
	Northern	6.70	6.75	0.68%
	Southern	7.28	7.13	-2.09%
	Prairie Mountain	6.83	7.08	3.76%
	Winnipeg	10.02	10.49	4.68%
NICU Admissions	Interlake-Eastern	8.12	7.22	-11.07%
	Northern	5.55	4.96	-10.65%
	Southern	4.99	5.06	1.49%
	Prairie Mountain	13.24	14.82	11.49%
	Winnipeg	8.80	8.43	-4.15%
Breastfeeding Initiation	Interlake-Eastern	78.89	77.56	-1.69%
	Northern	60.87	57.59	-6.89%
	Southern	89.70	90.09	0.44%
	Prairie Mountain	82.66	83.59	1.13%
	Winnipeg	85.36	84.24	-1.31%

Caesarean Delivery	Interlake-Eastern	22.63	24.09	6.45%
	Northern	19.69	21.35	8.44%
	Southern	25.34	26.64	5.13%
	Prairie Mountain	32.11	31.83	-0.89%
	Winnipeg	26.45	29.42	11.25%
Stillbirth	Interlake-Eastern	0.39	0.52	33.33%
	Northern	0.73	1.32	80.82%
	Southern	0.64	0.61	-4.69%
	Prairie Mountain	0.72	0.69	-4.17%
	Winnipeg	0.57	0.64	12.28%

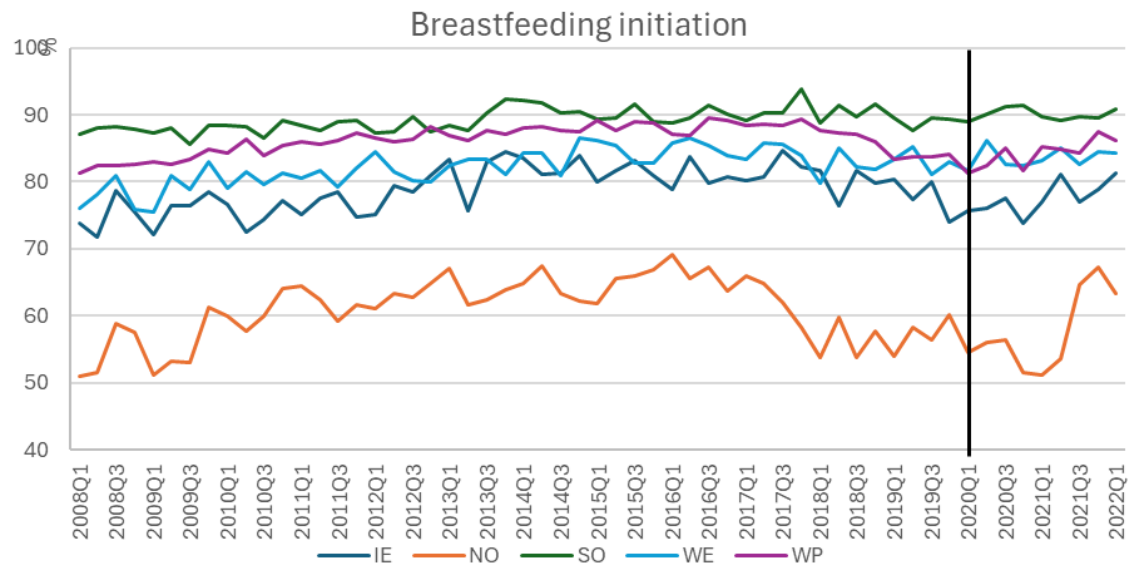
- Average before based on rates 2 years before pandemic: from March 2018 to March 2020
- *Relative percentage change = (Average Percentage 2 years during pandemic – Average Percentage 2 years before pandemic) / Average Percentage 2 years before pandemic * 100.*

Supplementary Figure S2.1. Trends of the seven perinatal outcomes by quarter by health region in Manitoba before and during the COVID-19 pandemic.

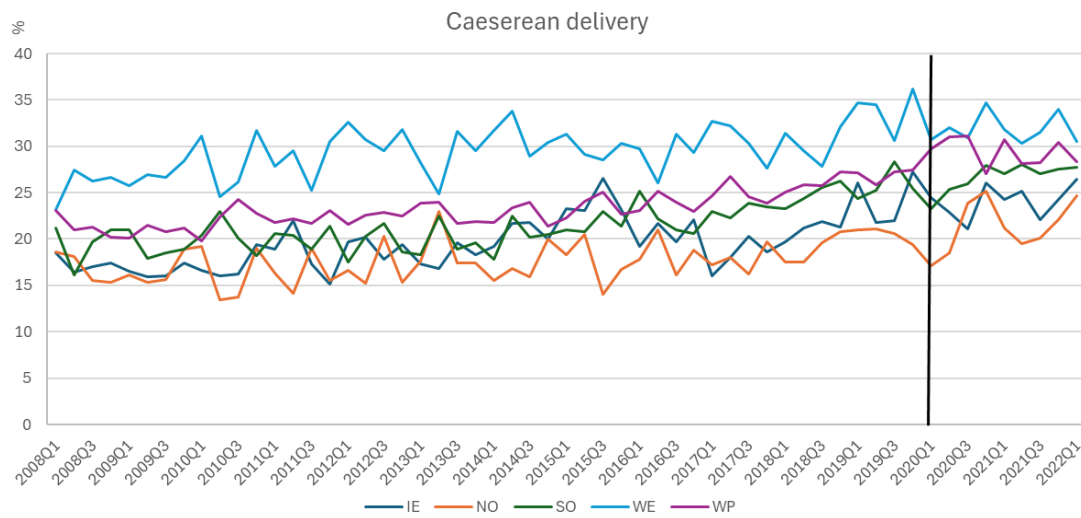
A)



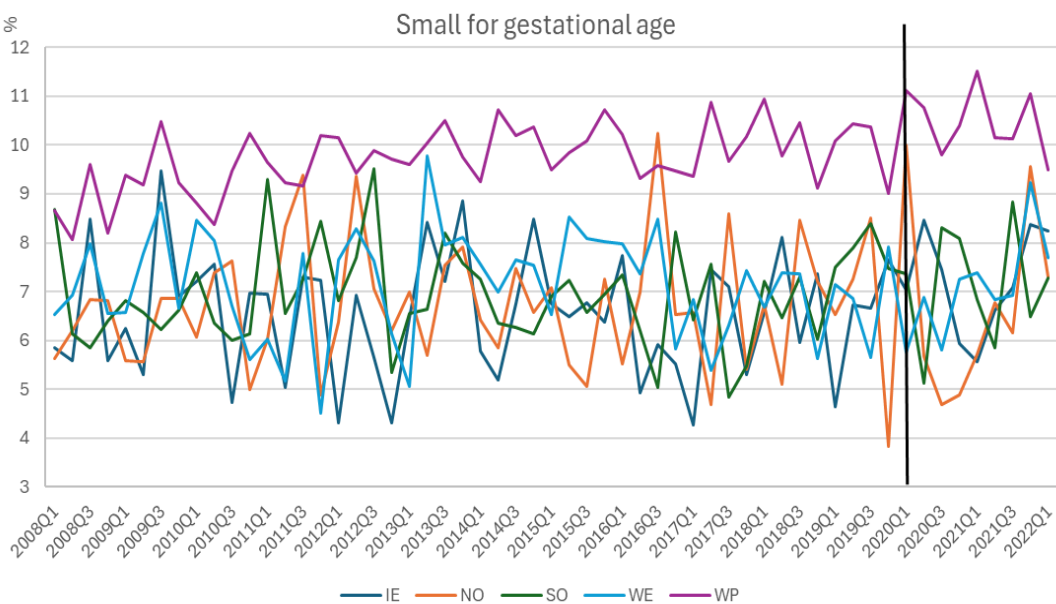
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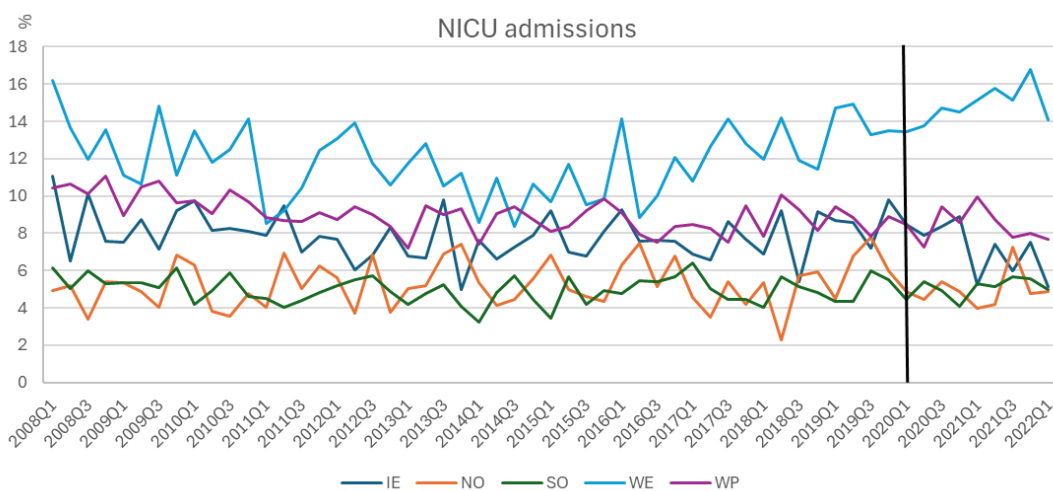
c)



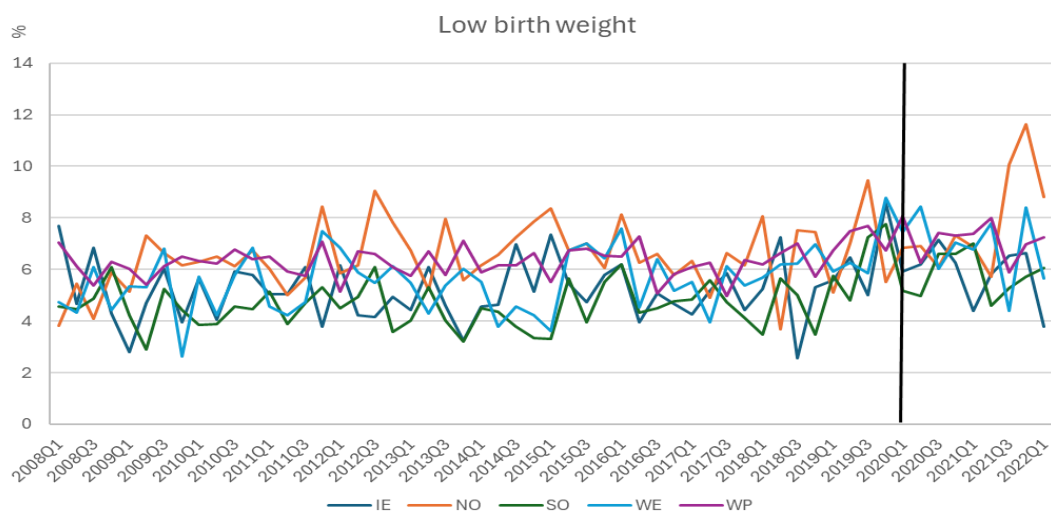
d)



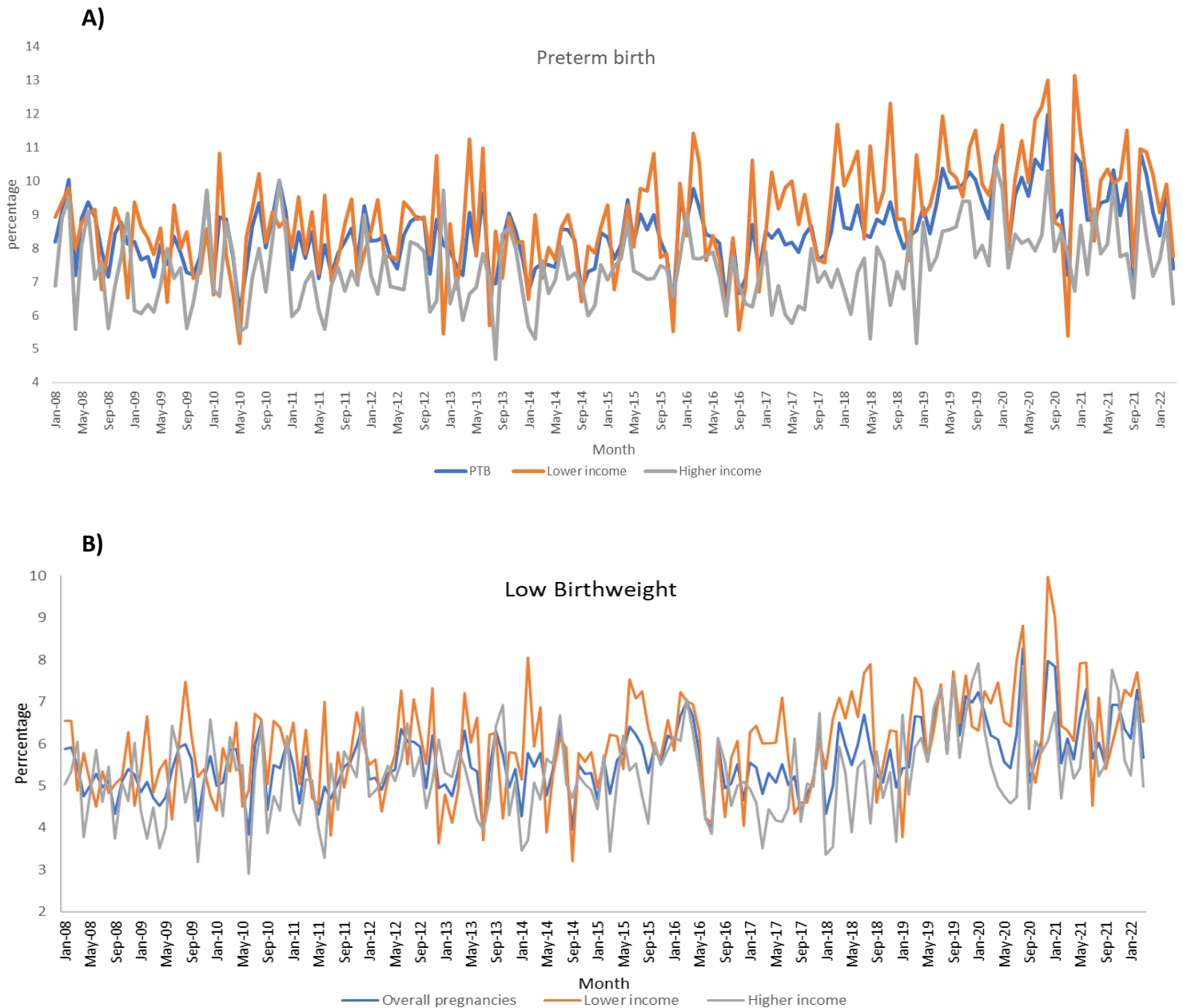
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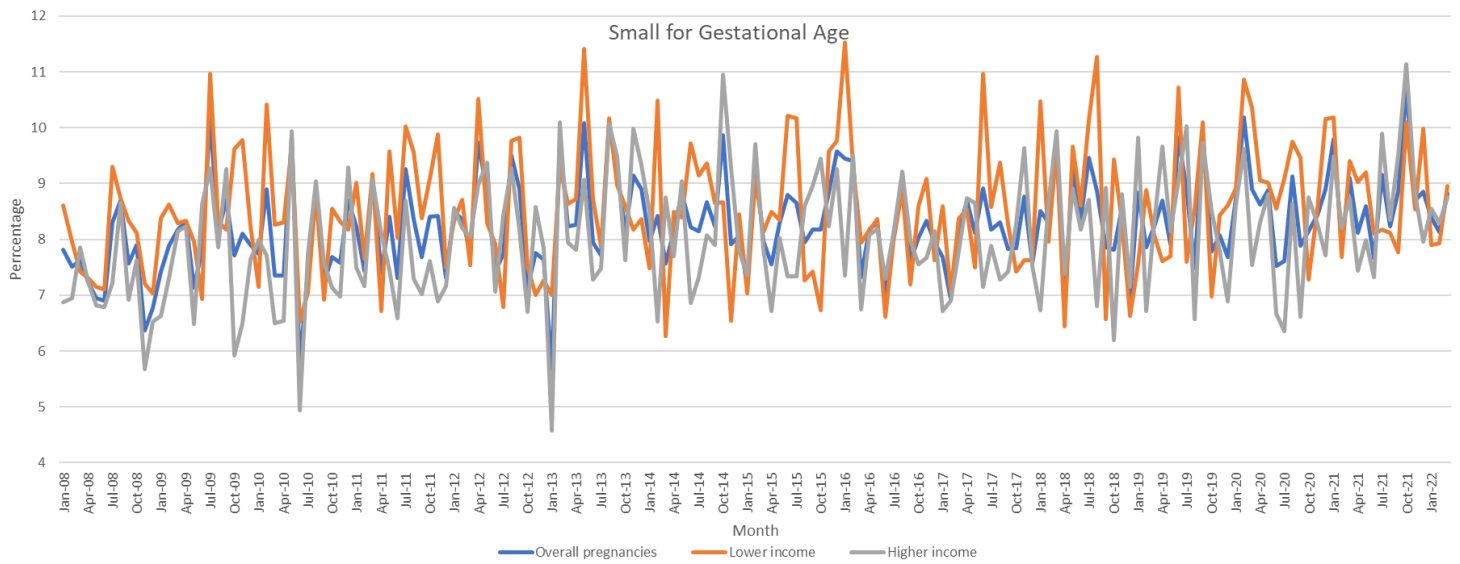
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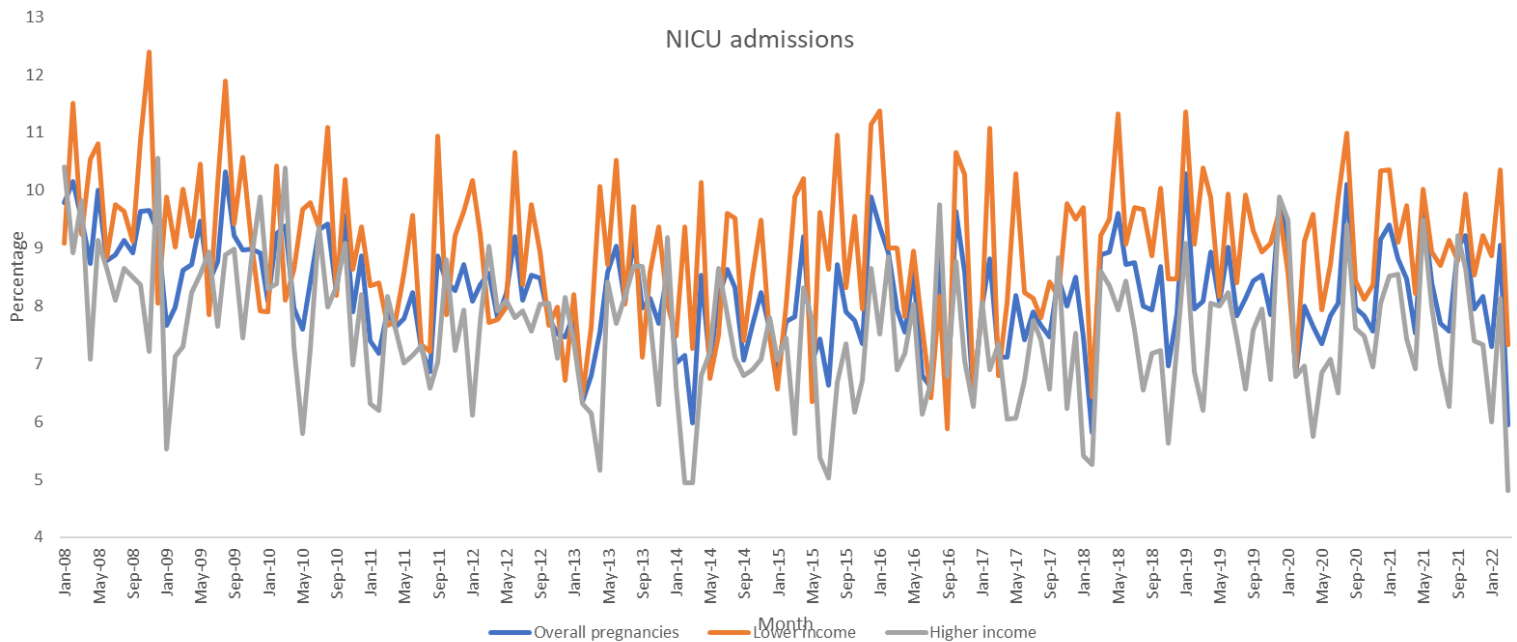
Supplementary Figure S2.2. Trends of the seven perinatal outcomes among all pregnancies and income groups Manitoba before (January 2008-February 2020) and during (March 2020-March 2022) the COVID-19 pandemic.



