Group B streptococcal disease in infants aged younger than 3 months: systematic review and meta-analysis

Karen M Edmond, Christina Kortsalioudaki, Susana Scott, Stephanie J Schrag, Anita K M Zaidi, Simon Cousens, Paul T Heath

Summary
Background Despite widespread use of intrapartum antibiotic prophylaxis, group B streptococcus remains a leading cause of morbidity and mortality in infants in Europe, the Americas, and Australia. However, estimates of disease burden in many countries outside of these regions is not available. We aimed to examine the current global burden of invasive disease and the serotype distribution of group B streptococcus isolates.

Methods We searched Medline, Embase, and Wholis databases for studies on invasive early-onset (day 0–6) and late-onset (day 7–89) group B streptococcal disease. Eligible studies were those that described incidence, deaths, or serotypes. We also reviewed reference lists and contacted experts to seek unpublished data and data missed by our search. Random effects meta-analysis was used to pool data.

Findings 74 studies met the inclusion criteria; 56 studies reported incidence, 29 case fatality, and 19 serotype distribution. An additional search for studies that reported serotype distribution from Jan 1, 1980, yielded a total of 38 articles. Only five low-income countries were represented in the review and contributed 5% weight to the meta-analysis. 47 (69%) studies reported use of any intrapartum antibiotic prophylaxis. Substantial heterogeneity existed between studies. Mean incidence of group B streptococcus in infants aged 0–89 days was 0·53 per 1000 livebirths (95% CI 0·44–0·62) and the mean case fatality ratio was 9·6% (95% CI 7·5–11·8). Incidence of early-onset group B streptococcus (0·43 per 1000 livebirths [95% CI 0·37–0·49]) and case fatality (12·1%, [6·2–18·3]) were two-times higher than late-onset disease. Serotype III (48·9%) was the most frequently identified serotype in all regions with available data followed by serotypes Ia (22·9%), Ib (7·0%), II (6·2%), and V (9·1%). Studies that reported use of any intrapartum antibiotic prophylaxis were associated with lower incidence of group B streptococcus (0·23 per 1000 livebirths [95% CI 0·13–0·59]) than studies in which patients did not use prophylaxis (0·75 per 1000 livebirths [0·58–0·89]).

Interpretation More high-quality studies are needed to accurately estimate the global burden of group B streptococcus, especially in low-income countries. A conjugate vaccine incorporating five serotypes (Ia, Ib, II, III, V) could prevent most global group B streptococcal disease.

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Introduction Group B streptococcus (Streptococcus agalactiae) is the most common cause of neonatal sepsis in high-income countries.7 Disease risk is highest during the first 3 months of life and declines substantially thereafter. Early-onset disease (day 0–6) is the result of vertical transmission from a colonised mother during or just before delivery.3 Late-onset disease (day 7–89) can be acquired from the mother or from environmental sources.11 Case fatality from both early-onset and late-onset disease is high, even with antibiotic therapy.3 Group B streptococcus is also an important cause of preterm delivery, antepartum and intrapartum stillbirth, and puerperal sepsis.12 Prevention of early-onset group B streptococcus has become a realistic option, through the use of intrapartum antibiotics given to pregnant women with risk factors or known carriage of the bacteria (intrapartum antibiotic prophylaxis).5 This prophylaxis has been implemented in most high-income countries since the late 1990s, but has been difficult to implement in many low-income countries and middle-income countries.13 Several group B streptococcus vaccines are also at various stages of testing and could allow prevention of both early-onset disease and late-onset disease.5–14 However, many challenges exist to obtaining accurate estimates of disease burden, especially for low-income and middle-income countries, including difficulties with obtaining specimens and poor laboratory capacity for diagnosis of group B streptococcus.

We aimed to estimate the incidence of group B streptococcal invasive disease and case fatality in infants aged 0–89 days in the era of intrapartum prophylaxis, estimate the incidence of early and late onset invasive disease, and estimate distribution of group B streptococcal serotypes in invasive disease specimens. Secondary objectives were to assess how the incidence of group B streptococcal disease varies with gross national income (GNI) per head and geographical region.

Methods Definitions and classification We defined invasive group B streptococcal disease as laboratory isolation of Streptococcus agalactiae from a normally sterile site in an infant aged 0–89 days with...
any signs of clinical disease (eg, sepsis, pneumonia, or meningitis).

**Search strategy and selection criteria**

We searched Medline, Embase, and Wholis databases using the search terms (“Streptococcus agalactiae”[Mesh] OR “Streptococcus Group B” OR “Group B Streptococcal”) AND Limits: Humans, Publication date 2000/01/01–2011/09/01. We restricted our search from January 2000, to maintain consistency and comparability with other publications from WHO Global Burden of Disease and the Child Health Epidemiology Reference Group aimed at producing disease burden estimates for 2000. To ensure we included all studies in which group B streptococcus was not isolated and incidence was zero we reviewed all reports that described incidence or case fatality from the concurrent neonatal infection search in the 2010 global burden of disease project. We also reviewed reference lists and contacted experts to seek unpublished data and data missed by our search. No language restrictions were used.

