Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden

Bronner P. Gonçalves
Simon R. Procée
Proma Paul
Jaya Chandna
Alexandra Lewin

See next page for additional authors

Follow this and additional works at: https://ecommons.aku.edu/eastafrica_ihd

Part of the Obstetrics and Gynecology Commons
Authors
Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden

Bronner P Gonçalves, Simon R Procter, Pruma Paul, Jaya Chandna, Alexandra Lewin, Farah Seedat, Artemis Koukounari, Ziyaad Danger, Shannon Leahy, Sridhar Santhanam, Hima B John, Justina Bramugy, Azucena Bardaji, Amina Abubakar, Carophine Nasambu, Romina Libster, Clara Sánchez Yanotti, Erzsébet Horváth-Puhó, Henrik T Sørensen, Diederik van de Beek, Merijn W Bijlsma, William M Gardner, Nicholas Kassebaum, Caroline Trotter, Quique Bassat, Shabir A Madhi, Philipp Lambach, Markjit J, Joy E Lawn*, on behalf of the GBS Danish and Dutch collaborative group for long term outcomes, GBS Low and Middle Income Countries collaborative group for long term outcomes, GBS Scientific Advisory Group, epidemiological sub-group, and CHAMPS team

Summary

Background Group B streptococcus (GBS) colonisation during pregnancy can lead to invasive GBS disease (iGBS) in infants, including meningitis or sepsis, with a high mortality risk. Other outcomes include stillbirths, maternal infections, and prematurity. There are data gaps, notably regarding neurodevelopmental impairment (NDI), especially after iGBS sepsis, which have limited previous global estimates. In this study, we aimed to address this gap using newly available multicountry datasets.

Methods We collated and meta-analysed summary data, primarily identified in a series of systematic reviews published in 2017 but also from recent studies on NDI and stillbirths, using Bayesian hierarchical models, and estimated the burden for 183 countries in 2020 regarding: maternal GBS colonisation, iGBS cases and deaths in infants younger than 3 months, children surviving iGBS affected by NDI, and maternal iGBS cases. We analysed the proportion of stillbirths with GBS and applied this to the UN-estimated stillbirth risk per country. Excess preterm births associated with maternal GBS colonisation were calculated using meta-analysis and national preterm birth rates.

Findings Data from the seven systematic reviews, published in 2017, that informed the previous burden estimation (a total of 515 data points) were combined with new data (17 data points) from large multicountry studies on neurodevelopmental impairment (two studies) and stillbirths (one study). A posterior median of 19.7 million (95% posterior interval 17.9–21.9) pregnant women were estimated to have rectovaginal colonisation with GBS in 2020. (2600–125800) infant deaths from GBS were estimated to have occurred. In an analysis assuming a higher case fatality rate in the absence of a skilled birth attendant, 91,900 (44,800–187,800) iGBS infant deaths were estimated; in an analysis without this assumption, 58,300 (26,500–125,800) infant deaths from GBS were estimated. 37,100 children who recovered from iGBS (14,600–96,200) were predicted to develop moderate or severe NDI. 40,500 (21,500–66,200) maternal iGBS cases and 46,200 (20,300–111,300) GBS stillbirths were predicted in 2020. GBS colonisation was also estimated to be potentially associated with considerable numbers of preterm births.

Interpretation Our analysis provides a comprehensive assessment of the pregnancy-related GBS burden. The Bayesian approach enabled coherent propagation of uncertainty, which is considerable, notably regarding GBS-associated preterm births. Our findings on both the acute and long-term consequences of iGBS have public health implications for understanding the value of investment in maternal GBS immunisation and other preventive strategies.

Funding Bill & Melinda Gates Foundation.

Copyright © 2022 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Neonatal infections are a major contributor to the global burden of diseases, with an estimated 6.9 million incident cases of presumed severe neonatal infections each year in low-income and middle-income countries alone, causing approximately half a million deaths worldwide in 2012. One of the leading pathogens causing these infections is group B streptococcus (GBS), which has been recognised for more than 5 decades as causing invasive GBS (iGBS) disease in young infants, with a high case fatality rate. A systematic review, published in 2012, described the iGBS incidence in infants for several regions, and the first set of global estimates for GBS, including maternal GBS disease, stillbirths due to GBS, and an association between preterm birth and GBS colonisation, were published in 2017 using data for 2015. In the context of the UN call for expanding effective preventive interventions targeting the main causes of neonatal mortality, an updated and comprehensive estimation of the full GBS burden is necessary to guide and accelerate the development of improved preventive strategies, including maternal GBS vaccines.
A notable gap identified in earlier estimates of the GBS-related burden of disease was the associated risk of neurodevelopmental impairment (NDI), with no data available to estimate the risk of NDI after iGBS sepsis, and few data on NDI after iGBS meningitis. In 2021, data on GBS sepsis, a more frequent clinical presentation of this infection compared with meningitis, have been published: a large cohort study in Denmark and the Netherlands showed that GBS sepsis also leads to an increase in NDI risk and special education needs. In that study, notably the high number of women with GBS infection during pregnancy supported some of the findings of the previous study and improved data for GBS-associated preterm risk as well as GBS-related stillbirths and NDI after iGBS sepsis, not just after meningitis, based on new data on NDI among patients with iGBS from an electronic cohort in Denmark and five low-income and middle-income countries (Argentina, India, Kenya, Mozambique, and South Africa), which increased the estimated annual number of patients recovering from moderate or severe NDI. The estimated number of stillbirths due to GBS is notable (46 000) and crucial to count. We also estimated, for the first time, the potential preterm burden associated with GBS. Although this is potentially substantial, at more than 0·5 million cases, there is wide uncertainty, and it still represents a small proportion (3·5%) of the overall preterm birth burden, at 15 million births per year.