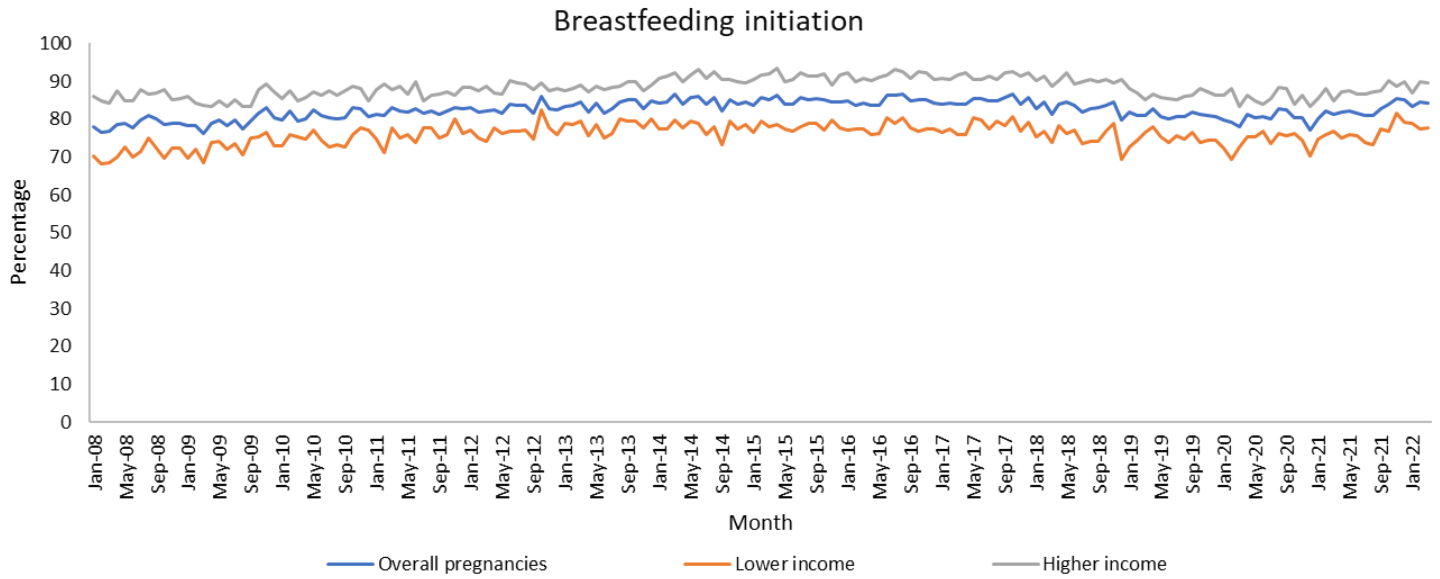
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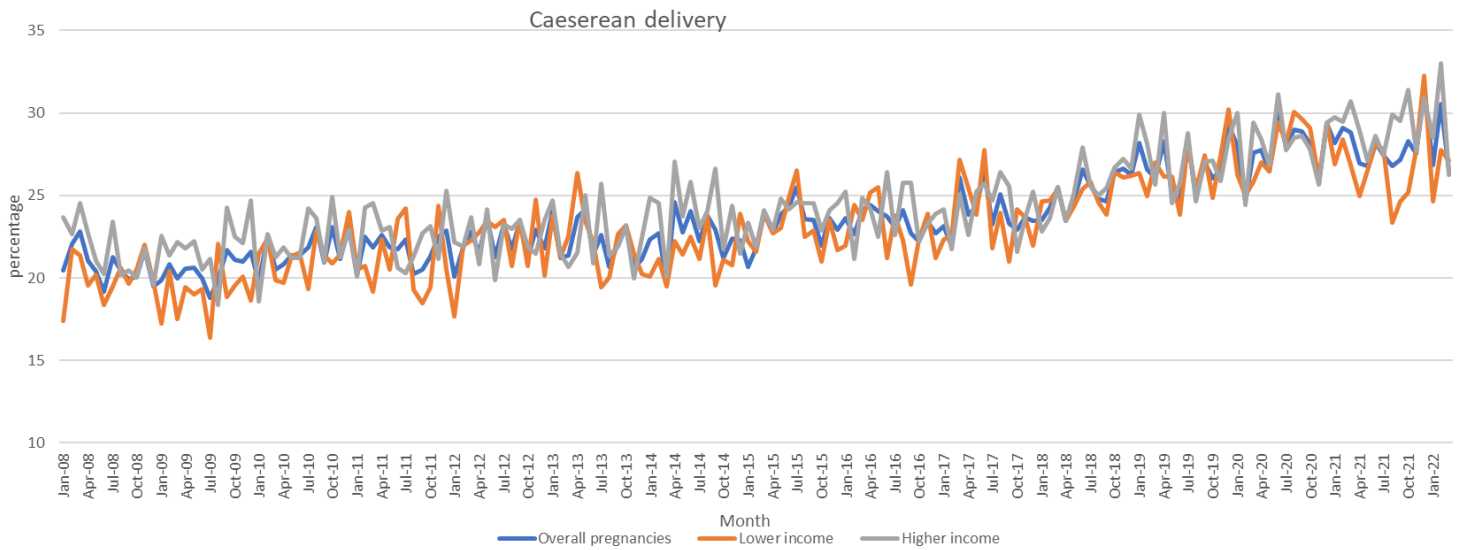
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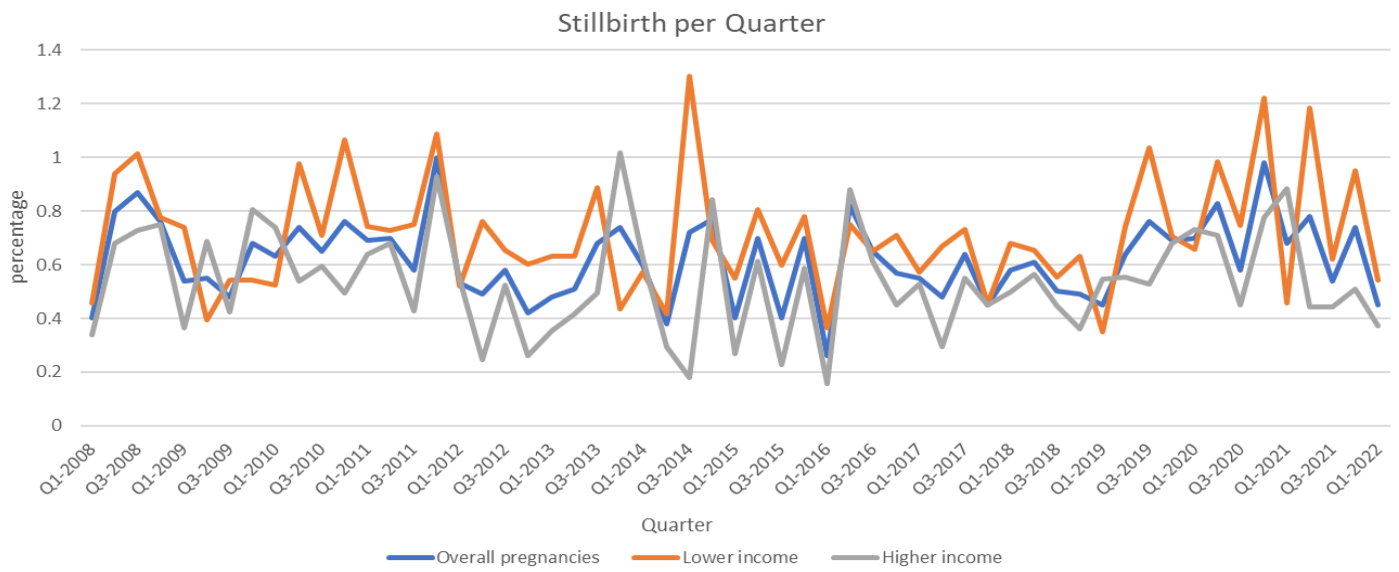
E)



F)



G)



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	59-60
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	60-61
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	61-63
Objectives	3	State specific objectives, including any prespecified hypotheses	63-64
Methods			
Study design	4	Present key elements of study design early in the paper	64
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	64-67
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	65-66
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	65-66
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	65-67
Bias	9	Describe any efforts to address potential sources of bias	66-69
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	67-70
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	67-70
		(b) Describe any methods used to examine subgroups and interactions	67-70
		(c) Explain how missing data were addressed	67-70
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	67-70

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	70
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	70
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	70-74
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	70-74
		(b) Report category boundaries when continuous variables were categorized	70-74
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	70-74
Discussion			
Key results	18	Summarise key results with reference to study objectives	74-75
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	78-79
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	75-78
Generalisability	21	Discuss the generalisability (external validity) of the study results	78-79
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	80-81

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Chapter 3. Trends and Determinants of Inequities in Prenatal Healthcare in the Canadian

Province of Manitoba: A Population-Based Cohort Study (2010–2022)

Aboulatta L, Kowalec K, Lix LM, Tadrous M, Delaney JA, Leong C, Falk J, Alessi-Severini S, Raimondi C, Kearns K, Haidar L, Peymani P, Tan Q, & Eltonsy S. Trends and Determinants of Inequities in Prenatal Healthcare in the Canadian Province of Manitoba: A Population-Based Cohort Study (2010–2022). Manuscript submitted for publication to Paediatric and Perinatal Epidemiology, November 2025

3.1. Overview

Between 2004 and 2009, Manitoba experienced a significant increase in inadequate care, a trend which was associated with underlying social inequalities at both individual and community levels. Population-based studies assessing prenatal care adequacy have been conducted in various settings and using different adequacy indices. This project presents the results of prenatal care utilization among pregnant women in Manitoba using a population-based cohort design and linked administrative databases. The study examined both the frequency of prenatal visits with a threshold of fewer than 5 visits and the adequacy of care using the Revised Graduated Prenatal Care Utilization Index (R-GINDEX). This study provides a comprehensive assessment of longitudinal trends, determinants, and the impact of the COVID-19 pandemic on prenatal care access. The overall trends were stable prior to 2020; however, the onset of the COVID-19 pandemic was associated with an increase in the proportion of women receiving inadequate care and fewer than five visits. Young maternal age, rural residence, lower socioeconomic status, multiparity, and previous healthcare use were associated with a higher risk of both inadequate care and fewer visits.

3.2. Abstract

Background

Adequate prenatal care is essential for optimal maternal and infant health outcomes. Exploring the clinical and demographic factors affecting the adequacy of prenatal care services can help support equitable access. This population-based study characterized trends in prenatal care utilization in Manitoba (2010–2022), with a focus on fewer than five visits (<5 visits) and adequacy of care measured by the Revised Graduated Prenatal Care Utilization Index (R-GINDEX). Determinants of fewer than five visits and R-GINDEX adequacy categories were examined. A secondary objective assessed the impact of COVID-19 pandemic measures on fewer than five visits and R-GINDEX-defined adequacy.

Methods

We conducted a cohort study using province-wide mother-infant-linked administrative health databases from January 2010 to March 2022. Prenatal care adequacy was assessed using the R-GINDEX, which classifies care into 6 mutually exclusive categories: adequate, inadequate, intermediate, intensive, missing and no care. Annual percentages of women receiving <5 visits, and R-GINDEX categories (adequate, intermediate, inadequate or intensive care) were estimated, and trends in these percentages were analyzed using linear regression. Sociodemographic and clinical determinants of <5 visits were examined using multivariable logistic regression, while determinants of adequacy of care were examined using multivariable multinomial logistic regression. The impact of the COVID-19 pandemic measures on fewer than five visits and R-GINDEX categories was evaluated using interrupted time series analyses with generalized linear models.

Results

Among 192,274 pregnancies, 3.9% (n=7,518) had <5 visits. R-GINDEX classification showed that 65,143 (33.9%) received adequate care, 90,732 (47.2%) intermediate, 19,926 (10.4%) inadequate and 15,275 (7.9%) intensive care. The percentage of women who received <5 visits ($p=0.58$) and inadequate care ($p=0.85$) remained stable between January 2010 and January 2020. Determinants of inadequate care included rural residence (aRR=1.42, 95% CI: 1.40-1.45), lower income (aRR=1.41, 95% CI: 1.39- 1.43), and multiparity (aRR=2.46, 95% CI: 2.42-2.50). Women with frequent ambulatory visits (≥ 4 visits) before pregnancy had a 41% lower risk of inadequate care (aRR=0.59, 95% CI: 0.58–0.61). Rural residence, lower income, psychological distress, multiparity, and previous hospital visits were significant determinants of fewer than five visits. During the first year of the COVID-19 pandemic, there was a relative increase in the percentage of women receiving <5 visits by 38.2% ($\beta_{100\%year1}=0.29, p=0.02$), and inadequate care by 2.3% ($\beta_{100\%year1}=0.2, p<0.01$) compared to the pre-pandemic period, while intensive prenatal care increased.

Conclusions

A substantial percentage of Manitoba women received inadequate or intermediate prenatal care, and this percentage increased during the COVID-19 pandemic. Significant inequities persist, with rural residence, lower income, and multiparity representing key barriers to adequate care. Targeted, equity-oriented interventions are warranted to mitigate structural barriers and improve prenatal care access for vulnerable populations, and subsequent studies should evaluate the downstream associations between inadequate care and maternal and neonatal outcomes.

3.3. Introduction

Ensuring high-quality healthcare during pregnancy is essential for improving health outcomes for both mothers and infants. Prenatal care utilization has been identified as a determinant of several maternal and neonatal health outcomes, including preterm birth, stillbirths, low birth weight, and other outcomes that can adversely affect infant development and long-term health(1–3). Regular prenatal visits can provide timely diagnosis and management of maternal health conditions such as gestational diabetes and hypertension, as well as screening and support for mental health concerns, thereby helping to control risk factors associated with pregnancy complications(4–7). Prenatal care should be tailored to the physical and psychosocial needs of the mother and fetus and to the healthcare context of each country. Notably, It is most effective when initiated early in pregnancy and continued at regular intervals to support timely assessment and intervention(8). The Society of Obstetricians and Gynecologists of Canada (SOGC) recommend prenatal care visits every 4–6 weeks early in pregnancy, every 2–3 weeks after 30 weeks, and every 1-2 weeks after 36 weeks of gestation(9). Similarly, the 2016 WHO recommendations shifted from a minimum of four visits to at least eight contacts, starting in the first trimester, with visits spaced across the second and third trimesters(10). Despite these recommendations, many pregnant women either initiate care after the first trimester or receive fewer contacts than recommended, with implications for preventable morbidity. In the United States, for instance, the percentage of women receiving inadequate care, defined either as care initiated during the second trimester or later, or having <50% of the recommended visits based on gestational age, has increased between 2018 and 2023(11). By 2023, approximately one in six U.S. infants (15.7%) was born to a mother receiving inadequate care(11). Studies have shown that inadequate prenatal care is associated

with increased risk of stillbirth, preterm birth, low birthweight and small for gestational age(12–14).

Multiple sociodemographic and geographic factors, such as maternal age, region of residence, marital status, and education, might influence the frequency and adequacy of prenatal care(8,15–23). Additionally, employment status and socioeconomic status, and chronic maternal health conditions have been identified as potential barriers to impact prenatal care visits(8,15–22). Between 2004 and 2009, Manitoba experienced a significant increase in inadequate care from 10.5% to 12.5%, a trend which was associated with underlying social inequalities at both individual and community levels(24). Recently, the COVID-19 pandemic exacerbated pre-existing social and regional disparities and led to limited access to healthcare services, including prenatal care(25,26). This study examined trends in prenatal care utilization among women who gave birth in Manitoba, focusing on: (1) frequency of prenatal visits, using a cutoff of fewer than five visits, and (2) adequacy of care classified by the Revised Graduated Prenatal Care Utilization Index (R-GINDEX categories: inadequate, intermediate, adequate, intensive, missing, or no care). We also investigated maternal clinical and sociodemographic determinants associated with: (1) having <5 visits and (2) adequacy of care (defined by R-GINDEX). As a secondary objective, we examined the impact of the COVID-19 pandemic measures on prenatal visit frequency (<5 visits) and the adequacy of care using R-GINDEX.

3.4. Methods

3.4.1. Study Design and Population

We conducted a population-based cohort study including all pregnant women giving birth, either live birth or stillbirth, in hospitals in the Canadian province of Manitoba from 1 January 2010 to 31 March 2022. Inclusion into the cohort was defined as the delivery date, identified using the delivery procedure code recorded in the hospital discharge abstract database(27,28). We excluded pregnancies ending in miscarriage (pregnancy loss before 20 weeks of gestation), ectopic pregnancies, and pregnancies where no linkage could be made between mother and baby.

3.4.2. Data Sources

We used the Population Research Data Repository hosted at the Manitoba Centre for Health Policy (MCHP), a secure provincial health and administrative database containing de-identified individual-level data for all residents eligible for health services in Manitoba. The reliability and validity of the MCHP Repository for epidemiological research have been well-established in previous studies(29–34). We used multiple linked databases to capture demographic, clinical, and socioeconomic information. Prenatal care visits, maternal age, and comorbidities were obtained from the hospital discharge abstract database, with diagnoses coded using the International Classification of Diseases (ICD) system, Tenth Revision, with Canadian enhancements (ICD-10-CA)(35). Physician billing records from the medical claims database were used to identify prenatal care visits and comorbidities, with diagnoses coded using ICD-9-CM(35). Age and area of residence were obtained from the Manitoba Health Insurance Registry. The

province of Manitoba has five regional health authorities (RHAs), each responsible for delivering healthcare within specific geographic areas based on the address of residents: Winnipeg (including Churchill), Interlake-Eastern, Prairie Mountain, Southern, and Northern. The Drug Program Information Network (DPIN) was used to capture prescription drug dispensations, and Statistics Canada census data provided information on household income used to define area-level income quintiles.

3.4.3. Prenatal Care Outcomes

(1) Frequency of Prenatal Care Visits

Prenatal care visits were defined as visits that occurred either in-person or virtual, between the health care provider and pregnant woman during the pregnancy period until the initiation of labour(36). We used the hospital discharge abstracts and medical claims databases to measure the number of prenatal care visits. Both in-person and virtual visits were identified using tariff codes recorded during gestation. In Manitoba, tariff codes are unique billing codes used within the provincial health insurance system to record physician and other provider services. Each code corresponds to a specific service and associated reimbursement amount, which are reliable and have been used in previous population-based studies to identify healthcare provider services(24,37). The list of tariff codes used to capture prenatal visits is provided in Supplementary **Table S3.1**. Having seven to eleven prenatal care visits in clinical settings is considered standard for low-risk pregnancies(38,39). Thus, we defined fewer than five visits during pregnancy (including both in-person and virtual visits) as a low number of visits. This cut-

off is consistent with previous literature, including Heaman et al. (2012), who developed and used indicators to assess prenatal care and categorized women receiving fewer than five visits within this group(38–42).

(2) Adequacy of prenatal care (R-GINDEX)

Several indices have been used to assess the adequacy of prenatal care utilization, such as the Adequacy of Prenatal Care Utilization (APNCU) index, Kessner Index, and the Revised Graduated Index of Prenatal Care Utilization (R-GINDEX), each using different algorithms to categorize adequacy of care and resulting in varying utilization patterns(43–45). Our study used the Revised Graduated Index of Prenatal Care Utilization (R-GINDEX) to assess the adequacy of prenatal care. R-GINDEX is based on the American College of Obstetricians and Gynecologists recommendations for prenatal visits, demonstrated reliable results, and was used in previous research in Manitoba and Canada(42,46–50). The R-GINDEX classifies utilization based on the month prenatal care began, total number of visits, and gestational age at delivery, yielding six categories: no care, missing, inadequate, intermediate, adequate, and intensive. For example, initiation in months 1–6 with fewer than eight total visits is classified as inadequate, whereas first-trimester initiation with 13–16 visits by 40 weeks' gestation is adequate. Intermediate indicates first 4 months' initiation with 50%–79% of expected visits; intensive reflects a higher-than-expected number of visits and may indicate elevated clinical need. The no care category encompasses pregnancies without recorded visits, recognizing that services delivered by salaried providers, midwives, or nursing stations may not generate fee-for-service claims captured in our data. Missing care is defined as missing information on prenatal care in the database.

3.4.4. Determinants of Fewer than Five Prenatal Visits and Adequacy of Care

The two primary outcomes examined in the determinant analyses were: (1) receiving fewer than five prenatal visits and (2) adequacy of care per R-GINDEX, categorized as inadequate, intermediate or intensive care. Based on the available literature, we examined the following determinants. Maternal age at delivery was categorized as: 19 years or younger, 20–34 years, and 35 years or older. Parity was classified as either primipara (0-1 prior birth) or multipara (>1 prior births)(51), and plurality was defined as singleton or multiple birth. Maternal residence was categorized as urban or rural, according to the geographic classification of the maternal postal code at delivery. As a proxy for maternal socioeconomic status, we used income quintile based on the median household income for Statistics Canada dissemination areas, the smallest geographic unit for which Census data are publicly released. These quintiles were subsequently grouped into three categories: lower income (1st and 2nd quintiles), higher income (3rd to 5th quintiles), and income unknown (for individuals who could not be assigned a neighborhood income quintile)(52). We captured maternal psychological distress defined as any form of diagnosed psychological distress (e.g., anxiety and/or depression) occurring during the eight months before giving birth using ICD-9-CM and ICD-10-CA codes(53). In addition, we assessed pre-existing physical comorbid conditions using validated definitions, including diabetes(54), hypertension(55), and chronic respiratory diseases (including asthma(56) and chronic obstructive pulmonary diseases(57)). For each comorbidity, a pre-specified look-back window before the delivery was applied to ascertain the presence of the diagnosis. Detailed definitions, ICD codes, and time frames used to define these conditions are provided in Supplementary **Table S3.2**. We identified outpatient (i.e., ambulatory) and inpatient healthcare contacts the year before the first

day of pregnancy. Ambulatory visits included the total number of visits to physicians and nurse practitioners. Hospital visits were defined as the total number of inpatient hospitalizations, including day surgeries. For analysis, ambulatory encounters were categorized as 0, 1–3, or ≥ 4 visits; hospital as 0, 1, or ≥ 2 admissions; categories were selected a priori and aligned with the empirical distribution of our data.

3.4.5. Pandemic Measures and Exposure Levels

The first COVID-19 case in Manitoba was reported on March 12, 2020, followed shortly by the declaration of a public health emergency and the introduction of widespread public health measures on social and healthcare services(58,59). These measures included limits on gathering sizes, physical-distancing requirements, lockdowns, modifications to health-care services, and suspension of non-urgent medical care(58,59). To capture the differential exposure lengths to pandemic measures, deliveries were grouped according to the approximate proportion of pregnancy spent under pandemic measures: unexposed (January 2010-March 2020); 25% exposed (April–May 2020); 50% exposed (June–August 2020); 75% exposed (September–November 2020); 100% exposed year 1 (December 2020-March 2021), and 100% exposed year 2 (April 2021-March 2022).

3.4.6. Statistical Analyses

Population Characteristics

Descriptive analyses were conducted for the characteristics of women receiving <5 visits and the four categories of the R-GINDEX: inadequate, intermediate, adequate, and intensive. Pregnancies

with missing (less than 0.05%) and no care (around 0.1%) were excluded from all the analyses, given their rarity.

Trend Analyses of Fewer than Five Prenatal Care Visits and R-GINDEX

We examined the yearly trend in the percentage of women receiving <5 visits and four R-GINDEX categories. The denominator included the total number of pregnancies each year, including live births, stillbirths, multiple births, and singletons. A linear regression model was used to assess linear trends over time from January 2010 to January 2020. Subgroup analyses of the percentage of women receiving <5 visits and four R-GINDEX categories across the five health regions in Manitoba were conducted.

Determinants of Fewer than Five Prenatal Care Visits and Adequacy of Care

A multivariable logistic regression model was used to identify determinants of women receiving <5 visits, with women receiving five or more visits as a reference group. A multivariable multinomial logistic regression model was used to examine the adequacy of prenatal care using the R-GINDEX. In this model, we examined the association between the predictors and women receiving inadequate, intermediate care, or intensive care with those receiving adequate care as reference group. The models included the following predictors: maternal age, residence, income group, parity, plurality, chronic respiratory diseases, epilepsy, hypertension, diabetes, psychological distress, ambulatory, and hospital visits. Adjusted odds ratios with 95% confidence intervals (CI) were calculated for each independent variable. We then derived adjusted relative risks (aRR) with 95% CI using the formula provided by Zhang and Yu(60).

Impact of COVID-19 Pandemic Measures

We conducted interrupted time series (ITS) analysis using generalized linear models, with March 2020 as the intervention point to examine the impact of the COVID-19 pandemic measures on trends of percentage of women receiving <5 visits and prenatal care adequacy (using the R-GINDEX categories). We used monthly percentages of outcomes in the ITS analyses when each month included ≥ 80 events. When monthly counts fell below 80, we aggregated the data into two-month intervals and applied this threshold consistently within each outcome across all time points. This recommended cut-off was applied to ensure that each time point contributed a sufficient number of outcome events to generate stable estimates, reduce random variation, and preserve the statistical power of the ITS models.(61–63) Our models estimated changes in outcomes based on varying lengths of exposure to pandemic measures by including a variable for exposure (6 categories: 0%, 25%, 50%, 75%, 100% year 1 and 100% year 2) and season (fall/winter/spring/summer) to account for a potential seasonality effect. Relative percentage change was calculated as the difference between the average percentage during each pandemic exposure period and the pre-pandemic percentage, expressed relative to the pre-pandemic percentage. The model fit was evaluated using the scaled deviance (deviance divided by the degree of freedom), with a value close to 1 indicating a good model fit. Model fit for ITS analyses using GLM was evaluated using the scaled deviance (deviance divided by the degrees of freedom). However, relying on a single statistic has limitations because scaled deviance primarily reflects overall dispersion and does not assess residual patterns, model misspecification, or the presence of autocorrelation. To further evaluate model assumptions, residual plots and autocorrelation diagnostics were examined to assess whether systematic patterns or serial correlation were

present. We compared the fit of different models using the Bayesian Information Criterion (BIC); the smaller the BIC, the better the fit. A nominal $\alpha = 0.05$ was used to assess statistical significance. All analyses were conducted using SAS software, version 9 (SAS Institute Inc., Cary, NC).

3.5. Results

Population Characteristics

The included study population and outcomes are summarized in **Figure 3.1**. A total of 192,274 pregnant women were examined during the study period (**Table 3.1**). Among women who had <5 visits, the majority were 20-34 years, lived in urban areas, or were in the lower socioeconomic group. By R-GINDEX, 47.2% received intermediate care (n= 90,732) and 10.4% (n= 19,926) received inadequate care; among those with inadequate care, 11.4% were aged ≥ 35 years, 12.6% were aged <20 years, 66.8% were in the lower-income group, and 12.3% had documented maternal psychological distress.

Trends of Fewer than Five Prenatal Care Visits and Adequacy of Care

Between January 2010 and January 2020, the percentage of women with <5 visits was stable (p=0.58). Based on the adequacy of care, the percentage of women who received adequate, intermediate, intensive, or inadequate care was stable during the study period (**Figure 3.1**, **supplementary Table S3.3**). Regional patterns for fewer than five visits and R-GINDEX categories across Manitoba's five health regions are shown in **supplementary Figure S3.1**.

