The health and economic impacts of Group B *Streptococcus* disease among infants in Ontario, Canada

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PREFACE

Statement of originality

I hereby certify that the content of this thesis is my original work. This thesis has not been submitted for any degree or any other purpose. I confirm that the intellectual content is the result of my own efforts, and that all assistance received in preparing this thesis, as well as all sources, have been duly acknowledged.

Ethical considerations

All analyses were conducted using data from ICES, Ontario. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Ethical approval for all research projects were obtained from the Children's Hospital of Eastern Ontario Research Ethics Board (CHEOREB# 20/11PE) and the ICES Privacy Office (TRIM 2023-0901-320-001). Additionally, an administrative review was also obtained from the University of Ottawa Research Ethics Board (H-10-24-8241).

Statement of financial support

I received financial support from the Canadian Institutes of Health Research (CIHR) through a Doctoral Research Award (GR002845) for three years of my studies, as well as through a stipend through the Children's Hospital of Eastern Ontario Research Institute (CHEO-RI). Additionally, I was awarded an excellence scholarship from the University of Ottawa, which covered my tuition throughout my doctoral program.

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In this study, I served as the first and corresponding author, taking the lead in the study's design with input from my co-authors. W. Petrcich provided analytical guidance and contributed to revisions concerning data sources at ICES. I was responsible for linking the administrative data sources and conducting all statistical analyses, with assistance from D. Fell. I interpreted the results and took the lead in developing the manuscript. D. Fell, D. El-Chaar, N. Thampi, K. Brown, and B. Sander contributed to the interpretation of the results and provided revisions to the manuscript. All co-authors contributed to data interpretation, revised the manuscript for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work.

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In this study, I served as the first and corresponding author, leading the research with contributions from my co-authors. N. Thampi assisted with the study's conception and design, while W. Petrcich provided the data cut from ICES and offered analytical guidance. I conducted all analyses and drafted the manuscript, with help from D. Fell, D. El-Chaar, N. Thampi, K. Brown, and B. Sander, who played key roles in interpreting the results and providing revisions. The remaining co-authors assisted with manuscript revisions. All co-authors reviewed the manuscript for important intellectual content, approved the final version for publication, and agreed to be accountable for all aspects of the work.

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In this study, I served as the first author, leading the research study with support from my co-authors. B. Sander and N. Thampi assisted with the study's conception, design, and provided analytical and clinical guidance. I led the statistical analyses and the overall analytic direction, with W. Petrcich running the costing algorithm at ICES and providing technical support as needed. I interpreted the results and drafted the manuscript. D. Fell, D. El-Chaar, N. Thampi, K. Brown, and B. Sander assisted with interpreting the findings and provided essential revisions to the manuscript. All co-authors reviewed the manuscript, approved the final version, and accepted responsibility for the work as a whole.

ABSTRACT

Group B *Streptococcus* (GBS) remains a leading cause of neonatal morbidity and mortality worldwide, despite preventive measures such as intrapartum antibiotic prophylaxis (IAP). Globally, an estimated 20 million pregnant individuals are colonized with GBS each year, leading to nearly 400,000 cases of infant GBS disease and over 90,000 infant deaths annually. While routine screening using rectovaginal swabs in the late third trimester and IAP have reduced the incidence of early-onset GBS disease (infection occurring within the first 6 days of life) in high-income countries like Canada, current strategies have important limitations: they are less effective against later-onset GBS disease (beyond the first week of life), may miss cases due to false-negative screening results or changes in maternal colonization status, and have limited impact on GBS-associated preterm births and stillbirths. Moreover, despite the widespread adoption of these prevention strategies in Canada, studies evaluating their effectiveness remain sparse, often relying on outdated or regionally limited data with small sample sizes. Important gaps also exist in fully understanding the true burden of GBS disease, its long-term neurodevelopmental consequences, and its broader economic impact. As maternal immunization with a GBS vaccine is being explored as a potential future prevention strategy, robust epidemiological and health economic data are critically needed to support vaccine development, inform policy decisions, and guide future implementation efforts.

This dissertation aimed to address these gaps by evaluating the epidemiological, clinical, and economic burden of infant GBS disease in Ontario, Canada. Leveraging real-world, population-wide health administrative and registry data, this research pursued three key objectives: (1) to estimate the burden of infant GBS disease, describe epidemiological trends, and assess the effectiveness of current prevention strategies; (2) to evaluate the risk of neurodevelopmental impairments (NDIs) in early childhood following infant GBS disease, while examining sex and prematurity as effect modifiers; and (3) to determine the healthcare costs associated with GBS disease in infancy.

The findings from this dissertation highlight the substantial health and economic burden of infant GBS disease in Ontario and reveal ongoing challenges with current prevention efforts. In the first study, despite demonstrating high maternal screening coverage, we identified missed opportunities for IAP administration, and the incidence of later-onset disease remained unchanged across the five-year study period. The second study found that survivors of infant GBS disease had approximately twice the risk of developing neurodevelopmental impairments by five years of age, with particularly elevated risks among preterm infants and males. The last study demonstrated that infant GBS disease was associated with substantial short-term healthcare costs, particularly during the first 30 days after disease onset. Collectively, these findings can support clinical and public health planning, inform cost-effectiveness analyses, and contribute to evidence-based policy development as Canada and other jurisdictions explore the potential introduction of maternal GBS vaccination in the future, should a vaccine become available, licensed, and recommended for use.

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This PhD journey has been one of the most challenging and rewarding experiences of my life, and I feel deeply grateful for the extraordinary people who supported and uplifted me along the way.

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TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 2

CHAPTER 4

CHAPTER 5

CHAPTER 6

LIST OF FIGURES

CHAPTER 2

CHAPTER 3

CHAPTER 4

CHAPTER 5

CHAPTER 6

LIST OF ABBREVIATIONS

aHR	Adjusted hazard ratio
aIRR	Adjusted incidence rate ratio
aOR	Adjusted odds ratio
BORN	Better Outcomes Registry & Network
CBCL	Child Behaviour Checklist
CCI	Canadian Classification of Health Interventions
CHEO	Children's Hospital of Easter Ontario
CI	Confidence interval
CIHI	Canadian Institute for Health Information
CSF	Cerebrospinal fluid
DAD	Discharge Abstract Database
DALY	Disability-adjusted life years
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EOD	Early-onset GBS disease
FY	Fiscal year
GBS	Group B Streptococcus
HR	Hazard ratio
IAP	Intrapartum antibiotic prophylaxis
ICD-10-CA	Canadian implementation of the International Classification of Diseases, 10th Revision
IKN	ICES key number
IRR	Incidence rate ratio
LOD	Late-onset GBS disease
MOH	Ministry of Health
NACRS	National Ambulatory Care Reporting System
NDI	Neurodevelopmental impairment
NICU	Neonatal intensive care unit

OHIP	Ontario Health Insurance Plan
OLIS	Ontario Laboratories Information System
ON-Marg	Ontario Marginalization Index
OR	Odds ratio
PPROM	Preterm premature rupture of membranes
PROM	Premature rupture of membranes
RAE	Research analytical environment
REB	Research ethics board
RERI	Relative excess risk due to interaction
R-GINDEX	Revised-Graduated Prenatal Care Utilization Index
RPDB	Registered Persons Database
UK	United Kingdom
ULOD	Ultra-late-onset GBS disease
UR	Uncertainty range
US	United States
WHO	World Health Organization

CHAPTER 1. INTRODUCTION

1.1 Background

Group B Streptococcus (GBS) is a leading cause of neonatal morbidity and mortality worldwide, despite the availability of preventive measures such as intrapartum antibiotic prophylaxis (IAP).[1,2] The global burden of maternal GBS colonization and infant GBS disease remains substantial, particularly in regions with limited surveillance and healthcare infrastructure.[3,4] A systematic review estimated that approximately 20 million pregnant individuals worldwide were colonized with GBS in 2020, with nearly 400,000 infants developing early- or late-onset disease and over 90,000 infant deaths annually.[5] In high-income countries like Canada, routine screening and antibiotic interventions have reduced early-onset infant disease; however, gaps remain in understanding the true burden of GBS, its long-term neurodevelopmental consequences, and its economic impact.[6,7] Recent studies suggest that GBS survivors face an increased risk of neurodevelopmental impairments (NDIs), with approximately 18% of infants who experience GBS meningitis developing moderate-to-severe impairments by 18 months of age.[8] Additionally, the healthcare costs associated with GBS disease are significant, with estimates ranging from $20,000 to $50,000 per affected infant in high-income settings.[9] As maternal immunization with a GBS vaccine is being pursued as a future potential prevention strategy,[10–12] robust epidemiological and health economic data are critically needed to inform vaccine development and future implementation. This dissertation aimed to address these gaps by evaluating the burden of infant GBS disease in Ontario, Canada, assessing its long-term effects on child health, and estimating its economic costs to guide future prevention strategies.

1.2 Research objectives

The overarching aim of this doctoral thesis was to evaluate the current health and economic burden of infant GBS disease in Ontario, Canada. Leveraging real-world, population-wide healthcare data from Ontario, this thesis addressed three specific objectives:

1) To estimate the burden of infant GBS disease, describe epidemiological trends, and evaluate current GBS prevention initiatives in Ontario, including the uptake of maternal GBS screening and intrapartum antibiotic prophylaxis (IAP) receipt, as well as the association of these preventive measures with the risk of infant GBS disease (*Chapter 4*).

2) To assess the risk of neurodevelopmental impairments (NDIs) in early childhood following GBS disease during infancy and examine how sex and prematurity independently modify the effect of GBS on NDI outcomes (*Chapter 5*).

3) To determine the healthcare costs attributable to GBS disease during infancy (*Chapter 6*).

1.3 Thesis organization

This dissertation follows an article-based format in accordance with the University of Ottawa's doctoral thesis guidelines. Having reviewed the background, research objectives, and organization of the thesis in this first chapter, the following sections provide an overview of the remaining chapters:

- **Chapter 2** presents a comprehensive literature review, identifying key knowledge gaps and providing the rationale for the thesis objectives.
- **Chapter 3** outlines key methodological aspects that are consistently applied across all studies.

- **Chapter 4** presents the first article of the thesis, titled "Burden of infant Group B *Streptococcus* disease and impact of maternal screening and antibiotic prophylaxis in Ontario, Canada: a population-based cohort study". This article is published in *The Lancet Regional Health – The Americas (*https://doi.org/10.1016/j.lana.2024.100914).
- **Chapter 5** presents the second article, titled "Group B *Streptococcus* disease during infancy and risk of subsequent neurodevelopmental impairments in young children: a population-based cohort study in Ontario, Canada". This article is published in *The Lancet Regional Health – The Americas* (https://doi.org/10.1016/j.lana.2025.101170).
- **Chapter 6** presents the final article, titled "Healthcare costs attributable to Group B *Streptococcus* disease during infancy: a population-based matched cohort study in Ontario, Canada", which is in preparation for submission to *Clinical Infectious Diseases*.
- **Chapter 7** summarizes the key findings from the three research studies, reviews the limitations of this dissertation, discusses the broader implications for clinical practice and policy, and outlines directions for future research.

CHAPTER 2. LITERATURE REVIEW AND RESEARCH RATIONALE

2.1 Characteristics, transmission and clinical manifestations of GBS

Streptococcus agalactiae, commonly known as Group B *Streptococcus* (GBS), is a β-haemolytic Gram-positive bacterium that is part of the normal microbial flora in both humans and animals.[13] First identified as a pathogen in 1887, GBS was initially linked to bovine mastitis.[1] By 1938, it was recognized as a cause of puerperal sepsis in humans,[14] and by the 1960s, it had become widely known as major cause of neonatal septicemia and meningitis.[15,16] While the exact reasons for the emergence of GBS remain unclear, several theories have been proposed including changes to dairy farming practices,[17] a possible host jump from bovines to humans,[18] and the spread of a virulent GBS clone, likely driven by the extensive use and subsequent resistance of tetracycline.[19,20]

As an encapsulated bacterium, GBS is coated with capsular polysaccharides (CPS) containing sialic acid, which serve as crucial virulence factors that inhibit phagocytosis and effectively protect GBS from the host immune system.[21] Based on its capsular composition, GBS is classified into ten serotypes (Ia, Ib, II-IX), five of which (Ia, Ib, II, III, and V) are responsible for the majority of GBS disease, collectively accounting for approximately 97% of serotypes detected globally.[22]

Colonization with GBS—sometimes referred to as GBS carriage—can be intermittent, transient or chronic.[2] In healthy adults, GBS colonization typically does not result in disease; however, rectal and vaginal colonization during pregnancy poses a significant risk of vertical transmission to newborns during delivery, potentially leading to severe illness. GBS often resides

in the gastrointestinal tract and can migrate to the genital tract, allowing infants to ingest GBS-laden fluids in utero or during delivery.[23] Neonates are particularly susceptible to severe illness from GBS due to their immature immune systems, which rely heavily on the placental transfer of maternal GBS antibodies for protection.[24]

Maternal GBS antibodies, primarily IgG, are crucial for neonatal protection against GBS disease. Higher maternal anti-GBS IgG levels correlate with reduced neonatal infection risk, with concentrations above 1 μg/mL significantly lowering the likelihood of early-onset GBS disease.[25,26] However, the presence of these antibodies does not necessarily indicate that the mother has cleared the infection or is no longer colonized.

GBS colonization is known to be dynamic, fluctuating over time despite stable antibody levels. Studies have shown that while GBS-specific IgG, particularly against capsular polysaccharides, remains relatively consistent, colonization status can change. For instance, Haeusler et al. demonstrated that GBS colonization can be intermittent, with individuals transitioning between colonized and non-colonized states over time.[27] Additionally, Manning et al. found that a significant proportion of pregnant individuals who were GBS positive at one point could become negative at a later time, and vice versa, indicating that colonization status is not static.[28] This suggests that the immune response may help limit bacterial invasion but does not necessarily eradicate colonization.

The timing of maternal colonization also influences neonatal protection. If an individual acquires a GBS infection mid-pregnancy, she typically has sufficient time to mount an immune

response and transfer protective antibodies to the fetus via the placenta, enhancing neonatal protection.[25,26] Conversely, if colonization occurs closer to delivery, there may not be enough time for adequate antibody production and transplacental transfer, resulting in lower neonatal protection.[26]

Invasive GBS disease among infants most commonly manifests as meningitis, sepsis or bacteremic pneumonia.[1] Early-onset GBS disease (EOD), occurring from birth to 6 days of life, typically results from vertical transmission during vaginal delivery.[29] In contrast, the transmission routes for late-onset GBS disease (LOD), occurring between 7 and 89 days of life, and ultra-late-onset GBS disease (ULOD), occurring from 90 to 365 days, are less well understood but thought to include maternal (e.g., breastmilk) and non-maternal (e.g., caregivers) sources.[29,30] A less commonly described form is prenatal-onset GBS disease, which occurs when fetal GBS infection arises prior to birth due to in utero acquisition (**Figure 1**).[31] Prenatal-onset GBS disease can lead to miscarriage, stillbirth, early rupture of membranes and preterm labour.[31]

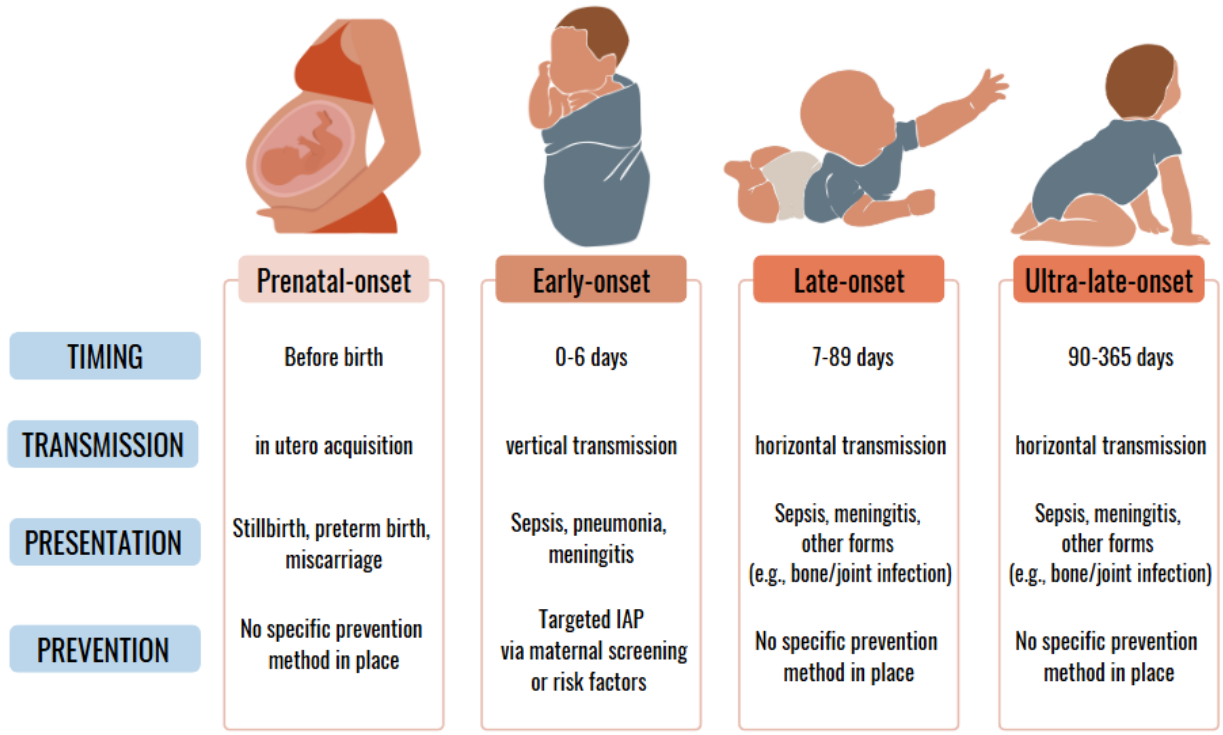

Figure 1. Comparison of key characteristics of prenatal-onset, early-onset, late-onset and ultra-late-onset Group B Streptococcus (GBS) disease

Abbreviations: IAP, Intrapartum antibiotic prophylaxis.

Elevated maternal colonization density significantly increases the risk of neonatal colonization at birth.[32–34] Beyond maternal GBS colonization, major risk factors for the development of EOD include preterm birth, prolonged rupture of membranes, intra-amniotic infection, GBS bacteriuria during pregnancy, and a history of GBS disease in a previous neonate.[35] Many of these obstetric and intrapartum risk factors have been used to guide targeted interventions to prevent EOD. Risk factors for LOD and ULOD, much like their transmission routes, remain poorly understood; however, evidence from observational studies indicates that maternal GBS colonization, ethnicity, prematurity, young maternal age and HIV infection may serve as potential risk factors.[30,36]

2.2 Global burden of maternal GBS colonization and infant GBS disease

In high-income settings, where routine laboratory surveillance is in place, GBS has increasingly been recognized as a leading cause of infant mortality, particularly during the early neonatal period (i.e., the first week of life).[3] However, obtaining accurate estimates of disease burden in low- and middle-income countries has been challenging due to issues related to specimen collection and inadequate laboratory capacity for GBS diagnosis.

In 2012, a systematic review estimated the global burden of infant GBS disease, reporting an overall incidence of 0.53 per 1,000 livebirths (95% CI: 0.41, 0.63) among infants under three months of age.[4] The highest incidence was reported in Africa (1.21 per 1,000 livebirths), followed by the Americas (0.67 per 1000 livebirths); however, no Canadian studies were included in this review.[4] The authors cautioned that the limited number of studies, along with their low quality and heterogeneous methods, likely resulted in an underestimation of the true burden of disease.[4]

In 2017, a comprehensive 11-article series published in *Clinical Infectious Diseases* compiled and evaluated all available global data—both published and unpublished—to better understand and contextualize the global burden of GBS.[2,11,17,19,25–3] This landmark series highlighted GBS as a leading contributor to adverse maternal and newborn outcomes, estimating at least 409,000 cases (uncertainty range [UR]: 144,000 - 573,000) of maternal, fetal and infant GBS disease globally, as well as an estimated 147,000 (UR: 47,000 - 273,000) GBS-associated stillbirths and infant deaths annually.[6] Across 90 studies included in one of the reviews from this series,[22] the pooled global incidence of infant GBS disease was slightly lower than previous

estimates (0.49 vs. 0.53 per 1,000 live births).[4,22] However, this figure likely continues to underestimate the true incidence due to ongoing challenges in case ascertainment, specimen collection, and processing—particularly in low-income settings, where blood cultures are used infrequently, and even when performed, fewer than 10% of neonates with suspected infections yield a positive result.[37,38] This is low positivity rate is mainly due to the limited sensitivity of blood cultures in neonates, which can result from small blood volumes collected, prior antibiotic exposure, low-level or intermittent bacteremia, and technical challenges in sample handling and processing.[1,5,10]

The prevalence of GBS rectovaginal colonization in pregnant individuals varies by geographic region, with a systematic review estimating a worldwide prevalence of 18% (95% CI: 17%, 19%).[39] While this pooled prevalence included data from 85 countries, over half of the United Nations member states had limited or no data for inclusion (**Figure 2**). Recent estimates suggest that in 2020, approximately 20 million pregnant individuals worldwide were colonized with GBS and nearly 400,000 infants presented with either EOD or LOD.[5] GBS was also responsible for over 90,000 infant deaths globally, nearly half of which occurred in Sub-Saharan Africa, despite the region representing about 15% of the world's population.[5] Low-income countries, which bear the highest risk of GBS disease, have the least available data, exacerbating the challenge of fully understanding the global burden of GBS.[1]

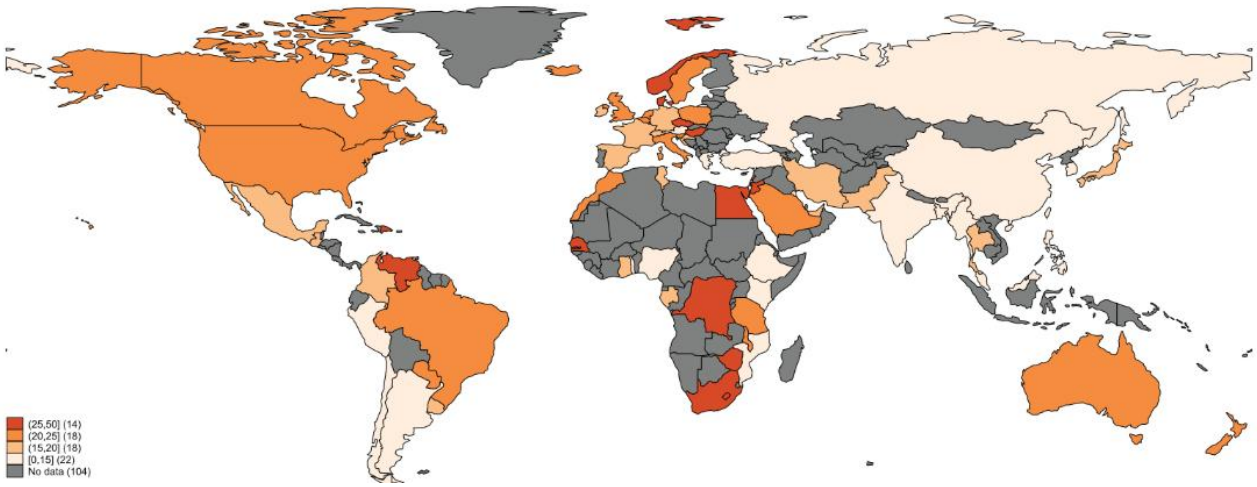

Figure 2. Prevalence of GBS colonization among pregnant individuals by country, adjusting for sampling site and laboratory culture method.

Figure source: Russell et al. (2017), Maternal Colonization with Group B Streptococcus and Serotype Distribution Worldwide: Systematic Review and Meta-analyses.[39]

The case-fatality rate of GBS varies by gestational age–while term infants have an estimated fatality rate of 1% to 3%, preterm infants have much higher rates (20% for EOD and 5% for LOD).[40] Among survivors, approximately 44% of those with GBS meningitis and 14% of those with GBS sepsis experience long-term disabilities.[9] Furthermore, GBS-associated neonatal encephalopathy occurs in 1.9 per 100,000 live births, doubling the risk of mortality compared to non-GBS-associated neonatal encephalopathy.[41]

2.3 Current methods of GBS diagnosis, prevention and treatment

To prevent the adverse outcomes associated with GBS, the most widely used and effective strategy is intrapartum antibiotic prophylaxis (IAP).[42] This can be implemented either through universal culture-based screening or a risk-based approach. In the culture-based screening method, IAP is administered to pregnant individuals who test positive for GBS in rectovaginal cultures, typically collected between 35 to 37 weeks of gestation as recommended

by the Society of Obstetricians and Gynaecologists of Canada (SOGC),[2] or between 36 to 37 weeks as advised by the American College of Obstetricians and Gynecologists (ACOG).[35] Alternatively, the risk-based approach offers IAP to pregnant individuals with specific risk factors, such as a history of GBS infection, a prior infant with GBS, GBS bacteriuria during pregnancy, preterm labour, or other conditions like fever or prolonged rupture of membranes.[43]

In 1996, the Centers for Disease Control and Prevention (CDC) released the first GBS screening guidelines,[44] recommending either universal culture-based screening or the risk-based approach. However, a 2002 multistate population-based study involving over 600,000 infants found that universal screening was more than 50% more effective in preventing perinatal GBS disease compared to the risk-based approach (attack rate per 1,000 live births: 0.33 vs. 0.59).[42] Based on these findings, the CDC,[45] the ACOG[46], and the SOGC[47] revised their guidelines to recommend universal screening followed by IAP for GBS carriers.

Despite the shift toward universal screening, some high-income countries, including New Zealand[48] and the United Kingdom (UK),[49] continue to favour the risk-based strategy. Concerns in these settings include the potential for antibiotic resistance, rare but serious side effects from antibiotics, and the logistical challenges of timely culture collection and analysis required for effective universal screening.[50–52] Both strategies have limitations, with missed opportunities for EOD prevention and concerns over antibiotic overuse remaining significant challenges. As a result, there is currently no international consensus on the optimal GBS prevention strategy.[53] A randomized controlled trial is currently underway in the UK (ISRCTN49639731) comparing routine GBS screening to the risk-based approach. The findings from this trial are expected to

provide robust evidence on the effectiveness and cost-efficiency of IAP directed by universal culture-based screening versus a risk-based approach.

Despite the effectiveness of IAP in reducing EOD, strict and universal implementation of current prevention strategies will not fully eliminate neonatal GBS disease. EOD can still occur among infants born to mothers who tested negative during screening or when no risk factors are present in labour. Moreover, targeted antibiotics do not prevent ascending infections during pregnancy or horizontal transmission, both of which contribute to LOD and ULOD disease.[54] Additionally, the timing of IAP administration limits its effectiveness in preventing GBS-associated stillbirths or preterm births.[10]

Concerns about the broader implications of IAP are growing. In the US, over 30% of infants are now exposed to intrapartum antibiotics, raising the risk of antibiotic resistance in GBS and other neonatal pathogens, as well as potential disruptions to the newborn microbiota.[55–58] Prenatal antibiotic exposure has been linked to alterations in the infant gut microbiome, which may carry long-term consequences, including an elevated risk of asthma, mood and anxiety disorders, autism, and attention deficit hyperactivity disorder.[59–61] These limitations of IAP highlight the pressing need for more effective and comprehensive strategies to address the burden of GBS disease in pregnant individuals and their infants.

2.4 Economic burden of GBS disease

GBS disease imposes a significant economic burden on both affected families and healthcare systems (**Table 1**). In the United States (US), short-term treatment costs for infant

GBS are substantial, averaging $20,000 for full-term infants and exceeding $50,000 for preterm infants.[9] Similarly, in England, the average health and social care cost during the first two years of life for infants with GBS was estimated at £11,968.90, compared to £6,260.70 for non-GBS controls—resulting in a difference of £5,708.20.[62] Beyond direct medical expenses, GBS also leads to considerable indirect costs, such as loss of family income and reduced productivity. For example, in the US, the total cost for a full-term infant with early-onset GBS sepsis, including direct and indirect expenses, can reach as high as $81,599.62.[63]

The costs of treating neonates and infants with sepsis or meningitis vary widely based on healthcare settings, patient age, and infection severity. A systematic review of 20 studies examining treatment costs found a broad range: from $55 to $129,632 for sepsis, $222 to $33,635 for meningitis, and $56,286 for meningococcal septicemia.[64] However, most of the included studies were conducted in high-income countries, with limited data from middle-income nations and none from low-income countries, highlighting a gap in the available literature. In middle-income countries, treatment costs were significantly lower, ranging from $55 to $3,607, compared to $64,047 to $129,632 in the US.[64] This discrepancy likely reflects differences in healthcare access, intensity of clinical management, and availability of services. In high-income settings, higher costs may stem from more comprehensive diagnostic workups, longer hospital stays, and use of advanced technologies, whereas lower costs in middle-income countries may reflect more constrained healthcare resources and underutilization of care.

In Denmark, children with a history of GBS infection within the first three months of life had significantly higher rates of outpatient visits (IRR 1.83, 95% CI 1.67 to 2.00) and hospital

admissions (IRR 1.43, 95% CI 1.37 to 1.50) by 10 years of age.[7] Similarly, a recent study conducted across five low- and middle-income countries found that GBS-exposed children had markedly higher odds of healthcare utilization, including more frequent healthcare visits, longer inpatient care stays, and higher out-of-pocket expenses compared to their unexposed counterparts.[65] In Canada, there is a notable lack of data on the economic impact of GBS on both infants and their families. Given the significant healthcare burden observed in other settings, there is a clear need for detailed estimates of the attributable costs of GBS in Canada. Such estimates could help guide resource allocation decisions and assess the potential economic benefits of preventive interventions, such as maternal GBS vaccination once a vaccine is available.

Table 1. Summary of existing studies estimating the healthcare costs or economic burden of infant Group B Streptococcus (GBS) disease

Reference	Country	Design	Sample size	Follow-up	GBS definition	Main findings
Schroeder et al., 2009[62]	England	Prospective matched cohort study	138 iGBS cases, 305 matched controls	First 2 years of life	Culture-confirmed iGBS (blood, CSF, or joint fluid) in infants <90 days old	Mean 2-year health and social care costs were nearly double for iGBS survivors (£11,969 vs. £6,261), driven primarily by initial hospital care.
Horváth-Puhó et al., 2021[7]	Denmark and Netherlands	National matched cohort study	2,258 GBS cases matched to 22,462 controls	Median 14 years (Denmark), 9 years (Netherlands)	Culture-confirmed iGBS (sepsis, meningitis, pneumonia) by 89 days of age.	iGBS disease was associated with more frequent outpatient clinic visits and hospital admissions in children 5 years or younger.
Seedat et al., 2024[65]	Argentina, India, Kenya, Mozambique, South Africa	Matched cohort study	161 iGBS survivors, 439 matched controls	1–20 years of age	Clinical iGBS with culture confirmation <90 days old	iGBS survivors had higher healthcare use and out-of-pocket costs in India, Mozambique, and Argentina, and worse HRQoL in children at follow-up.

Abbreviations: HRQoL, Health-Related Quality of Life; iGBS, Invasive Group B Streptococcus

2.5 Maternal immunization with a GBS vaccine

The limitations of current antibiotic-based prevention strategies—including their inability to address LOD/ULOD, prevent GBS-associated stillbirths and preterm births, and mitigate concerns of antibiotic resistance—underscore the need for alternative approaches. These challenges, coupled with potential disruptions to the infant microbiome, have made the development of a safe and efficacious vaccine a priority for improving pathogen control and reducing the burden of GBS disease.

Immunization during pregnancy (i.e., maternal immunization) is one promising strategy that could provide passive GBS protection to newborns during their most vulnerable stage of life. By transferring maternal antibodies to the fetus via active transport across the placenta, this approach could potentially prevent both EOD and LOD.[10] Factors influencing the level of protection include the efficiency of placental antibody transfer, vaccine efficacy, and the gestational timing of administration.[10] Despite its potential to protect newborns, children, and even adults, no vaccines are currently licensed for use against GBS.[11] Over the past three decades, vaccine development has progressed through various stages, with current efforts focused on two main approaches: capsular polysaccharide (CPS)-based and protein-based vaccines.[66]

Multivalent CPS vaccines have been designed to target the predominant disease-causing GBS serotypes, stimulating a CPS-specific IgG response. Several candidates are currently in various stages of development (**Table 2**).[67] Initial clinical trials with monovalent and bivalent

CPS vaccines conjugated with tetanus toxoid demonstrated safety and good tolerability.[68–71] Subsequent studies conducted in Belgium, Canada, South Africa, and Malawi assessed a trivalent vaccine (Ia, Ib, and III) conjugated to CRM197 in both pregnant and non-pregnant individuals.[72–75] These investigations confirmed the vaccine's acceptable safety profile, its ability to induce robust immune responses to the targeted serotypes, and effective transplacental antibody transfer to infants.

A Phase 1/2 clinical trial of the trivalent CRM197-conjugated vaccine in pregnant individuals reported higher levels of serotype-specific antibodies in newborns, with no safety concerns identified.[73] However, development of the monovalent and bivalent conjugates (TT and CRM197-CPS), as well as the trivalent CRM197-CPS vaccine, has been discontinued.[76]

Table 2. GBS vaccine candidates in the development pathway

Vaccine candidate	Serotype targets	Preclinical	Phase I	Phase II	Trials in pregnant individuals	Phase III
Polysaccharide conjugate vaccines						
TT Monovalent	Ia, Ib, II, III, IVa,V,VIa, VIIa, VIIIa	✓	✓	✓	✓	Discontinued
TT Bivalent	II, III	✓	✓	✓	✓	Discontinued
CRM197 Monovalent	V	✓	✓	✓	✓	Discontinued
Trivalent CRM197-CPS conjugates	Ia, Ib, III	✓	✓	✓	✓	Discontinued
Hexavalent CRM197-CPS conjugates	Ia, Ib, II, III, IV, V	✓	✓	✓	✓	Starting soon
Biotinylated CPS conjugates	Not specified	✓				
Protein-based vaccines						
N-terminal domains of the Rib and Alpha C proteins	N/A	✓	✓	✓	✓	Starting soon
Pilus proteins	N/A	✓				
Other proteins	N/A	✓				

N/A = not applicable

Since six GBS serotypes (Ia, Ib, II, III, IV, V) are responsible for the majority of the disease burden,[77] a hexavalent conjugate vaccine (GBS6) has been developed targeting these serotypes. In a Phase 1/2 placebo-controlled trial, GBS6—administered with or without aluminum phosphate— demonstrated good tolerability in healthy, non-pregnant adults (aged 18–49 years) and generated a sustained immune response lasting at least six months across all doses and formulations.[67] Recent findings from an ongoing Phase 2 trial (NCT03765073) involving 360 healthy pregnant individuals further highlight the vaccine's potential.[12] A single dose

administered in the late second or early third trimester was well-tolerated and elicited robust maternal antibody responses against all six targeted serotypes.[12] Notably, the induced antibody levels were comparable to naturally acquired protective levels, as observed in a parallel natural history study of over 18,000 mother-infant pairs.[12]

Protein subunit vaccines, which use isolated proteins from the GBS pathogen, offer the potential to target a broader range of GBS strains while addressing concerns about serotype replacement—an issue observed with CPS pneumococcal vaccines[78]—or capsular switching, which can occur during natural GBS infections.[79] Although several protein-based vaccines remain in preclinical development, one promising candidate, GBS-NN, targets the N-terminal domain of alpha-like surface proteins and has demonstrated safety and immunogenicity in a cohort of 240 healthy, non-pregnant adults.[80] Phase 2 trials are now underway to evaluate its safety and immunogenicity in pregnant individuals (NCT04596878, NCT05154578).

A recent systematic review summarized the evidence on the immunogenicity and safety of maternal GBS vaccines, analyzing data from 20 studies involving 5,765 participants, including 1,325 pregnant individuals.[81] The review found that the majority of participants who received conjugated CPS vaccines or surface subunit protein vaccines experienced significant increases in IgG geometric mean concentrations compared to the placebo group.[81] For individuals with low baseline antibody levels, a second dose further enhanced antibody concentrations. Notably, these elevated antibody levels were sustained well above baseline for at least 6 to 12 months, indicating a strong and lasting immune response. Moreover, placental transfer ratios of antibodies ranged from 0.4 to 1.4, suggesting effective transplacental transfer

and the potential for neonatal protection against GBS disease. Importantly, the number of reported reactogenic and serious adverse events among non-pregnant individuals, pregnant individuals, and infants was low, suggesting a favorable safety profile of these candidate vaccines—a critical factor for their future development and implementation.[81]

Despite these advancements, results from phase III clinical trials for these vaccine candidates are not yet available. Progress toward these trials has been hindered by several challenges, including the requirement for a large cohort of immunized pregnant individuals due to the low incidence of infant GBS disease and the absence of established correlates of protection.[82] Consequently, alternative licensing pathways are being considered, emphasizing the importance of studies aimed at identifying reliable correlates of protection or biomarkers associated with risk reduction.[78]

In 2015, the World Health Organization (WHO) recognized the urgent need for developing GBS vaccines for use in pregnancy[83] and proposed 15 steps to streamline and expedite the vaccine licensing process.[78] By 2021, the WHO, in collaboration with the Bill & Melinda Gates Foundation, released a comprehensive report titled *The Full Value of Vaccines Assessments*,[84] accompanied by a series of related papers.[85–93] This report presented updated epidemiological data on the global health impact of infant GBS disease, aiming to guide vaccine investment decisions and support countries in conducting financial and feasibility assessments for GBS vaccine candidates intended for use during pregnancy.

2.6 Longer-term health impacts of GBS disease

Infants who survive early-life GBS disease face a substantial risk of long-term neurodevelopmental impairments (NDIs). A 2017 meta-analysis estimated that approximately 18% (95% CI: 13–22%) of children who experience GBS meningitis develop moderate-to-severe NDIs by 18 months of age.[8] However, this figure likely underestimates the true burden due to the challenges of identifying NDIs in very young children and the scarcity of data from low- and middle-income countries (LMICs).

Recent cohort studies from high-income countries reinforce the long-term impact of GBS disease (**Table 3**). In Denmark and the Netherlands, children who survived GBS disease in the first three months of life were found to have increased risks of NDI by 10 years of age, with relative risks (RR) of 1.77 (95% CI: 1.44–2.18) and 2.28 (95% CI: 1.64–3.17) in these populations, respectively.[7] Similarly, a Norwegian study reported a threefold higher risk of NDIs among survivors by 12 years of age (RR: 3.49 [95% CI 3.05, 3.98]).[94]

Studies from LMICs highlight a comparable, if not greater, risk of NDIs following GBS disease in early infancy. In South Africa, survivors of infant GBS disease were found to have over five times the odds of moderate-to-severe NDIs by ages 5–8 years (adjusted OR [aOR]: 5.56, 95% CI: 1.07–28.93).[85] Similarly, in Mozambique, children who survived GBS infection in early infancy exhibited an eightfold increase in NDI risk by ages 0-5 years compared to matched controls (aOR: 8.41, 95% CI: 1.47–47.98).[86] In South India, a matched cohort study reported a 50% increased odds of NDIs among children aged 1–14 years who had a history of

GBS exposure in early infancy, though the wide confidence intervals included the null (OR: 1.51, 95% CI: 0.65–3.46), and no adjustments were made for confounders.[87]

Beyond neurodevelopmental outcomes, emotional and behavioural issues have been observed among GBS survivors. A multi-country cohort study across five LMICs found that school-aged survivors scored higher on the Child Behaviour Checklist (CBCL) for total problems and showed increased rates of DSM-5 psychological conditions such as anxiety, attention, and conduct disorders compared to controls.[88] Interestingly, these associations were not observed in preschool-aged survivors, suggesting that behavioural effects may become more apparent with age.[88]

In addition to developmental challenges, GBS survivors face an elevated risk of hospitalization and mortality in later childhood. An Australian study reported that survivors were three times more likely to die or require hospital care for chronic conditions, such as cerebral palsy, within the first 11 years of life.[95] Moreover, GBS-related sequelae may involve brain inflammation and edema, particularly in cases of meningitis and sepsis.[96] MRI findings frequently reveal abnormalities in neonates with GBS disease, with neonatal stroke being a common observation.[97] These neurologic injuries contribute to a heightened risk of subsequent disorders, including epilepsy. A Danish population-based cohort study demonstrated that neonatal GBS disease, particularly meningitis, was associated with a higher risk of childhood epilepsy, with prematurity, sex, and low maternal socioeconomic status acting as modifiers of this risk.[98]

Understanding the factors that modify the risk of NDIs in GBS survivors is essential for guiding targeted follow-up and improving clinical care. Evidence suggests that prematurity and sex may amplify the risk of NDIs, as indicated by cohort studies from Denmark and the Netherlands, which found that the elevated risk of NDIs was greater in preterm infants[89] and male children.[90] These findings highlight the importance of developing risk-specific interventions, particularly for vulnerable subgroups.

Recognizing the full scope of long-term consequences for GBS survivors is vital, as these data help better understand the full burden of GBS disease and influence metrics used to assess public health priorities such as disability-adjusted life years (DALYs). While vaccines for pathogens like pneumococcus and Haemophilus influenzae type B have significantly reduced the burden of similar infections in early infancy, the incidence of GBS disease has remained largely unchanged over the past two decades.[86,99] This highlights the urgent need for vaccine development and other strategies to mitigate the enduring impact of GBS on child health worldwide.

Table 3. Summary of existing observational studies on the association between infant Group B Streptococcus (GBS) disease and neurodevelopmental outcomes

Reference	Country	Design	Sample size	Follow-up	Exposure definition	Outcome definition	Main findings
Bramugy et al., 2022[86]	Mozambique	Prospective matched cohort study	39 iGBS survivors, 119 matched controls	Children aged 0–5 and 6–18 years	Culture-confirmed iGBS (blood or CSF) in infants <12 months old.	Malawi Developmental Assessment Tool (MDAT) and Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to assess cognitive, motor, language, and sensory function.	iGBS survivors aged 0–5 years had higher odds of any NDI (aOR 8.4); motor and cognitive impairments were common. No association was found in 6 to 18-year-olds.
Chandna et al., 2022[88]	Argentina, India, Kenya, Mozambique, South Africa	Matched, multicounty cohort study	iGBS defined by clinical signs of serious bacterial infection and GBS confirmed from sterile site in infants <90 days old	18 months to 17 years (school-aged children)	156 iGBS survivors, 417 matched non-iGBS children.	Emotional-behavioral problems measured using Child Behavior Checklist (CBCL), age-standardized T-scores	Among school-aged children, iGBS survivors had more emotional-behavioral problems than controls (especially internalizing problems like anxiety/withdrawal). No significant differences in preschool-aged group or in rates of clinical psychopathology per DSM-5.
Harden et al., 2022[85]	South Africa	Prospective matched cohort study	160 (43 iGBS, 117 non-iGBS)	Children assessed at ages 5 to 8 years.	Culture-confirmed invasive GBS disease (sepsis or meningitis) during infancy.	Griffiths Mental Development Scales-Extended Revised (GMDS-ER) scores to determine NDIs across motor, cognitive, vision, hearing and behavioral domains.	iGBS survivors had significantly higher odds of moderate/severe NDI compared to matched controls (aOR = 5.56, 95% CI: 1.07–28.93).
Horváth-Puhó et al., 2021[7]	Denmark and Netherlands	National matched cohort study	2,258 GBS cases matched	Median 14 years (Denmark), 9	Culture-confirmed iGBS (sepsis,	NDI defined using hospital diagnosis codes for motor, cognitive,	Any iGBS disease was associated with increased risk of NDI

			to 22,462 controls	years (Netherlands)	meningitis, pneumonia) by 89 days of age.	behavioral, or sensory impairments.	at 10 years of age in both countries; meningitis had the highest mortality and NDI risk.
Horváth-Puhó et al., 2021[89]	Denmark & Netherlands	Nationwide population-based matched cohort	Denmark: 1,432 iGBS to 1,4211 controls; Netherlands: 697 iGBS to 6,961 controls	Up to age 5 and 10 years	Denmark: ICD-10 codes for sepsis/meningitis; Netherlands: culture-confirmed GBS (CSF/blood)	Denmark: hospital diagnoses of NDI (ICD-10); Netherlands: need for special education	Prematurity significantly amplified the risk of NDIs following iGBS, with 36–60% of NDI risk in preterm iGBS cases attributable to the combined effect of prematurity and GBS exposure.
John et al., 2022[87]	South India	Prospective matched cohort study	35 iGBS survivors and 65 matched non-GBS children	1–14 years of age	Positive blood culture for GBS between 0–89 days of life (did not look at CSF).	NDI diagnosed by standardized tools by age (e.g., CBCL, BSID-III) and classified based on vision, hearing, cognition, language, motor, or behavior domains.	49% of iGBS survivors had any NDI vs. 38% in non-iGBS (not statistically significant); Higher odds of motor impairments in iGBS group (OR: 10.7; P=0.033), but not other domains.
Lykke et al., 2023[98]	Denmark	Population-based matched cohort	1,432 children with GBS matched to 14,211 children without GBS	Up to 22 years	Hospital-diagnosed iGBS (sepsis or meningitis) within 89 days of birth.	Epilepsy defined by ICD-10 codes and/or prescription codes for antiepileptic drugs.	Children with iGBS disease had an increased risk of developing epilepsy later in childhood, particularly following GBS meningitis (aHR: 15.7, 95% CI: 8.1–30.5). The association was modified by prematurity, male sex, and low maternal SES.
Mynarek et al., 2024[94]	Norway	National population-based cohort	1,415,625 live births (866 with	Mean age ~12 years (range 1.8–25.6 years	Culture-confirmed invasive GBS	Diagnosis of ≥1 neurodevelopmental disorder (NDD) via ICD-	GBS was associated with 3.5 times higher risk of any NDI,

		study using linked registries	invasive GBS infection)		(blood or CSF) within first year of life.	10 codes in hospital or primary care records. NDDs included: CP, epilepsy, hearing/vision loss, ADHD, ASD, or speech/motor delay	especially CP, epilepsy, hearing loss, ADHD, and PSDD. Risk was higher for LOD/VLOD and meningitis cases.
van Kassel et al., 2022[90]	Denmark & Netherlands	Nationwide population-based matched cohort	Denmark: 1,432 iGBS to 1,4211 controls; Netherlands: 697 iGBS to 6,961 controls	Up to age 5 and 10 years	Denmark: ICD-10 codes for sepsis/meningitis; Netherlands: culture-confirmed GBS (CSF/blood)	Denmark: hospital diagnoses of NDI (ICD-10); Netherlands: need for special education	Boys with iGBS had higher risk of NDI and greater educational support needs; evidence of effect modification by sex on the additive scale.
Yeo et al., 2019[95]	New South Wales, Australia	Population-based cohort study using linked administrative data	1,023,392 live births (1,206 with GBS)	Up to 11 years of age	ICD-10-AM diagnostic codes corresponding to GBS infection.	ICD-10-AM codes on hospitalisation episodes.	Children with GBS were significantly more likely to be re-admitted for neurological (OR 2.0) conditions such as epilepsy and cerebral palsy.

Abbreviations: ADHD, Attention-Deficit/Hyperactivity Disorder; aHR, Adjusted Hazard Ratio; aOR, Adjusted Odds Ratio; ASD, Autism Spectrum Disorder; BSID-III, Bayley Scales of Infant and Toddler Development, 3rd Edition; CBCL, Child Behavior Checklist; CI, Confidence Interval; CP, Cerebral Palsy; CSF, Cerebrospinal Fluid; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; GBS, Group B Streptococcus; GMDS-ER, Griffiths Mental Development Scales – Extended Revised; ICD-10, International Classification of Diseases, 10th Revision; MDAT, Malawi Developmental Assessment Tool; NDI, Neurodevelopmental Impairment; NDD, Neurodevelopmental Disorder; OR, Odds Ratio; PSDD, Psychomotor and Speech Developmental Disorders; SES, Socioeconomic Status; VLOD, Very Late-Onset Disease; WISC-V, Wechsler Intelligence Scale for Children, 5th Edition; WPPSI-IV, Wechsler Preschool and Primary Scale of Intelligence, 4th Edition.

2.7 GBS disease in Canada

Robust epidemiological data on the burden and incidence of GBS disease are essential for guiding GBS vaccine development and planning for effective implementation. However, data on GBS in the Canadian population are limited compared to other high-income countries; existing studies are small and mainly conducted in specialized facilities, which limits their generalizability.[83,100,101] Additionally, large variations in healthcare systems, GBS colonization rates and screening effectiveness highlight the need for localized assessments.[102]

Incidence rates of EOD and LOD vary across Canada based on the location and healthcare setting. For example, a study in Alberta examining the serotype distribution of invasive GBS disease reported an average annual incidence of neonatal GBS infections at 0.64 per 1,000 total births (liveborn and stillborn).[103] This retrospective analysis, which used laboratory data from 1993 to 1999, identified 168 cases of neonatal GBS disease, with 57% classified as EOD and a corresponding case fatality rate of 9%.[103] In contrast, a smaller study in the Greater Toronto Area, analyzing GBS isolates collected between 2009 and 2012, found an annual incidence of EOD at 0.19 per 1,000 live births.[104] According to cases reported to the Canadian Notifiable Disease Surveillance System, the incidence of infant GBS disease (per 100,000 births) steadily increased from 25.0 in 2009 to 38.1 in 2016.[105] However, data from the subsequent two years showed a slight decline, with incidence decreasing to 36.1 in 2017 and further to 24.7 in 2018.[105] While national mortality estimates for GBS in Canada are unavailable, one study reported a mortality rate of 14% for GBS meningitis.[106] Additionally, estimates of GBS colonization rates in Canada vary by population; a 1998 multicenter study found an overall colonization rate of 11%,[107] whereas a later study in British Columbia estimated a rate of 30%.[108]

Building on national surveillance data, a 2019 study in Ontario documented a higher burden of infant GBS disease than previously reported by public health surveillance systems.[109] Using cases captured in the mandatory reporting system, the incidence of neonatal GBS disease (up to 28 days of life) was initially estimated at 52.6 cases per year. However, when health administrative databases with ICD-10 codes specifically identifying GBS were used, this incidence slightly increased to 65.2 cases per year. To further uncover the hidden burden of GBS disease, the authors reviewed published epidemiological data to estimate the proportion of various newborn syndromes attributable to GBS. By applying these proportions and incorporating additional cases, the estimated incidence surged to 230.8 cases per year. Notably, the study found that 23% of infant cases (under 1 month of age) went unreported, suggesting that GBS estimates derived from public health surveillance may significantly underestimate the true burden of the disease.[109]

2.8 Knowledge gaps and research rationale

With several GBS vaccine candidates advancing into late-stage clinical trials, gathering real-world data on the health and economic impacts of GBS disease has become imperative. In Canada, where data on both short- and long-term outcomes following GBS disease in infancy is limited, this information is essential for shaping evidence-based health policies, optimizing patient care, and conducting robust cost-effectiveness evaluations for both current preventive measures and emerging vaccine candidates.

As discussed in the previous section, the true incidence of GBS disease in Canada remains unclear with reported estimates ranging from 0.19 to 0.64 per 1,000 births.[103,104] Moreover, findings from Ontario suggest that public health surveillance systems may substantially underestimate the burden, with nearly one-quarter of infant cases going unreported.[109] These gaps underscore the urgent need for more comprehensive, population-based data to support accurate infant GBS burden estimation in Canada. Further, despite universal maternal screening and IAP being well-established preventive measures in many high-income countries, Canadian studies evaluating their effectiveness remain limited in number and often rely on outdated or regionally limited data with small sample sizes.[6]

While the mortality risks associated with infant GBS infection are well established,[6] data on the long-term risk of NDIs among survivors remains limited. A 2017 meta-analysis found that 18% of infants who experienced GBS meningitis in the first three months of life developed moderate-to-severe NDIs by 18 months of age.[8] However, only five of the 18 included studies were conducted in the past two decades, and most lacked comparator groups needed to assess causality.[8] Additionally, these studies rarely examined outcomes beyond two years of age, and often overlooked clinical domains such as hearing, vision, or milder impairments like behavioural and cognitive deficits. Furthermore, the risk of NDIs following GBS sepsis could not be estimated due to the small number of available studies.[8] Although more recent population-based studies from Norway, Denmark and the Netherlands have provided valuable insights into long-term outcomes,[7,89-90,94,98] similar data from Canada are lacking.

In addition to the health burden, understanding the economic impact of infant GBS disease is essential for guiding resource allocation and evaluating the cost-effectiveness of prevention and treatment strategies. Currently, Canadian data on the economic burden of GBS is limited, leaving a gap in understanding the healthcare costs associated with managing acute GBS infections and addressing long-term complications among survivors. Estimating these costs is especially important as several GBS vaccine candidates advance toward potential approval, underscoring the need for robust data to inform investment decisions.

These key gaps, ranging from epidemiological data to long-term health and economic impacts, are summarized in **Figure 3**. This figure illustrates how the identified knowledge gaps were translated into specific research rationales, which in turn shaped the objectives for this thesis that are addressed in subsequent chapters.

