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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Summary

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' gestation) 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 1000 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.

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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.

Introduction

Group B *Streptococcus* (*S. 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 and 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.

Methods

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 <500 g, 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 Fig. 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 analyse health care and demographic data, without consent, for health system evaluation and improvement.

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 (≥500 g 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 hospitalisations (medical diagnoses and procedures); the CIHI National Ambulatory Care Reporting System (NACRS) for emergency department visits and outpatient clinics; the MOMBABY database for determining hospitalisation 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 marginalisation 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.

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.

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 cerebral spinal 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 Fig. 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 categorised 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. In rare instances where both blood and CSF cultures were positive within 24 h 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.

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 1000 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 marginalisation 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.

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 utilised multiple imputation.

Role of funding source

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Results

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 Fig. S1A). Of those with complete information (Supplementary Fig. 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 2012–2013), 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% [7692/93,872]), while those with PPROM had the highest (51.6% [2009/3894]). 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).

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 Fig. S1A). In this cohort, we identified 803 infants with GBS disease (1.03 per 1000 livebirths) across laboratory and health administrative databases (Supplementary Fig. 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 (Fig. 1). Incidence (per 1000 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 2012–2013 and 2017–2018, the overall incidence (per 1000 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 Fig. 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 marginalisation was observed. The incidence of GBS (per 1000 livebirths) was nearly three times higher among multiples (2.74) compared to

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	3890/15,937	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]				
2012–2013	108,916/118,607	91.8	25,678/115,444	22.2
2013–2014	109,011/117,424	92.8	26,458/119,764	22.1
2014–2015	111,470/118,188	94.3	24,276/117,107	20.7
2015–2016	111,413/117,710	94.7	24,000/114,814	20.9
2016–2017	111,533/117,541	94.9	23,438/114,384	20.5
2017–2018	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	7262/8646	84.0	1663/8734	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	6914/6991	98.9	931/4405	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 labour (spontaneous or induced)	85,588/90,105	94.5	21,345/88,304	24.2
Caesarean section without preceding labour	73,740/94,441	78.1	7692/93,872	8.2
Pre-existing maternal health conditions[e]				
Asthma	24,694/26,466	93.3	5929/26,193	22.6
Diabetes	5259/5997	87.7	1602/5984	26.8
Chronic hypertension	4929/5439	90.6	1274/5514	23.1
Heart disease	670/718	93.3	153/720	21.3
Thyroid disease	27,795/29,524	94.1	6267/28,709	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	2036/2925	69.6	300/2915	10.3
PROM	6538/6866	95.2	2050/6837	30.0
PPROM	2851/3830	74.4	2009/3894	51.6
Gestational diabetes	40,847/44,216	92.4	9669/43,567	22.2
Preeclampsia	5433/6047	89.9	1535/5992	25.6
Eclampsia	386/429	90.0	89/406	21.9
Gestational hypertension	23,287/24,862	93.7	6118/24,614	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	3583/17,606	20.4

(Table 1 continues on next page)

Characteristic	No. screened/total eligible[a]	Screening rate (per 100 eligible pregnancies)	No. received IAP/total eligible[a]	IAP rate (per 100 eligible pregnancies)
(Continued from previous page)				
Substance use during pregnancy[f]				
Yes	12,971/14,576	89.0	3504/14,631	24.0
No	621,886/662,137	93.9	138,157/653,073	21.2
Missing	28,934/29,779	97.2	5959/27,428	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
Neighbourhood 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	1942/2136	90.9	478/2147	22.3
Marginalization indices, quintile[g]				
Missing	6897/7709	89.5	1822/7765	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	8387/39,144	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	8912/49,471	18.0
Healthcare provider				
Midwife	67,816/73,176	92.7	12,694/72,233	17.6
CNS, NP, registered nurse	4155/4345	95.6	969/4269	22.7
Family doctor	54,757/56,465	97.0	12,614/55,687	22.7

(Table 1 continues on next page)

Characteristic	No. screened/total eligible[a]	Screening rate (per 100 eligible pregnancies)	No. received IAP/total eligible[a]	IAP rate (per 100 eligible pregnancies)
(Continued from previous page)				
Obstetrician	515,292/549,535	93.8	116,958/540,517	21.6
Other healthcare provider, resident, surgeon	16,768/17,675	94.9	3568/17,760	20.1
Unattended	820/991	82.7	15/1024	1.46
Missing	4183/4305	97.2	802/3642	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 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. [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 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.**

singletons (0.97), and over five times higher among preterm births (4.27) compared to term births (0.76).