Determinants of Fewer than Five Prenatal Care Visits and Adequacy of Care

Young maternal age (<20 years), multiparity, lower income, and maternal psychological distress were associated with an increased risk of both <5 visits and inadequate care (**Table 3.2**). Women

with frequent ambulatory care (≥ 4 visits) before pregnancy had a 68% lower risk of receiving < 5 visits (aRR= 0.32, 95% CI: 0.30–0.35) and a 41% lower risk of receiving inadequate care (aRR=0.59, 95% CI: 0.58–0.61), compared to those who had no ambulatory visits. In contrast, previous hospital visits were associated with increased risk for both outcomes. Women with one hospital visit had an aRR of 2.38 (95% CI: 2.25–2.52) for < 5 visits, and those with ≥ 2 hospital visits had an aRR of 2.76 (95% CI: 2.52–3.02) compared to pregnant women with no hospital visits. A similar pattern was observed for inadequate care, with increased relative risks in those with a history of hospital visits (**Table 3.2**). Women with maternal psychological distress had 21% higher risks of receiving intensive compared to those receiving adequate care. Determinants of women who received intermediate and intermediate care compared to adequate care are presented in **Supplementary Table S3.4**.

Impact of COVID-19 Pandemic Measures

The pandemic was associated with a 38.2% relative increase among women with < 5 visits exposed to pandemic measures for their entire pregnancies during the first year of the pandemic ($\beta_{100\% \text{ year1}}=0.29$, $p=0.02$; **Figure 3.3, Table 3.3**) compared to the pre-pandemic period. For adequacy of care using R-GINDEX, a 2.1% relative increase in inadequate care among those 75% exposed to pandemic measures followed by a 2.3% relative decrease among those who spent their entire pregnancies during first year of the pandemic ($\beta_{75\% \text{ exposed}}=0.22$; $\beta_{100\% \text{ year1}}=0.20$, both $p<0.01$, respectively) compared to the pre-pandemic period (**Figure 3.3, Table 3.3**). There was an 18.8% relative increase in intermediate care increased among those exposed 50% to pandemic measures ($\beta_{50\% \text{ exposed}}=0.07$, $p<0.01$), this was followed by a 6.2% relative decrease among

pregnancies that spanned the full term during the second year of the pandemic ($\beta_{100\% \text{ year}2} = -0.03$, $p=0.04$) compared to pre-pandemic period (**Figure 3.3, Table 3.3**).

3.6. Discussion

This population-based study showed that 10.4% of Manitoban women received inadequate prenatal care, while 3.9% had fewer than five prenatal visits throughout their pregnancy. Trends in prenatal care utilization were stable during the study period; however, the COVID-19 pandemic was associated with increased percentages of women receiving inadequate care. Young maternal age, living in rural areas, lower socioeconomic status, multiparous women and previous use of health care were associated with a higher risk of both inadequate care and receiving fewer than five visits throughout their pregnancy.

Our findings are consistent with prior Manitoba research (2004/05–2008/09), which documented inequities in prenatal care among younger, lower-income, and multiparous women(24). The previous study included 70,612 deliveries over five fiscal years and used the R-GINDEX to examine the adequacy of care across different geographical regions. That study assessed determinants such as maternal education and smoking/alcohol use that were not available in the present analysis. Our study extends previous work by incorporating preconception health service utilization and examining visit frequency using a <5 visit threshold. Despite Manitoba's universal coverage, the persistence of inequities over a decade indicates upstream system and structural barriers.

A study from Ontario, Canada, reported that 2.1% of pregnant women giving birth at major health care centers received inadequate care, defined as fewer than five visits or initiation

of care in the third trimester(64). Differential adequacy by migration status has also been reported in Ontario, with lower adequacy among government-assisted refugees than privately sponsored refugees(65). According to the Maternity Experience Survey, 18.9% of pregnant women in Canada received inadequate care, with Manitoba reporting a rate of 22.5%(66). In our study, the inadequate care percentage was lower (10.4%), which could be explained by differences in study designs and the index used to measure adequacy of care. The Maternity Experience Survey applied the Adequacy of Prenatal Care Utilization Index (APNCUI), whereas our study used the R-GINDEX. In our study, the percentage of inadequate care was comparable to findings from developed countries such as Southern Spain (16.5%)(67). However, international comparisons require caution because indices, data sources, and health system organization differ.

Several sociodemographic, clinical, structural barriers, and limitations within the healthcare system faced by women could limit their access to receiving the recommended prenatal care visits and adequate care(68,69). Consistent with prior literature, younger age, low income, higher parity, and rural residence were associated with inadequate utilization, highlighting the intersection of socioeconomic and geographic barriers within a publicly funded system(70–77). The persistence of these inequities demonstrates deeper structural challenges in Manitoba within the healthcare system that extend beyond individual factors(78,79). When health systems are strained, inequities widen as individuals with higher socioeconomic status often have the resources or flexible employment arrangements. In contrast, lower socioeconomic women face compounded barriers, exacerbating inequities in prenatal care access(80,81). Moreover, reliance of healthcare systems on outdated communication methods (e.g. busy phone lines and faxes), limited after-hours options, and lack of integrated service navigation may

disproportionately affect women balancing childcare, employment, and other social demands(80).

Healthcare infrastructure gaps in rural and underserved regions exacerbate disparities in access(82,83). Despite universal healthcare coverage, indirect costs such as transportation, time off work, and childcare for other children disproportionately affect low-income women. These economic barriers could explain why income remains a significant determinant within a publicly funded system(81,84). Shi et al. reported that geographic barriers, such as long travel distances and limited transportation options, impose substantial time and financial burdens on pregnant women, which can delay or prevent timely and adequate care(85). A U.S. study found that expanding maternity care clinicians in rural areas significantly increased prenatal visit counts(86). Provider availability and system capacity represent critical but often overlooked determinants of the adequacy of care. Rural physician shortages create capacity constraints affecting rural communities(83,86). Manitoba's health information systems rank among the lowest across Canada in interoperability, meaning women displaced by various circumstances often cannot transfer their prenatal information between providers(87). Limitations in health information interoperability may further impede continuity when care is fragmented across sites and providers, creating barriers to timely, coordinated prenatal care.

Psychological distress was associated with a higher risk of inadequate care in this cohort, consistent with prior Manitoba findings linking psychosocial adversity to lower adequacy(68). In Manitoba, prenatal services such as physiotherapy, psychology, and mental health care remain uninsured or fragmented, forcing women to resort to pharmacological alternatives because evidence-based non-pharmacological options are inaccessible or unaffordable. Integrating these

services into publicly insured perinatal care would address the most common complications of pregnancy, such as depression and anxiety(88).

Manitoba has foundational assets that strengthen access to prenatal care, including the Healthy Baby Prenatal Benefit Program, which has demonstrated improvements in utilization and neonatal outcomes through income supplementation and community supports(89). A 2007 study by Brownell et al. demonstrated the program's effectiveness, with over one-quarter of all mothers giving birth in Manitoba during the study period participating in the program(90). Another study, in 2011, reported that women receiving the prenatal benefit experienced fewer adverse neonatal outcomes and were more likely to breastfeed their infants(91). However, eligible women who were not part of the program were more likely to be younger than 18 years, live in rural areas, have had prior births, and no prenatal visits, highlighting persistent gaps in the program(90). To address these limitations, the Manitoba Government doubled the program's budget in 2024 to expand its reach and improve birth outcomes(92). Our study adds to this evidence by identifying specific sociodemographic and clinical characteristics of women receiving inadequate prenatal care in Manitoba, including the history of healthcare utilization as a key determinant of prenatal care frequency and adequacy. While the Healthy Baby Prenatal Benefit Program represents important policy innovation, the program's focus on financial support, while necessary, does not address structural barriers such as provider availability, transportation, or system navigation(93).

The COVID-19 pandemic revealed existing inequities in Manitoba's prenatal care and highlighted the structural barriers that had long affected women's access to care. During the first 2 years of the COVID-19 pandemic, our analysis showed an increase in the proportion of women

receiving fewer than five prenatal visits and a decline in the adequacy of care, while percentages of women receiving intensive care increased. In response to the COVID-19 pandemic, Manitoba implemented interim prenatal care schedules for low-risk pregnancies to reduce infection transmission by modifying the routine care, limiting in-person visits and transitioning to virtual visits(94). While these adaptations were intended to maintain care during the unprecedented pandemic period, the observed drop in adequacy of care could be attributed to pandemic-related challenges faced by pregnant women. While telehealth improved access for some women, women with limited internet access or lower digital literacy faced additional barriers to virtual care(95–97). This technological inequity likely contributed to the observed increase in inadequate care during the pandemic and suggests that system resilience requires not just alternative service delivery methods, but fundamental redesign to accommodate diverse pregnant women's needs and circumstances(95–97). Additionally, fear of infection and the implementation of public health measures, especially stay-at-home orders, gathering restrictions, and reduced access to family and social support, could have disrupted access to prenatal care and made pre-existing structural barriers more pronounced.

Building an adaptive prenatal capacity that equitably serves all women requires addressing structural determinants across multiple domains(78,79). In Manitoba, expanding midwifery services, aligning remuneration models between physicians and midwives, enabling collaborative care models, and implementing group prenatal care could be solutions to improve access. Developing innovative service delivery models is needed to address the longstanding challenge of travel for birth, especially in underserved communities. Thus, to address the

complex, multi-level barriers of prenatal care, the system should flexibly meet patient needs through integrated teams and locally accessible care.

Strengths of the current study include population-based coverage of all hospital deliveries in Manitoba, linkage across administrative data sources, parallel assessment of visit frequency and R GINDEX adequacy, and incorporation of preconception healthcare services utilization as a determinant. Finally, by pairing a clinically supported <5-visit cutoff with R-GINDEX, the study distinguishes care frequency from adequacy and enables complementary interpretation without conflating frequency with adequacy. Our study has several limitations to be acknowledged. We did not have information on important risk factors for prenatal care adequacy, such as smoking, marital status, and education. We assessed the adequacy of care using the R-GINDEX, one of several available indices. While the R-GINDEX has been used in previous studies and has demonstrated reliable results compared to other indices, it has not been formally validated(46,47). It is strictly a measure of utilization and captures the quantity and timing of prenatal care received and does not reflect the content or clinical adequacy of prenatal care. There is also potential for misclassification due to inaccuracies in gestational age estimations, as we relied on data recorded in hospital abstracts. In our study, the proportion of women recorded as having no prenatal care or with missing care was low, despite having a hospital delivery, which could be due to uncaptured care. For instance, the Medical Services data may not include all relevant prenatal care claims. Some women classified as receiving no care may have been seen by salaried physicians who did not submit billing claims or receive care from midwives or at nursing stations, which are services not captured in Medical Services data or hospital abstracts.

In addition, about 5–6% of births in Manitoba are attended by midwives, and fewer than 1% of births occur at home and were not included in this study (98).

3.7. Conclusions

This study highlights significant inequities in prenatal care in Manitoba, with maternal age, socioeconomic status, area of residence, and previous use of healthcare representing key determinants for inadequate care and fewer than five visits. The COVID-19 pandemic revealed structural barriers, with significant increases in inadequate care. Addressing these disparities presents an opportunity for system-level transformation that targets structural determinants alongside individual-focused interventions to improve prenatal care equity and outcomes, and support care models that are resilient to disruptions.

3.8. Ethical Approval

The study was approved by the University of Manitoba Health Research Ethics Board (HREB #: H2021:063), and access to data was approved by the Provincial Health Research Privacy Committee of Manitoba Health (HIPC #: 2020/2021-33). Informed consent was not required as the data are de-identified.

3.9. Disclaimer

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project # 2020-067 (HIPC # 2020/2021-33). The results and conclusions are those of the authors and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data

Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health. The authors declare no competing interests.

3.10. Data availability

Data cannot be shared publicly because of privacy restrictions. Data are available from the University of Manitoba and MCHP Institutional Data Access/Ethics Committee (contact via <https://umanitoba.ca/manitoba-centre-for-health-policy/>) for researchers who meet the criteria for access to confidential data.

3.11. Author contributions

LA, SE, KK conceptualized and designed the study, drafted the manuscript, carried out the initial analyses and interpretation, reviewed and revised the manuscript. LL, MT, JD, CL, JF, SAS, KK, CR contributed to study conception and design, reviewed and critically revised the manuscript. QT assisted in data acquisition, data analyses, and critically revised the manuscript. PP and LH contributed to the study design, reviewed and critically revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. This work was supported by a research grant from Research Manitoba and funding from the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate Scholarship.

3.12. Tables

Table 3.1. Characteristics of pregnant women included in the study, stratified by frequency of prenatal visits and adequacy of care using R-GINDEX categories.

Characteristics	Frequency of prenatal visits		R-GINDEX ⁺			
	<5 visits	≥5 visits	Adequate	Intermediate	Inadequate	Intensive
Numbers	7,518	184,756	65,143	90,732	19,926	15,275
Age (n, %)						
≤ 19 years	946 (12.6)	9,936 (5.4)	2,147 (3.3)	5,114 (5.6)	2,518 (12.6)	971 (6.4)
20-34 years	5,745 (76.5)	142,667 (77.2)	49,069 (75.3)	71,967 (79.3)	15,133(75.9)	11,321(74.1)
≥35 years	821 (10.9)	32,116 (17.4)	13,918 (21.4)	13,637 (15.0)	2,263 (11.4)	2,978 (19.5)
Residence* (n, %)						
Urban	2,607 (34.8)	104,433 (56.6)	41,957 (64.4)	48,489 (53.5)	7,218 (36.3)	8,819 (57.7)
Rural	4,883 (65.2)	80,254 (43.5)	23,176 (35.6)	42,216 (46.5)	12,657(63.7)	6,454 (42.3)
RHA** (n, %)						
Interlake Eastern	550 (7.3)	16,031 (8.7)	5,272 (8.1)	8,112 (8.9)	1,734 (8.7)	1,360 (8.9)
Northern	2,814 (37.6)	16,783 (9.1)	3,358 (5.2)	7,544 (8.3)	6,288 (31.6)	2,129 (13.9)
Southern	774 (10.3)	33,441 (18.1)	9,786 (15.0)	19,709 (21.7)	2,855 (14.4)	1,715 (11.2)
Prairie Mountain	912 (12.2)	22,951 (12.4)	8,834 (13.6)	10,270 (11.3)	2,266 (11.4)	2,354 (15.4)
Winnipeg	2,440 (32.6)	95,481 (51.7)	37,883 (58.2)	45,070 (49.7)	6,732 (33.9)	7,751 (50.5)
Parity (n, %)						
Primipara	3,049 (40.6)	129,591 (70.2)	50,204 (77.1)	61,734 (68.1)	9620 (48.3)	10,638 (69.7)
Multipara	4,455 (59.4)	55,105 (29.8)	14,937 (22.9)	28,987 (31.9)	10,298(51.7)	4,627 (30.3)
Income (n, %)						
Higher income	2,050 (27.3)	98,840 (53.5)	37,560 (57.7)	48,791 (53.8)	6,492 (32.6)	7,678 (50.3)
Lower income	5,413 (72.0)	85,353 (46.2)	27,430 (42.1)	41,669 (45.9)	13,303(66.8)	7,551 (49.4)
Comorbidities (n, %)						
Hypertension	948 (12.6)	26,024 (14.1)	11,309 (17.4)	10,248 (11.3)	2,191 (11)	3,057 (20)
Diabetes	639 (8.5)	15,915 (8.6)	7,063 (10.8)	5,689 (6.3)	1,449 (7.3)	2,263 (14.8)
Chronic respiratory diseases	3920 (52.1)	113,977 (61.7)	42,735 (65.6)	54,426 (60)	10,199(51.2)	9,859 (64.5)
Psychological distress	1,029 (13.7)	26,946 (14.6)	10,465 (16.1)	12,014 (13.2)	2,458(12.3)	2,890 (18.9)
Epilepsy	35 (0.5)	748 (0.4)	262 (0.4)	350 (0.4)	79 (0.5)	87 (0.6)
Previous Health care utilization						
Hospital visits (n, %)						
0	4646 (61.8)	148,574 (80.4)	54,145 (83.1)	72,876 (80.3)	13,511(67.8)	11,909 (77.9)
1	2247 (29.9)	29,984 (16.2)	9,136 (14.0)	14,899 (16.4)	5,150 (25.9)	2,710 (17.7)
≥2	625 (8.3)	6,198 (3.4)	1,862 (2.9)	2,957 (3.3)	1,265 (6.4)	656 (4.29)
Ambulatory visits (n, %)						
0	2231 (29.7)	29,579 (16)	7,144 (10.9)	15,940 (17.6)	6111 (30.7)	2,185 (14.3)
1 to 3	80 (31.7)	60,614 (32.8)	20,178 (30.9)	31,920 (35.2)	6,317 (31.7)	4,241 (27.8)
≥4	2907 (38.7)	94,536 (51.2)	37,821 (58.1)	42,872 (47.3)	7,498 (37.6)	8,849 (57.9)

*R-GINDEX: Revised Graduated Prenatal Care Utilization Index, which classifies adequacy of prenatal care as inadequate, intermediate, adequate, or intensive care based on the timing and number of visits adjusted for gestational age.

*Residence: urban = Winnipeg/Brandon; rural = all other Manitoba regions, **RHA: Manitoba Regional Health Authorities

Table 3.2. Adjusted Relative Risks and 95% Confidence Intervals for determinants of receiving fewer than five visits and receiving inadequate care.

Determinants	<5 visits ^a		Inadequate care ^b	
	Adjusted RR*	95% CI	Adjusted RR*	95% CI
Age group				
<20 vs. 20 - <35	2.6	2.41-2.81	3.38	3.17-3.61
>35 vs. 20 - <35	0.61	0.57-0.71	0.66	0.63-0.69
Income				
Lower vs. Higher	2.38	2.26-2.51	1.41	1.39-1.43
Parity				
Multi vs. primipara	1.21	1.16-1.27	2.46	2.42-2.50
Plurality				
Multiple births vs singleton	1.04	0.89-1.21	0.27	0.23-0.31
Residence**				
Rural vs Urban	1.79	1.70-1.88	1.42	1.40-1.45
Comorbidities				
Hypertension	0.97	0.90-1.04	0.81	0.77-0.85
Diabetes	0.83	0.77-0.90	0.61	0.58-0.65
Chronic Resp diseases	0.75	0.72-0.79	0.89	0.88-0.90
Psych. Distress	1.09	1.02-1.17	1.12	1.08-1.17
Epilepsy	1.18	0.85-1.65	1.21	0.92-1.57
Previous healthcare utilization				
Hospital visits 1 vs 0	2.38	2.25-2.52	2.08	2.01-2.15
Hospital visits ≥2 vs 0	2.76	2.52-3.02	2.45	2.27-2.64
Ambulatory visits 1-3 vs 0	0.53	0.50-0.57	0.69	0.67-0.71
Ambulatory visits ≥4 vs 0	0.32	0.30-0.35	0.59	0.58-0.61

^a <5 visits: determinants of women who received fewer than five prenatal visits with reference category women who received five or more prenatal visits.

^b Inadequate care: Determinants of women who received inadequate care with reference category women receiving adequate care as categorized by R-GINDEX.

*Adjusted RR: adjusted relative risk

**Residence: urban = Winnipeg/Brandon; rural = all other Manitoba regions

Table 3.3. Interrupted time series analyses examining the impact of pandemic measures on pregnant women receiving <5 visits and R-GINDEX categories by pandemic exposure percentage during pregnancy.

	Changes by exposure percentage ^a														
	25% (Deliveries between April-May 2020)			50% (Deliveries between June-August 2020)			75% (Deliveries between Sep-Nov 2020)			100% Year 1 (Deliveries between Dec2020-March 2021)			100% Year 2 (Deliveries between April 2021-March 2022)		
	Relative% change ^b	β _{25%}	p value	Relative% change ^b	β _{50%}	p value	Relative% change ^b	β _{75%}	p value	Relative% change ^b	β _{100%year1}	p value	Relative% change ^b	β _{100%year2}	p value
<5 visits*	29.2%	0.17	0.07	29.4%	0.19	0.16	27.6%	0.21	0.03	38.2%	0.29	0.02	14.3%	0.1	0.06
R-GINDEX ^c															
Adequate care	-16.7%	-0.18	<0.01	-22.6%	-0.25	<0.01	-22.6%	-0.28	<0.01	-16.9%	-0.17	<0.01	-10.4%	-0.11	<0.01
Intermediate Care	15.1%	0.04	0.15	18.8%	0.07	<0.01	25.8%	0.03	0.2	28.5%	-0.03	0.14	6.2%	-0.03	0.04
Inadequate Care	5.3%	0.13	0.06	7.9%	0.16	0.01	2.1%	0.22	<0.01	-2.3%	0.2	<0.01	-2.3%	0.04	0.21
Intensive care	22.5%	0.24	0.06	25.3%	0.25	0.02	53.4%	0.49	<0.01	50.3%	0.46	<0.01	48.9%	0.44	<0.01

*Interrupted time series analyses for R-GINDEX using monthly percentages, while for <5 visits, the percentages were aggregated every 2 months.

^a Change by exposure percentage to pandemic measures: Exposure 25%: Deliveries between April 2020-May2020, Exposure 50%: Deliveries between June 2020 to August 2020, Exposure 75%: Deliveries between Sep 2020 to Nov 2020, Exposure Year 1 100%: Deliveries between Dec 2020 to March 2021, and Exposure Year 2 100%: Deliveries between April 2021 to March 2022.

^b Relative %change: Calculated as: ((Average % of specified period of exposure – Average % pre-pandemic period)/ Average % pre-pandemic)

^c R-GINDEX: Revised Graduated Prenatal Care Utilization Index. ITS analysis for monthly categories of R-GINDEX.

3.13. Figures

Figure 3.1. Flow chart of the included pregnant women and study outcomes.