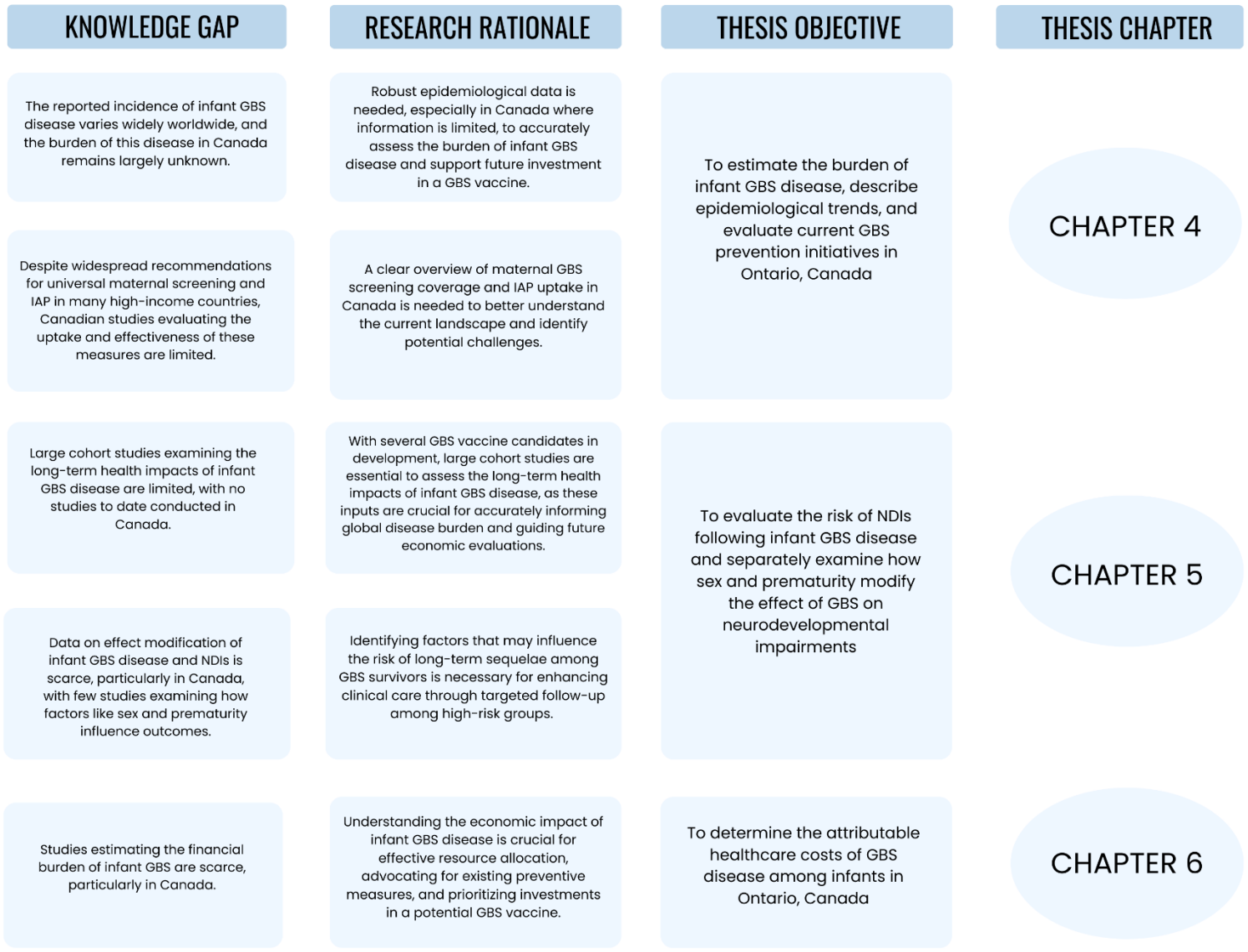

Figure 3. Overview of the knowledge gaps, research rationale and corresponding objectives of this thesis.

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CHAPTER 3. OVERVIEW OF METHODOLOGY COMMON TO ALL STUDIES

This chapter provides an overview of the core methodology and data sources used across all studies within this thesis. All three studies followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting of observational studies.[1]

3.1 Data sources

The Better Outcomes Registry & Network (BORN) Ontario was used to assemble the study population in all studies. This province-wide registry comprehensively gathers data on pregnancy, birth, and newborn outcomes for nearly all births (≥500 g or ≥20 weeks' gestation) in Ontario, Canada. Capturing approximately 140,000 births annually—representing about 40% of all births in Canada—BORN Ontario is the largest perinatal registry in the country, serving as a valuable resource for surveillance, quality improvement, performance measurement and research.[2]

To enable follow-up beyond infancy and supplement the data collected in BORN, the cohort was linked with health administrative data housed at ICES (www.ices.ca) (see **Figure 1**). ICES maintains a comprehensive provincial data repository containing longitudinal, coded, and linkable clinical and administrative records that capture nearly all interactions Ontario residents have with the publicly funded healthcare system. The linked databases used in this thesis varied somewhat by study, but consistently included the following core sources:

- *Ontario Laboratories Information System (OLIS):* Provides laboratory culture results.

- *Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD):* Contains data on hospitalizations, including medical diagnoses and procedures.
- *CIHI National Ambulatory Care Reporting System (NACRS):* Covers emergency department visits and outpatient clinic records.
- *Registered Persons Database (RPDB):* Provides information on healthcare eligibility and neighborhood income quintiles.
- *Ontario Health Insurance Plan (OHIP) Database:* Includes physician outpatient billing claims.
- *Ontario Marginalization Index (ON-Marg):* Provides data on area-level marginalization and socioeconomic status.

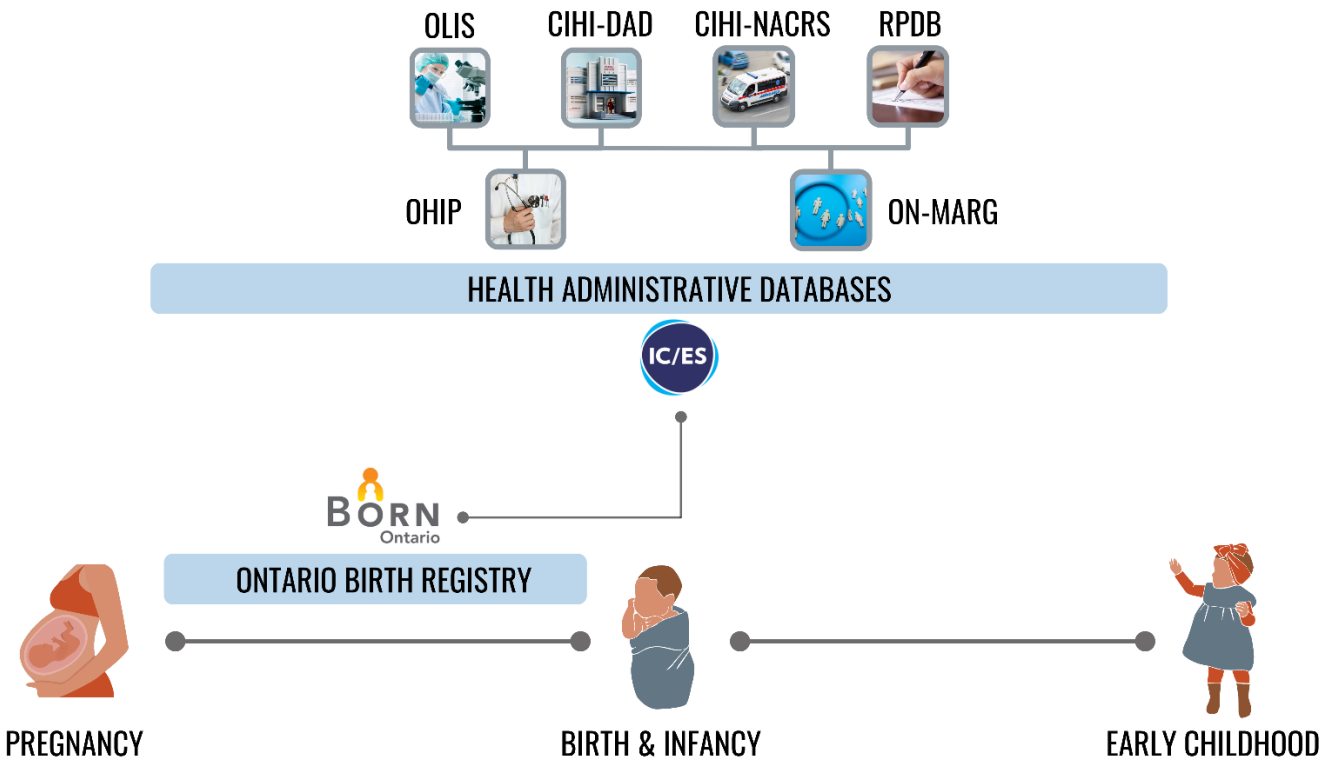

Figure 1. Illustration of data source linkages across perinatal continuum

Abbreviations: CIHI, Canadian Institute for Health Information; DAD, Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System; OHIP, Ontario Health Insurance Plan; OLIS, Ontario Laboratories Information System; ON-Marg, Ontario Marginalization Index; RPDB, Registered Persons Database.

3.2 Study population and follow-up

The study population for all three studies included all pregnancies and births in Ontario, Canada, between April 1, 2012, and March 31, 2018 (**Figure 2**). Distinct cohorts were used in each study to address specific research objectives, with follow-up periods tailored to the outcomes of interest.

The first study included two distinct cohorts, each serving a unique purpose (explained further in Chapter 4). ***Study 1 (Cohort #1)*** comprised pregnancies that ended in either a live birth

or stillbirth within the specified period, with one record retained per pregnancy (for multifetal pregnancies, a single record was included). Follow-up in this cohort concluded at birth. ***Study 1 (Cohort #2)*** was limited to only liveborn infants (one record per infant) from the same period, with follow-up extending to one year after birth.

Study 2 utilized a cohort of liveborn infants from the same timeframe as ***Study 1***, with follow-up extended to five years of age. This extended follow-up enabled the examination of longer-term health outcomes associated with GBS.

Finally, ***Study 3*** focused on liveborn infants from the same population but used a specific "index date," as described in Chapter 6, to mark the beginning of follow-up. Follow-up for this cohort continued for one year after the index date, allowing for the evaluation of healthcare utilization and costs attributable to GBS disease.

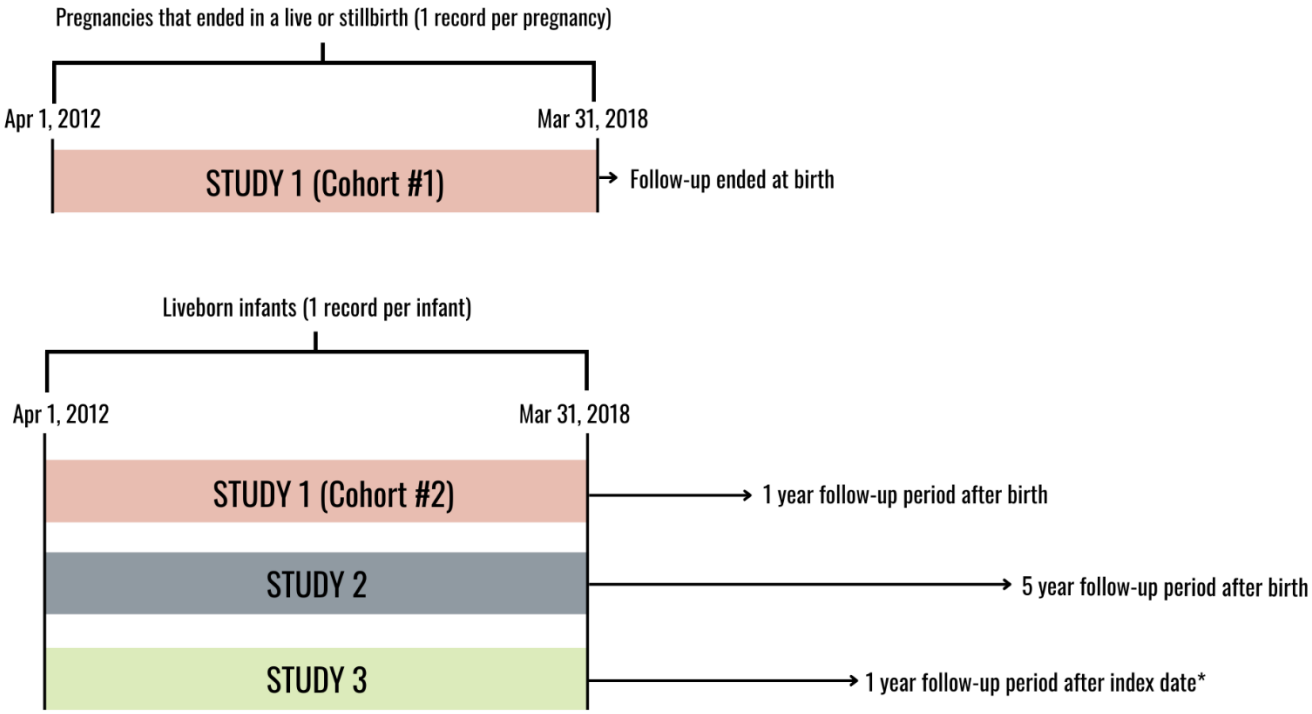

Figure 2. Overview of cohort formation and follow-up periods for each study
*The index date is explained in Chapter 6.

3.3 Ascertainment of GBS disease

In all studies, infant GBS disease was identified using a consistent methodology to ensure comparability across analyses. Infants were classified as having GBS disease if they met one of the following criteria: culture confirmation of GBS from a normally sterile site (such as blood or cerebrospinal fluid [CSF]) recorded in OLIS, the presence of one or more GBS-specific diagnostic codes (ICD-10-CA codes) in the health administrative databases (including DAD or NACRS), or both (**Figure 3**).

The primary reason for this dual capture approach was the variability in the initiation of data contributions to OLIS among participating hospitals, which resulted in incomplete specimen sample information during the earlier years of our study.[3] Additionally, research has shown that

blood culture sensitivity may be reduced among preterm infants and those exposed to antibiotics in utero.[4] Furthermore, not all infants with probable GBS sepsis undergo blood culture testing, and the necessary culture sites for capturing GBS in other forms (e.g., pneumonia) are not routinely collected.[5]

While no validation studies exist for diagnostic codes specific to GBS disease, the validity of a ICD-10-CA code for neonatal sepsis (P36) was evaluated by a Canadian validation study and reported a sensitivity of 38.4% and a specificity of 99.7% when validated against a clinical perinatal database.[6] Another population-based study from Switzerland evaluating ICD-10 codes for sepsis among pediatric patients with culture-confirmed bacterial or fungal infections reported a sensitivity of 60% and a positive predictive value (PPV) of 90%.[7]

For culture-confirmed GBS, infants were categorised as EOD (0–6 days), LOD (7–89 days) or ULOD (90–365 days) based on the specimen collection date in OLIS. When multiple specimens were collected, the date of the first positive culture was used to classify onset. For non-culture-confirmed cases identified through GBS-specific diagnostic codes, classification as EOD, LOD or ULOD was based on the date of the initial GBS-related visit (hospitalization or emergency department), referred to as the index GBS visit. The primary GBS presentation (e.g., sepsis, meningitis, pneumonia) was determined using the type of the earliest positive culture or the first instance of a diagnostic code on the index GBS visit when culture data were unavailable. In rare cases where both blood and CSF cultures were positive within 24 hours of each other, the case was classified as meningitis. Similarly, if both sepsis and meningitis codes were recorded during the same hospitalization, meningitis was assigned as the primary presentation. This approach ensured consistent classification of GBS across all cases, accounting for overlapping clinical presentations and variability in data availability.

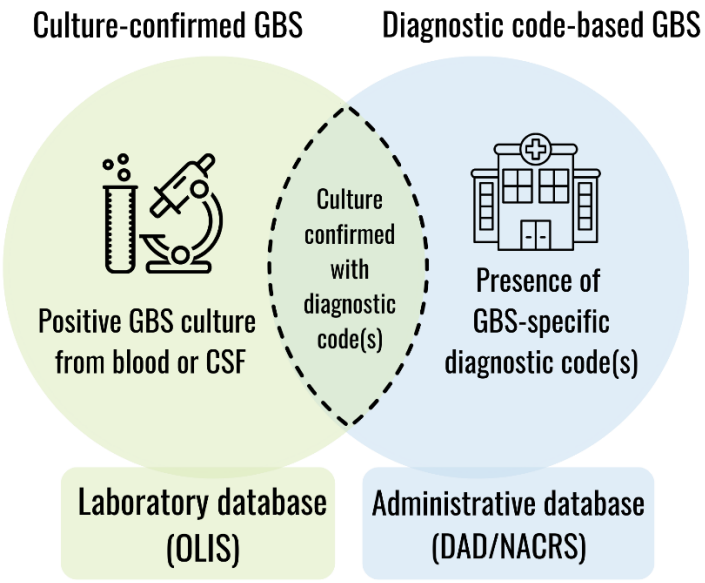

Figure 3. Overview of GBS case ascertainment using culture confirmation and diagnostic code(s).

Abbreviations: DAD, Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System; OLIS, Ontario Laboratories Information System.

3.4 References

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CHAPTER 4. MANUSCRIPT 1

Burden of infant Group B *Streptococcus* disease and impact of maternal screening and antibiotic prophylaxis in Ontario, Canada: a population-based cohort study

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https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(24)00241-2/fulltext

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4.1 Preface to chapter 4

This chapter presents the first manuscript, which estimates the burden of infant GBS disease in Ontario, Canada, and evaluates the association between current Canadian prevention methods (i.e., screening and intrapartum antibiotic prophylaxis) and infant disease rates. Following the abstract, a "Research in Context" section, required by *The Lancet Regional Health – The Americas*, situates this study within the broader evidence base, highlighting its added value and implications. Tables and figures accompanying the manuscript follow the references in Section 4.9, beginning on page 75. Author contributions are detailed on page 70, and the study appendix begins on page 90.

4.2 Abstract

Background: Group B *Streptococcus* (GBS) significantly contributes to neonatal sepsis and meningitis, with varying disease rates reported globally and limited population-based data. We estimated infant GBS disease burden in Ontario, Canada and assessed the association of maternal GBS screening (35-37 weeks) and intrapartum antibiotic prophylaxis (IAP) provision with infant disease rates.

Methods: Our population-based cohort study included pregnant individuals and their offspring from April 2012 to March 2018, utilising the provincial birth registry linked to health administrative data. GBS cases were ascertained through culture results and diagnostic codes. We calculated incidence rates for early-onset disease (EOD: 0-6 days), late-onset disease (LOD: 7-89 days), and ultra-LOD (ULOD: 90-365 days). Adjusted incidence rate ratios (aIRR) were derived via log-binomial regression to compare infant GBS rates according to screening and IAP-receipt.

Findings: Among 776,148 liveborn infants, we identified 803 with GBS, with multiples exhibiting a threefold incidence increase. Incidence rates of EOD, LOD and ULOD were 0.49, 0.46 and 0.07 per 1,000 livebirths, respectively. Of eligible pregnancies, 94% were screened; 23% screened positive, and 81% of them received IAP. Nearly 12% of term EOD infants had mothers who missed IAP despite screening positive. Maternal screening was associated with lower rates of any infant GBS disease (aIRR: 0.60; 95% CI: 0.45, 0.80). Among screen-positive births, IAP-receipt was associated with reduced rates of EOD (aIRR: 0.72, 95% CI: 0.48, 1.29) and LOD/ULOD (aIRR: 0.69; 95% CI: 0.46, 1.05), but confidence intervals included 1.0.

Interpretation: Our study, the largest Canadian investigation into infant GBS disease, highlights both widespread adoption and ongoing challenges of the current prevention strategy.

Funding: Canadian Institutes of Health Research.

Key Words: Group B *Streptococcus*; *Streptococcus agalactiae*; incidence; burden; estimate; early onset; late onset

4.3 Research in context

Evidence before this study

Group B Streptococcus (GBS) is a significant contributor to neonatal morbidity and mortality, surpassing the combined impact of other neonatal pathogens. We searched PubMed for studies reporting on the burden and epidemiologic trends of infant GBS disease, as well as studies evaluating the impact of screening and intrapartum antibiotic prophylaxis (IAP). Our search, conducted using key terms including "Group B Streptococcus", "Streptococcus agalactiae", "burden", "incidence", "epidemiology", "population-based study", "antibiotic prophylaxis", and "universal screening", was current as of February 26th, 2024. We focussed specifically on studies involving pregnant individuals and infants aged 0–12 months, with no language restrictions. Published incidence rates of infant GBS disease show considerable variability, ranging from 0.30 to 1.12 per 1000 live births, attributed to disparities in reporting practices, testing accessibility, genuine shifts in incidence, or ineffective preventive measures. A 2017 systematic review on the global burden of infant GBS emphasised the need for robust epidemiological data to accurately establish the true burden of disease and strengthen the rationale for future investment in a GBS vaccine. Despite the widespread recommendation and evaluation of universal maternal screening and IAP as preventive measures in numerous high-income countries, Canadian studies evaluating program effectiveness are notably scarce, often characterised by small sample sizes and outdated data. With several GBS vaccine candidates progressing into late-phase clinical trials, there is a renewed urgency to comprehend the current state of GBS screening capabilities and disease rates.

Added value of this study

With nearly 800,000 pregnancies included, this study stands as the largest Canadian investigation into infant GBS disease, providing an expansive landscape of maternal GBS screening coverage, IAP uptake and the epidemiology of infant GBS disease. Our study reveals a high maternal GBS screening coverage of 94%. While screening rates varied among certain demographic groups, no clear correlation with socioeconomic status emerged, suggesting successful program adherence across diverse populations in the region. However, opportunities for program improvement were apparent, particularly in enhancing IAP uptake among screen-positive individuals. Only 81% of screen-positive mothers received IAP and nearly 12% of term infants with early-onset GBS disease were born to mothers who missed the intervention entirely despite screening positive. Between 2012 and 2018 we identified 803 infants with GBS disease, an overall incidence rate of 1.0 per 1000 live births. While the incidence of early- onset exhibited a decline over the study period, incidences of late-onset disease and

ultra-late onset disease remained stable. Although several characteristics were associated with higher rates of infant GBS disease, the most notable was a nearly threefold increase in incidence among multiple births. Maternal screening was associated with a significant reduction in rates of both early- and late-onset disease, however, the protective association observed between IAP and these outcomes did not reach statistical significance, possibly due to misclassification of the exposure or outcome.

Implications of all the available evidence

Our findings underscore the widespread adoption of the current GBS screening prevention strategy while also revealing ongoing challenges. The incidence of late-onset GBS disease has remained unchanged over time, and a significant proportion of early-onset infants are born to mothers who fail to receive treatment despite testing positive during screening. These challenges highlight the need for alternative strategies, such as maternal vaccination, to provide more comprehensive protection against infant GBS disease.

4.4 Introduction

Group B *Streptococcus* (*Streptococcus agalactiae,* GBS) is a major contributor to neonatal morbidity and mortality, surpassing the combined neonatal deaths attributed to tetanus, pertussis, and respiratory syncytial virus.[1] Newborn GBS infections are categorised into early-onset disease (EOD: 0-6 days of life), late-onset disease (LOD: 7-89 days of life), and ultra-late onset disease (ULOD: 90-365 days of life). A less widely described form of GBS disease is prenatal-onset GBS disease, which occurs when GBS infection arises during pregnancy, prior to birth.[2] This form of GBS is associated with miscarriages and stillbirths (recent estimates indicate that GBS causes approximately 46,000 stillbirths annually[3]).

In many high-income countries, including Canada, the current prevention strategy involves universal culture-based screening of pregnant individuals between 35-37 weeks' gestation,

followed by intrapartum antibiotic prophylaxis (IAP) for positive culture results or certain risk factors.[4] However, challenges persist, including limited effectiveness against LOD, GBS-associated preterm births, and stillbirths.[3] Immunization with a GBS vaccine has been proposed as a potential solution and several candidates are in active development.[5,6]

Reported infant GBS disease rates vary widely due to differences in reporting and access to testing, genuine incidence shifts, or suboptimal preventive measures. Global burden estimates for GBS, published in 2017,[1,7] identified numerous epidemiological gaps, emphasizing the need for population-based data and analyses. Moreover, unlike other countries with universal GBS screening, Canadian studies assessing program effectiveness are scarce, small, and outdated.[8,9] With several vaccine candidates progressing into late-phase clinical trials,[6] there is a renewed need to understand the current state of GBS screening capabilities and disease rates.

We aimed to estimate the burden of infant GBS disease, describe epidemiological trends, and evaluate current GBS prevention initiatives in Ontario, Canada. Specifically, we assessed the uptake of maternal GBS screening and IAP-receipt and evaluated the association of these preventative measures with the risk of infant GBS disease.

4.5 Methods

4.5.1 Study population

We conducted a population-based retrospective cohort study in Ontario, Canada, covering registered births among individuals who delivered live or stillbirths, and their offspring, from April 1, 2012, to March 31, 2018. We excluded maternal records if they belonged to non-Ontario residents, mothers <12 or >50 years at delivery, those without continuous Ontario Health

Insurance Plan (OHIP) coverage during pregnancy, or records with administrative issues (e.g., invalid identifiers). For infants, we excluded records with mismatched birthdates, missing gestational age (if also absent on maternal record), lack of OHIP eligibility within 60 days of birth for liveborn infants, or gestational age <20 weeks or birth weight <500g, as these events are not systematically recorded in the registry.

Following these data exclusions, we created two separate cohorts to address each objective. Cohort #1 was used to describe the uptake of Canada's screening and IAP strategy and was therefore restricted to unique pregnancies (i.e., one record per pregnancy), regardless of whether the pregnancy ended in live or stillbirth or was a singleton or multifetal pregnancy. In cases of multifetal pregnancies, only one record was retained. Since screening is recommended between 35- and 37-weeks' gestation, this cohort was further limited to pregnancies eligible for screening (>35 weeks' gestation) to prevent incorrectly attributing pregnancies that were not eligible for screening to the unscreened group.

Cohort #2 was assembled to estimate infant GBS disease and evaluate the association between the screening/IAP use on the risk of GBS disease. This cohort was limited to liveborn infants (i.e., one record per infant), included multifetal births, and followed them from birth until one year, with the latest follow-up on March 31st, 2019. For details on cohort formation please refer to the supplement (Supplementary Figure S1).

This study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board (Protocol No. 20/11PE) and the ICES Privacy Office (Protocol 2023-0901-320-001). ICES is an

independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

4.5.2 Data sources

We used the Better Outcomes Registry & Network (BORN) Ontario to assemble the study population and capture sociodemographic and clinical data, including GBS screening status and IAP-receipt during delivery. This province-wide registry comprehensively documents births (≥500g or ≥20 weeks' gestation) from hospitals, birth centres, and midwifery practice groups (home births) across Ontario,[10] ensuring high-quality data as demonstrated in a validation study.[11]

To identify infant outcomes and supplement BORN data, we linked the cohort to eight health administrative databases at ICES (https://www.ices.on.ca/): the Ontario Laboratories Information System (OLIS) database for laboratory culture results; the Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) for hospitalizations (medical diagnoses and procedures); the CIHI National Ambulatory Care Reporting System (NACRS) for emergency department visits and outpatient clinics; the MOMBABY database for determining hospitalization episode information (e.g., length of stay); Registered Persons Database for healthcare eligibility and neighbourhood income quintiles; the Postal Code Conversion File for geographic information; the OHIP Database for physician outpatient billing claims; and the Ontario Marginalization Index for area-level marginalization and socioeconomic status. Data sets were linked by means of unique encoded identifiers and analysed at ICES. See Supplementary

Table S1 for details on each data source. We obtained diagnostic and procedural codes from the enhanced Canadian version of the *International Statistical Classification of Diseases and Related Health Problems*, *10th Revision* (ICD-10-CA) and the Canadian Classification of Health Interventions, respectively.

4.5.3 Exposures

The maternal GBS prevention strategy is captured through three components in BORN: 1) GBS screening completion (screened or unscreened); 2) GBS screening result (positive or negative); and 3) IAP-receipt (received IAP or did not receive IAP). The date that screening was conducted was not well documented, which limited our ability to confirm whether screening was completed within the recommended 35 to 37-week timeframe. Due to the absence of precise timing of GBS screening, Cohort #1 (used to assess screening/IAP uptake) included only pregnancies eligible for screening (delivered >35 weeks' gestation). Similarly, specific analyses related to screening/IAP evaluation in Cohort #2 were limited to births eligible for screening (>35 weeks' gestation). This approach aimed to exclude deliveries ineligible for GBS screening, thus preventing an incorrect inflation of the "unscreened" group with births not eligible for screening. Screening results were available only for those who were screened, while data on IAP-receipt were available regardless of the mother's GBS screening status due to potential administration for other indications (e.g., previous infant with GBS disease). Information on IAP type, dose, duration, or timing was not available.

4.5.4 Outcomes

The primary outcome, infant GBS disease, was identified through a dual capture approach: culture confirmation of GBS from a normally sterile site (blood or cerebrospinal fluid [CSF]) reported in the laboratory database (OLIS) and GBS-specific diagnostic codes (ICD-10-CA codes) in the health administrative databases (DAD, NACRS). Infants were included if either a culture confirmation or an ICD-10 code for GBS was identified (Supplementary Figure S2). This approach was chosen for several reasons. First, there were variations in the initiation of data contribution to OLIS among participating hospitals, leading to incomplete information on specimen samples in the earlier years of our study.[12] Second, research suggests reduced blood culture sensitivity among preterm births and infants exposed to antibiotics in-utero.[13] Lastly, not all infants with probable GBS sepsis undergo blood culture testing, and the required culture sites for capturing GBS in other forms (e.g., pneumonia) are not routinely collected.[14]

For culture-confirmed GBS, infants were categorized as EOD (0-6 days), LOD (7-89 days) or ULOD (90-365 days) based on the specimen collection date in OLIS. In instances with multiple specimens, we used the date of the first positive culture result. Non-culture-confirmed cases, identified through GBS-specific diagnostic codes (Supplementary Table S2), were classified as EOD, LOD or ULOD using the date for the initial GBS-related visit (hospitalization or emergency department), referred to as the index GBS visit. We defined the primary GBS presentation (GBS sepsis, meningitis, pneumonia) using the type of the earliest positive culture or the first instance of a diagnostic code on the index GBS visit if culture data were unavailable.

4.5.5 Statistical analyses

We described the study population using frequencies for categorical variables and medians (interquartile ranges) for continuous variables. Maternal screening and IAP rates were reported among Cohort #1 which included screening eligible pregnancies (>35 weeks' gestation). Using the live birth cohort (Cohort #2), GBS disease incidence rates (per 1,000 livebirths), including types (EOD, LOD, ULOD), were computed for the overall cohort and across various characteristics.

Next, using log-binomial regression, we calculated crude and adjusted incidence rate ratios (IRR) with 95% confidence intervals (CI) for infant GBS disease rates across each of the following groups: 1) Screened vs. Unscreened; 2) Screened positive with IAP vs. Screened positive without IAP; 3) Screened negative with IAP vs. Screened negative without IAP. As previously mentioned, these analyses were limited to screening eligible births (born >35 weeks' gestation) to prevent the incorrect inflation of the unscreened group with deliveries that were not eligible for screening. Models were adjusted for maternal age, parity, multiple birth, pre-existing maternal conditions, season and fiscal year of birth, prenatal care adequacy, area-level marginalization indices (residential instability, material deprivation, dependency and ethnic concentration), rurality, mode of delivery, smoking and substance use during pregnancy, and neighbourhood income quintile (definitions in Supplementary Table S3). We utilized generalised estimating equations with an independent correlation structure to account for more than one livebirth delivery from the same individual (for instance, subsequent pregnancies over time or multifetal pregnancies) throughout the study period (see Appendix S1 for details).

Prior to running log-binomial models, we employed multiple imputation (fully conditional specification, MI procedure in SAS Version 9.4)[15] to address missing values. Ten imputation cycles were conducted, pooling results from each dataset to incorporate variability introduced by imputed values. See Appendix S2 for details on MI methods and results. All analyses used SAS Enterprise Guide 8.3 (SAS Institute). In accordance with ICES privacy policies, cell sizes less than six could not be reported. Suppression of other cell counts, and corresponding percentages, was occasionally required to prevent recalculation of the unreportable small cell counts.

4.5.6 Sensitivity analyses

Relying solely on culture confirmation may underestimate GBS disease burden and overestimate prevention success, as not all GBS infections are confirmed through culture.[14] However, GBS diagnostic codes documented on infant records might be precautionary or premature, especially among infants with EOD where the birthing individual also screened positive. To assess the robustness of our findings, we conducted a sensitivity analysis, implementing validation checks for GBS infants identified solely based on diagnostic codes. We excluded infants who (i) only tested negative for blood or CSF in OLIS; (ii) tested positive for GBS only through a non-sterile specimen site (e.g., urine); (iii) had documented EOD but a length of stay <2 days; or (iv) had diagnostic code B95.1 (GBS as cause of disease) without any other specific GBS diagnostic codes. We reassessed associations between maternal exposure groups and GBS disease risk using the remaining infants, as well as other GBS subgroups, such as GBS-meningitis and GBS-sepsis cases.

We examined whether missing exposure information on screening completion or IAP-receipt were linked to other factors potentially impacting the validity of our findings using standardized differences, with an absolute difference >0.10 signalling an imbalance. Finally, we reassessed the relationship between maternal exposure groups and infant GBS risk through a complete case analysis, deviating from the primary analysis that utilized multiple imputation.

4.5.7 Role of funding source

This study was supported by the Canadian Institutes of Health Research (CIHR) through an operating grant (PJT-162338) awarded to NT, and a CIHR Doctoral Research award (GR002845) awarded to RF. MS is supported via salary awards from the BC Children's Hospital Foundation and Michael Smith Health Research BC. BS is supported by a Tier 2 Canada Research Chair in Economics of Infectious Diseases held by CRC-950-232429. The funder had no role in data collection, data analysis, data interpretation, or writing up of the manuscript. This work was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This document used data adapted from the Statistics Canada Postal CodeOM Conversion File, which is based on data licensed from Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from ©Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information compiled and provided by CIHI and the Ontario Ministry of Health. The analyses, conclusions, opinions and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. This study is based in part on data provided by Better Outcomes Registry and Network ("BORN"), part of the Children's

Hospital of Eastern Ontario. The interpretation and conclusions contained herein do not necessarily represent those of BORN Ontario.

4.6 Results

4.6.1 Uptake of maternal GBS screening and IAP (Cohort 1)

Following data exclusions, a total of 781,241 livebirths and stillbirths were captured between 2012 and 2018, of which 767,890 were unique pregnancies. Among these pregnancies, 742,549 (96.7%) were eligible for screening (delivered >35 weeks' gestation) and included in Cohort #1 (Supplementary Figure S1A). Of those with complete information (Supplementary Figure S1B), 94.0% (663,791/706,492) were screened and 23.4% screened positive for GBS (151,400/647,143).

Screening rates were lower among individuals who were older (≥35 years), delivered in an earlier year (fiscal year 2012-13), were multiparous, had a multiple birth or reported smoking or substance use during pregnancy (Table 1). Notably, individuals with caesarean deliveries before the onset of labour showed lower screening rates (78.1% [73,740/94,441]), compared to other birth types. There was no clear socioeconomic gradient, with screening rates remaining consistent across neighbourhood marginalization indices and income quintiles.

Among pregnancies in Cohort #1 with complete information on IAP-receipt, 21.2% received IAP (147,620/695,132), whereas among GBS screen-positive pregnancies, 81.2% (122,973/151,400) received IAP. Across all screening eligible pregnancies, individuals who delivered by caesarean without preceding labour had the lowest IAP rates (8.2% [7,692/93,872]), while those with PPROM had the highest (51.6% [2,009/3,894]). IAP-receipt did not exhibit a clear gradient for any other characteristics (Table 1). While screening and IAP rates were calculated exclusively

among those with complete data, sensitivity analyses indicated minimal impact from this exclusion on our overall interpretations (Supplementary Tables S5 and S6).

4.6.2 Incidence and trends of infant GBS disease (Cohort #2)

Of the 781,241 livebirths and stillbirths captured, 776,148 livebirths were included in Cohort #2 (Supplementary Figure S1A). In this cohort, we identified 803 infants with GBS disease (1.03 per 1,000 livebirths) across laboratory and health administrative databases (Supplementary Figure S2). Of these, 51.4% (413/803) were male and 48.76% (390/803) were female. Culture confirmation was present among 15.4% (124/803) of cases (Figure 1A). Incidence (per 1,000 livebirths) of EOD (n=383), LOD (n=360), and ULOD (n=60) was 0.49 (95% CI: 0.45,0.54), 0.46 (95% CI: 0.42,0.51) and 0.07 (95% CI: 0.06, 0.09), respectively. Between fiscal years 2012-13 and 2017-18, the overall incidence (per 1,000 livebirths) of EOD declined from 0.65 (95% CI: 0.51, 0.78) to 0.41 (95% CI: 0.30, 0.52), whereas LOD incidence and ULOD incidence remained stable (Supplementary Figure S3).

Maternal characteristics with higher infant GBS disease rates included younger age (20 to <25 years), nulliparity, smoking during pregnancy, having a caesarean delivery following the onset of labour (spontaneous or induced), and having chronic hypertension, PPROM, or preeclampsia (Table 2). No distinct gradient in area-level marginalization was observed. The incidence of GBS (per 1,000 livebirths) was nearly three times higher among multiples (2.74) compared to singletons (0.97), and over five times higher among preterm births (4.27) compared to term births (0.76).

4.6.3 Clinical characteristics of infant GBS disease (Cohort #2)

GBS disease was recorded within the first 3 months of life in over 90% of cases (n=743), with over 80% of EOD infants (n=321) captured within the first 24 hours (Figure 1B). The median age at diagnosis was 29 days (interquartile range [IQR]: 16-45) for LOD infants, and 121 days (IQR: 100-184) for ULOD infants. Of all GBS-infected infants (n=803), 24.5% required mechanical ventilation, with 12.0% necessitating long-term durations (≥96 hours) and 16.4% experiencing respiratory distress syndrome (Table 3). Infants with EOD exhibited a higher frequency of respiratory distress syndrome and a greater need for mechanical ventilation compared to those with LOD/ULOD. Preterm birth was more common among infants with EOD (40.5%), compared to those with LOD/ULOD (25.5%).

Approximately 82% (314/383) of infants with EOD required admission to a special care unit, compared to 26% (110/420) of LOD/ULOD infants. Most presentations were sepsis (63.5%), with higher proportions observed among EOD infants. In LOD/ULOD, initial presentation with meningitis was more common than in EOD, with rates of 18.3% (77/420) versus 5.7% (22/383). Early-onset presentations were more common among very preterm (<28 weeks) and moderate-to-late preterm (28 to <37 weeks) births, while late-onset presentations were more prevalent in term births. Ultra-late-onset presentations were consistent across all gestational age categories (Supplementary Table S7).

4.6.4 Impact of prevention strategies on rates of infant GBS disease (Cohort #2)

Among screening eligible births (>35 weeks' gestation) in Cohort #2, the incidence of any infant GBS disease (per 1,000 livebirths) was 0.75 in the screened group and 1.30 in the unscreened

group (adjusted IRR [aIRR]: 0.60, 95% CI: 0.45, 0.80). Similarly, screening was associated with a 44% reduction in the rate of EOD (aIRR: 0.56; 95% CI: 0.37, 0.86) and a 46% reduction in the rate of LOD/ULOD (aIRR: 0.54; 95% CI: 0.38, 0.78) (Table 4 and Supplementary Figure S4). Results remained consistent across all subcategories of GBS disease (Supplementary Table S8). The incidence of EOD (per 1,000 livebirths) among infants born to mothers who screened positive and received IAP was 0.71, compared to 0.92 among those who screened positive but did not receive IAP (IRR: 0.77, 95% CI: 0.49, 1.21). Even after controlling for confounding, the confidence intervals included the null value (aIRR: 0.72, 95% CI: 0.48, 1.29). Among screen-negative births, those who received IAP had a 35% reduction in the rate of EOD, compared to those who did not (IRR: 0.65, 95% CI: 0.10, 4.66); however, confidence intervals included 1.0. Results remained consistent even after adjusting for confounding (Table 4).

Among screen-positive births, IAP-receipt was associated with a reduction in the rate of LOD/ULOD, however confidence intervals included 1.0 (aIRR: 0.69, 95% CI: 0.46, 1.05). In almost all subgroups of GBS, the incidence was highest among screen-positive births that did not receive IAP and lowest among screen-negative births that received IAP (Table 4 and Supplementary Tables S8 and S9). An exception was among rates of LOD/ULOD, which were similar in screen-negative births that received IAP (0.25 per 1,000 livebirths) and did not receive IAP (0.23 per 1,000 livebirths). Similarly, in infants born to screen-negative mothers, the rates of GBS-meningitis were comparable in those who received (0.12 per 1,000 livebirths) and did not receive (0.13 per 1,000 livebirths) IAP (Supplementary Table S8). Results remained consistent across all sensitivity analyses examining various GBS subgroups (Supplementary Table S8), and

a complete cases analysis (Supplementary Table S9).

Among EOD infants born at term, 92.2% (202/219) had mothers who were screened. Of those with complete data (n=189), 43.4% screened positive and received IAP, while 11.6% did not receive IAP, despite screening positive. The remaining 85 EOD infants (45.0%), whose mothers screened negative, did not receive IAP (Supplementary Figure S5).

4.7 Discussion

In this population-wide study of nearly 800,000 pregnancies in Ontario, Canada, maternal GBS screening coverage was 94%. While screening rates were lower among certain groups (older age, earlier year of delivery, multiple births, etc.), no clear correlation with socioeconomic status was found, potentially indicating success in the current screening program. Opportunities for improving IAP uptake, however, were apparent, with only 81% of screen-positive individuals receiving IAP, and nearly 12% of term infants with EOD being born to mothers who missed the intervention despite screening positive for GBS. Between fiscal years 2012 and 2017, the overall incidence of infant GBS disease in the first year of life was 1.0 per 1,000 livebirths; the incidence of EOD declined over this period, while LOD and ULOD incidences remained stable. Several characteristics were associated with higher rates of infant GBS disease, including a nearly threefold increased incidence among multiple births. Maternal GBS screening was associated with a significantly lower incidence of EOD and LOD/ULOD disease. IAP-receipt was associated with a reduction in the rate of EOD, irrespective of the mother's screening results; however, the reduction was not statistically significant. Across almost all subcategories of GBS disease, the incidence was highest among screen-positive births without IAP and lowest

among screen-negative births with IAP. Exceptions were observed for outcomes of LOD/ULOD and GBS-meningitis, where IAP-receipt did not impact disease rates when the mother screened negative.

This is the largest Canadian study on infant GBS disease burden, revealing an overall incidence of 1.0 per 1,000 livebirths. Similar to previous reports,[16,17] over 90% of GBS cases in our study occurred in the first 3 months of life, with most EOD cases documented in the first 24 hours. While an earlier Canadian study reported a lower rate of GBS (0.58 per 1,000 livebirths in infants <90 days),[18] recent provincial estimates reported rates closer to 1.8 per 1,000 livebirths.[19] Only 15% of infants with GBS in our study were confirmed through culture. This was likely primarily due to incomplete capture of laboratory-diagnosed outcomes in the OLIS dataset, which has been documented in a previous study,[12] and supports our decision to supplement case ascertainment with GBS-diagnostic codes. Other factors include reduced sensitivity of blood cultures in preterm infants exposed to antibiotics in utero, variability in testing practices among infants with "probable" GBS sepsis, and irregular collection of cultures from GBS infection sites presenting in other forms such as pneumonia.[13,14] Nonetheless, our overall rate of EOD (0.49 per 1,000 livebirths) aligns with a recent meta-analysis reporting 0.37 (95% CI: 0.30, 0.44) for EOD in high-income countries.[17] While overall rates of LOD remained stable throughout our study, consistent with other studies,[20,21] other studies have found rising incidences of LOD.[22,23]
The incidence of GBS among multiple births was three times higher than in singleton births. Consistent with our findings, recent studies suggest that GBS disease in one sibling of a multiple birth increases the risk for the others by 17%, a rate tenfold higher than the risk attributed to maternal colonization.[24]

While GBS screening is universally recommended in Canada regardless of birthing method, our study found lower screening rates among those with caesarean sections without preceding labour. Although the risk of EOD among full-term neonates born via caesarean section performed before the onset of labour is low, it is crucial to recognize that caesarean delivery does not eliminate the risk of neonatal transmission, as GBS can cross intact membranes.[25] Moreover, prenatal-onset GBS disease can occur regardless of the mode of delivery.[2]

In the era of universal screening and IAP policies, determining EOD rates among infants whose mothers have GBS risk factors but lack exposure to IAP is challenging. Nevertheless, our study found that maternal screening completion was associated with a significant reduction in the risk of infant GBS disease up to one year of age. Screening may prompt mothers and healthcare providers to take necessary precautions during and after birth, such as increased surveillance and improved hygiene practices. While the reduction in EOD risk associated with maternal IAP-receipt among screen-positive individuals did not reach statistical significance in our study, the magnitude and direction of the point estimate were consistent with other studies.[26] Since we relied on the date of specimen collection or hospitalization as a proxy for symptom onset, there is a possibility that infants with EOD were incorrectly categorized as LOD. This misclassification would dilute the observed effect of IAP on EOD, making IAP appear less effective than it truly is. While existing reviews suggest that IAP reduces the risk of EOD,[26,27] evidence regarding its impact on LOD/ULOD rates remains limited. One Italian prospective cohort investigating 100 infants with LOD found that IAP was associated with delayed presentations and milder symptoms of LOD.[23]

Among screen-negative births, we observed a possible reduction in EOD rates with maternal IAP-receipt that was not seen with LOD/ULOD rates. Although the estimate was not statistically significant, this observed difference may be attributed to variations in GBS colonization dynamics between screen-positive and screen-negative mothers. Screen-negative mothers might have lower or intermittent colonization levels, potentially influencing the effectiveness of IAP.[23] Moreover, while IAP might be administered to screen-negative mothers due to specific EOD risk factors, its impact on LOD, which can occur through diverse transmission routes, might be less pronounced. Some studies suggest that IAP could delay LOD onset or mitigate its severity by altering the mode of acquisition from vertical to horizontal transmission.[22] However, given that GBS may persist for weeks after IAP administration, mothers could still serve as a postnatal source of transmission.[23]

An inherent assumption of the current screening approach is that GBS colonization at the time of screening is an acceptable predictor of colonization at delivery, adding to its practicality but also presenting challenges including unnecessary antibiotic treatment for if colonization is no longer present at delivery, the potential for false-negative results, and instances where individuals not colonized at the time of screening become colonized by delivery.[28] In our study, 45% of term infants with EOD had screen-negative mothers who did not receive IAP. Similarly, other studies have observed a substantial number of EOD infants born to mothers with inadequate IAP administration, mainly attributed to negative or unknown maternal GBS status.[20,29,30] These challenges highlight the need for alternative strategies such as maternal vaccination to provide more comprehensive protection against infant GBS disease.

The main strength of our study lies in the accessibility of population-based databases and a comprehensive registry, offering detailed sociodemographic and clinical information about mothers and their infants up to one year after birth. This allowed us to assemble a substantial sample of mother-infant pairs and identify 803 infants with GBS, even in the context of low incidence.

This study also has important limitations. Data on the duration, type, dose, and timing of IAP were lacking, limiting our ability to assess the validity of the variable, the appropriateness of IAP administration before delivery,[4] its effectiveness based on antibiotic type, and the reasons for non-administration of IAP. Additionally, some individuals may have received IAP based on risk factors for EOD that were not captured in our dataset. Furthermore, we lacked information regarding the exact timing of screening, GBS serotypes and antibiotic-associated side effects to the birthing individual. Given the retrospective nature of the study, misclassification of infant GBS disease, including the type (EOD, LOD, ULOD) is possible. As previously mentioned, we used the specimen collection date or hospital admission date as a proxy for the timing of disease onset, which may not accurately reflect the true onset. To cross-validate our approach, we compared cases with both culture and diagnostic code, and found that both specimen collection and hospital admission dates similarly defined the type of GBS disease. Nevertheless, infants may have still been misclassified, potentially affecting the early versus late-onset stratified analyses. As noted earlier, infants born to mothers who screened positive for GBS might be more likely to have a GBS diagnostic code as a precautionary measure. However, our findings remained consistent even after excluding GBS infants that potentially fell into this category. The

possibility of residual confounding in our findings due to unmeasured or unknown confounders cannot be dismissed. Finally, despite using multiple imputation to address missing data and conducting sensitivity analyses to understand its impact, we acknowledge the inherent limitation of assuming that our data was missing at random.

Our study stands as the largest Canadian investigation into infant GBS disease and marks the first population-based analysis of the impact of universal maternal GBS screening and IAP administration on infant disease rates. While our findings reveal widespread adoption of maternal GBS screening in Ontario with negligible socioeconomic disparities, opportunities for improving IAP uptake were apparent. Despite maternal screening being associated with significant reductions in rates of both EOD and LOD, the observed protective association between IAP and these outcomes did not reach statistical significance, possibly due to misclassification of the exposure or outcome. Nevertheless, inherent challenges of the current strategy suggest the need for exploring alternatives like maternal vaccination for broader protection against infant GBS disease.

Author contributors: **RF**, DBF, NT, DE, BS and KB, NC, TL and SB conceived the study protocol, study design and analytical approach. **RF** linked the administrative data sources to create the study cohort and performed the statistical analyses, which were supervised by DBF and DE. WP provided analytical guidance and revisions to data sources at ICES. **RF** and DBF drafted the manuscript. All authors contributed to data interpretation, revised the manuscript for important intellectual content, approved the final version to be published and agreed to be

accountable for all aspects of the work.

Data sharing statement: The dataset from this current study is held securely in coded form at ICES. Even though data-sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those meeting pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors on request, with the understanding that the computer programs may rely on coding templates or macros that are unique to ICES and, therefore, are inaccessible or may need modification.

Declaration of interests: MS has been an investigator on projects funded by Pfizer, Merck, Moderna, Sanofi Pasteur, and GlaxoSmithKline (all unrelated to study). All funds have been paid to his institute, and he has not received any personal payments. KW is the CEO of CANImmunize Inc and served as a member of the independent data safety monitoring committee for the Medicago COVD-19 vaccine trial. When this project was funded and initiated, DBF was employed by the University of Ottawa and had an academic appointment at the Children's Hospital of Eastern Ontario Research Institute; she is now employed by Pfizer and works on an unrelated topic. DEC has been an investigator on projects funded by Moderna and Pfizer. All funds have been paid to her institute, and she has not received any personal payments. AM has received research funds to her institution from Pfizer and Sanofi Pasteur and received personal fees for advisory boards and DSMBs from Astra-Zeneca, GlaxoSmithKline, Medicago, Merck, Moderna, Pfizer, Roche and Sanofi Pasteur. SB is the director of the Centre for Vaccine Preventable Diseases at the University of Toronto, which has received support from Merck,

Sanofi and Pfizer. All funds are paid to the institute and are subject to the University of Toronto's governance policies.

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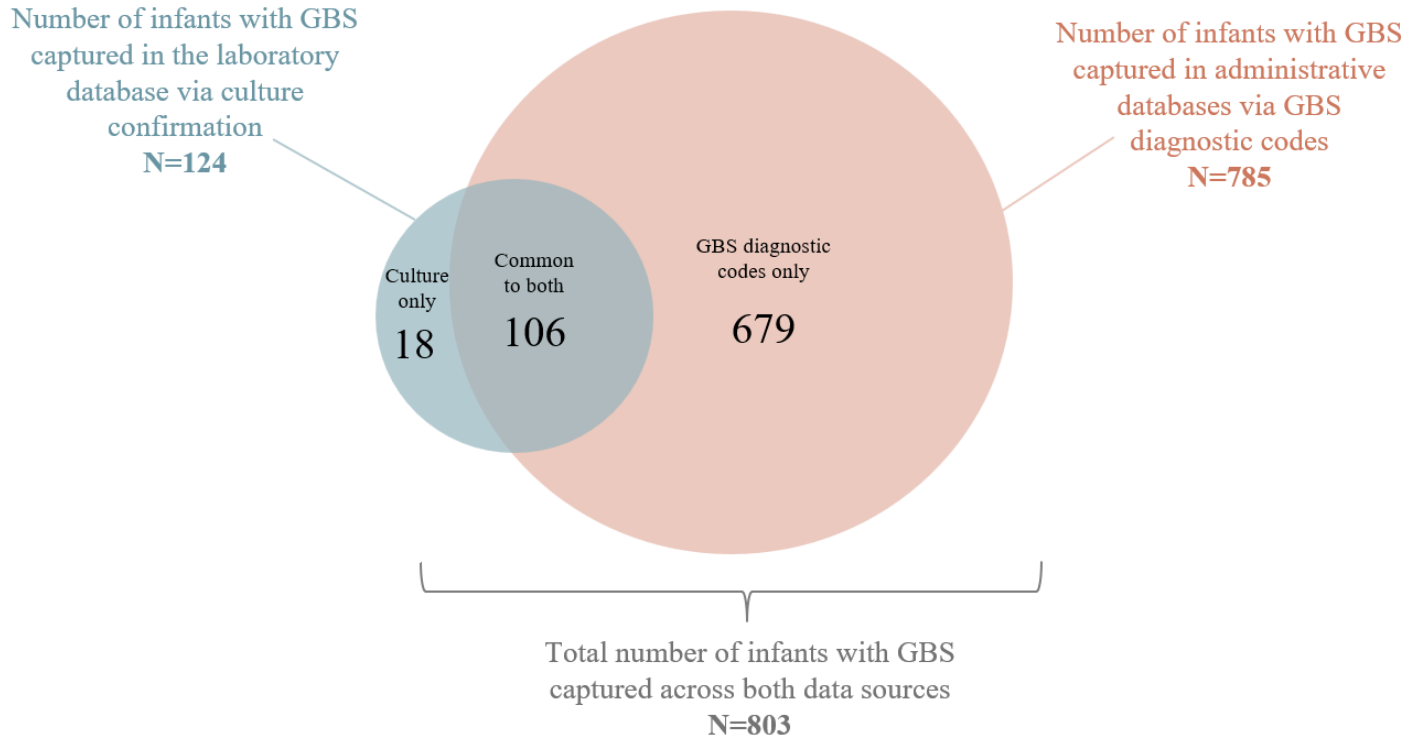
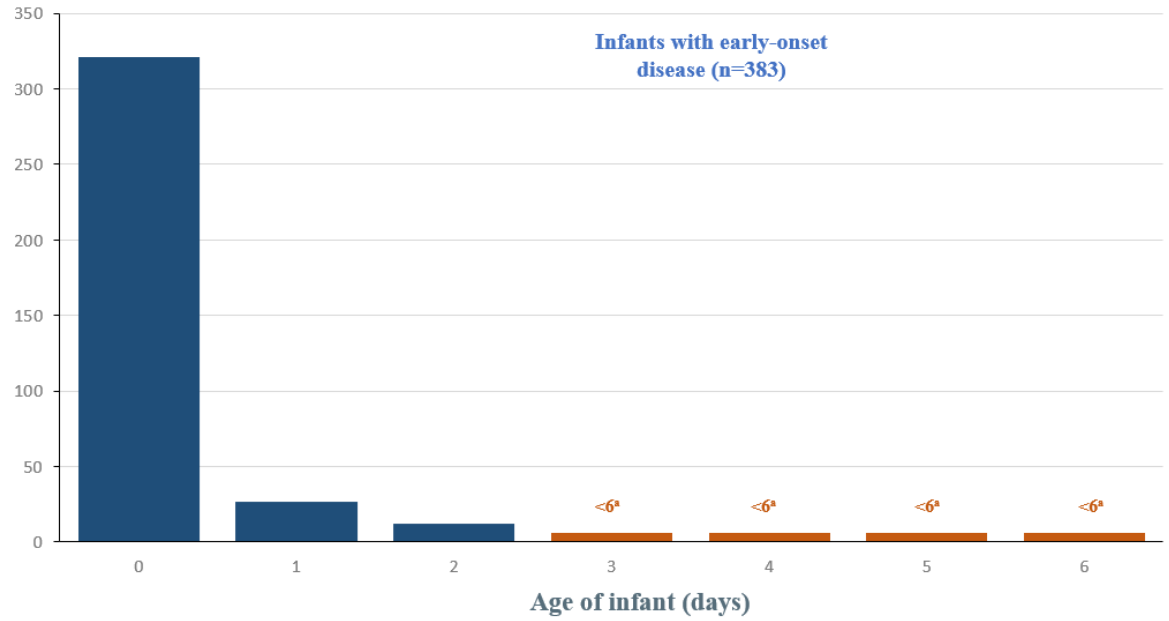
4.9 Manuscript tables and figures

A.



