

RESEARCH PAPER



The burden of infant group B streptococcal infections in Ontario: Analysis of administrative data to estimate the potential benefits of new vaccines

James Hartley^a, Ye Li^b, Liz Kunkel^a, and Natasha S. Crowcroft^a

^aApplied Immunization Research and Evaluation, Public Health Ontario, Toronto, Ontario, Canada; ^bKnowledge Services, Public Health Ontario, Toronto, Ontario, Canada

ABSTRACT

Group B *Streptococcus* (GBS) is a leading bacterial cause of neonatal sepsis and meningitis in many countries as well as an important cause of disease in pregnant women. Currently, serotype-specific conjugate vaccines are being developed.

We conducted an epidemiological analysis of health administrative data to estimate the burden of infant GBS disease in Ontario, Canada and combined these estimates with literature on serotype distribution to estimate the burden of disease likely to be vaccine-preventable.

Between 1st January 2005 and 31st December 2015, 907 of 64320 health care encounters in Ontario in patients under 1 year old had codes specifically identifying GBS as the cause of the disease, of which 717 were under one month of age. In addition, application of epidemiological data to the remaining patients allowed us to estimate a further 2322 cases and among them 1822 were under one month of age. In the same period, 579 confirmed neonatal invasive GBS cases in patients up to one month of age were reported to public health. Depending on serotype distribution, vaccination coverage and early versus late onset disease (0–6 days and 7–90 days of age respectively), the preventable fraction ranged widely. With a vaccine that is 90% effective and 60% immunization coverage, up to 52% of early and late onset disease could be prevented by forthcoming vaccines.

GBS is under-reported in Ontario. Uncertainty about the potential impact of vaccine indicates that further analysis and research may be needed to prepare for policy-decision making, including clinical validation studies and an economic evaluation of GBS vaccination in Ontario.

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Introduction

Group B *Streptococcus* (GBS), or *Streptococcus agalactiae*, remains a leading cause of neonatal sepsis and meningitis in many countries as well as an important cause of disease in pregnant women.¹ In addition, it also causes a range of conditions in vulnerable non-pregnant adults.² Infection in neonates can lead to both death and long term sequelae of meningitis,³ and disease in affected non-pregnant adults carries a high mortality.² The use of targeted intrapartum antibiotics has had some success in reducing the burden of early-onset (under seven days of life) GBS disease (EOD), but has no impact on late onset neonatal disease (LOD) or disease in older children and adults.⁴ Thus, improved control of this pathogen is desirable. One potential strategy is vaccination, and several vaccine candidates are currently under development and have been shown to be safe and immunogenic in trials.^{4–6} It has also been shown to be potentially cost effective in recent modelling analyses.⁷

Screening of all pregnant women and intrapartum antibiotic treatment for those who are positive is currently recommended in Ontario.⁸ Whilst GBS causing neonatal disease in infants up to 28 days of age has been a reportable disease in Ontario since 1995, other forms of infection are not reportable.⁹ In addition, the reporting rate of neonatal GBS amongst physicians has not been assessed. Understanding the burden of GBS disease in Ontario is important to evaluate the potential impact of

implementation of a vaccine, and may also serve as a model for other high income settings. Assessing the burden can be challenging because GBS causes multiple clinical syndromes and those syndromes have multiple infectious causes. The coding of administrative and other data does not always permit identification of specific infectious causes.¹⁰ We thus use a combination of epidemiological and administrative data to estimate the burden of GBS in Ontario.

Results

Reported incidence of GBS in infants

The Integrated Public Health Information System (iPHIS) contained records of 579 cases of GBS in infants up to 28 days of age in Ontario between January 2005 and December 2015. 551 of these were so-called EOD in infants aged 0–6 days, and 28 were cases of LOD in infants 7–28 days. This equates to an incidence of 50.1 cases of EOD per year and 2.54 cases of LOD per year, or 0.36 and 0.018 cases per 1000 live births respectively.

Incidence of confirmed GBS in administrative clinical data

It may be the case that not all confirmed cases of GBS are reported to iPHIS. In order to interrogate this, we searched administrative data in the Discharge Abstract Database

(DAD) and National Ambulatory Care Reporting System (NACRS) for clinical encounters associated with ICD-10 codes denoting the confirmed presence of GBS in infants up to 28 days of age in Ontario between January 2005 and December 2015. The full criteria of our search are presented in the Methods below.

In this time period, we identified 717 cases of GBS, 590 EOD and 127 LOD (Table 1). This equates to an average of 65.2 cases/year and an incidence of 0.47/1000 live births.

Table 1. NACRS/DAD patients with GBS confirmed codes in total over the eleven years studied (incidence/1000 live births).

	0– 6 days	7– 28 days	29– 365 days	Total
Sepsis	498 (0.33)	60 (0.04)	89 (0.06)	647 (0.7)
Pneumonia	63 (0.04)	4 (0.003)	3 (0.002)	70 (0.045)
GBS specific code with no specified condition	29 (0.02)	63 (0.04)	98 (0.06)	190 (0.12)
Total	590 (0.39)	127 (0.083)	190 (0.12)	.59

Table 2. The epidemiology and papers table.