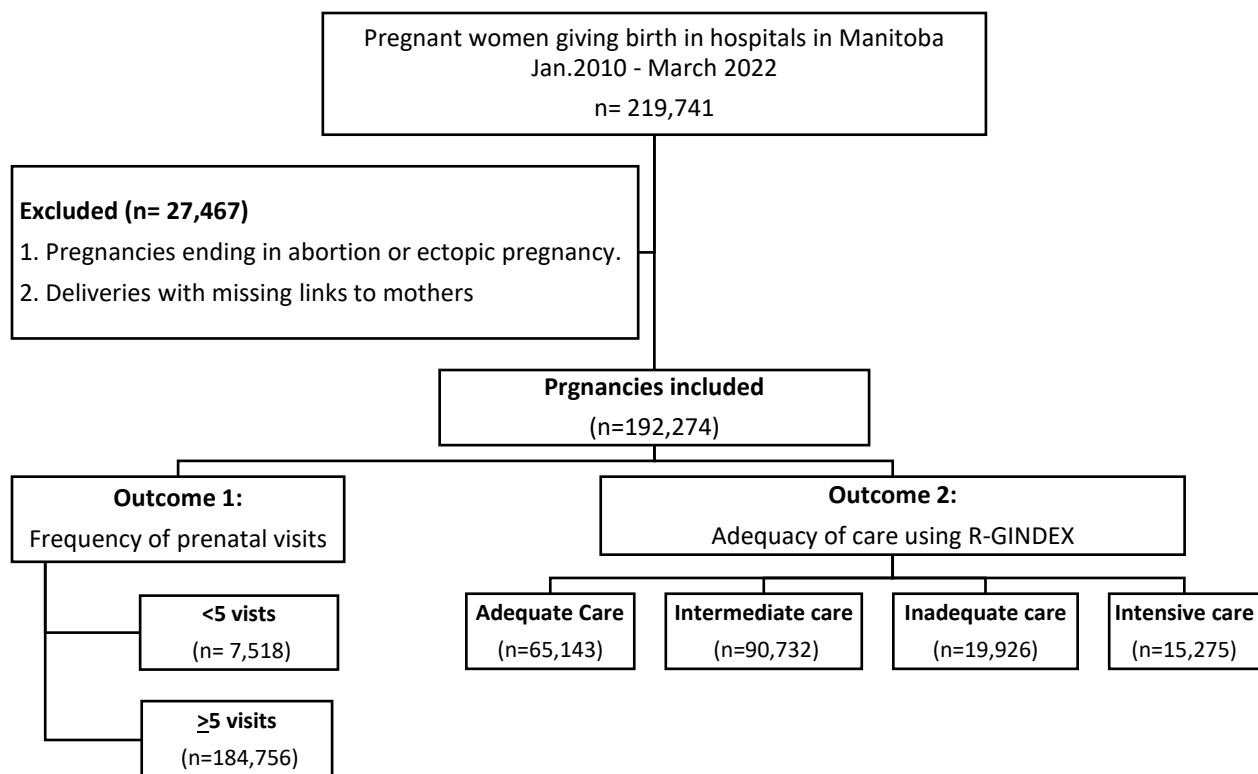
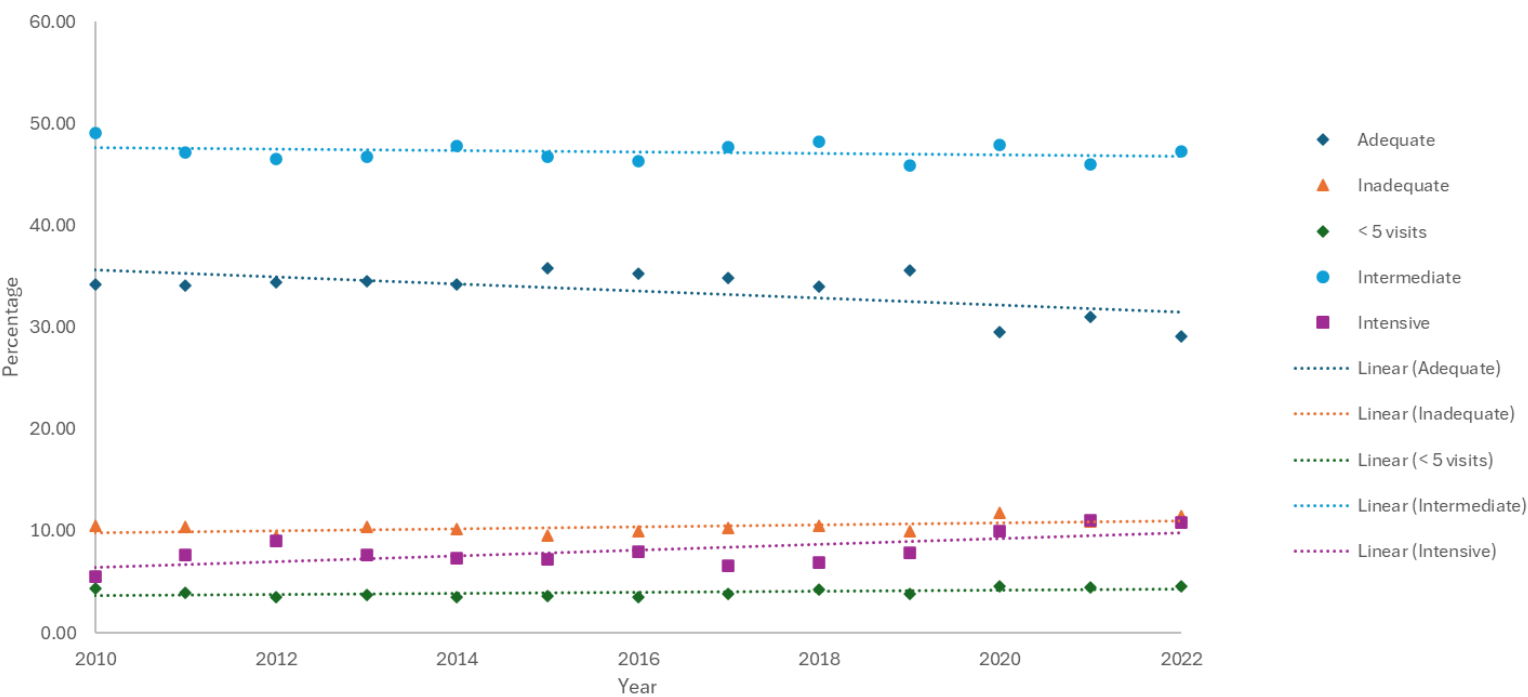
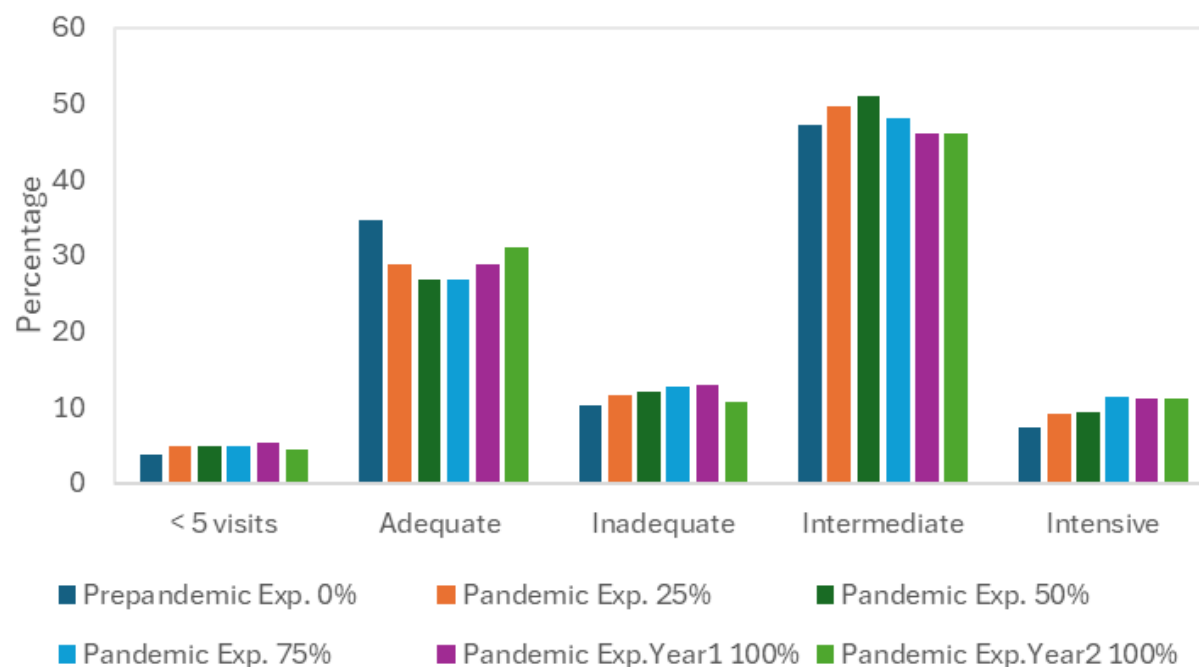


Figure 3.2. Trends in the annual percentage of pregnant women receiving <5 visits and R-GINDEX* categories during the study period.



*R-GINDEX: Revised Graduated Prenatal Care Utilization Index, which classifies adequacy of prenatal care as inadequate, intermediate, adequate, or intensive care based on the timing and number of visits adjusted for gestational age.

Figure 3.3. Percentage of pregnant women receiving <5 visits and R-GINDEX categories by change in exposure percentage during the pandemic measures*



*Change by exposure to pandemic measures: Exposure 25%: Deliveries between April 2020-May2020, Exposure 50%: Deliveries between June 2020 to August 2020, Exposure 75%: Deliveries between Sep 2020 to Nov 2020, Exposure Year 1 100%: Deliveries between Dec 2020 to March 2021, and Exposure Year 2 100%: Deliveries between April 2021 to March 2022.

3.14. Supplementary

Supplementary Table S3.1. Tariff codes to identify prenatal visits among pregnant women in Manitoba.

Category	Tariff Code(s)	Condition
Complete prenatal assessment	8400	-
Subsequent Prenatal visits	8401	-
Ambulatory visits	8501, 8507, 8509, 8529, 8540, 8550	Counted only if paired with pregnancy-related diagnosis (ICD-9-CM 630–679, V22, V23, V28)
Virtual visits	MCHP-defined virtual visit tariff codes (8001, 8005, 8100, 8101, 8321, 8442, 8480, 8481, 8527, 8535, 8478, 8479, 8533, 8655, 8786)	Counted only if paired with pregnancy-related diagnosis codes (ICD-9-CM 630–679, V22, V23, V28), restricted to physician visits during the gestational period.

Supplementary Table S3.2. Maternal comorbidities: Definitions, ICD codes, and look-back windows.

Variable	Definition	ICD Codes
1. Hypertension*	Individuals aged ≥ 19 diagnosed with hypertension within 1 year with any of the following: • ≥ 1 hospitalizations with a diagnosis of hypertension; OR • ≥ 1 physician visits with a diagnosis of hypertension; OR • ≥ 2 prescriptions for hypertension drugs Validated: Sensitivity: 77.5%, Specificity: 93.1%	ICD-9-CM: 401-405 ICD10-CA: I10-I13, I15
2. Diabetes*	Individuals aged ≥ 19 diagnosed with diabetes within 3 years with any of the following: ▪ ≥ 1 hospitalizations with a diagnosis of diabetes, or ▪ ≥ 2 physician visits with a diagnosis of diabetes, or ▪ ≥ 1 prescriptions for medications to treat diabetes. Validated: Sensitivity: 88.4 %, Specificity: 98.8 %	ICD-9-CM: 250 ICD-10-CA: E10-E14
3. Asthma*	Individuals with asthma within 2 years with any of the following: ▪ ≥ 1 physician visits; OR ▪ ≥ 1 hospitalization; OR ▪ ≥ 1 prescriptions for asthma treatment. Validated: Sensitivity: 68.6%, Specificity: 93 %	ICD-9-CM: 493 ICD-10-CA: J45, J46
4. Chronic Obstructive Pulmonary Disease (COPD)	Individuals with one of the following diagnoses: • ≥ 1 hospitalization in one year with a diagnosis of COPD or • ≥ 1 physician visits in one year with a diagnosis of COPD (ICD-9-CM codes as above).	ICD-9-CM: 490, 491, 492, 493, 496; ICD-10-CA: J40-J45

ICD: International Classification of Diseases; **ICD-9-CM:** International Classification of Diseases, Ninth Revision, Clinical Modification; **ICD-10-CA:** International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada.

*Validated definitions: **Source:** [Lix L, Yogendran M MJ. Defining and Validating Chronic Diseases: An Administrative Data Approach. An Update with ICD-10-CA. Manitoba Cent Heal Policy, Univ Manitoba. Published online 2008.](#)

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Supplementary Table S3.3. Linear trend analysis of the percentage of pregnant women receiving <5 Visits and R-GINDEX categories from January 2010 to January 2020.

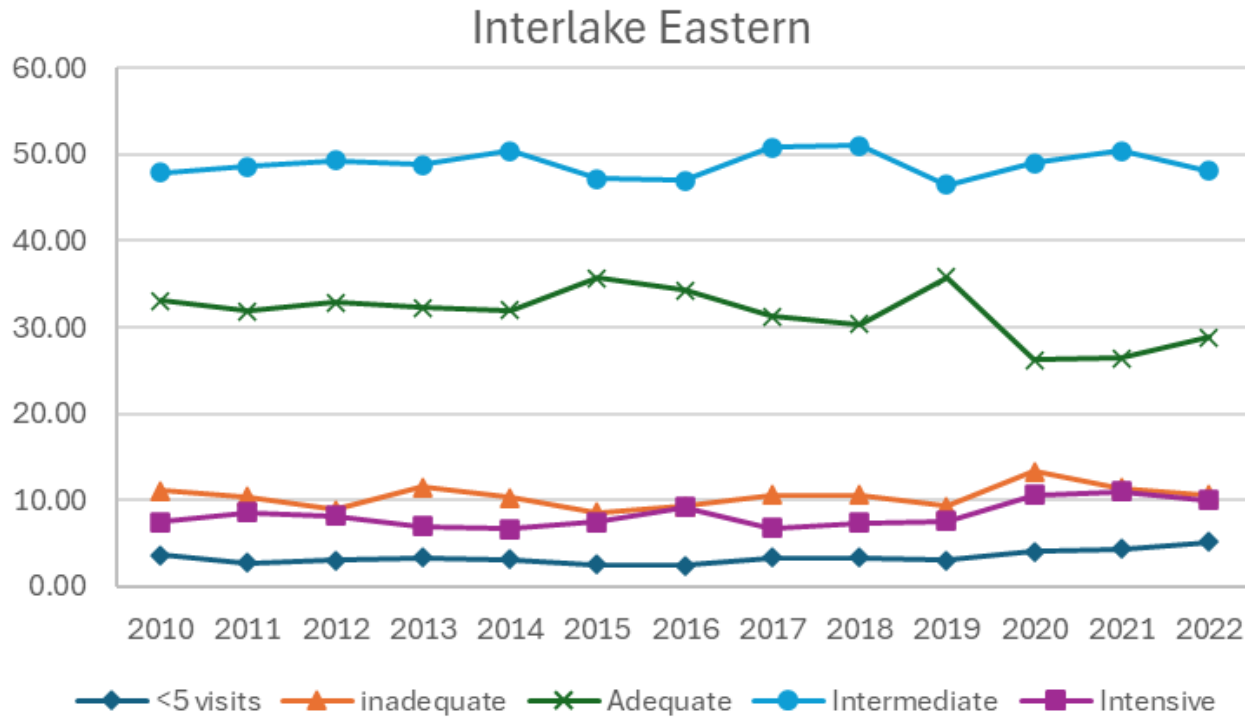
Prenatal care utilization	Parameter estimate	Standard error	p value
<5 visits	-0.02	0.03	0.58
R-GINDEX			
Adequate Care	0.09	0.07	0.23
Intermediate Care	-0.12	0.11	0.32
Inadequate Care	-0.01	0.04	0.85
Intensive Care	0.02	0.11	0.83

Supplementary Table S3.4. Adjusted Relative Risks (RR) and 95% Confidence Intervals (CI) for determinants of intermediate and intensive prenatal care relative to adequate care (R-GINDEX).

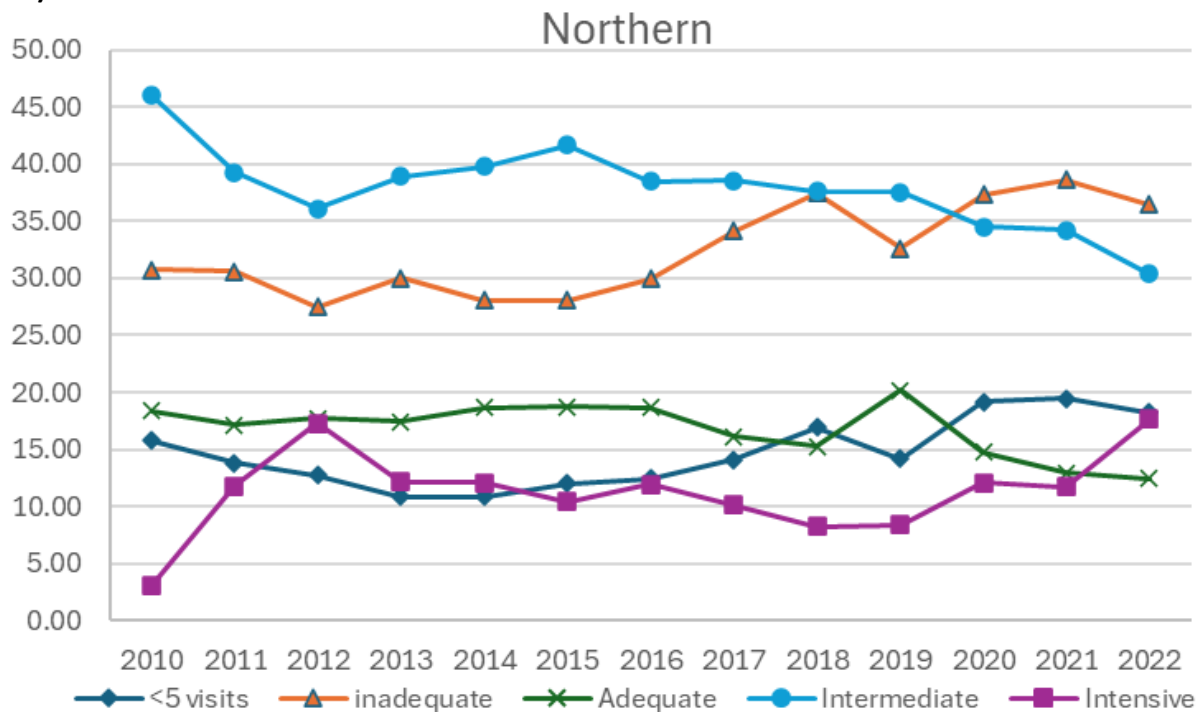
Determinants		Adjusted RR (95% CI)	
		Intermediate Care	Intensive Care
Age group			
	<20 vs. 20 - ≤35	0.79 (0.76–0.81)	0.96 (0.94–0.98)
	>35 vs. 20 - ≤35	1.61 (1.54–1.67)	1.88 (1.77–2.00)
SES			
	Lower vs. Higher	1.04 (1.03–1.05)	1.11 (1.09–1.13)
Parity			
	Multi vs. primipara	1.48 (1.45–1.50)	1.30 (1.26–1.35)
Plurality			
	Multiple births vs singleton	0.35 (0.33–0.38)	1.06 (0.97–1.15)
Residence			
	Rural vs Urban	1.18 (1.17–1.20)	1.11 (1.08–1.14)
Comorbidities			
	Hypertension	0.75 (0.73–0.77)	1.12 (1.08–1.17)
	Diabetes	0.62 (0.60–0.65)	1.29 (1.23–1.35)
	Chronic Resp diseases	0.96 (0.95–0.97)	0.98 (0.97–0.99)
	Psych. Distress	0.96 (0.93–0.98)	1.21 (1.16–1.25)
	Epilepsy	1.08 (0.92–1.27)	1.31 (1.03–1.67)
Previous healthcare utilization			
	Hospitalization 1 vs 0	1.24 (1.20–1.27)	1.24 (1.19–1.29)
	Hospitalization ≥2 vs 0	1.19 (1.12–1.27)	1.33 (1.21–1.45)
	Ambulatory visits 1-3 vs 0	0.91 (0.90–0.92)	0.89 (0.88–0.91)
	Ambulatory visits ≥4 vs 0	0.88 (0.87–0.89)	0.94 (0.92–0.95)

Supplementary Figure S3.1. Trends in the annual percentage of pregnant women receiving <5 visits and R-GINDEX categories during the study period across 5 regions of Manitoba: A) Interlake Eastern, B) Northern, C) Southern, D) Prairie Mountain, and E) Winnipeg.

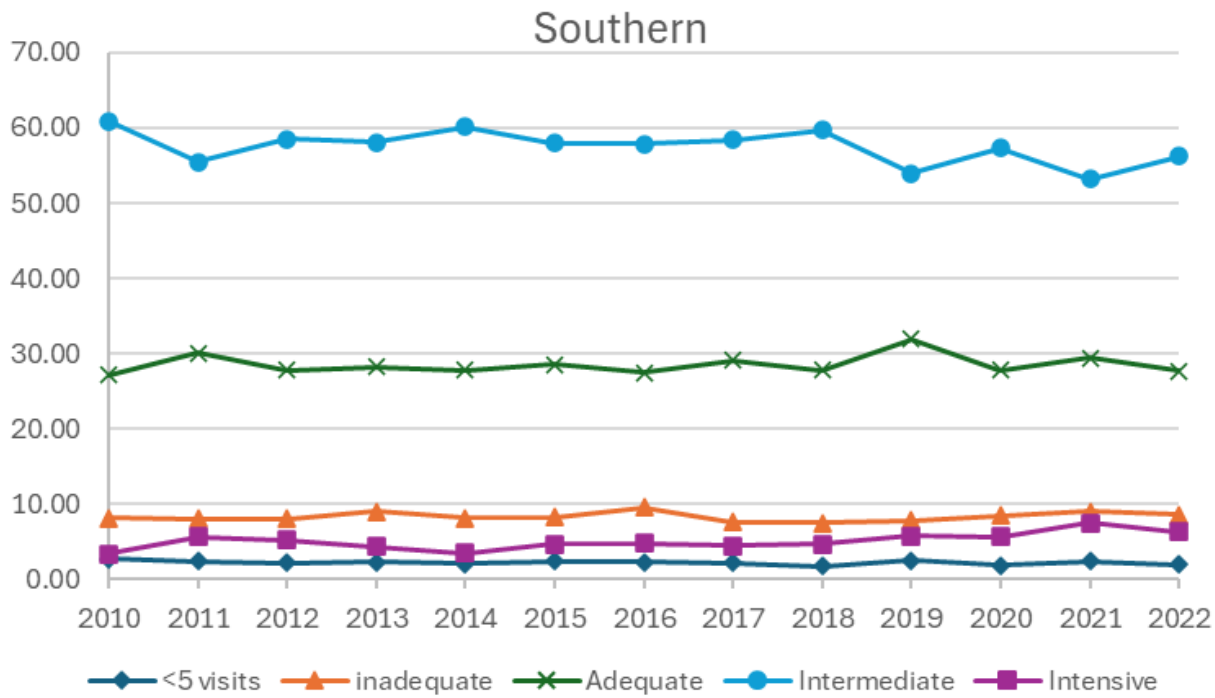
A)



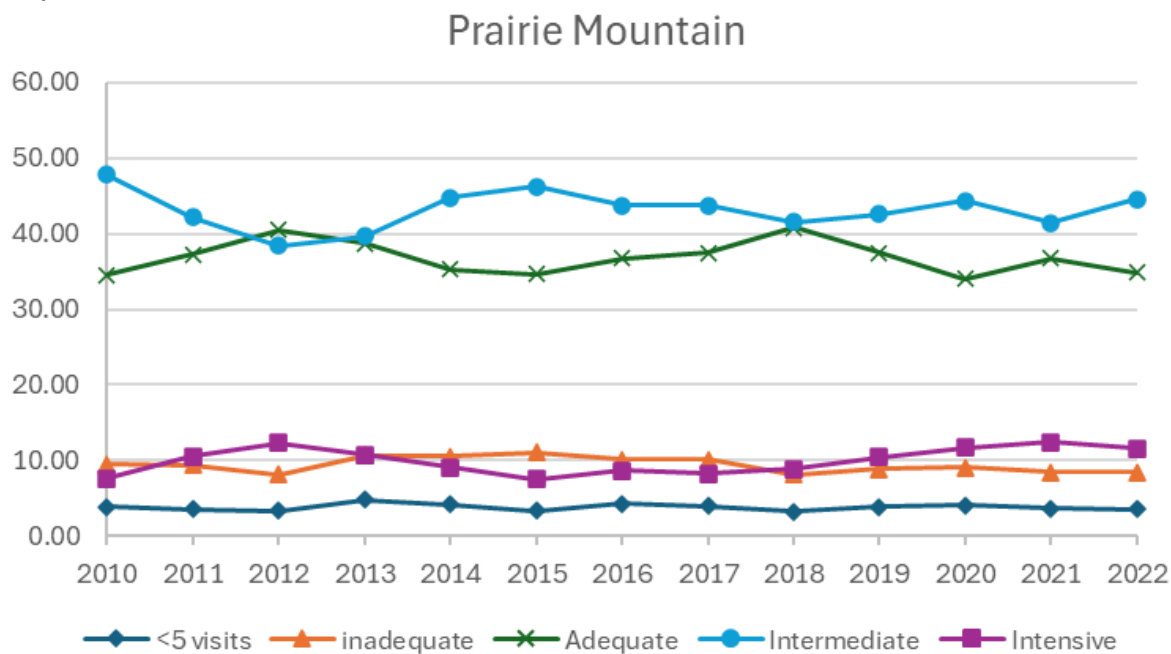
B)

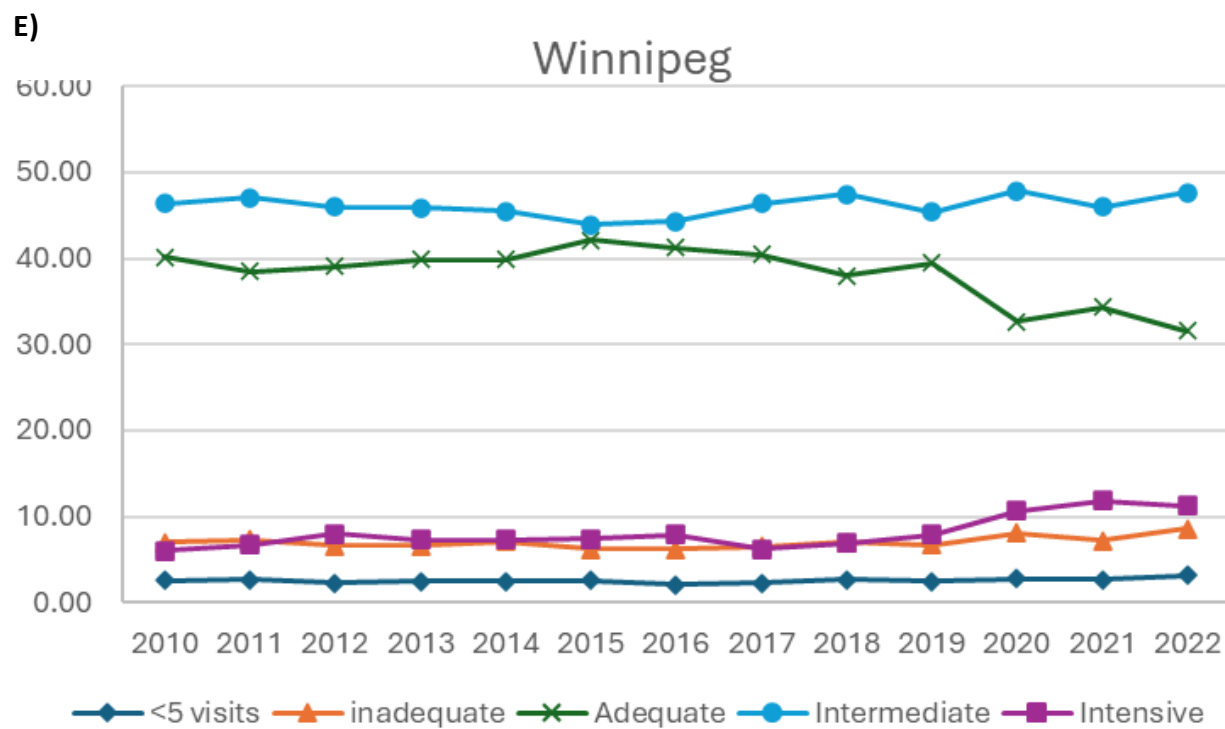


c)



d)





STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	114-115
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	115-116
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	117-118
Objectives	3	State specific objectives, including any prespecified hypotheses	118
Methods			
Study design	4	Present key elements of study design early in the paper	119
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	119-120
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	119-120
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	120-123
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	120-123
Bias	9	Describe any efforts to address potential sources of bias	120-123
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	123-126
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	123-126
		(b) Describe any methods used to examine subgroups and interactions	123-126
		(c) Explain how missing data were addressed	123-126
		(d) If applicable, explain how loss to follow-up was addressed	-

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	126
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	Fig 3.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	126
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	124-125
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	124-125
		(b) Report category boundaries when continuous variables were categorized	126-128
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	126-128
Discussion			
Key results	18	Summarise key results with reference to study objectives	128
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	133-134
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	128-132
Generalisability	21	Discuss the generalisability (external validity) of the study results	133-134
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	134-135

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Chapter 4: Antibiotic Utilization During Pregnancy in Manitoba: A 23-Year Population-Based Study

Aboulatta, L., Kowalec, K., Lix, L. M., Tadrous, M., Delaney, J. A., & Eltonsy, S. Antibiotic utilization during pregnancy in Manitoba: A 23-year population-based study. Manuscript to be submitted to the Journal of Antimicrobial Chemotherapy in March 2026.