Implications of all the available evidence
Our findings show a higher burden of iGBS than previously estimated, primarily because of the previously unquantified number of NDI cases after GBS sepsis. We note that, even in regions with good coverage of intrapartum antibiotic prophylaxis, antibiotic prophylaxis, usually given around the time of birth, is unlikely to prevent most stillbirths, GBS-associated preterm birth, or late-onset iGBS, which is more likely to present as meningitis and has a high risk of NDI. Notably, a high proportion of the burden is in low-income and middle-income countries, where intrapartum antibiotic administration is more challenging to implement. Data gaps in this area that are a priority require more ambitious studies; for example, multicountry pregnancy cohort studies from the first trimester with more frequent testing of GBS colonisation could improve data for GBS-associated preterm risk as well as GBS stillbirths and maternal sepsis, which have been understudied in all settings. Our results will enable the first global cost-effectiveness analysis for maternal GBS vaccination and provide an imperative for more rapid progress given several decades of vaccine development so far.

Methods
Overview
We collated aggregated data for all outcomes (cases of maternal colonisation, iGBS cases in the first 3 months of life, deaths among infants younger than 3 months
with iGBS, patients who recovered from iGBS with NDI, stillbirths caused by GBS, cases of maternal iGBS, and excess preterm births associated with maternal GBS colonisation). Most studies included were identified in a series of systematic reviews published in 2017,2-14,19,21 and we included new data on stillbirths and NDI. Note that the search strategy, selection criteria, data extraction, and assessment of study quality were described in the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews.

The search strategy, selection criteria, data extraction, and assessment of study quality were described in the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews. Bayesian hierarchical models22 were used to analyse the original publications of these systematic reviews.

For the UN World Population Prospects 2019 see https://population.un.org/wpp/ See Online for appendix.
Panel 1: Case definitions used for estimates

- Group B streptococcus (GBS) maternal colonisation: isolation by culture of GBS from either the vagina (high or low), rectum, or peri-anal region at any time during pregnancy
- Maternal GBS disease: laboratory isolation of GBS from sterile site in pregnant or post-partum women (up to 42 days post partum), with clinical signs of sepsis
- Stillbirth GBS invasive disease: birth of a fetus weighing >1000 g or ≥28 weeks’ gestational age, or both, with no signs of life and evidence of GBS invasive disease from a normally sterile site such as foetal blood, lung aspirate, or cerebrospinal fluid
- Neonatal and infant GBS invasive disease: laboratory isolation of Streptococcus agalactiae from a normally sterile site in an infant aged 0–89 days with signs of clinical disease, including meningitis, sepsis, or bacteraemic pneumonia
- Neurodevelopment impairment in children after GBS invasive disease: cognitive or motor, vision, or hearing, or a combination, impairment in patients who have recovered from invasive infant GBS disease isolated from a normally sterile site
- Preterm birth associated with GBS maternal colonisation: delivery before completion of 37 weeks of gestation from a mother with maternal GBS colonisation isolated from vaginal, cervical, or rectal swabs, or a combination

For the CHAMPS network see https://champshealth.org
For the Global Health Observatory data repository see https://www.who.int/data/gho
Maternal iGBS

GBS also causes disease in pregnant women. The little research on this, all from high-income countries, was reviewed by Hall and colleagues. We used data reported in that review, together with those from a study in England, to estimate the risk of GBS-related morbidity during pregnancy or post partum (up to 42 days after delivery). Of note, the inclusion of the 2020 study in England was not the result of a systematic search but was suggested by the project’s Scientific Advisory Group. Since these studies, which primarily reported cases where GBS was cultured from blood or cerebrospinal fluid, or both, did not estimate risk given maternal GBS carriage, we applied our estimates directly to country-specific number of births.

Excess preterm births associated with maternal GBS colonisation

Using previously reported data, we estimated the association between maternal GBS colonisation and preterm births. To incorporate all available evidence, we performed a meta-analysis on case-control studies and used the posterior distribution of the coefficient as a prior distribution in a meta-analysis model of cohort and cross-sectional studies. The overall odds ratio was used, together with country-level frequencies of preterm births, to calculate the excess number of preterm births associated with maternal GBS colonisation. Two different approaches were used for this calculation, which also required estimated country-level prevalence of maternal GBS colonisation; in the appendix (pp 21–22), we present the results of the meta-analyses and describe these approaches.