Syndrome	Identifying ICD-10-CA codes	Proportion caused by GBS	References
Early onset neonatal infection (0–6d)	P36, A021, A327, A392, A394, A400, A40, A41, A427, A483, B377, R572, R650, R651	16%	Cohen-Wolkowicz et al 2009 ²⁸ Stoll et al 2011 ²⁹
Late onset neonatal infection	P36, A021, A327, A392, A394, A400, A40, A41, A427, A483, B377, R572, R650, R651	12%	Cohen-Wolkowicz et al 2009 ²⁸ Stoll et al 2002 ³⁰ Byrington et al 2003 ³ Biondi et al 2013 ³ Greenhow et al 2014 ³³ Watt et al 2010 ³⁴ Ashkenazi-Hoffnung et al 2011 ³⁵ Cantey et al 2015 ³⁶ Cantey et al 2016 ³
Meningitis	G00, G01	< 1m: 18% 1m to < 3m: 39%. 3m to < 3y: 11%.	Nigrovic et al 2008 ³⁷ Stoll et al 2011 ²⁹
Congenital pneumonia	P23	-	No epidemiological data including GBS identified
Cellulitis and soft tissue infection	L03	0.6%	Noel et al 2008 ⁴⁰ Jones et al 2003 ⁴¹ Lark et al 2001 ⁴³ Rantala et al 2009 ⁴⁴
Osteomyelitis	M86	4%	Goergens et al 2005 ⁴⁵
Urinary tract infections	N10, N30.0	2%	Imirzalioglu et al 2008 ⁴⁶ contained GBS Laupland et al 2007 ⁴⁷ , reviewed in Foxman 2010. ⁴⁸ Ulett et al 2009 ⁴⁹ Bouza et al 2001 ⁵⁰ Jones et al 1999 ⁵¹ Mathai et al 2001 ⁵² Grude et al 2001 ⁵³ Flores-Mireles et al 2015 ⁵⁴ Zhan et al 2000 ⁵⁵
Peritonitis	K65.0	-	No epidemiological data available
Septic arthritis	M00	13%	Goergens et al 2005 ⁴⁵ Bono et al 2015 ⁵⁶ Binard et al 2006 ⁵⁷ Nolla et al 2003 ⁵⁸ Louthrenoo et al 2014 ⁵⁹ Van de Beek et al 2004 ⁶¹ Sambola et al 2002 ⁶² Durand 2017 ⁶³
Endocarditis	I33.0	1.70%	Jackson et al 2003 ⁶⁴
Endophthalmitis	hH44.0	5–10%	No epidemiological data including GBS available
Pneumonia	J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18,	-	No epidemiological data including GBS available
Pericarditis/myocarditis	I301, I400	-	No epidemiological data including GBS available

Using administrative data, we are also able to search for the infections occurring up to one year of age. In the 29–365 day age bracket, there are a further 190 cases of disease (Table 1).

Estimated further incidence of GBS

In addition to cases of GBS confirmed by laboratory investigation, there are cases that are clinically compatible with GBS but lacking laboratory confirmation. In order to assess this hidden burden of disease, we used epidemiological data to assess the proportion of various conditions likely to be caused by GBS. We then applied these proportions to the number of cases of the conditions observed in DAD/NACRS for the target time period, targeting only cases where no specific pathogen had been identified.

Reviewing the literature for our epidemiological data, we found data on the role of GBS in 13 different syndromes applicable to infants. We found sufficient sources to estimate the proportion of the syndrome caused by GBS in nine of these syndromes (Table 2).

Applying these proportions to the DAD/NACRS cases under 28 days of age with the corresponding syndrome but without an assigned pathogen gives an estimated further

Table 3. Additional estimated GBS cases from NACRS/DAD (incidence per 1000 live births).

	0–6 days	7–28 days	29–365 days	Total
Sepsis	1497.3 (1.06)	284.04 (0.20)	451.56 (0.32)	2232.9 (1.574)
Meningitis	8.82 (0.01)	27.3 (0.02)	14.74 (0.01)	50.86 (0.036)
Cellulitis	0.174 (0.00)	1.23 (0.00)	14.598 (0.01)	16.002 (0.01)
Renal	0.08 (0.00)	0.7 (0.00)	7.54 (0.01)	8.32 (0.01)
Endophthalmitis	0.35 (0.00)	1.7 (0.00)	3.85 (0.00)	5.9 (0.00)
Septic arthritis	0.13 (0.00)	0.26 (0.00)	4.81 (0.00)	5.2 (0.00)
Osteomyelitis	0.12 (0.00)	0.24 (0.00)	2.8 (0.00)	3.16 (0.00)
Infective endocarditis	0.034 (0.00)	0 (0.00)	0.085 (0.00)	0.119 (0.00)
Total	1507.008 (1.06)	315.47 (0.22)	499.983 (0.35)	2322.461 (1.64)

Table 4. Total NACRS/DAD patients with GBS over 11 years studied (incidence per 1000 live births).