4.1. Overview

This study was conducted to examine antibiotic utilization patterns during pregnancy over a 23-year period in Manitoba. Antibiotics are among the most commonly used medications in pregnancy, which are used to treat infections. This project aimed to investigate the overall antibiotic use during pregnancy, classified by trimester, as well as within 90 days before pregnancy and after delivery. This project also examined the impact of the COVID-19 pandemic on antibiotic utilization during pregnancy. We observed a relatively stable trend in antibiotic use over time, followed by a temporary decline after the onset of the COVID-19 pandemic in 2020. Approximately one in three pregnancies were exposed to at least one antibiotic, with β -lactam penicillins remaining the most prescribed antibiotic class throughout the study period.

4.2. Abstract

Background

During pregnancy, women are at a higher risk of infections, and untreated infections can lead to maternal and neonatal complications. Therefore, antibiotics are commonly used in pregnancy. Evaluating patterns of prenatal use is imperative to optimizing prescribing practices among this vulnerable population. This study aimed to examine trends in antibiotic utilization among pregnant women in Manitoba, Canada.

Methods

A population-based cohort study was conducted using linked administrative databases from Manitoba, Canada, to identify all pregnancies from 2000 to 2023. Prescriptions for systemic antibiotics filled during pregnancy were identified and categorized into nine major classes. Annual prevalence and average annual percentage change were estimated, and 95% confidence intervals (CIs) for at least one prescription at any point during pregnancy, by trimester, and in the 90 days before pregnancy and after delivery. Secondly, the potential impact of the COVID-19 pandemic on antibiotic utilization was examined using interrupted time series analysis.

Results

Of 474,054 pregnancies, 33.1% filled at least one antibiotic prescription during pregnancy, with a slight annual increase of 0.19% (95% CI 0.02 to 0.35) over a 23-year period. β -lactam penicillins were the most prescribed class throughout the study period; however, there was a decreasing trend in their use from 2000 to 2023 (Annual Percentage Change (APC) = -0.76% , 95%CI: -1.01 to -0.50). Annual declines were observed for macrolides (APC = -1.39% , 95%CI: -1.74 to -1.04) and sulfonamides and trimethoprim (APC = -4.73% , 95 % CI -4.73 to -3.94). Across different

trimesters, 18% (n=86,393) of women were exposed to antibiotics during the first trimester, 13% (n=62,011) during the second, and 11% (n=52,226) during the third trimester. Across the study period, amoxicillin remained the most prescribed antibiotic during pregnancy and in the 90 days before pregnancy. However, during the 90 days following delivery, cefalexin was the most prescribed antibiotic, accounting for 30% of all pregnancies with an antibiotic prescription by 2023. Immediately after the onset of the COVID-19 pandemic, there was a temporary decline in the overall antibiotic use of 4.6% ($\beta_{\text{immediate change}} = -0.17$, $p < 0.01$), followed by a rebound increase by 0.2% during the 2-year pandemic period ($\beta_{\text{change during pandemic}} < 0.01$, $p = 0.04$).

Conclusions

Antibiotic use during pregnancy in Manitoba remained largely stable from 2000 to 2023, with approximately one in three pregnant women prescribed at least one antibiotic. β -lactam penicillins remained the most prescribed class but showed a gradual decline, while non-penicillin β -lactams increased over the study period. Ongoing research should assess the determinants, safety outcomes, and effects of antimicrobial stewardship initiatives on prescribing in pregnancy.

4.3. Introduction

Pregnant women are at higher risk of severe infections due to their unique physiological and immunological characteristics.(1) In 2017, the World Health Organization (WHO) reported approximately 11.9 million cases of maternal infections, of which 5.7 million women experienced sepsis during or after pregnancy or during childbirth).(2,3) Common infections during pregnancy including urinary tract infections, respiratory tract infections, and sexually transmitted infections(4–7), if untreated, these infections can lead to severe maternal and neonatal morbidity and mortality.(4,8) However, these complications can be prevented through appropriate antibiotic use and adherence to the antimicrobial stewardship framework.(4)

Optimal antibiotic use is challenging as it requires balancing maternal benefits with maximal fetal safety while mitigating infection-related risks to both.(1,9) While some antibiotics, such as penicillin, are known for their safety, others should be carefully considered, weighing their benefits against potential risks to both mother and fetus.(1,9) Evidence on the short- and long-term effects of prenatal antibiotic exposure remains conflicting and varies across outcomes, timing, and frequency of exposure. Few observational studies have reported potential link between prenatal exposure to specific antibiotics and congenital malformations(10,11), neurological development(10), childhood obesity(12,13), and asthma(14,15); however, findings are inconsistent. Since antibiotics are widely used during pregnancy, treatment choices depend on the specific drug and gestational stage, as even small increases in fetal risk can have significant implications for perinatal health. For example, the use of certain macrolides during the first trimester has been associated with an increased risk of major congenital malformations.(10,16)

More than 25% of pregnant women receive antibiotics either during pregnancy or prophylactically during delivery.(17) In a Canadian study of four provinces, nearly two-thirds of pregnant women (61%) were prescribed medications during pregnancy, and among these, 89% of the prescriptions were in the first trimester, and 26% were antibiotics.(18) In Manitoba, the proportion of pregnancies with at least one prescribed medication increased from 62.3% in 2001 to 68.8% in 2013, with amoxicillin, nitrofurantoin, and cefalexin among the most prescribed medications.(19) While previous studies in Manitoba have investigated the overall medication use during pregnancy, the trend of antibiotic use during pregnancy has not been examined. The aim of this study was to examine the trends in antibiotic utilization before, during, and after pregnancy from 2000 to 2023, and stratified by trimester and antibiotic class. A secondary objective assessed the impact of the COVID-19 pandemic on the monthly antibiotic use between March 2017 and March 2023.

4.4. Methods

4.4.1. Study Design and Data Source

This retrospective cohort study used the de-identified, linked administrative health data from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy (MCHP). The Repository contains information for nearly all Manitobans and has been validated and used in health services and pharmacoepidemiological studies.(20–25) The Manitoba Health Insurance Registry provided demographic information, including maternal age and area of residence. Hospital discharge abstracts were used to identify maternal and pregnancy-related

characteristics, such as gestational age, comorbidities, and infections diagnosed during pregnancy, which were coded using the International Classification of Diseases, Tenth Revision, Canadian Enhancement (ICD-10-CA). The physician claims database captured healthcare contacts, comorbidities, and infections diagnosed during pregnancy, coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).(26) Prescription drug data (by Anatomical Therapeutic Chemical (ATC) code) were obtained from the Drug Product Information Network (DPIN), which captures all outpatient prescription dispensations for Manitobans regardless of insurance coverage. However, drugs dispensed during inpatient hospitalizations are not captured in the DPIN database. The Canada census data were used to provide information on neighborhood-level average household income.

4.4.2. Study Population

The cohort included all pregnancies concluding in live births, stillbirths, abortions, or miscarriages in Manitoba from January 1, 2000, to March 31, 2023. Pregnancies were required to have continuous Manitoba health coverage from at least one year prior to conception through 90 days postpartum. Conception date is calculated by subtracting the weeks of gestation at delivery from the infant's date of birth. Pregnancies were excluded if health data were unavailable for the one-year preconception period or the 90-day post-pregnancy interval. Overall, 6.3% of eligible pregnancies were excluded due to incomplete coverage during the required observation windows.

4.4.3. Study Medications and variables

Antibiotic use was defined as at least one prescription filled during the specified exposure windows identified from the DPIN. The exposure window included anytime during pregnancy (from the first day of gestation to the end of pregnancy), and the pregnancy period was divided into three trimesters: first trimester (first day of gestation to the end of week 14), second trimester (weeks 15–25), and third trimester (week 26 to the end of pregnancy). Antibiotic use was also examined during the pre-pregnancy period (defined as 90 days before the first day of gestation) and the post-delivery period (defined as 90 days after delivery). The 90-day window was selected to capture both acute and recurrent antibiotic prescribing and ensure comprehensive ascertainment of antibiotic prescriptions proximal to delivery. All systemic outpatient antibiotics (administration either via oral, IM, IV, or inhalation routes) were identified using the ATC classification index (ATC J01) and were categorized into 9 major groups: β -lactam penicillins, non-penicillin β -lactams, macrolides, lincosamides, sulfonamides and trimethoprim, tetracyclines, fluoroquinolones, aminoglycosides, and other antibiotics. A complete list of included antibiotics and corresponding ATC codes is provided in Supplementary **Table S4.1**.

Characteristics of the study cohort were documented including maternal age at delivery, and maternal income quintile based on the median household income for Statistics Canada dissemination areas, which were categorized as: lower income (1st and 2nd quintiles), higher income (3rd to 5th quintiles), and income unknown (for individuals who could not be assigned a neighborhood income quintile).(27) We also examined residence location, categorized as urban (Winnipeg and Brandon) or rural (all other regions), based on the geographic classification of the maternal postal code at delivery. Parity was classified as either primipara (0-1 prior birth) or

multipara (>1 prior birth)(28) and cesarean delivery was defined using the Canadian Classification of Health Interventions (CCI) code (5MD60), both identified from the hospital abstract database.(29) In addition, we assessed existing comorbidities frequently affecting pregnant women, including diabetes(30), hypertension(31), and asthma(32). For each comorbidity, a pre-specified look-back window before the delivery was applied to ascertain the presence of the comorbid condition (Supplementary **Table S4.2**).

Four common infections during pregnancy that are associated with antibiotic use were studied: respiratory, urinary tract, sexually transmitted, and intestinal infections, based on evidence from previous studies.(4–7) Infection episodes were identified via diagnosis codes from physician claims and hospital discharge data. A 14-day window was applied to define a single infection episode, with repeat diagnoses within 14 days considered the same episode. Definitions and ICD codes used to identify the infections are provided in Supplementary **Table S4.2**.

4.4.4. Statistical Analyses

Descriptive analyses were conducted to compare sociodemographic and clinical characteristics of antibiotic users and non-users during pregnancy.

We calculated the annual prevalence (per 100 pregnancies) and 95% confidence interval (CI) for overall antibiotic use anytime during pregnancy and at each trimester of pregnancy. The prevalence was expressed as the percentage of pregnancies that received at least one antibiotic prescription during the specified window. Annual prevalence by calendar year was estimated for overall antibiotics, by antibiotic class, and by individual antibiotics. We also examined annual prevalence for the ten most commonly used antibiotics during pregnancy, as well as use within

90-day windows before pregnancy and after delivery. The denominator for the top ten antibiotics was the total number of pregnancies with at least one antibiotic prescription during each respective window (pregnancy, pre-pregnancy, or post-delivery).

Infection prevalence was calculated as the percentage of pregnancies with recorded respiratory, urinary, sexually transmitted, or intestinal infection diagnoses per calendar year. The infection was examined descriptively, and we did not link or associate it with antibiotic utilization.

We investigated annual trends in antibiotic utilization from January 2000 to December 2019, which were modelled using a generalized linear model (GLM) with a negative binomial distribution, to examine the pre-pandemic trends.(33,34) A Poisson distribution was first considered; however, the yearly counts of pregnancies with antibiotic prescriptions showed overdispersion, so the negative binomial distribution was more appropriate for modelling the variance and better fit our data. The dependent variable was the yearly count of pregnancies with antibiotic prescriptions, and the independent variable was calendar year treated as a categorical variable. Models were fitted using a log link, and the log of the total number of pregnancies in each calendar year was included as an offset to model annual rates. Model fit was assessed using the scaled deviance, calculated as the deviance divided by the degrees of freedom, where values close to 1 indicate a good fit. Annual percent change (APC) and 95% CIs were derived by exponentiating model coefficients. Trend analyses were conducted for overall antibiotic use and stratified by trimester, 90 days before pregnancy and after delivery, and by antibiotic class.

Secondly, we estimated immediate and delayed changes in monthly antibiotic use following the onset of the COVID-19 pandemic. We conducted interrupted time series analyses (ITS) using

monthly data from March 2017 to March 2023, providing a 3-year pre-intervention baseline and a 3-year pandemic period. A negative binomial GLM was fitted with March 2020 as the intervention point. The ITS model included an indicator variable for the pandemic onset (1=pandemic, 0=pre-pandemic) to examine the immediate change. In addition, a continuous variable for the months during the pandemic (March 2017 to March 2020=0, April 2020=1 to March 2023=36) was included to examine the change during the 3-year pandemic period. Season variable (fall/winter/spring/summer) was included to account for a potential seasonality effect. Model fit was assessed using the deviance-to-degrees-of-freedom ratio, with a value close to 1 indicating a good model fit. Model fit for ITS analyses using GLM was evaluated using the scaled deviance (deviance divided by the degrees of freedom). However, relying on a single statistic has limitations because scaled deviance primarily reflects overall dispersion and does not assess residual patterns, model misspecification, or the presence of autocorrelation. To further evaluate model assumptions, residual plots and autocorrelation diagnostics were examined to assess whether systematic patterns or serial correlation were present.

All analyses were conducted using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA). Statistical significance was defined as a p-value of <0.05.

4.5. Results

Overall, 474,054 pregnancies representing 195,627 women were captured during the study period. At least one antibiotic was prescribed during one third (n=156,791) of pregnancies (**Table 4.1**). Comorbidities were more prevalent among antibiotic users; asthma was nearly twice as common amongst users compared to non-users (11.8% vs. 6.7%). Among pregnant women

who received antibiotics, the most common infections were urinary tract infections (21.7%), followed by sexually transmitted infections (2.8%) and respiratory tract infections (1.2%). (**Table 4.1, Figure S4.1**).

The overall prevalence of pregnancies with at least one antibiotic prescribed remained stable between 2000 and 2019, with a small average annual increase of 0.19% (95% CI 0.02–0.35) (**Table 4.2, Figure 4.1**). β -lactam penicillins were the most prescribed antibiotic class throughout the study period; however, their use decreased from 2000 to 2023 (APC= –0.76%, 95% CI –1.01 to –0.50, **Table 4.2**). Non-penicillin β -lactams prescribed during pregnancy increased from 4.5% in 2000 to 11.2% in 2023, becoming the second most frequently used antibiotic class during pregnancy (APC=3.74%, 95% CI 3.30 to 4.19). In contrast, annual declines were observed for macrolides prescribed during pregnancy (APC=–1.39%, 95% CI –1.74 to –1.04) and sulfonamides and trimethoprim (APC=–4.73%, 95% CI –4.73 to –3.94). Tetracyclines, fluoroquinolones, and lincosamide prescribed during pregnancy accounted for less than 2% of all antibiotics prescribed during pregnancy (**Table 4.2, Figure 4.1**). Supplementary **Table S4.3** illustrates the prevalence of pregnancies with at least one antibiotic prescription 90 days before pregnancy, during pregnancy (by trimester), and 90 days after delivery.

Overall, 18% (n=86,393) of women were exposed to antibiotics during the first trimester, 13% (n=62,011) during the second trimester, and 11% (n=52,226) during the third trimester. **Figure 4.2** illustrates the trends in the percentage of pregnancies that received at least one antibiotic prescription within 90 days before pregnancy, during each trimester, and 90 days post-delivery. There were no significant annual changes across trimesters for antibiotic use (APC = 0.11% for the first trimester; 0.78% for the second trimester; and –0.57% for the third trimester,

Table 4.2). During pregnancy, β -lactam penicillins were most commonly used across all trimesters, peaking at 9% in the first trimester. Non-penicillin β -lactams and macrolides were the second most commonly prescribed antibiotics in the first trimester; macrolide use declined across prenatal period from 3.2% (first trimester) to 1.3% (third trimester). Use of tetracyclines, lincosamide, fluoroquinolones, and sulfonamides/trimethoprim declined throughout pregnancy to under 0.6% in the third trimester (**Figure 4.3**).

The most frequently prescribed antibiotics during pregnancy were amoxicillin, azithromycin, cefalexin and amoxicillin– β -lactamase inhibitor combinations (**Figure 4.4 A**). Across the 24-year study period, amoxicillin remained the most prescribed antibiotic during pregnancy and in the 90 days before pregnancy. In contrast, during the 90 days following pregnancy, cefalexin surpassed amoxicillin to become the most prescribed antibiotic by 2023 (**Figures 4.4 (B) and (C)**). **Table 4.3** summarizes the frequency and percentage of pregnancies with at least one antibiotic prescription across exposure windows, further by medication class and individual antibiotic.

Following the onset of the COVID-19 pandemic, an immediate 4.6% decline in the overall antibiotic use occurred ($\beta_{\text{immediate change}} = -0.17$, $p < 0.01$), followed by a monthly rebound increase of 0.2% ($\beta_{\text{change during pandemic}} = 0.002$, $p = 0.04$) (Supplementary **Table S4.4**).

4.6. Discussion

This population-based study spanning 23 years, including 474,054 pregnancies, found that approximately one in three pregnancies in Manitoba filled at least one antibiotic prescription. Overall antibiotic use remained stable, with a slight annual increase before a temporary decline during the COVID-19 pandemic and a gradual rebound thereafter. Prescribing patterns shifted

over time, with the most commonly prescribed class, the β -lactam penicillins, declining steadily, whereas use of non-penicillin β -lactams more than doubled by 2023. Antibiotic use also differed across trimesters, with the highest use observed during the first trimester.

Our findings showed that rates in Manitoba were stable, consistent with previous research. Broe et al. analyzed nearly one million pregnancies and reported a steady increase in antibiotic use, with more than 38% filling at least one prescription during pregnancy.(35) In addition, the use of systemic antibiotics increased from 28.4% in 2000 to 37.0% in 2010 in Denmark, and was similar in an Italian study.(36) Penicillins were the most frequently prescribed class, and macrolide prescriptions peaked during the second trimester, reaching 5.1% (95% CI 5.0–5.1).(36) In contrast, a French population-based study reported a decreasing trend in antibiotic use during pregnancy, from 38.0% in 2010 to 32.1% in 2019, with trimester-specific prevalence ranging from 16% to 20%.(37) A meta-analysis of 116 studies estimated a pooled global prevalence of 23.6% (95% CI 20.1–27.5) of pregnant women who received antibiotic prescriptions, with regional variation ranging from 34.4% in the Western Pacific to 8.2% in South-East Asia.(38) While these percentages are comparable to our findings, the meta-analysis reported lower percentages than those observed in our study and other large population-based cohorts. In the Americas, antibiotic use was higher in the United States than in Canada (37.4% vs. 26.2%, respectively).(38) Variations in infection epidemiology, sociodemographic factors, obstetric practices, and surveillance methods may explain the observed differences. The current perinatal stewardship literature indicates that reductions in antibiotic exposure are often achievable without measurable harm; however, there is no evidence-based target rate for antibiotic use during pregnancy.(39)

Consistent with our results, a Canadian study by members of our team across four provinces, including Manitoba, reported that antibiotics accounted for 26% of all prenatal medications.(18) Similarly, data from the French Pregnancy Cohort in Quebec showed that antibiotics were the most commonly prescribed medication during pregnancy, accounting for 26% of all prescriptions.(40) In British Columbia, 30.5% of prescriptions filled during pregnancy were antibiotics, with penicillin or penicillin-derived antibiotics most frequently used.(41) In Manitoba, a cohort study observed an increase in the proportion of all prenatal medication prescriptions between 2001 and 2013, with amoxicillin, nitrofurantoin, and cefalexin among the five most prescribed medications.(19) Our findings are similar to results across the Canadian provinces, indicating a consistent national pattern of clinical practice. Although pregnant women are at a higher risk of infections than the general population, and antibiotics are commonly used and clinically appropriate, it is essential to monitor the overall antibiotic use. The rise in antimicrobial resistance and the potential impacts of fetal exposure reinforce the need for optimal prescribing to ensure antibiotics are used when indicated while maintaining maternal and fetal safety.

The overall antibiotic prescribing rates during pregnancy were stable in this study; however, there was a concurrent shift toward broader-spectrum antibiotics (such as amoxicillin–clavulanate, third-generation cephalosporins, or macrolides), while β -lactam penicillins declined steadily over time. This change in prescribing patterns may be attributed to increasing resistance to narrow-spectrum antibiotics, greater reliance on empiric antibiotic prescribing, evolving guidelines, or prescriber preferences.(42–44) However, as we did not examine prescribing indications, we cannot definitively determine the underlying reasons for these trends. Furthermore, our study observed a temporary decline in antibiotic use following the onset of the

COVID-19 pandemic, followed by a rebound increase over the subsequent two years. This pattern parallels trends in the general population in Manitoba(45), suggesting that reduced transmission of common respiratory pathogens and changes in care-seeking behavior may have limited antibiotic prescribing. Because this study did not capture indications or infection types, it remains uncertain whether the COVID-19-related reduction in antibiotic use represented improved stewardship or untreated infections.

