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

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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 We also reviewed reference lists and contacted experts to seek unpublished data and data missed by our search.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 early-onset 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.[1,2] 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.[4,5] Case fatality from both early-onset and late-onset disease is high, even with antibiotic therapy.[2,3] Group B streptococcus is also an important cause of preterm delivery, antepartum and intrapartum stillbirth, and puerperal sepsis.[6,7]

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).[8–10] 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.[11–13] 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.[6,14] 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 streptococcus 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.[15,16] 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.[16] 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.

	2000–11 (all articles)				1980–2011 (38 serotype articles)
	Total (68 papers)	Incidence (56 papers)	Case fatality (29 papers)	Serotypes (19 papers)	
WHO region					
Americas	16 (24%)	16 (29%)	9 (31%)	5 (26%)	9 (24%)
Africa	6 (9%)	4 (7%)	3 (10%)	1 (5%)	2 (5%)
Southeast Asia	5 (7%)	5 (9%)	0	0	0
Europe	24 (35%)	20 (36%)	12 (41%)	10 (53%)	19 (50%)
Eastern Mediterranean	4 (6%)	4 (7%)	3 (10%)	0	1 (3%)
Western Pacific	13 (19%)	7 (13%)	5 (17%)	3 (16%)	7 (18%)
Gross national income (in $US per head)					
High income (>12 196)	49 (72%)	41 (73%)	23 (79%)	17 (89%)	33 (87%)
High-middle income (3946–12 195)	5 (7%)	5 (9%)	1 (3%)	2 (11%)	3 (8%)
Low-middle income (996–3945)	9 (13%)	7 (13%)	2 (7%)	0	2 (5%)
Low income (<995)	5 (7%)	3 (5%)	3 (10%)	0	0
Skilled attendance at delivery					
≥70%	59 (87%)	49 (88%)	26 (90%)	19 (100%)	37 (97%)
<70%	9 (13%)	7 (13%)	3 (10%)	0	1 (3%)
Study design					
Prospective	29 (43%)	27 (48%)	8 (28%)	8 (42%)	14 (37%)
Retrospective	39 (57%)	29 (52%)	21 (72%)	11 (58%)	24 (63%)
Site of delivery					
Inborn	62 (91%)	27 (93%)	51 (91%)	19 (100%)	34 (89%)
Outborn	6 (9%)	5 (9%)	2 (7%)	0	4 (11%)
Reporting period					
Complete	44 (65%)	37 (66%)	18 (62%)	17 (89%)	26 (68%)
Incomplete	24 (35%)	19 (34%)	11 (38%)	2 (11%)	12 (32%)
Specimen type					
All sterile sites	54 (79%)	45 (80%)	26 (90%)	17 (58%)	33 (87%)
Blood only	14 (21%)	11 (20%)	3 (10%)	2 (11%)	5 (13%)
Intrapartum antibiotic prophylaxis					
Any intrapartum antibiotic prophylaxis used	47 (69%)	43 (77%)	19 (66%)	13 (68%)	17 (45%)
No intrapartum antibiotic prophylaxis used	21 (31%)	13 (23%)	10 (34%)	6 (32%)	21 (55%)
Low birthweight*					
<20%	17 (25%)	13 (23%)	10 (34%)	1 (5%)	3 (8%)
20–39%	51 (75%)	43 (77%)	19 (66%)	18 (95%)	35 (92%)
≥40%	0	0	0	0	0

*Proportion of infants with group B streptococcus who had low birthweight.

Table 1: **Characteristics of included studies**

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.[15–17] 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,