	0–6 days	7–28 days	29–365 days	Total
Sepsis	1995.3 (1.31)	344.04 (0.23)	540.56 (0.36)	2879.9 (1.89)
No specified condition	29 (0.02)	63 (0.04)	98 (0.06)	190 (0.12)
Pneumonia	63.174 (0.04)	5.23 (0.00)	17.598 (0.01)	86.002 (0.06)
Meningitis	8.82 (0.01)	27.3 (0.02)	14.74 (0.01)	50.86 (0.03)
Cellulitis	0.174 (0.00)	1.23 (0.00)	14.598 (0.01)	16.002 (0.01)
Renal	0.08 (0.00)	0.7 (0.00)	7.54 (0.00)	8.32 (0.01)
Endophthalmitis	0.35 (0.00)	1.7 (0.00)	3.85 (0.00)	5.9 (0.00)
Septic arthritis	0.13 (0.00)	0.26 (0.00)	4.81 (0.00)	5.2 (0.00)
Osteomyelitis	0.12 (0.00)	0.24 (0.00)	2.8 (0.00)	3.16 (0.00)
Total	2097.008 (1.38)	442.47 (0.29)	689.983 (0.45)	3229.46 (2.12)

Table 5. Estimated proportion of Ontario serotypes covered by different vaccines.

Vaccine serotypes covered in vaccine	References concerning vaccine	Estimated Ontario proportion (%)		
		Infants 0–3d	Infants 3–90d	Children (90d–18y)
Ia, Ib, III	^{5,6,11}	73.5	89.9	87.5
III	^{5,6,12}	44.1	74.6	37.5
V	¹²	14.70	5.10	0
II	¹³ (secondary source)	8.8	1.7	0
Ia, Ib, II, III, V	hypothetical	97	96.7	87.5

1822.5 cases of likely GBS disease, 1507 EOD and 315.5 LOD (1.0 and 0.21 per 1000 live births). A further 499.98 (0.33/1000 live births) can be estimated in the 29 to 365 day old group (Table 3).

This gives a grand total of 2539.5 cases of GBS in 0–28 day year olds combining those with GBS specific codes with the estimated number of missed cases – 230.8 per year and 1.8/1000 live births (Table 4). This is considerably more than the 52.6 and 0.38/1000 taken from iPHIS data.

Vaccine impact

Combining the above estimates of GBS disease burden with estimates of 90% vaccine efficacy against serotypes included in the vaccine (Table 5, further details in Methods) and a population coverage of 90% suggests that a vaccine may avert up to 116.4 cases of GBS per year in 0–6 day olds and 35.12 cases in 7–28 day olds, with a further 54.8 cases in 29 to 395 day olds. Comparing 3-

component, monocomponent serotype III and a universal vaccine, estimates of the benefit for different age groups would vary from 0–53% (Table 5).

Discussion

This study represents one of the first large scale population-based evaluations of the total burden of disease caused by GBS in a developed nation setting taking account of non-laboratory confirmed cases and including cases up to the age of 1 year, thus giving a unique perspective on the amount of illness caused by this pathogen. Our use of health administrative data as well as legally mandated reports of cases and of an epidemiological model to estimate the number of non-culture confirmed cases aims to overcome the limitation of incomplete reporting of neonatal GBS and of the lack of microbiological confirmation or documentation for a proportion of all GBS infection. Our approach is likely more sensitive than previous methods, though it may be more likely to overestimate incidence, particularly if there is positive selection bias in the literature on which our estimates were based. The integration of recently published data on the serotype distribution around Ontario with our data on disease burden also allows for an up-to-date evaluation of potential vaccine program impact.

Our findings suggest that the actual burden of GBS disease in neonates may be somewhat higher than previously believed, and higher than that suggested by legally mandated reporting. Comparing the data from iPHIS to Table 1 reveals that 38 culture-confirmed infant GBS cases were not captured by the mandatory reporting system, 6% of the total number. In addition, further non-culture confirmed cases and cases in infants up to one month of age were not captured – an extra 1962 cases. Furthermore, cases with GBS occurred in every month of age up to 1 year of age. Thus, whilst the mandatory reporting gives the incidence of GBS disease in up to 28 day olds to be 0.38/1000 live births, our estimate gives an upper bound of 1.8/1000 live births. This suggests two things – first, GBS surveillance may need strengthening in Ontario if a vaccine is implemented, including increased use of culture and serogrouping and an extension of the age group included under surveillance. Second, the impact of a GBS vaccine in Ontario would likely be greater than suggested by current surveillance. A further observation is that this high estimate of GBS burden in Ontario occurs in the context of good screening and intrapartum antibiotic practices; other areas with less screening and antibiotic coverage may have an even higher hidden burden of GBS.

This increased incidence is especially relevant given recent estimates of the cost effectiveness of a GBS vaccine in the United States by Kim and colleagues.⁷ The amount of morbidity and mortality a vaccine prevents, and hence its cost effectiveness, rises with the incidence of the disease: whilst at an incidence of EOD of 0.7/1000 births, a 90% effective vaccine is predicted to save 4876 Quality Adjusted Life Years (QALYs) each year, increasing the incidence to 1.1/1000 enlarges this number to 6762 at a lower cost per QALY. Further QALYs can be saved, though at additional

cost, by combining vaccination with current screening programmes. Our estimates of incidence are higher than the upper end of the incidence range used in this model, raising the possibility of an even larger vaccine impact.