There is growing evidence that perinatal antibiotic exposure can disrupt the developing microbiome, promote antimicrobial resistance, and have lasting consequences for fetal health.(46,47) Despite the WHO's 2016 call for global action to address antimicrobial resistance by increasing surveillance and research on antibiotic use, gaps in perinatal antimicrobial stewardship remain.(42) Given the high prevalence of urinary tract infections in pregnancy, emerging resistance to penicillins has intensified efforts to curb inappropriate antibiotic use. Recent evidence from high-risk pregnancies in Korea (2015–2020) showed an increased use of antibiotics and resistant pathogens, which was associated with higher rates of early-onset neonatal sepsis.(48) Therefore, maternal antimicrobial stewardship is required to ensure effective treatment while avoiding unnecessary antibiotic use that increases the risk of infants carrying resistant bacteria.(49)

Canada's national antimicrobial stewardship framework, released in 2014 and implemented provincially in 2017–2018, was reinforced by the 2023 Pan-Canadian Action Plan on Antimicrobial Resistance.(50,51) However, these national efforts did not translate into measurable trend changes in our data. Antibiotic use during pregnancy in Manitoba remained stable, with a slight upward trend, which indicates the limited impact of stewardship on

prescribing during pregnancy. This limited impact could be potentially influenced by variations in implementation across provinces, with Manitoba experiencing limited or a lack of stewardship implementation due to funding limitations and other systemic challenges. Given the shifting resistance patterns and pathogen profiles over time, pregnancy-specific stewardship strategies in Manitoba are needed to optimize antibiotic use in this vulnerable population. Rather than focusing on reducing overall use, optimal antibiotic stewardship in pregnancy is achieved by indication-specific appropriateness, monitoring antibiotic selection and treatment duration, and prioritize narrow-spectrum, pregnancy-safe first-line options, when susceptibility permits, to better define safe thresholds for antibiotic exposure.(39) This approach aims to avoid unnecessary broad-spectrum antibiotic exposure, which can contribute to antimicrobial resistance and may have long-term health effects on the infant. In this study, infections affected approximately 10–12% of pregnant women annually. Although antibiotics are necessary for managing these infections, studies have reported association between prenatal antibiotic exposure and several short- and long-term infant outcomes. (10,10–15) Thus, the optimal use of antibiotics in pregnancy is challenging as it requires balancing maternal benefits with fetal safety.

Over the study period, penicillins and non-penicillin beta-lactams remained the predominant antibiotic classes, consistent with their well-established safety profiles.(39,52) Penicillins are first-line treatment for various infections during pregnancy; thus, appropriate labelling for penicillin allergy is essential.(53) The gradual rise in cephalosporin use, particularly cefalexin, in this study is likely attributed to their safety and suitability for patients with mild penicillin allergy.(54) As part of antimicrobial stewardship in clinical practice, routine penicillin allergy testing is recommended to prevent the use of broad-spectrum antibiotics, which may be

less effective, increase maternal or neonatal adverse effects, and rise in antibiotic-resistant bacteria.(53,55) In the postpartum period, our findings indicate that by 2023, cefalexin had surpassed amoxicillin as the most commonly prescribed antibiotic within 90 days following delivery. This shift may be attributed to its use in managing surgical site and urinary tract infections after childbirth.(54)

Antibiotic classes differ in their associated risks during pregnancy. Several antibiotic classes, including sulfamethoxazole-trimethoprim, tetracyclines, aminoglycosides and fluoroquinolones, are recommended only for restricted use due to well-established fetal risks.(39) Our study indicates that these higher-risk antibiotics were prescribed infrequently, with use declining across trimesters. Thus, there is a need for ongoing monitoring and pregnancy-specific stewardship. Nitrofurantoin showed a modest upward trend in overall use during pregnancy. Within pregnancy, nitrofurantoin use declined from 2.6% in the first trimester to 2.3% in the second and 1.8% in the third trimester. This pattern is consistent with clinical safety recommendations: nitrofurantoin is considered safe for the treatment of urinary tract infections in the first and second trimesters, whereas its use in the third trimester or at term is generally avoided due to the risk of hemolytic anemia in the newborn.(56) Concerns have also been raised about possible associations with congenital anomalies when used in the first trimester.(39) However, recent guidelines continue to recommend nitrofurantoin as a first-line treatment for urinary tract infections in the first and second trimesters, provided the benefits outweigh the risks.(57)

In contrast, sulfamethoxazole-trimethoprim, an antibiotic widely used to treat urinary tract infections, was infrequently prescribed (2.2% overall, 1.4% first trimester) in our study

during pregnancy, consistent with recommendations to avoid during the first and late trimesters due to potential association with birth defects.(39,56) However, for some infections, such as pneumocystis pneumonia, sulfamethoxazole-trimethoprim is considered first-line treatment regardless of pregnancy status. In this case, folic acid supplementation is recommended during the first trimester to reduce the risk of birth defects.(39)

Our data showed that the percentage of tetracycline use during pregnancy is very low, dropping to less than 0.1% in the third trimester, consistent with evidence on their teratogenic risks.(39) Tetracyclines should be avoided during pregnancy and used only for certain infections, such as tick-borne infections, for which doxycycline is the recommended therapy. Aminoglycosides should be avoided throughout pregnancy due to the risk to the fetus, unless the benefits outweigh the risks, such as in the treatment of pyelonephritis.(39) Aminoglycosides are commonly used for severe gram-negative bacterial infections, but are not commonly prescribed in outpatient settings due to the risks of nephrotoxicity and ototoxicity.(39) For these reasons, aminoglycosides were rarely used before and during pregnancy in our study. Fluoroquinolones are broad-spectrum antibiotics used to treat a wide variety of infections, including urinary tract, respiratory tract, gonorrhea, and gastrointestinal infections. However, the prevalence of fluoroquinolone prescriptions during pregnancy was very low, consistent with published data on the safety of these agents. This class should be avoided in pregnant women and used only during pregnancy if no alternatives are available and the benefits outweigh the risks.(39,58)

Macrolides are commonly used in pregnancy to treat respiratory tract infections, skin and soft tissue infections, urethritis, gonorrhea, chlamydial infections, as well as in cases of suspected penicillin allergy.(9,58–60) Concerns over the years about their safety during pregnancy, including

possible associations with major congenital malformations, cardiovascular defects, cerebral palsy, and miscarriage, have led to more cautious prescribing.(10,16,61,62) These concerns were reflected in our data, which showed a decline in overall macrolide use, specifically a decrease in erythromycin use, with an increase in azithromycin. In 2020, updated UK recommendations for prescribing macrolides during pregnancy advised avoiding erythromycin and clarithromycin during the first trimester and recommended azithromycin only if needed, such as for the treatment of gonorrhea or chlamydia.(58)

Our study has several strengths: first, we used a comprehensive provincial database that captures all pregnancies, without restrictions on income, age, drug insurance coverage, or pregnancy outcome, providing complete coverage of Manitobans and improving the study's generalizability. Second, the longitudinal nature of the data allowed examination of long-term trends spanning more than two decades. However, several limitations must be considered. Prescription dispensing may not accurately reflect actual medication use, potentially leading to exposure misclassification.(63) DPIN captures outpatient prescriptions dispensed from community pharmacies but does not capture antibiotics administered during inpatient hospital stays, resulting in incomplete ascertainment of overall antibiotic exposure. This limitation is particularly relevant for third-trimester exposure assessment, as intrapartum antibiotic prophylaxis routinely administered in hospital at the time of delivery and is therefore not captured in DPIN, thus exposure may be systematically underestimated which may introduce non-differential exposure misclassification and could partially explain lower observed dispensing prevalence near term. However, perinatal hospitalizations (without delivery) were relatively uncommon in Manitoba, with 11 per 100 pregnancies in 2008-2009, and any antibiotics

prescribed at discharge are captured in the administrative data.(64) In addition, we did not differentiate between acute and prolonged antibiotic use, nor did we assess treatment duration. The assumption that prescriptions filled within a trimester correspond to use during that period may introduce temporal misclassification. Additionally, the absence of clinical indication data limits the assessment of prescription appropriateness and the ability to differentiate between therapeutic, prophylactic, or empiric uses of antibiotics. While this does not introduce confounding in a utilization study, it substantially constrains interpretation of observed patterns, especially when examining trimester-specific trends and should be taken into account when interpreting prevalence estimates and temporal trends. In addition, comparisons across time periods or settings are further limited by unmeasured variation in infection epidemiology, obstetric practices, care-seeking behaviors, or antimicrobial resistance patterns.

4.7. Conclusions

Our study demonstrates that antibiotic use during pregnancy in Manitoba has remained largely stable for more than two decades, with approximately one in three pregnancies exposed to an antibiotic. A temporary decline in antibiotic prescribing was observed following the onset of the COVID-19 pandemic. While β -lactam penicillins continued as the most prescribed class, their usage steadily decreased, contrasted by a marked increase in non-penicillin β -lactam prescriptions. Future research should focus on elucidating the determinants of antibiotic use in pregnancy and critically evaluate the effectiveness of prenatal stewardship interventions to enhance appropriate antibiotic prescribing and safeguard maternal and infant health.

4.8. Ethical Approval

The study was approved by the University of Manitoba Health Research Ethics Board (HREB #: H2020:411), and access to data was approved by the Provincial Health Research Privacy Committee (PHRPC #: 2020/2021-70). Informed consent was not required as the data are de-identified.

4.9. Acknowledgment and Disclaimer

The authors acknowledge the Manitoba Centre for Health Policy for use of data contained in the Manitoba Population Research Data Repository under project #2020-411 (PHRPC No. 2020/2021-70). The results and conclusions are those of the authors, and no official endorsement by the Manitoba Centre for Health Policy, Manitoba Health, or other data providers is intended or should be inferred. Data used in this study are from the Manitoba Population Research Data Repository housed at the Manitoba Centre for Health Policy, University of Manitoba and were derived from data provided by Manitoba Health.

4.10. Data availability

Data cannot be shared publicly because of privacy restrictions. Data are available from the University of Manitoba and MCHP Institutional Data Access/Ethics Committee (contact via <https://umanitoba.ca/manitoba-centre-for-health-policy/>) for researchers who meet the criteria for access to confidential data.

4.11. Author contributions

LA, SE, KK conceptualized and designed the study, drafted the manuscript, carried out the initial analyses and interpretation, reviewed and revised the manuscript. LL, MT, JD contributed to study conception and design, reviewed and critically revised the manuscript. RD assisted in data

acquisition, data analyses, and critically revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. This work was supported by a research grant from Research Manitoba and funding from the Canadian Institutes of Health Research (CIHR) Vanier Canada Graduate scholarship.

4.12. Tables

Table 4.1. Characteristics of the included population during the study period.

Characteristics*	Antibiotic use during pregnancy	No Antibiotic use during pregnancy
	N= 156,791	N= 317,263
Maternal age , Mean $\pm$ SD	27.09 (6.2)	27.82 (6.2)
Residence^a , N (%)		
Urban	88,189 (56.3%)	189,585 (59.8%)
Rural	68,602 (43.8%)	127,678 (40.2%)
Income , N (%)		
Higher income(Q3-Q5)	74,369 (47.4%)	166,733 (52.6%)
Lower income(Q1-Q2)	81,804 (52.2%)	149,666 (47.2%)
Unknown income	618 (0.4%)	864 (0.3%)
Parity^b , N (%)		
Primipara	40,638 (25.9%)	78,516 (24.8%)
Multipara	75,826 (48.4%)	127,665 (40.2%)
Mode of Delivery , N (%)		
Cesarean deliveries	26,721 (22.8%)	44,368 (21.4%)
Comorbidities , N (%)		
Asthma	18,560 (11.8%)	21,188 (6.7%)
Hypertension	3,887 (2.5%)	5,448 (1.7%)
Diabetes	4,950 (3.2%)	6,538 (2.1%)
Infections , N (%)		
Urinary tract infection	33,948 (21.7%)	6,151 (1.9%)
Sexually transmitted infection	4,311 (2.8%)	3,591 (1.1%)
Intestinal infection	1,331 (0.9%)	1,248 (0.4%)
Respiratory tract infection	1,915 (1.2%)	450 (0.1%)

*Characteristics of included pregnancies at delivery.

^aResidence: urban = Winnipeg/Brandon; rural = all other Manitoba regions

^bParity: Primipara include pregnant women with 0-1 prior birth and multipara include pregnant women with >1 prior births.

Table 4.2. Trend analysis and annual percent change of pregnancies with ≥ 1 antibiotic prescription, overall and stratified by antibiotic class and exposure window (2000–2019).

	Estimate ^a	P-value	Annual Percentage Change ^b	
			%	95% CI
Overall antibiotic use	0.002	0.03	0.19	(0.02 to 0.35)
By class*				
β -lactam penicillin	-0.008	<0.01	-0.76	(-1.01 to -0.50)
Other β -lactams	0.037	<0.01	3.74	(3.30 to 4.19)
Lincosamide	0.055	<0.01	5.69	(4.55 to 6.84)
Macrolides	-0.014	<0.01	-1.39	(-1.74 to -1.04)
Fluoroquinolones	0.012	0.03	1.18	(-0.73 to 3.12)
Sulfonamides	-0.044	<0.01	-4.33	(-4.73 to -3.94)
Tetracyclines	-0.012	0.03	-1.15	(-2.20 to -0.09)
Other classes	0.025	<0.01	2.54	(2.05 to 3.03)
By exposure window				
Pre-pregnancy	-0.010	<0.01	-0.96	(-1.29 to -0.62)
Trimester 1	0.001	0.44	0.11	(-0.18 to 0.40)
Trimester 2	-0.001	0.78	-0.05	(-0.43 to 0.32)
Trimester 3	-0.006	0.03	-0.57	(-1.09 to -0.05)
Post-delivery	-0.015	<0.01	-1.44	(-1.79 to -1.08)

*Aminoglycosides were excluded due to very low counts across multiple years; trends were not estimated for this class.

^aEstimate is the log rate ratio per 1-year change.

^bAnnual Percentage Change calculated as $100 \times [\exp(\text{estimate}) - 1]$.

Table 4.3. Frequency (%) of pregnancies using antibiotics by medication classes.

Antibiotics	No. of pregnancies using antibiotics (%)					
	Pre-pregnancy	During pregnancy	First trimester	Second trimester	Third trimester	Post-delivery
1) β-lactam penicillins						
Ampicillin	70 (<0.1)	615 (0.1)	199 (<0.1)	211 (<0.1)	230 (<0.1)	189 (<0.1)
Amoxicillin	25,976 (5.5)	81,909 (17.3)	38,078 (8.0)	29,555 (6.2)	27,960 (5.9)	27,322 (5.8)
Cloxacillin	2,668 (0.6)	3,950 (0.8)	2,055 (0.4)	1,035 (0.2)	1,010 (0.2)	8,605 (1.8)
Amoxicillin and β -lactamase inhibitor	3,516 (0.7)	6,883 (1.5)	3,484 (0.7)	2,092 (0.4)	1,575 (0.3)	6,569 (1.4)
2) Other β-lactams						
Cefalexin	7,829 (1.7)	30,910 (6.5)	12,177 (2.6)	10,414 (2.2)	11,536 (2.4)	27,291 (5.8)
Cefadroxil	S	S	S	S	S	S
Cefuroxime	795 (0.2)	2,101 (0.4)	884 (0.2)	634 (0.1)	669 (0.1)	1,063 (0.2)
Cefprozil	740 (0.2)	1,273 (0.3)	639 (0.1)	376 (0.1)	307 (0.1)	637 (0.1)
Cefixime	996 (0.2)	2,640 (0.6)	1,305 (0.3)	945 (0.2)	513 (0.1)	991 (0.2)
Aztreonam	S	S	S	S	S	S
3) Lincosamide						
Clindamycin	2,807 (0.6)	4,850 (1.0)	2,609 (0.6)	1,439 (0.3)	1,017 (0.2)	5,567 (1.2)
4) Macrolides						
Erythromycin	3,751 (0.8)	8,852 (1.9)	3,751 (0.8)	2,570 (0.5)	2,302 (0.5)	3,050 (0.6)
Azithromycin	9,843 (2.1)	16,192 (3.4)	8,650 (1.8)	4,831 (1.0)	3,561 (0.8)	7,080 (1.5)
Clarithromycin	3,717 (0.8)	3,525 (0.7)	2,414 (0.5)	814 (0.2)	410 (0.1)	2,254 (0.5)
5) Fluoroquinolones						
Ciprofloxacin	7,264 (1.5)	6,103 (1.3)	4,772 (1.0)	1,137 (0.2)	332 (0.1)	6,812 (1.4)
Norfloxacin	264 (<0.1)	220 (<0.1)	171 (<0.1)	40 (<0.1)	10 (<0.1)	156 (<0.1)
Moxifloxacin	324 (0.1)	237 (<0.1)	194 (<0.1)	36 (<0.1)	9 (<0.1)	193 (<0.1)
Levofloxacin	675 (0.1)	548 (0.1)	434 (0.1)	92 (0.02)	28 (<0.1)	599 (0.1)
6) Sulfonamides and trimethoprim						
Trimethoprim	27 (<0.1)	54 (<0.1)	20 (<0.1)	10 (<0.1)	26 (<0.1)	24 (<0.1)
Sulfamethoxazole and trimethoprim	9,100 (1.9)	10,517 (2.2)	6,702 (1.4)	2,866 (0.6)	1,346 (0.3)	7,783 (1.6)
7) Tetracyclines						
Doxycycline	2,672 (0.6)	2,289 (0.5)	1,536 (0.3)	793 (0.2)	19 (<0.1)	3,929 (0.8)
Tetracycline	661 (0.1)	527 (0.1)	463 (0.1)	87 (<0.1)	9 (<0.1)	428 (0.1)
8) Aminoglycoside						
Other AG	S	S	S	S	S	S
Tobramycin	S	S	S	S	S	S
Amikacin	S	S	S	S	S	S
9) Other classes						
Colistin	S	S	S	S	S	S
Nitrofurantoin	5,842 (1.2)	28,896 (6.1)	12,458 (2.6)	10,945 (2.3)	8,717 (1.8)	5,852 (1.2)
Others	93 (<0.1)	478 (<0.1)	226 (<0.1)	119 (<0.1)	148 (<0.1)	92 (<0.1)
Linezolid	S	S	S	S	S	S
Fosfomycin	S	S	S	S	S	S
Chloramphenicol	S	S	S	S	S	S

S: suppressed. Data are suppressed (not revealed or published) when the number of persons or events involved is five or fewer in order to avoid potential identification of individuals in an area.

4.13. Figures

Figure 4.1. Annual trends in the percentage of pregnancies with at least one antibiotic prescription, overall and by antibiotic class, in Manitoba, 2000–2023.

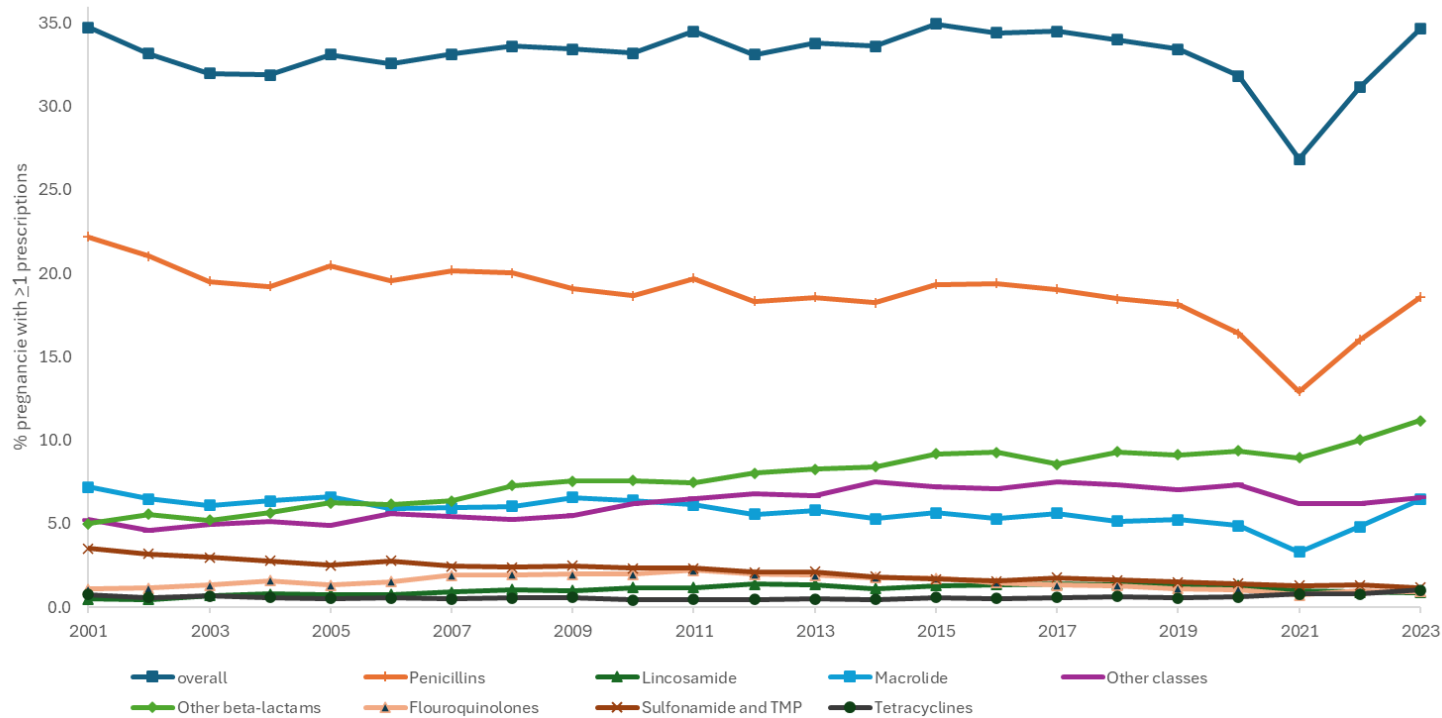


Figure 4.2. Trends in the percentage of pregnancies that received at least one antibiotic prescription within 90 days pre-pregnancy, during each trimester, and 90 days post-delivery.

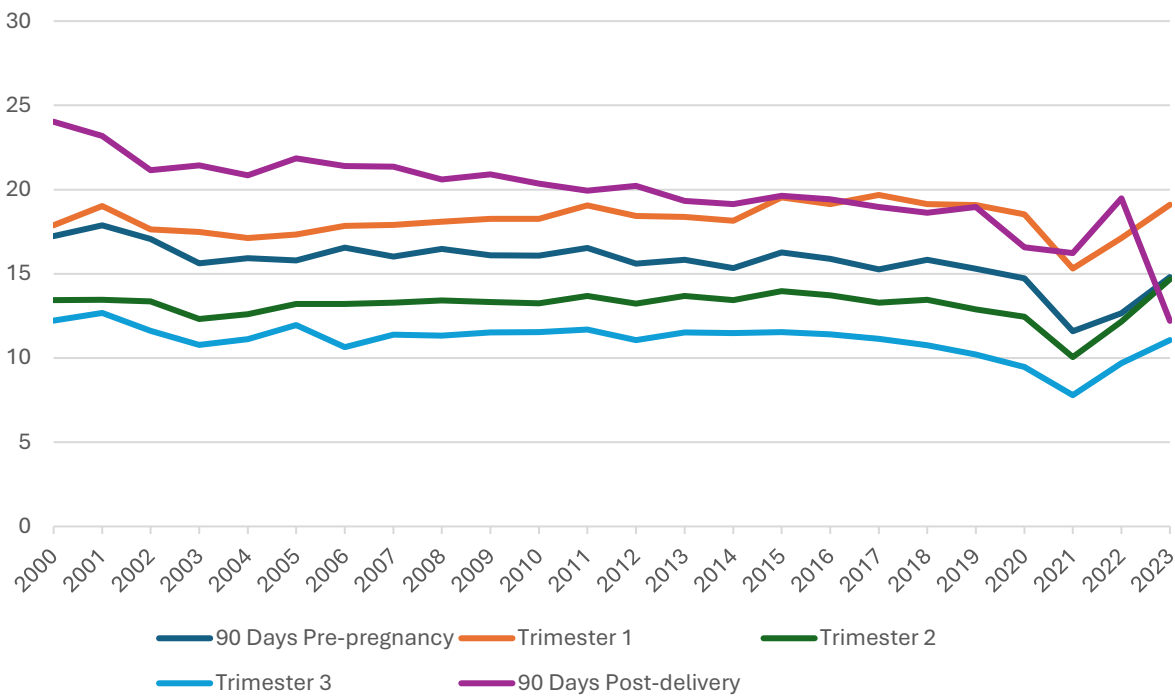


Figure 4.3. Percentage of pregnancies with antibiotic use by class and exposure window (90 days pre-pregnancy, by trimester, and 90 days post-delivery), Manitoba, 2000–2023.