Bayesian models

All analyses were done using the Hamiltonian Monte Carlo algorithm in PyStan (version 2.19), the interface for the Stan libraries in Python (version 3.7). Details on the models are presented in the appendix (pp 4–22, 43), including additional assumptions in our analyses and probable limitations.

Study ethics approval

For the primary data collection in high-income, low-income, and middle-income countries, the overarching protocol for the observational study was granted ethics approval at the London School of Hygiene & Tropical Medicine (approval number 16246). Institutional review

<table>
<thead>
<tr>
<th>Parameter(s) modelled</th>
<th>Data included</th>
<th>Input data overview</th>
<th>Level of estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal GBS colonisation</td>
<td>Prevalence</td>
<td>325 studies from 82 countries</td>
<td>Country</td>
</tr>
<tr>
<td>EOGBS risk</td>
<td>Risk of EOGBS in babies born to mothers who were GBS colonised (regression used to measure this risk using intrapartum antibiotic prophylaxis covariate)</td>
<td>28 studies assessing the risk of EOGBS in babies born to mothers who were GBS colonised</td>
<td>Country</td>
</tr>
<tr>
<td>LOGBS risk</td>
<td>Proportion of all iGBS cases that are LOGBS</td>
<td>20 studies that directly assess both EOGBS and LOGBS incidence</td>
<td>Region</td>
</tr>
<tr>
<td>Death among infants with iGBS</td>
<td>Case fatality rates for EOGBS and LOGBS cases</td>
<td>47 studies were used to estimate the case fatality rate for EOGBS cases and 29 studies were used to estimate the case fatality rate for LOGBS cases</td>
<td>Region</td>
</tr>
<tr>
<td>Patients who recovered from iGBS (meningitis) with NDI</td>
<td>Risk of moderate or severe NDI in those who recovered from iGBS (meningitis)</td>
<td>20 studies</td>
<td>Global</td>
</tr>
<tr>
<td>Patients who recovered from iGBS (sepsis) with NDI</td>
<td>Risk of moderate or severe NDI in those who recovered from iGBS (sepsis)</td>
<td>Nine studies (five in high-income countries and four in low-income and middle-income countries),</td>
<td>Region</td>
</tr>
<tr>
<td>Stillbirths due to GBS</td>
<td>Proportion of stillbirths with evidence of GBS infection</td>
<td>Data from six studies done after 2000, in addition to data from the CHAMPS network on seven local studies (ten countries in total)</td>
<td>Region</td>
</tr>
<tr>
<td>Maternal iGBS</td>
<td>Risk of GBS-related maternal disease</td>
<td>Five studies</td>
<td>Global</td>
</tr>
<tr>
<td>Excess preterm births associated with maternal GBS colonisation</td>
<td>Odds ratio of the association between preterm births and maternal GBS colonisation</td>
<td>Nine case-control studies and 28 cohort and cross-sectional studies</td>
<td>Global</td>
</tr>
</tbody>
</table>

For more details of input data see the appendix. EOGBS=early-onset iGBS. GBS=group B streptococcus. iGBS=innovative GBS. LOGBS=late-onset iGBS. NDI=neurodevelopmental impairment.

Table 1: Summary of the input data for the estimation for each parameter relevant to GBS burden in pregnancy and infancy
Figures 2: Global burden of outcomes related to GBS in pregnancy and infancy

(A) Number of pregnant women who were GBS colonised by Sustainable Development Goal regions. The height of the orange bars represents the median, and 2.5–97.5%, 25–75%, and 40–60% percentile intervals are presented by error bars with different widths. The blue bars correspond to the total number of births in each region.

(B) Estimated global burden of GBS cases, deaths, and NDIs. In the top panel, global numbers (posterior median and 95% posterior interval) of patients with iGBS (maternal, EOGBS, and LOGBS) are shown. The bottom left plot presents the number of children estimated to develop moderate and severe NDI after iGBS in 2020; and the bottom right panel shows the estimated numbers of stillbirths and deaths in infants with iGBS in 2020. In the top panel, EOGBS (2) corresponds to estimates that included both direct and indirect data on incidence; and in the bottom right panel, deaths (2) corresponds to the sensitivity analysis that did not assume a higher mortality in infants with iGBS. EOGBS cases in the absence of skilled birth attendance. EOGBS = early-onset iGBS; GBS = group B streptococcus; iGBS = invasive GBS; LOGBS = late-onset iGBS; NDI = neurodevelopmental impairment.

Results

Input data per parameter are summarised in table 1. Maternal GBS colonisation had the most data, in terms of number of studies, and subsequent variables have fewer inputs, notably maternal infection and stillbirths. Some regions are markedly under-represented; for example, only one study was identified on GBS diagnosis in stillbirths in Asia (Bangladesh), with none from Asia for maternal infection. Most studies assessing the risk of EOGBS in babies born to mothers who were GBS colonised and all studies on GBS-related maternal morbidity were from high-income countries.