B.


Infants with early-onset disease (n=383)
350
300
250
200
150
100
50
0
<6[a]
<6[a]
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0
1
2
3
4
5
6
Age of infant (days)

C.

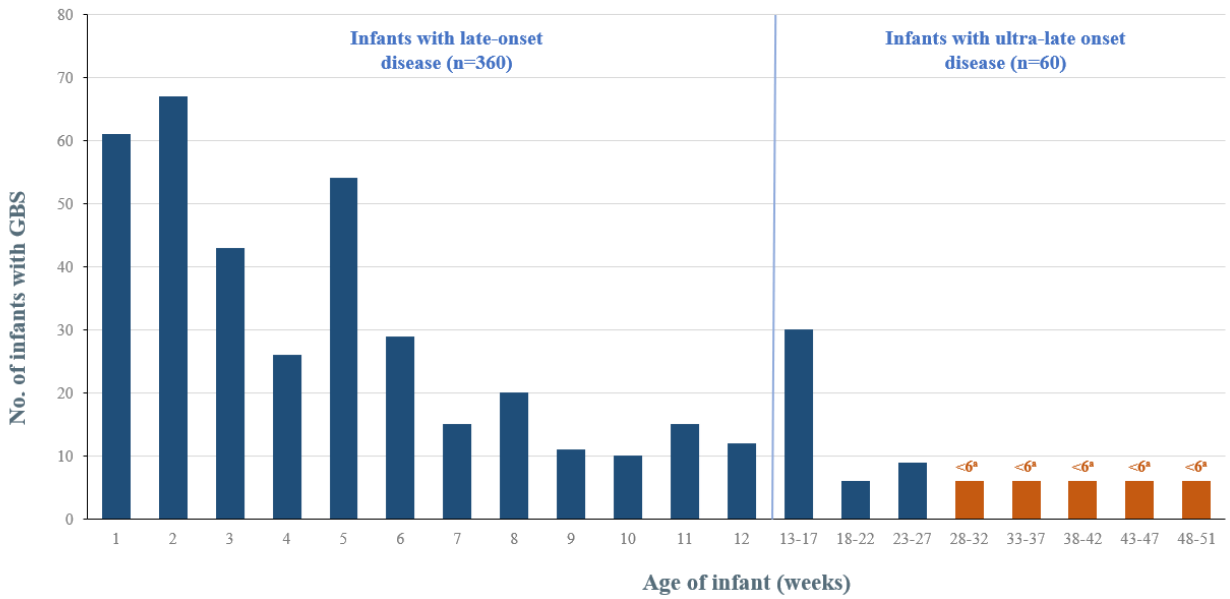


Figure 1. Distribution of infant Group B Streptococcus (GBS) disease occurrences by data source and infant age. (A) Venn diagram illustrating overlap of cases with respect to laboratory (OLIS) and health administrative (DAD, NACRS) databases. (B) Histogram showing infants with early-onset disease by infant age in days. (C) Histogram showing infants with late- and ultra-late onset disease by infant age in weeks. Each week represents a 7-day interval, starting from day 7 (e.g., week 1 includes days 7 to <14, week 2 includes days 14 to <21, etc.). [a] The orange histogram bars have been suppressed and set to a constant value of 6 due to small cell counts (n < 6)

Table 1. Maternal Group B *Streptococcus* (GBS) screening and intrapartum antibiotic prophylaxis (IAP) rates, among screening eligible pregnancies (>35 weeks' gestation) in Cohort #1, by sociodemographic, pregnancy and birth characteristics

Characteristic	No. screened / total eligible [a]	Screening rate (per 100 eligible pregnancies)	No. received IAP / total eligible [a]	IAP rate (per 100 eligible pregnancies)
Overall	663,791 / 706,492	94·0	147,620 / 695,132	21·2
Maternal age, years				
<20	15,042 / 15,947	94·3	3,890 / 15,937	24·1
20 - <25	70,999 / 75,508	94·0	16,896 / 75,036	22·5
25 - <30	181,349 / 191,867	94·5	40,039 / 188,821	21·2
30 - <35	246,211 / 261,336	94·2	53,948 / 256,190	21·1
>=35	150,190 / 161,834	92·8	32,847 / 159,148	20·6
Fiscal year of birth [b]				
2012-13	108,916 / 118,607	91·8	25,678 / 115,444	22·2
2013-14	109,011 / 117,424	92·8	26,458 / 119,764	22·1
2014-15	111,470 / 118,188	94·3	24,276 / 117,107	20·7
2015-16	111,413 / 117,710	94·7	24,000 / 114,814	20·9
2016-17	111,533 / 117,541	94·9	23,438 / 114,384	20·5
2017-18	111,448 / 117,022	95·2	23,770 / 113,619	20·9
Season of birth				
Fall	172,955 / 184,001	94·0	38,863 / 181,111	21·5
Spring	159,293 / 169,632	93·9	35,420 / 167,422	21·2
Summer	166,547 / 177,359	93·9	36,669 / 174,149	21·1
Winter	164,996 / 175,500	94·0	36,668 / 172,450	21·3
Multiple birth [c]				
Yes	7,262 / 8,646	84·0	1,663 / 8,734	19·0
No	656,529 / 697,846	94·1	145,957 / 686,398	21·3
Parity				
Nulliparous	286,520 / 297,340	96·4	67,474 / 293,481	23·0
Multiparous	370,357 / 402,161	92·1	79,215 / 397,246	19·9
Missing	6,914 / 6,991	98·9	931 / 4,405	21·1
Type of birth [d]				
Assisted vaginal	62,009 / 63,383	97·8	14,665 / 62,085	23·6

Spontaneous vaginal	442,454 / 458,563	96·5	103,918 / 450,871	23·1
Caesarean section after labor (spontaneous or induced)	85,588 / 90,105	94·5	21,345 / 88,304	24·2
Caesarean section without preceding labor	73,740 / 94,441	78·1	7,692 / 93,872	8·2
Pre-existing maternal health conditions [e]				
Asthma	24,694 / 26,466	93·3	5,929 / 26,193	22·6
Diabetes	5,259 / 5,997	87·7	1,602 / 5,984	26·8
Chronic hypertension	4,929 / 5,439	90·6	1,274 / 5,514	23·1
Heart disease	670 / 718	93·3	153 / 720	21·3
Thyroid disease	27,795 / 29,524	94·1	6,267 / 28,709	21·8
Any pre-existing maternal health condition	60,635 / 65,111	93·1	14,452 / 64,119	22·5
Obstetrical complication				
Placenta abruption	685 / 774	88·5	154 / 779	19·8
Placenta previa	2,036 / 2,925	69·6	300 / 2,915	10·3
PROM	6,538 / 6,866	95·2	2,050 / 6,837	30·0
PPROM	2,851 / 3,830	74·4	2,009 / 3,894	51·6
Gestational diabetes	40,847 / 44,216	92·4	9,669 / 43,567	22·2
Preeclampsia	5,433 / 6,047	89·9	1,535 / 5,992	25·6
Eclampsia	386 / 429	90·0	89 / 406	21·9
Gestational hypertension	23,287 / 24,862	93·7	6,118 / 24,614	24·9
HELLP	447 / 528	84·7	142 / 529	26·8
Smoked during pregnancy				
Yes	64,398 / 70,283	91·6	15,701 / 70,214	22·4
No	581,813 / 618,088	94·1	128,336 / 607,312	21·1
Missing	17,580 / 18,121	97·0	3,583 / 17,606	20·4
Substance use during pregnancy [f]				
Yes	12,971 / 14,576	89·0	3,504 / 14,631	24·0
No	621,886 / 662,137	93·9	138,157 / 653,073	21·2
Missing	28,934 / 29,779	97·2	5,959 / 27,428	21·7
Rural residence				
Yes	67,870 / 73,379	92·5	14,842 / 73,513	20·2
No	595,206 / 632,334	94·1	132,625 / 620,854	21·4

Missing	715 / 779	91·8	153 / 765	20·0
Neighborhood median family income quintiles				
1 (Lowest)	141,409 / 151,810	93·2	32,997 / 151,032	21·9
2	132,232 / 140,966	93·8	29,611 / 138,206	21·4
3	136,530 / 145,349	93·9	30,044 / 141,466	21·2
4	140,119 / 148,337	94·5	30,469 / 145,693	20·9
5 (Highest)	111,559 / 117,894	94·6	24,021 / 116,588	20·6
Missing	1,942 / 2,136	90·9	478 / 2,147	22·3
Marginalization indices, quintile [g]				
Missing	6,897 / 7,709	89·5	1,822 / 7,765	23·5
Residential instability				
1 (least marginalized)	141,062 / 149,505	94·4	30,726 / 144,859	21·2
2	122,408 / 130,202	94·0	27,314 /137,870	21·4
3	117,877 / 125,822	93·7	26,156 / 124,136	21·1
4	123,299 / 131,562	93·7	27,801 / 130,329	21·3
5 (most marginalized)	152,248 / 161,692	94·2	33,801 / 160,173	21·1
Material deprivation				
1 (least marginalized)	125,384 / 132,406	94·7	26,654 / 129,632	20·6
2	128,299 / 135,990	94·3	27,952 / 133,538	20·9
3	125,445 / 133,407	94·0	27,375 / 130,494	21·0
4	126,359 / 134,591	93·9	28,227 / 130,494	21·4
5 (most marginalized)	151,407 / 162,389	93·2	35,590 / 161,524	22·0
Dependency				
1 (least marginalized)	220,437 / 233,427	94·4	48,618 / 226,768	21·4
2	138,170 / 146,916	94·1	30,625 / 144,231	21·2
3	112,751 / 120,119	93·9	25,334 / 118,952	21·3
4	99,514 / 106,134	93·8	21,939 / 105,485	20·8
5 (most marginalized)	86,022 / 92,187	93·3	19,282 / 91,931	21·0

Ethnic concentration				
1 (least marginalized)	89,438 / 96,654	92·5	19,670 /96,661	20·4
2	99,691 / 107,294	92·9	21,992 / 107,259	20·5
3	112,478 / 119,918	93·8	24,769 / 118,657	20·9
4	138,416 / 146,316	94·6	30,724 / 143,838	21·4
5 (most marginalized)	216,871 / 228,601	94·9	48,643 / 220,952	22·0
Prenatal care index [h]				
Intensive	37,851 / 39,716	95·3	8,387 / 39,144	21·4
Adequate	236,781 / 249,905	94·8	53,598 / 245,813	21·8
Intermediate	254,106 / 268,697	94·6	56,430 / 263,658	21·4
Inadequate	90,212 / 98,276	91·8	20,293 / 97,046	20·9
No care captured/Missing	44,841 / 49,898	89·9	8,912 / 49,471	18·0
Healthcare provider				
Midwife	67,816 / 73,176	92·7	12,694 / 72,233	17·6
CNS, NP, registered nurse	4,155 / 4,345	95·6	969 / 4,269	22·7
Family doctor	54,757 / 56,465	97·0	12,614 / 55,687	22·7
Obstetrician	515,292 / 549,535	93·8	116,958 / 540,517	21·6
Other healthcare provider, resident, surgeon	16,768 / 17,675	94·9	3,568 / 17,760	20·1
Unattended	820 / 991	82·7	15 / 1,024	1·46
Missing	4,183 / 4,305	97·2	802 / 3,642	22·0

Note: CNS=clinical nurse specialist; HELLP= Hemolysis, Elevated Liver enzymes and Low Platelets syndrome; No.=Number; NP=nurse practitioner; PPROM=Preterm Premature Rupture of Membranes; PROM= Premature Rupture of Membranes·

[a] The screening and IAP rates presented are limited to the screening eligible population (i.e., pregnancies >35 weeks). We excluded records where screening completion status was unknown (n=36,057) for the evaluation of screening rates. Similarly, we excluded records where data on IAP-receipt was unknown (n=47,417) for the evaluation of IAP rates. See Supplementary Tables S5 and S6) for a description of these excluded records.

[b] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[c] Missing values for multiple births were combined with the "no" multiple birth category due to small cell sizes (n<6).

[d] Assisted vaginal birth refers to instances where forceps and/or vacuum extractor were used. Caesarean section after labor onset refers to instances where the procedure is performed after labor has begun, either spontaneously or through induction. Caesarean section without labor refers to instances where the procedure is performed without indication of preceding labor.

[e] The sum of each individual condition does not equal the total number of individuals with any condition because categories were not mutually exclusive.

[f] Self-reported cannabis, opioid or alcohol use during pregnancy.

[g] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see Supplementary Table S3 for complete descriptions of what is captured in each of these 4 dimensions.

[h] Adequacy of prenatal care characterized with the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX). See the Supplementary Tables S3 and S4, Appendix S3 for

more details. “No care” refers to individuals who either did not receive prenatal care or received it solely from midwives or other healthcare providers not typically recorded in the physician billing database, excluding family physicians and obstetricians. Missing values for prenatal care were combined with “No care” category due to small cell sizes (n<6).

Table 2. Incidence of infant Group B Streptococcus (GBS) disease by maternal and infant characteristics (Cohort 2)

Characteristic	All livebirths No. (col %)	No. infants with GBS [a]	Incidence of GBS, per 1,000 livebirths (95% CI) [a]	Crude IRR [a,b] (95% CI)
Overall	776,148 (100·0)	803	1·03 (1·00, 1·11)	-
Maternal characteristics				
Maternal age, years				
<20	17,265 (2·2)	26	1·51 (0·93, 2·08)	1·47 (0·98, 2·22)
20 - <25	81,283 (10·5)	117	1·44 (1·18, 1·70)	1·41 (1·12, 1·77)
25 - <30	207,361 (26·7)	215	1·04 (0·90, 1·17)	1·01 (0·83, 1·23)
30 - <35	286,599 (36·9)	257	0·90 (0·80, 1·01)	0·88 (0·73, 1·06)
>=35	183,640 (23·7)	188	1·02 (0·88, 1·17)	Ref
Fiscal year of birth [c]				
2012-13	131,363 (16·9)	161	1·23 (1·04, 1·41)	1·20 (0·96, 1·52)
2013-14	130,100 (16·8)	152	1·17 (0·98, 1·35)	1·15 (0·91, 1·45)
2014-15	129,809 (16·7)	114	0·88 (0·72, 1·04)	0·86 (0·67· 1·11)
2015-16	128,974 (16·6)	130	1·01 (0·83, 1·18)	0·99 (0·78, 1·26)
2016-17	128,105 (16·5)	116	0·91 (0·74, 1·07)	0·89 (0·69, 1·14)
2017-18	127,797 (16·5)	130	1·02 (0·84, 1·19)	Ref
Season of birth				
Fall	202,374 (26·1)	187	0·92 (0·78, 1·06)	Ref
Spring	186,348 (24·0)	188	1·01 (0·86, 1·15)	1·09 (0·89, 1·34)
Summer	194,325 (25·0)	207	1·07 (0·92, 1·21)	1·15 (0·95, 1·40)
Winter	193,101 (24·9)	221	1·14 (0·99, 1·30)	1·24 (0·99, 1·50)
Multiple birth [d]				
Yes	26,296 (3·4)	72	2·74 (2·11, 3·37)	2·81 (2·21, 3·58)
No	749,852 (96·7)	731	0·97 (0·90, 1·05)	Ref
Parity				
Nulliparous	325,697 (42·0)	397	1·22 (1·09, 1·34)	1·34 (1·17, 1·54)
Multiparous	441,374 (56·9)	400	0·91 (0·82, 0·99)	Ref
Missing	9,077 (1·2)	< 6	-	-
Type of birth [e]				
Assisted vaginal	67,922 (8·7)	69	1·01 (0·78, 1·26)	1·10 (0·86, 1·42)
Spontaneous vaginal	488,995 (63·0)	450	0·92 (0·83, 1·00)	Ref

Caesarean section after labour (spontaneous or induced)	102,927 (13·3)	177	1·72 (1·47, 1·97)	1·87 (1·57, 2·22)
Caesarean section without preceding labour	116,304 (15·0)	107	0·92 (0·74, 1·09)	1·00 (0·81, 1·23)
Pre-existing maternal health conditions [f]				
Asthma	28,569 (3·7)	35	1·22 (0·82, 1·63)	1·19 (0·85, 1·67)
Diabetes	7,386 (0·1)	13	1·76 (0·80, 2·72)	1·71 (0·99, 2·96)
Heart disease	833 (0·1)	< 6	-	-
Chronic hypertension	7,294 (0·9)	21	2·88 (1·65, 4·11)	2·83 (1·84, 4·36)
Thyroid disease	32,023 (4·1)	26	0·82 (0·50, 1·12)	0·78 (0·53, 1·15)
Any pre-existing maternal health condition	72,503 (9·3)	90	1·24 (0·99, 1·50)	1·22 (0·98, 1·53)
Obstetrical complication				
Placenta abruption	1,115 (0·1)	< 6	-	-
Placenta previa	3,799 (0·5)	< 6	-	-
PROM	7,267 (0·9)	9	1·24 (0·43, 2·05)	1·20 (0·62, 2·31)
PPROM	7,621 (1·0)	35	4·59 (3·07, 6·11)	4·60 (3·28, 6·44)
Gestational diabetes	49,795 (6·4)	48	1·04 (0·96, 1·11)	0·93 (0·69, 1·24)
Gestational hypertension	27,787 (3·6)	32	1·15 (0·75, 1·55)	1·12 (0·79, 1·59)
Preeclampsia	8,316 (1·1)	29	3·49 (2·22, 4·75)	3·46 (2·40, 5·01)
Eclampsia	578 (0·1)	< 6	-	-
HELLP	977 (0·1)	< 6	-	-
Smoked during pregnancy				
Yes	76,899 (9·9)	110	1·43 (1·16, 1·70)	1·49 (1·21, 1·82)
No	670,258 (86·4)	645	0·96 (0·88, 1·04)	Ref
Missing	28,991 (3·7)	48	1·66 (1·19, 2·12)	1·72 (1·28, 2·31)
Substance use during pregnancy [g]				
Yes	16,440 (2·2)	23	1·40 (0·83, 1·97)	1·41 (0·93, 2·13)
No	716,291 (92·3)	712	0·99 (0·92, 1·07)	Ref
Missing	43,417 (5·6)	68	1·57 (1·19· 1·93)	1·58 (1·23, 2·02)
Rural residence [d]				
Yes	78,925 (10·2)	67	0·85 (0·65, 1·05)	0·80 (0·63, 1·03)
No	697,223 (89·8)	736	1·06 (0·98, 1·13)	Ref
Neighborhood median family income quintiles				
1 (Lowest)	166,935 (21·5)	180	1·08 (0·92, 1·24)	1·21 (0·96, 1·52)

2	154,571 (19·9)	180	1·16 (0·99, 1·33)	1·30 (0·99, 1·65)
3	159,582 (20·6)	172	1·08 (0·92, 1·24)	1·21 (0·95, 1·53)
4	162,735 (21·0)	153	0·94 (0·79, 1·09)	1·05 (0·83, 1·34)
5 (Highest)	129,967 (16·8)	116	0·89 (0·73, 1·05)	Ref
Missing	2,358 (0·3)	< 6	-	-
Marginalization Indices, quintile [h]				
Missing	8,393 (1·1)	< 6	-	-
Residential instability				
1 (least marginalized)	165,966 (21·4)	181	1·09 (0·93, 1·25)	Ref
2	141,306 (18·2)	145	1·03 (0·86, 1·19)	0·94 (0·76, 1·17)
3	136,884 (17·6)	133	0·97 (0·81, 1·14)	0·89 (0·71, 1·11)
4	144,068 (18·6)	145	1·01 (0·84, 1·17)	0·92 (0·74, 1·15)
5 (most marginalized)	179,531 (23·1)	194	1·09 (0·93, 1·23)	0·99 (0·81, 1·21)
Material deprivation quintile				
1 (least marginalized)	145,292 (18·7)	135	0·93 (0·77, 1·09)	Ref
2	148,098 (19·1)	140	0·95 (0·79, 1·10)	1·02 (0·80, 1·29)
3	146,434 (18·9)	134	0·92 (0·76, 1·07)	0·98 (0·78, 1·25)
4	149,065 (19·2)	192	1·28 (1·11, 1·47)	1·39 (1·11, 1·73)
5 (most marginalized)	178,866 (23·1)	197	1·10 (0·95, 1·26)	1·19 (0·95, 1·48)
Dependency quintile				
1 (least marginalized)	259,424 (33·4)	274	1·06 (0·93, 1·18)	Ref
2	161,634 (20·8)	168	1·04 (0·88, 1·20)	0·98 (0·81, 1·19)
3	131,282 (16·9)	134	1·02 (0·84, 1·19)	0·97 (0·79, 1·19)
4	115,312 (14·9)	116	1·01 (0·82, 1·18)	0·95 (0·77, 1·18)
5 (most marginalized)	100,103 (12·9)	106	1·06 (0·86, 1·26)	1·00 (0·80, 1·25)
Ethnic concentration quintile				
1 (least marginalized)	103,883 (13·4)	93	0·90 (0·71, 1·08)	Ref
2	115,710 (14·9)	125	1·08 (0·89, 1·27)	1·21 (0·93, 1·58)
3	130,692 (16·8)	116	0·89 (0·73, 1·05)	0·99 (0·78, 1·30)
4	161,656 (20·8)	161	1·00 (0·84, 1·15)	1·11 (0·86, 1·44)
5 (most marginalized)	255,814 (33·0)	303	1·18 (1·05, 1·32)	1·32 (1·05, 1·67)
Prenatal care index [i]				
Intensive	47,019 (6·1)	56	1·19 (0·88, 1·50)	0·95 (0·60, 0·94)
Adequate	282,444 (36·4)	353	1·25 (1·12, 1·38)	Ref
Intermediate	291,399 (37·5)	253	0·87 (0·76, 0·98)	0·69 (0·59, 0·82)

Inadequate	103,834 (13·4)	97	0·93 (0·75, 1·12)	0·75 (0·60, 0·94)
No care captured/Missing	51,452 (6·6)	44	0·86 (0·60, 1·11)	0·68 (0·50, 0·94)
Infant characteristics				
Male sex	397,753 (51·3)	413	1·04 (0·94, 1·14)	1·01 (0·88, 1·17)
Female sex [d]	378,395 (48.7)	390	1.03 (0.93, 1.13)	Ref
Preterm (<37 weeks)	61,346 (7·9)	262	4·27 (3·75, 4·79)	5·64 (4·87, 6·54)
Apgar score (5 min)				
0-3	2,943 (0·4)	37	12·57 (8·54, 16·60)	15·18 (10·92, 21·10)
4-7	23,873 (3·1)	134	5·61 (4·67, 6·56)	6·78 (5·63, 8·16)
8-10	741,108 (95·5)	614	0·83 (0·70, 0·89)	Ref
Missing	8,224 (1·1)	18	2·19 (1·18, 3·20)	2·64 (1·65, 4·22)
5-minute Apgar score <7	14,553 (1·9)	115	7·90 (6·46, 9·34)	8·89 (7·30, 10·82)

Note: Col=Column; HELLP= Hemolysis, Elevated Liver enzymes and Low Platelets syndrome; IRR=Incidence rate ratio; No.=Number; Ref=reference group; PPROM=Preterm Premature Rupture of Membranes; PROM= Premature Rupture of Membranes.

[a] Due to a contractual agreement with the data provider, small cell sizes (n<6) cannot be reported and have been suppressed.

[b] For incidence rate ratio calculations, the "no" category served as the reference category when not explicitly indicated.

[c] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[d] Due to small cell sizes (n<6), missing values for certain variables were combined with the 'no' category. For infant sex, missing values were combined with the 'female sex' category. [e] Assisted vaginal birth refers to instances where forceps and/or vacuum extractor were used. Caesarean section after labour onset refers to instances where the procedure is performed after labour has begun, either spontaneously or through induction. Caesarean section without labour refers to instances where the procedure is performed without indication of preceding labour.

[f] The sum of each individual condition does not equal the total number of individuals with any condition because categories were not mutually exclusive.

[g] Self-reported cannabis, opioid or alcohol use during pregnancy.

[h] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see Supplementary Table S3 for complete descriptions of what is captured in each of these 4 dimensions.

[i] Adequacy of prenatal care characterized with the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX). See Supplementary Tables S3 and S4, Appendix S3) for more details. “No care” refers to individuals who either did not receive prenatal care or received it solely from midwives or other healthcare providers not typically recorded in the physician billing database, excluding family physicians and obstetricians. Missing values for prenatal care were combined with “No care” category due to small cell sizes (n<6).

Table 3. Clinical characteristics of infants with Group B Streptococcus (GBS) disease identified in laboratory and health administrative databases (n=803)

Characteristics	All infants with GBS *n*=803	Early-onset [a] *n*=383	Late- and ultra-late onset [a] *n*=420
	No. (%) [b]	No. (%) [b]	No. (%) [b]
Respiratory distress syndrome	132 (16·4)	106 (27·7)	26 (6·2)
Mechanical ventilation required	197 (24·5)	139 (36·3)	58 (13·8)
Short-term (<96 hours)	101 (12·6)	67 (17·5)	34 (8·1)
Long-term (≥96 hours)	96 (12·0)	72 (18·8)	24 (5·7)
Admitted to a special care unit	424 (52·8)	314 (82·0)	110 (26·2)
Median length of stay, days (IQR)	10 (3 – 26)	10 (4 – 23)	8 (3 – 38)
5-minute Apgar score <7	115 (14·3)	85 (22·2)	29 (7·1)
Median gestational age, weeks (IQR)	39 (34 – 40)	38 (31 – 40)	39 (37 – 40)
Preterm birth	262 (32·6)	155 (40·5)	107 (25·5)
Initial GBS presentation [c]			
Sepsis	510 (63·5)	297 (77·6)	213 (50·7)
Meningitis	99 (12·3)	22 (5·7)	77 (18·3)
Pneumonia [d]	34 (4·2)	27 (7·1)	7 (1·7)
Other GBS infection [d,e]	160 (19·9)	37 (9·7)	123 (29·3)
Age at diagnosis, days (median, IQR)	9 (0 – 38)	0 (0 – 1)	38 (17 – 63)

Note: GBS=Group B Streptococcus; IQR= interquartile range; No.=Number.

[a] Early-onset: 0 to <7 days; Late-onset: 7 to ≤365 days. We combined late-onset (7 to <90 days) and ultra-late onset (90 to ≤365 days) disease categories due to small cell sizes.

[b] Column percentages are shown, unless otherwise stated.

[c] Initial GBS presentation represents the primary GBS diagnosis, defined using the type of earliest positive culture or first instance of diagnostic code on index GBS hospitalization (i.e., first GBS-related hospitalization) if culture data was not available.

[d] Note: these conditions are not captured in the laboratory database (OLIS) and only captured in the administrative database.

[e] These are instances where the diagnostic code "B95.1" appeared first which represents "GBS as the cause of disease classified elsewhere". Examples of accompanying diseases included urinary tract infections, cellulitis, colitis, kidney infections etc.

Table 4. Association between maternal Group B Streptococcus (GBS) prevention methods and rates of infant GBS disease up to 1 year of age, among screening eligible births (>35 weeks), capturing cases identified in laboratory and health administrative databases

	No· GBS infants/total [a,b]	Incidence of GBS, per 1,000 livebirths	Crude IRR [c] (95% CI)	Adjusted IRR [c] (95% CI)
Any infant GBS disease				
Screened for GBS	524 / 702,122	0·75	0·57 (0·43, 0·74)	0·60 (0·45, 0·80)
Unscreened	63 / 48,551	1·30	Ref	Ref
Screened positive, received IAP	240 / 140,371	1·71	0·78 (0·58, 1·04)	0·74 (0·54, 1·01)
Screened positive, did not receive IAP	55 / 24,943	2·20	Ref	Ref
Screened negative, received IAP	-	0·38	0·88 (0·28, 2·76)	0·99 (0·25, 4·06)
Screened negative, did not receive IAP	-	0·43	Ref	Ref
Early-onset disease [d]				
Screened for GBS	226 / 702,122	0·32	0·59 (0·40, 0·89)	0·56 (0·37, 0·86)
Unscreened	26 / 48,551	0·54	Ref	Ref
Screened positive, received IAP	99 / 140,371	0·71	0·77 (0·49, 1·21)	0·72 (0·48, 1·29)
Screened positive, did not receive IAP	23 / 24,943	0·92	Ref	Ref
Screened negative, received IAP	-	0·12	0·65 (0·10, 4·66)	0·63 (0·10, 4·53)
Screened negative, did not receive IAP	-	0·19	Ref	Ref
Late- and ultra-late onset disease [d]				
Screened for GBS	298 / 701,896	0·42	0·55 (0·39, 0·77)	0·54 (0·38, 0·78)
Unscreened	37 / 48,525	0·76	Ref	Ref
Screened positive, received IAP	141 / 140,272	1·00	0·78 (0·53, 1·15)	0·69 (0·46, 1·05)
Screened positive, did not receive IAP	32 / 24,920	1·28	Ref	Ref
Screened negative, received IAP	-	0·25	1·08 (0·27, 3·38)	1·00 (0·25, 4·06)
Screened negative, did not receive IAP	-	0·23	Ref	Ref

Note: CI= confidence interval; GBS= Group B *Streptococcus*; IAP=intrapartum antibiotic prophylaxis; IRR=Incidence Rate Ratios; Ref= reference group.

[a] Analysis was restricted to screening eligible births (>35 weeks' gestation). Multiple imputation was used to address missing values, and consequently, the presented incidence values (per 1,000 livebirths) represent an average across all ten imputations. However, the reported number of cases and totals were obtained from the first of ten imputed datasets. Refer to Supplementary Figure S4 for a flow diagram illustrating the number of GBS cases by maternal screening, result and IAP status.

[b] In accordance with ICES privacy policies, we are unable to report cell sizes less than six. As the number of cases in the 'Screened negative, received IAP' group is small (n<6), we have suppressed these values. Additional suppression of other cell counts in this group was required to prevent recalculation of the unreportable small cell counts, while still allowing for the illustration of incidence rates.
[c] Point estimates shown are risk ratios generated using a log-binomial regression model. Model adjusted for: maternal age, parity, multiple births, pre-existing maternal health conditions, season of birth, fiscal year of birth, adequacy of prenatal care, marginalization indices, rurality, mode of delivery, smoking/substance use during pregnancy, and income quintile.
[d] Early-onset: 0 to <7 days; Late-onset: 7 to ≤365 days. We combined late-onset (7 to <90 days), and ultra-late onset (90 to ≤ 365 days) disease categories due to small cell counts and to allow for model convergence. Infants with early-onset disease were excluded in the analysis of late-onset disease.

4.10 Supplementary materials

Table S1. Description and purpose of each data source utilised in the study

Database	Description	Information collected
Better Outcomes Registry & Network (BORN) Ontario	Captures all births ≥500 grams or ≥20 weeks' gestation in the province of Ontario. Routine data collection includes information on maternal demographic variables; pre-existing maternal health conditions; obstetric factors affecting the pregnancy; and birth outcomes (Murphy et al., 2021).[112]	Used to ascertain information related to GBS screening (completion, results), intrapartum antibiotic prophylaxis (IAP) receipt during delivery, as well as other sociodemographic, pregnancy and birth characteristics.
Registered Persons Database (RPDB)	Demographic repository containing information on all Ontario residents eligible for publicly funded health care in the province.	Used to establish the duration for which each participant was eligible to receive health care services, as well as obtain demographic information regarding neighborhood income quintiles.
Postal Code Conversion File (PCCF)	The Postal Code Conversion File (PCCF) facilitates the matching of six-digit postal codes with standardized census geographies. These resulting small-area geographies serve various purposes, such as aggregating data to widely used administrative boundaries and comprehending socio-economic status at the neighborhood level.	Used to obtain geographic information for variables such as rural location and neighbourhood income quintiles by converting Ontario postal codes into Statistics Canada standard geographical areas.
Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)	Captures demographic and clinical information regarding hospital admissions from all acute care institutions throughout Ontario. Contains medical diagnoses (most responsible diagnosis and up to 24 secondary diagnoses), interventions received, length of hospital stay and other data elements. Medical diagnoses are coded using the Canadian implementation of the International Classification of Diseases, 10th Revision (ICD-10-CA). Medical interventions are documented through Canadian Classification of Health Interventions (CCI) codes.	Used to obtain information regarding hospital admissions, including medical diagnoses (e.g., GBS outcomes) and medical procedures (e.g., mechanical ventilation). We also used this database to obtain information on admissions and discharges to any special care units (e.g., neonatal intensive care unit).
Canadian Institute for Health Information (CIHI) National Ambulatory Care Reporting System (NACRS)	Captures data originating from outpatient clinics and urgent visits to emergency departments in Ontario. Up to 10 clinical diagnoses on each abstract are coded using ICD-10-CA.	Used to supplement data from the CIHI-DAD and capture additional medical diagnoses (e.g., GBS outcomes).

MOMBABY Database	Contains inpatient admission records for delivering mothers and their respective newborns (including stillbirths), linked by a unique matching identifier on each hospitalization record. This administrative dataset, maintained and annually updated at ICES, links approximately 98% of maternal-infant records for in-hospital deliveries in Ontario.	The MOMBABY database was utilized to obtain birth-record keys, which were subsequently extracted from the CIHI-DAD along with other relevant records related to mother length of stay (LOS), baby LOS, and neonatal intensive care unit (NICU) data. This was essential to accurately identify birth records within the CIHI-DAD and determine episode information, especially distinguishing between a discharge to another facility within a series of records versus the end of a hospitalization episode.
Ontario Health Insurance Plan (OHIP) Database	Contains health care billing information made by physicians, or other health care providers, for service reimbursement. This database includes information on the diagnosis (i.e., reason for the visit), type of service received, and the associated billing code.	Used to capture prenatal care visits via OHIP fee codes (see Supplementary Table S4).
Ontario Marginalization Index (ON-Marg)	Data tool that quantifies the level of marginalization occurring in Ontario. This multifaceted index uses data from Statistics Canada's Census and consists of four dimensions that indicate area-level marginalization: residential instability, material deprivation, dependency and ethnic concentration. Scores corresponding to each of these four dimensions were previously divided into quintiles, where quintile 1 represents areas that are the least marginalized and quintile 5 represents the most marginalized areas.	Provided information regarding the four indices of area-level marginalization.
Ontario Laboratories Information System (OLIS) Database	OLIS is an electronic repository of the province's laboratory test results. This system was implemented to allow health care providers timely access to laboratory test results from both community- and hospital-based laboratories. According to eHealth Ontario, as of Dec. 31, 2017, 134 of the 262 hospital sites across the province were using OLIS, and 13 of the 14 Local Health Integration Networks (LHINs) were included (https://ehealthontario.on.ca/files/public/support/DataContributorsOLIS.pdf).	Used to identify laboratory-confirmed instances of infant GBS disease. We utilized cleaned observation codes for bacterial culture results that had an organism code of 53 (*Streptococcus* agalactiae) and a specimen source of either blood or cerebrospinal fluid.

Table S2. Infant Group B *Streptococcus* (GBS) outcome definitions

GBS Outcome Category	Laboratory Database (OLIS) ‡	Health administrative databases (DAD, NACRS)*‡	References
Sepsis	Positive blood culture for GBS	ICD-10-CA codes (up to 365 days of life): - A40.1 (Sepsis due to GBS) - P36.0 (Sepsis of newborn due to GBS)	Horváth-Puhó 2021[7] Lykke 2023[96]
Meningitis	Positive cerebrospinal fluid (CSF) for GBS	ICD-10-CA codes (up to 365 days of life): - G00.2 (*Streptococcal* meningitis) - Patients with sepsis codes above AND G00.9 (bacterial meningitis, unspecified) or G03.9 (meningitis, unspecified)	Horváth-Puhó 2021[7] Lykke 2023[96]
Pneumonia	Not captured	ICD-10-CA codes (up to 365 days of life): - J15.3 (Pneumonia due to GBS) - P23.3 (Congenital pneumonia due to GBS)	Horváth-Puhó 2021[7]
Other GBS infection	N/A	ICD-10-CA codes (up to 365 days of life): - B95.1 (*Streptococcus*, group B, as the cause of disease classified elsewhere), Examples include: urinary tract infections, cellulitis, kidney infections etc.	Yeo 2019 [93]
Early-onset disease (EOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was within the period from birth to 6 days of life.	Admission date for the first GBS-related hospitalization was within the period from birth to 6 days of life.	N/A
Late-onset disease (LOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was from 7 days of life to 89 days of life.	Admission date for the first GBS-related hospitalization was within the period from 7 days of life to 89 days of life.	N/A
Ultra-late-onset disease (ULOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was from 90 days of life to 1 year of age.	Admission date for the first GBS-related hospitalization was within the period from 90 days of life to 1 year of age.	N/A

DAD=Discharge Abstract Database; N/A=not applicable; NACRS=National Ambulatory Care Reporting System; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; OLIS=Ontario Laboratories Information System Database.

*Records with a diagnostic code for GBS on any of the 25 fields within DAD or 10 fields within NACRS were selected.
‡ For cases with culture-confirmation, infants were categorized as EOD, LOD or ULOD based on the date of specimen collection in OLIS. In instances of multiple specimen collections, we used the date of the first positive culture result. Among GBS infants without culture confirmation (identified only in DAD/NACRS), we used the admission date for the first GBS-related visit (hospitalization or emergency department visit), referred to as the index GBS visit, to determine the classification of GBS disease as EOD, LOD, or ULOD. The initial clinical presentation of GBS (sepsis, meningitis, pneumonia) was defined using the type of earliest positive culture or the first instance of a diagnostic code on the index GBS visit if culture data were unavailable. In rare instances where both blood and CSF cultures were positive within 24 hours of each other, meningitis was assigned. Similarly, if both sepsis and meningitis codes were recorded during the same hospitalization, the case was classified as meningitis.

Table S3. Definitions and diagnostic/procedural codes used to define all other study variables

Study Variable	Patient record	Definition	Data source, ICD-10-CA diagnostic code, and/or CCI procedure code
Exposure variables			
GBS screening completion (screened vs. unscreened)	Mother	Indicates whether maternal GBS screening was performed (screened), meaning that a swab was collected from the mother, or not (unscreened). Individuals could be categorized as "screened" even if the screening result was unknown/missing.	Measured using "groupbstrepscreenresult_id" in BORN.
GBS screening result (screened positive vs. screened negative)	Mother	Indicates whether the GBS screening result was positive or negative. Was only available among those that were screened.	Measured using "groupbstrepscreenresult_id" in BORN.
IAP receipt (received IAP vs. did not receive IAP)	Mother	Indicates whether the mother received or did not receive antibiotics (IAP) for GBS during delivery. Information on type, timing, dose, duration was not available.	Measured using "group_b_strep_antibiotic_id" variable in BORN.
Maternal characteristics			
Maternal age	Mother	Age of the mother at the time of giving birth.	Calculated using from "m_bdate" variable in BORN.
Parity	Mother	Total number of previous pregnancies (live births and stillbirths) that reached a viable gestational age.	Measured using "parity" variable in BORN.
Pre-existing maternal health condition(s)	Mother	Mother had any one or combinations of the following pre-existing conditions: asthma, chronic hypertension, diabetes, heart disease or thyroid disease.	Using the "mat_pre_exist_heatlh_cond_id" variable in BORN, we generated specific flags for each individual condition and a composite flag that captured the presence of 1 or more conditions.
Multiple birth	Mother	Total number of fetuses in the current pregnancy.	Measured using "number_of_fetuses" variable in BORN.
Type of birth	Mother	Refers to the mode of delivery and type of labor experienced by the mother:	Measured using "birth_type_id" variable in BORN.

		- Assisted vaginal: Vaginal birth that required assistance of forceps and/or vacuum extractor - Spontaneous vaginal: Vaginal birth that did not require assistance of forceps and/or vacuum extractor. - Caesarean section after labor onset: Caesarean section with induced (artificial initiation of labor by any intervention/s before the spontaneous onset of the latent phase of labour) or spontaneous (active labour achieved without any induction measures) labour - No labour caesarean section: Caesarean section with no indication of labour	
Obstetrical complication(s)	Mother	Includes: placenta abruption, placenta previa, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), gestational diabetes, gestational hypertension, preeclampsia, eclampsia an Hemolysis, Elevated Liver enzymes and Low Platelets syndrome (HELLP)	We generated specific flags for each individual condition using the "complication_id" variable in BORN.
Smoking during pregnancy	Mother	Self-reported smoking use at first prenatal care visit and/or at time of labour/admission.	Measured using "mat_smoking_at_adm_for_birth_id" and "matsmokingatfirstprenvisit_id" variables in BORN.
Substance use during pregnancy	Mother	Self-reported cannabis, opioid or alcohol use during pregnancy.	Measured using "expos_drug_and_subst_id" variable in BORN.
Season of birth	Mother and infant	Refers to the season that the infant was born.	Grouped into Fall, Spring, Summer or Winter based on infant's date of birth.
Fiscal year of birth	Mother and infant	Refers to the fiscal year that the infant was born.	Grouped using infant's date of birth where a fiscal year begins on Apr. 1 and ends on Mar. 31.

Revised Graduated Prenatal Care Index (R-GINDEX)	Mother	Categorizes adequacy of prenatal care into 6 groups: inadequate, intermediate, adequate, intensive, no care captured, and missing.	Derived from a combination of gestational age of the infant at birth (**GEST**), trimester when prenatal care began (**TCPB**), and total number of prenatal care visits (**PCV**). The index is based on work from Alexander and Kotelchuck.[113,114] The fee codes associated with prenatal care visits are shown in **Supplementary Table S4** and the algorithm is shown in **Appendix S3**. Note: Prenatal care provided solely from midwives or other healthcare providers not typically recorded in the physician billing database, excluding family physicians and obstetricians, were not captured.
Rural residence	Mother	Rurality determined using second digit of postal code from Canada Post Corporation.	Measured using rural flag variable from postal code conversion file in RPDB.
Income quintile	Mother	Nearest Census Based Neighborhood Income Quintile.	Measured using "INCQUINT" variable within RPDB.
Dependency	Mother	Refers to area-level concentrations of people who don't have income from employment.	Measured using "dependency factor score" variable within the ON-Marg database.
Ethnic concentration	Mother	Refers to high area-level concentrations of recent immigrants and people belonging to a 'visible minority' group.	Measured using "ethnic concentration factor score" variable within the ON-Marg database.
Material deprivation	Mother	Refers to inability for individuals and communities to access and attain basic material needs. This dimension is closely connected to poverty.	Measured using "material deprivation factor score" variable within the ON-Marg database.
Residential instability	Mother	Refers to area-level concentrations of people who experience high rates of family or housing instability.	Measured using "residential instability factor score" variable within the ON-Marg database.

Healthcare provider	Mother	Refers to the healthcare provider that caught/delivered (had hands on) the baby. The language "caught" refers to midwifery, while "delivered" refers to hospital settings. Births are considered "unattended" if the person who caught/delivered the baby is not a health care provider.	Measured using "provider_who_caught_baby_id" variable in BORN.
Infant characteristics			
Preterm birth	Mother and infant	Live birth prior to 37 weeks of gestation.	Measured using gestational age variable in BORN.
Apgar score (5-minute)	Infant	5-minute Apgar score	Measured using BORN variable. Flag variable created for infants with 5-minute Apgar score <7.
Baby's sex	Infant	Infant's sex.	Measured using "b_sex" variable in BORN.
Mechanical ventilation, Respiratory System	Infant	Mechanical ventilation codes are accompanied by an extent code to flag if the duration was long (≥96 hours) or short (<96 hours). This flag variable within the DAD was used to classify if duration was short or long-term.	Measured using CCI procedural codes (1.GZ.31.CAND; 1.GZ.31. CAEP; 1.GZ.31.CAPK; 1.GZ.31.CRND; 1.GZ.31.GPND) in the DAD.
Respiratory distress syndrome (RDS) of newborn	Infant	Difficulty in breathing experienced by a newborn including Hyaline membrane disease and Idiopathic respiratory distress syndrome (IRDS).	Measured using ICD-10-CA code P22.0 in DAD.
Special care unit	Infant	Infant admitted to the special care nursery or neonatal intensive care unit.	Measured using "SCU (special care unit)" variables in DAD.

Note: BORN=Better Outcomes Registry & Network; DAD=Discharge Abstract Database; NACRS=National Ambulatory Care Reporting System; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; RPDB=Registered Persons Database.

Table S4. Ontario Health Insurance Plan (OHIP) fee codes associated with a prenatal visit*

OHIP fee code	Description
A920	Medical management of early pregnancy, initial visit
A921	Medical management of early pregnancy, subsequent visit
A005	Consultation
A006	Re-consultation
A665	Prenatal consult
Q606	Prenatal care - gen. Assess - major prenatal visit
Q607	Prenatal care - min. Assess - subsequent prenatal visit
P002	High risk prenatal assessment
P003	Obstetric prenatal care-general assess - major prenatal visit
P004	Obstetric prenatal care-minor prenatal assess - subsequent prenatal visit
P005	Antenatal health screen

* Prenatal visits were defined by limiting to one record per person per type of doctor per day. Only visits with an associated OHIP fee code related to prenatal care were included in this definition. Prenatal care provided solely from midwives or other healthcare providers not typically recorded in the physician billing database, excluding family physicians and obstetricians, were not captured.

Table S5. Maternal baseline characteristics of records with and without data on screening completion

Maternal Characteristics	Data on screening completion available (*n*=731,833)	Data on screening completion not available (*n*=36,057)	SD [b]
	no.(%) [a]	no.(%) [a]	
Maternal age, years			
<20	16,681 (2·3)	604 (1·7)	0·04
20 - <25	78,123 (10·7)	3,787 (10·5)	0·01
25 - <30	197,965 (27·1)	7,657 (21·2)	0·14
30 - <35	269,957 (36·9)	15,244 (42·3)	0·07
>=35	169,107 (23·1)	8,765 (24·3)	0·03
Fiscal year of birth [c]			
2012-13	122,955 (16·8)	6,709 (18·6)	0·05
2013-14	121,668 (16·6)	6,827 (18·9)	0·06
2014-15	122,417 (16·7)	5,965 (16·5)	0·00
2015-16	121,913 (16·7)	5,801 (16·1)	0·02
2016-17	121,762 (16·6)	5,206 (14·4)	0·06
2017-18	121,118 (16·5)	5,549 (15·4)	0·03
Season of birth			
Fall	190,495 (26·0)	9,615 (26·7)	0·01
Spring	175,768 (24·0)	8,588 (23·8)	0·00
Summer	183,692 (25·1)	8,607 (23·9)	0·03
Winter	181,878 (24·9)	9,247 (25·6)	0·02
Multiple birth [d]			
Yes	12,376 (1·7)	1,028 (2·9)	0·08
No	719,457 (98·3)	35,029 (97·1)	0·08
Parity			
Nulliparous	309,481 (42·3)	12,396 (34·4)	0·16
Multiparous	415,033 (56·7)	22,022 (61·1)	0·09
Missing	7,319 (1·0)	1,639 (4·5)	0·22
Type of birth			
Assisted vaginal	64,096 (8·8)	2,704 (7·5)	0·05
Spontaneous vaginal	472,527 (64·6)	24,967 (69·2)	0·04
Caesarean section after labour onset	95,493 (13·0)	4,404 (12·2)	0·03

No labour caesarean section	99,717 (13·6)	3,982 (11·0)	0·06
Pre-existing maternal health conditions [e]			
Asthma	27,530 (3·8)	719 (2·0)	0·11
Diabetes	6,773 (0·9)	595 (1·7)	0·06
Chronic hypertension	6,429 (0·9)	748 (2·1)	0·10
Heart disease	783 (0·1)	44 (0·1)	0·00
Thyroid disease	30,757 (4·2)	747 (2·1)	0·12
Any pre-existing maternal health condition	68,878 (9·4)	2,675 (7·4)	0·07
Obstetrical complication			
Placenta abruption	1,095 (0·1)	65 (0·2)	0·01
Placenta previa	3,321 (0·5)	434 (1·2)	0·08
PROM	7,119 (1·0)	91 (0·3)	0·09
PPROM	7,007 (1·0)	314 (0·9)	0·01
Gestational diabetes	46,039 (6.3)	2,803 (7.8)	0.06
Preeclampsia	7,583 (1·0)	388 (1·1)	0·00
Eclampsia	543 (0·1)	29 (0·1)	0·00
Gestational hypertension	26,080 (3·6)	1,086 (3·0)	0·03
HELLP	877 (0·1)	38 (0·1)	0·00
Smoking during pregnancy			
Yes	73,791 (10·1)	2,680 (7·4)	0·09
No	637,739 (87·1)	25,075 (69·5)	0·44
Missing	20,303 (2·8)	8,302 (23·0)	0·63
Drug or substance use during pregnancy [f]			
Yes	15,679 (2·1)	734 (2·0)	0·01
No	683,180 (93·4)	25,586 (71·0)	0·61
Missing	32,974 (4·5)	9,737 (27·0)	0·65
Rural residence			
Yes	75,712 (10·3)	2,509 (7·0)	0·12
No	655,299 (89·5)	33,512 (92·9)	0·12
Missing	822 (0·1)	36 (0·1)	0·00
Neighborhood median family income quintiles			
1 (Lowest)	158,138 (21·6)	7,597 (21·1)	0·01
2	146,158 (20·0)	6,888 (19·1)	0·02

3	150,541 (20·6)	7,370 (20·4)	0·00
4	153,145 (20·9)	7,597 (21·1)	0·00
5 (Highest)	121,619 (16·6)	6,500 (18·0)	0·04
Missing	2,232 (0·3)	105 (0·3)	0·00
Marginalization Indices, quintile [g]			
Missing	8,030 (1·1)	349 (1·0)	0·01
Residential instability			
1 (least marginalized)	154,755 (21·1)	9,208 (25·5)	0·10
2	134,417 (18·4)	5,198 (14·4)	0·11
3	130,236 (17·8)	5,075 (14·1)	0·10
4	136,464 (18·6)	6,189 (17·2)	0·04
5 (most marginalized)	167,931 (22·9)	10,038 (27·8)	0·11
Material deprivation			
1 (least marginalized)	136,539 (18·7)	6,811 (18·9)	0·01
2	140,431 (19·2)	5,853 (16·2)	0·08
3	138,045 (18·9)	6,845 (19·0)	0·00
4	139,670 (19·1)	7,814 (21·7)	0·06
5 (most marginalized)	169,118 (23·1)	8,385 (23·3)	0·00
Dependency			
1 (least marginalized)	241,951 (33·1)	14,620 (40·5)	0·16
2	152,211 (20·8)	7,673 (21·3)	0·01
3	124,374 (17·0)	5,446 (15·1)	0·05
4	109,810 (15·0)	4,335 (12·0)	0·09
5 (most marginalized)	95,457 (13·0)	3,634 (10·1)	0·09
Ethnic concentration			
1 (least marginalized)	99,886 (13·6)	2,946 (8·2)	0·18
2	110, 867 (15·1)	3,537 (9·8)	0·16
3	123,989 (16·9)	5,153 (14·3)	0·07
4	151,553 (20·7)	8,193 (22·7)	0·05
5 (most marginalized)	237,508 (32·5)	15,879 (44·0)	0·24
Prenatal care index [h]			
Intensive	41,482 (5·7)	2,643 (7·3)	0·07
Adequate	263,920 (36·1)	14,061 (39·0)	0·06
Intermediate	275,155 (37·6)	15,128 (42·0)	0·09
Inadequate	100,453 (13·7)	3,321 (9·2)	0·14

No care captured/Missing	50,823 (6·9)	904 (2·5)	0·13
Healthcare provider			
Midwife	73,405 (10·0)	935 (2·6)	0·31
CNS, NP, registered nurse	4,645 (0·6)	83 (0·2)	0·06
Family doctor	56,903 (7·8)	2,022 (5·6)	0·09
Obstetrician	572,367 (78·2)	31,185 (86·5)	0·22
Other healthcare provider, resident, surgeon	18,615 (2·5)	348 (1·0)	0·12
Unattended	1,098 (0·2)	78 (0·2)	0·02
Missing	4,800 (0·7)	1,406 (3·9)	0·22

Note: CNS=clinical nurse specialist; HELLP= Hemolysis, Elevated Liver enzymes and Low Platelets syndrome; No.=Number; NP=nurse practitioner; PPROM=Preterm Premature Rupture of Membranes; PROM= Premature Rupture of Membranes; SD, standardized difference.

[a] Column percentages are shown except when noted otherwise.

[b] Absolute standardized difference comparing those with and without data on screening completion. Shaded cells indicate an imbalance (>0.10) between the two groups.