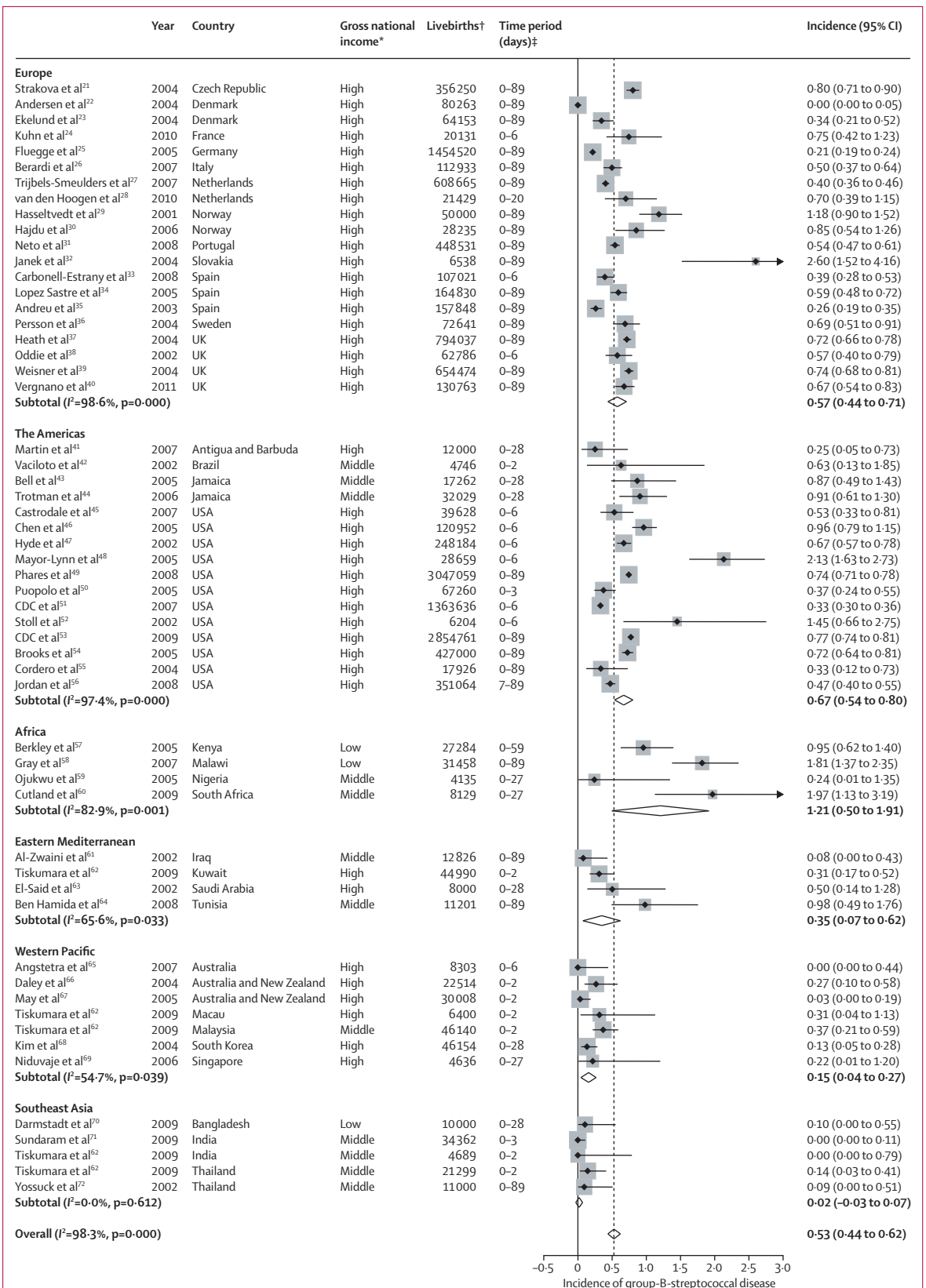

***Figure 1*: Meta-analysis of studies that reported incidence of group B streptococcus in infants with disease onset 0–89 days, 2000–11, by region**
*Gross national income in US$ per head. †Number of livebirths in the denominator of the study. ‡Data collection time period in days since the birth of the infant.

high-middle income, high income), and high versus low (≥70% *vs* <70%) skilled attendance at birth according to WHO criteria.[15]

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 specimens) versus blood only.[18,19] 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,[20] 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.