19.7 million (95% posterior interval, 17.9–21.9) pregnant women were estimated to be colonised with GBS globally in 2020, with the highest numbers in sub-Saharan Africa (6.1 million [5.7–5.2]; figure 2A; appendix p 24) and central and south Asia (4.4 million [3.7–5.2]; figure 2A; appendix pp 35–36). After accounting for intrapartum antibiotic prophylaxis policy coverage, we estimated 231800 (114100–455000) neonates developed EOGBS, with 90800 (43000–186600) cases estimated to occur in sub-Saharan Africa, and 4300 (2000–7600) in Europe and north America (table 2). In a secondary analysis for the same countries, which included both direct and indirect evidence on incidence, the estimated number of global EOGBS cases was 222500 (138000–353300; appendix p 24). Using region-specific proportions of iGBS cases presenting as EOGBS (appendix p 37), we estimated that 162200 (70200–394400) infants developed LOGBS (table 2). Figure 3A shows the relative distribution of infant and maternal GBS cases by region. We present the combined incidence of EOGBS and LOGBS cases in different regions in the appendix (p 24).

Assuming a higher case fatality rate in the absence of a skilled birth attendant, an estimated 91900 (44800–187800) deaths occurred in infants with either EOGBS or LOGBS globally (figure 2B, 3B; table 2; institutional review board of WHO (approval number ERC.0003169). The Danish electronic cohort study was approved by the Danish Data Protection Agency (record number 2015–57–0002). In the Netherlands, the study protocol (EPI-408) was submitted to the Centre for Clinical Expertise at the National Institute for Public Health and the Environment. The study protocol was exempted from further approval by an ethics research committee, according to Dutch law for medical research involving human patients. This study was reviewed by the Centers for Disease Control and Prevention and was conducted consistent with applicable federal law and Centers for Disease Control and Prevention policy.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
are predicted to develop moderate or severe NDI, which sepsis in low-income and middle-income countries
excess number of preterm births associated with GBS
specific preterm risk estimates and our estimates of
income countries, and 9·2% (2·4–22·8) with GBS
combined), 3·3% (1·0–7·6) with GBS sepsis in high-
(16·1–25·6) of those with GBS meningitis (all countries
infection in 2020.
www.thelancet.com/lancetgh
(300–111 000) stillbirths resulted from in utero GBS
2020. Of the patients who recovered from iGBS, 20–7% (16·1–25·6) of those with GBS meningitis (all countries combined), 3·3% (1·0–7·6) with GBS sepsis in high-income countries, and 9·2% (2·4–22·8) with GBS sepsis in low-income and middle-income countries are predicted to develop moderate or severe NDI, which amounts to 37 100 children (146 000–96 200; figure 2B; panel 2). Using the risk of moderate and severe NDI in children with no history of iGBS15 as a counterfactual, we also crudely estimated the excess number of children with NDI due to iGBS, which was 30 400 (10 900–84 300; appendix pp 13–16).

The risk of GBS maternal disease was 0·29 (0·15–0·47) per 1000 deliveries and was assumed to be the same in all countries. Note that no studies in this analysis were done outside of Europe and North America. We applied this risk to the country-specific numbers of births to calculate the global number of maternal GBS cases: 40 500 (21 500–66 200; figure 2).

We estimated the meta-analytical odds ratio for the association between maternal GBS colonisation and prematurity to be 1·30 (1·02–1·71). We used country-specific preterm risk estimates and our estimates of maternal GBS colonisation prevalence to quantify the excess number of preterm births associated with GBS colonisation: 518 100 (36 900–1 142 300) globally, of which 172 300 (12 300–380 000) were in sub-Saharan Africa and 125 100 (84 000–281 200) were in central and south Asia (table 3), which corresponded to 3·5% (0·2–7·7%) of preterm births globally.

Discussion
We present the most comprehensive estimates to date, to the best of our knowledge, of the global burden of GBS disease related to pregnancy. Our results suggest that the burden is even higher than previously quantified, in part because of novel data enabling the estimation of NDI cases after GBS sepsis and not just meningitis. It is likely that more than 200 000 infants developed EOGBS, and approximately 160 000 developed LOGBS in 2020. Globally, 91 900 deaths were estimated to have occurred in children with iGBS, with the highest numbers in sub-Saharan Africa and Asia. More data on the risk of moderate and severe NDI after GBS meningitis and novel findings on NDI after GBS sepsis allowed for a more comprehensive quantification of these outcomes. New data from Africa and Asia also allowed for a better estimation of stillbirths due to GBS. Finally, we estimated the potential annual burden of GBS-associated preterm births for the first time, at 0·5 million, with a wide uncertainty range. Altogether, these results highlight the large burden of GBS infection, better informing public health action, especially for prevention, and highlight a need for improved epidemiological data, including prospective multicentre pregnancy cohort studies in the highest burden regions, to reduce uncertainty in estimates.