[c] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[d] Missing values for multiple births were combined with the "no" multiple birth category due to small cell sizes (n<6).

[e] The sum of each individual condition does not equal the number of mothers with any condition, as categories were not mutually exclusive.

[f] Self-reported cannabis, opioid or alcohol use during pregnancy.

[g] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see the Supplement (Table S3) for complete descriptions of what is captured in each of these 4 dimensions.

[h] Adequacy of prenatal care characterized with the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX). See the Supplement (Tables S3 and S4, Appendix S3) for more details. "No care" refers to individuals who either did not receive prenatal care or received it solely from midwives or other healthcare providers not typically recorded in the physician billing database, excluding family physicians and obstetricians. Missing values for prenatal care were combined with "No care" category due to small cell sizes (n<6).

Table S6. Maternal baseline characteristics of records with and without data on intrapartum antibiotic prophylaxis (IAP) receipt

Maternal Characteristics	Data on IAP receipt available (*n*=695,132)	Data on IAP receipt not available (*n*=47,417)	SD [b]
	no.(%) [a]	no.(%) [a]	
Maternal age, years			
<20	15,937 (2·3)	614 (1·3)	0·08
20 - <25	75,036 (10·8)	3,259 (6·9)	0·14
25 - <30	188,821 (27·2)	12,703 (26·8)	0·02
30 - <35	256,190 (36·9)	18,390 (38·8)	0·04
>=35	159,148 (2·9)	12,451 (26·2)	0·09
Fiscal year of birth [c]			
2012-13	119,199 (16·6)	10,465 (20·1)	0·09
2013-14	123,552 (17·3)	4,943 (9·5)	0·23
2014-15	120,619 (16·8)	7,763 (14·9)	0·05
2015-16	118,130 (16·5)	9,584 (18·4)	0·05
2016-17	117,676 (16·4)	9,292 (17·9)	0·04
2017-18	116,734 (16·3)	9,933 (19·1)	0·07
Season of birth			
Fall	181,111 (26·1)	12,505 (26·4)	0·01
Spring	167,422 (24·1)	10,798 (22·8)	0·03
Summer	147,149 (25·1)	11,817 (24·9)	0·00
Winter	172,450 (24·8)	12,297 (25·9)	0·03
Multiple birth [d]			
Yes	8,734 (1·3)	940 (2·0)	0·06
No	686,398 (98·7)	46,477 (98·0)	
Parity			
Nulliparous	293,481 (42·2)	16,255 (34·3)	0·16
Multiparous	397,246 (57·1)	26,937 (56·8)	0·01
Missing	4,405 (0·6)	4,225 (8·9)	0·40
Type of birth			
Assisted vaginal	62,085 (8·9)	4,002 (8·4)	0·02
Spontaneous vaginal	450,871 (64·9)	28,659 (60·4)	0·04
Caesarean section after labour onset	88,304 (12·7)	6,205 (13·1)	0·01
No labour caesarean section	93,872 (13·6)	8,551 (18·0)	0·08

Pre-existing maternal health conditions [e]			
Asthma	26,193 (3·8)	992 (2·1)	0·09
Diabetes	5,984 (0·9)	608 (1·3)	0·04
Chronic hypertension	5,514 (0·8)	673 (1·4)	0·06
Heart disease	720 (0·1)	42 (0·1)	0·00
Thyroid disease	28,709 (4·1)	1,562 (3·3)	0·04
Any pre-existing maternal health condition [e]	64,119 (9·2)	3,667 (7·7)	0·05
Obstetrical complication			
Placenta abruption	779 (0·1)	60 (0·1)	0·00
Placenta previa	2,915 (0·4)	444 (0·9)	0·06
PROM	6,837 (1·0)	120 (0·3)	0·08
PPROM	3,894 (0·6)	250 (0·5)	0·00
Gestational diabetes	43,567 (6·3)	3,452 (7·3)	0·04
Preeclampsia	5,992 (0·9)	443 (0·9)	0·01
Eclampsia	406 (0·1)	52 (0·1)	0·02
Gestational hypertension	24,614 (3·5)	1,334 (2·8)	0·04
HELLP	529 (0·1)	37 (0·1)	0·00
Smoking during pregnancy			
Yes	70,214 (10·1)	2,749 (5·8)	0·16
No	607,312 (87·4)	35,851 (75·6)	0·31
Missing	17,606 (2·5)	8,817 (18·6)	0·54
Drug or substance use during pregnancy [f]			
Yes	14,631 (2·1)	679 (1·4)	0·05
No	653,073 (93·9)	34,650 (73·1)	0·59
Missing	27,428 (3·9)	12,088 (25·5)	0·64
Rural residence			
Yes	73,513 (10·6)	2,375 (5·0)	0·20
No	620,854 (89·3)	44,992 (94·9)	0·20
Missing	765 (0·1)	50 (0·1)	0·00
Neighborhood median family income quintiles			
1 (Lowest)	151,032 (21·7)	8,375 (17·1)	0·09
2	138,206 (19·9)	9,648 (20·3)	0·01
3	141,466 (20·4)	11,253 (23·7)	0·08
4	145,693 (21·0)	10,241 (21·6)	0·02

5 (Highest)	116,588 (16·8)	7,806 (16·5)	0·01
Missing	2,147 (0·3)	94 (0·2)	0·02
Marginalization Indices, quintile [g]			
Missing	7,765 (1·1)	293 (0·6)	0·05
Residential instability			
1 (least marginalized)	144,859 (20·8)	13,854 (29·2)	0·19
2	127,870 (18·4)	7,530 (15·9)	0·07
3	124,136 (17·9)	6,761 (14·3)	0·10
4	130,329 (18·7)	7,422 (15·7)	0·08
5 (most marginalized)	160,173 (23·0)	11,557 (24·4)	0·03
Material deprivation			
1 (least marginalized)	129,632 (18·6)	9,585 (20·2)	0·04
2	133,538 (19·2)	8,305 (17·5)	0·04
3	130,494 (18·8)	9,758 (20·6)	0·05
4	132,179 (19·0)	10,226 (21·6)	0·06
5 (most marginalized)	161,524 (23·2)	9,250 (19·5)	0·09
Dependency			
1 (least marginalized)	226,768 (33·2)	17,279 (36·4)	0·06
2	144,231 (20·7)	10,358 (21·8)	0·03
3	118,952 (17·1)	6,613 (13·9)	0·09
4	105,485 (15·2)	6,984 (14·7)	0·03
5 (most marginalized)	91,931 (13·2)	5,890 (12·4)	0·05
Ethnic concentration			
1 (least marginalized)	96,661 (13·9)	4,939 (10·4)	0·07
2	107,259 (15·4)	5,572 (11·7)	0·08
3	118,657 (17·1)	7,414 (15·6)	0·06
4	143,838 (20·7)	10,671 (22·5)	0·04
5 (most marginalized)	220,952 (31·8)	18,528 (39·1)	0·08
Prenatal care index [h]			
Intensive	39,144 (5·6)	3,215 (6·8)	0·05
Adequate	245,813 (35·4)	18,153 (38·3)	0·06
Intermediate	263,658 (37·9)	3,215 (6·8)	0·05
Inadequate	97,046 (14·0)	4,551 (9·6)	0·14
No care captured/Missing	49,471 (7·1)	1,331 (2·8)	0·20
Healthcare provider			

Midwife	72,233 (10·4)	1,878 (4·0)	0·25
CNS, NP, registered nurse	4,269 (0·6)	159 (0·3)	0·04
Family doctor	55,687 (8·0)	2,800 (5·9)	0·08
Obstetrician	540,517 (77·8)	40,203 (84·8)	0·18
Other healthcare provider, resident, surgeon	17,760 (2·6)	263 (0·6)	0·16
Unattended	1,024 (0·1)	45 (0·1)	0·02
Missing	3,642 (0·5)	2,069 (4·4)	0·25

Note: CNS=clinical nurse specialist; HELLP= Hemolysis, Elevated Liver enzymes and Low Platelets syndrome; No.=Number; NP=nurse practitioner; PPROM=Preterm Premature Rupture of Membranes; PROM= Premature Rupture of Membranes; SD, standardized difference.

[a] Column percentages are shown except when noted otherwise.

[b] Absolute standardized difference comparing those with and without data on screening completion. Shaded cells indicate an imbalance (>0.10) between the two groups.

[c] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[d] Missing values for multiple births were combined with the "no" multiple birth category due to small cell sizes (n<6).

[e] The sum of each individual condition does not equal the number of mothers with any condition, as categories were not mutually exclusive.

[f] Self-reported cannabis, opioid or alcohol use during pregnancy.

[g] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see the Supplement (Table S3) for complete descriptions of what is captured in each of these 4 dimensions.

[h] Adequacy of prenatal care characterized with the Revised-Graduated Prenatal Care Utilization Index (R-GINDEX). See the Supplement (Tables S3 and S4, Appendix S3) for more details. "No care" refers to individuals who either did not receive prenatal care or received it solely from midwives or other healthcare providers not typically recorded in the physician billing database, excluding family physicians and obstetricians.

Missing values for prenatal care were combined with "No care" category due to small cell sizes (n<6).

Table S7. Characteristics of infant Group B Streptococcus (GBS) disease identified through both laboratory and health administrative databases, stratified by gestational age at birth

Characteristics	All infants with GBS *n*=803	<28 weeks *n*=108	28 to <37 weeks *n*=154	≥37 weeks *n*=541
	no.(%) [a]	no.(%) [a]	no.(%) [a]	no.(%) [a]
Early-onset	383 (47·7)	70 (64·8)	85 (55·2)	228 (42·1)
Late-onset	360 (44·8)	29 (26·9)	57 (37·0)	274 (50·7)
Ultra-late onset	60 (7·5)	9 (8·3)	12 (7·8)	39 (7·2)
Initial GBS presentation [b]				
Sepsis	510 (63·5)	82 (76·0)	107 (69·5)	321 (59·3)
Meningitis	99 (12·3)	12 (11·1)	17 (11·0)	70 (12·9)
Pneumonia [c]	34 (4·2)	6 (5·6)	7 (4·6)	21 (3·9)
Other GBS infection [c,d]	160 (19·9)	8 (7·4)	23 (14·9)	129 (23·8)
Age at diagnosis, days (median, IQR)	9 (0 – 38)	0 (0 – 31)	1·0 (0 – 38)	13 (0 – 39)

Note: GBS=Group B Streptococcus; IQR= interquartile range; No.=number.
Early-onset: 0 to <7 days; Late-onset: 7 to <90 days; Ultra-late-onset: 90 to ≤365 days.
[a] Column percentages are shown, unless otherwise stated.
[b] Initial GBS presentation represents the primary GBS diagnosis, defined using the type of earliest positive culture or first instance of diagnostic code on index GBS hospitalization (i.e., first GBS-related hospitalization) if culture data was not available.
[c] Note: these conditions are not captured in the laboratory database (OLIS) and only captured in the administrative database.
[d] These are other forms of GBS infections where the diagnostic code "B95.1" appeared first which represents "GBS as the cause of disease classified elsewhere". Examples of accompanying diseases included urinary tract infections, cellulitis, colitis, kidney infections etc.

Table S8. Results of sensitivity analyses looking at the association between Group B *Streptococcus* (GBS) prevention methods and rates of various GBS disease subgroups, among screening eligible births (>35 weeks)

	No. GBS infants/total [a,b]	Incidence of GBS, per 1,000 livebirths	Crude IRR [c] (95% CI)	Adjusted IRR [c] (95% CI)
Infants with GBS disease captured in administrative databases				
Screened for GBS	516 / 702,122	0·73	0·56 (0·43,0·73)	0·54 (0·41, 0·72)
Unscreened	63 / 48,551	1·30	Ref	Ref
Screened positive, received IAP	238 / 140,371	1·70	0·80 (0·59, 1·08)	0·75 (0·54, 1·04)
Screened positive, did not receive IAP	53 / 24,943	2·12	Ref	Ref
Screened negative, received IAP	-	0·25	0·60 (0·15, 2·40)	0·57 (0·14, 2·28)
Screened negative, did not receive IAP	-	0·42	Ref	Ref
Infants with GBS disease initially presenting with sepsis				
Screened for GBS	310 / 702,122	0·44	0·59 (0·42, 0·84)	0·56 (0·39, 0·80)
Unscreened	36 / 48,551	0·74	Ref	Ref
Screened positive, received IAP	143 / 140,371	1·02	0·85 (0·57, 1·25)	0·80 (0·52, 1·22)
Screened positive, did not receive IAP	30 / 24,943	1·20	Ref	Ref
Screened negative, received IAP	-	0·13	0·50 (0·06, 3·50)	0·47 (0·06, 3·39)
Screened negative, did not receive IAP	-	0·26	Ref	Ref
Infants with GBS disease initially presenting with meningitis				
Screened for GBS	70 / 702,122	0·10	0·53 (0·27, 1·07)	0·52 (0·26, 1·11)
Unscreened	9 / 48,551	0·19	Ref	Ref
Screened positive, received IAP	26 / 140,371	0·19	0·69 (0·30, 1·58)	0·61 (0·25, 1·52)
Screened positive, did not receive IAP	7 / 24,943	0·28	Ref	Ref
Screened negative, received IAP	-	0·12	0·95 (0·13, 5·87)	1·01 (0·14, 5·30)
Screened negative, did not receive IAP	-	0·13	Ref	Ref
Infants with GBS disease remaining after validation exclusions [d]				
Screened for GBS	329 / 701,882	0·47	0·56 (0·40, 0·77)	0·53 (0·37, 0·74)
Unscreened	41 / 48,574	0·84	Ref	Ref

Screened positive, received IAP	146 / 140,233	1·04	0·78 (0·53, 1·14)	0·71 (0·48, 1·08)
Screened positive, did not receive IAP	33 / 249,22	1·32	Ref	Ref
Screened negative, received IAP	-	0·25	0·89 (0·22, 3·59)	0·90 (0·23, 3·65)
Screened negative, did not receive IAP	-	0·28	Ref	Ref

Note: CI= confidence interval; GBS= Group B *Streptococcus*; IAP=intrapartum antibiotic prophylaxis; IRR=Incidence Rate Ratios; Ref= reference group.

[a] Multiple imputation was used to address missing values, and consequently, the presented incidence values (per 1,000 livebirths) represent an average across all ten imputations. However, the reported number of cases and totals were obtained from the first of ten imputed datasets.

[b] In accordance with ICES privacy policies, we are unable to report cell sizes less than six. As the number of cases in the 'Screened negative, received IAP' group is small (n<6), we have suppressed these values. Additional suppression of other cell counts in this group was required to prevent recalculation of the unreportable small cell counts, while still allowing for the illustration of incidence rates.

[c] Point estimates shown are risk ratios generated using a log-binomial regression model. Model adjusted for: maternal age, parity, multiple births, pre-existing maternal health conditions, season of birth, fiscal year of birth, adequacy of prenatal care, marginalization indices, rurality, mode of delivery, alcohol/substance use during pregnancy, and income quintile.

[d] We excluded infants with GBS disease that were identified solely through diagnostic codes (without culture confirmation) if they had: i) only tested negative for blood or cerebrospinal fluid in the laboratory database; ii) only tested positive for another specimen source that was not blood or cerebrospinal fluid (e.g., urine); iii) early-onset disease but had a length of stay less than 2 days; or iv) the diagnostic code B95.1 (GBS as cause of disease) without any additional corresponding GBS condition (e.g., sepsis, meningitis or pneumonia).

Table S9. Complete case analysis of the association between maternal Group B Streptococcus (GBS) prevention methods and rate of infant GBS disease up to 1 year of age among births >35 weeks, capturing cases identified in laboratory and health administrative databases

	No. GBS infants/total [a,b]	Incidence of GBS, per 1,000 livebirths	Crude IRR [c] (95% CI)	Adjusted IRR [c] (95% CI)
Any infant GBS disease				
Screened for GBS	501 / 669,971	0·75	0·56 (0·43, 0·72)	0·53 (0·40, 0·70)
Unscreened	59 / 43,817	1·35	Ref	Ref
Screened positive, received IAP	220 / 123,956	1·77	0·80 (0·60, 1·08)	0·71 (0·51, 0·98)
Screened positive, did not receive IAP	55 / 24,939	2·21	Ref	Ref
Screened negative, received IAP	-	0·38	0·92 (0·30, 2·87)	0·96 (0·31, 3·01)
Screened negative, did not receive IAP	-	0·41	Ref	Ref
Early-onset disease [d]				
Screened for GBS	217 / 669,971	0·32	0·59 (0·39, 0·90)	0·54 (0·34, 0·85)
Unscreened	24 / 43,817	0·55	Ref	Ref
Screened positive, received IAP	89 / 123,956	0·72	0·78 (0·49, 1·23)	0·70 (0·42, 1·16)
Screened positive, did not receive IAP	23 / 24,939	0·92	Ref	Ref
Screened negative, received IAP	-	0·13	0·69 (0·10, 4·93)	0·65 (0·10, 4·52)
Screened negative, did not receive IAP	-	0·18	Ref	Ref
Late- and ultra-late onset disease [d]				
Screened for GBS	284 / 669,754	0·42	0·53 (0·37, 0·75)	0·52 (0·36, 0·75)
Unscreened	35 / 43,793	0·80	Ref	Ref
Screened positive, received IAP	131 / 123,867	1·06	0·82 (0·56, 1·21)	0·71 (0·46, 1·09)
Screened positive, did not receive IAP	32 / 24,916	1·28	Ref	Ref
Screened negative, received IAP	-	0·25	1·10 (0·27, 4·48)	1·04 (0·25, 4·23)
Screened negative, did not receive IAP	-	0·23	Ref	Ref

Note: CI= confidence interval; GBS= Group B Streptococcus; IRR=Incidence Rate Ratios; Ref= reference group.

[a] Analysis was restricted to screening eligible births (>35 weeks' gestation).

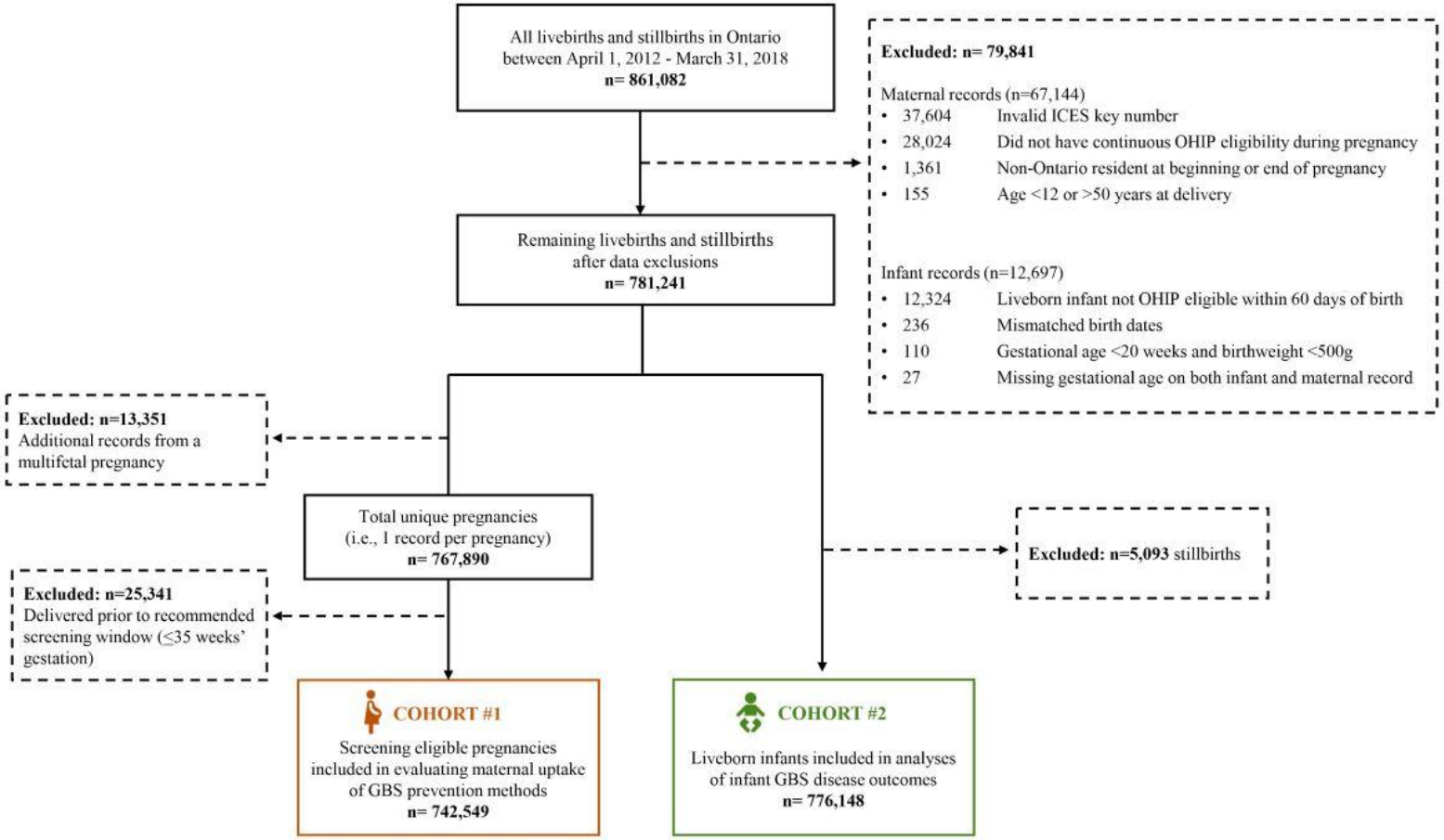
[b] In accordance with ICES privacy policies, we are unable to report cell sizes less than six. As the number of cases in the 'Screened negative, received IAP' group is small (n<6), we

have suppressed these values. Additional suppression of other cell counts in this group was required to prevent recalculation of the unreportable small cell counts, while still allowing for the illustration of incidence rates.

[c] Point estimates shown are risk ratios generated using a log-binomial regression model. Model adjusted for: maternal age, parity, multiple births, pre-existing maternal health conditions, season of birth, fiscal year of birth, adequacy of prenatal care, marginalization indices, rurality, mode of delivery, smoking/substance use during pregnancy, and income quintile.

[d] Early-onset: 0 to <7 days; Late-onset: 7 to ≤365 days. We combined late-onset (7 to <90 days), and ultra-late onset (90 to ≤ 365 days) disease categories to allow for model convergence. Infants with early-onset disease were excluded in the analysis of late-onset disease.

A.


All livebirths and stillbirths in Ontario between April 1, 2012 - March 31, 2018
n= 861,082
Excluded: n= 79,841
Maternal records (n=67,144)
• 37,604 Invalid ICES key number
• 28,024 Did not have continuous OHIP eligibility during pregnancy
• 1,361 Non-Ontario resident at beginning or end of pregnancy
• 155 Age <12 or >50 years at delivery
Infant records (n=12,697)
• 12,324 Liveborn infant not OHIP eligible within 60 days of birth
• 236 Mismatched birth dates
• 110 Gestational age <20 weeks and birthweight <500g
• 27 Missing gestational age on both infant and maternal record
Remaining livebirths and stillbirths after data exclusions
n= 781,241
Excluded: n=13,351
Additional records from a multifetal pregnancy
Total unique pregnancies (i.e., 1 record per pregnancy)
n= 767,890
Excluded: n=5,093 stillbirths
Excluded: n=25,341
Delivered prior to recommended screening window (≤35 weeks' gestation)
COHORT #1
Screening eligible pregnancies included in evaluating maternal uptake of GBS prevention methods
n= 742,549
COHORT #2
Liveborn infants included in analyses of infant GBS disease outcomes
n= 776,148

B.

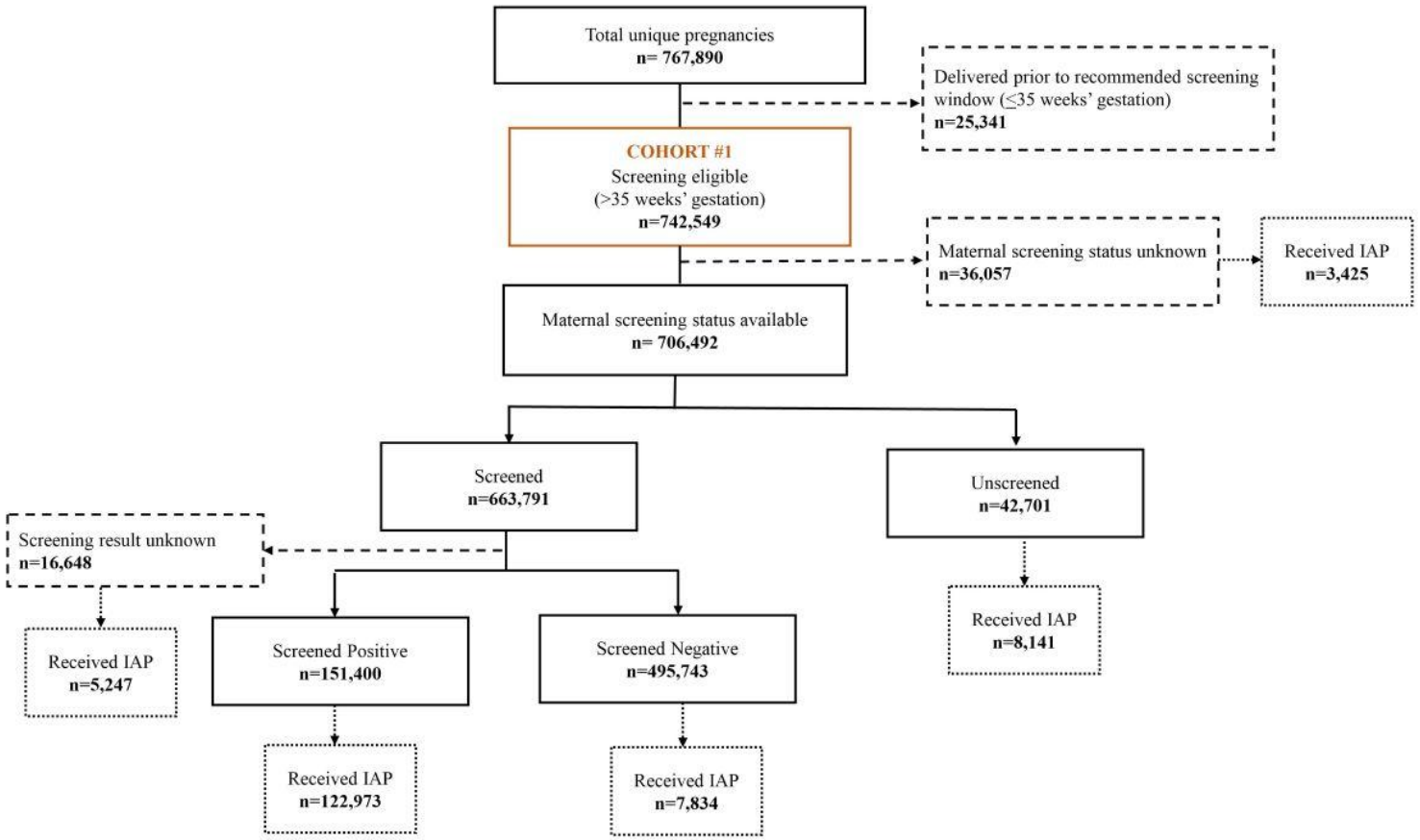


Figure S1. Flow diagram illustrating the creation of the two study cohorts (A) and screening/IAP distribution in Cohort #1 (B).

Note for Panel A: The difference between Cohort #1 (n=742,549) and Cohort #2 (n=776,148) is due to multifetal pregnancies. Cohort #1 counts one record per pregnancy, while Cohort #2 includes each liveborn infant. A total of 13,351 additional records from multifetal pregnancies were excluded from Cohort #1.
Note for Panel B: IAP-receipt was unknown among n=47,417 records in Cohort #1 that are not explicitly illustrated here.
Abbreviations: GBS=Group B Streptococcus; IAP=intrapartum antibiotic prophylaxis; OHIP=Ontario Health Insurance Plan.

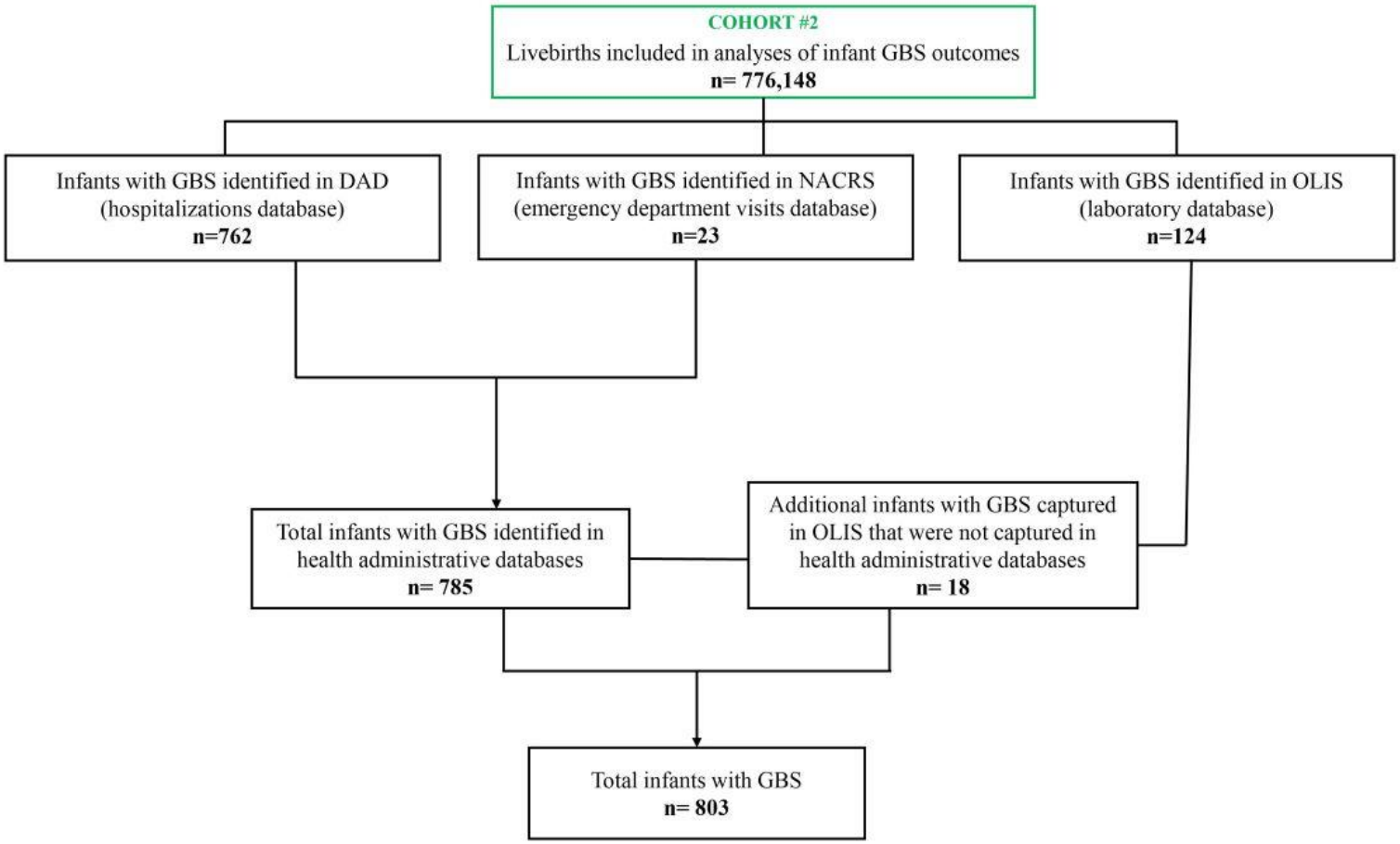


Figure S2. Flow diagram illustrating the linkage process for identifying Group B Streptococcus (GBS) cases from laboratory (OLIS) and health administrative (DAD, NACRS) databases.

Abbreviations: DAD= Discharge Abstract Database; NACRS=National Ambulatory Care Reporting System; OLIS=Ontario Laboratory Information System.

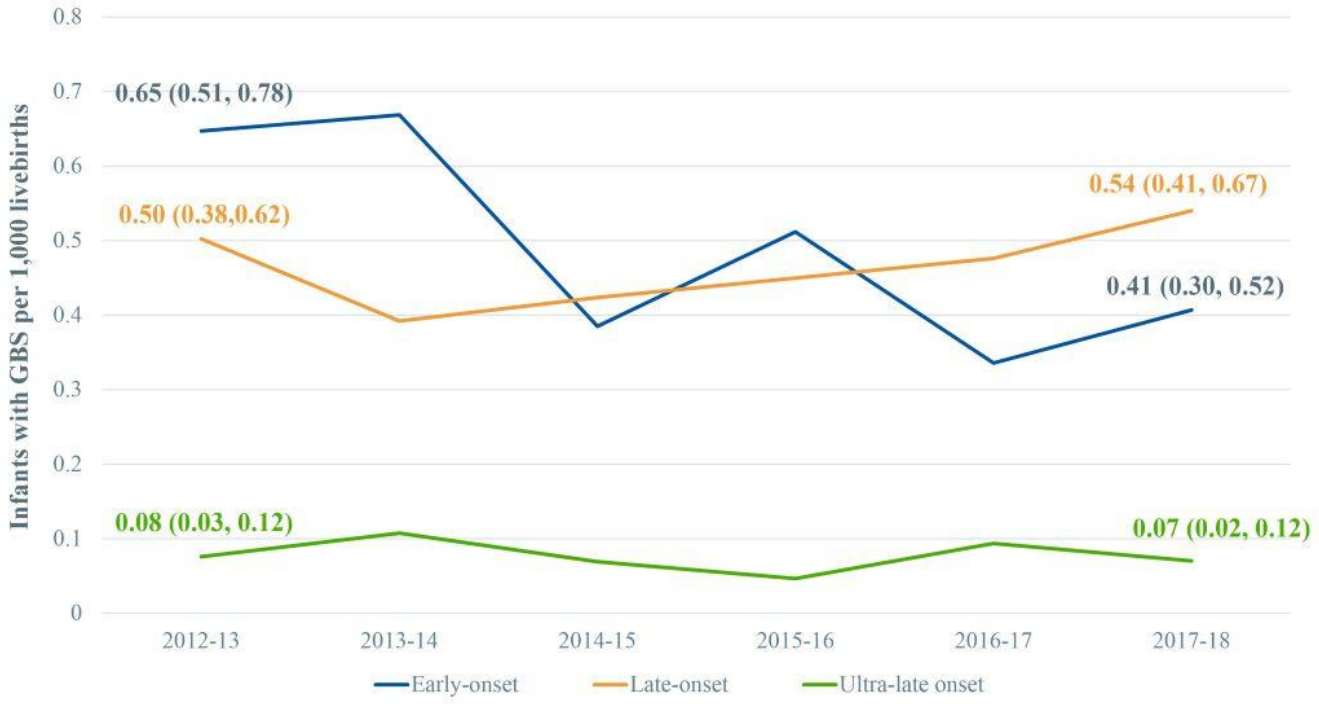


Figure S3. Incidence of infant Group B Streptococcus (GBS) disease (per 1,000 livebirths) by fiscal year of birth.

Note: incidence rates and 95% confidence intervals for the first and last fiscal years are presented for each GBS subtype. Early-onset: 0 to <7 days; Late-onset: 7 to <90 days; Ultra-late onset: 90 to <365 days.

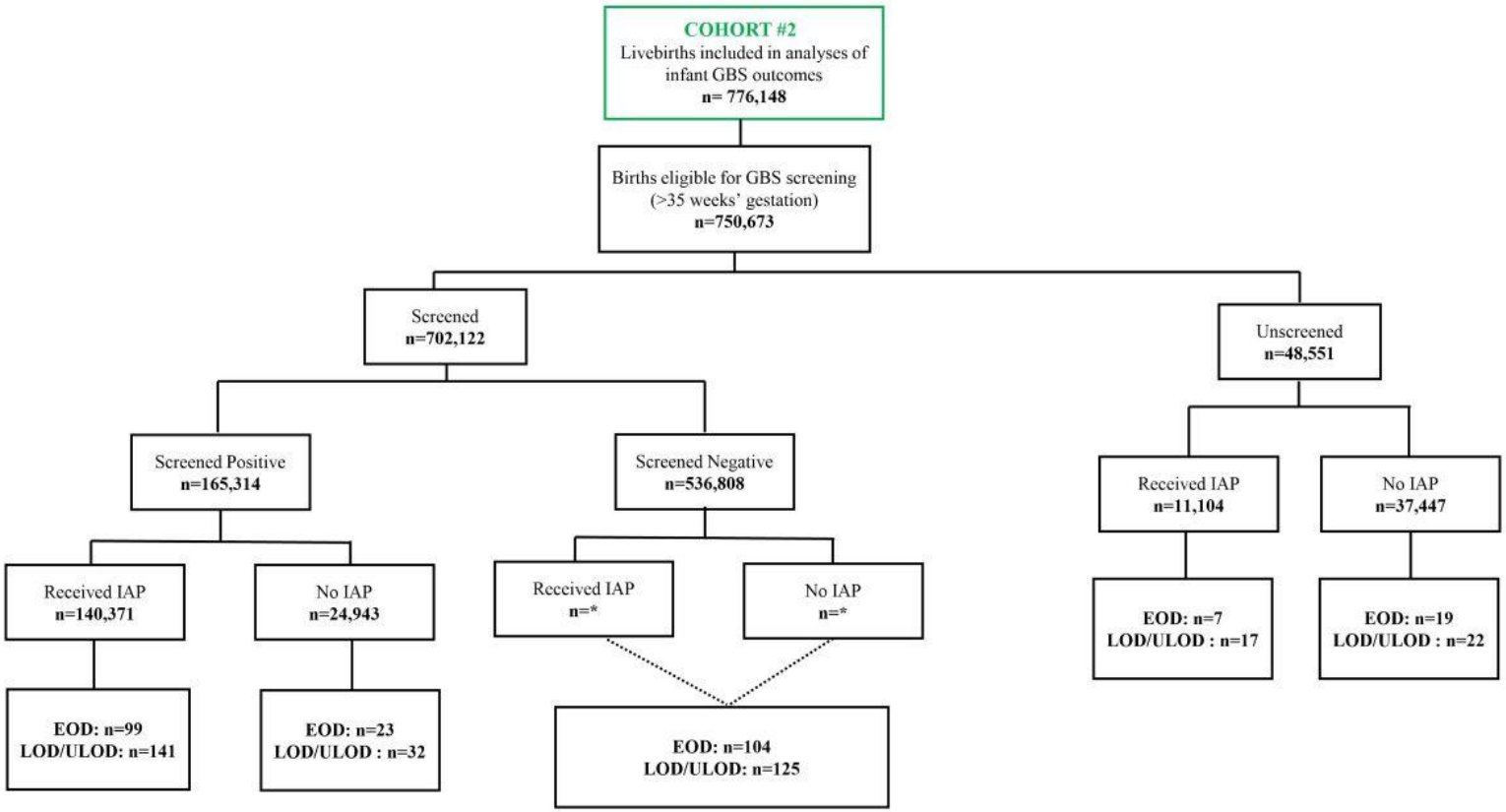


Figure S4. Number of EOD and LOD/ULOD cases by maternal screening, result and IAP status among screening eligible births (>35 weeks' gestation) in Cohort #2.

Early-onset (EOD): 0 to <7 days; Late-onset (LOD): 7 to <90 days; Ultra-late onset (ULOD): 90 to <365 days.
Note: This flow diagram visually complements the values presented in Table 4 of the manuscript. Since multiple imputation was used to address missing values in the analyses shown in Table 4, the reported number of cases and totals in that table and this flow diagram are derived from the first of the ten imputed datasets.
* In accordance with ICES privacy policies, we are unable to report cell sizes less than six. As the number of cases in the 'Screened negative, received IAP' group is small (n<6), we have suppressed these values. Additional suppression of other cell counts in this group was required to prevent recalculation of the unreportable small cell counts, while still allowing for the illustration of incidence rates in Table 4.

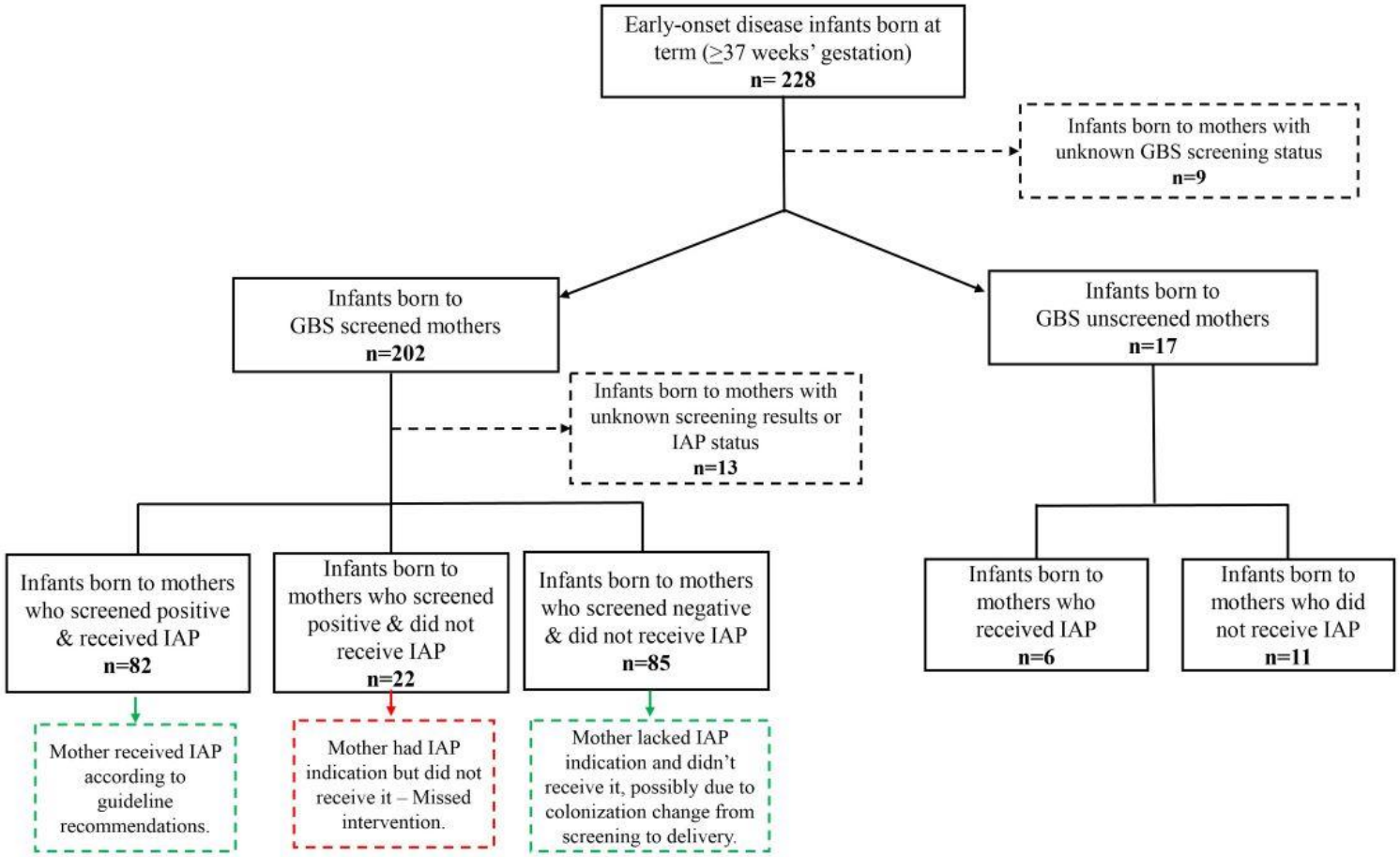


Figure S5. Description of missed opportunities for intrapartum antibiotic prophylaxis (IAP) among infants with early-onset disease born at term (> 37 weeks' gestation).

Note: IAP=intrapartum antibiotic prophylaxis. Early-onset: 0 to <7 days.

Appendix S1. Overview of Generalized Estimating Equation (GEE) Methods

In this study, we utilized Generalized Estimating Equations (GEE) to account for >1 livebirth deliveries belonging to the same mother over the study time period. GEE is particularly suited for analyzing correlated data, such as repeated measures or clustered data. Multifetal pregnancies as well as subsequent pregnancies from the same mother are inherently correlated. Using the GEE approach ensured robust standard error estimates and accurate inference despite the inherent dependencies in the data.
For the purpose of this study, ">1 livebirth delivery" referred to either of the following scenarios:

1. The individual had more than one pregnancy resulting in a live birth recorded in our birth registry (≥500g or ≥20 weeks' gestation) over the study period.

2. The individual had a single pregnancy with multiple deliveries (e.g., twins), each resulting in a live birth captured in our birth registry (≥500g or ≥20 weeks' gestation).

We ran our log-binomial models using the GEE method to account for correlated observations. We used the "repeated statement" in our model and specified the clustering variable as the mother's identification variable (M_IKN), which is unique to each mother in our dataset. We specified an independent correlation structure, meaning that we assumed no correlation between the clusters themselves but within cluster correlations are accounted for by robust standard errors (corrw). All analyses presented in Tables 4, Supplementary Tables S8 and S9 have GEE incorporated into their models. Since Cohort #2 was used in this analysis, which was limited to livebirth deliveries, the GEE model only accounted for >1 livebirth delivery belonging to the same mother.

Appendix S2. Multiple Imputation Methods and Outputs

Missing Data Overview
Approximately 8.2% (63,314 / 776,148) of live birth records were missing information for one or more of the variables included in our initial set of covariates. The percentage of missing data for any individual covariate was low (range 0-5.6%). With inclusion of our three exposure variables (screening completion, screening results, intrapartum antibiotic prophylaxis [IAP]), the proportion of records with missing data rose to 10.9% (84,568 / 776,148). In our final analysis, each exposure group was assessed within certain subgroups (e.g., association between screening result and infant Group B Strep disease was assessed among those screened), so this proportion was lower.
Handing Missing Data
As analyses based on subjects with complete information only (i.e., complete case analysis) has been shown to yield biased results,[115] we opted to address missing covariate values with multiple imputation methodology. We operated under the assumption of a "missing at random" mechanism, indicating that the likelihood of data being missing was unrelated to the specific missing value for the variable but was associated with the values of other observed variables.[115]
Imputation Methodology

We used the MI procedure in Statistical Analysis Software (SAS) Version 9.4 (SAS Institute Inc., Cary, NC) specifying the fully conditional specification. This approach defines the multivariate imputation model on a variable-by-variable basis through a series of conditional densities,

where each incomplete variable has its own specified density.[116] This strategy is particularly advantageous for large datasets with intricate data structures and in situations where missing data includes both categorical and continuous variables.

Covariates

The imputation models included the following covariates: maternal age, parity, mode of delivery, smoking during pregnancy, substance use during pregnancy, rural residence multiple birth, pre-existing maternal health conditions (asthma, chronic hypertension, diabetes, heart disease, thyroid disease), neighborhood income quintile, marginalization indices (material deprivation, residential instability, ethnic concentration, dependency), fiscal year of birth, season of birth, adequacy of prenatal care index, screening completion, screening result and IAP. Please refer to **Supplementary Table S3** for clear definitions of these covariates.

Imputation Process

We generated ten imputed datasets using PROC MI and then combined the results from each imputed dataset using PROC MIANALYZE to account for the uncertainty of multiply imputed values. The distribution of variables with missing values in the crude and first five imputed datasets are shown in the table below**:**

Distribution of variables with missing values in original and first five imputed datasets among livebirths in Cohort 2 (n=776,148)

Characteristic	Non-imputed dataset	Imputation #1	Imputation #2	Imputation #3	Imputation #4	Imputation #5
	col %	col %	col %	col %	col %	col %
Screened for GBS [a]						
Yes	89·3	93·5	93·5	93·4	93·5	93·4
No	5·8	6·5	6·5	6·6	6·5	6·6
Missing	4·9	-	-	-	-	-
Screening result [b]						
Positive	22·8	23·5	23·6	23·5	23·5	23·5
Negative	74·7	76·5	76·4	76·5	76·5	76·5
Missing	2·6	-	-	-	-	-
IAP receipt [c]						
Yes	81·2	83·6	83·7	83·6	83·6	83·7
No	16·3	16·4	16·3	16·4	16·4	16·3
Missing	2·5	-	-	-	-	-
Parity						
Nulliparous	42·0	42·4	42·3	42·4	42·5	42·4
Multiparous	56·9	57·6	57·5	57·6	57·5	57·6
Missing	1·2	-	-	-	-	-
Smoked during pregnancy						

Yes	9·9	10·2	10·1	10·2	10·2	10·2
No	86·4	89·8	89·9	89·8	89·8	89·8
Missing	3·7	-	-	-	-	-
Substance use during pregnancy [d]						
Yes	2·1	2·4	2·4	2·4	2·3	2·4
No	92·3	97·6	97·6	97·6	97·7	97·6
Missing	5·6	-	-	-	-	-
Rural residence						
Yes	10·2	10·2	10·2	10·2	10·2	10·2
No	89·7	89·8	89·8	89·8	89·8	89·8
Missing	0·1	-	-	-	-	-
Neighborhood median family income quintiles						
1 (Lowest)	21·5	21·6	21·6	21·6	21·6	21·6
2	19·9	20·0	19·9	20·0	20·0	20·0
3	20·6	20·6	20·7	20·6	20·6	20·6
4	21·0	21·0	21·0	21·0	21·0	21·0
5 (Highest)	16·8	16·8	16·8	16·8	16·8	16·8
Missing	0·3	-	-	-	-	-
Marginalization indices, quintile [e]						
Missing	1·1	-	-	-	-	-
Residential instability						
1	21·4	21·5	21·5	21·5	21·5	21·5
2	18·2	18·3	18·4	18·3	18·4	18·3
3	17·6	17·8	17·8	17·8	17·8	17·8
4	18·6	18·8	18·8	18·8	18·8	18·8
5	23·1	23·6	23·5	23·5	23·5	23·5
Material deprivation						
1	18·7	18·8	18·8	18·8	18·8	18·8
2	19·1	19·2	19·2	19·2	19·2	19·2
3	18·9	19·0	19·0	19·0	19·0	19·0

4	19·2	19·4	19·4	19·4	19·4	19·4
5	23·1	23·5	23·6	23·6	23·5	23·6
Dependency						
1	33·4	33·6	33·6	33·6	33·6	33·6
2	20·8	21·0	21·0	21·0	21·0	21·0
3	16·9	17·1	17·1	17·1	17·1	17·1
4	14·9	15·1	15·1	15·1	15·1	15·1
5	12·9	13·2	13·2	13·2	13·2	13·2
Ethnic concentration						
1	13·4	13·8	13·8	13·8	13·8	13·9
2	14·9	15·1	15·2	15·1	15·1	15·1
3	16·8	17·0	16·9	17·0	17·0	17·0
4	20·8	21·0	20·9	21·0	20·9	20·9
5	33·0	33·1	33·2	33·1	33·1	33·1

Note: Col=Column %

[a] Limited to births eligible for GBS screening (i.e., born >35 weeks' gestation) (non-imputed dataset: n=750,673)

[b] Limited to births with completed maternal GBS screening (non-imputed dataset: n=669,971)

[c] Limited to births with positive maternal GBS screening results (non-imputed dataset: n=152,745)

[d] Self-reported cannabis, opioid or alcohol use during pregnancy.

[e] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see the Supplement (Table S3) for complete descriptions of what is captured in each of these 4 dimensions.