This said, there are a number of limitations in this study and further work which needs to be done. One aspect of this study was to review the epidemiological literature providing data about the aetiology of a number of syndromes GBS has been reported to cause. However, for some key syndromes, no epidemiological studies which reported the contribution of GBS in particular were available, and these were therefore excluded; this was the case for pneumonia, congenital pneumonia, chorioamnionitis and septic abortion. Together, these syndromes accounted for 36,899 records of clinical encounters potentially caused by GBS in under 1-year-olds – 57% of the total. In particular, pneumonia accounts for 34,209 encounters (53% of the total). The proportion of cases of pneumonia which is caused by GBS is likely small, but pneumonia has a high burden, so the omission of estimates of numbers of GBS pneumonia cases may cause systematic under-estimation of GBS burden. This highlights a gap which potential further research could fill. Obtaining this information would also allow refinement of the estimate yielded by these methods.

An important further limitation is introduced by the methodology of applying published epidemiological data to administrative data. Whilst every effort was made to select publications in which the studied patient population would be similar to Ontario, it is likely that differences will exist. Some epidemiological studies only focussed on culture confirmed cases of conditions rather than clinically diagnosed; some argue this may underestimate the burden of GBS disease.¹⁴ Moreover, the proportion of cases attributable to GBS is assumed to be constant over Ontario, which may not be accurate, especially given the observed year-to-year variation. The same limitation may apply to the assumption that the GBS serotype distribution recorded for the Greater Toronto Area is representative of Ontario as a whole. However, a meta-analysis of serotype distribution globally across three decades found a relatively consistent pattern of serotype predominance across multiple continents, with serotype III followed by Ia universally constituting the majority of disease in infants.¹⁵ Likewise, a separate study looking at GBS serotypes in adults in East Africa found a similar pattern to that in adults in Toronto, with a preponderance of disease caused by serotypes III and V followed by Ib, II and IV.¹⁶ This homogeneity over global and long term temporal scales suggests that it is reasonable to assume homogeneity between Toronto and Ontario as a whole. Furthermore, the application of epidemiological proportions to health care administrative data may create bias: we apply the proportions to a subpopulation where no infectious cause for the disease was positively identified by culture. However, they were necessarily created from a different subpopulation where at least a proportion of cases were culture positive. The proportion of GBS in the “uncultured” case population might be different to the “total” case population, but we cannot say whether it might be higher or lower. The nature of the data used also introduces a number of limitations to the study. The diagnosis codes used in IntelliHEALTH data may not always be

accurate or complete, and data quality may vary by region. Challenges in analysis are created by records with multiple diagnosis codes corresponding to different syndromes, and by records without associated patient numbers making it hard to tell whether they are duplicates. We chose to take a conservative approach by excluding such records. This may also introduce some bias and under-estimate some outcomes more than others if certain syndromes are associated with multiple codes. Finally, our estimate of the impact of a vaccine uses the assumption that a licensed vaccine will have an efficacy of 90%. Whilst this is not unreasonable as it is a goal of many vaccines, it may be that vaccines of lower efficacy coupled with an excellent safety profile would still be recommended and widely used. In this case, the impact of the vaccine in terms of cases averted would be lower. Using our simple approach, the impact would be reduced in proportion with the efficacy of the vaccine. For example, if vaccine efficacy were 80% rather than 90%, all estimates of benefit would be reduced by 10%.

Reassuringly, a recent paper in CID by Seale and colleagues made similar estimates to ours using a different approach which somewhat validates our methods.¹⁷ Rather than working from data recording the number of cases of different clinical conditions, the authors started with demographic data and used epidemiological data on the colonisation of mothers by GBS and probabilities of exposure leading to neonatal disease to calculate likely case rates. This compartmental model has the advantage of requiring little direct data from regions studied, allowing them to make estimates of worldwide GBS incidence including in countries where surveillance is poor. They also included in their model estimates of GBS burden in terms of stillbirth and ongoing impairment following disease. Overall, they produced an estimate of 10900 cases of EOD and 6000 cases of LOD in developed countries in 2015, for an estimated 13.4 million live births. This corresponds to incidences of 0.81 and 0.44 per 1000 live births respectively, compared to ours of 1.38 and 0.29 for Ontario. Their model explicitly estimated “invasive neonatal disease” – primarily meningitis, sepsis, or bacterial pneumonia. It did not include the rare conditions covered by our method – cellulitis, urinary tract infections, septic arthritis, endophthalmitis and osteomyelitis. However, as these contributed only 5 of the 2787 cases we estimated, this is unlikely to account for the higher overall incidence in our model. The discrepancy may thus be due to region-specific differences in GBS occurrence, in which case our use of local data would render our estimate more reliable for Ontario, or alternatively because of differing bias and weaknesses of the two models.

Overall, then, the estimates of GBS burden created in this study are just that – estimates. They highlight gaps and opportunities for further research and place bounds on likely vaccine impact, but are only a starting point for more precise estimates of burden.

Our review of the literature provided bounds on the impact of a vaccine in terms of the proportion of disease averted. However, as noted above, it does not take account of herd immunity, the amplified benefit that immunising mothers to protect multiple children may have, antibiotic resistance in the face of continued screen-and-treat strategies, or changing

serotype prevalence in the face of the vaccine (as seen with pneumococcal disease). A more full assessment would require these elements, and may require more dynamic models to do so.