Infants in sub-Saharan Africa have the highest burden of iGBS, with nearly half of all global GBS-related deaths occurring there, reflecting high colonisation rates, a near absence of intrapartum antibiotic prophylaxis policy adoption, and a mortality due to GBS of 23% (12–38%). Stillbirths caused by GBS are also high in sub-Saharan Africa, whereas in Asia there are few data available on GBS diagnosis in stillbirths. Of note, the stillbirth outcome was modelled as the proportion with evidence of GBS infection in a sterile site, and applied to the latest UN estimates by country for stillbirth rate. We note that the global estimated number of stillbirths has decreased from 2·6 million38 in 2015 to the current 2 million since the year 2019 by the UN and region-specific proportions of stillbirths caused by GBS infection (appendix pp 36, 41), we estimate that globally, 46 200 (20 300–111 300) stillbirths resulted from in utero GBS infection in 2020.

Articles

<table>
<thead>
<tr>
<th>Region</th>
<th>Stillbirths (9000–40 500)</th>
<th>EOGBS (43 000–186 600)</th>
<th>LOGBS (30 000–218 700)</th>
<th>Infant deaths after iGBS (2·4–22·8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sub-Saharan Africa</td>
<td>20 300</td>
<td>90 800</td>
<td>78 100</td>
<td>50 600 (23 800–108 400)</td>
</tr>
<tr>
<td>North Africa and west Asia</td>
<td>2300 (1000–5800)</td>
<td>29 000 (12 800–58 700)</td>
<td>20 800 (84 000–52 800)</td>
<td>9600 (4300–20 800)</td>
</tr>
<tr>
<td>Central and south Asia</td>
<td>14 700 (6600–51 500)</td>
<td>47 200 (24 300–89 900)</td>
<td>23 600 (6100–68 600)</td>
<td>16 700 (8200–33 500)</td>
</tr>
<tr>
<td>East and southeast Asia</td>
<td>4600 (1100–16 200)</td>
<td>45 700 (21 600–92 900)</td>
<td>22 500 (5700–68 200)</td>
<td>9700 (4200–22 600)</td>
</tr>
<tr>
<td>Latin America and the Caribbean</td>
<td>1800 (300–11 700)</td>
<td>12 800 (6700–24 400)</td>
<td>8 400 (2700–29 200)</td>
<td>3600 (1600–8200)</td>
</tr>
<tr>
<td>Oceania</td>
<td>100 (20–600)</td>
<td>700 (300–15 000)</td>
<td>400 (100–26 000)</td>
<td>300 (100–900)</td>
</tr>
<tr>
<td>Europe and North America</td>
<td>700 (200–1800)</td>
<td>4300 (2000–7600)</td>
<td>2500 (1000–5300)</td>
<td>400 (200–800)</td>
</tr>
<tr>
<td>Global</td>
<td>46 200 (20 300–111 300)</td>
<td>231 800 (114 100–455 000)</td>
<td>162 200 (70 200–394 400)</td>
<td>91 900 (44 800–187 800)</td>
</tr>
</tbody>
</table>

Data shown as posterior medians (95% posterior intervals) of GBS-related stillbirths, EOGBS cases, LOGBS cases, and infant deaths during iGBS in 2020 by region. The last two digits in each number were rounded down, except for numbers less than 100, as done in previous estimates. EOGBS=early-onset iGBS. GBS=group B streptococcus. iGBS=inverse GBS. LOGBS=late-onset iGBS.

Table 2: Sustainable Development Goal region estimates of acute and long-term outcomes

www.thelancet.com/lancetgh Vol 10 June 2022 e813
numbers of stillbirths estimated by the UN for 2019, and
the apparent decrease in GBS stillbirth estimates is partly
because of lower UN stillbirth rate estimates. Given that
maternal GBS colonisation presumably is a necessary
step for GBS-related stillbirths, studies comparing the
stillbirth risk in pregnant women with GBS colonisation
versus pregnant women with no evidence of GBS
colonisation, and that adjust for potential confounders,
would probably improve the quantification of GBS
stillbirth risk. Notably, our estimates highlight the
importance of this public health problem, which in most
settings is unrecognised partly because of the limited
laboratory capacity to diagnose infections in stillbirths,
but also because of the absence of an investigation of the
causes of stillbirth, even in high-income settings.