Reports were excluded if they did not describe data collected between Jan 1, 2000, and Sept 1, 2011, human infants aged 0–89 days at onset of infection episode, specimens obtained from a sterile site, laboratory investigation for common bacterial pathogens such as group B streptococcus, original data (ie, reviews or repeated datasets were excluded), denominator data (eg, case series were excluded); and data representative of the whole population of infants (eg, studies containing only information on very high-risk groups [eg, preterm infants] were excluded).

Only 19 articles with data on serotypes of group B streptococcus fulfilled the inclusion criteria for the search from Jan 1, 2000 to Sept 1, 2011, thus an additional search for reports with serotype data from Jan 1, 1980, to Sept 1, 2011 was done with the same search strategy outlined above.

**Data extraction**

Two reviewers (CK, KME) examined titles, abstracts, and articles independently with identical case definitions, data abstraction forms, and selection criteria. Disagreements were resolved by consensus between the two reviewers and the lead authors (CK, KME, PTH).

We gathered basic data on author, country and group B streptococcal cases, deaths, and serotypes ascertained for three age groups: 0–89 days, 0–6 days, and 7–89 days. We also gathered data on livebirths in the study population. If a study only included inborn babies (babies born in the study hospital) then the number of livebirths for the whole hospital was used as denominator data. If a study included outborn babies (babies who were not born in the study hospital but born at home or another health facility) then the number of livebirths in the whole study population (including community births) was used.

We also gathered data on potential explanatory variables (ie, variables that might explain variance in incidence or risk of group B streptococcus; table 1).

First, we obtained data from 2009 World Bank, WHO, and Child Health Epidemiology Reference Group data sets. These data were used to categorise countries into WHO region (African, southeast Asia, western Pacific, eastern Mediterranean, European, and American), gross national income in $US per head, and child health epidemiology region data sets.

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We also gathered data on potential explanatory variables (ie, variables that might explain variance in incidence or risk of group B streptococcus; table 1). First, we obtained data from 2009 World Bank, WHO, and Child Health Epidemiology Reference Group data sets. These data were used to categorise countries into WHO region (African, southeast Asia, western Pacific, eastern Mediterranean, European, and American), gross national income in $US per head from 2009 (low income, low-middle income, etc.) and the child health epidemiology region data sets.
Figure 1: Meta-analysis of studies that reported incidence of group B streptococcus in infants with disease onset 0–89 days, 2000–11, by region

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gross national income</th>
<th>Livebirth</th>
<th>Time period (days)</th>
<th>Incidence (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>India</td>
<td>Low</td>
<td>34 362</td>
<td>0–2</td>
<td>0·35 (0·21 to 0·53)</td>
</tr>
<tr>
<td>2009</td>
<td>Bangladesh</td>
<td>Low</td>
<td>10 000</td>
<td>0–28</td>
<td>0·31 (0·24 to 0·41)</td>
</tr>
<tr>
<td>2009</td>
<td>Saudi Arabia</td>
<td>High</td>
<td>80 000</td>
<td>0–5</td>
<td>0·24 (0·16 to 0·36)</td>
</tr>
<tr>
<td>2009</td>
<td>Norway</td>
<td>High</td>
<td>26 140</td>
<td>0–2</td>
<td>0·74 (0·64 to 0·84)</td>
</tr>
<tr>
<td>2009</td>
<td>India</td>
<td>Low</td>
<td>80 263</td>
<td>0–28</td>
<td>0·47 (0·32 to 0·66)</td>
</tr>
<tr>
<td>2009</td>
<td>Japan</td>
<td>High</td>
<td>80 000</td>
<td>0–2</td>
<td>0·35 (0·29 to 0·43)</td>
</tr>
<tr>
<td>2009</td>
<td>Turkey</td>
<td>High</td>
<td>79 400</td>
<td>0–2</td>
<td>0·47 (0·40 to 0·54)</td>
</tr>
<tr>
<td>2009</td>
<td>UK</td>
<td>High</td>
<td>72 640</td>
<td>0–2</td>
<td>0·67 (0·54 to 0·81)</td>
</tr>
<tr>
<td>2009</td>
<td>Bangladesh</td>
<td>Low</td>
<td>32 029</td>
<td>0–27</td>
<td>0·22 (0·15 to 0·31)</td>
</tr>
<tr>
<td>2009</td>
<td>Australia and New Zealand</td>
<td>High</td>
<td>8129</td>
<td>0–5</td>
<td>0·35 (0·27 to 0·44)</td>
</tr>
<tr>
<td>2009</td>
<td>Sweden</td>
<td>High</td>
<td>80 263</td>
<td>0–2</td>
<td>0·78 (0·68 to 0·88)</td>
</tr>
<tr>
<td>2009</td>
<td>USA</td>
<td>High</td>
<td>35 647</td>
<td>0–2</td>
<td>0·40 (0·32 to 0·49)</td>
</tr>
<tr>
<td>2009</td>
<td>USA</td>
<td>High</td>
<td>74 900</td>
<td>0–2</td>
<td>0·40 (0·30 to 0·50)</td>
</tr>
<tr>
<td>2009</td>
<td>USA</td>
<td>High</td>
<td>8129</td>
<td>0–5</td>
<td>0·35 (0·27 to 0·44)</td>
</tr>
</tbody>
</table>