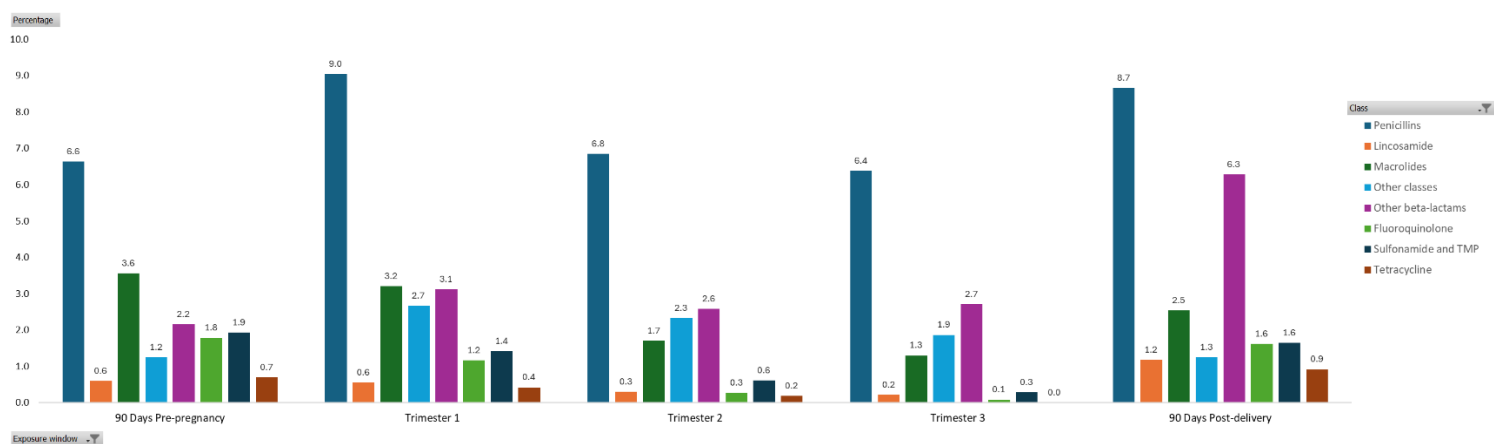
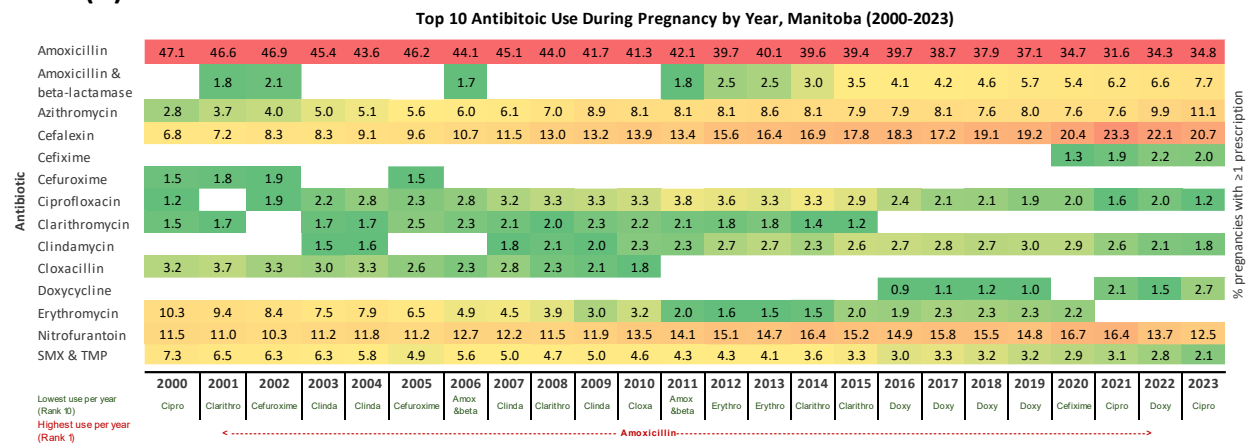
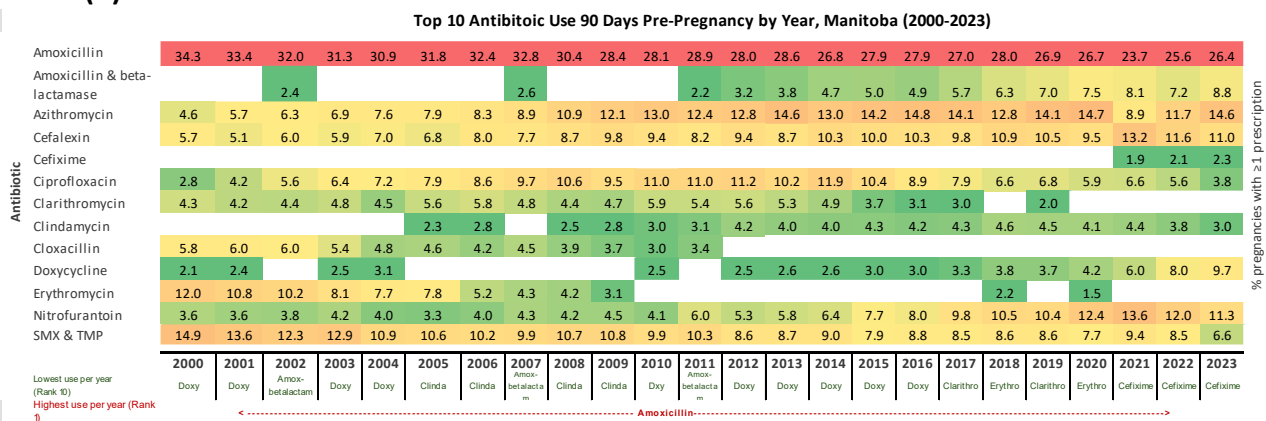


Figure 4.4. Top 10 antibiotic drugs utilization A) During pregnancy, B) 90 days pre-pregnancy, and C) 90 days post-delivery per year in Manitoba (2000-2023).

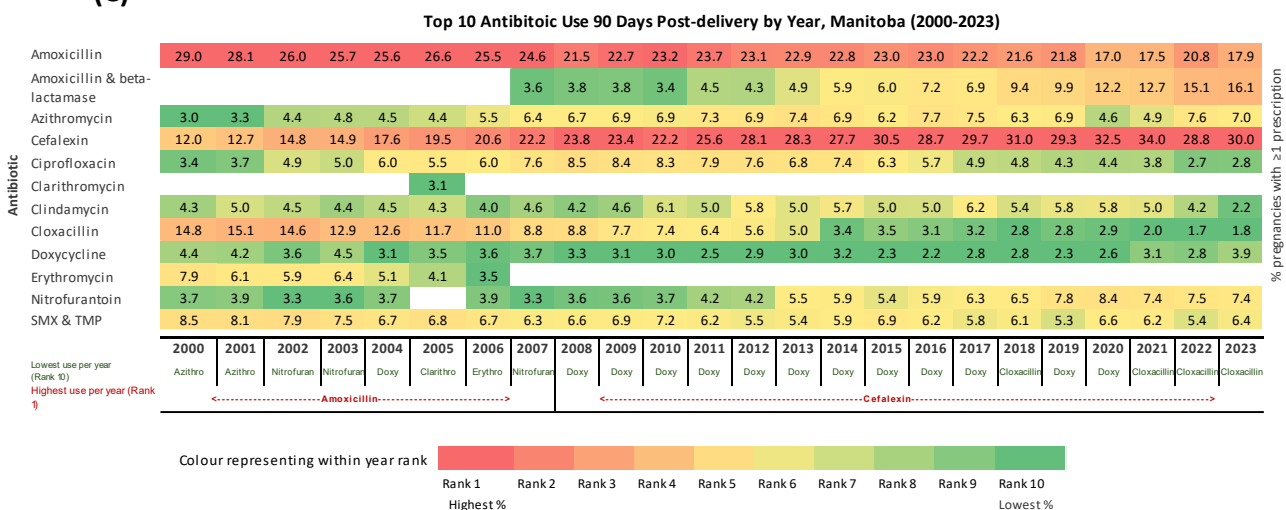
(A)



(B)



(C)



*Ranks calculated for each year

Each column represents one year. *Colours correspond to within-year ranks (red = highest, green = lowest). The bottom panel lists the antibiotics with the highest (Rank 1) and lowest (Rank 10) use for each year.

4.14. Supplementary

Supplementary Table S4.1. Systemic antibiotics and corresponding ATC codes included in the study.

Systemic antibiotics	ATC codes
1) β-lactam penicillins	J01C
Ampicillin	J01CA01
Amoxicillin	J01CA04
Pivmecillinam	J01CA08
Cloxacillin	J01CF02
Amoxicillin and beta-lactamase inhibitor	J01CR02
2) Other β-lactams	J01D
Cefalexin	J01DB01
Cefadroxil	J01DB05
Cefuroxime	J01DC02
Cefprozil	J01DC10
Cefixime	J01DD08
Aztreonam	J01DF01
3) Lincosamide	J01FF
Clindamycin	J01FF01
4) Macrolides	J01FA
Erythromycin	J01FA01
Azithromycin	J01FA10
Clarithromycin	J01FA09
5) Fluoroquinolone	J01M
Ciprofloxacin	J01MA02
Norfloxacin	J01MA06
Moxifloxacin	J01MA14
Levofloxacin	J01MA12
6) Sulfonamides and trimethoprim	J01E
Trimethoprim	J01EA01
Sulfamethoxazole and trimethoprim	J01EE01
7) Tetracyclines	J01A
Doxycycline	J01AA02
Tetracycline	J01AA07
8) Aminoglycoside	J01G
Other AG	J01GB
Tobramycin	J01GB01
Amikacin	J01GB06
9) Other classes	J01X
Nitrofurantoin	J01XE01
Others	J01XX
Linezolid	J01XX08
Fosfomicin	J01XX01
Amphenicols	J01BA
Chloramphenicol	J01BA01

Supplementary Table S4.2. Definitions and ICD codes for existing comorbidities and infections.

Condition	Definitions/ICD Codes
Infections	
Intestinal Infectious	ICD-10-CM: A00–A09 ICD-9-CM: 001–009
Respiratory Infections ^a	ICD-9-CM: 480–486 ICD-10-CM: J12–J18
Sexually Transmitted Infections (STIs) ^b	ICD-10-CM: A50–A64 (infections with a predominantly sexual mode of transmission) ICD-9-CM: 090–099 (syphilis and other venereal diseases); V01.6 (contact or exposure to venereal diseases)
Urinary Tract Infections (UTIs) ^c	ICD-10-CM: N39.0 ICD-9-CM: 599.0 (unspecified urinary tract infection) <i>NB: Before 2015, ICD-9-CM 599 was used from medical claims database due to the absence of 4 digits codes.</i>
Comorbidities	
Asthma ^d	Definition: Individuals diagnosed with asthma within 2 years based on any of the following criteria: • >1 physician visit; OR • >1 hospitalization; OR • >1 prescription for asthma treatment. Validation: Sensitivity = 68.6%, Specificity = 93.0%. ICD-9-CM: 493 ICD-10-CA: J45, J46
Diabetes ^e	Definition: Individuals aged >19 years diagnosed with diabetes within 3 years based on any of the following criteria: • >1 hospitalization with a diagnosis of diabetes; OR • >2 physician visits with a diagnosis of diabetes; OR • >1 prescription for diabetes medication. Validation: Sensitivity = 88.4%, Specificity = 98.8%. ICD-9-CM: 250 ICD-10-CA: E10–E14
Hypertension ^f	Definition: Individuals aged >19 years diagnosed with hypertension within 1 year based on any of the following criteria: • >1 hospitalization with a diagnosis of hypertension; OR • >1 physician visit with a diagnosis of hypertension; OR • >2 prescriptions for antihypertensive medications. Validation: Sensitivity = 77.5%, Specificity = 93.1%. ICD-9-CM: 401–405 ICD-10-CA: I10–I13, I15

ICD: International Classification of Diseases; **ICD-9-CM:** International Classification of Diseases, Ninth Revision, Clinical Modification; **ICD-10-CA:** International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada.

*Validated definitions: **Source:** [Lix L, Yogendran M MJ. Defining and Validating Chronic Diseases: An Administrative Data Approach. An Update with ICD-10-CA. Manitoba Cent Heal Policy, Univ Manitoba. Published online 2008.](#)

^a**Respiratory Infections:** Systematic review: specificity >90% and sensitivity <80%.

Hanquet G, Theilacker C, Vietri J, et al. Best Practices for Identifying Hospitalized Lower Respiratory Tract Infections Using Administrative Data: A Systematic Literature Review of Validation Studies. *Infect Dis Ther*. 2024;13(4):921-940. doi:10.1007/s40121-024-00949-8

^b**Sexually Transmitted Infections:** Positive predictive value for using ICD-9 codes alone to identify clinical pelvic inflammatory diseases was 79%. The positive predictive values for chlamydia, gonorrhea, and unspecified STI ICD-10-CM codes were 87.6%, 85.0%, and 32.0%. Sensitivities were low for chlamydia and gonorrhea.

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^c**Urinary Tract Infections:** ICD-9 and ICD-10 diagnoses codes validation: Positive predictive value 85% (95% CI 81.1–88.2%)

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^dTerm: Asthma | MCHP Concept Dictionary and Glossary for Population-Based Research | Max Rady College of Medicine | University of Manitoba.

<http://mchpappserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=102278>.

^eTerm: Diabetes - Measuring Prevalence | MCHP Concept Dictionary and Glossary for Population-Based Research | Max Rady College of Medicine | University of Manitoba.

<http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1085>.

^fTerm: Hypertension Prevalence | MCHP Concept Dictionary and Glossary for Population-Based Research | Max Rady College of Medicine | University of Manitoba.

<http://mchp-appserv.cpe.umanitoba.ca/viewDefinition.php?definitionID=104903>.

Supplementary Table S4.3. Prevalence of pregnancies with at least one antibiotic prescription 90 days before pregnancy, during Pregnancy (by trimester), and 90 days after delivery, 2000–2023.

Year	Pre-pregnancy Percentage (95% CI)	First trimester Percentage (95% CI)	Second trimester Percentage (95% CI)	Third trimester Percentage (95% CI)	Post-delivery Percentage (95% CI)
2000	17.23 (16.64–17.83)	17.88 (17.29–18.50)	13.44 (12.92–13.97)	12.23 (11.74–12.74)	24.02 (23.33–24.74)
2001	17.87 (17.28–18.49)	19.03 (18.41–19.67)	13.46 (12.95–14.00)	12.68 (12.17–13.20)	23.18 (22.50–23.88)
2002	17.06 (16.47–17.67)	17.64 (17.04–18.26)	13.35 (12.83–13.89)	11.60 (11.12–12.11)	21.14 (20.49–21.82)
2003	15.63 (15.07–16.20)	17.48 (16.89–18.09)	12.31 (11.82–12.83)	10.78 (10.32–11.26)	21.44 (20.79–22.11)
2004	15.92 (15.35–16.52)	17.13 (16.53–17.74)	12.59 (12.08–13.12)	11.11 (10.63–11.61)	20.84 (20.18–21.52)
2005	15.80 (15.22–16.39)	17.33 (16.73–17.96)	13.21 (12.68–13.75)	11.95 (11.45–12.47)	21.86 (21.18–22.56)
2006	16.56 (15.99–17.14)	17.84 (17.25–18.45)	13.21 (12.71–13.73)	10.65 (10.20–11.12)	21.40 (20.76–22.07)
2007	16.02 (15.47–16.58)	17.90 (17.32–18.49)	13.28 (12.79–13.80)	11.39 (10.93–11.87)	21.35 (20.72–22.00)
2008	16.47 (15.92–17.04)	18.08 (17.51–18.68)	13.41 (12.92–13.93)	11.33 (10.88–11.81)	20.61 (19.99–21.24)
2009	16.10 (15.56–16.65)	18.27 (17.70–18.86)	13.33 (12.84–13.83)	11.51 (11.06–11.98)	20.90 (20.28–21.53)
2010	16.08 (15.55–16.64)	18.26 (17.68–18.85)	13.24 (12.76–13.75)	11.54 (11.08–12.01)	20.36 (19.75–20.99)
2011	16.53 (15.99–17.09)	19.05 (18.47–19.65)	13.68 (13.18–14.19)	11.69 (11.24–12.16)	19.93 (19.33–20.55)
2012	15.61 (15.09–16.15)	18.44 (17.87–19.03)	13.23 (12.75–13.72)	11.07 (10.63–11.52)	20.22 (19.62–20.83)
2013	15.83 (15.31–16.38)	18.37 (17.80–18.95)	13.69 (13.20–14.20)	11.51 (11.07–11.98)	19.32 (18.74–19.92)
2014	15.34 (14.83–15.87)	18.14 (17.58–18.72)	13.44 (12.96–13.94)	11.48 (11.03–11.94)	19.14 (18.56–19.73)
2015	16.26 (15.73–16.81)	19.53 (18.95–20.14)	13.97 (13.47–14.48)	11.54 (11.09–12.01)	19.64 (19.05–20.24)
2016	15.88 (15.35–16.43)	19.13 (18.54–19.73)	13.73 (13.24–14.24)	11.40 (10.95–11.87)	19.42 (18.83–20.03)
2017	15.26 (14.74–15.80)	19.68 (19.09–20.29)	13.28 (12.79–13.78)	11.14 (10.69–11.60)	18.96 (18.38–19.56)
2018	15.83 (15.30–16.37)	19.14 (18.56–19.73)	13.46 (12.98–13.96)	10.76 (10.33–11.21)	18.61 (18.04–19.20)
2019	15.31 (14.79–15.84)	19.07 (18.50–19.67)	12.88 (12.41–13.37)	10.20 (9.78–10.64)	18.97 (18.39–19.56)
2020	14.73(14.21–15.26)	18.52(17.95–19.12)	12.45 (11.98–12.94)	9.47 (9.06–9.90)	16.57 (16.02–17.13)
2021	11.59 (11.13–12.06)	15.31 (14.79–15.86)	10.05 (9.63–10.50)	7.79 (7.42–8.18)	16.24 (15.69–16.80)
2022	12.65 (12.16–13.16)	17.12 (16.55–17.71)	12.16 (11.68–12.66)	9.69 (9.26–10.13)	19.47 (18.87–20.10)
2023	14.80 (13.73–15.96)	19.10 (17.88–20.41)	14.67 (13.60–15.82)	11.07 (10.15–12.08)	12.21 (11.23–13.26)

Supplementary Table S4.4. Interrupted time series analyses for antibiotic monthly utilization before and during the pandemic periods in the Canadian province of Manitoba (March 2017–March 2023).

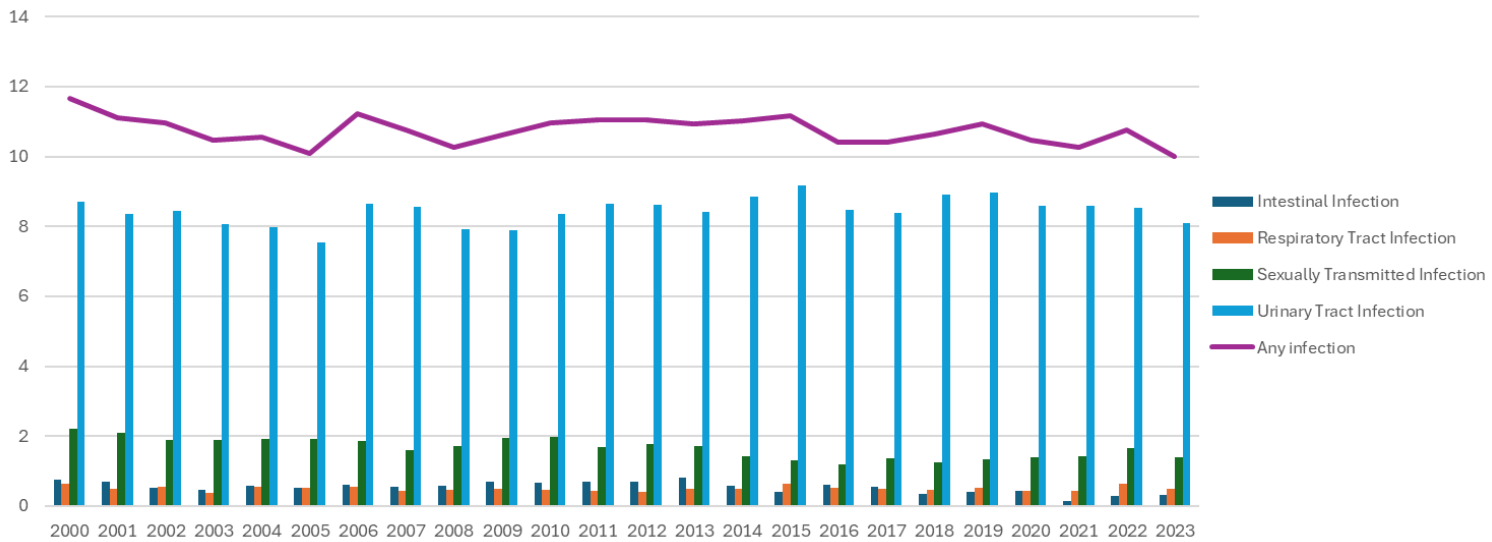
Systemic antibiotic*	Immediate level change ^a		Change in trend estimate during the pandemic vs. before pandemic ^b	
	Estimate	p-Value	Estimate	p-Value
Overall	−0.168	<0.001	0.002	0.04
β-lactam Penicillins	−0.266	<0.001	−0.011	0.034
Other β-lactams	−0.005	0.119	0.005	<0.001
Macrolides	−0.339	<0.001	0.008	0.01
Other antibiotic classes	−0.008	0.839	0.006	<0.001

*Interrupted time series analyses were not conducted for lincosamides, fluoroquinolones, tetracyclines, sulfonamides, or aminoglycosides because the monthly number of prescriptions in these classes was too low to support stable model estimation

^aImmediate change examines the change in level immediately after the onset of the pandemic in outcomes rates compared to pre-pandemic period.

^bChange during pandemic examines the change in slope during the pandemic in outcomes rates compared to the pre-pandemic period.

Supplementary Figure S4.1. Prevalence of infections anytime during pregnancy per calendar year during study period (2000-2023).



Any Infection prevalence was calculated as the count of infections (respiratory, urinary, sexually transmitted, or intestinal) diagnosis across all pregnancies per calendar year

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	161
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	162-163
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	164-165
Objectives	3	State specific objectives, including any prespecified hypotheses	165
Methods			
Study design	4	Present key elements of study design early in the paper	165
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	165-166
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	166-168
		(b) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	166-168
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	165-166
Bias	9	Describe any efforts to address potential sources of bias	166-168
Study size	10	Explain how the study size was arrived at	-
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	162-163
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	168-170
		(b) Describe any methods used to examine subgroups and interactions	168-170
		(c) Explain how missing data were addressed	-
		(d) If applicable, explain how loss to follow-up was addressed	-
		(e) Describe any sensitivity analyses	-

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	170-171
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	170-171
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	-
Outcome data	15*	Report numbers of outcome events or summary measures over time	171-172
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	171-172
		(b) Report category boundaries when continuous variables were categorized	171-172
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	171-172
Discussion			
Key results	18	Summarise key results with reference to study objectives	172-173
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	179-180
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	173-179
Generalisability	21	Discuss the generalisability (external validity) of the study results	179-180
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	181-182

4.15. References

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Chapter 5: Conclusions and Future Recommendations

Pregnancy represents a unique period where healthcare delivery, medication safety, and social determinants of health intersect to shape maternal and perinatal outcomes. This thesis addressed three major objectives that provided real-world evidence on maternal and perinatal health in Manitoba using linked administrative data. The COVID-19 pandemic disrupted access to essential services and highlighted existing inequities in maternal care. In Manitoba, leveraging linked administrative data to evaluate prenatal care adequacy, pandemic-related impacts, and antibiotic use provides evidence to guide policy and strengthen equitable, resilient maternal–infant health systems and contribute to understanding how structural conditions and health system pathways shape maternal and infant health.