Furthermore, fully judging the value of introducing a new vaccine will require a comprehensive cost-benefit analysis. Oster et al 2014 estimated the cost of a trivalent Group B streptococcus vaccine to be US\$91,321 per QALY, in the same range as other vaccines such as teenage meningococcal vaccines. They concentrated solely on neonatal GBS disease, using a sophisticated model to estimate the morbidity and mortality caused not only by the primary disease but by complications such as neurological sequelae. A more recent paper by Kim and colleagues has considered the cost effectiveness of a pentavalent vaccine in further detail as discussed above.⁷ However, extending the conclusions from the US to the Canadian healthcare system might not be valid.

Our paper provides the data to create rigorous estimates of the type found in Oster et al for the Canadian context. The specific data on Ontario matched with specific data on the GBS serotype distribution in the region provide a robust estimator of the proportion of disease a vaccine might prevent. We also consider a wider range of vaccine efficacies, in line with more recent research on the vaccine itself; and furthermore, we set the scene for inclusion of data and estimates on all age groups which might be affected by vaccination rather than only neonates. Using this research to complete a rigorous cost-benefit analysis is the next step in evaluating the GBS vaccine for use.

Conclusions

Our research has three main outcomes. First, we have assessed the burden of GBS disease in the under one year old population in Ontario and estimated it to be higher than that drawn from official public health surveillance data. This highlights the need for changes to surveillance to consistently capture this burden. Second, in a review of the literature, we have identified gaps in our current knowledge of the epidemiology of GBS, which may be filled by further studies. Third, we have estimated the likely impact of various GBS vaccines, setting the scene for a more extensive cost-benefit analysis for making decisions concerning vaccine implementation.

Patients and methods

The overall approach we took was to combine administrative data with statistics from specific epidemiological studies to estimate the full impact of GBS. This information was then combined with a review of published literature of serotype prevalence and vaccine efficacy to estimate the value of vaccination for GBS in Ontario in different patient groups.

Patient data

The IntelliHEALTH information system was used to obtain patient data.¹⁸ Two kinds of data were obtained – inpatient discharge summary data from the Discharge Abstract Database System (DAD) and outpatient data from the

National Ambulatory Care Reporting System (NACRS). The populations in these databases include ambulatory patients, hospital in-patients, and patients visiting physicians in their practices or clinics, all occurring within the region of Ontario, Canada.¹⁹ The data available in these systems is in the forms of individual encounters with the health care system (as opposed to entries for individual patients). Duplicate records of the same episode – taken to be records of the same patient appearing within 30 days of a previous record's discharge date, or admission date if discharge date was unavailable, or within 30 days of an admission of a patient with the same hospital, age in days and diagnosis if a patient identifier was not available – were eliminated. Data was restricted to the eleven year period from January 2005 to 31st December 2015. Data in these systems was extracted by ICD-10-CA diagnosis code, using a range of codes audited by each author and designed to capture the full range of syndromes potentially caused by GBS (Table 2).

In addition to the above DAD and NACRS data, the Integrated Public Health information System (iPHIS) was used to obtain data on all cases of confirmed or likely invasive group B streptococcus infections in neonates mandatorily reported to public health units in Ontario, with cases defined as laid out in Appendix B of the Ontario Infectious Diseases protocol.²⁰

Published epidemiological data

As part of this study, we carried out two separate searches of literature. The first focused on finding epidemiological studies which provided data on what proportion of given clinical syndromes were likely to be caused by GBS. The second took a wider view and aimed to review the current state of vaccine development, likely vaccine effectiveness, and the serotype distribution of GBS in Ontario. Both searches were conducted on PubMed and Medline. Appendix 1 gives details of the search terms used in each search, and Table 2 catalogues the results pertaining to the first search (proportions of syndromes caused by GBS). An expanded version of Table 2 giving details on each paper included is available in Appendix 2.

Statistical analysis

Analysis of data was performed using R.²¹

The patient records from the IntelliHEALTH data was divided by ICD-10-CA code into groups depending on the designated syndrome, as shown in Table 2.

Some patients were expected to be associated with multiple diagnosis codes signifying more than one of the syndromes delineated in Table 2. Determining which of these diagnosis codes was the most important clinically was not possible with the data available. After considering several methods to accommodate these records, it was decided to simplify the analysis by excluding them.

Subsets were then analysed by dividing them into age specific groups and applying epidemiological data to estimate GBS case numbers as above. Incidence rates were calculated by combination with census data for Ontario 2005 to 2015, thus using the figure of 139203.3 live births per year on average over that time.

Estimation of vaccine coverage

We estimated the likely coverage a GBS vaccine would achieve in Ontario by modelling it as:

- similar to current coverage of GBS screening in pregnant mothers
- likely to be similar to that of other vaccines given in pregnant e.g. flu and pertussis
- similar to other childhood and adult vaccines given (not specifically in pregnancy).

Data relevant to each of these models was obtained by searching PubMed for publications which measured the uptake of the comparative vaccines, or looking at the online vaccine uptake data for Canada or comparable developed countries.