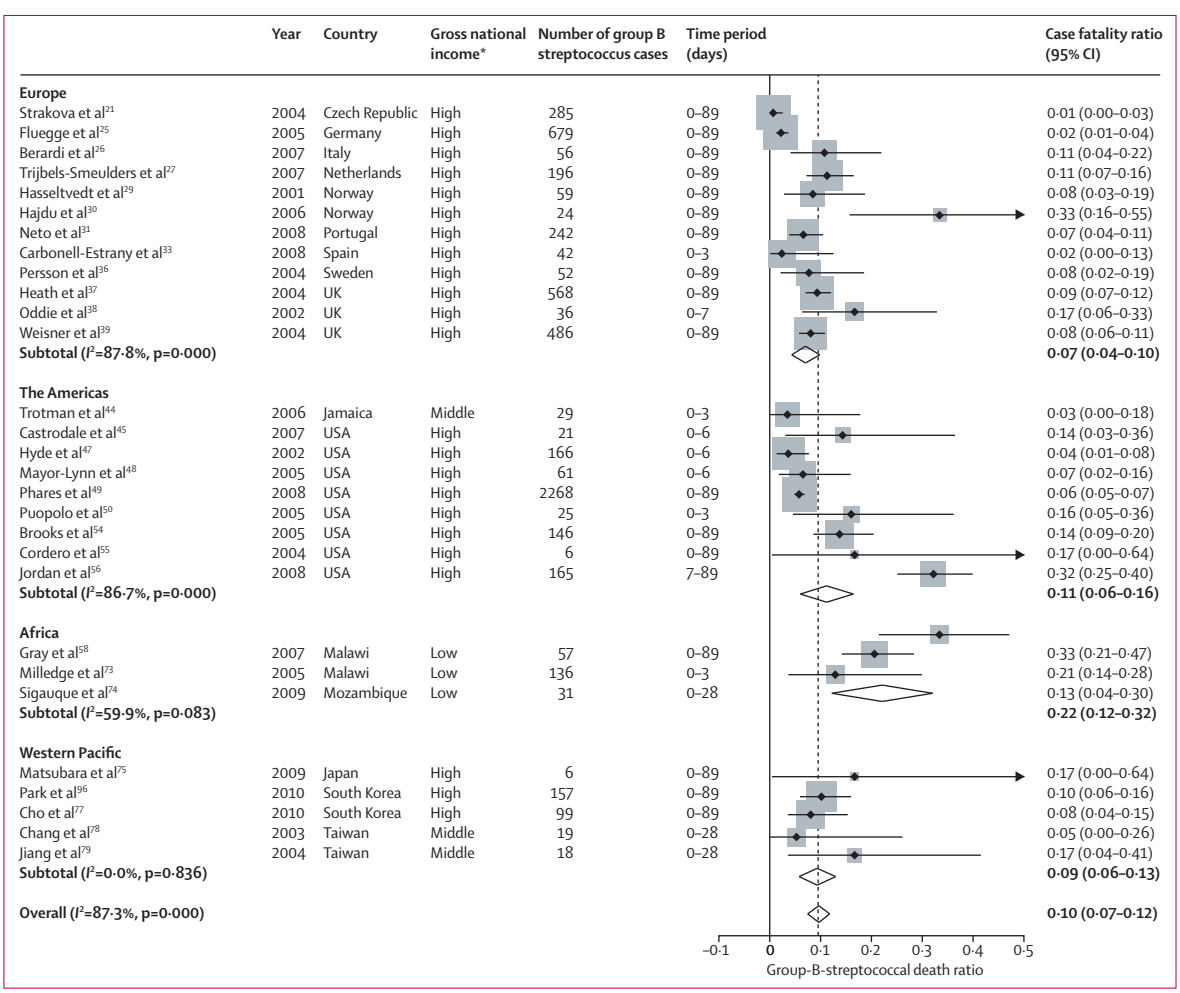

***Figure 2*: Meta-analysis of studies that reported data for case fatalilty caused by group B streptococcus in infants with disease onset 0–89 days, 2000–11, by region**
*Gross national income in US$ per head. †Data collection time period in days since the birth of the infant.

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). 56 studies reported incidence data,[21–72] 29 reported case fatality data,[21,25–27,29–31,33,36–39,44,45,47–50,54–56,58,73–79] and 19 reported serotype data (webappendix pp 1–11). The serotype search from 1980–2011 yielded a total of 38 papers (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 (webappendix 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).

56 papers reported incidence data for the overall period 0–89 days (table 1). Studies from low-income countries carried only 5% weight in the meta-analysis. Mean incidence was 0·53 per 1000 livebirths (95% CI 0·44–0·62; figure 1). Incidence was highest in Africa followed by the Americas and Europe. Southeast Asia had the lowest incidence. The studies were very heterogeneous in both the overall analysis and within regions (p<0·0001), except for southeast Asia (p=0·612). Even within countries a great deal of heterogeneity existed.