Overall (p=0·000) 0·53 (0·44 to 0·62)
high-middle income, high income), and high versus low (≥70% vs <70%) skilled attendance at birth according to WHO criteria.

We categorised studies as prospective (data gathered while the infant was still unwell or in hospital) versus retrospective (data gathered after the infant had been discharged from hospital). Data on site of delivery were also gathered because inborn babies have different risk factors for infection than do babies who are outborn. Also, delay in specimen collection from outborn babies can be longer than in inborn babies. The reporting period was categorised as complete versus incomplete. For example, we looked for data on early-onset incidence over the whole period from day 0–6. If data for this period was available it was classified as complete. However, if information was only available for day 0–2 then data were still recorded but classified as incomplete. Data on specimen type were grouped as specimens from all sterile sites (blood, cerebrospinal fluid, bone and joint specimen type) versus blood only. Only limited information was available for intrapartum antibiotic prophylaxis and studies could only be categorised into use of any intrapartum antibiotic prophylaxis versus no use of intrapartum antibiotic prophylaxis. Infants with low birthweight should comprise 20–30% of all infants with group B streptococcus, thus we also divided studies into three categories of low birthweight: 20% or less, 20–39%, 40% or more.

Group B streptococcal disease is rapidly progressive and under-ascertainment can result if specimens are not obtained within 24 h of disease onset. Thus, we examined articles for indicators such as proportion of specimens collected during the first day of illness or on the day of birth or careseeking and referral on day one of life, but no data were available. Poor laboratory techniques can also cause under-ascertainment of group B streptococcus, so we also searched for information on specimen volume, transport conditions, and culture techniques; but data were disparate and could not be pooled. We also looked for data on HIV status but this was not available in most articles or could not be synthesised.

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gross national income*</th>
<th>Number of group B streptococcal cases</th>
<th>Time period (days)</th>
<th>Case fatality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Czech Republic</td>
<td>High</td>
<td>285</td>
<td>0–89</td>
<td>0.01 (0.00–0.03)</td>
</tr>
<tr>
<td>2005</td>
<td>Germany</td>
<td>High</td>
<td>639</td>
<td>0–89</td>
<td>0.02 (0.01–0.04)</td>
</tr>
<tr>
<td>2007</td>
<td>Italy</td>
<td>High</td>
<td>56</td>
<td>0–89</td>
<td>0.11 (0.04–0.22)</td>
</tr>
<tr>
<td>2016</td>
<td>Netherlands</td>
<td>High</td>
<td>196</td>
<td>0–89</td>
<td>0.11 (0.07–0.16)</td>
</tr>
<tr>
<td>2001</td>
<td>Norway</td>
<td>High</td>
<td>59</td>
<td>0–89</td>
<td>0.08 (0.05–0.13)</td>
</tr>
<tr>
<td>2006</td>
<td>Norway</td>
<td>High</td>
<td>24</td>
<td>0–89</td>
<td>0.33 (0.16–0.55)</td>
</tr>
<tr>
<td>2008</td>
<td>Portugal</td>
<td>High</td>
<td>242</td>
<td>0–89</td>
<td>0.07 (0.04–0.11)</td>
</tr>
<tr>
<td>2008</td>
<td>Spain</td>
<td>High</td>
<td>42</td>
<td>0–3</td>
<td>0.02 (0.00–0.03)</td>
</tr>
<tr>
<td>2004</td>
<td>Sweden</td>
<td>High</td>
<td>52</td>
<td>0–28</td>
<td>0.08 (0.02–0.19)</td>
</tr>
<tr>
<td>2004</td>
<td>UK</td>
<td>High</td>
<td>568</td>
<td>0–89</td>
<td>0.09 (0.07–0.12)</td>
</tr>
<tr>
<td>2002</td>
<td>Japan</td>
<td>High</td>
<td>36</td>
<td>0–7</td>
<td>0.17 (0.06–0.33)</td>
</tr>
<tr>
<td>2004</td>
<td>UK</td>
<td>High</td>
<td>486</td>
<td>0–89</td>
<td>0.07 (0.06–0.11)</td>
</tr>
</tbody>
</table>