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 h (Fig. 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 h) 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) vs. 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).

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 1000 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 Fig. S4). Results remained consistent across all subcategories of GBS disease (Supplementary Table S8).

The incidence of EOD (per 1000 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

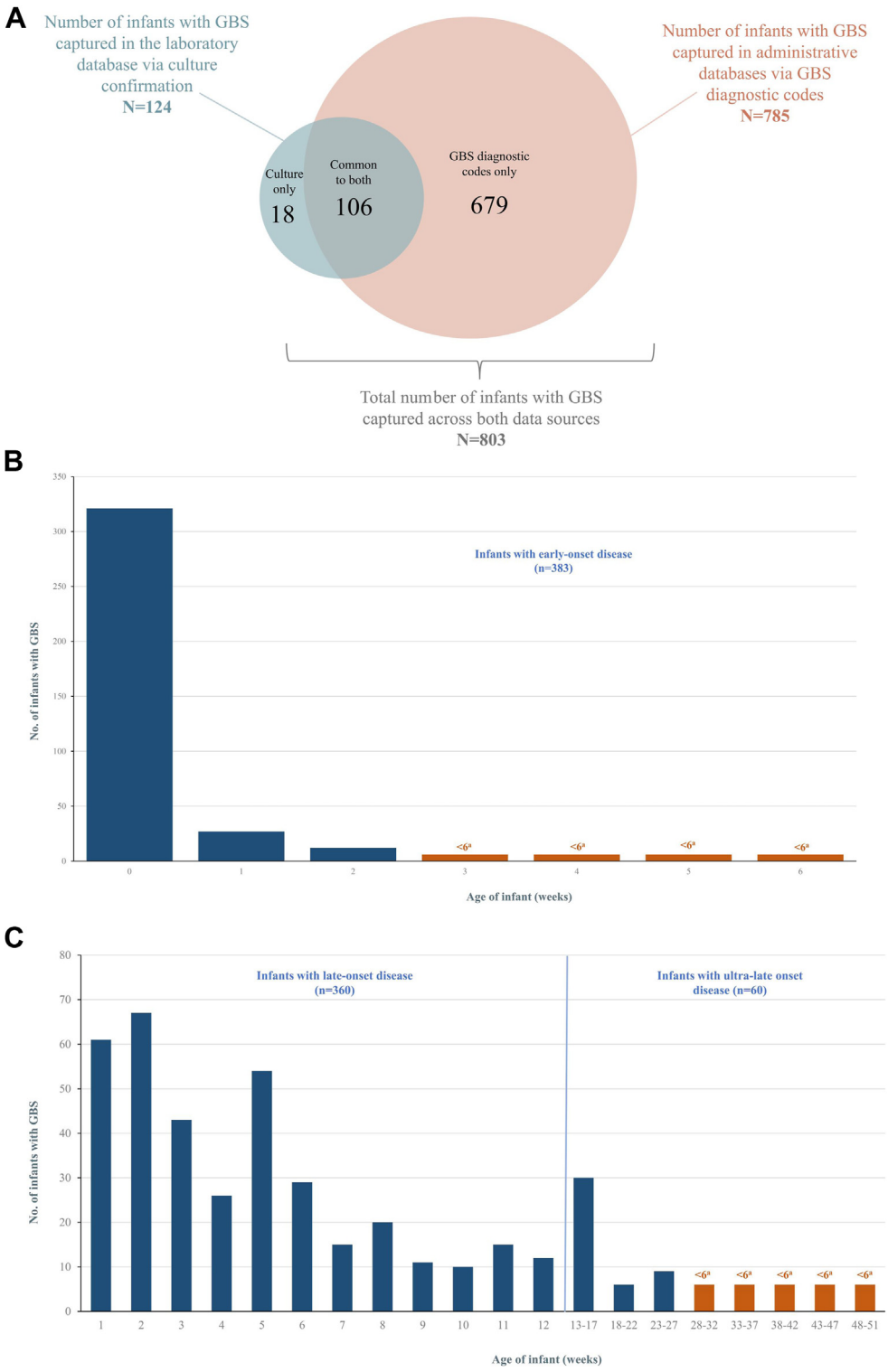

Fig. 1: **Distribution of infant Group B Streptococcus (GBS) disease occurrences by data source and infant age.** (A) Venn diagram illustrating overlap of cases with respect to laboratory (OLIS) and health administrative (DAD, NACRS) databases. (B) Histogram showing infants with early-onset disease by 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).

Characteristic	All livebirths No. (col %)	No. infants with GBS[a]	Incidence of GBS, per 1000 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]				
2012–2013	131,363 (16.9)	161	1.23 (1.04, 1.41)	1.20 (0.96, 1.52)
2013–2014	130,100 (16.8)	152	1.17 (0.98, 1.35)	1.15 (0.91, 1.45)
2014–2015	129,809 (16.7)	114	0.88 (0.72, 1.04)	0.86 (0.67. 1.11)
2015–2016	128,974 (16.6)	130	1.01 (0.83, 1.18)	0.99 (0.78, 1.26)
2016–2017	128,105 (16.5)	116	0.91 (0.74, 1.07)	0.89 (0.69, 1.14)
2017–2018	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	9077 (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	7386 (0.1)	13	1.76 (0.80, 2.72)	1.71 (0.99, 2.96)
Heart disease	833 (0.1)	<6	–	–
Chronic hypertension	7294 (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	1115 (0.1)	<6	–	–
Placenta previa	3799 (0.5)	<6	–	–
PROM	7267 (0.9)	9	1.24 (0.43, 2.05)	1.20 (0.62, 2.31)
PPROM	7621 (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	8316 (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)

(Table 2 continues on next page)

Characteristic	All livebirths No. (col %)	No. infants with GBS[a]	Incidence of GBS, per 1000 livebirths (95% CI)[a]	Crude IRR[a,b] (95% CI)
(Continued from previous page)				
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
Neighbourhood 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	2358 (0.3)	<6	–	–
Marginalization Indices, quintile[h]				
Missing	8393 (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)

(Table 2 continues on next page)