Appendix S3. Coding algorithm for Revised Graduated Prenatal Care Utilization Index (R-GINDEX)

Key Variables:
GEST = Gestational Age (18-45 weeks based on LMP)
PCV = Number of Prenatal Care Visits (0 = None)
TPCB = Trimester Prenatal Care Began (0 = None, 1-3 trimesters) *
GINDEX = Graduated Prenatal Care Utilization Index

***NOTE:** Trimester 1 = (0-13 weeks or 1-91 days)
Trimester 2 = (14-27 weeks or 92-189 days)
Trimester 3 = (28+ weeks or 190+ days)

INTENSIVE PRENATAL CARE UTILIZATION;

```
IF (TPCB=1) &
      (((18<=GEST<=21) & (11=<PCV))       |   ((22<=GEST<=25) & (13=<PCV))
      | ((26<=GEST<=29) & (14=<PCV))      |   ((30<=GEST<=31) & (15=<PCV))
      | ((32<=GEST<=36) & (16=<PCV))      |   ((37<=GEST<=40) & (17<=PCV))
      | ((41<=GEST<=42) & (18=<PCV))      |   ((43<=GEST<=45) & (19<=PCV)))
THEN GINDEX = 'INTENSIVE (1st Trimester)';
IF (TPCB=2) &
      (((18<=GEST<=21) & (10=<PCV))       |   ((22<=GEST<=25) & (11=<PCV))
      | ((26<=GEST<=31) & (12=<PCV))      |   ((32<=GEST<=35) & (13=<PCV))
      | ((36<=GEST<=37) & (14=<PCV))      |   ((38<=GEST<=40) & (15=<PCV))
      | ((41<=GEST<=42) & (16=<PCV))      |   ((43<=GEST<=45) & (17<=PCV)))
THEN GINDEX = 'INTENSIVE (2nd Trimester)';
IF (TPCB=3) &
      (((GEST=25) & (9=<PCV))             |   ((26<=GEST<=31) & (10=<PCV))
      | ((32<=GEST<=35) & (11=<PCV))      |   ((36<=GEST<=37) & (12=<PCV))
      | ((38<=GEST<=40) & (13=<PCV))      |   ((41<=GEST<=42) & (14=<PCV))
      | ((43<=GEST<=45) & (15=<PCV)))
 THEN GINDEX = 'INTENSIVE (3rd Trimester)';
```

ADEQUATE PRENATAL CARE UTILIZATION CRITERIA;

```
IF (TPCB=1) &
      (((18<=GEST<=21) & (3=<PCV<=10))    |   ((22<=GEST<=25) & (4=<PCV<=12))
```

```
      | ((26<=GEST <=29) & (5=<PCV<= 13))  |      ((30<=GEST<=31) & (6=<PCV<= 14))
      | ((32<=GEST<=33)  & (7=<PCV<=15))  |      ((34<=GEST<=35) & (8=<PCV<=15))
      | ((GEST=36)      & (9=<PCV<=15))   |     ((GEST =37) & (10<=PCV<=16))
      | ((GEST=38)      & (11=<PCV<=16))  |      ((GEST =39) & (12<=PCV<=16))
      | ((GEST=40) & (13=<PCV<=16))       |      ((GEST =41) & (14<=PCV<=17))
      | ((GEST=42) & (15=<PCV<=17))       |      ((43<=GEST<=45) & (16<=PCV<=18)))
THEN GINDEX = 'ADEQUATE (1st Trimester)';

INTERMEDIATE PRENATAL CARE UTILIZATION CRITERIA;

IF (TPCB=1) &
      (((18<=GEST<=21) & (1<=PCV<=2))      |    ((22<=GEST<=25) & (2=<PCV<=3))
      | ((26<=GEST<=29) & (2=<PCV<=4))     |    ((30<=GEST<=31) & (3=<PCV<=5))
      | ((32<=GEST<=33) & (4=<PCV<=6))     |    ((34<=GEST<=35) & (5=<PCV<=7))
      | ((GEST=36) & (5=<PCV<=8))          |    ((GEST=37) & (6=<PCV<=9))
      | ((GEST=38) & (7=<PCV<=10))         |    ((GEST=39) & (7=<PCV<=11))
      | ((GEST=40) & (8=<PCV<=12))         |    ((GEST=41) & (8=<PCV<=13))
      | ((GEST=42) & (9=<PCV<=14))         |    ((43<=GEST<=45) & (9=<PCV<=15)))
THEN GINDEX = 'INTERMEDIATE (1st Trimester)';
IF (TPCB=2) &
      (((18<=GEST<=21) & (1=<PCV<=9))      | ((22<=GEST<=25) & (2=<PCV<=10))
      | ((26<=GEST<=29) & (2=<PCV<=11))    | ((30<=GEST<=31) & (3=<PCV<=11))
      | ((32<=GEST<=33) & (4=<PCV<=12))    | ((34<=GEST<=35) & (5=<PCV<=12))
      | ((36<=GEST<=37) & (6=<PCV<=13))    | ((38<=GEST<=39) & (7=<PCV<=14))
      | ((GEST=40) & (8=<PCV<=14))         | ((GEST =41)    & (8=<PCV<=15))
      | ((GEST=42) & (9=<PCV<=15))         | ((43<=GEST<=45) & (9=<PCV<=16)))
THEN GINDEX = 'INTERMEDIATE (2nd Trimester)';

INADEQUATE PRENATAL CARE UTILIZATION CRITERIA;
IF (TPCB=1) &
      (((22<=GEST<=29) & (PCV=1))          |   ((30<=GEST<=31) & (1<=PCV<=2))
      | ((32<=GEST<=33) & (1<=PCV<=3))     |   ((34<=GEST<=36) & (1<=PCV<=4))
      | ((GEST=37) & (1<=PCV<=5))          |   ((38<=GEST<=39) & (1<=PCV<=6))
      | ((40<=GEST<=41) & (1<=PCV<=7))     |   ((42<=GEST<=45) & (1<=PCV<=8)))
THEN GINDEX = 'INADEQUATE (1St Trimester)';
IF (TPCB=2) &
```

(((22<=GEST<=29) & (PCV=1)) | ((30<=GEST<=31) & (1<=PCV<=2))
| ((32<=GEST<=33) & (1<=PCV<=3)) | ((34<=GEST<=35) & (1<=PCV<=4))
| ((36<=GEST<=37) & (1<=PCV<=5)) | ((38<=GEST<=39) & (1<=PCV<=6))
| ((40<=GEST<=41) & (1<=PCV<=7)) | ((42<=GEST<=45) & (1<=PCV<=8)))
THEN GINDEX = **'INADEQUATE (2nd Trimester)'**;
IF (TPCB=3) &
(((GEST =25) & (1<=PCV<=8)) | ((26<=GEST<=31) & (1<=PCV<=9))
| ((32<=GEST<=35) & (1<=PCV<=10)) | ((36<=GEST<=37) & (1<=PCV<=11))
| ((38<=GEST<=40) & (1<=PCV<=12)) | ((41<=GEST<=42) & (1<=PCV<=13))
| ((43<=GEST<=45) & (1<=PCV<=14)))
THEN GINDEX = **'INADEQUATE (3rd Trimester)'**;

MISSING PRENATAL CARE CRITERIA;
IF (((PCV=.) & (TPCB^=0)) | ((TPCB=3) & (1<=GEST<=24))
| ((TPCB=2) & (1<=GEST<=11)) | ((GEST=.) & (PCV^=0))
| ((TPCB=.) & (PCV^=0)) | (TPCB=0 & (PCV>0)))
THEN GINDEX = **'MISSING'**;

NO PRENATAL CARE UTILIZATION;
IF (PCV=0) | (TPCB=0 & PCV=.)
THEN GINDEX = **'NOCARE'**;

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CHAPTER 5. MANUSCRIPT 2

Group B *Streptococcus* disease during infancy and risk of subsequent neurodevelopmental impairments in young children: a population-based cohort study in Ontario, Canada

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5.1 Preface to chapter 5

This chapter presents the second manuscript of this dissertation, focusing on the risk of neurodevelopmental impairments (NDIs) following GBS disease in early infancy and examining whether sex and prematurity influence this risk. Following the abstract, a "Research in Context" section, required by *The Lancet Regional Health – The Americas*, positions this study within the existing evidence base, underscoring its unique contributions and implications. Tables and figures supporting the manuscript appear after the references in Section 5.9, beginning on page 156, with author contributions outlined on page 150 and the study appendix starting on page 162.

5.2 Abstract

Background: Group B *Streptococcus* (GBS) is a leading infectious cause of neonatal morbidity and mortality worldwide, yet data on longer-term outcomes in children remain limited. We aimed to assess the risk of neurodevelopmental impairments (NDIs) in GBS survivors and to explore effect modification by sex and prematurity.

Methods: We performed a population-based cohort study of liveborn infants in Ontario between April 2012 and March 2018, using linked birth registry, laboratory, and health administrative databases. GBS disease in the first year of life was ascertained through culture results and diagnostic codes. NDIs, encompassing cognitive, motor, sensory (hearing, vision), and social/behavioural domains, were ascertained up to five years of age using diagnostic codes. Cox regression was used to estimate adjusted hazard ratios (aHR) for overall, domain-specific, and multidomain NDIs, comparing children with and without GBS disease during infancy.

Findings: Of 764,934 infants, 771 had a history of GBS disease. GBS survivors had a twofold increased risk of any NDI (adjusted hazard ratio [aHR]: 2.18 [95% CI 1.88, 2.54]) and higher rates of cognitive (aHR: 2.79 [95% CI 2.37, 3.30]), motor (aHR: 7.08 [95% CI 2.93, 17.08]), social/behavioural (aHR: 1.60 [95% CI 1.20, 2.14]), and sensory (aHR: 1.64 [95% CI 1.02, 2.64]) impairments. Male children and those born preterm (<37 weeks) had disproportionately higher risks of GBS-associated NDIs.

Interpretation: GBS disease in infancy is associated with a higher risk of NDIs by age five years, particularly for male children and those born preterm. Primary prevention strategies are

needed to mitigate long-term developmental impacts of early-life GBS disease.

Funding: Canadian Institutes of Health Research.

Key Words: Group B *Streptococcus*; *Streptococcus agalactiae*; neurodevelopmental impairments; effect modification; sex differences; prematurity

5.3 Research in context

Evidence before the study

Group B Streptococcus (GBS; Streptococcus agalactiae) remains a leading cause of neonatal and infant morbidity and mortality worldwide. While the mortality risk from GBS infections in infancy is well documented, the long-term neurodevelopmental impairments (NDIs) faced by survivors are less understood. Additionally, research on how infant sex and prematurity influence long-term outcomes after GBS disease is limited. We conducted a PubMed search using key terms such as "Group B Streptococcus," "Streptococcus agalactiae," "neurodevelopmental impairment," "effect modification," and "sex differences," with no language restrictions. Our search, current as of September 4, 2024, focused on studies investigating NDIs in infants who survived GBS disease.

A 2017 meta-analysis estimated that 18% of infants with GBS meningitis experienced moderate-to-severe NDIs by 18 months of age, with more recent studies suggesting a similarly high prevalence of NDIs among survivors of GBS sepsis. However, many of these studies lacked comparator groups, and few extended follow-up beyond two years. Population-based cohort studies from Denmark, the Netherlands, and Norway have reported a significantly increased risk of NDIs among survivors of infant GBS disease, though North American studies remain scarce. Furthermore, limited research has explored how infant sex, or prematurity might modify the risk of NDIs following GBS disease. As maternal GBS vaccines progress in development, larger cohort studies are essential to better quantify long-term outcomes following GBS disease and inform global burden estimates and economic evaluations.

Added value of this study

This population-based cohort study provides novel insights into the long-term neurodevelopmental impairments (NDIs) associated with infant Group B Streptococcus (GBS) disease, specifically in a North American context where data are limited. By examining close to 770,000 children in Ontario, Canada, we offer comprehensive estimates of NDI incidence across multiple domains, including cognitive, motor, sensory, and social/behavioural outcomes, for survivors of GBS disease up to 5 years of age. We also provide new insights into the differences in NDI risk between early-onset disease and late-onset disease, identifying that both subgroups face significantly elevated risks, but with particularly high risks for motor impairments in the early-onset group. Moreover, we conducted effect modification analyses, showing that male children and those born premature are disproportionately

affected by NDIs following GBS disease, with a significant proportion of their risk attributable to the interaction of these factors with GBS.

Implications of all the available evidence

Current evidence suggests that infant GBS disease not only poses a significant risk of mortality but also has lasting impacts on survivors' neurodevelopment. The findings from our study, along with those from recent cohort studies in Denmark, the Netherlands, and Norway, emphasize the elevated risk of NDIs among GBS survivors. It underscores the need for preventive measures, such as maternal vaccination, to reduce the burden of GBS-related NDIs. Furthermore, our findings reveal that boys and preterm infants are particularly vulnerable to these impairments, suggesting the need for targeted interventions to mitigate these risks.

5.4 Introduction

Group B *Streptococcus* (GBS; *Streptococcus agalactiae*) is an important cause of severe bacterial infections among neonates and infants globally.[1] While the mortality risk from GBS infections in infancy is well documented,[2,3] research on the potential for neurodevelopmental impairments (NDIs) among children who survive GBS disease remains limited.[3] A 2017 meta-analysis estimated that 18% of infants with GBS meningitis in first 3 months of life had moderate-to-severe NDIs, including cognitive, motor, hearing and visual impairments, by 18 months of age.[4] The majority of extant studies have lacked comparator groups needed to understand causality, and few have assessed outcomes beyond 2 years of age. Among the higher-quality studies, a 77% higher risk of NDIs by age ten following GBS disease in infancy (risk ratio [RR]: 1.77 [95% CI 1.44, 2.18]) was reported by a Danish cohort study, while another from the Netherlands found an even higher risk (RR: 2.28 [95% CI 1.64, 3.17]).[5] Additionally, a Norwegian study reported a threefold higher risk of NDIs by age 12 years and 10 months (RR: 3.49 [95% CI 3.05, 3.98]).[6]

In addition to quantifying the risk of long-term sequelae following GBS disease in infancy, identifying factors that may influence this risk is necessary for enhancing clinical care through targeted follow-up among high-risk groups. In a cohort study from Denmark and the Netherlands, the excess risk of NDIs following early-life GBS disease was found to be amplified among those born preterm [7] and among male children (compared with term-born and female children, respectively).[8] The combined effect of GBS disease with either prematurity or male sex on NDIs exceeded what would be expected from each factor alone, suggesting a synergistic increase in NDI risk.[8]

With several GBS vaccine candidates in development,[9] large cohort studies are needed to assess long-term health impacts of infant GBS disease, as these inputs are essential for informing global disease burden and economic evaluations. In this province-wide cohort study from Ontario, Canada, we evaluated the risk of NDIs following infant GBS disease and separately examined how sex and prematurity modified any risk of GBS on NDIs.

5.5 Methods

5.5.1 Study design, population and data sources

We conducted a population-based retrospective cohort study in the Canadian province of Ontario, where universal publicly funded healthcare covers almost all residents, including newborns. We identified infants born between April 1, 2012, to March 31, 2018 using the Better Outcomes Registry & Network (BORN) Ontario birth registry, which captures all hospital and home births ($\geq$500g or $\geq$20 weeks' gestation) in the province, representing ≈40% of Canadian births.[10] The registry routinely collects data on sociodemographics, health behaviours, pre-existing conditions, obstetrical complications and birth outcomes, with ongoing quality checks to ensure high data integrity.[11]

We linked this birth cohort with laboratory and health administrative databases to ascertain infant GBS disease and pediatric health outcomes over a five-year follow-up period. Databases were linked using unique encoded identifiers and analyzed at ICES (https://www.ices.on.ca). The databases included the Ontario Laboratories Information System (OLIS) database for laboratory culture results, Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD) for hospitalizations, CIHI National Ambulatory Care Reporting System (NACRS) for

emergency department (ED) visits and outpatient clinics, the Registered Persons Database for healthcare eligibility and neighbourhood income quintiles, Postal Code Conversion File for geographic information, Ontario Health Insurance Plan (OHIP) Database for physician outpatient billing claims and Ontario Marginalization Index for area-level marginalization and socioeconomic status. We used diagnostic and procedural codes from the Canadian version of the *International Statistical Classification of Diseases and Related Health Problems*, *10th Revision* (ICD-10-CA) and Canadian Classification of Health Interventions (CCI), respectively (details on data sources provided in Supplementary Table S1).

We excluded infant records with invalid identifiers/birthdates and those lacking Ontario healthcare eligibility within 60 days of birth. Infants born to individuals not continuously eligible for Ontario healthcare during pregnancy, non-Ontario residents, under 12 or over 50 years of age at delivery, or had invalid identifiers were also excluded. Follow-up for NDI outcomes began at 18 months of age, as this timing aligns with standard neurodevelopmental assessment practices in clinical care and captures a period when NDIs can be more reliably identified.[12,13] Accordingly, children were considered at risk for NDIs starting at 18 months, and any NDI diagnoses recorded before this age were not counted toward the outcome unless a diagnosis was also recorded at or after 18 months. Children who died or lost healthcare eligibility before 18 months were excluded from the analysis.

5.5.2 Exposure measurement

Infant GBS disease in the first year of life was identified through a dual capture approach: (i) culture confirmation of GBS from a normally sterile site (blood or cerebral spinal fluid [CSF]) in the laboratory database (OLIS), or (ii) GBS-specific diagnostic codes (ICD-10-CA codes) in

health administrative databases (DAD, NACRS). Infants were considered GBS-exposed if either a culture confirmation or an ICD-10-CA code for GBS was identified (Supplementary Table S2); this method was chosen due to inconsistencies in data contributions to OLIS by Ontario hospitals, leading to incomplete specimen information in early years of our study.[14] Moreover, blood culture sensitivity is lower among preterm infants and those exposed to antibiotics in-utero,[15] not all infants with probable GBS sepsis are tested, and culture sites necessary for identifying other GBS manifestations (e.g., pneumonia) are not routinely collected.[13]

For culture-confirmed GBS, infants were categorized as early-onset disease (EOD, 0–6 days of life), late-onset disease (LOD, 7–89 days), or ultra-late-onset disease (ULOD, 90–365 days) based on the specimen collection date in OLIS. In instances with multiple specimens, we used the date of the first positive culture result. Non-culture-confirmed GBS cases (i.e., identified through GBS-specific diagnostic codes [Supplementary Table S2]), were classified as EOD, LOD or ULOD using the date for the initial GBS-related visit (hospitalization or emergency department). The primary GBS presentation (GBS sepsis, meningitis, or pneumonia) was classified based on the earliest positive culture or, if unavailable, the GBS-related diagnostic code documented during the first hospitalization. If both blood and CSF cultures were positive within 24 hours of each other, the GBS disease was classified as meningitis—the more severe condition—to reflect instances where both specimen types were collected during the same clinical episode. Similarly, if both sepsis and meningitis codes were recorded during the same hospitalization, the GBS disease was classified as meningitis.

5.5.3 Outcome measurement

The primary outcome, NDIs diagnosed between 18 months and 5 years of age, was defined using diagnostic, procedural, and physician codes for mental, behavioural and nervous system disorders, consistent with definitions and case-finding algorithms from previous NDI research.[4–6,12,16]

We applied an algorithm requiring at least one hospitalization or ED encounter (DAD or NACRS) with an NDI diagnostic (ICD-10-CA) or procedural (CCI) code, and/or at least two physician (OHIP) visits with an NDI diagnosis during follow-up. This approach, validated in prior health administrative research on neurodevelopmental outcomes,[17] helps mitigate a limitation of the OHIP data set, which permits only one diagnostic code per claim; relying solely on a single physician visit might misclassify children assessed for an NDI who did not qualify for the diagnosis. For autism spectrum disorder, the two or more physician visits must have been made by a pediatrician or psychiatrist.[12]

We evaluated cognitive, motor, sensory (hearing, vision), and social/behavioural domains, categorizing impairments by severity (mild, moderate, severe, or uncategorized). An NDI was defined as an impairment in any single domain, while multidomain NDI involved impairments across multiple ($\geq$2) domains. Uncategorized conditions were included in "any NDI" and "multidomain NDI" definitions but not in the severity subgroups. Severity subgroups were defined as: mild (1–2 mild domains AND no moderate/severe domains), and moderate-to-severe ($\geq$3 mild domains OR $\geq$1 moderate/severe domains). See Supplementary Table S3 for details.

5.5.4 Statistical analyses

We described study population characteristics using frequencies and compared baseline characteristics between exposure groups using standardized differences, considering values below 0.10 as well-balanced.[18] Follow-up began at 18 months and continued until the child became ineligible for Ontario healthcare (owing to emigration or death), experienced an NDI, or reached five years of age, whichever came first. NDI rates were expressed per 1,000 person-years. We used Cox proportional hazards models to estimate unadjusted and adjusted hazard ratios (aHR), with 95% confidence intervals (CI). A Kaplan-Meier curve was generated to compare the probability of remaining free from NDI between children with and without GBS disease during infancy (Supplementary Fig. S1).

The proportional hazards assumption was assessed and deemed valid through examination of Schoenfeld residual plots and Wald tests for interactions between GBS exposure status and time (Appendix S1). Estimates were adjusted for infant sex, maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, area-level marginalization indices and neighbourhood income quintile (definitions in Supplementary Table S4). Adjusted models excluded observations with missing covariate information (5.5% had missing information on $\geq$1 covariate included in the models). We assessed risks of overall, domain-specific, and multidomain NDIs, comparing children with/without GBS during infancy, and across different subgroups, considering GBS timing (EOD, LOD, GBS in the first 89 days of life) and primary diagnosis (sepsis, meningitis).

We separately evaluated whether infant sex and prematurity (<37 weeks' gestation) modified the effect of GBS on NDI, using both additive and multiplicative scales. On the additive scale, effect

modification occurs when the absolute risk difference between exposed and unexposed groups varies by the potential modifier, while on the multiplicative scale it occurs if the relative measures of association (HRs) differ across levels of the potential modifier.

We assessed effect modification on the additive scale using the relative excess risk due to interaction (RERI), a preferred measure for time-to-event outcomes.[19] For infant sex, we used females without GBS as the reference group and calculated RERI as: $HR_{GBS+/Male} - HR_{GBS+/Female} - HR_{GBS-/Female} + 1$. We also calculated the attributable proportion due to interaction as $RERI/(HR_{GBS+/Male}) \times 100\%$. Effect modification on the multiplicative scale was assessed by including a product term (sex × GBS) in the multivariable models.

For prematurity, we used term children without GBS as the reference group and calculated RERI as: $RERI = HR_{GBS+/Preterm} - HR_{GBS+/Term} - HR_{GBS-/Preterm} + 1$. The attributable proportion due to interaction was calculated as $RERI / HR_{GBS+/Preterm} \times 100\%$. Multiplicative scale modification was assessed by including the product term "preterm birth × GBS" in the multivariable models. See Appendix S2 for further details. All analyses used SAS Enterprise Guide 8.3 (SAS Institute).

5.5.5 Sensitivity analyses

Due to uncertainty about whether preterm birth is a consequence of, or a risk factor for GBS, we did not adjust for prematurity in our primary analysis, considering its potential role as a mediator on the causal pathway;[6,20,21] however, recognizing the complexity of this relationship,[21] we additionally adjusted for gestational age in a sensitivity analysis. To address concerns about GBS cases without culture confirmation, we applied validation checks for infants classified solely by diagnostic codes, excluding infants who: (i) only tested negative for GBS through blood or CSF

in OLIS; (ii) tested positive for GBS only through non-sterile sites (e.g., urine); (iii) had EOD but a hospital stay <2 days (accounting for hospital transfers); or (iv) were assigned diagnostic code B95.1 without any other specific GBS-related codes. To improve the specificity of the primary outcome, we excluded children with uncategorized NDI conditions (captured in the cognitive and sensory domains) to focus on well-defined NDI categories. We also performed a post-hoc sensitivity analysis additionally adjusting for maternal history of neuropsychiatric conditions (defined in Supplementary Table S4). Recognizing that NDI risk may vary by gestational age within preterm births, we divided into early preterm (<32 weeks) and late preterm (32 to <37 weeks); this enabled us to explore whether the combined effect of preterm birth and GBS on NDI differed between early and late preterm infants. Finally, as our adjusted models excluded children with missing covariate data, we compared the distribution of key characteristics between those with and without complete covariate data to evaluate whether excluded children were similar to those included in our analyses; the incidence of GBS and NDI outcomes between these groups was also evaluated.

5.6 Results

5.6.1 Study population

Of the 855,849 livebirths in Ontario between April 1, 2012 and March 31 2018, 773,945 remained after exclusions (Figure 1). We further excluded 9,011 children who either lost Ontario healthcare eligibility (n=6,287) or died (n=2,724) before reaching 18 months of age, leaving a final cohort of 764,934 children who were followed up to five years of age. Of these, 771 had a history of GBS disease in the first year of life. During the follow-up period, 364 children died and 10,408 lost healthcare eligibility and were censored.

5.6.2 Characteristics of children with GBS disease

Among 771 children with GBS disease during infancy, 15.7% (n=121) had culture confirmation (Supplementary Fig. S2). Among these culture-confirmed cases, 107 had sepsis (defined by a positive blood culture) and 14 had meningitis (positive CSF culture). Overall, of those with GBS, 57.7% (n=445) had sepsis, 18.2% (n=140) had meningitis, 4.0% (n=31) had pneumonia, and 20.1% (n=155) had other GBS disease types (i.e., those identified by diagnostic code B95.1 without any other specific GBS-related codes). Regarding GBS onset, 46.6% (n=359) experienced EOD, 46.0% (n=355) had LOD, and 7.4% (n=57) had ULOD. Children with a history of GBS during infancy were more likely to have mothers who were younger at delivery (20 to <25 years), nulliparous, had a multi-fetal pregnancy, smoked during pregnancy, and experienced higher material deprivation (quintile 4), than children without a history of GBS (Table 1).

5.6.3 Relationship between any GBS disease during infancy and NDIs

The incidence of any NDI (per 1,000 person years) was 53.4 (95% CI 46.1, 61.5) among children with GBS and 23.6 (95% CI 23.4, 23.8) in those without (Table 2). After adjustment, children who survived GBS had a twofold increased risk of any NDI by age five years compared to those without (aHR: 2.18 [95% CI 1.88, 2.54]). Children with GBS experienced higher rates of mild NDIs than those without GBS (13.1 vs. 7.93 per 1,000 person-years, aHR: 1.72 [95% CI 1.28, 2.32]). The rate of moderate-to-severe NDIs was also higher in children with GBS than those without (aHR: 1.66 [95% CI 1.21, 2.29]). Additionally, multidomain NDIs were more than double in children with GBS compared to those without (7.25 vs. 3.29 per 1,000 person-years; aHR: 2.09 [95% CI 1.39, 3.16]). GBS survivors were also at increased risk of cognitive (aHR: 2.79 [95% CI 2.37, 3.30]), motor (aHR: 7.08 [95% CI 2.93, 17.08]), social/behavioural (aHR: 1.60 [95% CI 1.20, 2.14]) and sensory (aHR: 1.64 [95% CI 1.02, 2.64]) disorders, compared to children without a history of GBS during infancy.

5.6.4 Exposure subgroup analyses

The association between GBS disease in the first 89 days of life and NDI outcomes was comparable to our primary results (Supplementary Table S5). Hazard ratios for any NDI suggested increased risks for both EOD (aHR: 2.29 [95% CI: 1.83, 2.85]) and LOD (2.10 [95% CI: 1.68, 2.63]), compared to unexposed children. For moderate-to-severe NDI, the hazard ratio was 2.04 (95% CI: 1.33, 3.12) for EOD and 1.50 (95% CI: 0.92, 2.45) for LOD. Estimates for multi-domain NDIs also showed increased risks for EOD (aHR: 2.24 [95% CI: 1.24, 4.04]) and LOD (aHR: 2.31 [95% CI: 1.32, 4.07]), compared to children without GBS. Estimates for domain-specific NDIs generally indicated an increased risk in both EOD and LOD subgroups

compared to no GBS (Supplementary Table S5). The estimate for motor impairments was the highest in the EOD subgroup (aHR: 9.45 [95% CI: 3.05, 29.33]).

Approximately 24.5% (109/445) of GBS sepsis survivors and 28.6% (40/140) of GBS meningitis survivors experienced an NDI. Compared to unexposed children, those with GBS sepsis or GBS meningitis had an increased NDI risk (Supplementary Table S6). Risks for moderate-to-severe NDIs were higher for the GBS sepsis subgroup (aHR: 2.06 [95% CI: 1.42, 2.99]) than for the GBS meningitis subgroup (aHR: 1.11 [95% CI: 0.42, 2.95]). The hazard ratio for multi-domain NDI was 2.13 (95% CI: 1.26, 3.59) for the GBS sepsis group and 1.13 (95% CI: 0.28, 4.52) for the GBS meningitis group. Domain-specific NDI estimates showed increased risks for children with GBS sepsis or GBS meningitis compared to those without, with the highest hazard ratios for motor impairments in both groups (Supplementary Table S6).

5.6.5 Effect modification by infant sex and prematurity

Compared to the reference category of female children without GBS, higher risks of any NDI and moderate-to-severe NDIs were observed in males without GBS, males with GBS, and females with GBS (Table 3). There was evidence of effect modification on the additive scale for any NDI (RERI: 0.53 [95% CI 0.23, 0.84]). Approximately 14% of NDI risk and 15% of moderate-to-severe NDI was attributable to the combined effect of GBS and male sex. There was no evidence of effect modification by infant sex on the multiplicative scale for any NDI (P value=0.31) or moderate-to-severe NDIs (P value=0.72) (Table 3).

Compared to term children without GBS, the risk of any NDI was highest in preterm children with GBS (aHR: 3.74 [95% CI: 2.99, 4.67]), and similar for term children with GBS (aHR: 1.78 [95% CI: 1.45, 2.19]) and preterm children without GBS (aHR: 1.77 [95% CI: 1.73, 1.80]). Evidence of effect modification on the additive scale was found for both any NDI (RERI: 1.18 [95% CI 0.88, 1.49]) and moderate-to-severe NDIs (RERI: 2.13 [95% CI 1.48, 2.78]), indicating that the combined effect of GBS and prematurity exceeds the sum of their individual effects. Approximately 32% of any NDI risk and 58% of moderate-to-severe NDI risk in preterm infants with GBS was attributable to the interaction between GBS and prematurity. There was no evidence of effect modification by prematurity on the multiplicative scale for any NDI (P value=0.27); however, it was observed for moderate-to-severe NDIs (P value=0.008).

5.6.6 Sensitivity analyses

Adjustment for gestational age yielded estimates that were closely aligned with our primary estimates for all outcomes (Supplementary Table S7). Excluding GBS cases identified only through diagnostic codes that did not meet our validation criteria reduced the total from 771 to 506. Specifically, 265 of the 650 diagnostic-code-only GBS cases were excluded, leaving 385 validated diagnostic cases, which together with 121 culture-confirmed cases, comprised the final sensitivity cohort. This restriction generally did not change the interpretation of our findings and often resulted in higher estimates (Supplementary Table S7). Excluding uncategorized conditions from the cognitive and sensory NDI domains attenuated the original estimates but the overall interpretation was unchanged (Supplementary Table S7). Although children born at early preterm gestation with a history of GBS had a higher incidence of NDI than children born at late preterm gestation (107.5 vs. 63.2 per 1,000 person-years; Supplementary Table S8), the risk of

NDI compared to children with no history of GBS during infancy was slightly lower among early preterm infants than among late preterm infants (aHR: 1.36 [95% CI: 1.03, 1.78] and aHR: 1.76 [95% CI: 1.19, 2.60], respectively). Additionally adjusting for maternal history of neuropsychiatric conditions had minimal impact on primary estimates across all outcomes (Supplementary Table S7).

Characteristics of children with and without complete covariate data were not meaningfully different (Supplementary Table S9) and incidence of infant GBS disease and NDI outcomes was comparable between those included in the adjusted models and those excluded due to missing data (Supplementary Table S10).

5.7 Discussion

In this large, population-based cohort study, we found that children who survived infant GBS disease had higher rates of NDIs by five years of age compared to those with no history of GBS during infancy. Specifically, GBS survivors had a twofold increased risk of an NDI and exhibited elevated risks for cognitive, motor, social/behavioural, and sensory impairments. We also observed higher rates of multi-domain and moderate-to-severe NDIs among GBS survivors. Infant sex and prematurity were observed to significantly modify the risk of NDIs following infant GBS disease, with male and preterm children being particularly vulnerable.

Our study corroborates existing literature on long-term impacts of GBS disease during infancy, which has been linked to NDIs,[4–8,22–25] epilepsy,[26] recurrent hospitalizations[27] and mortality.[5,6,27] Despite this, there are few large studies on NDI risk following GBS disease. Consistent with

recent findings from a Danish and Dutch cohort study,[5] we found that survivors of GBS sepsis and GBS meningitis face considerably higher risks of NDIs than unexposed children. Our subgroup analysis also indicated that this elevated NDI risk was evident in both EOD and LOD cases.[5]

While few studies have examined NDIs across different domains,[5,6,23–25] our research provides detailed estimates of domain-specific NDIs for various GBS subtypes based on primary diagnosis and timing of onset. Similar to previous reports, we found that survivors of GBS meningitis had higher rates of cognitive and motor impairments compared to those without GBS.[5,6,28] Uniquely, our study found that children with a history of EOD had over nine times the risk of developing motor impairments than unexposed children. While risk of motor impairments was high across all subgroups, it was particularly elevated among those who experienced EOD, possibly due to disruptions in neurodevelopment during the earliest stages of post-natal brain growth.[29]

A systematic review reported that 32% of GBS meningitis survivors experienced any NDI at a median follow-up of over 18 months,[4] aligning with our estimate of 29%. We identified a higher risk of moderate-to-severe NDIs at five years of age among those who experienced GBS sepsis (aHR: 2.06 [95% CI 1.42, 2.99]), compared to unexposed children. The similarity in NDI risk between GBS sepsis and GBS meningitis was somewhat unexpected, given prior evidence suggesting more severe outcomes following meningitis. One possible explanation is that some GBS meningitis cases may have been misclassified as sepsis due to unperformed lumbar punctures, negative CSF cultures following early antibiotic use,[30] or incomplete diagnostic

coding. This misclassification may have diluted the observed difference in NDI outcomes between the two groups. Additionally, neonatal sepsis itself can cause systemic inflammation and brain injury, particularly in preterm infants, which may contribute to long-term neurodevelopmental impairments, even in the absence of meningitis.[31] Such neurological damage may not be immediately apparent in the neonatal period but can still lead to persistent developmental consequences.[32]

Our findings align with previous studies, indicating that male children who had GBS disease during infancy have an excess risk of NDI.[8] This is consistent with preclinical studies demonstrating that GBS-exposed male offspring exhibit social, communication, and sensory deficits compared to their unexposed counterparts, mirroring behavioural traits similar to autism spectrum disorder.[29] Our study also observed an excess risk of NDI among children born preterm who had GBS disease during infancy.[7] The excess risk of NDI following GBS disease during infancy was higher for both early and late preterm births, compared to term births, but highest among children born at early preterm gestation. Numerous preclinical and clinical studies have linked perinatal infection, inflammation and preterm birth to brain damage, contributing to motor and psychiatric disorders.[33,34] These results on effect modification highlight the importance of continuing follow-up care beyond infancy for preterm and male children survivors of GBS to facilitate early NDI identification and provide necessary support, including educational interventions. Additionally, these findings offer valuable insights for public health discussions regarding the potential impact of preventive measures.

The universal maternal GBS screening (between 35 to 37 weeks' gestation) and intrapartum antibiotic prophylaxis (IAP) (for those who screen positive) currently adopted as a primary prevention strategy by many high-income countries presents several challenges, including limited effectiveness against LOD/ULOD and GBS-associated preterm births, as well as rising antibiotic resistance.[35] Further, recent Canadian findings also suggest insufficiencies in IAP administration, with a large proportion of infants with EOD being born to mothers who either did not receive IAP due to screening negative or who screened positive but were missed entirely.[36] This highlights the importance of primary prevention of infant GBS disease, such as potentially through maternal vaccination. In addition to preventing EOD and LOD, a maternal GBS vaccine could also delay new maternal colonization, potentially reducing the risk of preterm delivery.[7] Based on the excess NDI incidence attributable to GBS disease in this setting (i.e., 29.8 cases per 1,000 person-years), a GBS vaccine with 90% efficacy could potentially prevent approximately 26.8 NDI cases per 1,000 person-years. Applying this to the total person-time among GBS-exposed children in our cohort (3,446.7 person-years) yields an estimated 92 NDI cases potentially averted, which corresponds to approximately 12.1 NDI cases averted per 100,000 births in this population.[37]

A major strength of our study is the availability of a large, population-based cohort with comprehensive follow-up data, enhancing the generalizability of our findings. Additionally, the linkage of multiple health administrative databases allowed for robust identification of GBS cases and neurodevelopmental outcomes.

Our study has several limitations. Most GBS cases were identified through diagnostic codes rather than culture, primarily due to incomplete availability of laboratory data in the early years of the study. This could have introduced exposure misclassification, particularly if some diagnostic-code-only cases were false positives. Such misclassification would likely be non-differential, generally biasing HRs toward the null. However, our sensitivity analysis which excluded cases that did not meet our validation criteria did not change our overall findings.
We used specimen collection or hospital admission dates as proxies for disease onset, which may not accurately reflect true onset timing and could have impacted the EOD/LOD subgroup analyses. While this would not impact the overall GBS-NDI association, it may have introduced misclassification into the subgroup analyses, potentially attenuating differences between EOD and LOD categories.

NDIs were primarily identified using diagnostic codes from hospital and emergency department encounters, which may have led to outcome misclassification, particularly by underestimating milder conditions that do not result in hospital-based care. This under-ascertainment would likely be non-differential by GBS exposure status and would bias the HRs toward the null. To mitigate this, we supplemented NDI ascertainment with physician billing and specialist codes where possible. It is possible that NDIs were diagnosed earlier or more frequently in children who survived a GBS infection due to increased clinical surveillance or healthcare-seeking behaviour. However, the observed associations between GBS disease and NDIs remained consistent across all levels of NDI severity—including moderate-to-severe impairments—where diagnoses are less likely to be influenced by differential healthcare use and detection. Finally, while we adjusted for many confounders, residual confounding by unmeasured factors remains possible.

Our study demonstrated that infant GBS disease is associated with an increased risk of NDIs by five years of age. The heightened risks were evident across various NDI domains, particularly in male children and those born at preterm gestation. Future research should investigate mechanisms by which neurodevelopmental domains may be differentially affected in these subgroups. Long-term studies beyond early childhood are also needed to understand the lifelong consequences of infant GBS infection**.** These findings highlight the need for preventive strategies, such as vaccination, to improve long-term health outcomes for infants affected by GBS disease.

Contributors: RF, DBF, NT, DE, BS and KB, NC, TL and SB conceived the study protocol, study design and analytical approach. **RF** linked the administrative data sources to create the study cohort and performed the statistical analyses, which were supervised by DBF and DE. WP provided analytical guidance and revisions to data sources at ICES. **RF** and DBF drafted the manuscript. All authors contributed to data interpretation, revised the manuscript for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work.

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Declaration of interests: MS has been an investigator on projects funded by Pfizer, Merck, Moderna, Sanofi Pasteur, and GlaxoSmithKline (all unrelated to study). All funds have been paid to his institute, and he has not received any personal payments. KW is the CEO of CANImmunize Inc and served as a member of the independent data safety monitoring committee for the Medicago COVD-19 vaccine trial. When this project was funded and initiated, DBF was employed by the University of Ottawa and had an academic appointment at the Children's Hospital of Eastern Ontario Research Institute; she is now employed by Pfizer and works on an unrelated topic. DEC has been an investigator on projects funded by Moderna and Pfizer. All funds have been paid to her institute, and she has not received any personal payments. AM has received research funds to her institution from Pfizer and Sanofi Pasteur and received personal fees for advisory boards and DSMBs from Astra-Zeneca, GlaxoSmithKline, Medicago, Merck, Moderna, Pfizer, Roche and Sanofi Pasteur. SB is the director of the Centre for Vaccine Preventable Diseases at the University of Toronto, which has received support from Merck, Sanofi and Pfizer. All funds are paid to the institute and are subject to the University of Toronto's governance policies.

Ethics: This study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board (Protocol No. 20/11PE) and the ICES Privacy Office (Protocol 2023-0901-320-001). ICES is an independent, non-profit research institute whose legal status under Ontario's health

information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

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Data sharing statement: The dataset from this current study is held securely in coded form at ICES. Even though data-sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those meeting pre-specified criteria for confidential access, available at https://www.ices. on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors on request, with the understanding that the computer programs may rely on coding templates or macros that are unique to ICES and, therefore, are inaccessible or may need modification.

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5.9 Manuscript tables and figures

Table 1. Characteristics of children with and without a history of Group B *Streptococcus* disease in the first year of life (n=764,934)

Characteristic	GBS disease (n=771)	No GBS disease (764,163)	SD [a]
	n (%)	n (%)	
Primary GBS syndrome			
Sepsis	445 (57·7)	N/A	-
Meningitis	140 (18·2)	N/A	-
Pneumonia	31 (4·0)	N/A	-
Other GBS infection [b]	155 (20·1)	N/A	-
Timing of GBS onset [c]			
Early-onset	359 (46·6)	N/A	-
Late-onset	355 (46·0)	N/A	-
Ultra-late-onset	57 (7·4)	N/A	-
Sex			
Female	371 (48·1)	372,035 (48·7)	0·01
Male	396 (51·4)	391,508 (51·2)	0·00
Missing [d]	<6	620 (0·1)	0·07
Gestational age at birth, weeks			
<28	95 (12·3)	2,064 (0·3)	0·51
28 - <37	147 (19·1)	56,243 (7·4)	0·35
>= 37	529 (68·6)	705,856 (92·4)	0·63
Maternal age, years			
<20	26 (3·4)	16,886 (2·2)	0·07
20 - <25	111 (14·4)	79,626 (10·4)	0·12
25 - <30	207 (26·8)	204,111 (26·7)	0·00
30 - <35	249 (32·3)	282,578 (37·0)	0·10
>=35	178 (23·1)	180,962 (23·7)	0·01
Fiscal year of birth [e]			
2012-13	154 (20·0)	129,031 (16·9)	0·08
2013-14	145 (18·8)	127,884 (16·7)	0·05
2014-15	109 (14·1)	127,970 (16·7)	0·07
2015-16	124 (16·1)	127,125 (16·6)	0·01
2016-17	114 (14·8)	126,259 (16·5)	0·05
2017-18	125 (16·2)	125,894 (16·5)	0·01

Season of birth			
Fall	181 (23·5)	199,301 (26·1)	0·06
Spring	175 (22·7)	183,510 (24·0)	0·03
Summer	199 (25·8)	191,363 (25·0)	0·02
Winter	216 (28·0)	189,989 (24·9)	0·07
Multifetal pregnancy [f]			
Yes	70 (9·1)	25,452 (3·3)	0·24
No	701 (90·0)	738,711 (96·7)	0·24
Mode of delivery			
Vaginal	502 (65·1)	548,173 (71·7)	0·14
Cesarean	269 (34·9)	215,990 (28·3)	0·14
Parity			
Nulliparous	378 (49·0)	320,583 (42·0)	0·14
Multiparous	387 (50·2)	434,659 (56·9)	0·13
Missing	6 (0·8)	8,921 (1·2)	0·04
Smoked during pregnancy			
Yes	107 (13·9)	75,265 (9·8)	0·12
No	619 (80·3)	660,538 (86·4)	0·17
Missing	45 (5·8)	28,360 (3·7)	0·09
Maternal history of neuropsychiatric conditions [g]			
Yes	81 (10·5)	66,466 (8·7)	0.06
No	690 (89·5)	697,697 (91·3)	0.06
Rural residence			
Yes	67 (8·7)	77,802 (10·2)	0·05
No	704 (91·3)	685,511 (89·7)	0·05
Missing	0 (0·0)	850 (0·1)	0·05
Neighborhood median family income quintiles			
1 (Lowest)	174 (22·6)	163,593 (21·4)	0·03
2	175 (22·7)	51,963 (19·9)	0·07
3	166 (21·5)	157,310 (20·6)	0·02
4	146 (18·9)	160,699 (21·0)	0·05
5 (Highest)	108 (14·0)	128,293 (16·8)	0·08
Missing [d]	<6	2305 (0·3)	0·01

Marginalization indices, quintile [h]			
Missing [d]	<6	8,259 (1·1)	0·05
Residential instability			
1 (least marginalized)	174 (22·6)	163,903 (21·4)	0·03
2	138 (17·9)	139,481 (18·3)	0·01
3	127 (16·5)	134,966 (17·7)	0·03
4	139 (18·0)	141,757 (18·6)	0·01
5 (most marginalized)	188 (24·4)	175,797 (23·0)	0·03
Material deprivation			
1 (least marginalized)	127 (16·5)	143,449 (18·8)	0·06
2	134 (17·4)	146,095 (19·1)	0·05
3	127 (16·5)	144,344 (18·9)	0·06
4	187 (24·3)	146,563 (19·2)	0·12
5 (most marginalized)	191 (24·8)	175,453 (23·0)	0·04
Dependency			
1 (least marginalized)	262 (34·0)	255,487 (33·4)	0·01
2	160 (20·8)	159,144 (20·8)	0·00
3	131 (17·0)	129,203 (16·9)	0·00
4	113 (14·7)	113,553 (14·9)	0·01
5 (most marginalized)	100 (13·0)	98,517 (12·9)	0·00
Ethnic concentration			
1 (least marginalized)	92 (11·9)	102,349 (13·4)	0·04
2	119 (15·4)	113,990 (14·9)	0·01
3	111 (14·4)	128,743 (16·8)	0·07
4	154 (20·0)	159,217 (20·8)	0·02
5 (most marginalized)	290 (37·6)	251,605 (32·9)	0·10

Abbreviations: GBS=Group B *Streptococcus*; N/A=not applicable; SD=Standardized difference

[a] Shaded cells highlight standardized differences greater than 0.10, indicating a meaningful difference between individuals with and without GBS disease.

[b] Other GBS infection was defined using ICD-10-CA code B95.1. Refer to Supplement Table S2 for the complete definitions of GBS disease.

[c] Early-onset: 0 to <7 days; Late-onset: 7 to <90 days; Ultra-late-onset: 90 to <365 days

[d] Due to a contractual agreement with the data provider, small cell sizes (n=<6) cannot be reported and have been suppressed.

[e] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[f] Missing values for the multifetal pregnancy variable were combined with the "no" category due to small cell sizes (n=<6).

[g] Includes diagnoses of neurodevelopmental disorders (e.g., intellectual disability, autism spectrum disorder) and/or mental health conditions (e.g., depression, anxiety, bipolar disorder) documented on the mother's birth record.

[h] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see the Supplement (Table S4) for complete descriptions of what is captured in each of these 4 dimensions.

Table 2. Association between Group B *Streptococcus* disease in the first year of life and neurodevelopmental impairments in early childhood (n=764,934)

Outcome	GBS disease (n=771) [a]		No GBS disease (764,163)		Crude HR (95% CI)	Adjusted HR (95% CI)[b] No. of events
	No. of events	Incidence rate (95% CI) per 1,000 person-years	No. of events	Incidence rate (95% CI) per 1,000 person-years		
Any domain NDI[c,d]	184	53·4 (46·1, 61·5)	85,796	23·6 (23·4, 23·8)	2·33 (2·02, 2·69)	2·18 (1·88, 2·54)
Mild	45	13·1 (9·63, 17·3)	28,843	7·93 (7·84, 8·02)	1·72 (1·28, 2·30)	1·72 (1·28, 2·32)
Moderate-to-severe	42	12·2 (8·89, 16·3)	25,732	7·07 (6·98, 7·16)	1·76 (1·30, 2·38)	1·66 (1·21, 2·29)
Multi-domain NDI[e]	25	7·25 (4·79, 10·5)	11,979	3·29 (3·23, 3·35)	2·23 (1·51, 3·30)	2·09 (1·39, 3·16)
Domain specific NDI						
Cognitive	139	40·3 (34·0, 47·5)	53,173	14·6 (14·5, 14·7)	2·79 (2·37, 3·30)	2·56 (2·15, 3·05)
Motor	6	1·74 (0·71, 3·62)	751	0·21 (0·19, 0·22)	8·40 (3·76, 18·76)	7·08 (2·93, 17·08)
Social/behavioural	48	13·9 (10·4, 18·3)	32,386	8·90 (8·81, 9·00)	1·64 (1·24, 2·18)	1·60 (1·20, 2·14)
Sensory (Hearing, Vision)	18	5·22 (3·19, 8·09)	12,053	3·31 (3·25, 3·37)	1·63 (1·03, 2·58)	1·64 (1·02, 2·64)

Abbreviations: CI= confidence interval; GBS=Group B *Streptococcus*; HR=hazard ratio; NDI=neurodevelopmental impairment.

[a] Refer to Supplement Tables S5 and S6 to see the breakdown of GBS disease by timing (i.e., early-onset, late-onset) and type (i.e., sepsis, meningitis)

[b] Hazard ratios adjusted for infant sex, maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, marginalization indices, income quintile. Complete case analysis was used for the adjusted models (n=722,404), where records with missing covariate data were excluded.

[c] Any domain NDI: Child has an impairment in any NDI domain and severity group (including uncategorized conditions). Mild: 1-2 domains mildly affected, 0 domains moderately/severely affected; Moderate-Severe: $\geq$3 domains mildly affected OR $\geq$1 domain moderately/severely affected.

[d] 31,318 infants with only 'uncategorized' NDIs were included in the definition of 'any NDI' but not in the severity subgroups (n=97 with GBS, n=31,221 without GBS).

[e] Multi-domain NDI: child has more than one affected NDI domain (any severity group, including uncategorized conditions).

Table 3. Effect modification by sex and prematurity of neurodevelopmental impairment outcomes after Group B *Streptococcus* disease

Subgroups/Outcome	No. of events	Incidence rate per 1,000 person-years (95% CI)	Analyses with common reference group (additive interaction)		Stratified analyses (multiplicative interaction)	
			Adjusted HR [a] (95% CI)	RERI (95% CI); AP, %	Adjusted HR [a] (95% CI)	P value for interaction term
Infant Sex [b]						
Any NDI						
GBS-/Female	29,810	16·6 (16·4, 16·8)	1·00 (reference)	0·53 (0·23, 0·84); 14·2%	1·00 (reference)	0·31
GBS+/Female	72	42·6 (33·6, 53·4)	2·41 (1·89, 3·06)		2·39 (1·88, 3·04)	
GBS-/Male	55,899	30·4 (30·1, 30·6)	1·85 (1·82, 1·88)		1·00 (reference)	
GBS+/Male	111	63·8 (52·7, 76·5)	3·79 (3·12, 4·61)		2·06 (1·69, 2·50)	
Moderate-to-severe NDI						
GBS-/Female	7,778	4·33 (4·24, 4·43)	1·00 (reference)	0·55 (-0·12, 1·22); 15·2%	1·00 (reference)	0·72
GBS+/Female	14	8·28 (4·72, 13·6)	1·81 (1·05, 3·11)		1·82 (1·06, 3·14)	
GBS-/Male	17,934	9·74 (9·60, 9·88)	2·26 (2·20, 2·32)		1·00 (reference)	
GBS+/Male	28	16·1 (10·9, 22·9)	3·62 (2·44, 5·36)		1·59 (1·08, 2·36)	
Preterm birth						
Any NDI						
GBS-/Term	74,618	22·1 (21·9, 22·3)	1·00 (reference)	1·18 (0·88, 1·49); 31·8%	1·00 (reference)	0·27
GBS+/Term	94	38·6 (31·4, 47·1)	1·78 (1·45, 2·19)		1·78 (1·45, 2·19)	
GBS-/Preterm	11,178	41·9 (41·2, 42·7)	1·77 (1·73, 1·80)		1·00 (reference)	
GBS+/Preterm	90	88·8 (71·9, 108·7)	3·74 (2·99, 4·67)		2·12 (1·70, 2·65)	
Moderate-severe NDI						
GBS-/Term	22,729	6·74 (6·65, 6·83)	1·00 (reference)	2·13 (1·48, 2·78); 58·4%	1·00 (reference)	0·008
GBS+/Term	15	6·16 (3·58, 9·94)	0·98 (0·59, 1·63)		0·98 (0·59, 1·62)	
GBS-/Preterm	3,003	11·3 (10·9, 11·7)	1·54 (1·48, 1·61)		1·00 (reference)	
GBS+/Preterm	27	26·7 (17·9, 38·3)	3·65 (2·42, 5·50)		2·35 (1·56, 3·55)	

Abbreviations: AP=attributable proportion due to interaction; CI= confidence interval; GBS=Group B *Streptococcus*; HR=hazard ratio; NDI=neurodevelopmental impairment; RERI=relative excess risk due to interaction

[a] Hazard ratios adjusted for maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, marginalization indices, income quintile. For preterm birth analysis, hazard ratios also adjusted for infant sex.

[b] Records with missing data on infant sex (n=624) were not included.

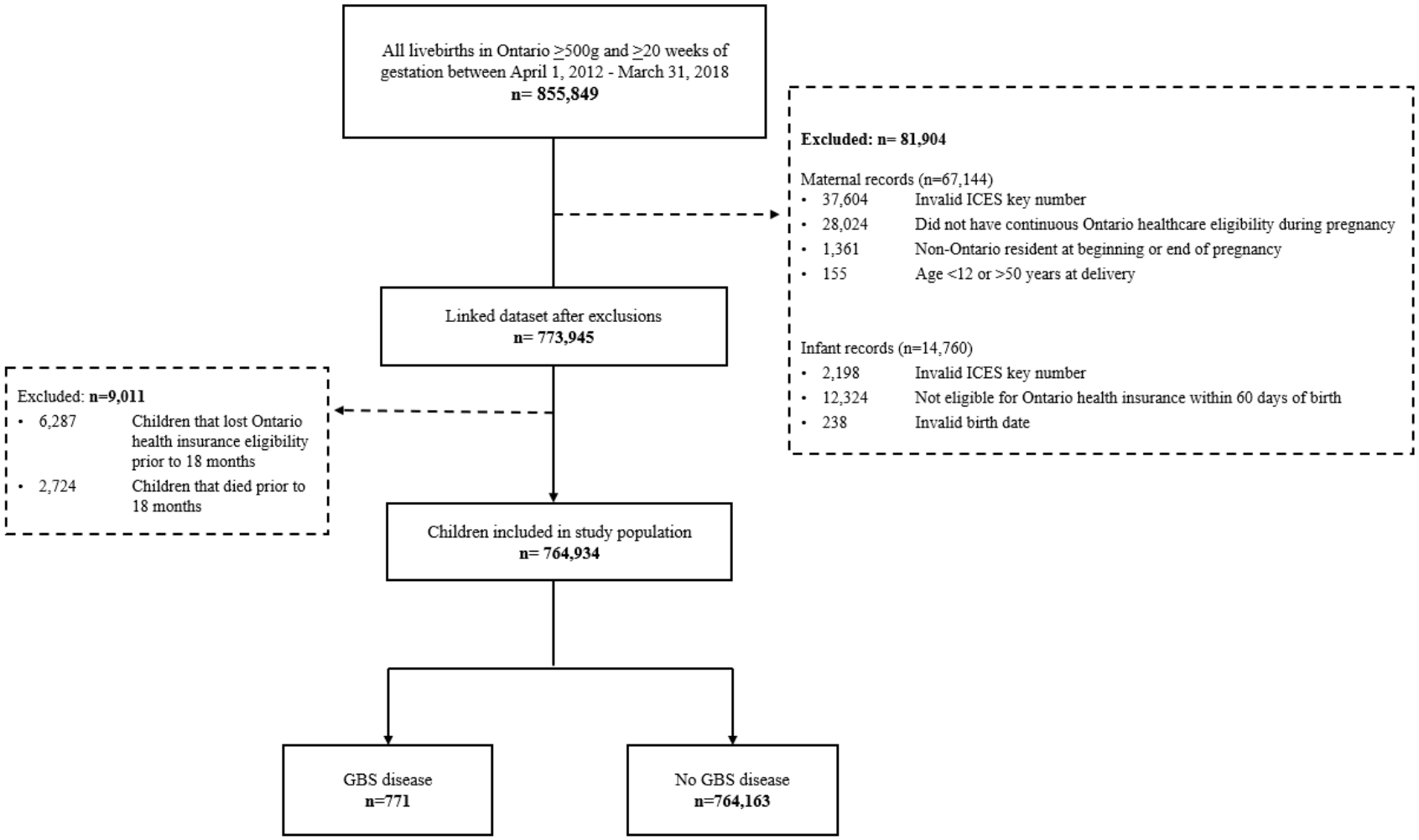


Figure 1. Flow diagram illustrating creation of study cohort
Abbreviations: GBS=Group B *Streptococcus*

5.10 Supplementary materials

Table S1. Description and purpose of each data source utilized in the study

Database	Description	Information collected
Better Outcomes Registry & Network (BORN) Ontario	Captures all births ≥500 grams or ≥20 weeks' gestation in the province of Ontario. Routine data collection includes information on maternal demographic variables; pre-existing maternal health conditions; obstetric factors affecting the pregnancy; and birth outcomes (Murphy et al., 2021).[1]	Used to ascertain sociodemographic, pregnancy and birth characteristics.
Registered Persons Database (RPDB)	Demographic repository containing information on all Ontario residents eligible for publicly funded health care in the province.	Used to establish the duration for which each participant was eligible to receive health care services, as well as obtain demographic information regarding neighborhood income quintiles.
Postal Code Conversion File (PCCF)	The Postal Code Conversion File (PCCF) facilitates the matching of six-digit postal codes with standardized census geographies. These resulting small-area geographies serve various purposes, such as aggregating data to widely used administrative boundaries and comprehending socio-economic status at the neighborhood level.	Used to obtain geographic information for variables such as rural location and neighbourhood income quintiles by converting Ontario postal codes into Statistics Canada standard geographical areas.
Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)	Captures demographic and clinical information regarding hospital admissions from all acute care institutions throughout Ontario. Contains medical diagnoses (most responsible diagnosis and up to 24 secondary diagnoses), interventions received, length of hospital stay and other data elements. Medical diagnoses are coded using the Canadian implementation of the International Classification of Diseases, 10th Revision (ICD-10-CA). Medical interventions are documented through Canadian Classification of Health Interventions (CCI) codes.	Used to obtain information regarding hospital admissions, including medical diagnoses and procedures, for defining exposures and outcomes.
Canadian Institute for Health Information (CIHI) National Ambulatory Care Reporting System (NACRS)	Captures data originating from outpatient clinics and urgent visits to emergency departments in Ontario. Up to 10 clinical diagnoses on each abstract are coded using ICD-10-CA.	Used to supplement data from the CIHI-DAD and capture additional medical diagnoses captured at emergency department visits and outpatient clinics for exposure and outcome information.