This thesis is organized around the WHO Commission on Social Determinants of Health framework, which distinguishes structural determinants from intermediary pathways and positions the health system infrastructure as a determinant through access and quality of care. Using this framework, the thesis delivers evidence that aligns with WHO priorities for ending preventable maternal mortality. The first project contributes evidence on how pandemic measures can affect pregnancy and birth outcomes over time. The second project shows that prenatal care inequities can persist and worsen during the COVID-19 pandemic measures even with universal health insurance, and the third project provides long-term baseline evidence and first step relevant to antimicrobial stewardship in pregnancy.

5.1 Conclusions

The first population-based study, presented in Chapter 2, examined the impact of COVID-19 pandemic measures and exposure duration to pandemic measures on perinatal outcomes among 222,636 pregnancies in Manitoba. My findings showed that the length of exposure to pandemic measures had differential effects on adverse perinatal outcomes, as longer exposure to the pandemic measures was associated with higher rates of preterm birth and cesarean delivery. These observations could be attributed to changes in access and adequacy of care, increased socioeconomic vulnerability in certain groups, or other unknown mechanisms. However, the rates of small for gestational age births, NICU admissions, and breastfeeding initiation remained stable over the two-year pandemic period.

The second study of this thesis, chapter 3, examined trends and determinants of prenatal care utilization in Manitoba from January 2010 to March 2022. I found persistent inequities in access and adequacy despite universal healthcare coverage in Manitoba. In 192,274 pregnant women, over 12 years, approximately one in ten women received inadequate prenatal care, while one in twenty-six attended fewer than five prenatal visits. Younger women, and those with lower income, multiparity, and rural residence were at higher risk of inadequate care and receiving fewer than five visits throughout their pregnancy. While the overall pre-pandemic trends were stable and like other Canadian provinces(166–168), the COVID-19 pandemic was associated with increased rates of inadequate care. Our findings emphasize the need to develop innovative service delivery models to overcome the complex and multi-level barriers influencing prenatal care. The health system should adapt flexibly to improve prenatal care through system-level transformation that targets structural determinants alongside individual-focused interventions.

The third study, presented in Chapter 4, investigated annual trends in the use of antibiotics before, during and after pregnancy over a 23-year period. Approximately one in three pregnancies filled at least one systemic antibiotic, and the overall prevalence of use remained stable over the 23-year study period. A temporary decline was observed following the onset of pandemic measures, followed by a rebound during the subsequent two years. Across trimesters, antibiotic use was highest in the first trimester, then second and third trimesters. β -lactam penicillins remained the most prescribed class but declined steadily over time, while the use of other β -lactams more than doubled, becoming the second most common class by 2023. Amoxicillin was the leading drug throughout pregnancy, whereas cefalexin surpassed amoxicillin as the most prescribed antibiotic in the post-delivery period. These findings provide essential baseline data for evaluating antibiotic safety studies and antimicrobial-stewardship initiatives to optimize antibiotic use in pregnant women.

The three studies in this thesis illustrate how maternal and perinatal health outcomes are influenced by interactions between healthcare systems, clinical practices, and broader social determinants. The perinatal outcomes analysis captured the overall population-level impact of pandemic measures on birth outcomes, while the prenatal care study demonstrated persistent inequities in access to prenatal services across socioeconomic and geographic groups. The antibiotic utilization study provided long-term evidence on patterns of medication use during pregnancy and established baseline trends relevant for future medication safety and antimicrobial stewardship research. These results indicate that the prenatal health system was under stress and that existing inequities were further intensified during the COVID-19 pandemic. First, pandemic measures disproportionately affected perinatal outcomes, and the dose-response

relationships suggest that prolonged exposure to disrupted health systems had cumulative effects. Second, universal health insurance does not guarantee equitable access to care. Structural, geographic, and socioeconomic barriers continue to shape who receives prenatal care. Third, antibiotic prescribing during pregnancy remained relatively stable overall, but the increasing use of broader-spectrum antibiotics, despite the implementation of a national antimicrobial stewardship framework, suggests that pregnancy-specific stewardship strategies may be needed. These findings indicate that maternal and perinatal health outcomes are shaped not only by individual clinical care but also requires health systems that are resilient, equitable and capable of adapting to the needs of pregnant women, especially during times of crisis.

Sensitivity analyses were conducted by restricting prenatal care visits to clinician-virtual prenatal care billing codes only, changing intervention points (February 2020 and April 2020), and restricting the study period to two years before and two years after the intervention. Results were consistent with the primary analyses, indicating that the findings were robust to alternative specifications of prenatal care visits, intervention timing, and the study period.

5.2. Interpretation of Findings within the CSDH Framework

The findings of this thesis suggest that maternal and perinatal health outcomes are shaped by interactions between structural determinants and intermediary pathways operating through the healthcare system. The COVID-19 pandemic measures represent a major structural shock that influenced healthcare delivery, healthcare utilization patterns, and broader social conditions affecting pregnant individuals.

The observed decline in prenatal care adequacy during the pandemic, together with persistent disparities by income, rural residence, age, and parity, is consistent with the framework that structural inequalities shape access to healthcare services. Even within a universal healthcare system, structural and geographic barriers can influence the ability of individuals to obtain timely and adequate prenatal care, particularly during periods when healthcare systems are under stress.

In addition, perinatal outcomes, such as preterm birth and cesarean delivery, appeared sensitive to prolonged exposure to pandemic-related disruptions, whereas other outcomes remained stable during the same period. These patterns could be linked to the pandemic-related changes, including changes in healthcare access, modifications in health-seeking behaviours, changes in clinical practice, and broader social disruptions. In this thesis the analyses estimated the overall population-level impact of pandemic measures rather than evaluating specific causal pathways linking structural factors to outcomes. Prenatal care utilization was examined as a separate outcome and was not modelled as an intermediary variable between pandemic measures and perinatal outcomes. Similarly, the analysis of antibiotic utilization did not examine infections or clinical indications for antibiotic use. Thus, the observed associations should be interpreted with caution reflecting the combined influence of multiple pathways that may have operated simultaneously during the pandemic period.

Several mechanisms relevant to the CSDH framework could not be directly measured using administrative health data. These include structural and social factors such as culturally unsafe care, housing insecurity, food insecurity, and other lived barriers that influence healthcare access. The absence of these measures limits the ability to attribute observed inequities to specific

mechanisms and highlights the need for future research integrating administrative data with qualitative and community-engaged approaches.

5.3. Comparison with Findings from Other Canadian Jurisdictions

Reports from Canada on the effects of COVID-19 pandemic measures on perinatal outcomes have been conflicting.(181–185) Three retrospective cohort studies conducted in the province of Ontario examined the influence of first-wave pandemic lockdown measures on perinatal outcomes and reported no significant changes in preterm birth (PTB) or stillbirth rates (182–184). Similarly, other adverse perinatal outcomes, including NICU admission and 28-day neonatal death, did not change significantly during the pandemic period.(182,184) A national Canadian study study, using the Discharge Abstract Database (excluding Quebec), examined 136,445 singleton births during the pandemic and also found no change in PTB rates, although cesarean delivery rates declined (185). The observed changes in adverse pregnancy and neonatal outcomes across different periods highlight the varying impact of the pandemic on pregnant women. Pandemic measures, such as restrictions on healthcare access, reduced social support, changes in hospital policies, shifts in hygiene practices, and physical distancing, may have differentially impacted perinatal outcomes across different regional and socio-economic settings.

Our findings are consistent with previous research in Manitoba, which documented persistent inequities in prenatal care among younger, lower-income, and multiparous women.(80) Despite universal healthcare coverage, these disparities have remained over time, suggesting the presence of upstream structural and health system barriers. Similar patterns have been observed in other Canadian jurisdictions. A study from Ontario reported that 2.1% of pregnant women received inadequate prenatal care, defined as fewer than five visits or late initiation of care(74)

and differences in adequacy have also been reported by migration status.(224) National survey data further indicate that 18.9% of pregnant women in Canada received inadequate care, with Manitoba reporting a higher rate of 22.5%.(225) In the present study, the proportion of inadequate care was lower (10.4%), which may reflect differences in study design and measurement indices.

A Canadian study across four provinces, including Manitoba, reported that antibiotics accounted for 26% of all prenatal medications.(10) Similarly, data from the French Pregnancy Cohort in Quebec showed that antibiotics were the most commonly prescribed medication during pregnancy, accounting for 26% of all prescriptions.(226) In Manitoba, a cohort study observed an increase in the proportion of all prenatal medication prescriptions between 2001 and 2013, with amoxicillin, nitrofurantoin, and cefalexin among the five most prescribed medications.(107) Our findings are similar to results across the Canadian provinces, indicating a consistent national pattern of clinical practice

5.4. Strengths and Limitations

This thesis has several strengths. This thesis represents a comprehensive population-based examination of perinatal health in Manitoba spanning 12-23 years, utilizing validated linkages across administrative health databases to capture all registered births. The use of rigorous quasi-experimental methods, including interrupted time series analysis, enabled examining pandemic effects while controlling pre-existing trends, and the categorization of pandemic exposure by duration of pregnancy spent under measures revealed dose-response relationships not captured

in prior studies. A particular strength is the focus on health equity across studies, stratifying analyses by income and geography, examining demographic characteristics to identify vulnerable populations and demonstrating that universal health insurance alone has not eliminated inequities in prenatal care access or perinatal outcomes.

Limitations of this thesis should be acknowledged. Administrative data lack clinical detail, severity information, medication indications, and important social determinants, including race, ethnicity, education, marital status, and behavioral factors (e.g. smoking), preventing assessment of quality of prenatal care. While breastfeeding initiation was defined as any exclusive or partial breastfeeding within the first 3 days postpartum, breastfeeding initiation after hospital discharge was not captured, and continuation of breastfeeding could therefore not be assessed (227). Measures of prenatal care visits and adequacy (using the R-GINDEX) were derived from physician visits identified through hospital records and physician medical claims. Some women classified as receiving no care may have been seen by salaried physicians who did not submit billing claims, or by midwives or at nursing stations, services not captured in medical services data or hospital abstracts(228,229). As a result, prenatal care utilization may be underestimated, potentially leading to underestimation of prenatal care visits and misclassification of prenatal care adequacy. However, this misclassification would likely be non-differential and bias estimates toward the null. While the R-GINDEX has been used in previous studies and has demonstrated reliable results compared to other indices, it has not been formally validated(61). It is strictly a measure of utilization and captures the quantity and timing of prenatal care received and does not reflect the content or clinical adequacy of prenatal care. There is also potential for misclassification due to inaccuracies in gestational age estimations, as we relied on data recorded in hospital abstracts.

In addition, Prescription dispensing may not accurately reflect actual medication use, potentially leading to exposure misclassification(230). DPIN captures outpatient prescriptions dispensed from community pharmacies but does not capture antibiotics administered during inpatient hospital stays, resulting in incomplete ascertainment of overall antibiotic exposure. This limitation is relevant for third-trimester exposure assessment, as intrapartum antibiotic prophylaxis routinely administered in hospital at the time of delivery and is therefore not captured in DPIN, thus exposure may be underestimated. This may introduce non-differential exposure misclassification and could explain lower observed prescriptions near term(230). In addition, the absence of clinical indication data limits the assessment of prescription appropriateness and the ability to differentiate between therapeutic, prophylactic, or empiric uses of antibiotics. While this does not introduce confounding in a utilization study, it constrains interpretation of observed patterns when examining trimester-specific trends. Comparisons across time periods are also limited by unmeasured variation in infection epidemiology, obstetric practices, care-seeking behaviors, and antimicrobial resistance patterns.

While the interrupted time series analysis examines the intervention (i.e. pandemic) effects, the study design cannot definitively identify specific causal mechanisms (i.e. observed outcome changes could be due to healthcare disruption, psychosocial stress, or behavioral changes). Although ITS designs are considered one of the strongest quasi-experimental approaches for evaluating population-level interventions, they remain susceptible to bias from time-varying confounding and concurrent events occurring around the time of the intervention. One approach to strengthen internal validity in ITS analyses is the inclusion of a nonequivalent dependent variable or control outcome that is not expected to be affected by the intervention but is

measured over the same time period(231). In this thesis, a control outcome was not included, which limits the ability to rule out the influence of time-varying confounders. In this thesis, I used the ITS models which accounted for underlying secular trends and seasonal variation; however, residual bias from unmeasured time-varying factors cannot be completely excluded. Moreover, model fit for ITS analyses was evaluated using the scaled deviance (deviance divided by the degrees of freedom). Although the scaled deviance is commonly used to assess goodness-of-fit in generalized linear models, relying on a single statistic has limitations because it primarily reflects overall dispersion and does not assess residual patterns, model misspecification, or the presence of temporal dependence. To further evaluate model assumptions, residual plots and autocorrelation diagnostics were examined to assess whether systematic patterns or autocorrelation were present. Generalizability to jurisdictions without universal insurance or with different healthcare systems, provincial policies, pandemic responses, and sociodemographic characteristics is limited. Although Canadian provinces implemented similar public health measures during the COVID-19 pandemic, such as lockdowns, gathering restrictions, school closures, and physical distancing, the timing, stringency, and duration of these measures differed across provinces (232,233). Differences in provincial policy measures and disruptions to the healthcare system may therefore influence healthcare access and utilization. Additionally, Manitoba's population structure might respond differently to healthcare disruptions compared to other Canadian provinces. Therefore, caution is needed when applying these findings to other Jurisdictions.

5.5. Clinical and Policy Implications and Future Directions

The findings from this thesis have implications for clinical practice, health policy, and system planning. Persistent inequities in prenatal care access highlight the need to redesign how prenatal care is delivered. Manitoba's universal insurance alone is not sufficient; flexible service models such as expanding midwifery services, community outreach programs, and hybrid virtual-and-in-person care can help address both geographic and social barriers. The consistent finding that lower-income and rural women are at higher risk of inadequate care, even within a universal system, suggests that financial coverage without concurrent removal of non-financial barriers such as travel distance, limited provider availability, and inflexible appointment scheduling is insufficient to achieve equitable prenatal care utilization. Manitoba's Healthy Baby Prenatal Benefit remains an important policy initiative, but financial support should be linked with coordinated clinical and mental health care to better support families. Given that maternal psychological stress is a determinant for inadequate care, integrating mental health screening and support into prenatal care, rather than treating them as separate services, could address an important gap in current practice. Rural residence emerged as a consistent determinant of inadequate care; transportation represents a primary obstacle. Policy solutions include mobile clinic provision and subsidized transportation to regional centers, leveraging existing social service infrastructure where feasible.

The COVID-19 pandemic has exposed weaknesses in the perinatal care system and shown how access to prenatal care can be disrupted. The dose-response relationship between exposure to pandemic measures and few adverse perinatal outcomes observed in Chapter 2 underscores that even temporary disruptions in health service delivery can have cumulative consequences,

reinforcing the need to maintain uninterrupted access to essential prenatal services during future crises. Strengthening preparedness for future public health crises requires incorporating equity considerations into emergency response plans and ensuring that all women, regardless of geography or income, can continue to access care. The rapid shift to virtual prenatal care demonstrated that hybrid models are possible; however, they should be systematically developed and implemented. The hybrid approach should be developed with attention to digital literacy and equitable technological access so that it enhances rather than restricts care access for vulnerable populations. Adaptability should include investments in prenatal care infrastructure and provider support to maintain continuity of care under changing conditions.

Our findings provide comprehensive, real-world evidence on antibiotic utilization during pregnancy that will serve as a foundation for future research on medication safety and antimicrobial stewardship. The stability of antibiotic prescribing over more than two decades with shift from penicillins to broader-spectrum β -lactams, despite the implementation of the national antimicrobial stewardship framework in 2017, suggests that current stewardship strategies are not reaching prenatal prescribing contexts and that pregnancy-specific audit-and-feedback programs targeting obstetric and primary care providers are needed. The observed shift from penicillins to broader spectrum antibiotics may increase the risk of antimicrobial resistance and alter the maternal and neonatal microbiome, with potential adverse effects on infants' health. Integrating pregnancy-specific antimicrobial stewardship, including penicillin allergy delabelling (i.e. confirming and removing inaccurate allergy labels), and standardized postpartum protocols, can reduce unnecessary broad-spectrum exposure while maintaining safety.

Administrative data captures *what* occurred but provides limited insight into *why*. Qualitative research involving in-depth interviews with women who received inadequate prenatal care should explore patient perspectives on barriers, including structural barriers (transportation, childcare, appointment availability), financial barriers, healthcare system factors (provider attitudes, communication quality, cultural responsiveness), and personal factors (competing priorities, health literacy, cultural beliefs about prenatal care). This rich qualitative data should inform intervention design to address the actual barriers women face.

Further investigation into regional and socioeconomic disparities in Manitoba is warranted to better understand the underlying mechanisms and to guide evidence-based maternal and neonatal healthcare policies for vulnerable populations in future public health crises. Significant inequities persist, with rural residence, lower income, and multiparity representing key barriers to adequate care. Targeted, equity-oriented interventions are warranted to mitigate structural barriers and improve prenatal care access for vulnerable populations.

This thesis documented prescribing patterns for antibiotic use in pregnancy, but not appropriateness. Chart review or primary data collection with clinical indication validation for a representative sample of antibiotic prescriptions would enable assessment of prescribing appropriateness, identify common patterns of inappropriate prescribing (e.g., use of broad-spectrum agents), and quantify potential for stewardship interventions.

This thesis quantified inadequate prenatal care utilization but did not directly assess consequences. Subsequent research should link inadequate prenatal care identified in these analyses to downstream maternal and infant outcomes, including maternal morbidity (postpartum hemorrhage, infection, readmission, severe complications), infant outcomes

(developmental milestones at 12 and 24 months, healthcare utilization, emergency department visits), and long-term neurodevelopmental and metabolic outcomes. Understanding the magnitude of harm flowing from inadequate care in Manitoba's population strengthens the public health and policy case for prenatal care system transformation and provide evidence needed to justify resource allocation for prenatal care system transformation in terms of avoidable adverse outcomes and downstream healthcare expenditures.

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<https://canadaspremiers.ca/covid-19/>

Appendix A: Research ethics (HERB)



University of Manitoba | Research Ethics and Compliance

Research Ethics Bannatyne
P126-770 Bannatyne Avenue
Winnipeg, MB R3E 0W3
T: 204 789 3255
F: 204 789 3414
bannreb@umanitoba.ca

HEALTH RESEARCH ETHICS BOARD (HREB)

CERTIFICATE OF ANNUAL APPROVAL

PRINCIPAL INVESTIGATOR: Laila Aboulatta	INSTITUTION/DEPARTMENT: U of M and MCHP/Pharmacy	ETHICS #: HS24655 (H2021:063)
HREB MEETING DATE (If applicable): NA	APPROVAL DATE: February 10, 2025	EXPIRY DATE: February 26, 2026
STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (If applicable): Sherif Eltonsy		
PROTOCOL NUMBER: NA	PROJECT OR PROTOCOL TITLE: The impact of COVID-19 pandemic lockdown measures on perinatal outcomes: a population-based cohort study - Linked to HS24111 (H2020:335)	
SPONSORING AGENCIES, FUNDING AGENCIES AND/OR COORDINATING GROUPS: Start-Up Fund		
Submission Date of Investigator Documents: January 20, 2025		HREB Receipt Date of Documents: January 21, 2025

REVIEW CATEGORY OF ANNUAL REVIEW: Full Board Review ☐ Delegated Review ☒

THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:

Document Name (if applicable)	Version (if applicable)	Date
-------------------------------	-------------------------	------

Annual approval

Annual approval implies that the most recent **HREB approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.

Consent and Assent Form(s):

CERTIFICATION

The University of Manitoba (UM) Health Research Board (HREB) has reviewed the annual study status report for the research study/project named on this **Certificate of Annual Approval** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, UM HREB, per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

HREB ATTESTATION

The University of Manitoba (UM) Health Research Board (HREB) is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, the HREB complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada and carries out its functions in a manner consistent with Good Clinical Practices.

QUALITY ASSURANCE

The University of Manitoba Research Quality Management Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

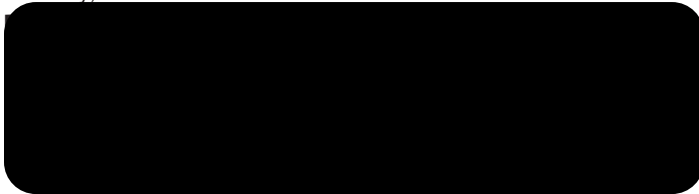
CONFLICT OF INTEREST

Any Principal or Co-Investigators of this study who are members of the UMHREB did not participate in the review or voting of this study.

CONDITIONS OF APPROVAL:

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. ***For logistics of performing the study, approval must be sought from the relevant institution(s).***
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has the responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. A Bannatyne Campus Annual Study Status Report** must be submitted to the REB within 15-30 days of this expiry date.
5. Any changes of the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to the HREB for consideration in advance of implementation of such changes on the **Bannatyne Campus Research Amendment Form**.
6. Adverse events and unanticipated problems must be reported to the REB as per Bannatyne Campus Research Boards Standard Operating procedures.
7. The UM HREB must be notified regarding discontinuation or study/project closure on the **Bannatyne Campus Final Study Status Report**.

Sincerely,



Appendix B: Research ethics (HIPC/PHRPC)



April 23, 2021

Laila Aboulatta
University of Manitoba, College of Pharmacy
65 Notre Dame Avenue R3E 0M2
aboulatl@uryumanitoba.ca

HIPC No. 2020/2021- 81

File number to be quoted on
correspondence

**Re: The impact of COVID-19 pandemic lockdown measures on perinatal outcomes:
a population-based cohort study**

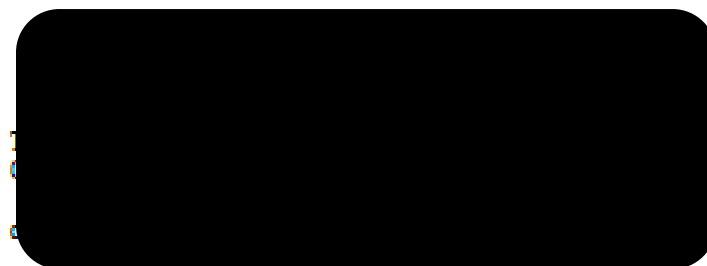
Dear Ms. Aboulatta,

The Health Information Privacy Committee has considered and *approved* your request for access to data for the purposes of the above named project.

Any significant changes to the proposed study design should be reported to the Chair/HIPC for consideration in advance of their implementation. Also, please be reminded that any manuscripts and presentation materials resulting from this study must be submitted to Manitoba Health, Seniors and Active Living for review. Specifically, manuscripts must be submitted *at least 30 calendar days* prior to the intended publication and presentation materials must be submitted *at least 10 calendar days* prior to the presentation.

Researcher Agreement will need to be completed before work on this project can commence. This will be initiated by MCHP. If you have any questions or concerns, please do not hesitate to contact Saila Parveen, Committee Coordinator at (204)786-7204.

Yours truly,



Manitoba
spirited energy



Provincial Health Research Privacy Committee (PHRPC)
Amendment Approval

October 14, 2025

PHRPC No. 2020/2021-70
file number to be quoted on all correspondence

Application date: August 29, 2025

Submission received: September 8, 2025

Approval date: October 8, 2025

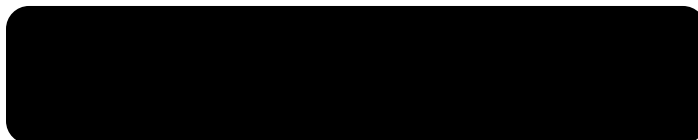
Researcher name: Dr. Sherif Eltonsy

Project title: Canadian Mother-Child Cohort Active Surveillance (CAMCCO) [Linked to H2020:412]

Thank you for submitting the protocol **amendment** form for the proposed protocol changes for this project named above. The Provincial Health Research Privacy Committee (PHRPC) has **approved** your revisions and you may consider this message as official notification of amendment approval.

If you have any questions or concerns, please do not hesitate to contact the RITHIM Program Officer (PHRPC Lead) at PHRPC@researchmb.ca.

Yours truly,



Vice-Chair, Provincial Health Research Privacy Committee (PHRPC)

PLEASE ALWAYS USE THE MOST RECENT VERSION OF PHRPC FORMS FROM THE PHRPC WEBSITE

- see 'Forms & Guides' at <https://www.rithim.ca/phrpc-submission-information>