Characteristic	All livebirths No. (col %)	No. infants with GBS[a]	Incidence of GBS, per 1000 livebirths (95% CI)[a]	Crude IRR[a,b] (95% CI)
(Continued from previous page)				
Apgar score (5 min)				
0–3	2943 (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	8224 (1.1)	18	2.19 (1.18, 3.20)	2.64 (1.65, 4.22)
5-min 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 2: **Incidence of infant Group B *Streptococcus* (GBS) disease by maternal and infant characteristics (Cohort 2).**

LOD/ULOD, which were similar in screen-negative births that received IAP (0.25 per 1000 livebirths) and did not receive IAP (0.23 per 1000 livebirths). Similarly, in infants born to screen-negative mothers, the rates of GBS-meningitis were comparable in those who received (0.12 per 1000 livebirths) and did not receive (0.13 per 1000 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 Fig. S5).

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 h)	101 (12.6)	67 (17.5)	34 (8.1)
Long-term (≥96 h)	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-min 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 3: **Clinical characteristics of infants with Group B *Streptococcus* (GBS) disease identified in laboratory and health administrative databases (n = 803).**

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 1000 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

	No. GBS infants/total[a,b]	Incidence of GBS, per 1000 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 1000 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 Fig. 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.

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.**

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 sub-categories 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 1000 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 h. While an earlier Canadian study reported a lower rate of GBS (0.58 per 1000 livebirths in infants <90 days),[18] recent provincial estimates reported rates closer to 1.8 per 1000 livebirths.[19] Only 15% of infants with GBS in our study were confirmed through culture. This was likely primary 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 1000 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 vs. 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.

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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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2024.100914.

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