Ontario Health Insurance Plan (OHIP) Database	Contains health care billing information made by physicians, or other health care providers, for service reimbursement. This database includes information on the diagnosis (i.e., reason for the visit), type of service received, and the associated billing code.	Used to capture physician billing claims to define certain neurodevelopmental conditions.
Ontario Marginalization Index (ON-Marg)	Data tool that quantifies the level of marginalization occurring in Ontario. This multifaceted index uses data from Statistics Canada's Census and consists of four dimensions that indicate area-level marginalization: residential instability, material deprivation, dependency and ethnic concentration. Scores corresponding to each of these four dimensions were previously divided into quintiles, where quintile 1 represents areas that are the least marginalized and quintile 5 represents the most marginalized areas.	Provided information regarding the four indices of area-level marginalization.
Ontario Laboratories Information System (OLIS) Database	OLIS is an electronic repository of the province's laboratory test results. This system was implemented to allow health care providers timely access to laboratory test results from both community- and hospital-based laboratories. According to eHealth Ontario, as of Dec. 31, 2017, 134 of the 262 hospital sites across the province were using OLIS, and 13 of the 14 Local Health Integration Networks (LHINs) were included (https://ehealthontario.on.ca/files/public/support/DataContributorsOLIS.pdf).	Used to identify laboratory-confirmed instances of infant GBS disease. We utilized cleaned observation codes for bacterial culture results that had an organism code of 53 (*Streptococcus* agalactiae) and a specimen source of either blood or cerebrospinal fluid.

Table S2. Infant Group B *Streptococcus* (GBS) definitions

GBS Category	Laboratory Database (OLIS) ‡	Health administrative databases (DAD, NACRS)*‡	References
Sepsis	Positive blood culture for GBS	ICD-10-CA codes (up to 365 days of life): - A40.1 (Sepsis due to GBS) - P36.0 (Sepsis of newborn due to GBS)	Horváth-Puhó (2021) [2] Lykke (2023) [3]
Meningitis	Positive cerebrospinal fluid (CSF) for GBS, with or without a positive blood culture for GBS	ICD-10-CA codes (up to 365 days of life): - G00.2 (*Streptococcal* meningitis) - Patients with sepsis codes above AND G00.9 (bacterial meningitis, unspecified) or G03.9 (meningitis, unspecified)	Horváth-Puhó (2021) [2] Lykke (2023) [3]
Pneumonia	Not captured	ICD-10-CA codes (up to 365 days of life): - J15.3 (Pneumonia due to GBS) - P23.3 (Congenital pneumonia due to GBS)	Horváth-Puhó (2021) [2]
Other GBS infection	N/A	ICD-10-CA codes (up to 365 days of life): - B95.1 (*Streptococcus*, group B, as the cause of disease classified elsewhere), Examples include: urinary tract infections, cellulitis, kidney infections etc.	Yeo (2019) [4]
Early-onset disease (EOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was within the period from birth to 6 days of life.	Admission date for the first GBS-related hospitalization was within the period from birth to 6 days of life.	N/A
Late-onset disease (LOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was from 7 days of life to 89 days of life.	Admission date for the first GBS-related hospitalization was within the period from 7 days of life to 89 days of life.	N/A
Ultra-late-onset disease (ULOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was from 90 days of life to 1 year of age.	Admission date for the first GBS-related hospitalization was within the period from 90 days of life to 1 year of age.	N/A

DAD=Discharge Abstract Database; N/A=not applicable; NACRS=National Ambulatory Care Reporting System; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; OLIS=Ontario Laboratories Information System Database.

*Records with a diagnostic code for GBS on any of the 25 fields within DAD or 10 fields within NACRS were selected.

‡ For cases with culture-confirmation, infants were categorized as EOD, LOD or ULOD based on the date of specimen collection in OLIS. In instances of multiple specimen

collections, we used the date of the first positive culture result. Among GBS infants without culture confirmation (identified only in DAD/NACRS), we used the admission date for the first GBS-related visit (hospitalization or emergency department visit), referred to as the index GBS visit, to determine the classification of GBS disease as EOD, LOD, or ULOD. The initial clinical presentation of GBS (sepsis, meningitis, pneumonia) was defined using the type of positive culture, or diagnostic code on the index GBS visit if culture data were unavailable. If an infant had both blood and CSF (or both sepsis and meningitis ICD codes) on the same collection date or index hospitalization, then meningitis was assigned.

Table S3. Neurodevelopmental impairment (NDI) definitions

Domain	**Definition and identifying ICD-10-CA/OHIP diagnostic code(s), CCI procedural code(s) and/or OHIP fee code(s) ***	**References for definitions**
Any domain NDI	An impairment in any single domain and severity group (including uncategorized). Severity categories*: - **Mild:** 1-2 domains mildly affected AND no domains moderately or severely affected - **Moderate-to-severe:** ≥3 domains mildly affected OR ≥1 domain moderately affected OR ≥1 domain severely affected *Infants with only "uncategorized" conditions were included in the definition of "any NDI" but not in the severity categories.	Horváth-Puhó (2021) [2] Paul (2022) [5]
Multi-domain NDI	An impairment in more than one affected domain and severity group (including uncategorized conditions).	Horváth-Puhó (2021) [2]
Cognitive	**Mild:** - **ICD-10-CA codes (≥1 occurrence):** F70 [mild mental retardation], F80.0 [speech articulation disorder], F80.1 [expressive language disorder], F80.2 [receptive language disorder], F80.9 [developmental disorder of speech and language], F81.0 [specific reading disorder], F81.1 [specific	Horváth-Puhó (2021) [2] Kohli-Lynch (2017) [6] Robinson (2021) [7] Dodds (2009) [8] Lin (2013) [9] Corsi (2020) [10]

	spelling disorder], F81.2 [specific disorder of arithmetical skills] **Moderate:** - **ICD-10-CA codes (≥1 occurrence):** F83 [mixed specific developmental disorders], F84.0 [childhood autism], F84.1 [atypical autism], F84.3 [other childhood disintegrative disorder], F84.5 [Asperger's syndrome], F71 [moderate mental retardation], F81.3 [mixed disorder of scholastic skills] - **OHIP diagnostic codes (≥ 2 occurrences with physician specialty codes 19 or 26 for pediatrician or psychiatrist):** 299 [autism] **Severe:** - **ICD-10-CA codes (≥1 occurrence):** F72 [severe mental retardation], F73 [profound mental retardation], F80.3 [acquired aphasia with epilepsy], F84.2 [Rett's syndrome], F84.4 [Overactive disorder associated with mental retardation and stereotyped movements] **Uncategorized:** - **ICD-10-CA codes (≥1 occurrence):** F78 [other mental retardation], F79 [unspecified mental retardation], F84.8 [other pervasive developmental disorders], F84.9 [pervasive developmental disorder, unspecified], F88 [other disorders of psychological development], F80.8 [other developmental disorders of speech and language], F81.8 [other developmental disorders of scholastic skills], F81.9 [developmental disorder of scholastic skills, unspecified] - **OHIP diagnostic code (≥ 2 occurrences):** 319 [mental retardation, unspecified]	

Motor	**<u>Mild:</u>** - **ICD-10-CA codes (≥1 occurrence):** F82 [developmental disorder of motor function], R27.0 [ataxia], R27.8 [other lack of coordination], R26.0 [ataxic gait], R26.1 [paralytic gait], G24.9 [dystonia], G25.9 [extrapyramidal and movement disorder] **<u>Moderate:</u>** - **ICD-10-CA codes (≥1 occurrence):** G80.1 [spastic diplegic cerebral palsy], G80.3 [dyskinetic cerebral palsy], G80.4 [ataxic cerebral palsy], G80.8 [other cerebral palsy], G80.9 [cerebral palsy, unspecified] **<u>Severe:</u>** - **ICD-10-CA codes (≥1 occurrence):** G80.0 [spastic quadriplegic cerebral palsy]	Horváth-Puhó (2021) [2] Kohli-Lynch (2017) [6]
Sensory	***<u>Hearing conditions:</u>*** **<u>Mild:</u>** - **ICD-10-CA codes (≥1 occurrence):** H90.1 [conductive hearing loss, unilateral with unrestricted hearing on the contralateral side], H90.4 [sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side], H90.7 [Mixed conductive and sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side] **<u>Severe:</u>** - **ICD-10-CA codes (≥1 occurrence):** H90.0 [conductive hearing loss, bilateral], H90.3 [sensorineural hearing loss, bilateral], H90.6	Horváth-Puhó (2021) [2] Kohli-Lynch (2017) [6] Robinson (2021) [7] Laverty (2021) [11] Ray (2016) [12]

	[mixed conductive and sensorineural hearing loss, bilateral], Z45.3 [adjustment and management of implanted hearing device] - **OHIP diagnostic codes (≥ 2 occurrences):** 389 [deafness] - **OHIP fee codes (≥2 occurrences):** E341 [cochlear implants], E346 [hearing aid insertion] - **CCI codes (≥1 occurrence)**: 1DM53 [implantation of internal device, cochlea] **Uncategorized:** - **ICD-10-CA codes (≥1 occurrence):** Z97.4 [presence of external hearing aid], Z46.1 [fitting and adjustment of hearing aid], H90.2 [conductive hearing loss, unspecified], H90.5 [sensorineural hearing loss, unspecified], H90.8 [mixed conductive and sensorineural hearing loss, unspecified], H91 [other hearing loss] - **CCI codes (≥1 occurrence)**: 1DZ37 [installation of external appliance, ear NEC, not elsewhere classified], 1DL53 [implantation of internal device, mastoid process], 6PA10 [counseling, hearing loss], 6TA10 [counseling, sight or other sensory loss], 7SF18TD [measuring and fitting, service for other assistive/adaptive device (e.g. hearing aid)] ***Vision conditions:*** **Mild:** - **ICD-10-CA codes (≥1 occurrence):** H53.0 [amblyopia ex anopsia], H53.1 [subjective visual disturbances], H53.2 [diplopia], H53.4 [visual field defects], H54.5 [blindness, monocular],	

	H54.6 [visual impairment, monocular] **<u>Moderate:</u>** - **ICD-10-CA codes (≥1 occurrence):** H54.2 [visual impairment, binocular] **<u>Severe:</u>** - **ICD-10-CA codes (≥1 occurrence):** H54.0 [blindness, binocular], H54.1[severe visual impairment, binocular] **<u>Uncategorized:</u>** - **ICD-10-CA codes (≥1 occurrence):** H47 [Other disorders of optic (2nd) nerve and visual pathways], H48.8 [other disorders of optic nerve and visual pathways in diseases classified elsewhere]	
Social/behavioural	**<u>Mild:</u>** - **ICD-10-CA codes (≥1 occurrence):** F90.0 [disturbance of activity and attention (attention-deficit hyperactivity disorders)], F90.1 [hyperkinetic conduct disorder], F90.8 [other hyperkinetic disorders], F90.9 [hyperkinetic disorder, unspecified], F91.0 [conduct disorder confined to the family context], F91.1 [unsocialized conduct disorder], F91.2 [socialized conduct disorder], F91.3 [oppositional defiant disorder], F91.8 [other conduct disorders], F91.9 [conduct disorder, unspecified], F92.0 [depressive conduct disorder], F92.8 [other mixed disorders of conduct and emotions], F92.9 [mixed disorder of conduct and emotions, unspecified], F93.0 [separation anxiety disorder of childhood],	Horváth-Puhó (2021) [2] Kohli-Lynch (2017) [6] Robinson (2021) [7] Corsi (2020) [10] Miller (2013) [13]

	F93.1 [phobic anxiety disorder of childhood], F93.2 [social anxiety disorder of childhood], F93.3 [sibling rivalry disorder], F93.8 [other childhood emotional disorders], F93.9 [childhood emotional disorder, unspecified], F94.1 [reactive attachment disorder of childhood], F94.2 [disinhibited attachment disorder of childhood], F94.8 [other childhood disorders of social functioning], F94.9 [childhood disorder of social functioning, unspecified], F95.1 [chronic motor or vocal tic disorder], F95.2 [combined vocal and multiple motor tic disorder], F95.8 [Other tic disorders], F95.9 [Tic disorder, unspecified], F98.0 [nonorganic enuresis], F98.1 [nonorganic encopresis], F98.2 [feeding disorder of infancy and childhood], F8.3 [pica of infancy and childhood], F40 [phobic anxiety disorders], F41 [other anxiety disorders], F42 [obsessive-compulsive disorder], F48.8 [other neurotic disorders (fatigue syndrome)], F48.9 [neurotic disorder, unspecified], F38 [other mood disorders], F39 [Unspecified mood disorder] - **OHIP diagnostic code (≥ 2 occurrences):** 296 [manic depressive psychosis, involutional melancholia], 300 [anxiety disorders], 301 [personality disorders], 309 [anxiety disorders (adjustment reaction)], 311 [depressive or other non-psychotic disorders], 313 [behaviour disorders of childhood and adolescence], 314 [hyperkinetic syndrome of childhood]	

Abbreviations: CCI= Canadian Classification of Health Interventions; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; Ontario Health Insurance Plan (OHIP)

*For ICD-10-CA codes and CCI codes at least one occurrence was required to meet the definition. For OHIP codes, two or more occurrences during the follow-up period were required to meet the definition.

Table S4. Definitions of all other study variables

Study Variable	Patient record	Definition	Source of variable
Maternal characteristics			
Maternal age	Mother	Age of the mother at the time of giving birth.	Calculated using from "m_bdate" variable in BORN.
Parity	Mother	Total number of previous pregnancies (live births and stillbirths) that reached a viable gestational age.	Measured using "parity" variable in BORN.
Multifetal pregnancy	Mother	The total number of fetuses in the current pregnancy. If the pregnancy included more than one fetus, it was classified as multifetal.	Measured using "number_of_fetuses" variable in BORN.
Mode of delivery	Mother	Refers to the mode of delivery (vaginal or cesarean section) experienced by the mother.	Measured using "birth_type_id" variable in BORN.
Smoking during pregnancy	Mother	Self-reported smoking use at first prenatal care visit and/or at time of labor/admission.	Measured using "mat_smoking_at_adm_for_birth_id" and "matsmokingatfirstprenvisit_id" variables in BORN.
Season of birth	Mother and infant	Refers to the season that the infant was born.	Grouped into Fall, Spring, Summer or Winter based on infant's date of birth.
Fiscal year of birth	Mother and infant	Refers to the fiscal year that the infant was born.	Grouped using infant's date of birth where a fiscal year begins on Apr. 1 and ends on Mar. 31.
Maternal history of neuropsychiatric conditions	Mother	Refers to whether the mother had a record of neurodevelopmental disorders (e.g., Autism, hearing disorder, vision disorder, learning disability, developmental delay) or mental health conditions (e.g., depression, anxiety, bipolar disorder, schizophrenia) at or prior to delivery.	Measured using "mat_pre_exist_health_cond_id" (limited to neurodevelopmental conditions) and "mental_health_concern_id" variables in BORN.

Rural residence	Mother	Rurality determined using second digit of postal code from Canada Post Corporation.	Measured using rural flag variable from postal code conversion file in RPDB.
Income quintile	Mother	Nearest Census Based Neighborhood Income Quintile.	Measured using "INCQUINT" variable within RPDB.
Dependency	Mother	Refers to area-level concentrations of people who don't have income from employment.	Measured using "dependency factor score" variable within the ON-Marg database.
Ethnic concentration	Mother	Refers to high area-level concentrations of recent immigrants and people belonging to a 'visible minority' group.	Measured using "ethnic concentration factor score" variable within the ON-Marg database.
Material deprivation	Mother	Refers to inability for individuals and communities to access and attain basic material needs. This dimension is closely connected to poverty.	Measured using "material deprivation factor score" variable within the ON-Marg database.
Residential instability	Mother	Refers to area-level concentrations of people who experience high rates of family or housing instability.	Measured using "residential instability factor score" variable within the ON-Marg database.
Infant characteristics			
Preterm birth	Mother and infant	Live birth prior to 37 weeks of gestation.	Measured using gestational age variable in BORN.
Baby's sex	Infant	Infant's sex.	Measured using "b_sex" variable in BORN.

Note: BORN=Better Outcomes Registry & Network; DAD=Discharge Abstract Database; NACRS=National Ambulatory Care Reporting System; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; RPDB=Registered Persons Database.

Table S5. Association between subgroups of GBS, based on timing of GBS onset, and NDIs

Outcome	GBS disease (≤89 days)[a] (n=714)		Early-onset disease (≤6 days) (n=359)		Late-onset disease (7 to ≤ 89 days)[b] (n=355)	
	Crude HR (95% CI)	Adjusted HR[c] (95% CI)	Crude HR (95% CI)	Adjusted HR[c] (95% CI)	Crude HR (95% CI)	Adjusted HR[c] (95% CI)
Any domain NDI[d,e]	2·34 (2·02, 2·72)	2·19 (1·87, 2·57)	2·41 (1·95, 2·96)	2·29 (1·83, 2·85)	2·28 (1·84, 2·82)	2·10 (1·68, 2·63)
Mild	1·82 (1·35, 2·44)	1·83 (1·36, 2·47)	1·40 (0·87, 2·26)	1·42 (0·87, 2·33)	2·24 (1·54, 3·24)	2·20 (1·51, 3·21)
Moderate-to-severe	1·86 (1·37, 2·52)	1·76 (1·27, 2·43)	2·17 (1·46, 3·24)	2·04 (1·33, 3·12)	1·55 (0·97, 2·49)	1·50 (0·92, 2·45)
Multi-domain NDI[f]	2·42 (1·63, 3·57)	2·28 (1·52, 3·43)	2·30 (1·31, 4·05)	2·24 (1·24, 4·04)	2·53 (1·47, 4·35)	2·31 (1·32, 4·07)
Domain specific NDI						
Cognitive	2·78 (2·34, 3·31)	2·54 (2·11, 3·05)	3·03 (2·39, 3·82)	2·84 (2·22, 3·65)	2·55 (1·98, 3·30)	2·26 (1·72, 2·97)
Motor	9·08 (4·07, 20·26)	7·68 (3·18, 18·52)	9·00 (2·90, 27·95)	9·45 (3·05, 29·33)	9·12 (2·94, 28·35)	6·98 (1·49, 23·99)
Social/behavioural	1·72 (1·30, 2·30)	1·70 (1·26, 2·28)	1·19 (0·73, 1·93)	1·11 (0·65, 1·87)	2·28 (1·61, 3·25)	2·26 (1·59, 3·21)
Sensory (Hearing, Vision)	1·67 (1·02, 2·65)	1·67 (1·03, 2·73)	2·13 (1·18· 3·84)	2·10 (1·13, 3·91)	1·18 (0·53, 2·62)	1·25 (0·56, 2·79)

Abbreviations: CI= confidence interval; GBS=Group B Streptococcus; HR=hazard ratio; NDI=neurodevelopmental impairment.

[a] Those with ultra-late onset disease (90 to ≤365 days) were excluded from analysis (n=57).

[b] Those with early-onset disease (n=359) were excluded from analysis of late-onset disease.

[c] Hazard ratios adjusted for infant sex, maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, marginalization indices, income quintile. Complete case analysis was used for the adjusted models (n=722,404), where records with missing covariate data were excluded.

[d] Any domain NDI: Child has an impairment in any NDI domain and severity group (including uncategorized conditions). Mild: 1-2 domains mildly affected, 0 domains moderately/severely affected; Moderate-to-severe: ≥3 domains mildly affected OR ≥1 domain moderately/severely affected.

[e] Infants with only 'uncategorized' NDIs (n=31,318) were included in the definition of 'any NDI' but not in the severity subgroups.

[f] Multi-domain NDI: child has more than one affected NDI domain (any severity group, including uncategorized conditions).

Table S6. Association between subgroups of GBS, based on primary diagnosis of GBS, and NDIs

Outcome	GBS sepsis (n=445)		GBS meningitis (n=140)	
	Crude HR (95% CI)	Adjusted HR[a] (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Any domain NDI[b,c]	2·40 (1·99, 2·89)	2·16 (1·77, 2·62)	2·87 (2·11, 3·92)	2·75 (1·96, 3·84)
Mild	1·99 (1·39, 2·84)	1·91 (1·33, 2·76)	1·55 (0·74, 3·24)	1·66 (0·79, 3·48)
Moderate-to-severe	2·26 (1·59, 3·21)	2·06 (1·42, 2·99)	1·21 (0·51, 2·89)	1·11 (0·42, 2·95)
Multi-domain NDI[d]	2·32 (1·40, 3·84)	2·13 (1·26, 3·59)	1·51 (0·49, 4·68)	1·13 (0·28, 4·52)
Domain specific NDI				
Cognitive	2·68 (2·14, 3·35)	2·34 (1·84, 2·96)	3·67 (2·60, 5·19)	3·39 (2·31, 4·98)
Motor	7·26 (2·34, 22·54)	7·20 (2·32, 22·39)	7·88 (1·12, 55·66)	7·55 (1·07, 53·43)
Social/behavioural	1·88 (1·33, 2·66)	1·76 (1·23, 2·51)	1·37 (0·65, 2·86)	1·49 (0·71, 3·12)
Sensory (Hearing, Vision)	2·18 (1·29, 3·68)	2·16 (1·25, 3·71)	1·54 (0·50, 4·76)	1·80 (0·59, 5·55)

Abbreviations: CI= confidence interval; GBS=Group B Streptococcus; HR=hazard ratio; NDI=neurodevelopmental impairment.

[a] Hazard ratios (HRs) adjusted for infant sex, maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, marginalization indices, income quintile. Complete case analysis was used for the adjusted models (n=722,404), where records with missing covariate data were excluded.

[b] Any domain NDI: Child has an impairment in any NDI domain and severity group (including uncategorized group). Mild: 1-2 domains mildly affected; Moderate-to-severe: $\geq$3 domains mildly affected OR $\geq$1 domain moderately affected OR $\geq$1 domain severely affected.

[c] Infants with only 'uncategorized' NDIs (n=31,318) were included in the definition of 'any NDI' but not in the severity subgroups.

[d] Multi-domain NDI: child has more than one affected NDI domain (any severity group, including uncategorized conditions).

Table S7. Sensitivity analyses for the association between Group B Streptococcus disease and neurodevelopmental impairments

Outcome	Results from primary analysis [a]	Additionally adjusting for gestational age [b]	Validation exclusions for GBS definition [c]	Excluding only 'uncategorized' NDI conditions [d]	Additionally adjusting for maternal history of neuropsychiatric conditions
	Adjusted HR (95% CI)	Adjusted HR (95% CI) [a]	Adjusted HR (95% CI) [a]	Adjusted HR (95% CI) [a]	Adjusted HR (95% CI) [a]
Any domain NDI[e,f]	2·18 (1·88, 2·54)	1·93 (1·66, 2·24)	2·38 (1·99, 2·85)	1·70 (1·37, 2·11)	2·18 (1·87, 2·53)
Mild	1·72 (1·28, 2·32)	1·63 (1·22, 2·20)	1·87 (1·32, 2·66)	N/A	1·71 (1·27, 2·30)
Moderate-to-severe	1·66 (1·21, 2·29)	1·51 (1·10, 2·08)	1·81 (1·24, 2·64)	N/A	1·66 (1·21, 2·28)
Multi-domain NDI[g]	2·09 (1·39, 3·16)	1·80 (1·20, 2·71)	1·53 (0·84, 2·76)	2·02 (1·33, 3·06)	2·09 (1·39, 3·14)
Domain specific NDI					
Cognitive	2·56 (2·15, 3·05)	2·14 (1·79, 2·54)	2·63 (2·13, 3·26)	1·98 (1·45, 2·70)	2·55 (2·14, 3·04)
Motor	7·08 (2·93, 17·08)	5·12 (2·12, 12·37)	6·44 (2·07, 20·04)	N/A	7·03 (2·92, 16·97)
Social/behavioural	1·60 (1·20, 2·14)	1·51 (1·13, 2·02)	1·72 (1·21, 2·43)	N/A	1·59 (1·19, 2·13)
Sensory (Hearing, Vision)	1·64 (1·02, 2·64)	1·51 (0·94, 2·43)	1·90 (1·11, 3·28)	1·98 (1·45, 2·70)	1·63 (1·02, 2·63)

Abbreviations: CI= confidence interval; GBS=Group B Streptococcus; HR=hazard ratio; N/A=not applicable; NDI=neurodevelopmental impairment.

[a] Hazard ratios adjusted for infant sex, maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, marginalization indices, income quintile. Complete case analysis was used for the adjusted models (n=722,404), where records with missing covariate data were excluded.

[b] Estimates additionally adjusted for gestational age (<28 weeks, 28-<37 weeks, ≥37 weeks).

[c] Infants with GBS disease that were identified solely through diagnostic codes (without culture confirmation) were excluded if they had: i) only tested negative for blood or cerebral spinal fluid in the laboratory database; ii) only tested positive for another specimen source that was not blood or cerebral spinal fluid (e.g., urine); iii) early-onset disease but had a length of stay less than 2 days; or iv) the diagnostic code B95.1 (GBS as cause of disease) without any additional corresponding GBS condition (e.g., sepsis, meningitis or pneumonia). The number of infants with GBS went from 771 to 506.

[d] Infants exclusively with 'uncategorized' NDIs were excluded from the outcome definition. Domains without 'uncategorized' conditions in their definition are denoted as 'N/A' as their estimates remained unchanged in this sensitivity analysis.

[e] Any domain NDI: Child has an impairment in any NDI domain and severity group (including uncategorized conditions). Mild: 1-2 domains mildly affected, 0 domains moderately/severely affected; Moderate-to-severe: ≥3 domains mildly affected OR ≥1 domain moderately/severely affected.

[f] For the sensitivity analyses adjusting for preterm birth, applying validation exclusions, and maternal history of neuropsychiatric conditions, infants with only 'uncategorized' NDI conditions (n=31,318) were included in the definition of 'any NDI' but not in the severity subgroups.

[g] Multi-domain NDI: child has more than one affected NDI domain (any severity group, including uncategorized).

Table S8. Sensitivity analysis of effect modification by prematurity, distinguishing between early (<32 weeks) and late (32 to <37 weeks) preterm birth

Subgroups/Outcome	No. of events	Incidence rate per 1,000 person-years (95% CI)	Analyses with common reference group (additive interaction)		Stratified analyses (multiplicative interaction)	
			Adjusted HR [a] (95% CI)	RERI (95% CI); AP, %	Adjusted HR [a] (95% CI)	P value for interaction term
Any NDI						
GBS-/Term	74,618	22·1 (21·9, 22·3)	1·00 (reference)	-	1·00 (reference)	-
GBS+/Term	94	38·6 (31·4, 47·1)	1·78 (1·45, 2·19)	-	1·78 (1·45, 2·19)	-
GBS-/Late Preterm	8,808	37·3 (36·5, 38·1)	1·58 (1·54, 1·62)	0·46 (0·22, 0·91); 16·4%	1·00 (reference)	0·32
GBS+/Late Preterm	27	63·2 (42·5, 90·8)	2·83 (1·91, 4·19)		1·76 (1·19, 2·60)	
GBS-/Early Preterm	2,370	78·5 (75·4, 81·7)	3·29 (3·14, 3·45)	0·37 (0·17, 0·71); 8·3%	1·00 (reference)	0·048
GBS+/Early Preterm	63	107·5 (83·3, 136·6)	4·45 (3·40, 5·82)		1·36 (1·03, 1·78)	

Early Preterm: Infant born prior to 32 weeks' gestation. Late Preterm: Infant born between 32 and <37 weeks' gestation.
Abbreviations: AP=attributable proportion due to interaction; CI= confidence interval; GBS=Group B *Streptococcus*; HR=hazard ratio; NDI=neurodevelopmental impairment; RERI=relative excess risk due to interaction
[a] Hazard ratios adjusted for maternal age, infant birth month and year, parity, smoking during pregnancy, rurality, multifetal pregnancy, marginalization indices, income quintile and infant sex.

Table S9. Distribution of key characteristics among those with and without complete covariate data

Characteristic	Complete covariate data (n=722,404)	Incomplete covariate data (n=42,530)	SD[a]
	n (%)	n (%)	
Sex			
Female	351,969 (48·7)	20,437 (48·1)	0·01
Male	370,435 (51·3)	21,469 (50·5)	0·02
Missing	0	624 (1·5)	-
Gestational age at birth, weeks			
<28	1,816 (0·30)	343 (0·80)	0·07
28 - <37	52,092 (7·2)	4,298 (10·1)	0·08
>= 37	668,496 (92·5)	37,889 (89·1)	0·10
Maternal age, years			
<20	15,474 (2·1)	1,438 (3·4)	0·08
20 - <25	75,458 (10·4)	4,279 (10·1)	0·01
25 - <30	193,426 (26·7)	10,892 (25·6)	0·01
30 - <35	267,614 (37·0)	15,213 (35·8)	0·03
>=35	170,432 (23·6)	10,708 (25·1)	0·03
Fiscal year of birth [b]			
2012-13	120,503 (16·7)	8,682 (20·4)	0·06
2013-14	120,630 (17·0)	7,399 (17·4)	0·00
2014-15	121,389 (16·8)	7,501 (17·6)	0·02
2015-16	119,748 (16·6)	7,662 (18·0)	0·04
2016-17	119,959 (16·6)	6,414 (15·1)	0·04
2017-18	120,175 (16·6)	5,844 (13·7)	0·05
Season of birth			
Fall	187,659 (26·0)	11,823 (27·8)	0·04
Spring	173,765 (24·1)	9,920 (23·3)	0·02
Summer	180,997 (25·1)	10,565 (24·8)	0·00
Winter	179,983 (24·9)	10,222 (24·0)	0·02
Multifetal pregnancy			
Yes	23,550 (3·3)	1,972 (4·6)	0·07
No	698,854 (96·7)	40,554 (95·4)	0·07
Missing [c]	0	<6	-
Delivery type			

Vaginal	519,570 (71·9)	29,105 (68·4)	0·08
Cesarean	202,834 (28·1)	13,425 (31·6)	0·08
Parity			
Nulliparous	306,215 (42·4)	14,746 (34·7)	0·16
Multiparous	416,189 (57·6)	18,857 (44·3)	0·27
Missing	0	8,927(21·0)	-
Smoked during pregnancy			
Yes	71,514 (9·9)	3,853 (9·1)	0·03
No	650,890 (90·1)	10,267 (24·1)	0·46
Missing	0	28,405 (66·8)	-
Rural residence			
Yes	74,549 (10·3)	3,320 (7·8)	0·06
No	648,669 (89·7)	38,360 (90·1)	0·01
Missing	0	850 (2·0)	-
Neighborhood median family income quintiles			
1 (Lowest)	152,920 (21·2)	10,847 (25·5)	0·10
2	145,459 (20·1)	6,679 (15·7)	0·09
3	150,504 (20·8)	6,972 (16·4)	0·09
4	152,907 (21·2)	7,938 (18·7)	0·06
5 (Highest)	120,614 (16·7)	7,787 (18·3)	0·04
Missing	0	2,307	-
Marginalization indices, quintile [d]			
Missing	0	8,264 (19·4)	-
Residential instability			
1 (least marginalized)	156,176 (21·6)	7,901 (18·6)	0·08
2	134,891 (18·7)	4,728 (11·1)	0·21
3	130,516 (18·1)	4,577 (10·8)	0·21
4	136,479 (18·9)	5,417 (12·7)	0·17
5 (most marginalized)	1564,342 (22·7)	11,643 (27·4)	0·09
Material deprivation			
1 (least marginalized)	135,111 (18·8)	8,065 (19·0)	0·01
2	140,150 (19·4)	6,079 (14·3)	0·14
3	138,268 (19·1)	6,203 (14·6)	0·10
4	139,943 (19·4)	6,807 (16·0)	0·09

5 (most marginalized)	168,532 (23·3)	7,112 (16·7)	0·17
Dependency			
1 (least marginalized)	240,986 (33·4)	14,763 (34·7)	0·03
2	151,755 (21·0)	7,549 (17·7)	0·08
3	124,190 (17·2)	5,144 (12·1)	0·14
4	109,875 (15·2)	3,791 (8·9)	0·19
5 (most marginalized)	95,598 (13·2)	3,019 (7·1)	0·19
Ethnic concentration			
1 (least marginalized)	99,236 (13·7)	3,205 (7·5)	0·12
2	112,045 (15·5)	2,064 (4·9)	0·31
3	124,076 (17·2)	4,778 (11·2)	0·09
4	150,043 (20·8)	9,328 (21·9)	0·03
5 (most marginalized)	237,004 (32·8)	14,891 (35·0)	0·04

[a] Shaded cells highlight standardized differences greater than 0.10, indicating a meaningful difference between individuals with and without complete covariate data.
[b] A fiscal year begins on Apr. 1 and ends on Mar. 31.
[c] Due to a contractual agreement with the data provider, small cell sizes (n=<6) cannot be reported and have been suppressed.
[d] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. See Supplementary Table S4 for complete descriptions of what is captured in each of these 4 dimensions.

Table S10. Incidence of exposure and outcome among those with and without complete covariate data

Characteristic	Complete covariate data (n=722,404)		Incomplete covariate data (n=42,530)	
	No. of events	Incidence rate (95% CI) per 1,000 person years	No. of events	Incidence rate (95% CI) per 1,000 person years
Exposure				
Infant with GBS disease	715	0·20 (0·19, 0·22)	56	0·26 (0·20, 0·34)
Outcomes				
Any domain NDI[a]	80,587	23·43 (23·27, 25·59)	5,393	26·8 (25·46, 27·6)
Mild	27,083	7·87 (7·78, 8·79)	1,805	8·98 (8·57, 9·41)
Moderate-to-severe	24,292	7·06 (6·97, 7·15)	1,482	7·38 (7·01, 7·76)
Multi-domain NDI[b]	11,212	3·26 (3·20, 3·32)	792	3·94 (3·67, 4·22)
Domain specific NDI				
Cognitive	49,820	14·48 (14·36, 16·61)	3,492	17·38 (16·41, 18·97)
Motor	701	0·20 (0·19, 0·22)	56	0·27 (0·21, 0·35)
Social/behavioural	30,392	8·83 (8·74, 9·89)	2,042	10·16 (9·73, 10·61)
Sensory (Hearing, Vision)	11,432	3·32 (3·26, 3·39)	639	3·18 (2·94, 3·44)

Abbreviations: CI= confidence interval; GBS=Group B Streptococcus; HR=hazard ratio; NDI=neurodevelopmental impairment.

[a] Any domain NDI: Child has an impairment in any NDI domain and severity group (including uncategorized conditions). Mild: 1-2 domains mildly affected, 0 domains moderately/severely affected; Moderate-to-severe: $\geq$3 domains mildly affected OR $\geq$1 domain moderately/severely affected.

[b] Multi-domain NDI: child has more than one affected NDI domain (any severity group, including uncategorized).

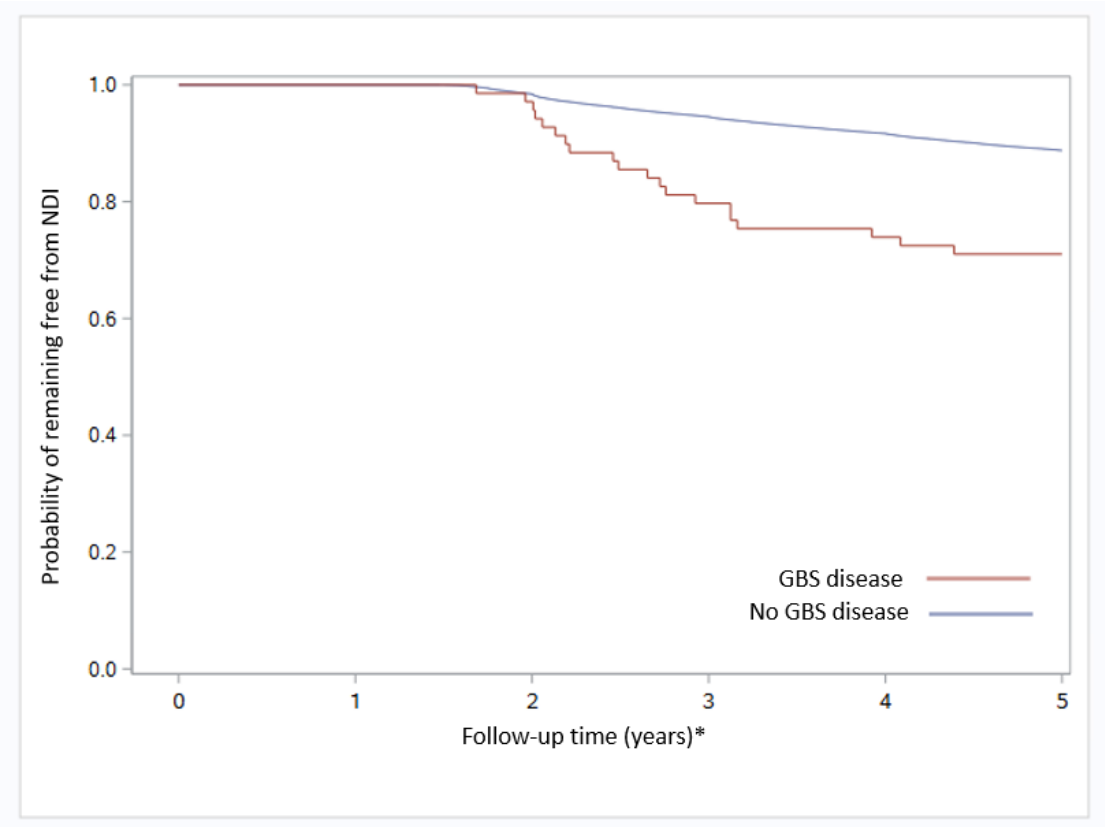


Figure S1. Kaplan-Meier Curve for primary NDI outcome by GBS disease during infancy
*Follow-up for NDI outcomes began at 18 months of age.

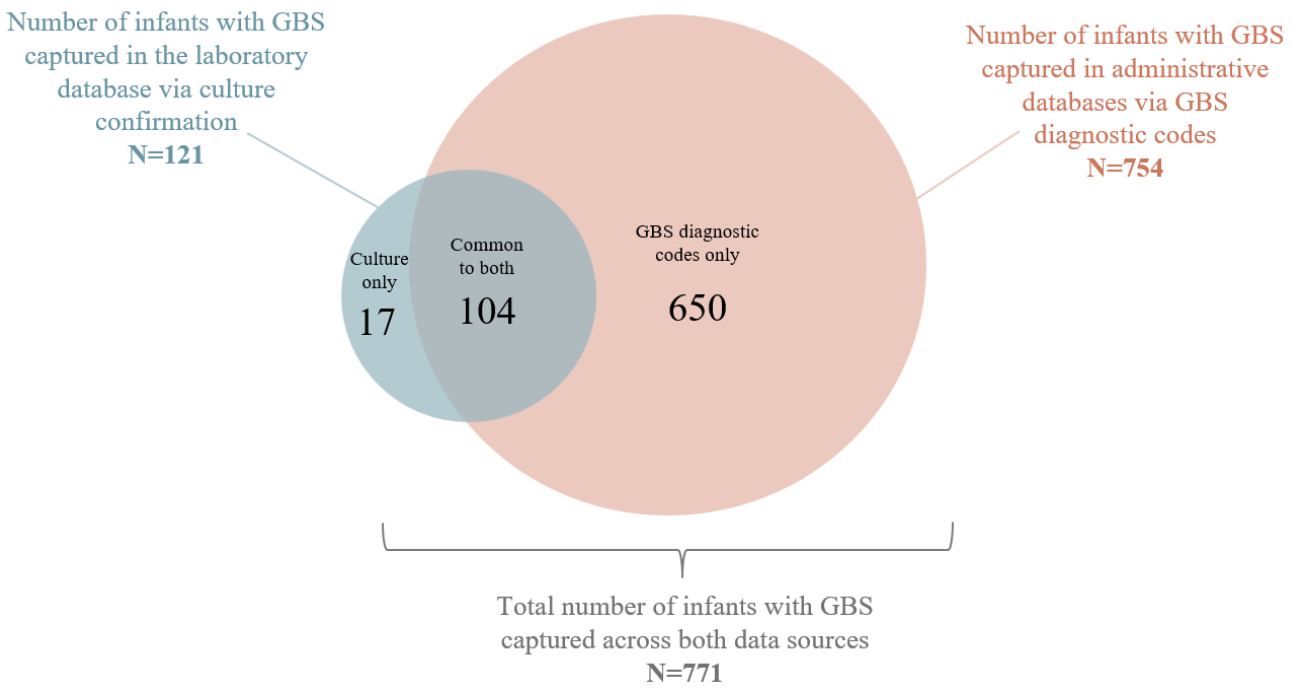


Figure S2. Overlap of Group B Streptococcus (GBS) cases identified in laboratory (OLIS) and health administrative (DAD, NACRS) databases**.**

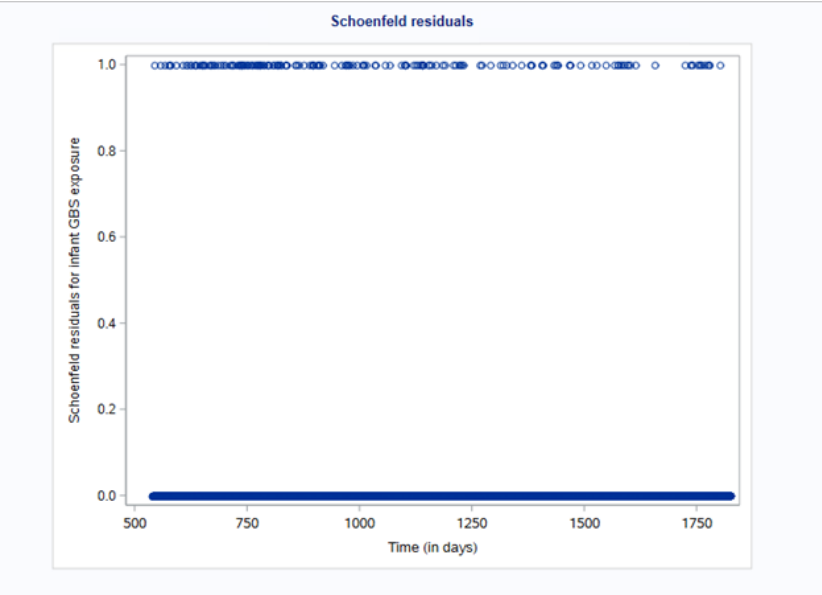
DAD= Discharge Abstract Database; NACRS=National Ambulatory Care Reporting System; OLIS=Ontario Laboratory Information System.
Note: The low number of confirmed GBS cases in our dataset is mainly attributable to incomplete OLIS data from the earlier years of our cohort. This incompleteness resulted from variability in data contributions from participating hospitals and other health information custodians to Ontario Health's repositories. Not all health facilities consistently submitted data, leading to gaps in the available information (https://ehealthontario.on.ca/files/public/support/DataContributorsOLIS.pdf).

Appendix S1. Assessment of the proportional hazards assumption

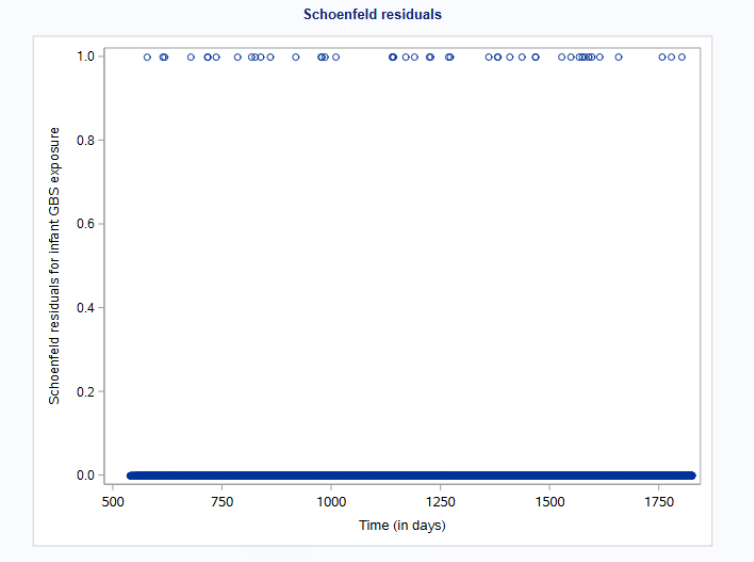
We assessed the proportional hazards (PH) assumption using Schoenfeld residual plots and Wald test for interactions between GBS exposure and time. We also assessed the PH assumption for all covariates included in the adjusted models. None showed evidence of violation, and therefore individual plots for covariates are not presented.

Outcome	**Schoenfeld residual plot**	**GBS exposure*time interaction p-value**
Any domain neurodevelopmental impairment	No violation of PH assumption (see plot A)	0.5734
Mild neurodevelopmental impairment	No violation of PH assumption (see plot B)	0.4652
Moderate-severe neurodevelopmental impairment	No violation of PH assumption (see plot C)	0.4872
Multi-domain neurodevelopmental impairment	No violation of PH assumption (see plot D)	0.3964

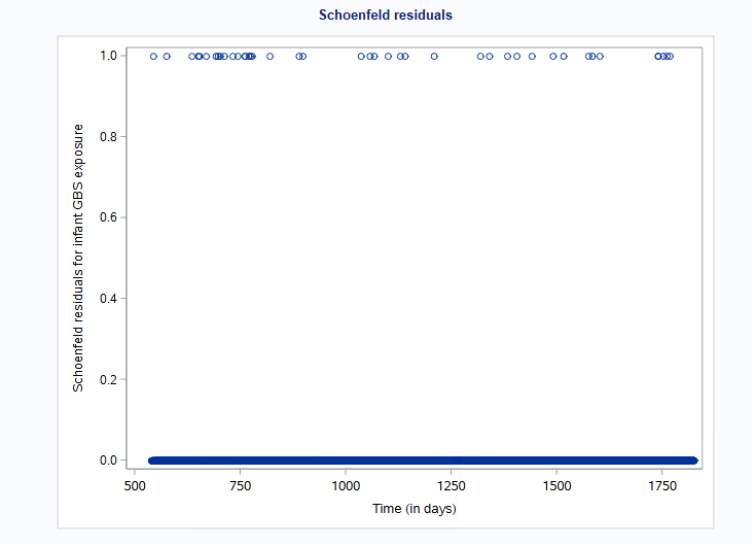
A.



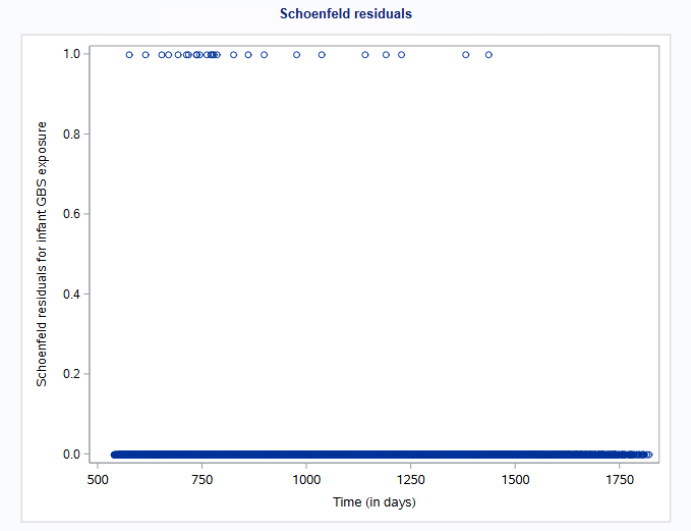
B.


Schoenfeld residuals
Schoenfeld residuals for infant GBS exposure
1.0
0.8
0.6
0.4
0.2
0.0
500
750
1000
1250
1500
1750
Time (in days)

C.


Schoenfeld residuals
Schoenfeld residuals for infant GBS exposure
1.0
0.8
0.6
0.4
0.2
0.0
500
750
1000
1250
1500
1750
Time (in days)

D.



Appendix S2. Effect modification methods overview

Effect modification overview	Effect modification occurs when the association between an exposure and a health outcome varies depending on the levels of a third variable, known as the effect modifier. This variation across levels of the effect modifier helps identify subgroups where a risk factor is particularly significant and clarifies a multifactorial causal relationship. Effect modification can be assessed on both additive and multiplicative scales, and it is recommended to analyze it on both scales.[14,15] In this study we aimed to examine whether the effect of GBS on NDIs differs for i) male and female children; and ii) children born at term or preterm. We performed the following analyses: 1) Stratified analyses by sex and prematurity, where the risk of NDIs after GBS was analyzed separately for male/female and preterm/term children.

	2) Single reference category analyses, using non-GBS female children (for sex analysis) and non-GBS term children (for prematurity analysis) as the reference categories. 3) Calculated measures of effect modification on additive scale (RERI) and multiplicative scale (interaction term of sex*GBS and preterm*GBS in Cox regression models).
Infant sex analysis	In the stratified analyses by sex, NDI rates among children with a history of GBS were compared to non-GBS children. In the single reference category analyses, we estimated hazard ratios (HRs) based on the common reference group of non-GBS females (GBS-/Female). All hazard ratios were adjusted for maternal age, infant birth month and year, parity, smoking during pregnancy, rural, multifetal pregnancy, marginalization indices, income quintile. **Additive scale:** Effect modification on the additive scale was examined by calculating the relative excess risk due to interaction (RERI), using the common reference group of non-GBS girls (GBS-/Female) and the HRs estimated in the single reference category analyses: $RERI = HR_{GBS+/Male} - HR_{GBS+/Female} - HR_{GBS-/Male} + 1$. Additionally, we calculated the attributable proportion due to interaction as $RERI/(HR_{GBS+/Male}) \times 100\%$. **Multiplicative scale:** On the multiplicative scale, modification occurs if the hazard ratios (HRs) between GBS and NDI differ by sex. Therefore, we included the interaction term (sex*GBS) in the Cox regression models.
Prematurity analysis	In the stratified analyses by prematurity, NDI rates among children with a history of GBS were compared to non-GBS children. In the

	single reference category analyses, we estimated HRs based on the common reference group of non-GBS term infants (GBS-/Term). All hazard ratios were adjusted for infant sex, maternal age, infant birth month and year, parity, smoking during pregnancy, rural, multifetal pregnancy, marginalization indices, income quintile. **Additive scale:** Effect modification on the additive scale was examined by calculating the relative excess risk due to interaction (RERI), using the common reference group non-GBS term infants (GBS-/Term) and the HRs estimated in the single reference category analyses: RERI = $HR_{GBS+/Preterm} - HR_{GBS+/Term} - HR_{GBS-/Preterm} + 1$. Additionally, we calculated the attributable proportion due to interaction as RERI / ($HR_{GBS+/Preterm}$) x 100%x 100%. **Multiplicative scale:** On the multiplicative scale, modification occurs if the hazard ratios (HRs) between GBS and NDI differ by prematurity. Therefore, we included the interaction term (preterm*GBS) in the Cox regression models.

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CHAPTER 6. MANUSCRIPT 3

Healthcare costs attributable to Group B *Streptococcus* disease during infancy: a population-based matched cohort study in Ontario, Canada

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The article presented in this chapter is being prepared for submission to *Clinical Infectious Diseases*.

6.1 Preface to chapter 6

This chapter presents the third and final manuscript of this thesis which estimates the healthcare costs attributable to GBS disease in infancy. Tables and figures supporting the manuscript appear after the references in Section 6.8, beginning on page 212. Author contributions are outlined on page 208 and the study appendix starts on page 225.

6.2 Abstract

Background: Group B *Streptococcus* (GBS) is a leading cause of infant morbidity and mortality, yet its economic burden remains largely unmeasured. We aimed to estimate the publicly funded healthcare costs attributable to GBS disease in infancy using real-world population-based data from Ontario, Canada.