NDI risk after GBS sepsis was a major data gap,
and multicountry studies have allowed a more accurate
estimation of the long-term consequences of iGBS than
was feasible in the previous global estimate. On one
hand, the risk of moderate or severe NDI after GBS
sepsis is lower compared with the risk in children who
had GBS meningitis, with the risk of NDI after GBS
meningitis being similar to the risk after severe
neonatal meningitis due to any bacterial pathogen.\textsuperscript{39}
On the other hand, since sepsis is a more common
presentation, our analysis suggests that the number of
moderate or severe NDI cases is probably considerably
higher than previously estimated. One limitation is that
most studies on NDI after iGBS did not include a
comparator group. As a crude approach to estimating

Figure 3: Region-specific relative distribution of GBS burden
(A) Cases of EOGBS and LOGBS as well as maternal iGBS. (B) Deaths during EOGBS or LOGBS and stillbirths. The map is coloured showing Sustainable Development
Goal regions. The areas of the pie charts are proportional to region-specific numbers. The pie charts present the proportions of cases in different regions that affect
babies and women. Posterior medians were used for each of the outcomes; uncertainty in the proportions is therefore not presented. EOGBS=early-onset iGBS.
GBS=group B streptococcus. iGBS=invasive GBS. LOGBS=late-onset iGBS.
the excess number of moderate or severe NDI cases due to GBS, we used the risk of NDI of children who had no history of iGBS in Denmark as a counterfactual risk. The risk was assumed to be fixed, ignoring the uncertainty in this parameter and probable variation that might occur in different settings. One meta-analysis of studies performed in low-income and middle-income countries, for example, estimated a lower prevalence of NDI in the general population in some settings, whereas other data, collected using sensitive tools for NDI assessment, suggest a higher baseline risk of moderate or severe NDI than the baseline risk estimated in the Denmark study (1–25% in studies with more than ten participants). Another limitation of our analysis is that different studies recruited children at different ages and used different NDI assessment tools or epidemiological designs, which might partly explain the substantial between-study variability in risk (appendix pp 29–32). Furthermore, unlike the previous estimates, we did not quantify neonatal encephalopathy with GBS to avoid double counting. Notably, NDI after iGBS will deeply affect children’s lives, in particular those with moderate or severe impairment, as well as affect their parents, and will have economic consequences to society broadly. Our findings confirm the necessity of including support to and aftercare for those who recover from bacterial meningitis as one of the pillars of the Defeating Meningitis roadmap.

Prematurity has been shown to be associated with GBS colonisation, and there are plausible mechanisms for this. However, the most careful review to date highlighted the heterogeneity in estimates of this association from epidemiological studies, which might be related to differences between studies in terms of the timing of screening for GBS. Some cohort studies assessed the exposure of GBS colonisation late in the third trimester of pregnancy, hence missing preterm births occurring earlier in pregnancy and potentially underestimating the association. Given this challenge and the wide uncertainty range, although in our analysis we incorporated all the evidence available from observational studies, our estimates of the associated excess numbers need to be carefully interpreted. Although the number appears to be high, it is a small proportion (approximately 3.5%) of the approximately 15 million preterm births each year. We note that, in addition, preterm babies have a higher risk of iGBS, especially LOGBS, which we have not estimated.

Maternal iGBS was estimated at 0.29 per 1000 births, and a total of 40,500 cases per year, which might represent a considerable proportion of all iGBS cases in mothers and babies. However, all included studies were from high-income countries and, by using these data to represent all countries, we are likely to have underestimated the magnitude of this public health problem. Moreover, the few data on the fatality risk during these episodes prevented the estimation of maternal deaths, which might be higher where data are absent.

Incidence of EOGBS reflects both the prevalence of maternal GBS colonisation and the risk of disease in babies born to mothers who are GBS colonised. By inferring case numbers from these two sources, we attempted to avoid the underestimation consistently described for studies and routine data on EOGBS or LOGBS incidence. In addition to our primary analysis, we used a Bayesian evidence synthesis model that combined direct incidence data with studies on maternal GBS colonisation and EOGBS risk conditional on GBS colonisation; this alternative approach resulted in a slightly lower estimated incidence. More studies with enhanced case capture, similar to one study in the UK, 

<table>
<thead>
<tr>
<th>Panel 2: Estimated numbers of children with moderate and severe neurodevelopmental impairment after invasive group B streptococcus in 2020 by Sustainable Development Goal region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data shown as posterior median and 95% posterior intervals. The last two digits in each number were rounded down, as done in previous estimates, except for numbers below 100.</td>
</tr>
<tr>
<td><strong>Excess preterm births associated with GBS colonisation (%)</strong></td>
</tr>
<tr>
<td><strong>Sub-Saharan Africa</strong></td>
</tr>
<tr>
<td><strong>North Africa and west Asia</strong></td>
</tr>
<tr>
<td><strong>Central and south Asia</strong></td>
</tr>
<tr>
<td><strong>East and southeast Asia</strong></td>
</tr>
<tr>
<td><strong>Latin America and the Caribbean</strong></td>
</tr>
<tr>
<td><strong>Oceania</strong></td>
</tr>
<tr>
<td><strong>Europe and North America</strong></td>
</tr>
<tr>
<td><strong>Global</strong></td>
</tr>
<tr>
<td><strong>Data shown as posterior medians (95% posterior intervals). The last two digits in each number were rounded down, except for numbers less than 100, as was done in previous estimates. GBS=group B streptococcus.</strong></td>
</tr>
</tbody>
</table>
and that also assess maternal GBS colonisation status would allow for a direct comparison between these approaches to inform burden estimation. Underascertainment and under-reporting also apply to LOGBS; hence, we estimated the region-specific proportions of iGBS cases occurring after the first week of life and applied these to the estimated numbers of EOGBS cases to calculate the LOGBS incidence. An underlying assumption is that EOGBS and LOGBS are equally likely to be identified in incidence studies; if EOGBS cases are missed more often than LOGBS cases, it is possible that our analysis might have overestimated the number of LOGBS cases.