Subtotal (p=87.8%, p=0.000)

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gross national income*</th>
<th>Number of group B streptococcal cases</th>
<th>Time period (days)</th>
<th>Case fatality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Jamaica</td>
<td>Middle</td>
<td>29</td>
<td>0–3</td>
<td>0.01 (0.00–0.018)</td>
</tr>
<tr>
<td>2007</td>
<td>USA</td>
<td>High</td>
<td>21</td>
<td>0–6</td>
<td>0.14 (0.03–0.36)</td>
</tr>
<tr>
<td>2002</td>
<td>USA</td>
<td>High</td>
<td>166</td>
<td>0–6</td>
<td>0.04 (0.01–0.08)</td>
</tr>
<tr>
<td>2005</td>
<td>USA</td>
<td>High</td>
<td>61</td>
<td>0–6</td>
<td>0.07 (0.02–0.16)</td>
</tr>
<tr>
<td>2008</td>
<td>USA</td>
<td>High</td>
<td>2268</td>
<td>0–89</td>
<td>0.06 (0.05–0.07)</td>
</tr>
<tr>
<td>2005</td>
<td>USA</td>
<td>High</td>
<td>25</td>
<td>0–3</td>
<td>0.16 (0.05–0.36)</td>
</tr>
<tr>
<td>2005</td>
<td>USA</td>
<td>High</td>
<td>146</td>
<td>0–89</td>
<td>0.14 (0.09–0.20)</td>
</tr>
<tr>
<td>2004</td>
<td>USA</td>
<td>High</td>
<td>8</td>
<td>0–89</td>
<td>0.17 (0.00–0.64)</td>
</tr>
<tr>
<td>2008</td>
<td>USA</td>
<td>High</td>
<td>165</td>
<td>7–89</td>
<td>0.32 (0.25–0.40)</td>
</tr>
</tbody>
</table>

Subtotal (p=86.7%, p=0.000)

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gross national income*</th>
<th>Number of group B streptococcal cases</th>
<th>Time period (days)</th>
<th>Case fatality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>Malawi</td>
<td>Low</td>
<td>57</td>
<td>0–89</td>
<td>0.33 (0.21–0.47)</td>
</tr>
<tr>
<td>2005</td>
<td>Malawi</td>
<td>Low</td>
<td>136</td>
<td>0–3</td>
<td>0.21 (0.14–0.28)</td>
</tr>
<tr>
<td>2009</td>
<td>Mozambique</td>
<td>Low</td>
<td>31</td>
<td>0–28</td>
<td>0.13 (0.04–0.30)</td>
</tr>
</tbody>
</table>

Subtotal (p=59.9%, p=0.003)

<table>
<thead>
<tr>
<th>Year</th>
<th>Country</th>
<th>Gross national income*</th>
<th>Number of group B streptococcal cases</th>
<th>Time period (days)</th>
<th>Case fatality ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>Japan</td>
<td>High</td>
<td>6</td>
<td>0–89</td>
<td>0.17 (0.00–0.64)</td>
</tr>
<tr>
<td>2010</td>
<td>South Korea</td>
<td>High</td>
<td>157</td>
<td>0–89</td>
<td>0.10 (0.06–0.16)</td>
</tr>
<tr>
<td>2010</td>
<td>South Korea</td>
<td>High</td>
<td>99</td>
<td>0–89</td>
<td>0.08 (0.04–0.15)</td>
</tr>
<tr>
<td>2003</td>
<td>Taiwan</td>
<td>Middle</td>
<td>19</td>
<td>0–28</td>
<td>0.05 (0.00–0.26)</td>
</tr>
<tr>
<td>2004</td>
<td>Taiwan</td>
<td>Middle</td>
<td>18</td>
<td>0–28</td>
<td>0.17 (0.04–0.43)</td>
</tr>
</tbody>
</table>

Subtotal (p=0.0%, p=0.036)

Overall (p=87.3%, p=0.000)

Figure 2: Meta-analysis of studies that reported data for case fatality caused by group B streptococcus in infants with disease onset 0–89 days, 2000–11, by region

*Gross national income in US$ per head. †Data collection time period in days since the birth of the infant.
Statistical analyses
We used random-effects meta-analysis to calculate weighted mean estimates across studies and 95% CIs for incidence of group B streptococcus, case fatality, and serotype distribution. Random-effects logistic regression was used to investigate the effect of gross national income, WHO region, and other explanatory variables for group B streptococcus estimates while taking account of within-study and within-country correlations. We decided a priori that all effect measures should be adjusted for study design, delivery site, reporting period, specimen type, intrapartum antibiotic use, and proportion of low birthweight infants in the final model. However, we judged that gross national income, WHO region, and skilled attendance would be highly correlated and only gross national income should be included in the final model. Crude and adjusted odds ratios and their 95% CIs were calculated. Statistical analyses were done with STATA (version 11).