Vaccination coverage in pregnancy in Canada are poorly documented. However, during the 2009 H1N1 epidemic it was shown that uptake of a vaccine for the pandemic strain in pregnant women reached 40%,¹³ likely providing a high estimate of normal levels because of increased concern and attention to the pandemic strain. More complete vaccine uptake records can be found for other comparable nations such as the US and UK. In the UK, average coverage for flu vaccination in pregnancy was found to be 42.3% between September 2015 and January 2016, whilst pertussis vaccination in pregnancy averaged 56.4% over April 2014 to March 2015.^{11,12} Meanwhile, in the US, influenza vaccine uptake in pregnancy during October 2014-January 2015 was 50.3%, and 53.4% of recently pregnant women across 16 states and New York City in 2011 reported being vaccinated against pertussis, including 13.9% before pregnancy, 9.9% during pregnancy, and 30.5% after delivery.²² Considering these numbers led us to our wide estimate of GBS vaccine coverage in pregnant mothers as likely between 20 and 80%.

GBS serotype distribution in ontario

GBS serotype distribution in Ontario can be estimated from recent data looking at the serotypes causing disease in the greater Toronto area, as published by Teatero et al.²³ Of the ten GBS capsular serotypes (Ia, Ib and II-IX), they found disease in humans to be dominated by three (III, V and Ia). The relative predominance of each strain varied by age of patient.

Vaccine serotypes

Various vaccines for GBS are in development, as discussed in recent reviews.^{4,24} The most advanced candidate, found safe and immunogenic in phase 1b/2 trials, is a toxoid conjugated trivalent vaccine covering serotypes Ia, Ib and III.^{5,6,25} This would potentially prevent 73.5% and 89.9% of 0–3 day old and 3–90 day old in infants respectively, as well as 87.5%, 57.4% and 48.7% of childhood, adult and older adult disease. Other studies have also looked at vaccines including serotypes II and V,^{24,26} and a pentavalent vaccine covering these in addition to Ia, Ib and III may also be feasible, providing

extended protection particularly against disease in adults (Table 5).

Vaccine efficacy and effectiveness

As phase 3 trials have not been completed, vaccine efficacy is as yet unknown. We assumed that any GBS vaccine to be implemented will have at least 90% efficacy for the direct effect of maternal immunization at preventing disease caused by serotypes included in the vaccine in infants up to 1 year of age.

The estimates of vaccine efficacy, coverage, and coverage of serotypes in Ontario can be combined to produce an estimate of the preventable proportion of disease as suggested in O'Loughlin et al.²⁷

$$\text{Proportion Preventable} = \text{Efficacy} (\%) \times \text{Coverage} (\%) \times \text{SP}$$

Where SP represents the proportion of disease accounted for by serotypes included in the vaccine. Using this formula we conducted a sensitivity analysis using a range of potential vaccine coverage values, high and low estimates of disease and vaccine efficacy, and proportions of serotypes covered by different vaccine formulations at different ages (from Table 5). We assessed the sensitivity of the results to the vaccine type by assessing the difference in proportional impact between the different vaccines (Table 5) with the theoretical vaccine that includes all serotypes.

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No potential conflict of interest was reported by the authors.

ORCID

Ye Li  <http://orcid.org/0000-0001-6338-7474>

Liz Kunkel  <http://orcid.org/0000-0003-3997-0525>

Natasha S. Crowcroft  <http://orcid.org/0000-0002-6761-8783>

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Appendix 1. Literature searches

As part of this study, we carried out two separate searches of literature. The first focussed on finding epidemiological studies which provided data on what proportion of given clinical syndromes were likely to be caused by GBS. The second took a wider view and aimed to review the current state of vaccine development, likely vaccine effectiveness, and the serotype distribution of GBS in Ontario. Both searches were conducted on PubMed and Medline.

The first search used using combinations of the search terms “group B streptococcus”, “streptococcus agalactiae”, “beta-haemolytic streptococcus”, “epidemiology”, “Canada” and the names of syndromes as printed in Table 2. Results were restricted to papers published in the year 2000 onwards. Bibliographies of identified papers were searched for further useful publications. The most recent and relevant to our data in

terms of location and time period were selected, and when appropriate data were combined to improve the reliability of estimated statistics. The results of this search are catalogued in Table 2, an expanded version of which is available in Appendix 2.

The second search used two sets of search terms, first “group B streptococcus” (and its synonyms) AND “vaccin*” AND “2000:2016 [dp]”, and second “group B streptococcus” AND (“Serotype*” OR “Strains”) AND “2000:2016[dp]”. Results were informally screened to look for primary studies and recent reviews pertinent to recent developments in the development of GBS vaccines, or for epidemiological studies relevant to ascertaining the distribution of GBS serotypes causing disease in Ontario, Canada. References of selected studies were also perused for additional useful publications. Finally, the most relevant and recent papers from the created pool were informally selected for reference in this report.