Our analyses have strengths and limitations. We were able to advance the previous GBS global burden estimates, particularly with new studies on NDI from either high-income countries or low-income and middle-income countries, which were funded as a result of the gaps shown in the first study. The Bayesian approach has many advantages compared with the previous estimation approach, including the propagation of uncertainty for several parameter estimates, although, as mentioned earlier, a few of these parameters were assumed to be fixed.

However, there are still some data gaps. The sample sizes of some of the studies, in particular the studies on NDI outcomes after GBS meningitis in low-income and middle-income countries, were small, which highlights the difficulty in performing these studies in some settings and the need to improve surveillance to identify those who recover from iGBS. Intrapartum antibiotic prophylaxis coverage data are also few, and our analysis is informed by a literature review with data for 92 countries. Currently, our estimates do not incorporate uncertainty for this variable; but a sensitivity analysis (appendix pp 6–7) indicates how the overestimation or underestimation of intrapartum antibiotic prophylaxis coverage might have influenced estimation. Studies that quantify intrapartum antibiotic prophylaxis policy coverage in different countries would improve our estimates and help to better capture between-country variability. There were few data on maternal iGBS and related maternal mortality. We also did not quantify the global effect of iGBS on educational needs for children with GBS-associated NDI, a problem that was identified in a large cohort study in the Netherlands, because data from different settings are not available. Another limitation in our estimates is the few data on fatality rates during iGBS for children who have limited access to care and antibiotics. Although our assumptions were similar to those made in previous analyses, we also presented results where all children, including those with limited access to care, were assumed to have similar fatality rates during iGBS as those reported in observational studies. Furthermore, for parameters estimated at the global level (ie, assumed to be the same for all countries), it is probable that the uncertainty was underestimated and point estimates might have been biased when applied to specific settings. For example, more data on NDI after GBS meningitis were available for high-income countries, which implies, in addition to the potential bias (eg, an underestimation of NDI risk after GBS meningitis when this global risk is applied to low-income settings), that uncertainty in settings with fewer studies would be higher; data from low-income and middle-income countries are necessary to allow robust region-specific estimations. As is common in many burden estimation exercises, the data used to inform most outcomes were typically before the year of estimation (2020) and might have been influenced by the COVID-19 pandemic.

In summary, our estimates show that pregnancy-related GBS results in a considerable disease burden worldwide, with the highest absolute burden in sub-Saharan Africa and Asia. Effective interventions could reduce the high incidence of iGBS, and prevent the devastating long-term consequences on neurodevelopment, but also need to be implementable at high coverage in the wide range of settings where GBS infection is a public health problem; it is likely that maternal GBS vaccines could be more scalable than intrapartum antibiotic prophylaxis in the lowest resource settings. Interventions that have a preventive effect earlier in a pregnancy than intrapartum antibiotic prophylaxis, which is given around the time of birth, would have the added value of reducing stillbirths, maternal infections, and potentially GBS-associated preterm births. Our results can be used to refine cost-effectiveness analyses regarding maternal GBS vaccines under clinical development, through the inclusion of NDI and other long-term consequences of infection, in addition to mortality. Our data and analyses on NDI underlie the necessity of follow-up and providing care to those who recover from iGBS. However, there are still substantial data gaps. We hope that before another round of estimates is undertaken, well designed studies could address the top epidemiological data gaps regarding stillbirths, maternal iGBS, and preterm risk.
Reference Laboratory for Bacterial Meningitis, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands), Susan J M Halmé (Centre for International Health, National Institute for Public Health and the Environment, Bilthoven, Netherlands).

GBS low-income and middle-income country collaborative group for long-term outcomes
Shabir A Madhi (Medical Research Council, Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; Ziyad Dangor (Medical Research Council, Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Shannon Leahey (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Lois M Harden (Brain Function Research Group, School of Physiology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Azra Ghoor (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Sarah Lowick (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Barbara Laughton (Department of Paediatrics and Child Health, Stellenbosch University, Tygerberg, Western Cape, South Africa), Tamara Jaye (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Sanjay G Lal (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Jacqueline Msayi (Medical Research Council, Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Amina Abubakar (Neuroscience Research Group, Department of Clinical Sciences, University of the Witwatersrand, Johannesburg, South Africa), Sarah Lowick (Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), Madagascar), Qazi Sadeq-ur Rahman (Maternal and Child Health Division, International Centre for Diarrhoeal Diseases Research, Dhaka, Bangladesh), Asma Khalil (Foetal Medicine Unit, St. George’s University of London, London, UK), Pamela Sithole (Medical Research Council, Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa), and Paul T Heath (Vaccine Institute & Paediatric Infectious Diseases Research Group, St. George’s, University of London, London, UK).