Role of the funding source
The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
2709 papers were identified from the Medline and Wholis search from Jan 1, 2000, to Sept 1, 2011, and 423 titles were retained. No additional articles were obtained from the Embase search, 111 titles were obtained from the concurrent WHO Global Burden of Disease neonatal-infection search, and 114 titles were obtained from experts in neonatal care and reference lists. No unpublished data that met our inclusion criteria were identified. 74 papers were retained after the abstracts were reviewed and our inclusion criteria were applied (webappendix pp 1–11).


Overall, 8718 infants were positive for group B streptococcus in 36 countries (median number of infants per study 21.5 [IQR 3.5–92.5]; table 1). 47 (69%) studies reported use of intrapartum antibiotic prophylaxis (web appendix p 12). This proportion was higher in Europe (22 [92%] of 24) and the Americas (13 [81%] of 16) than in the eastern Mediterranean (one [25%] of four) and Africa (one [17%] of six). No studies in low-income countries reported use of intrapartum antibiotic prophylaxis.

To assess whether any publication bias was likely in our study we did scatter plots of incidence and case fatality rate against sample size and SE to determine whether any correlation existed. These analyses yielded non-significant results both for data on incidence (p=0.223) and case fatality (p=0.206).

42 studies reported incidence data for early-onset (0–6 days) group B streptococcus; 31 (74%) had data for the complete period (0–6 days) and 34 (81%) reported use of intrapartum antibiotic prophylaxis. Only three low-income countries (Kenya, Malawi, Bangladesh) had data for early-onset group B streptococcus. The mean

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Figure 3: Global distribution of group B streptococcus serotypes, 1980–2011
Distribution of group B streptococcus serotypes (A). Distribution of group B streptococcus serotypes by region and disease onset (B).
incidence of early-onset disease was 0·43 (95% CI 0·37–0·49). Incidence was highest in studies from Africa (0·53, 95% CI 0·15–0·92) followed by the Americas (0·50, 0·43–0·57) and Europe (0·45, 0·34–0·56). Studies from southeast Asia reported the lowest incidence (0·11, 95% CI 0·012–0·220).

18 papers reported any data for incidence of late-onset (7–89 days) group B streptococcus. The average incidence of late-onset disease was 0·24 (95% CI 0·17–0·30). Incidence was again highest in Africa (0·71, 95% CI 0·38–1·04) followed by the Americas (0·31, 95% CI 0·16–0·89).

29 papers reported data for case fatality in infants aged 0–89 days; 484 deaths occurred in 6135 infants positive for group B streptococcus (table 1). The mean case fatality ratio was 9·6% (95% CI 7·5–11·8; figure 2). Early-onset case fatality (12·1%, 95% CI 6·2–18·3) was twice as high as late-onset death (6·8%, 4·3–9·4). The case fatality ratio was three times higher in low-income countries (12·6%, 95% CI 10·8–14·9) than in high-income countries (4·6%, 2·1–9·1).

### Table 2: Regression analyses of the effect of explanatory variables on incidence of group B streptococcus in infants with disease onset 0–89 days, 2000–11