Appendix 2. Expanded Table 2, giving details on each epidemiological paper included

Table 1.2: Proportion of various syndromes caused by GBS from epidemiological data

Syndrome	Identifying ICD-10-CA codes	Proportion caused by GBS	References
Infant disease			
Early onset neonatal infection (0-6d)	P36	16%	Cohen-Wolkowicz et al 200928: Looked retrospectively at cases of blood culture confirmed early onset neonatal sepsis, defined as < 3d of age, in neonatal ICUs in the United States in late preterm infants; found 120/531 cases of early onset cases to be culture positive for GBS Stoll et al 201129: Looked prospectively at culture confirmed early onset sepsis and early onset meningitis cases in a cohort of 400,000 live births under 72h of age in the US 2006 to 2009; found 159 out of 370 confirmed cases of sepsis to be caused by GBS, or 167/611 if one considers sepsis and meningitis and includes those cultures where the organism was considered a contaminant or contained solely coagulase negative staph. All infants in the study were treated with ≥ 5 days antibiotics or died on antibiotics at < 8d.
Late onset neonatal infection	Sepsis codes for infants 3d to 90d of age	5% based on all numbers including the low birth weight infants; 12% based on all numbers excluding the low birth weight papers; 22% according to the Cantey review	Cohen-Wolkowicz et al 200928: Looked retrospectively at cases of culture confirmed late onset neonatal sepsis, defined as 4–120 days of age, in neonatal ICUs in the United States in late preterm infants; found 26/803 cases of early onset cases to be culture positive for GBS Stoll et al 200230: looked retrospectively at culture confirmed LOS in very low birth weight infants in the US 1998–2002; found 30/1313 blood culture positive cases to be caused by GBS Byington et al 20033: Retrospectively looked at infants up to 90d of age on Salt Lake City, Utah, 1999 to 2002 with fever; found 6/105 blood culture positive cases to be GBS, out of 1298 infants who were evaluated for fever and had not had antibiotics in the preceding 24 hours and “Approximately 1800” evaluated for fever Biondi et al 20133: Retrospectively looked at 3-90d old infants in the US, mainly NYC, and found 41/181 blood culture positive cases to be positive for GBS Greenhow et al 20143: Retrospectively analysed blood, urine and CSF 2005 to 2011 at a hospital in ne California on full term previously healthy infants aged 1 week to 3 months; 23/129 cases of bacteraemia (18%) were GBS. Watt et al 201034: Retrospective review of 668 infants with fever without localising source ≤ 90d 1997 to 2006 (in 2 5y blocks). Out of 20 and 52 patients with serious infections evaluated by culture, 5 (25%) and 1 (1.9%) had GBS, or 6/668 of infants evaluated for fever without localising source. Ashkenazi-Hoffnung et al 201135: GBS was found to cause 1/151 culture positive cases of fever, or 1/1584 cases of fever before evaluation of culture, in children under 90 days old, studied 2005 to 2009 in Israel Cantey et al 201536: retrospective study in Dallas looking at all lab confirmed sepsis on children under 60 days of age May 2011 to December 2013; 30/265 cases associated with GBS (11.3%) Cantey et al 20163: a review including the seven papers above; they aggregate the data to say that 22% of cases of bacteraemia in 529 infants ≤ 90d was caused by GBS
Childhood meningitis	G00, G01	< 1m: 18% 1m to < 3m: 39%. 3m to < 3y: 11%. 3y to < 10y: 5%. 10y to 19y: 8%.	Nigrovic et al 200837: looked at 231 cases of lab confirmed meningitis (by CSF culture, blood culture or CSF latex agglutination) in the US in children 1m to 19y; found total 42 of 231 CSF cultures GBS positive, divided by age as given. Stoll et al 201129: Looked prospectively at culture confirmed early onset sepsis and early onset meningitis cases in a cohort of 400,000 live births in the US 2006 to 2009 for infants < 3d; found 3 out of 16 confirmed cases of meningitis to be caused by GBS.
Congenital pneumonia	P23	-	No epidemiological data including GBS available