Methods: We conducted a population-based matched cohort study using Ontario's provincial birth registry linked to health administrative data from April 2012 to March 2018. GBS disease was identified using laboratory-confirmation and diagnostic codes. Infants with GBS were matched to up to three infants without GBS using a combination of hard and propensity score matching. Early-onset disease (EOD) and late-/ultra-late-onset disease (LOD/ULOD) groups were matched and analyzed separately. Infants were assigned to phases of care based on clinical trajectory. Phase-specific mean 10-day costs, as well as cumulative 30-, 180-, and 365-day mean costs, were estimated using a weighted generalized estimating equation model that accounted for matched pairs. Attributable costs were defined as the difference in mean costs between infants with and without GBS disease.

Results: A total of 634 infants with GBS (EOD: n=299; LOD/ULOD: n=344) were matched to 1,781 infants without GBS. In the first 30 days following diagnosis, cumulative mean attributable costs were $9,403 (95% CI: $7,008 to $11,798) for EOD and $19,282 (95% CI: $17,185 to $21,379) for LOD/ULOD, with the highest costs incurred in the initial 10-day period ($4,534 for EOD and $12,124 for LOD/ULOD). Mean 10-day costs during the acute care phase were also elevated for both GBS groups—$9,952 for infants with EOD and $7,254 for infants

with LOD/ULOD—driven primarily by inpatient hospitalizations and physician services. Among infants with LOD/ULOD, elevated mean 10-day attributable costs persisted into the post-acute ($202; 95% CI: $64 to $340) and ongoing care phases ($179; 95% CI: $81 to $276).

Conclusions: Our findings highlight the substantial healthcare costs associated with infant GBS disease, particularly in the early acute period, and reinforce the value of ongoing screening and intrapartum antibiotic prophylaxis programs, as well as the potential of maternal vaccination as a preventive strategy.

Key Words: Group B *Streptococcus*; *Streptococcus agalactiae;* Health Care Costs; Healthcare Utilization; Phase-of-care costing

Funding: Canadian Institutes of Health Research

6.3 Introduction

Group B *Streptococcus* (GBS; *Streptococcus agalactiae*) is a leading cause of invasive bacterial infections in neonates and young infants, often resulting in significant morbidity and mortality due to conditions such as sepsis and meningitis.[1,2] In 2020, global estimates indicated that approximately 20 million pregnant individuals were colonized with GBS, resulting in nearly 400,000 pediatric cases of GBS disease and around 90,000 infant deaths.[1] Additionally, approximately 40,000 surviving infants each year develop moderate-to-severe neurodevelopmental impairments due to GBS infection.[3]

Despite the well-documented health consequences of GBS, its economic burden remains under characterized. A study in the United Kingdom (UK) examining children diagnosed with GBS disease within the first 90 days of life found that healthcare and social care costs over the subsequent two years following diagnosis were twice as high as those for children without GBS disease.[4] Similarly, in Denmark, children with previous GBS infection experienced significantly higher rates of outpatient visits (incidence rate ratio [IRR] 1.83, 95% confidence interval [CI] 1.67 to 2.00) and hospital admissions (IRR 1.43, 95% CI 1.37 to 1.50) by age 10 years, with the highest healthcare utilization observed during the first year of life.[5] In low- and middle-income countries, children with GBS disease had greater odds of healthcare utilization, including more frequent healthcare visits, longer inpatient stays, and higher out-of-pocket payments compared to children without GBS disease.[6]

Given the substantial healthcare burden associated with GBS disease documented in various settings, detailed estimates of its attributable costs are essential to guide resource allocation and

thoroughly evaluate the economic benefits of implementing new preventive strategies, such as maternal GBS vaccines, which are currently in late-stage clinical development.[7,8]

While our previous work described the epidemiology of infant GBS disease in Ontario,[9] its economic implications remain unquantified in the Canadian context. This study aims to address this gap by leveraging comprehensive and population-based real-world data to estimate the healthcare costs attributable to infant GBS disease in the first year following diagnosis in Ontario, Canada.

6.4 Methods

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for reporting of observational studies.[10]

6.4.1 Study design, data sources and participants

We conducted a population-based matched cohort study of infants with GBS disease during the first year of life to examine attributable costs from the provincial healthcare payer perspective in Ontario, Canada (Ontario Ministry of Health). Follow-up continued for one year after the infant's GBS diagnosis to capture healthcare costs over this period. We included infants born between April 1, 2012, to March 31, 2018 using the Better Outcomes Registry & Network (BORN) Ontario birth registry, which captures all hospital and home births ($\geq$500g or $\geq$20 weeks' gestation) in the province, representing ≈40% of births in Canada.[11]

Data on healthcare resource utilization and costs covered by the Ontario Ministry of Health were obtained through ICES, a research institute with the legal authority to collect healthcare and

demographic data without consent for the purposes of health system evaluation and improvement. Our birth cohort was linked to various health administrative databases at ICES, including the Registered Persons Database (healthcare eligibility); Ontario Health Insurance Plan database (physician billings); Discharge Abstract Database (DAD; hospital admissions); National Ambulatory Care Reporting System (NACRS; ambulatory care including emergency department visits); Same Day Surgery (same-day surgery); Ontario Drug Benefits claims (universal drug insurance for those on social assistance and >65 years of age); National Rehabilitation Reporting System (rehabilitation); Home Care Database (home care); Continuing Care Reporting System (long-term or continuing care); the Ontario Mental Health Reporting System (designated mental health inpatient services); the Ontario Laboratories Information System database (OLIS; laboratory culture results); the Postal Code Conversion File (geographic information); and the Ontario Marginalization Index (area-level marginalization and socioeconomic status). Please refer to Supplementary Table S1 for details on each data source. Databases were linked using unique encoded identifiers and analyzed at ICES (https://www.ices.on.ca).

We excluded infants with invalid identifiers or birthdates, as well as those without continuous Ontario healthcare eligibility or who died during the study follow-up. Additionally, we excluded infants with mothers who lacked continuous Ontario healthcare eligibility during pregnancy, were non-Ontario residents, were under 12 or over 50 years old at delivery or had invalid identifiers.

6.4.2 Exposure

The primary exposure—GBS disease in the first year of life—was identified using a combination of culture results from a normally sterile site (blood or cerebrospinal fluid [CSF]) in the provincial laboratory database (OLIS) and GBS-specific diagnostic codes (*International Statistical Classification of Diseases and Related Health Problems*, *10th Revision* [ICD-10-CA]) in health administrative databases (DAD, NACRS). Infants were classified as having GBS disease if either a culture confirmation or an ICD-10-CA code for GBS was identified (Supplementary Table S2). This approach, as previously described,[9] was adopted due to inconsistencies in data contributions to OLIS by Ontario hospitals over time, leading to incomplete specimen information in the early years of our study.[12]

For culture-confirmed GBS, the index date was assigned based on the specimen collection date of the first positive culture. For non-culture-confirmed GBS cases, identified through GBS-specific diagnostic codes, we assigned the first instance of emergency department visit or hospitalization for GBS as the index date. Infants were categorized as having early-onset disease (EOD, 0-6 days), late-onset disease (LOD, 7-89 days) or ultra-late-onset disease (ULOD, 90-365 days) based on their index date. The index dates for the infants without GBS disease were randomly assigned based on the distribution of index dates among infants with GBS disease.

6.4.3 Outcomes

The primary outcome was the mean total publicly funded healthcare costs attributable to infant GBS disease within 1 year of the index date. We used a person-level costing algorithm developed and validated at ICES to estimate healthcare costs accrued for each infant. In-depth

details regarding this methodology have been previously described.[13] Briefly, this method utilizes administrative data to determine the total healthcare costs per patient by summing the individual cost components involved in providing the service. Healthcare service categories included inpatient hospitalizations, emergency department visits, physician services, and other costs such as same-day surgeries, ambulatory care, inpatient rehabilitation, complex continuing care, long-term care, inpatient mental health services, home care, eligible prescription medications, and medical devices (see Supplementary Table S3 for details). Costs are presented in 2023 Canadian dollars and adjusted for inflation using the healthcare-specific Consumer Price Index (CPI) reported by Statistics Canada.[14]

6.4.4 Statistical analyses

To address confounding, each infant with GBS disease was matched to three infants without GBS disease using a combination of hard and propensity score matching. Hard matching was based on index date (± 30 days), infant age at index (in days, ± 7 days), gestational age at birth, and average daily healthcare costs prior to index date (± $200). Propensity scores were generated using a logistic regression model estimating the probability of GBS disease, conditional on the following covariates: infant sex, maternal age, fiscal year of birth, income, rural residence, area-level marginalization indices, gestational age at birth, birthweight, multifetal pregnancy, parity, mode of delivery, presence of one or more pre-existing maternal medical conditions, neonatal intensive care unit (NICU) admission at birth, and presence of one or more newborn congenital anomalies (variable definitions in Supplementary Table S4). To improve balance, key cost-driving variables, such as pre-index costs and gestational age at birth were included in both hard and propensity score matching.

Nearest neighbor greedy matching was used with a caliper width of 0.2 standard deviations of the logit of the propensity score. Balance in the matched sets was assessed by examining standardized differences across matching variables, with values below 0.10 indicating good balance.[15] Propensity score matching was conducted separately for the EOD and LOD/ULOD groups, with LOD and ULOD combined due to small counts. As a sensitivity analysis, LOD was also modeled separately to assess the impact of this grouping.

Using the phase-of-care approach, we estimated phase-specific attributable costs for each exposure group. This method assigns the observation time of each patient into distinct phases consistent with the disease or treatment trajectory.[16,17] Infants could enter the analysis at any phase and contribute data to more than one phase. We defined the four phases—pre-index phase (10 days prior to GBS diagnosis [day 0]), acute care phase (days 0 to 30), post-acute care phase (days 31 to 180) and ongoing care phase (days 181 to 365)—using joinpoint analysis, combined with clinical expertise (Figure 1). Clinical judgment informed the interpretation of joinpoint analysis by considering the typical healthcare trajectory for infants with GBS, including timing of diagnosis, hospitalization patterns, follow-up care, and recovery. The pre-index phase captured healthcare use leading up to diagnosis, the acute care phase included initial treatment and hospitalization, the post-acute care phase reflected follow-up care and recovery, and the ongoing care phase captured additional follow-up and support needs within the first year. Given that nearly 90% of EOD infants in our cohort were diagnosed within 24 hours of delivery, we did not include a pre-index costing phase for this group. Additionally, due to the low number of infant deaths in our cohort, particularly among infants with GBS (n=15), and the one-year

follow-up of the study, we did not include a terminal phase of care. As a result, infants who died during follow-up were excluded from the analysis.

We estimated mean 10-day healthcare costs for each phase of care, as well as cumulative 30-, 180- and 365-day mean costs, using a weighted generalized estimating equation model that accounted for clustering within the matched sets. Attributable costs were defined as the difference between costs among GBS-infected infants and those among uninfected infants. Mean and attributable healthcare costs were reported with 95% confidence intervals (CIs).
All analyses used SAS Enterprise Guide 8.3 (SAS Institute). In compliance with ICES privacy policies, cell counts fewer than six could not be disclosed. In some instances, additional data suppression or category collapsing was necessary to prevent the derivation of suppressed values from other reported figures.

6.4.5 Ethics approval

This study was approved by the Children's Hospital of Eastern Ontario Research Ethics Board (Protocol No 20/11PE) and the ICES Privacy Office (Protocol 2023-0901-320-001). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse health care and demographic data, without consent, for health system evaluation and improvement.

6.5 Results

6.5.1 Study population

There were 855,849 live births in Ontario between April 1, 2012, and March 31, 2018 (Figure 2); after applying administrative exclusions (n=87,777), the linked dataset included 768,072 infants. Further exclusions were applied to remove infants who died within one year of birth (n=1,446) and those with missing data on key matching variables (n=21,864), yielding a study population of 744,762 infants prior to matching.

Among the study cohort, 752 infants were identified with GBS disease, categorized as EOD (n=347) and LOD/ULOD (n=405). Prior to matching, infants with GBS (EOD or LOD/ULOD) were more likely to be preterm (<37 weeks' gestation), part of a multifetal pregnancy, admitted to NICU at birth, and have one or more congenital anomalies compared to infants without GBS (Tables 1 and 2).

Matching was performed separately for EOD and LOD/ULOD groups, with each infant with GBS disease matched to up to three uninfected infants using hard and propensity score matching. A total of 109 infants with GBS (EOD: n=48, LOD/ULOD: n=61) could not be matched and were excluded. Compared to matched GBS infants, unmatched GBS infants were more likely to be born preterm, part of a multifetal pregnancy, delivered via cesarean section, have a lower birthweight, have a congenital anomaly, and require NICU admission (Supplement Table S5). These patterns were consistently observed when comparing matched and unmatched infants within both the EOD and LOD/ULOD subgroups (data not shown due to small cell counts). The

final matched cohort consisted of 634 infants with GBS disease (EOD: n=299; LOD/ULOD: n=344) and 1,781 infants without GBS disease (Figure 2).

In the matched cohort, baseline characteristics were comparable between infants with EOD and their matched counterparts (Table 1). Similarly, characteristics for infants with LOD/ULOD and their matched counterparts were generally well-balanced, with only a modest difference observed for parity and least marginalized areas based on ethnic concentration (Table 2; standardized difference = 0.11).

6.5.2 Healthcare costs by phases of care

In the acute care phase (0–30 days post-diagnosis), infants with EOD incurred higher mean 10-day healthcare costs compared to their matched counterparts, with mean 10-day attributable cost of $2,958 (95% CI: $2,119 to $3,798). This difference was primarily driven by higher hospitalization costs ($2,481) and physician services ($452) (Table 3). In the post-acute care phase (days 31–180), the mean 10-day total costs for infants with EOD were higher than their matched unexposed counterparts ($1,301 vs. $1,269) and mainly driven by inpatient hospitalizations. In the ongoing care phase (days 181–365), mean 10-day total costs were similar for infants with EOD and their matched counterparts (mean 10-day attributable cost: $3; 95% CI: –$209 to $216).

The mean 10-day total cost in the pre-index period for infants who later developed LOD/ULOD was $1,968, compared to $2,394 for their matched uninfected counterparts, with hospitalizations accounting for the largest proportion of costs (Table 3). During the acute care phase, infants with

LOD/ULOD had higher mean 10-day total costs ($7,254) compared to their matched unexposed infants ($6,315), with an attributable mean cost of $939 (95% CI: $407 to $1,471). This was largely due to inpatient hospitalizations and physician services. Attributable costs in the post-acute and ongoing care periods were notably lower than in the acute phase but remained higher among infants with LOD/ULOD compared to their matched counterparts (Table 3). Findings remained consistent in a sensitivity analysis restricted to infants with LOD (n=304), with slightly higher attributable costs observed (Supplement Table S6).

6.5.3 Cumulative healthcare costs

Cumulative healthcare costs were highest in the first 30 days following diagnosis. Among infants with EOD, the mean 30-day cumulative cost was $29,838 (95% CI: $26,874 to $32,802), compared to $20,434 (95% CI: $17,375 to $23,494) for matched uninfected infants, resulting in an attributable cost of $9,403 (95% CI: $7,008 to $11,798). For infants with LOD/ULOD, the mean 30-day cumulative cost was $21,706 (95% CI: $19,474 to $23,937), compared to $2,423 (95% CI: $1,145 to $3,700) for uninfected infants, resulting in an attributable cost of $19,282 (95% CI: $17,185 to $21,379). Within this 30-day period, attributable costs were highest in the first 10 days post-diagnosis: $4,534 for EOD and $12,124 for LOD/ULOD (Figure 3 and Table 4).

Cumulative mean attributable 180- and 365-day costs for EOD, compared to their uninfected counterparts, were $10,724 (95% CI: $2,673 to $18,775) and $11,547 (95% CI: $1,392 to $21,703), respectively. Among infants with LOD/ULOD, cumulative attributable costs were $22,706 (95% CI $19,306 to $26,107) over 180 days and $23,519 (95% CI $19,901 to $27,136)

over 365 days following the index date. When restricting the analysis to infants with LOD only, results were consistent with the main findings, with slightly higher attributable mean costs observed (Supplement Table S7).

6.6 Discussion

In this Canadian population-based cohort study, we provide a comprehensive analysis of healthcare costs attributable to GBS disease during infancy, across distinct phases of care in the first year following diagnosis. We found that among infants with either EOD or LOD/ULOD, GBS infection was associated with substantial short-term healthcare costs, particularly during the 30-day acute care phase, with the highest costs incurred in the first 10 days following diagnosis. Cost differences were primarily driven by increased expenses related to inpatient hospitalizations and physician services. Among infants with EOD, we found that costs declined markedly after the acute phase, with small cost differences observed in the post-acute and ongoing care phases. In contrast, infants with LOD/ULOD exhibited elevated attributable healthcare costs not only during the acute care phase but also persisting into the post-acute and ongoing care phases.
Few studies have directly estimated the healthcare costs attributable to GBS disease in infancy, as most existing economic literature has focused on modeling cost-effectiveness of prevention and treatment strategies.[18–24] However, based on the limited evidence available, our findings are largely consistent with prior research.

A UK study similarly reported that initial hospitalizations made up the largest portion of healthcare costs among infants with GBS (<90 days), with mean health and social care costs nearly doubling in the first two years of life (£11,969) compared to unexposed infants (£6,261).[4]

However, this study combined infants with early- and late-onset GBS into a single group, potentially masking important differences in disease timing, severity and care needs that become more evident when these subgroups are examined separately. While direct cost comparisons are difficult due to differences in healthcare systems, the relative magnitude of cost differences between infants with and without GBS disease in the two studies are comparable.

A matched cohort study of Dutch and Danish children found that those with a history of GBS disease had significantly higher rates of outpatient visits and hospital admissions up to 10 years of age.[5] Although our study was limited to one year of follow-up, we similarly observed ongoing care costs that remained higher among infants with GBS disease, compared to non-GBS infants, particularly in the LOD/ULOD group.

The larger attributable healthcare costs observed among the LOD/ULOD group, compared to the EOD group, may be driven by both clinical factors and differences in baseline health status between matched groups. LOD/ULOD typically presents after hospital discharge, which can delay diagnosis and lead to more severe illness and complications.[25] Prior studies have shown that LOD is more frequently associated with meningitis—an outcome requiring prolonged specialist care, neuroimaging, and rehabilitative services[26–28]—and infants with GBS meningitis have been found to experience longer treatment durations and higher rates of neurological complications compared to those with GBS sepsis.[25] In contrast, EOD generally presents within the first 48 hours of life while infants are still hospitalized, allowing for earlier diagnosis and management. Despite higher absolute 1-year healthcare costs among infants with EOD, compared to infants with LOD/ULOD, the smaller attributable cost difference in this group may

be due to the elevated baseline healthcare needs of their matched counterparts. Since EOD often co-occurs with early-life complications such as prematurity and low birthweight,[29] infants matched to EOD cases were likely sicker than average, resulting in higher healthcare use even in the absence of GBS. This likely attenuated the observed differences in healthcare costs. In comparison, infants in the LOD/ULOD group typically appeared healthy prior to infection, which may explain the larger relative increase in healthcare costs following GBS diagnosis.

A recent systematic review highlighted the substantial economic burden of neonatal and infant sepsis and meningitis, with treatment costs ranging from $55 to $129,632 for sepsis and $222 to $33,635 for meningitis.[30] The wide cost variability reported, reflects differences in healthcare settings, patient age, and disease severity.[30] However, the review did not report costs specific to GBS disease, highlighting the need for pathogen-specific evaluations to guide resource allocation and inform cost-effectiveness analyses of prevention strategies.

Our study has several strengths. The population-based approach enhances the generalizability of our findings, as the results reflect a diverse population across demographic and geographic subgroups in a large population. The use of individually linked administrative datasets allowed for the assembly of a substantial cohort of infants with GBS disease and enabled the inclusion of a wide range of publicly funded healthcare services, ensuring a comprehensive analysis of direct healthcare costs. Additionally, the matched cohort design accounted for baseline healthcare utilization, reducing potential confounding and strengthening the validity of our cost estimates. Finally, the phase-of-care approach allowed for a comparison of costs across distinct periods

within the first year after diagnosis, while joinpoint regression provided a data-driven method for defining phase durations.

Our study also has several limitations. The analysis focused solely on direct medical costs from the perspective of the Ontario healthcare system, which does not capture broader societal costs such as caregiver time off work or lost productivity. Furthermore, we were unable to match all infants with GBS disease, which may introduce selection bias and limit comparability between groups. Unmatched GBS infants tended to have indicators of higher baseline risk and greater healthcare needs, and their exclusion may have led to an underestimation of the overall cost burden of GBS. The exclusion of infant deaths during the follow-up period may also underestimate the true economic and societal impact by omitting end-of-life care costs. Additionally, we observed lower pre-index healthcare costs among infants who later developed LOD/ULOD compared to their matched unexposed counterparts. This may reflect residual confounding (i.e., differences in healthcare-seeking behavior) or under-recognition of early symptoms.

This study provides important insight into the healthcare burden of infant GBS disease, offering a clearer understanding of when and where healthcare resources are most heavily utilized. Characterizing this burden is critical not only for informing health system planning and resource allocation, but also because healthcare costs and utilization patterns can serve as indirect indicators of disease severity and care complexity. Our findings offer valuable inputs for cost-effectiveness models evaluating GBS prevention strategies, such as maternal vaccination. Given that the highest costs occur shortly after diagnosis and are largely driven by inpatient

hospitalizations, reducing the incidence of infant GBS disease could lead to significant healthcare savings for the Canadian healthcare system. Future work should incorporate indirect costs, such as family caregiving and long-term impacts, to more fully capture the societal burden of GBS.

Author contributions: RF, DBF, NT, DE, BS and KB conceived the study protocol, study design and analytical approach. **RF** and WP performed the statistical analyses, which were supervised by DBF and DE. **RF**, BS and DBF drafted the manuscript. All authors contributed to data interpretation, revised the manuscript for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work.

Data sharing statement: The dataset from this current study is held securely in coded form at ICES. Even though data-sharing agreements prohibit ICES from making the data set publicly available, access can be granted to those meeting pre-specified criteria for confidential access, available at www.ices.on.ca/ DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors on request, with the understanding that the computer programs may rely on coding templates or macros that are unique to ICES and, therefore, are inaccessible or may need modification.

Potential conflicts of interest: When this project was funded and initiated, DBF was employed by the University of Ottawa and had an academic appointment at the Children's Hospital of Eastern Ontario Research Institute; she is now employed by Pfizer and works on an unrelated topic. DEC has been an investigator on projects funded by Moderna and Pfizer. All funds have been paid to her institute, and she has not received any personal payments.

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6.8 Manuscript tables and figures

Table 1. Baseline characteristics of the study population before and after hard and propensity score matching of infants with and without early-onset disease (EOD)

Characteristic	Study population prior to matching (n=744,357) [a]			Matched cohort (n=1,119)		
	Infants with EOD n=347	Infants without EOD n=744,010	SD	Infants with EOD n=299	Infants without EOD n=820	SD [b]
	n(%)	n(%)		% [c]	% [c]	
Sex						
Female	160 (46.1)	362,395 (48.7)	0.05	47.2	43.3	0.08
Male	187 (53.9)	381,615 (51.3)	0.05	52.8	56.7	0.08
Gestational age at birth, weeks						
<28	54 (15.6)	1,883 (0.3)	0.59	2 – 12	2 – 12	0.00
28 - <37	77 (22.2)	54,440 (7.3)	0.43	18 – 28	18 – 28	0.00
>= 37	216 (62.2)	687,687 (92.4)	0.77	65 – 75	65 – 75	0.00
NICU admission during birth hospitalization						
Yes	205 (59.1)	88,094 (11.8)	1.14	58.9	59.3	0.01
No	142 (40.9)	655,916 (88.2)	1.14	41.1	40.7	0.01
Birthweight (grams) [d]						
<1500	67 (19.3)	5,826 (0.8)	0.65	5 – 15	5 – 15	0.01
1500 - <2500	53 (15.3)	40,401 (5.4)	0.33	12 – 22	12 – 22	0.09
>=2500	227 (65.4)	697,783 (93.8)	0.75	73.2	69.3	0.09
Presence of one or more newborn congenital anomalies [e]						
Yes	34 (9.8)	8,927 (1.2)	0.38	2 – 12	2 – 12	0.07
No	313 (90.2)	735,083 (98.8)	0.38	88 – 98	88 – 98	0.07
Maternal age, years [d]						
<25	53 (15.3)	92,472 (12.4)	0.08	15.1	14.4	0.01
25 - <30	90 (25.9)	199,316 (26.8)	0.02	25.4	28.1	0.06
30 - <35	118 (34.0)	276,064 (37.1)	0.06	33.8	32.8	0.02

>=35	86 (24.8)	176,158 (23.7)	0.03	25.8	24.7	0.02
Fiscal year of birth [f]						
2012-13	79 (22.8)	124,714 (16.8)	0.15	22.7	23.0	0.01
2013-14	81 (23.3)	124,938 (16.8)	0.16	22.4	22.5	0.00
2014-15	43 (12.4)	123,817 (16.6)	0.12	7 – 17	7 – 17	0.01
2015-16	57 (16.4)	124,061 (16.7)	0.01	12 – 22	12 – 22	0.00
2016-17	41 (11.8)	123,263 (16.6)	0.14	7 – 17	7 – 17	0.01
2017-18	46 (13.3)	123,217 (16.6)	0.09	9 – 19	9 – 19	0.01
Multifetal pregnancy						
Yes	30 (8.6)	24,725 (3.3)	0.23	2 – 12	2 – 12	0.09
No	317 (91.4)	719,285 (96.7)	0.23	88 – 98	88 – 98	0.09
Mode of delivery						
Vaginal	225 (64.8)	533,575 (71.7)	0.15	66.2	64.2	0.04
Cesarean	122 (35.2)	210,435 (28.3)	0.15	33.8	35.8	0.04
Parity						
Nulliparous	177 (51.0)	316,435 (42.5)	0.17	50.5	54.3	0.08
Multiparous	170 (49.0)	427,575 (57.5)	0.17	49.5	45.7	0.08
Rural residence						
Yes	33 (9.5)	71,616 (9.6)	0.00	4 – 14	4 – 14	0.02
No	314 (90.5)	672,394 (90.4)	0.00	86 – 97	86 – 97	0.02
Neighborhood median family income quintiles						
1 (Lowest)	77 (22.2)	157,277 (21.1)	0.03	22.7	21.0	0.04
2	79 (22.8)	149,485 (20.1)	0.07	22.4	20.6	0.04
3	77 (22.2)	154,536 (20.8)	0.03	21.1	24.6	0.09
4	68 (19.6)	157,197 (21.1)	0.04	14 – 24	14 – 24	0.01
5 (Highest)	46 (13.3)	125,515 (16.9)	0.10	9 – 19	9 – 19	0.01
Marginalization indices, quintile [g]						
Residential instability						
1 (least marginalized)	82 (23.6)	160,534 (21.6)	0.05	22.7	21.9	0.02
2	58 (16.7)	137,693 (18.5)	0.05	12 – 22	12 – 22	0.01
3	53 (15.3)	133,419 (17.9)	0.07	11 – 21	11 – 21	0.02
4	64 (18.4)	139,964 (18.8)	0.01	13 – 23	13 – 23	0.04
5 (most marginalized)	90 (25.9)	172,400 (23.2)	0.06	26.1	24.3	0.04
Material deprivation						

1 (least marginalized)	53 (15.3)	141,197 (19.0)	0.10	12-22	12-22	0.01
2	63 (18.2)	144,139 (19.4)	0.03	16.1	17.7	0.04
3	60 (17.3)	142,038 (19.1)	0.05	13 – 23	13 – 23	0.04
4	85 (24.5)	143,785 (19.3)	0.13	23.4	23.5	0.00
5 (most marginalized)	86 (24.8)	172,851 (23.2)	0.04	25.8	22.7	0.07
Dependency						
1 (least marginalized)	121 (34.9)	249,990 (33.6)	0.03	35.1	36.1	0.02
2	74 (21.3)	156,673 (21.1)	0.01	20.4	20.0	0.01
3	51 (14.7)	127,470 (17.1)	0.07	10 – 20	10 – 20	0.01
4	52 (15.0)	112,273 (15.1)	0.00	10 – 20	10 – 20	0.04
5 (most marginalized)	49 (14.1)	97,604 (13.1)	0.03	10 – 20	10 – 20	0.01
Ethnic concentration						
1 (least marginalized)	44 (12.7)	101,900 (13.7)	0.09	8 – 18	8 – 18	0.03
2	59 (17.0)	113,278 (15.2)	0.05	16.7	18.7	0.05
3	46 (13.3)	127,263 (17.1)	0.11	8 – 18	8 – 18	0.03
4	64 (18.4)	156,403 (21.0)	0.06	19.1	22.2	0.08
5 (most marginalized)	134 (38.6)	245,166 (33.0)	0.12	37.8	34.4	0.07
Presence of one or more pre-existing maternal medical conditions [h]						
Yes	48 (13.8)	69,975 (9.4)	0.14	9 – 19	9 – 19	0.06
No	299 (86.2)	674,215 (90.6)	0.14	81 – 91	81 – 91	0.06

Abbreviations: EOD=early-onset disease; IQR=interquartile range; LOD=late-onset disease; NICU=neonatal intensive care unit; SD=standardized difference; ULOD=ultra-late-onset disease.

[a] Infants with LOD/ULOD (n=405) were excluded from the pre-match cohort.

[b] Absolute standardized difference. Shaded cells indicate an imbalance (> 0.10) between exposed and unexposed infants.

[c] Data were weighted using matching weights, which accounted for the number of infants without GBS matched to each infant with GBS. Due to a contractual agreement with the data provider, some percentages are given as a range to prevent the ability of back calculation of small cell sizes (n <6).

[d] Due to small cell sizes (n <6), some categories were collapsed in this table.

[e] Refer to Supplementary Table S4 for description of which newborn congenital anomalies were included.

[f] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[g] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see Supplementary Table S4 for complete descriptions of what is captured in each of these 4 dimensions.

[h] Pre-existing maternal health conditions included: asthma, diabetes, heart disease, chronic hypertension and thyroid disease.

Table 2. Baseline characteristics of the study population before and after hard and propensity score matching of infants with and without late- and ultra-late-onset disease (LOD/ULOD)

Characteristic	Study population prior to matching (n=744,415) [a]			Matched cohort (n=1,305)		SD [b]
	Infants with LOD/ULOD n=405	Infants without LOD/ULOD n=744,010	SD	Infants with LOD/ULOD n=344	Infants without LOD/ULOD n=961	
	n(%)	n(%)		% [c]	% [c]	
Sex						
Female	202 (49.9)	362,395 (48.7)	0.02	49.4	49.5	0.00
Male	203 (50.1)	381,615 (51.3)	0.02	50.6	50.5	0.00
Gestational age at birth, weeks [d]						
<37	67 (16.5)	54,440 (7.3)	0.29	9 – 19	9 – 19	0.01
>= 37	305 (75.3)	687,687 (92.4)	0.48	81 – 91	81 – 91	0.01
NICU admission during birth hospitalization						
Yes	137 (33.8)	88,094 (11.8)	0.54	25.9	25.9	0.00
No	268 (66.2)	655,916 (88.2)	0.54	74.1	74.1	0.00
Birthweight (grams) [d]						
<1500	55 (13.6)	5,826 (0.8)	0.51	1 – 9	1 – 9	0.03
1500 - <2500	47 (11.6)	40,401 (5.4)	0.22	5 – 13	5 – 13	0.02
>=2500	303 (74.8)	697,783 (93.8)	0.54	85.8	85.4	0.01
Presence of one or more newborn congenital anomalies [e]						
Yes	23 (5.7)	8,927 (1.2)	0.25	1 – 8	1 – 8	0.03
No	382 (94.3)	735,083 (98.8)	0.25	92 – 99	92 - 99	0.03
Maternal age, years [d]						
<25	78 (19.3)	92,472 (12.4)	0.19	19.5	17.8	0.03
25 - <30	115 (28.4)	199,316 (26.8)	0.04	28.2	29.6	0.03
30 - <35	122 (30.1)	276,064 (37.1)	0.15	31.1	31.0	0.00
>=35	90 (22.2)	176,158 (23.7)	0.03	21.2	21.6	0.00
Fiscal year of birth [f]						
2012-13	75 (18.5)	124,714 (16.8)	0.05	18.3	18.5	0.01
2013-14	63 (15.6)	124,938 (16.8)	0.03	14.2	14.1	0.01

2014-15	58 (14.3)	123,817 (16.6)	0.06	10 – 20	10 – 20	0.00
2015-16	61 (15.1)	124,061 (16.7)	0.04	12 – 22	12 – 22	0.00
2016-17	71 (17.5)	123,263 (16.6)	0.03	12 – 22	12 – 22	0.01
2017-18	77 (19.0)	123,217 (16.6)	0.06	14 – 24	14 – 24	0.01
Multifetal pregnancy						
Yes	38 (9.4)	24,725 (3.3)	0.25	2 – 12	2 – 12	0.01
No	367 (90.6)	719,285 (96.7)	0.25	88 – 98	88 – 98	0.01
Mode of delivery						
Vaginal	261 (64.4)	533,575 (71.7)	0.16	69.5	39.5	0.00
Cesarean	144 (35.6)	210,435 (28.3)	0.16	30.5	30.5	0.00
Parity						
Nulliparous	192 (47.4)	316,435 (42.5)	0.10	45.3	51.0	0.11
Multiparous	213 (52.6)	427,575 (57.5)	0.10	54.7	49.0	0.11
Rural residence						
Yes	31 (7.7)	71,616 (9.6)	0.07	2 – 12	2 – 12	0.05
No	374 (92.3)	672,394 (90.4)	0.07	88 – 98	88 – 98	0.05
Neighborhood median family income quintiles						
1 (Lowest)	92 (22.7)	157,277 (21.1)	0.04	23.8	25.6	0.04
2	95 (23.5)	149,485 (20.1)	0.08	24.1	22.3	0.04
3	85 (21.0)	154,536 (20.8)	0.01	20.9	21.2	0.01
4	75 (18.5)	157,197 (21.1)	0.07	14 – 24	14 – 24	0.03
5 (Highest)	58 (14.3)	125,515 (16.9)	0.07	8 – 18	8 – 18	0.04
Marginalization indices, quintile [g]						
Residential instability						
1 (least marginalized)	89 (22.0)	160,534 (21.6)	0.01	22.4	21.1	0.03
2	79 (19.5)	137,693 (18.5)	0.03	12 – 22	12 – 22	0.06
3	71 (17.5)	133,419 (17.9)	0.01	12 – 22	12 – 22	0.05
4	73 (18.0)	139,964 (18.8)	0.02	15 – 25	15 – 25	0.01
5 (most marginalized)	93 (23.0)	172,400 (23.2)	0.00	23.0	23.8	0.02
Material deprivation						
1 (least marginalized)	70 (17.3)	141,197 (19.0)	0.04	12 - 22	12 - 22	0.04
2	70 (17.3)	144,139 (19.4)	0.05	16.6	17.9	0.03
3	65 (16.0)	142,038 (19.1)	0.08	11 – 21	11 – 21	0.02
4	97 (24.0)	143,785 (19.3)	0.11	23.3	23.4	0.00

5 (most marginalized)	103 (25.4)	172,851 (23.2)	0.05	27.6	28.1	0.01
Dependency						
1 (least marginalized)	135 (33.3)	249,990 (33.6)	0.01	32.6	32.3	0.01
2	80 (19.8)	156,673 (21.1)	0.03	19.5	21.8	0.06
3	79 (19.5)	127,470 (17.1)	0.06	15 – 25	15 – 25	0.01
4	61 (15.1)	112,273 (15.1)	0.00	10 – 20	10 – 20	0.05
5 (most marginalized)	50 (12.3)	97,604 (13.1)	0.02	8 – 18	8 – 18	0.02
Ethnic concentration						
1 (least marginalized)	48 (11.9)	101,900 (13.7)	0.06	8 – 18	8 – 18	0.11
2	60 (14.8)	113,278 (15.2)	0.01	14.2	14.9	0.02
3	61 (15.1)	127,263 (17.1)	0.06	9 – 19	9 – 19	0.01
4	89 (22.0)	156,403 (21.0)	0.02	20.9	24.3	0.08
5 (most marginalized)	147 (36.3)	245,166 (33.0)	0.07	37.5	37.2	0.01
Presence of one or more pre-existing maternal medical conditions [h]						
Yes	36 (8.9)	69,795 (9.4)	0.02	4 – 14	4 – 14	0.02
No	369 (91.1)	674,215 (90.6)	0.02	86 – 96	86 – 96	0.02

Abbreviations: EOD=early-onset disease; IQR=interquartile range; LOD=late-onset disease; NICU=neonatal intensive care unit; SD=standardized difference; ULOD=ultra-late-onset disease.

[a] Infants with EOD (n=347) were excluded from the pre-match cohort.

[b] Absolute standardized difference. Shaded cells indicate an imbalance (> 0.10) between exposed and unexposed infants.

[c] Data were weighted using matching weights, which accounted for the number of infants without GBS matched to each infant with GBS. Due to a contractual agreement with the data provider, some percentages are given as a range to prevent the ability of back calculation of small cell sizes (n <6).

[d] Due to small cell sizes (n <6), some variable categories were collapsed in this table.

[e] Refer to Supplementary Table S4 for description of which newborn congenital anomalies were included.

[f] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[g] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Please see Supplementary Table S4 for complete descriptions of what is captured in each of these 4 dimensions.

[h] Pre-existing maternal health conditions included: asthma, diabetes, heart disease, chronic hypertension and thyroid disease.

Table 3. Mean 10-day healthcare costs per infant with early-onset (EOD) or late-/ultra-late-onset disease (LOD/ULOD) and their matched unexposed counterparts, stratified by phases of care

Cost Category	Infants with EOD (n=299)	Matched infants without EOD (n=820)	Attributable mean cost, $ (95% CI) [a,b]	Infants with LOD/ULOD (n=344)	Matched infants without LOD/ULOD (n=961)	Attributable mean cost, $ (95% CI) [a,b]
	Mean cost, $ (95% CI) [a]			Mean cost, $ (95% CI) [a]		
Pre-index phase [c]						
n	-	-	-	267	567	-
Inpatient hospitalizations	-	-	-	1,390 (910 to 1,870)	1,991 (1,299 to 2,684)	-602 (-922 to -281)
ED visits	-	-	-	189 (158 to 220)	19 (12 to 27)	169 (137 to 202)
Physician services	-	-	-	301 (238 to 364)	299 (225 – 374)	2 (-56 to 59)
Other costs	-	-	-	88 (67 to 110)	75 (59 to 91)	13 (-12 to 38)
Total costs	-	-	-	1,968 (1,437 to 2,500)	2,394 (1,623 to 3,166)	-426 (-803 to -49)
Acute care phase [d]						
n	299	820	-	344	756	-
Inpatient hospitalizations	8,578 (7,679 to 9,476)	6,097 (5,092 to 7,102)	2,481 (1,727 to 3234)	6,005 (5,327 to 6,683)	776 (276 to 1,276)	5,229 (4,580 to 5,878)
ED visits	20 (13 to 27)	11 (8 to 14)	9 (1 to 17)	149 (136 to 161)	9 (7 to 12)	139 (126 to 152)
Physician services	1,254 (1,144 to 1,363)	802 (691 to 913)	452 (347 to 557)	932 (848 to 1,016)	112 (72 to 152)	820 (736 to 904)
Other costs	98 (75 to 123)	73 (58 to 86)	26 (1 to 51)	164 (138 to 189)	31 (22 to 39)	133 (106 to 160)
Total costs	9,952 (8,959 to 10,945)	6,994 (5,881 to 8,108)	2,958 (2,119 to 3,798)	7,254 (6,505 to 8,003)	939 (407 to 1,471)	6,315 (5,598 to 7,032)
Post-acute care phase						
n	292	804	-	338	929	-
Inpatient hospitalizations	1,106 (710 to 1,502)	1,093 (261 to 1,925)	13 (583 to 608)	235 (150 to 321)	108 (10 to 227)	127 (6 to 248)

ED visits	9 (7 to 12)	6 (5 to 7)	4 (1 to 6)	10 (8 to 12)	5 (4 to 6)	5 (3 to 8)
Physician services	148 (109 to 186)	144 (73 to 216)	4 (-47 to 55)	67 (56 to 78)	33 (24 to 43)	34 (22 to 46)
Other costs	51 (39 to 63)	45 (31 to 58)	6 (-8 to 21)	63 (45 to 80)	24 (15 to 34)	38 (21 to 56)
Total costs	1,301 (851 to 1751)	1,269 (328 to 2,210)	32 (-632 to 695)	375 (272 to 478)	173 (33 to 312)	202 (64 to 340)
Ongoing care phase						
n	286	786	-	332	915	-
Inpatient hospitalizations	60 (-19 to 139)	82 (-85 to 249)	-22 (-216 to 172)	36 (14 to 58)	19 (8 to 30)	17 (-8 to 41)
ED visits	6 (4 to 7)	4.7 (3.9 to 5.5)	0.9 (-0.7 to 2.5)	8 (7 to 10)	5 (4 to 7)	3 (1 to 5)
Physician services	33 (21 to 45)	30 (23 to 38)	3 (-12 to 18)	30 (25 to 35)	21 (16 to 26)	9 (3 to 16)
Other costs	37 (18 to 56)	17 (-3 to 36)	21 (-10 to 51)	26 (20 to 31)	14 (10 to 18)	11 (5 to 18)
Total costs	134 (41 to 226)	130 (-47 to 308)	3 (-209 to 216)	100 (71 to 130)	60 (40 to 81)	40 (6 to 74)

Abbreviations: CI=confidence interval; ED=emergency department; EOD=early-onset disease; LOD=late-onset disease; ULOD=ultra-late-onset disease.

Note: Pre-index phase: 10 days before index date; Acute care phase: Days 0 to 30; Post-acute care phase: Days 31to180; Ongoing care phase: Days 181 to 365.

[a] Costs standardized to 10 days and adjusted to 2023 Canadian dollars. Weighted means were calculated using matched sample weights to account for variable-ratio matching.

[b] Attributable cost = (cost of exposed) - (cost of unexposed). Attributable costs were estimated using generalized estimating equations (GEE) accounting for matched pairs.

[c] Infants with EOD were not assigned a pre-index costing phase.

[d] There were <6 infants without EOD that did not contribute cost data during the acute phase. Due to contractual agreements with our data provider, these small cell counts have been suppressed.

Table 4. Cumulative mean healthcare costs for infants with early-onset (EOD) or late-/ultra-late-onset disease (LOD/ULOD) and their matched unexposed counterparts in the 30-, 180- and 365-days following index date

Cost duration	Infants with EOD (n=299)	Matched infants without EOD (n=820)	Attributable mean cost, $ (95% CI) [a,b]	Infants with LOD/ULOD (n=344)	Matched infants without LOD/ULOD (n=961)	Attributable mean cost, $ (95% CI) [a,b]
	Mean cost, $ (95% CI) [a]			Mean cost, $ (95% CI) [a]		
0 to 30 days	29,838 (26,874 to 32,802)	20,434 (17,375 to 23,494)	9,403 (7,008 to 11,798)	21,706 (19,474 to 23,937)	2,423 (1,145 to 3,700)	19,282 (17,185 to 21,379)
0 to 10 days	15,612 (14,584 to 16,640)	11,078 (9,945 to 12,211)	4,534 (3,629 to 5,439)	13,101 (12,181 to 14,021)	977 (513 to 1,441)	12,124 (11,300 to 12,948)
11 to 20 days	8,616 (7,497 to 9,735)	5,132 (4,091 to 6,174)	3,484 (2,494 to 4,474)	5,865 (5,007 to 6,722)	677 (267 to 1,088)	5,187 (4,334 to 6,040)
21 to 30 days	5,608 (4,544 to 6,672)	4,129 (3,108 to 5,149)	1,479 (609 to 2,350)	2,729 (2,046 to 3,413)	719 (313 to 1,125)	2,010 (1,337 to 2,684)
0 to 180 days	51,652 (42,810 to 60,493)	40,927 (31,073 to 50,781)	10,724 (2,673 to 18,775)	27,240 (23,876 to 30,604)	4,533 (2,006 to 7,059)	22,706 (19,306 to 26,107)
0 to 365 days	54,571 (44,261 to 64,882)	43,024 (32,715 to 53,332)	11,547 (1,392 to 21,703)	29,130 (25,542 to 32,719	5,611 (3,042 to 8,181)	23,519 (19,901 to 27,136)

Abbreviations: CI=confidence interval; EOD=early-onset disease; LOD=late-onset disease; ULOD=ultra-late-onset disease.

[a] Costs are adjusted to 2023 Canadian dollars. Weighted means were calculated using matched sample weights to account for variable-ratio matching.

[b] Attributable cost = (cost of exposed) - (cost of unexposed). Attributable costs were estimated using generalized estimating equations (GEE) accounting for matched pairs.

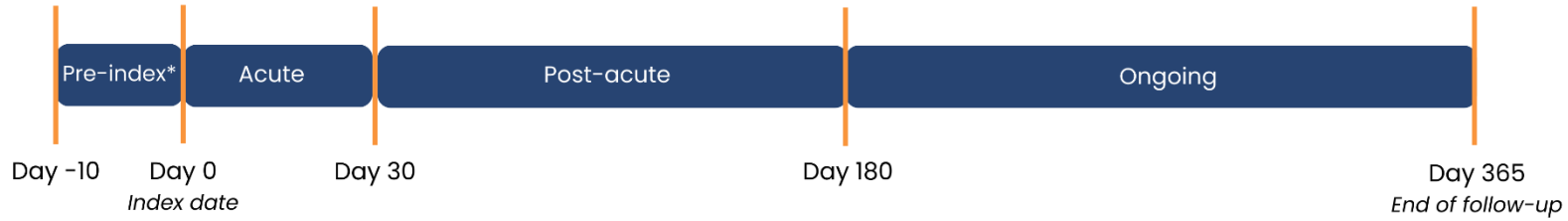


Figure 1. Phases of care for exposed infants with early-onset (EOD) or late-/ultra-late-onset disease (LOD/ULOD) and matched unexposed infants. *Infants with EOD and their matched unexposed counterparts were not assigned a pre-index care phase.

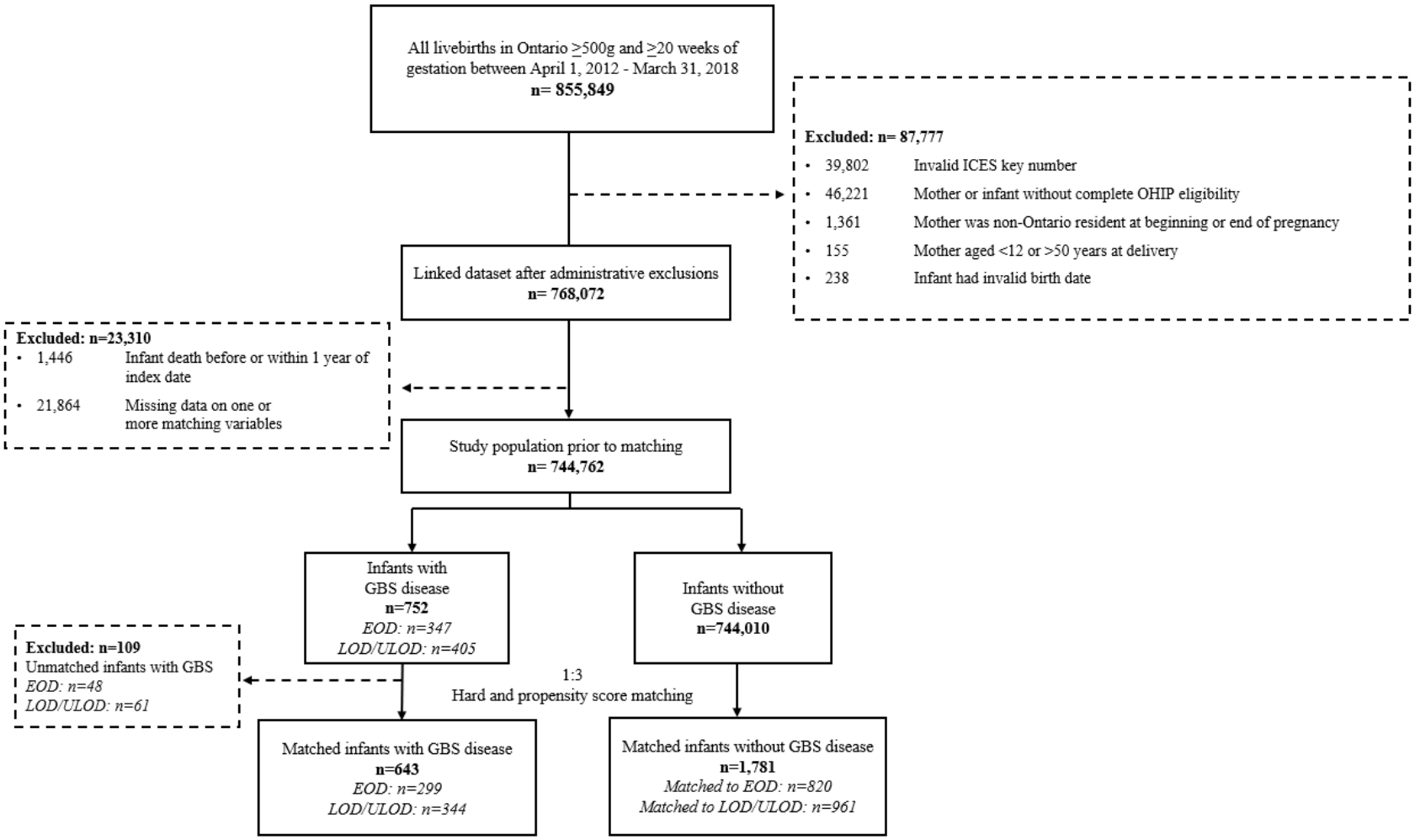
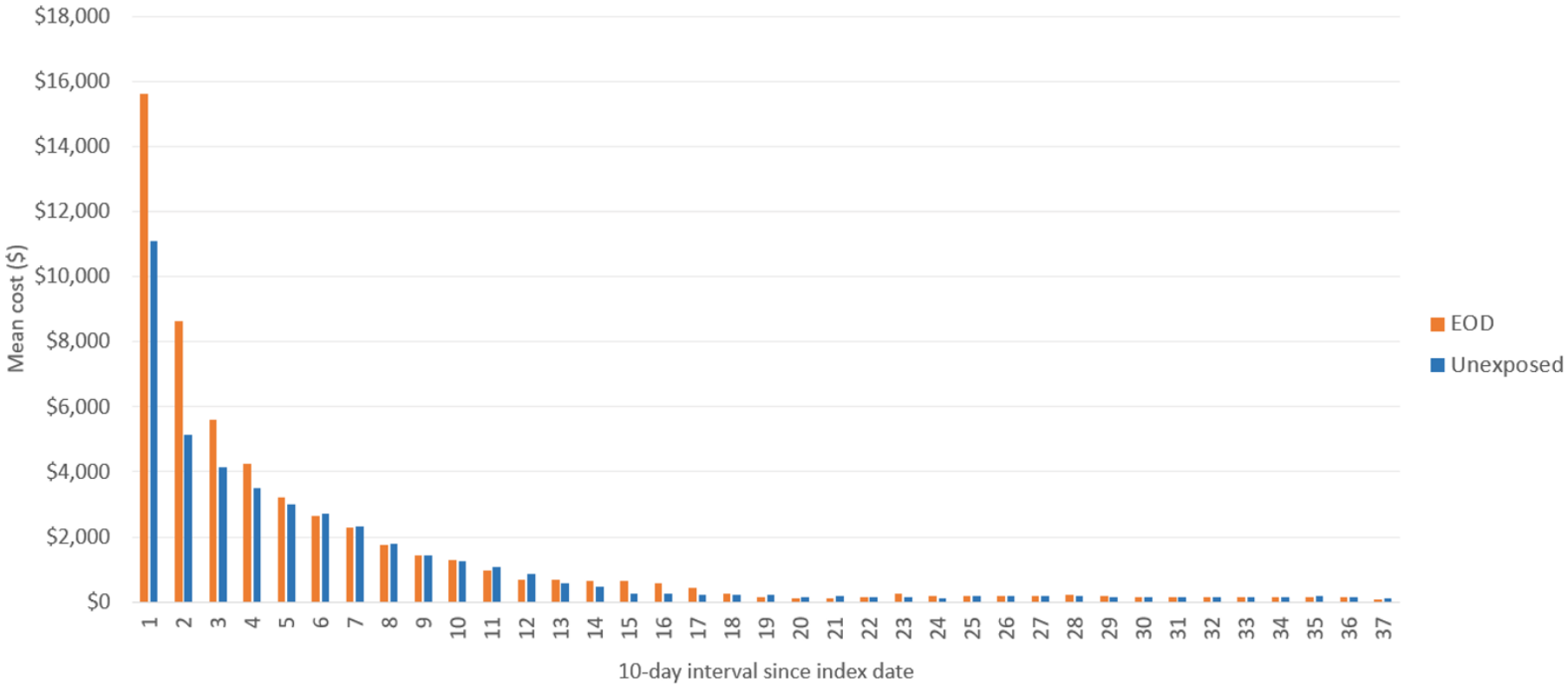


Figure 2. Study flow diagram

Abbreviations: EOD=early-onset disease; GBS=Group B Streptococcus; LOD=late-onset disease; OHIP=Ontario Health Insurance Plan; ULOD=ultra-late-onset disease

A.


$18,000
$16,000
$14,000
$12,000
$10,000
$8,000
$6,000
$4,000
$2,000
$0
Mean cost ($)
1
2
3
4
5
6
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32
33
34
35
36
37
10-day interval since index date
EOD
Unexposed

B.