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Studies</th>
<th>Participants</th>
<th>Subgroup estimates; incidence (95% CI)</th>
<th>Univariable regression; odds ratio (95% CI)*</th>
<th>Multivariable regression; adjusted odds ratio† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americas</td>
<td>16</td>
<td>8 638 370</td>
<td>5849</td>
<td>0·67 (0·54–0·80)</td>
<td>1</td>
</tr>
<tr>
<td>Africa</td>
<td>7</td>
<td>71 006</td>
<td>100</td>
<td>1·21 (0·50–1·91)</td>
<td>1·82 (0·77–4·45)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>5</td>
<td>81 350</td>
<td>5</td>
<td>0·016 (0·033–0·065)</td>
<td>0·087 (0·025–0·30)</td>
</tr>
<tr>
<td>Europe</td>
<td>20</td>
<td>5 396 048</td>
<td>2 701</td>
<td>0·57 (0·448–0·71)</td>
<td>0·86 (0·45–1·63)</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>4</td>
<td>77 017</td>
<td>30</td>
<td>0·35 (0·073–0·62)</td>
<td>0·60 (0·24–1·52)</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>4</td>
<td>164 155</td>
<td>33</td>
<td>0·15 (0·042–0·27)</td>
<td>0·26 (0·11–0·62)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Gross national income ($US per head)</td>
<td></td>
<td></td>
<td></td>
<td>p=0·691</td>
<td>p=0·710</td>
</tr>
<tr>
<td>High income (≥12 195)</td>
<td>41</td>
<td>14 151 386</td>
<td>8537</td>
<td>0·56 (0·47–0·66)</td>
<td>1</td>
</tr>
<tr>
<td>High-middle income (3946–12 195)</td>
<td>5</td>
<td>108 306</td>
<td>80</td>
<td>0·83 (0·42–1·23)</td>
<td>1·92 (0·76–4·89)</td>
</tr>
<tr>
<td>Low-middle income (996–3945)</td>
<td>7</td>
<td>99 512</td>
<td>17</td>
<td>0·17 (0·013–0·33)</td>
<td>0·33 (0·12–0·89)</td>
</tr>
<tr>
<td>Low income (&lt;995)</td>
<td>3</td>
<td>68 742</td>
<td>84</td>
<td>0·94 (0·040–1·91)</td>
<td>1·77 (0·59–5·31)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Skilled attendance at delivery</td>
<td></td>
<td></td>
<td></td>
<td>p=0·236</td>
<td></td>
</tr>
<tr>
<td>≥70%</td>
<td>49</td>
<td>14 304 018</td>
<td>8630</td>
<td>0·65 (0·11–1·19)</td>
<td>1</td>
</tr>
<tr>
<td>&lt;70%</td>
<td>7</td>
<td>123 928</td>
<td>88</td>
<td>0·56 (0·47–0·64)</td>
<td>0·66 (0·25–1·76)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>27</td>
<td>6 529 308</td>
<td>3 793</td>
<td>0·47 (0·34–0·60)</td>
<td>1</td>
</tr>
<tr>
<td>Retrospective</td>
<td>29</td>
<td>7 898 638</td>
<td>4 925</td>
<td>0·65 (0·54–0·75)</td>
<td>1·03 (0·66–1·59)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Delivery site</td>
<td></td>
<td></td>
<td></td>
<td>p=0·682</td>
<td>p=0·130</td>
</tr>
<tr>
<td>Inborn</td>
<td>51</td>
<td>14 223 575</td>
<td>8 625</td>
<td>0·57 (0·49–0·66)</td>
<td>1</td>
</tr>
<tr>
<td>Outborn</td>
<td>5</td>
<td>204 371</td>
<td>93</td>
<td>0·40 (0·14–0·65)</td>
<td>0·81 (0·30–2·20)</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Reporting period</td>
<td></td>
<td></td>
<td></td>
<td>p=0·219</td>
<td>p=0·026</td>
</tr>
<tr>
<td>Complete</td>
<td>37</td>
<td>14 016 126</td>
<td>8 556</td>
<td>0·64 (0·55–0·74)</td>
<td>1</td>
</tr>
<tr>
<td>Incomplete</td>
<td>19</td>
<td>411 820</td>
<td>162</td>
<td>0·35 (0·23–0·46)</td>
<td>0·71 (0·41–1·23)</td>
</tr>
<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>Specimen type</td>
<td></td>
<td></td>
<td></td>
<td>p=0·608</td>
<td>p=0·901</td>
</tr>
<tr>
<td>All sterile sites</td>
<td>45</td>
<td>13 999 368</td>
<td>8 430</td>
<td>0·557 (0·47–0·65)</td>
<td>1</td>
</tr>
<tr>
<td>Blood only</td>
<td>11</td>
<td>428 578</td>
<td>288</td>
<td>0·60 (0·34–0·86)</td>
<td>1·15 (0·68–1·92)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intrapartum antibiotic prophylaxis</td>
<td></td>
<td></td>
<td></td>
<td>p=0·968</td>
<td>p=0·112</td>
</tr>
<tr>
<td>Any intrapartum antibiotic prophylaxis used</td>
<td>43</td>
<td>13 831 239</td>
<td>8 279</td>
<td>0·55 (0·48–0·64)</td>
<td>1</td>
</tr>
<tr>
<td>No intrapartum antibiotic prophylaxis used</td>
<td>13</td>
<td>596 707</td>
<td>439</td>
<td>0·64 (0·37–0·90)</td>
<td>1·02 (0·50–2·08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low birthweight*</td>
<td></td>
<td></td>
<td></td>
<td>p=0·014</td>
<td>p=0·005</td>
</tr>
<tr>
<td>20–39%</td>
<td>43</td>
<td>12 893 707</td>
<td>7 859</td>
<td>0·69 (0·60–0·78)</td>
<td>1</td>
</tr>
<tr>
<td>&lt;20%</td>
<td>13</td>
<td>15 343 239</td>
<td>859</td>
<td>0·38 (0·28–0·57)</td>
<td>0·57 (0·36–0·89)</td>
</tr>
</tbody>
</table>

Data are number or incidence (95% CI), odds ratio (95% CI), or adjusted odds ratio (95% CI). *Proportion of infants with group B streptococcus who were low birthweight. †Adjusted for gross national income, design, delivery site, reporting period, specimen type, use of intrapartum antibiotic prophylaxis, and proportion of infants with low birthweight.
38 serotype studies published from Jan 1, 1980 to June 1, 2011, fulfilled the inclusion criteria (table 1, figure 3). Serotype III accounted for almost half of all isolates followed by serotypes Ia, Ib, I, II, and V; a small proportion of serotypes were non-typeable (figure 3).