GBS Scientific Advisory Group, epidemiological sub-group
Margaret Ip (Department of Microbiology, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China), Anna Seale (Maternal, Adolescent, Reproductive & Child Health Centre, London School of Hygiene & Tropical Medicine, London, UK), Robert A DuPont (First Aid Medical, Inc., Seattle, WA, USA), Emily J Wharton (Contact Tracing and Evaluation, Department of Global Health and Health Metrics Sciences, and Department of Anesthesiology & Pain Medicine, University of Washington, Seattle, WA, USA), William M Gardner (Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK), William M Gardner (Institute for Health Metrics and Evaluation, University of Washington, Seattle, WA, USA), David M Murray (The Lancet, Commission on Global Health, London, UK), and Shabir A Madhi (Medical Research Council, Vaccines and Infectious Diseases Analytical Unit, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa).
Contributors

JEL conceived the idea, obtained the funding, and oversaw the process. BPG designed and performed the Bayesian analyses with inputs from SRP, AL, AK, and MJ. PP, FS, and JC were responsible for the NDI data from the multicentre study. ZD and SL provided NDI risk data from South Africa. SS and HBJ provided NDI risk data from India. AA and CN provided risk data from Kenya. RL and CSY provided data from Argentina. QB, JB, and AB provided data from Mozambique. EH-P and HTS provided data on NDI risk in Denmark. DvdB and MWB generated special education risk data in the Netherlands, which are not reported here, but were jointly analysed with the Danish cohort data. QB and SAM provided CHAMPS data on stillbirths. BPG prepared the first draft of the manuscript with JEL. BPG and JEL had the final responsibility for the decision to submit for publication. MJ, CT, WMG, and NK provided conceptual input to the epidemiological modelling. All authors provided input to the content of the paper, reviewed each draft of the paper, and reviewed and approved the final version. BPG and SRP had access to and verified the data.

Declaration of interests

The Department of Clinical Epidemiology of Aarhus University receives funding from private and public institutions in the form of institutional research grants to (and administered by) Aarhus University; none of these grants has any relation to the present study. SAM declares funding from Astrazeneca, the Bill & Melinda Gates Foundation, GlaxoSmithKline, Minevax, Novavax, Pfizer, and the South Africa Medical Research Council; in particular, SAM denies funding to his institution from Pfizer for epidemiology studies on group B streptococcus (GBS) and a clinical trial on the GBS vaccine, and from the Bill & Melinda Gates Foundation on GBS epidemiology. FS declares employment by the UK National Screening Committee, which developed the policy recommendation for maternal GBS screening. CT declares a consulting fee from WHO for drafting a report on the Full Value of Vaccine Assessment for GBS vaccines, which is related to the current manuscript. RL declares participation on an advisory board for Jansen and Pfizer; payment for lectures from Reckitt; and grants to Fundación INFANT from the Bill & Melinda Gates Foundation and PATH. All other authors declare no competing interests.

Data sharing

Datasets with published data used in the meta-analyses are available upon request (either Bronner Gonzalez or Proma Paul can be contacted; the emails are bronner.gonzalez@lshtm.ac.uk and proma.paul@lshtm.ac.uk) or directly from the appendices of the systematic literature reviews cited in this paper. Unpublished data, including new datasets on NDI or stillbirths, from the CHAMPS network require communication with the investigators leading these specific studies.

Acknowledgments

We thank the teams working in the CHAMPS network, that provided data allowing us to update our estimates on stillbirths caused by GBS infection. We are also grateful to members of the project’s Scientific Advisory Group. We thank Simon Cousens for insightful advice on epidemiological variables. We are grateful to the authors of the previous estimation work for advice regarding previous input datasets, notably Fiorella Bianchi and Neil Russell. We thank Claudia da Silva for administrative support. The findings and conclusions in this report are those of the authors, and do not necessarily represent the official position of any of the agencies or organisations listed. In particular, the findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry. This work was supported by a grant (number OP1180644) from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine (principal investigator, Joy Lawn). The Bill & Melinda Gates Foundation also provided financial support to the WHO Immunization, Vaccines, and Biologicals department (grant number INV-1175247). PL works for WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of WHO.

Editorial note: the Lancet Group takes a neutral position with respect to organisations listed. In particular, the findings and conclusions in this report are those of the authors, and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the Agency for Toxic Substances and Disease Registry. This work was supported by a grant (number OP1180644) from the Bill & Melinda Gates Foundation to the London School of Hygiene & Tropical Medicine (principal investigator, Joy Lawn). The Bill & Melinda Gates Foundation also provided financial support to the WHO Immunization, Vaccines, and Biologicals department (grant number INV-1175247). PL works for WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions, policy, or views of WHO.

References