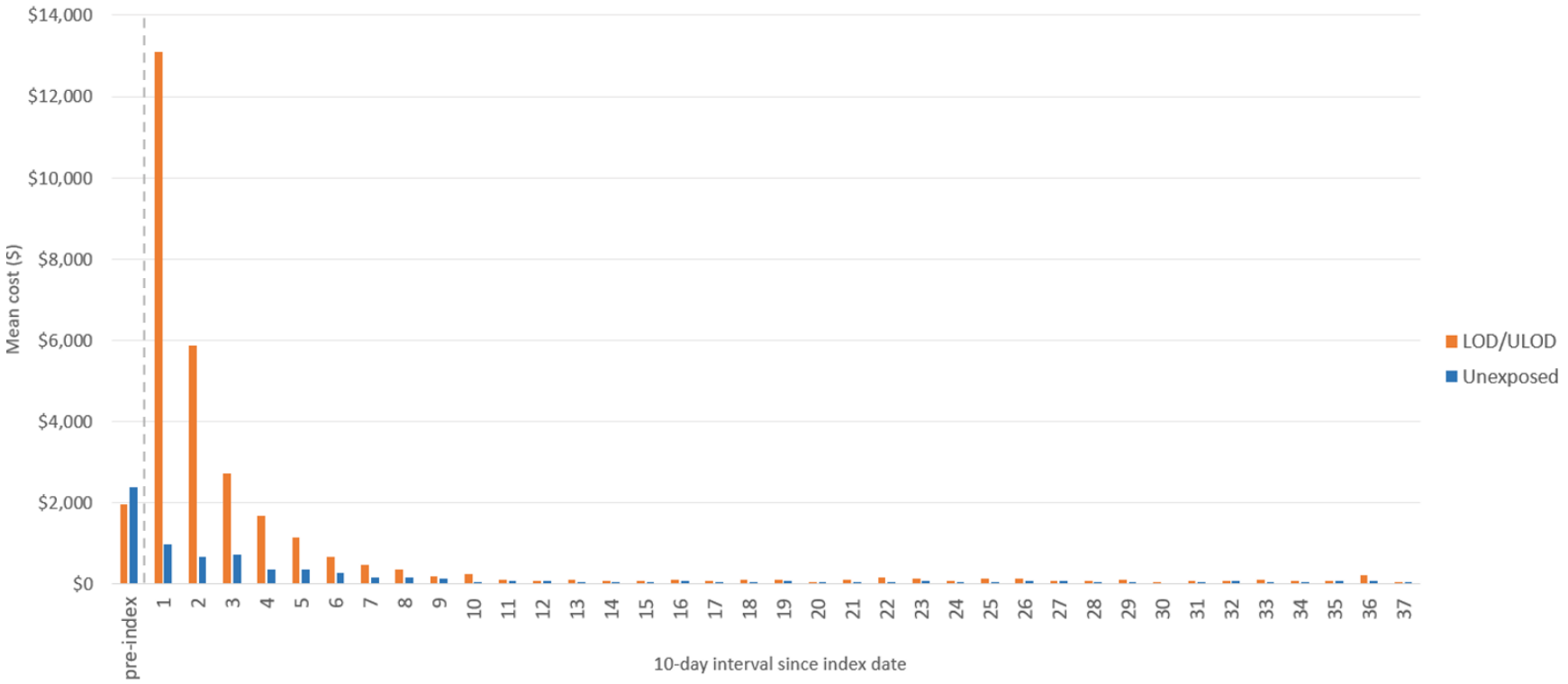

Figure 3. Mean healthcare costs per infant, shown in 10-day intervals, for infants with early-onset disease (EOD) (Panel A) and late-/ultra-late-onset disease (LOD/ULOD) (Panel B) and their matched unexposed counterparts. Each bar represents the average cost over a 10-day period following the index date. In Panel B, the dotted line indicates the index date, with the pre-index period representing the 10 days prior to diagnosis. Costs are presented in 2023 Canadian dollars.

6.9 Supplementary materials

Table S1. Description and purpose of each data source utilized in the study

Database	Description	Information collected
Better Outcomes Registry & Network (BORN) Ontario	Captures all births ≥500 grams or ≥20 weeks' gestation in the province of Ontario. Routine data collection includes information on maternal demographic variables; pre-existing maternal health conditions; obstetric factors affecting the pregnancy; and birth outcomes (Murphy et al., 2021).	Used to ascertain sociodemographic, pregnancy and birth characteristics.
Registered Persons Database (RPDB)	Demographic repository containing information on all Ontario residents eligible for publicly funded health care in the province.	Used to establish the duration for which each participant was eligible to receive health care services, as well as obtain demographic information regarding neighborhood income quintiles.
Postal Code Conversion File (PCCF)	The Postal Code Conversion File (PCCF) facilitates the matching of six-digit postal codes with standardized census geographies. These resulting small-area geographies serve various purposes, such as aggregating data to widely used administrative boundaries and comprehending socio-economic status at the neighborhood level.	Used to obtain geographic information for variables such as rural location and neighbourhood income quintiles by converting Ontario postal codes into Statistics Canada standard geographical areas.
Canadian Institute for Health Information (CIHI) Discharge Abstract Database (DAD)	Captures demographic and clinical information regarding hospital admissions from all acute care institutions throughout Ontario. Contains medical diagnoses (most responsible diagnosis and up to 24 secondary diagnoses), interventions received, length of hospital stay and other data elements. Medical diagnoses are coded using the Canadian implementation of the International Classification of Diseases, 10th Revision (ICD-10-CA). Medical interventions are documented through Canadian Classification of Health Interventions (CCI) codes.	Used to obtain information regarding hospital admissions, including medical diagnoses and procedures, for defining exposures and outcomes.
Canadian Institute for Health Information (CIHI) National Ambulatory Care Reporting System (NACRS)	Captures data originating from outpatient clinics and urgent visits to emergency departments in Ontario. Up to 10 clinical diagnoses on each abstract are coded using ICD-10-CA.	Used to supplement data from the CIHI-DAD and capture additional medical diagnoses captured at emergency department visits and outpatient clinics for exposure and outcome information.

Ontario Health Insurance Plan (OHIP) Database	Contains health care billing information made by physicians, or other health care providers, for service reimbursement. This database includes information on the diagnosis (i.e., reason for the visit), type of service received, and the associated billing code.	Used to capture physician billing claims to define certain neurodevelopmental conditions.
Ontario Marginalization Index (ON-Marg)	Data tool that quantifies the level of marginalization occurring in Ontario. This multifaceted index uses data from Statistics Canada's Census and consists of four dimensions that indicate area-level marginalization: residential instability, material deprivation, dependency and ethnic concentration. Scores corresponding to each of these four dimensions were previously divided into quintiles, where quintile 1 represents areas that are the least marginalized and quintile 5 represents the most marginalized areas.	Provided information regarding the four indices of area-level marginalization.
Ontario Laboratories Information System (OLIS) Database	OLIS is an electronic repository of the province's laboratory test results. This system was implemented to allow health care providers timely access to laboratory test results from both community- and hospital-based laboratories. According to eHealth Ontario, as of Dec. 31, 2017, 134 of the 262 hospital sites across the province were using OLIS, and 13 of the 14 Local Health Integration Networks (LHINs) were included (https://ehealthontario.on.ca/files/public/support/DataContributorsOLIS.pdf).	Used to identify laboratory-confirmed instances of infant GBS disease. We utilized cleaned observation codes for bacterial culture results that had an organism code of 53 (*Streptococcus* agalactiae) and a specimen source of either blood or cerebrospinal fluid.
Same Day Surgery	Contains records of same-day surgical procedures performed in hospitals across Ontario.	Includes surgical procedure codes, patient demographics, and postoperative outcomes. Used to calculate healthcare costs for surgeries using resource intensity weights (RIWs) and costs per weighted case (CPWC).
Ontario Drug Benefits claims	Contains claims for prescription drugs covered under the Ontario Drug Benefit (ODB) program, primarily for residents aged 65 and older.	Captures data on prescription drug costs, dispensing fees, and amounts paid for medications. These costs are calculated based on the amount paid per prescription.
National Rehabilitation Reporting System	Contains client data from adult inpatient rehabilitation facilities, including admission and discharge data, health and functional characteristics.	Collects information on rehabilitation admissions, functional outcomes, and lengths of stay. Costs are calculated using rehabilitation cost weights (RCWs) and costs per weighted case (CPWC).

Ontario Mental Health Reporting System	Contains data on patients admitted to adult inpatient mental health beds in acute care and psychiatric facilities across Ontario. Includes administrative data such as admission and discharge dates, diagnoses, and service utilization.	Captures details of inpatient mental health admissions, including length of stay, diagnoses coded using ICD-10-CA, and case mix indices (CMI). Costs are calculated based on days of stay, case mix indices, and costs per weighted day (CPWD).

Table S2. Infant Group B *Streptococcus* (GBS) definitions

GBS Category	Laboratory Database (OLIS) ‡	Health administrative databases (DAD, NACRS)*‡
GBS disease	Positive blood or cerebrospinal fluid (CSF) culture for GBS	ICD-10-CA codes (up to 365 days of life): - A40.1 (Sepsis due to GBS) - P36.0 (Sepsis of newborn due to GBS) - G00.2 (*Streptococcal* meningitis) - Patients with sepsis codes above AND G00.9 (bacterial meningitis, unspecified) or G03.9 (meningitis, unspecified) - J15.3 (Pneumonia due to GBS) - P23.3 (Congenital pneumonia due to GBS) - B95.1 (*Streptococcus*, group B, as the cause of disease classified elsewhere), Examples include: urinary tract infections, cellulitis, kidney infections etc.
Early-onset disease (EOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was within the period from birth to 6 days of life.	Admission date for the first GBS-related hospitalization was within the period from birth to 6 days of life.
Late-onset disease (LOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was from 7 days of life to 89 days of life.	Admission date for the first GBS-related hospitalization was within the period from 7 days of life to 89 days of life.
Ultra-late-onset disease (ULOD)	The specimen collection date of the first positive GBS culture (blood or CSF) was from 90 days of life to 1 year of age.	Admission date for the first GBS-related hospitalization was within the period from 90 days of life to 1 year of age.

CSF= cerebrospinal fluid; DAD=Discharge Abstract Database; NACRS=National Ambulatory Care Reporting System; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; OLIS=Ontario Laboratories Information System Database.

*Records with a diagnostic code for GBS on any of the 25 fields within DAD or 10 fields within NACRS were selected.
‡ For cases with culture-confirmation, infants were categorized as EOD, LOD or ULOD based on the date of specimen collection in OLIS. In instances of multiple specimen collections, we used the date of the first positive culture result. Among GBS infants without culture confirmation (identified only in DAD/NACRS), we used the admission date for the first GBS-related visit (hospitalization or emergency department visit), referred to as the index GBS visit, to determine the classification of GBS disease as EOD, LOD, or ULOD.

Table S3. Cost components and data sources

Cost Category	**Cost component and/or data source**
Inpatient hospitalizations	Canadian Institute for Health Information hospital Discharge Abstract Database (CIHI-DAD)
Emergency department	National Ambulatory Care Reporting System (NACRS)
Physician services	Including fee-for-service and most of the shadow billings: Ontario Health Insurance Plan (OHIP)
Other costs	- Complex continuing care facilities: Continuing Care Reporting System (CCRS) National - Rehabilitation services: National Rehabilitation Reporting System (NRS) - Longterm care facilities: Long term care (CCRS) - Ambulatory care (e.g., same day surgery, dialysis, cancer care clinics): National Ambulatory Care Reporting System (NACRS) - Home care: Home Care Database (HCD) - Medical devices: Assistive Devices Program (ADP) - Outpatient prescriptions for adults aged 65 and older and those required social assistance: Ontario Drug Benefit (ODB) - Admissions to designated mental health beds: Ontario Mental Health Reporting System (OMHRS)

Table S4. Definitions of matching variables

Study Variable	Patient record	Definition	Source of variable
Variables included in hard matching			
Index date	Infant	Exposed GBS infants: Index date determined by the specimen collection date for culture-confirmed cases or the admission date of hospitalization/visit for non-culture-confirmed cases. Unexposed infants: Index date randomly assigned based on the distribution of index dates among exposed infants. Caliper of ±30-days was used for matching.	Exposed GBS infants: OLIS database (specimen collection date), DAD or NACRS databases (hospitalization/visit dates). Unexposed infants: Distribution derived from exposed infants.
Infant age	Infant	The age of the infant (in days) from date of birth. Caliper of ±7-days was used for matching.	Calculated using date of birth.
Pre-index healthcare costs	Infant	Average daily healthcare costs from birth to index date. Caliper of ± $200 per day was used for matching.	Calculated using total cost from validated GETCOST algorithm at ICES.
Gestational age at birth	Mother and infant	The number of completed weeks of gestation at the time of delivery, calculated from the first day of the mother's last menstrual period or estimated based on ultrasound measurements.	Categorical variable was created using the gestational age variable in BORN (<28, 28-<37, ≥ 37 weeks).
Variables included in propensity score model			
Infant sex	Infant	Infant's biological sex assigned at birth.	Measured using "b_sex" variable in BORN.
Maternal age	Mother	Age of the mother at the time of giving birth.	Calculated using from "m_bdate" variable in BORN.
Fiscal year of birth	Mother and infant	Refers to the fiscal year that the infant was born.	Grouped using infant's date of birth where a fiscal year begins on Apr. 1 and ends on Mar. 31.

Parity	Mother	Total number of previous pregnancies (live births and stillbirths) that reached a viable gestational age.	Measured using "parity" variable in BORN.
Income quintile	Mother	Nearest Census Based Neighborhood Income Quintile.	Measured using "INCQUINT" variable within RPDB.
Rural residence	Mother	Rurality determined using second digit of postal code from Canada Post Corporation.	Measured using rural flag variable from postal code conversion file in RPDB.
Dependency	Mother	Refers to area-level concentrations of people who don't have income from employment.	Measured using "dependency factor score" variable within the ON-Marg database.
Ethnic concentration	Mother	Refers to high area-level concentrations of recent immigrants and people belonging to a 'visible minority' group.	Measured using "ethnic concentration factor score" variable within the ON-Marg database.
Material deprivation	Mother	Refers to inability for individuals and communities to access and attain basic material needs. This dimension is closely connected to poverty.	Measured using "material deprivation factor score" variable within the ON-Marg database.
Residential instability	Mother	Refers to area-level concentrations of people who experience high rates of family or housing instability.	Measured using "residential instability factor score" variable within the ON-Marg database.
Gestational age at birth	Mother and infant	The number of completed weeks of gestation at the time of delivery, calculated from the first day of the mother's last menstrual period or estimated based on ultrasound measurements.	Categorical variable was created using the gestational age variable in BORN (<28, 28-<37, ≥ 37 weeks).
Birthweight	Infant	Infant birth weight (grams).	Measured using birthweight variable in BORN.
Multifetal pregnancy	Mother	The total number of fetuses in the current pregnancy. If the pregnancy included more than one fetus, it was classified as multifetal.	Measured using "number_of_fetuses" variable in BORN.
Mode of delivery	Mother	Refers to the mode of delivery (vaginal or cesarean section) experienced by the mother.	Measured using "birth_type_id" variable in BORN.
Presence of one or more pre-existing maternal medical conditions	Mother	Mother had any one or combinations of the following pre-existing conditions: asthma, chronic hypertension, diabetes, heart disease or thyroid disease.	Using the "mat_pre_exist_heatlh_cond_id" variable in BORN, we generated specific flags for each individual condition and a composite flag that captured the presence of 1 or more conditions.

Presence of one or more newborn congenital anomalies	Infant	Presence of one or more congenital anomalies confirmed/diagnosed in the newborn period.	Measured using the "congenital_anomalies_confirmed" variable in BORN Ontario, which captures confirmed diagnoses of congenital anomalies in newborns, including but not limited to neural tube defects, orofacial clefts, limb deficiencies, chromosomal abnormalities (e.g., Down syndrome), congenital heart defects (e.g., Tetralogy of Fallot, Hypoplastic Left Heart Syndrome), and gastrointestinal anomalies (e.g., gastroschisis).
Neonatal Intensive Care Unit (NICU) admission at birth hospitalization.	Infant	Identifies whether infant was admitted to the neonatal intensive care unit (NICU) during their birth hospitalization.	Measured using “SCU (special care unit)” variables in DAD and nicu_admission_flag variable in BORN.

Note: BORN=Better Outcomes Registry & Network; DAD=Discharge Abstract Database; NACRS=National Ambulatory Care Reporting System; ICD-10-CA=Canadian implementation of the International Classification of Diseases, 10th Revision; RPDB=Registered Persons Database.

Table S5. Characteristics of matched compared to unmatched infants with GBS

Characteristic	Matched GBS infants n=643	Unmatched GBS infants n=109	SD
	n(%)	n(%)	
Sex			
Female	311 (48.4)	51 (46.8)	0.03
Male	332 (51.6)	58 (53.2)	0.03
Gestational age at birth, weeks			
<28	24 (3.7)	63 (57.8)	1.45
28 - <37	113 (17.6)	31 (28.4)	0.26
>= 37	506 (78.7)	15 (13.8)	1.72
NICU admission during birth hospitalization			
Yes	265 (41.2)	77 (70.6)	0.62
No	378 (58.8)	32 (29.4)	0.62
Birthweight (grams) [a]			
<1000	18 (2.8)	63 (57.8)	1.49
1000 - <1500	25 (3.9)	16 (14.7)	0.38
1500 - <2500	86 (13.4)	14 (12.8)	0.02
>=2500	514 (79.9)	16 (14.7)	1.73
Presence of one or more newborn congenital anomalies [b]			
Yes	32 (5.0)	25 (22.9)	0.54
No	611 (95.0)	84 (77.1)	0.54
Maternal age, years [a]			
<25	112 (17.4)	19 (17.4)	0
25 - <30	173 (26.9)	32 (29.4)	0.05
30 - <35	208 (32.3)	32 (29.4)	0.06
>=35	150 (23.3)	26 (23.9)	0.01
Fiscal year of birth [c]			
2012-13	131 (20.4)	23 (21.1)	0.02
2013-14	116 (18.0)	24 (22.0)	0.07
2014-15	89 (13.8)	12 (11.0)	0.08

2015-16	105 (16.3)	13 (11.9)	0.12
2016-17	96 (14.9)	16 (14.7)	0.01
2017-18	106 (16.5)	21 (19.2)	0.04
Multifetal pregnancy			
Yes	44 (6.8)	24 (22.0)	0.44
No	599 (93.2)	85 (78.0)	0.44
Mode of delivery			
Vaginal	437 (68.0)	49 (45.0)	0.48
Cesarean	206 (32.0)	60 (55.0)	0.48
Parity			
Nulliparous	336 (52.3)	47 (43.1)	0.18
Multiparous	307 (47.7)	62 (56.9)	0.18
Rural residence			
Yes	52 (8.1)	12 (11.0)	0.09
No	591 (91.9)	97 (89.0)	0.09
Neighborhood median family income quintiles			
1 (Lowest)	150 (23.3)	19 (17.4)	0.15
2	150 (23.3)	24 (22.0)	0.03
3	135 (21.0)	27 (24.8)	0.09
4	124 (19.3)	19 (17.4)	0.05
5 (Highest)	84 (13.1)	20 (18.3)	0.15
Marginalization indices, quintile [d]			
Residential instability			
1 (least marginalized)	145 (22.6)	26 (23.9)	0.03
2	110 (17.1)	27 (24.8)	0.19
3	109 (17.0)	15 (13.8)	0.09
4	122 (19.0)	14 (12.8)	0.14
5 (most marginalized)	157 (24.4)	26 (23.9)	0.01
Material deprivation			
1 (least marginalized)	108 (16.8)	15 (13.8)	0.08
2	105 (16.3)	28 (25.7)	0.23
3	108 (16.8)	17 (15.6)	0.03
4	150 (23.3)	32 (29.4)	0.14
5 (most marginalized)	172 (26.7)	17 (15.6)	0.28

Dependency			
1 (least marginalized)	217 (33.7)	39 (35.8)	0.04
2	128 (19.9)	26 (23.9)	0.10
3	115 (17.9)	15 (13.8)	0.10
4	99 (15.4)	14 (12.8)	0.07
5 (most marginalized)	84 (13.1)	15 (13.8)	0.02
Ethnic concentration			
1 (least marginalized)	85 (13.2)	7 (6.4)	0.23
2	99 (15.4)	20 (18.3)	0.08
3	88 (13.7)	19 (17.4)	0.10
4	129 (20.1)	24 (22.0)	0.05
5 (most marginalized)	242 (37.6)	39 (35.8)	0.04
Presence of one or more pre-existing maternal medical conditions [e]			
Yes	73 (11.4)	11 (10.1)	0.04
No	570 (88.6)	98 (89.9)	0.04

Abbreviations: EOD=early-onset disease; IQR=interquartile range; LOD=late-onset disease; NICU=neonatal intensive care unit; SD=standardized difference; ULOD=ultra-late-onset disease.

[a] Due to small cell sizes (n <6), some categories for birthweight and maternal age were collapsed in this table.

[b] Refer to Supplementary Table S4 for description of which newborn congenital anomalies were included.

[c] A fiscal year begins on Apr. 1 and ends on Mar. 31.

[d] Scores corresponding to each of these 4 dimensions were previously divided into quintiles, where quintile 1 represents the least marginalized areas, and quintile 5, the most marginalized areas. Refer to Supplementary Table S4 for complete descriptions of what is captured in each of these 4 dimensions.

[e] Pre-existing maternal health conditions included: asthma, diabetes, heart disease, chronic hypertension and thyroid disease.

Table S6. Sensitivity analysis: Mean 10-day attributable healthcare costs per infant with late-onset disease (LOD) and matched unexposed infants, stratified by phases of care

Cost Category	Infants with LOD n=304	Matched infants without LOD n=854	Attributable mean cost, $ (95% CI) [a,b]
	Mean cost, $ (95% CI) [a]		
Pre-index phase			
n	233	538	-
Inpatient hospitalizations	1,494 (957 to 2,031)	2,279 (1,495 to 3,062)	-785 (-1,137 to -432)
ED visits	159 (129 to 190)	21 (13 to 30)	138 (106 to 170)
Physician services	301 (233 to 369)	341 (256 to 425)	-40 (-101 to 21)
Other costs	79 (57 to 101)	84 (66 to 102)	-5 (-31 to 21)
Total costs	2,036 (1,443 to 2,629)	2,739 (1,866 to 3,612)	-703 (-1,112 to -293)
Acute care phase			
n	304	691	-
Inpatient hospitalizations	6,160 (5,420 to 6,900)	887 (316 to 1,458)	5,273 (4,564 to 5,982)
ED visits	148 (135 to 161)	10 (7 to 13)	138 (125 to 151)
Physician services	904 (822 to 986)	124 (78 to 171)	780 (698 to 862)
Other costs	152 (126 to 178)	31 (22 to 40)	121 (93 to 149)
Total costs	7,370 (6,559 to 8,181)	1,064 (455 to 1,673)	6,306 (5,532 to 7,080)
Post-acute care phase [c]			
n	304	825	-
Inpatient hospitalizations	235 (142 to 327)	122 (-13 to 257)	113 (-21 to 246)
ED visits	9	4	4

	(6 to 11)	(3 to 5)	(2 to 6)
Physician services	64 (53 to 75)	36 (26 to 47)	28 (16 to 40)
Other costs	56 (39 to 74)	27 (16 to 38)	29 (12 to 47)
Total costs	364 (254 to 475)	192 (33 to 352)	172 (20 to 323)
Ongoing care phase			
n	293	814	-
Inpatient hospitalizations	36 (12 to 59)	18 (7 to 30)	17 (-9 to 44)
ED visits	8 (6 to 10)	5 (4 to 7)	3 (1 to 5)
Physician services	30 (24 to 35)	22 (16 to 27)	8 (1 to 15)
Other costs	24 (18 to 30)	15 (10 to 19)	9 (3 to 16)
Total costs	97 (66 to 129)	60 (37 to 83)	37 (1 to 74)

Abbreviations: CI=confidence interval; ED=emergency department; LOD=late-onset disease

Note: Pre-index phase: 10 days before index date; Acute care phase: Days 0 to 30; Post-acute care phase: Days 31–180; Ongoing care phase: Days 181 to 365.

[a] Costs standardized to 10 days and adjusted to 2023 Canadian dollars. Weighted means were calculated using matched sample weights to account for variable-ratio matching.

[b] Attributable cost = (cost of exposed)-(cost of unexposed). Attributable costs were estimated using generalized estimating equations (GEE) accounting for matched pairs.

[c] There were <6 infants with LOD that did not contribute cost data during the post-acute phase. Due to contractual agreements with our data provider, these small cell counts have been suppressed.

Table S7. Sensitivity analysis: Mean cumulative healthcare costs for infants with late-onset disease (LOD) and matched unexposed infants in the 30-, 180-days and 365 days following index date

Cost duration	Infants with LOD n=304	Matched infants without LOD n=854	Attributable mean cost, $ (95% CI) [a,b]
	Mean cost, $, (95% CI) [a]		
0 to 30 days	22,032 (19,619 to 24,445)	2,739 (1,278 to 4,199)	19,292 (17,037 to 21,549)
0 to 10 days	13,250 (12,266 to 14,234)	1,110 (578 to 1,643)	12,140 (11,271 to 13,009)
11 to 20 days	6,017 (5,090 to 6,944)	762 (294 to 1,230)	5,255 (4,332 to 6,178)
21 to 30 days	2,752 (2,006 to 3,498)	809 (346 to 1,272)	1,943 (1,208 to 2,677)
0 to 180 days	27,338 (23,729 to 30,948)	5,044 (2,148 to 7,939)	22,294 (18,631 to 25,957)
0 to 365 days	29,170 (25,313 to 33,026)	6,113 (3,175 to 9,051)	23,056 (19,157 to 26,956)

Abbreviations: CI=confidence interval; LOD=late-onset disease

[a] Costs adjusted to 2023 Canadian dollars. Weighted means were calculated using matched sample weights to account for variable-ratio matching.

[b] Attributable cost = (cost of exposed) - (cost of unexposed). Attributable costs were estimated using generalized estimating equations (GEE) accounting for matched pairs.

CHAPTER 7. DISCUSSION

GBS disease remains a significant global public health concern, placing a substantial burden on affected infants, straining healthcare systems, and impacting the well-being of families and caregivers. Despite decades of research and existing preventive options, such as maternal screening and IAP, GBS disease continues to contribute to severe infant outcomes, including sepsis and meningitis, with long-term health consequences among survivors. Moreover, the economic burden of GBS disease—including in the Canadian context—has been underexplored, limiting the ability to evaluate the full impact of this condition. Real-world data on the health and economic burden of GBS disease are critical, as they provide a foundation for evaluating both the effectiveness of current prevention strategies and the potential benefits of emerging preventive interventions in development, such as maternal GBS vaccination.

The overarching aim of this doctoral thesis was to comprehensively assess the health and economic burden of GBS disease among infants in Ontario, Canada. Through three population-based studies, this thesis has generated the first Canadian estimates of GBS disease impacts, addressing critical evidence gaps on both the short- and long-term burden on affected infants and the healthcare system.

Chapter 2 reviewed the existing literature on GBS disease, detailing its clinical characteristics, global estimates of disease and economic burden, long-term health impacts, current preventive options, and the potential future preventive option of maternal GBS vaccination. This chapter also highlighted key evidence gaps, particularly the lack of Canadian-

based research and the need for larger population-based epidemiological studies. Chapters 4 to 6 presented the three population-based cohort studies conducted for this thesis, each with a distinct objective focused on understanding the current landscape of infant GBS disease in Ontario, Canada. This Discussion chapter summarizes the key findings from all three studies, reviews the overarching limitations of the dissertation, discusses implications for clinical practice and policy, and outlines priorities for future research.

7.1 Summary of key findings

Burden of infant Group B Streptococcus disease and impact of maternal screening and antibiotic prophylaxis in Ontario, Canada: a population-based cohort study—The first study, presented in Chapter 4 and published in Lancet Regional Health—The Americas, estimated the burden of infant GBS disease and evaluated the effectiveness of current prevention methods in Ontario, Canada.[1] Using data from nearly 800,000 pregnancies, this is the largest Canadian study of its kind, providing a comprehensive assessment of maternal GBS screening coverage, IAP uptake, and infant GBS disease epidemiology.

Our study revealed a high maternal screening coverage of 94%, with minimal socioeconomic disparity, indicating widespread adherence to screening recommendations. Despite high screening rates, important gaps in IAP administration were identified. Only 81% of screen-positive mothers received IAP, and among term infants with EOD, 12% were born to mothers who had screened positive but did not receive the recommended prophylaxis. This suggests that even with high screening coverage, lapses in IAP administration may contribute to preventable cases of EOD. Similar challenges have been observed internationally: Bianco et al.

(2016) reported that although 91% of eligible individuals received IAP in Italy, only 36% adhered to full CDC guideline criteria, with delayed administration (<4 hours before delivery) being the most common issue.[2] A 2017 systematic review found that although many high-income countries have adopted universal screening and IAP policies, implementation and coverage vary significantly, with no international consensus on the optimal approach.[3]

In our study, the overall incidence of infant GBS disease in Ontario was 1.0 per 1,000 live births. While the incidence of EOD declined over time, the incidence of LOD and ULOD remained stable, which is consistent with existing knowledge about the limitations of IAP-based strategies, as it does not prevent GBS disease beyond the early neonatal period.[4] The observed decline in EOD incidence may correspond with the broader implementation of universal maternal GBS screening and IAP protocols in Canada during the early 2000s; however, this has not been evaluated empirically. Although maternal screening was significantly associated with reduced incidence of both EOD and LOD/ULOD, the protective association between IAP receipt and EOD did not reach statistical significance. This may be due to limited statistical power resulting from the small number of exposed cases, although exposure or outcome misclassification may also have played a role. Nonetheless, the direction of our point estimates aligns with previous research demonstrating a protective effect of IAP against EOD.[5]

Group B Streptococcus disease during infancy and risk of subsequent neurodevelopmental impairments in young children: a population-based cohort study in Ontario, Canada—The second study, presented in Chapter 5, evaluated the risk of NDIs in children by five years of age following GBS disease during infancy and examined whether sex and prematurity modified this

risk. Using a population-based cohort of over 770,000 children in Ontario, we found that survivors of infant GBS disease had approximately twice the risk of NDIs by five years, compared to children without a history of GBS.

GBS survivors exhibited significantly higher rates of impairments across cognitive, motor, sensory, and social/behavioural domains, as well as greater likelihood of moderate-to-severe and multi-domain NDIs. These findings are consistent with previous studies showing that GBS disease is associated with long-term sequelae such as cerebral palsy, hearing loss, and intellectual disability.[6] Importantly, our study distinguished between EOD and LOD. While both groups faced elevated NDI risks, early-onset GBS survivors were especially vulnerable to motor impairments, possibly due to disruptions in neurodevelopment during the earliest stages of post-natal brain growth.[7] Similarly, survivors of GBS-meningitis in our study had a higher risk of cognitive impairments, which is likely due to the direct involvement of the central nervous system and resulting inflammation during a critical period of brain development.[6]

We also found that prematurity and male sex significantly modified the risk of NDIs. Among survivors, preterm infants experienced a notably higher burden of impairment, aligning with prior research showing that the combination of prematurity and neonatal infection substantially increases neurodevelopmental vulnerability.[8,9] Male infants were also more likely to experience impairments across multiple domains, a pattern similarly observed in other GBS-related studies on neurodevelopment outcomes.[10] Together, these findings highlight the substantial long-term impact of infant GBS disease and underscore the importance of prevention, not only to reduce acute morbidity, but also to mitigate lasting developmental consequences.

They also point to the need for early developmental screening and tailored clinical follow-up for high-risk groups, particularly male infants and those born preterm who survive GBS disease.

Healthcare costs attributable to Group B Streptococcus disease during infancy: a population-based matched cohort study in Ontario, Canada — The third, and final, study presented in Chapter 6, estimated the healthcare costs attributable to infant GBS disease during the first year following diagnosis. Using a matched cohort design, we compared 634 infants diagnosed with GBS to 1,781 unexposed infants. This study found that infant GBS disease was associated with substantial short-term healthcare costs, particularly during the acute 30-day period following diagnosis.

Attributable costs were highest within the first 10 days and largely driven by inpatient hospitalizations and physician services, highlighting the intensity of care required during the early phase of illness. Infants with EOD incurred higher healthcare costs than uninfected infants during the acute phase (days 0 to 30), but these differences diminished in the post-acute (days 31 to 180) and ongoing care (days 181 to 365) periods. In contrast, infants with LOD or ULOD had consistently elevated attributable costs throughout all phases of care, suggesting more prolonged and complex healthcare needs.

This pattern aligns with previous studies showing that LOD is more often associated with meningitis, which often requires extended specialist care, neuroimaging, and rehabilitative services.[11–13] LOD and ULOD typically occur after hospital discharge, which may delay diagnosis and result in more complications.[14] This is in contrast to EOD, which generally

presents quickly following birth while infants are still hospitalized, allowing for earlier recognition and intervention. Although previous studies have suggested that GBS meningitis requires longer treatment duration and higher rates of neurological complications compared to GBS sepsis,[11–13] findings from our second study showed similar NDI risks across these two subgroups. This difference may reflect heterogeneity in case definitions, outcome measurement, and study power.

Further evidence from a population-based study from Australia found that infants with GBS were significantly more likely than unexposed infants to experience rehospitalization and to have longer hospital stays throughout early childhood, particularly within the first five years of life.[15] While the study did not differentiate between early- and late-onset disease, it found higher rates of hospitalizations for conditions such as epilepsy, cerebral palsy, and genitourinary disorders among GBS survivors, reflecting a sustained burden on the healthcare system beyond the neonatal period.[15]

Given the limited number of studies directly estimating the healthcare costs of infant GBS disease, our findings provide valuable real-world evidence from Canada. These estimates can support future cost-effectiveness analyses and health technology assessments by organizations such as Canada's Drug Agency when evaluating emerging prevention strategies—such as maternal vaccination—against current approaches like screening and IAP.

7.2 Limitations

While each study's specific limitations are addressed in Chapters 4 to 6, this section provides a broader overview of the limitations across the entire dissertation.

7.2.1 Data availability and scope

Although the use of population-level databases and registries strengthened our studies, many of these data sources were not originally designed for research purposes. Consequently, the variables available for evaluation and adjustment were limited to the information collected within these datasets. For instance, information on GBS serotypes was unavailable, which would have been valuable for estimating the incidence of various GBS serotypes in Ontario (Study 1) and exploring their potential association with NDI outcomes (Study 2). Additionally, the lack of data on the duration, type, dose, and timing of IAP in Study 1 limited our ability to fully understand its role in preventing infant GBS disease. Without this information, we were unable to assess the validity of the variable, evaluate the appropriateness of IAP administration before delivery, determine its effectiveness based on antibiotic type, or investigate reasons for non-administration. We also did not have data on whether antibiotics were administered to the newborn to treat GBS infection. Further, while we had data on maternal GBS screening completion, we lacked information on colonization levels—which are not routinely captured clinical data collection—and the precise timing of screening beyond confirmation that it occurred after 35 weeks' gestation.

In Study 3, our analysis was limited to direct medical costs captured in the health administrative databases, excluding broader societal costs such as caregiver time, out-of-pocket expenses, and productivity losses. This likely underestimates the full economic burden of infant GBS disease.

Finally, across all studies, data on race, ethnicity, and individual-level socioeconomic status were unavailable. We relied on neighbourhood income quintiles and the Ontario Marginalization Index (ON-MARG), which uses area-level marginalization data from Statistics Canada's Census to estimate four indices of marginalization: Households and dwellings (previously called 'Residential instability'), Material resources (previously called 'Material deprivation'), Age and labour force (previously called 'Dependency'), and Racialized and newcomer populations **(**previously called 'Ethnic concentration').[16] However, area-based measures may not accurately reflect individual-level characteristics, and the possibility of residual confounding due to unmeasured variables cannot be ruled out.

7.2.2 Misclassification of GBS disease

A key limitation across all studies in this dissertation relates to the availability and accuracy of data used to identify infant GBS cases, which may have introduced misclassification. Culture results in the laboratory database (OLIS) were incomplete in the earlier years of the study period, and GBS diagnoses made via polymerase chain reaction (PCR) were also unavailable in OLIS, limiting our ability to identify cases using more sensitive diagnostic methods. As a result, GBS case identification relied primarily on diagnostic codes. Approximately 15% of cases had microbiological confirmation, and among these, 85% also had

a corresponding diagnostic code, suggesting that diagnostic coding likely captured the majority of culture-confirmed cases. This case definition approach was informed by previous real-world evidence studies using administrative data to identify invasive GBS disease,[17] as well as expert input from pediatric and microbiology specialists on our study team.

Nonetheless, misclassification of GBS disease is possible across all three studies, particularly for cases lacking microbiological confirmation. In Study 1, where GBS disease was the outcome, infants born to screen-positive mothers may have been more likely to receive a GBS diagnosis code due to heightened clinical suspicion, even in the absence of laboratory confirmation. This would primarily affect the classification of EOD and could have introduced differential misclassification of the outcome, potentially biasing the observed association between IAP and EOD toward the null. However, our results remained consistent even after excluding GBS cases that were identified solely through diagnostic codes and may have potentially fallen into this category, supporting the robustness of the findings.

In Study 2, where GBS was the exposure, heightened clinical monitoring and increased healthcare-seeking behaviour among parents of infants with GBS disease may have increased the likelihood of NDI detection, particularly for milder impairments. This could have introduced differential outcome misclassification and led to an overestimation of the true association. However, the increased risk of NDI observed among GBS-exposed children was also evident across more severe outcomes—such as moderate-to-severe impairments—where detection is less likely to be influenced by follow-up intensity or parental health-seeking behaviours, supporting the robustness of the association.

In Study 3, where GBS was also the exposure and the outcome was healthcare costs, any exposure misclassification would likely be non-differential with respect to the cost outcome. Because cost data are derived from administrative billing systems and are not influenced by exposure classification, errors in identifying GBS cases would likely dilute observed cost differences between exposed and unexposed infants, biasing estimates toward the null.

Another limitation was the reliance on index hospitalization date and specimen collection date as proxies for the true timing of GBS infection. These were necessary to classify cases as early-, late-, or ultra-late-onset disease, but may not accurately reflect the actual onset of illness. If specimen collection was delayed relative to symptom onset, this could result in misclassification from earlier to later GBS subtypes. In Study 1, where GBS subtype (EOD, LOD, or ULOD) was part of the outcome, this misclassification would likely be non-differential with respect to exposure (e.g., IAP receipt) and would bias subtype-specific estimates toward the null. For example, if some true EOD cases were misclassified as LOD due to delayed specimen collection, this non-differential misclassification would reduce differences in EOD incidence between IAP-exposed and unexposed groups, thereby attenuating the observed protective association between IAP and EOD.

In Study 2, where GBS subtype served as the exposure when examining NDI risk, misclassification between EOD and LOD could obscure potential differences in NDI outcomes. If EOD cases were incorrectly grouped with LOD cases, this would reduce our ability to detect subtype-specific risks. As this misclassification is likely non-differential with respect to the NDI outcome, it would likely bias subtype-specific risk estimates toward the null and obscure

potential differences in NDI profiles between EOD and LOD survivors. Similarly, in Study 3, misclassification of true EOD cases as LOD would lead to underestimation of EOD-related costs and inflation of LOD-related costs, thereby attenuating observed differences in healthcare utilization between subtypes.

7.2.3 Misclassification of other study variables

As with most large database studies, a potential limitation across our work is the risk of misclassification due to coding errors or inconsistencies in data capture. In Study 1, maternal GBS screening results recorded in the birth registry may have changed between the time of initial screening and delivery. If rescreening occurred or results were updated after initial data entry, mothers may have been incorrectly classified as screen-positive or screen-negative. This type of exposure misclassification is likely non-differential with respect to infant GBS outcomes and would bias the observed association between screening and disease incidence toward the null, underestimating the effectiveness of screening in preventing GBS disease.

In Study 2, NDIs were primarily identified using diagnostic codes from hospital and emergency department records, which may not capture milder impairments that do not require acute care. While we attempted to improve case ascertainment by including physician billing and specialist visit data where available, this approach may still underestimate the true prevalence of NDIs. If under-ascertainment was similar between GBS-infected and non-infected groups, the resulting non-differential outcome misclassification would likely attenuate the observed association between GBS exposure and NDI risk. Conversely, if GBS-exposed infants were more closely followed clinically—leading to increased detection of mild impairments—this could have

introduced differential misclassification and inflated the observed association. However, as previously noted, the elevated NDI risk was observed across the full spectrum of severity, including moderate-to-severe impairments, which are less likely to be influenced by healthcare-seeking behavior or intensive of clinical observation.

7.2.4 Restricting to liveborn infants

In all studies, the population was restricted to liveborn infants. As with many perinatal epidemiological studies, our data sources did not capture early fetal losses or miscarriages occurring before 20 weeks' gestation, limiting our ability to account for these outcomes. Additionally, routine culture testing for GBS among stillbirth cases is not standard practice in Canada or other jurisdictions, preventing identification and accurate estimation of GBS-related stillbirths. This restriction is most relevant to Study 1, which aimed to estimate the incidence of GBS disease, as it may have underestimated the broader impact of prenatal GBS exposure. However, this limitation is unlikely to have influenced our assessment of the association between prevention strategies and infant GBS disease, since IAP is not expected to prevent GBS-associated stillbirth, which typically results from infection occurring before labor.[18] Improving surveillance and microbiological testing for GBS in stillbirth cases remains essential to fully understand the burden of GBS and to inform the development and implementation of preventive strategies such as maternal vaccination.

Lastly, the exclusion of infants who died during the follow-up period in Study 3 may have led to an underestimation of total healthcare costs by omitting high-cost end-of-life care.

7.3 Policy implications and future directions

7.3.1 Enhancing GBS surveillance and data infrastructure

The burden of GBS disease in Canada is likely higher than currently recognized due to limitations in surveillance and case capture.[17] To better reflect the true incidence and impact of GBS infections, enhanced data collection and reporting mechanisms are needed. Future research should prioritize validation studies comparing GBS diagnostic codes (e.g., ICD-10) against detailed clinical records to assess their accuracy and reliability.

Existing registries like BORN Ontario, which already collect standardized perinatal and infant health data across the province, are well positioned to enhance GBS surveillance. This could be achieved by adding mandatory fields in the perinatal record specifically for reporting infant GBS disease status, such as whether the infant had culture-confirmed GBS, the timing of diagnosis, and any related complications. Strengthening data-sharing agreements between BORN Ontario and public health agencies, such as Public Health Ontario, could enable better integration of clinical and laboratory data, reducing duplication and improving completeness. Additionally, linking BORN with electronic health records from hospitals and primary care could allow for more timely and accurate identification of GBS cases across the continuum of care, ensuring cases diagnosed outside of birth hospitals or after discharge are not missed. Together, these improvements would support more accurate and comprehensive surveillance of infant GBS disease in Ontario.

Currently, GBS surveillance efforts are primarily focused on EOD and LOD, often excluding ULOD, which occurs beyond three months of age. Expanding surveillance definitions

to include ULOD could offer a more complete picture of the GBS disease burden across infancy. Incorporating these later-onset cases would enhance estimates of GBS-related morbidity and mortality and help inform development and implementation of more effective prevention strategies, including maternal vaccination.

7.3.2 Challenges and future considerations for IAP-based strategies

While screening and IAP currently remains the cornerstone of GBS prevention, challenges related to uptake, compliance, and effectiveness persist.[2,19,20] Failures in IAP delivery have been linked to incorrect antibiotic choice, delayed administration, or suboptimal dosing, which point to the need for strengthened clinical protocols and provider training.[21] A 2017 systematic review also highlights the global inconsistency in IAP policies and implementation, underscoring the need for standardized strategies that ensure more uniform prevention efforts.[3]

Internationally, GBS prevention strategies vary widely. In contrast to Canada, where universal screening is standard practice, some countries like the UK, Denmark and the Netherlands currently employ a risk-based approach to IAP administration.[22] This approach involves administering antibiotics based on clinical risk factors rather than conducting routine universal GBS screening during pregnancy. The GBS3 trial—a large, randomized controlled trial involving 71 hospitals across the UK (ISRCTN49639731)— is currently evaluating the clinical and cost-effectiveness of culture-based screening at 35–37 weeks' gestation, intrapartum PCR testing at the onset of labour, and risk factor-based prevention strategies. Results from the GBS3 trial are expected in the coming months and will inform policy decisions in the UK, with potential implications for international screening guidelines.

While universal GBS screening is recommended in Canada, we observed disparities in screening rates among individuals undergoing caesarean sections without labor (Study 1), which suggests that clinical decision-making may not always align with guidelines. Addressing this gap requires targeted education for both healthcare providers and patients to ensure that screening is not bypassed based on anticipated mode of delivery. Further, the possibility of maternal GBS colonization status changing between screening and delivery raises questions about the reliability of a single third-trimester test.[23] Culture-based screening also carries a risk of false negatives due to intermittent colonization or low bacterial load, which may lead to missed opportunities for IAP administration.[22] Future research should explore the feasibility and benefits of adopting rapid PCR-based testing at the time of labour, which can offer real-time results and improved sensitivity.

Another limitation of IAP-based strategies is their inability to prevent maternal colonization or postnatal transmission, which are key factors in the development of late- and ultra-late-onset disease. While we observed an association between IAP and reduced risk of later-onset GBS disease in our study, further investigation is needed to confirm this finding and understand the underlying mechanisms. Specifically, large studies with complete, high-resolution data on IAP timing, dosage, and antibiotic type are needed. In parallel, long-term follow-up studies are needed to evaluate the potential downstream effects of perinatal antibiotic exposure on infant microbiota, antimicrobial resistance, and other health outcomes, to ensure that the benefits of IAP continue to outweigh any unintended consequences.

From an implementation perspective, ethical and logistical concerns also arise with universal IAP-based strategies. Unequal access to prenatal care or intrapartum services may exacerbate disparities in GBS prevention, particularly in underserved or remote communities. These challenges are further magnified in low-resource countries, where universal screening and IAP administration are often logistically unfeasible.[24] In such contexts, alternative strategies such as a potential maternal GBS vaccine or microbiome-based interventions (e.g., probiotics or bacteriophage therapy)[25,26] may offer more scalable and sustainable solutions in the future. These considerations point to the need for a more nuanced and flexible approach to GBS prevention—one that balances short-term efficacy with long-term safety, addresses variability in healthcare access, and evolves alongside emerging technologies and interventions.

7.3.3 Long-term impacts and high-risk groups

My second study demonstrated that infants who survive neonatal GBS disease are at increased risk for NDIs in early childhood, with particularly elevated risks among boys and preterm infants. These findings highlight the importance of early identification and close developmental monitoring of GBS survivors to facilitate timely intervention and support. Given the critical period of early brain development, NDIs may stem from both the direct effects of invasive infection (e.g., meningitis or sepsis) and secondary consequences such as systemic inflammation, hypoxia, or prolonged hospitalization.[27]

Building on this, my findings also revealed important GBS subtype-specific differences in both neurodevelopmental outcomes and associated healthcare needs. In my second study, infants with EOD were more likely to experience moderate-to-severe NDIs, consistent with the

potential for early systemic infection and inflammation to disrupt critical neurodevelopmental processes.[28] In contrast, LOD survivors were at higher risk for milder impairments, particularly in social and behavioural domains, which may reflect neurological effects of postnatal meningitis.[29] While these impairments may not meet the threshold for moderate-to-severe NDI, they can result in persistent developmental challenges that require behavioural, educational, or outpatient support, thereby generating substantial long-term healthcare needs.[30] These differences were mirrored in my third study, where LOD cases incurred higher attributable healthcare costs that extended beyond the acute period, likely due to delayed diagnoses, complications, and the need for ongoing specialist care, follow-up, and rehabilitation services. Collectively, these findings emphasize the importance of tailored long-term care strategies and the need to consider GBS subtype in both clinical management and ongoing research.

Future research should extend follow-up into adolescence and beyond to capture the full trajectory of GBS-related outcomes and assess functional impacts during school years and adulthood. Long-term data are especially limited for late- and ultra-late-onset cases, as well as for children born preterm who may face compounded developmental risks. The observed sex differences in NDI risk point to underlying biological or social mechanisms that remain poorly understood, emphasizing the need for longitudinal studies that examine sex-specific vulnerabilities in neurodevelopment following neonatal infection.

Preventive strategies remain critical to reducing this long-term burden. In addition to maternal vaccination, which is a promising prevention method, other emerging interventions such as oral probiotics and bacteriophage therapy may offer new avenues to reduce GBS-related

complications, including preterm birth and associated developmental risks.[31] Continued evaluation of these new strategies, alongside efforts to improve post-discharge follow-up and access to early developmental services, is essential in mitigating the lasting impact of GBS disease.

7.3.4 Economic burden and the case for maternal GBS vaccination

Despite the documented clinical burden of infant GBS disease, real-world data on its economic impact remain limited, both within Canada and globally. My third study addressed this gap by providing population-based cost estimates in Ontario, yet comparable data from other provinces and countries are sparse. These estimates are critical in informing economic evaluations, particularly as new preventive strategies become available.

Importantly, healthcare costs represent only part of the picture. My second study found that preterm infants with GBS disease face a significantly higher risk of NDIs, which are known to require long-term medical care, educational support, and social services. These lifelong needs translate into substantial societal costs, including caregiver burden and lost productivity, which are not captured in traditional studies of health system costs. Capturing these downstream costs are essential for a comprehensive understanding of the economic burden of GBS.

Further emphasizing this broader burden of disease, a UK-based survey study (n=531) examining the impact of LOD on families found that many caregivers experienced lasting psychological distress and financial strain as a result of their child's illness.[30] Notably, 67% of

families reported that their child's late-onset GBS infection had affected the planning or enjoyment of subsequent pregnancies. Additionally, 69% reported that they had never heard of GBS prior to their child's diagnosis, highlighting persistent gaps in awareness and the critical importance of preventive strategies. These findings underscore the far-reaching effects of GBS, extending beyond clinical outcomes to include the emotional and informational support needs of affected families.[30]

Maternal vaccination offers a promising strategy to address this multifaceted burden. In addition to preventing both early- and late-onset invasive GBS disease, maternal immunization could potentially prevent GBS-associated preterm births or stillbirths—if administered early enough in pregnancy, ideally between 24 and 34 weeks' gestation[32,33]—a key factor in both NDI risk and healthcare costs.[34] A recent global modeling study found that maternal GBS vaccination could be cost-effective in many settings, particularly if it prevents even a modest proportion of preterm births and associated complications.[35] Investing in maternal vaccination research and surveillance infrastructure will be essential for accurately assessing the full potential public health value of a GBS vaccine and supporting regulatory and policy decision-making worldwide.

7.4 Final conclusions

By examining the health consequences and associated costs of infant GBS disease, this thesis provides novel evidence to inform public health strategies in Canada. Through three large population-based studies, I quantified the burden of GBS disease, evaluated the effectiveness of current prevention methods, described the neurodevelopmental consequences for survivors, and estimated the short-term healthcare costs attributable to infection. Collectively, these studies also

highlight gaps in Canada's current prevention approach and underscore the considerable health and economic burden faced by affected infants and their families.

The evidence presented supports an urgent need for enhanced surveillance, more consistent implementation of existing prevention guidelines, and the development of new strategies—most notably, maternal GBS vaccination. A maternal vaccine has the potential to address several current limitations by preventing both early- and late-onset disease, reducing GBS-related preterm birth and stillbirth, and improving long-term outcomes. As Canada may explore the potential introduction of maternal GBS immunization in the future, the findings from my thesis can help inform future cost-effectiveness analyses, support clinical and public health planning, and contribute to evidence-based policy development should a vaccine become available and recommended for use.

7.5 References

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APPENDIX A: CERTIFICATES OF ETHICAL APPROVAL

All three studies included in this dissertation were reviewed and approved by the following Research Ethics Boards (REBs) and privacy offices:

- Children's Hospital of Eastern Ontario Research Ethics Board (CHEOREB#20/11PE)
- ICES Privacy Office (TRIM 2023-0901-320-001)
- University of Ottawa Research Ethics Board (H-10-24-8241)
- Better Outcomes Registry and Network (BORN) Ontario Project Approval (see below)

IC/ES Data Discovery Better Health

Project Approval Request Form

For Use of Data from Better Outcomes Registry and Network (BORN)

This Project Approval Request Form is used to request and document approval for use of BORN (Niday and BIS) data in an ICES Project. Project approval is required under the agreement between BORN and ICES.

Project teams should email this completed form to the Strategic Partnerships Director, at DataPartnerships@ices.on.ca, with the project proposal and if possible, the dataset creation plan.
Please note "BORN APPROVAL NEEDED" in the email's subject line.

Requests will be reviewed by BORN for approval, facilitated by a Strategic Partnerships liaison. Once approved, BORN will send the approved form back to Strategic Partnerships, after which the Strategic Partnerships liaison would email the fully signed and appoved form back to the respective project team (and carbon copy the Compliance inbox).

PART 1 – PROJECT DESCRIPTION				
Title	Health and Economic Impacts of Infant Group B Streptococcal (GBS) Disease			
Objectives *(brief summary)*	Using real-world Ontario data, this doctoral program of research aims to:1) Measure the incidence of infant GBS disease in Ontario and assess uptake and effectiveness of GBS screening and IAP in preventing EOD; 2) Determine healthcare resource use and costs attributable to infant GBS disease; 3) Compare various GBS prevention strategies with respect to short and long-term health and economic outcomes; 4) Assess longer-term health outcomes following invasive GBS disease.			
Project Proposal	Attached ☒		Pending ☐	
Dataset Creation Plan	Attached ☐		Pending ☒	
Principal Investigator	**Name**	Romina Fakhraei		
	Affiliation	University of Ottawa		
Contact for Questions	Name:		Same as above ☒	
	Email:	[redacted]	[redacted]	
PART 2 - REVIEW & APPROVAL				
ICES *(Director, Strategic Partnerships)*	**Decision**	Approved ☒		Declined ☐
	Name	Sujitha Ratnasingham	SR	
	Date	23/3/22		
BORN *(Manager, Health Outcomes or designate)*	**Decision**	Approved ☒		Declined ☐
	Name	Nicole Roberts	[redacted]	
	Date	March 21 2022		

PART 3 – BORN DATA

Note for Project Teams: *Please list the correct variables and years of data below for Niday and BIS, by referring to the "BORN" entry in the ICES Data Dictionary, datadictionary.ices.on.ca. Niday and BIS cover different years and have different variable names.*

BIS			
Variable Name	**Description**	**Proposed Use (e.g. covariate)**	**Year(s)**
Cohort creation			