No serotype studies from southeast Asia were identified, and only one study from the eastern Mediterranean region (Morocco) and two studies from Africa (Nigeria and South Africa) were recorded. Distribution of group B streptococcus serotypes seemed to be similar across WHO regions (figure 3). Five serotypes (Ia, Ib, II, III, V) accounted for more than 85% of serotypes in all regions with serotype data (Africa 98% [112], Americas 96% [2152], Europe 93% [2295], western Pacific 89% [569], eastern Mediterranean 88% [51]).

33 serotype studies were from high-income countries. Five studies from middle-income countries (South Africa, Nigeria, Morocco, Romania, and Argentina) reported serotypes; 94 (43%) of 221 cases in middle-income countries were serotype III. However, no serotype studies from low-income countries were identified.

We also examined serotype distribution by disease onset (figure 3). 221 (37%) of 604 early-onset serotypes were type III compared with 347 (53%) of 653 late-onset serotypes. 242 (40%) early-onset serotypes were type I compared with 196 (30%) of late-onset serotypes. By contrast, serotype distribution did not seem to change substantially over the three decades of data collection. Serotype III accounted for 48% (1324) of isolates in the 1980s, 49% (822) of isolates in the 1990s, and 50% (544) of isolates from 2000–10. Serotype V accounted for 9% (245) of isolates in the 1980s, 9% (143) of isolates in the 1990s, and 10% (112) of isolates from 2000–10.

The only explanatory variables that seemed to be strongly predictive of group B streptococcus risk were the proportion of infants positive for group B streptococcus who had low birthweight and reporting period (table 2). Studies with less than 20% of infants with low birthweight reported lower odds of group B streptococcal infection than did studies with proportions ranging from 20–39%. Studies with incomplete reporting recorded lower odds of group B streptococcal infection than did studies with complete reporting.

Infants in countries with low gross national income had higher odds of group B streptococcal infection than did those in countries with high gross national income, but this result was not significant (table 2). No association was reported between incidence of group B streptococcus and gross national income (adjusted odds ratio 0.99, 95% CI 0.97–1.01, p=0.071). Incidence of group B streptococcus in infants aged 0–89 days was higher in studies that reported no use of intrapartum antibiotic prophylaxis than in infants in studies that reported any intrapartum antibiotic prophylaxis, but this effect was not significant (table 2).

We also constructed a multivariable model to closely investigate the effect of WHO region. In this analysis only the Asian region had a significantly different risk of group B streptococcus than the baseline group (Americas; adjusted odds ratio 0.077, 95% CI 0.023–0.260) after adjusting for all variables in the initial model except for gross national income.

We also repeated the analyses, assessing the effect of all explanatory variables on early-onset incidence of group B streptococcus. The only variable with an important association with risk of early-onset disease was use of intrapartum antibiotic prophylaxis. No use of prophylaxis was associated with a 2.2 times increased odds of early-onset group B streptococcal infection (odds ratio 2.20, 95% CI 1.59–3.40; incidence of early-onset disease 0.23 per 1000 livebirths in studies with any intrapartum antibiotic prophylaxis compared with 0.75 per 1000 livebirths in studies with no intrapartum antibiotic prophylaxis).

### Discussion

More studies are needed to accurately estimate the global burden of group B streptococcus, especially in low-income countries. We judge our overall estimate of group B streptococcus incidence (0.53 per 1000 livebirths) to be an underestimate of the global incidence. Incidence and case fatality were two-times higher in infants who had group B streptococcal disease in the first week of life (0–6 days) compared with later infancy (7–89 days). The disease is often rapidly fulminating and many cases can be missed because of difficulties with obtaining specimens before babies die. This issue is especially important in African and Asian countries with high case-fatality rates due to group B streptococcus. Our estimate also mirrors the current use of intrapartum antibiotic prophylaxis in high-income countries as it was used in almost 70% of the studies. This intervention has high efficacy in preventing early-onset group B streptococcus and has substantially reduced the incidence of early-onset disease since its introduction in the 1990s.8,9,10

Risk of group B streptococcal disease was two-times less in studies with small proportions (<20%) of infected low-birthweight infants than in studies with proportions ranging from 20–39%. Infants with low birthweight have a high risk of group B streptococcal infection and under-representation in a study sample can lead to substantial underestimations.6 Studies done in the UK and USA report an eight-times greater risk of group B streptococcal infection in infants under 1.5 kg and up to three-times greater risk in infants 1.4–2.5 kg than babies with normal birthweight.6,15

Studies done in Africa reported the highest incidence of group B streptococcal disease; almost three-times higher than in the Americas. By contrast, studies done in southeast Asia reported the lowest risk and two studies in this region reported no group B streptococcus. The disparities between Africa and Asia are striking. The low incidence in Asia could be a true regional estimate or could be due to high previous antibiotic use, high case fatality before specimen collection, or study design...
issues including small sample sizes and incomplete periods for data collection.