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Maternal disease			
Maternal sepsis/ Puerperal fever	O75.3, O85	Antepartum 9.7%; postpartum 7.4%	Acosta et al 201438: Looked at pregnant women in the UK with clinical sepsis (including those in whom there was no eventual confirmation by lab testing or in which the organism remained unknown). 13/134 and 17/231 women with pre and postpartum sepsis had GBS on culture respectively. No epidemiological data available
Chorioamnionitis	O23.5, O42.11, O42.12, O42.13, O42.19	-	No epidemiological data available
Septic abortion	O03.0, O03.5	-	No epidemiological data available
Stillbirth	P95	0 – 12.1%; 2.3%	Nan et al 201539: Systematic review of stillbirth puts the proportion associated with GBS infection to be 0–12.1%, with the most recent US paper available giving 2.3%
All patient groups (data mostly from non-pregnant adults)			
Cellulitis and soft tissue infection	L03	0.6%	Noel et al 200840: Multicentre study in the US identifying complicated skin and soft tissue infections in > 18 year olds caused by confirmed or suspected gram positive bacteria in multiple countries between October 2004 and December 2005. Ten out of 784 detected cases before microbiological evaluation were caused by GBS (70 by gram negative infections). Jones et al 20034: Used retrospective data from The Surveillance Network to look at culture confirmed skin and soft tissue infections in the USA and EU through the entirety of 2001; found GBS to cause 92/26233 cases registered in the USA and 434/58865 in the EU. Diekema et al 20024: Study using North American SENTRY programme to identify 25,745 culture positive bloodstream infections January 1997 to 2000; found 922 (3.6%) to be caused by beta haemolytic streptococci. Lark et al 20014: Seattle study collecting data on blood culture positive community acquired bacteraemia 1994 to 1997; found 8/387 episodes to be caused by beta haemolytic strep Rantala et al 20094: Study in Pirkanmaa, India looking at sensitivity of different beta haemolytic strep to antibodies, using blood stream infection samples. Showed that 76/314 cases of bloodstream infection cultured were due to GBS. This proportion can be used to modify the percentage of beta haemolytic strep causing bacteraemia in the above study to estimate the burden of GBS.
Bacteraemia without focus	A40, A41, A42.7, A22.7, B37.7, A26.7, A28.2, A54.86, A32.7, A39.2, A39.3, A39.4, A21.7, R57.2, A48.3, A02.1, R65.1	1%	Goergens et al 200545: Australian study looking at one hospital 1998-2002, found GBS to account for 2/102 cases of acute haematogenous osteomyelitis in patients less than 16 years of age from January 1998 to June 2002 Imirzalioglu et al 200846: Analysed 1613 urine samples from patients in Giessen, Germany with culture and PCR. 5/165 of those in which an infection was identified (3%) contained GBS Laupland et al 20074, Study which 40618 UTI samples 2004–2005 in Calgary, Canada, in which organisms could be identified; of the ambulatory patients, 2% had GBS; inpatients 4.9%; nursing home residents, 2.0%. Reviewed, with excellent visualisations of the data, in Foxman 2010.8 Ulett et al 200949: Looked for GBS in the urine of 34367 patients >18 with clinically suspected UTI in Birmingham house hospital, University of Alabama. 387 (1.1%) had GBS in their urine. Bouza et al 200150: One day point prevalence questionnaire in multiple European hospitals 29th February 2000 asking about lab confirmed nosocomially acquired UTIs. Identified 522; in the EU, GBS was not reported as a cause, but in non-EU countries, GBS accounted for 1.6% of cases. Jones et al 19995: Looked at organisms from 1698 cases of lab confirmed UTI (1308 US; 390 Canada) Jul-Sep 1997; beta haemolytic strep accounted for 1.2% of the total. Mathai et al 20015: Looked at organisms from 1510 cases of lab confirmed UTI in the US and Canada, 1998, 9 of which were GBS (0.6%) Grude et al 20015: Looked at 52350 urine samples processed in Norway June 1997 to October 1999, 28066 of which had bacteria present; of these, inpatient samples revealed 0.8% to contain GBS (41/53252) and outpatients outpatients 1.5% (349/22714) Flores-Mireles et al 20155: Nature Microbiology Review with a figure citing GBS as the cause of 3% of uncomplicated UTI and 2% of complicated UTI. Zhanel et al 20005: Collected 2000 UTI isolates from 10 tertiary care Canadian hospitals Jan-Sep '98, and found 0.5% (10) to contain GBS.
Osteomyelitis	M86	4%	
Urinary tract infections	N10, N30.0	10% for pyelonephritis in pregnancy; 2% of UTIs	
Peritonitis	K65.0	?	No epidemiological data available

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Septic arthritis	M00	13% of children <16; 14% adults	Goergens et al 200545: Australian study looking at clinical cases of septic arthritis in patients <16 years of age in one hospital 1998-2002; found GBS to account for 1/47 of septic arthritis in children. Bono et al 201556: Retrospectively looked at cases of septic arthritis in children younger than three months in a hospital in Ohio from 1994 to 2010; identified 14 cases, 5 of which were positive for GBS on aspirate or blood culture. Binard et al 200657: Retrospectively identified cases of septic arthritis in patients of any age in Brest Hospital, France between May 2000 and May 2004; Analysed 48 patients with septic arthritis and found 5 (10.4%) of the cases were caused by group B streptococcus Nolla et al 200358: Collected all microbiologically proven cases of septic arthritis in patients over 20 years of age, January 1992 to December 2001 in a hospital in Barcelona; found 11/112 patients cases to be associated with GBS infection Louthrenoo et al 201459: A study looking retrospectively at 244 septic arthritis patients in Thailand between July 1990 and December 2010, finding 38 (15.57%) to be caused by GBS
Meningitis	G00, G01	2%	Domingo et al 199760: Isolated GBS from 12/278 (4.3%) cases of clinically diagnosed acute bacterial meningitis in patients over 15 years of age 1982 to 1996 in Barcelona and Terrassa . Van de Beek et al 20046: Study looking at 683 patients >16 yoa in the Netherlands 1998 to 2002 with culture confirmed acute bacterial meningitis; 5 were due to GBS (0.73%)
Endocarditis	I33.0	1.70%	Sambola et al 20026: Study in 4 Spanish hospitals 1975 to 1998 describing 1771 episodes of endocarditis in patients over 18 years, finding 30 to be caused by GBS.
Endophthalmitis	H44.0	5–10%	Durand 20176: Review paper; states 9% of infectious endophthalmitis is caused by streptococci. Jackson et al 20036: Prospectively in St Thomas' Hospital, London, and through literature search identified culture positive cases of endogenous bacterial endophthalmitis from 1986 to 2001. 4/19 prospectively identified cases and 14/267 review cases were caused by GBS.
Pneumonia	J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18,	?	No epidemiological data including GBS available
Pericarditis/ myocarditis	I301, I400	?	No epidemiological data including GBS available
Unspecified bacterial infection	A49.1, A49.9	NA	Initially included in search but later decided to be too non-specific to be useful