Distribution of group B streptococcus serotypes was strikingly similar across the WHO regions and no evidence was shown that distribution had changed over the past 30 years. Serotype III accounted for almost half of all the isolates followed by serotype Ia, II, and V. Five studies from middle-income countries (South Africa, Nigeria, Morocco, Romania, and Argentina) reported on distribution of serotypes. However, no studies in southeast Asia and in low-income countries were identified and serotypes might be different in these countries.

Our review had some limitations. Infants born to HIV-positive mothers have a high risk of late-onset group B streptococcal disease, but we were unable to assess the effect of HIV status in our meta-analysis due to insufficient data. We also were only able to include five studies from low-income countries and five studies from Asia and calculation of representative estimates of global or regional incidence of group B streptococcus were not possible. We also had few indicators of study quality. We were not able to obtain data on the proportion of specimens taken within 24 h of disease onset and had no clear measures of laboratory accuracy and reliability.

We also did not provide estimates of group B streptococcal cases and deaths by WHO region because we judged the studies to be too heterogeneous. This heterogeneity was due to the wide range of data sources retained, especially in the studies from low-income countries. However, we did adjust our regression analyses for important explanatory variables and presented both unadjusted and adjusted effect measures. Also, an important strength of our study was our comprehensive search strategy. We included all papers from the concurrent global burden of disease neonatal infection study regardless of whether group B streptococcus was isolated or not. Our study also seems to be the first synthesis of global group B streptococcus incidence, case fatality, and serotype data. Previous Cochrane reviews have only assessed the effect of important preventive interventions such as intrapartum antibiotic prophylaxis and vaginal chlorhexidine.

We included both inborn and outborn babies but all studies had to include contact with a hospital that could undertake laboratory investigations for common bacterial pathogens such as group B streptococcus. These studies are biased towards patients with severe disease, and more babies with group B streptococcal infection could have been included in these studies than those in the total population, thereby inflating our incidence estimate. Families who attend hospitals also have better access to health care and higher socioeconomic status than do those who do not attend hospitals. However, we showed that studies with lowest levels of skilled attendance at delivery (<70%) and lowest gross national income reported the highest risk of group B streptococcal infection. This finding contrasts with other studies that suggest that mothers with the highest socioeconomic status have the highest risk of infection.

This study has important implications for research and policy development. Low-income countries had the highest risk of group B streptococcus disease and mortality, yet little incidence and serotype data were available from these countries. High-quality group B streptococcus data are urgently needed from low-income countries, especially from Asia. These data are required to formulate prevention policies including the optimum use of intrapartum antibiotic prophylaxis and the potential use of group B streptococcus vaccines.

A simple risk-based algorithm for use of intrapartum antibiotic prophylaxis in preterm deliveries, premature rupture of membranes, and maternal pyrexia could be applied in health facilities in low-income countries. However, because of logistical issues, very few low-income countries are implementing any intrapartum antibiotic policies despite their known efficacy; and even when policies are implemented, they are often limited. Intrapartum antibiotic prophylaxis also is not currently reaching the women most in need—those with high-risk home deliveries. Emphasis must be placed on improving use of intrapartum antibiotic prophylaxis in low-income settings.

Our data also indicate that a conjugate vaccine incorporating five serotypes (Ia, Ib, II, III, V) could prevent over 85% of global group B streptococcal disease in infants aged younger than 3 months. Serotype distribution seems to be similar in Africa, western Pacific, Europe, the Americas, and the eastern Mediterranean regions and has not changed over the past 30 years. This finding contrasts with the regional variation in serotype distribution seen with other vaccine preventable diseases. Group B streptococcus conjugate vaccines are at advanced stages of testing and phase 3 trials will soon begin in Africa. Vaccination of pregnant women also has the potential to reduce premature births, stillbirths, and puerperal sepsis caused by group B streptococcus.

Contributors

PTH was responsible for the initial concept. KME, PTH, and SJS wrote the first draft. All authors reviewed the final version. AKMZ and KME designed the data abstraction system. CK and KME undertook the data abstraction. SS and SC undertook the statistical analyses.

Conflicts of interest

PTH is an investigator for clinical trials done on behalf of St George’s, University of London, London, UK, sponsored by vaccine manufacturers including Novartis vaccines and is a consultant to Novartis on group B streptococcus vaccines. Industry-sourced honoraria for consultancy by PTH are paid to an educational/administrative fund held by St George’s, University of London, London, UK. All other authors declare no conflicts of interests.

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