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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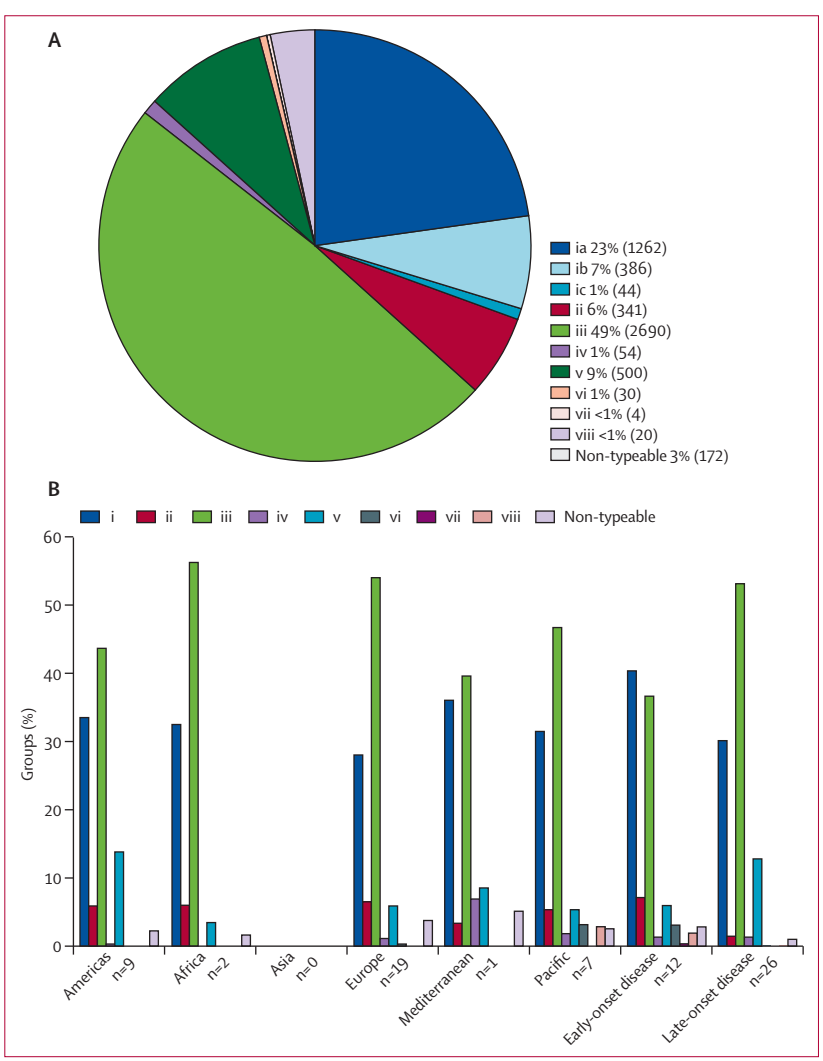

***Figure 3*: Global distribution of group B streptococcus serotypes, 1980–2011**
Distribution of group B streptococcus serotypes (A). Distribution of group B streptococcus serotypes by region and disease onset (B).

	Studies	Participants		Subgroup estimates; incidence (95% CI)	Univariable regression; odds ratio (95% CI)*	Multivariable regression; adjusted odds ratio*† (95% CI)
		Live births	Group B streptococcus			
WHO region					p=0·035	
Americas	16	8 638 370	5849	0·67 (0·54–0·80)	1	..
Africa	7	71 006	100	1·21 (0·50–1·91)	1·85 (0·77–4·45)	..
Southeast Asia	5	81 350	5	0·016 (0·033–0·065)	0·087 (0·025–0·30)	..
Europe	20	5 396 048	2701	0·57 (0·448–0·71)	0·86 (0·45–1·63)	..
Eastern Mediterranean	4	77 017	30	0·35 (0·073–0·62)	0·60 (0·24–1·52)	..
Western Pacific	4	164 155	33	0·15 (0·042–0·27)	0·26 (0·11–0·62)	..
Gross national income ($US per head)					p=0·691	p=0·710
High income (≥12 196)	41	14 151 386	8537	0·56 (0·47–0·65)	1	1
High-middle income (3946–12 195)	5	108 306	80	0·83 (0·42–1·23)	1·92 (0·76– 4·89)	1·759 (0·68–4·57)
Low-middle income (996–3945)	7	99 512	17	0·17 (0·013–0·33)	0·33 (0·12–0·89)	0·190 (0·066–0·54)
Low income (<995)	3	68 742	84	0·94 (0·040–1·91)	1·77 (0·59–5·31)	1·802 (0·60–5·42)
Skilled attendance at delivery					p=0·236	
≥70%	49	14 304 018	8630	0·65 (0·11–1·19)	1	..
<70%	7	123 928	88	0·56 (0·47–0·64)	0·66 (0·25–1·76)	..
Study design					p=0·906	p=0·902
Prospective	27	6 529 308	3793	0·47 (0·34–0·60)	1	1
Retrospective	29	7 898 638	4925	0·65 (0·54–0·75)	1·03 (0·66–1·59)	0·975 (0·66–1·44)
Delivery site					p=0·682	p=0·130
Inborn	51	14 223 575	8625	0·57 (0·49–0·66)	1	1
Outborn	5	204 371	93	0·40 (0·14–0·65)	0·81 (0·30–2·20)	0·50 (0·20–1·23)
Reporting period					p=0·219	p=0·026
Complete	37	14 016 126	8556	0·64 (0·55–0·74)	1	1
Incomplete	19	411 820	162	0·35 (0·23–0·46)	0·71 (0·41–1·23)	0·54 (0·32–0·93)
Specimen type					p=0·608	p=0·901
All sterile sites	45	13 999 368	8430	0·557 (0·47–0·65)	1	1
Blood only	11	428 578	288	0·60 (0·34–0·86)	1·15 (0·68–1·92)	1·03 (0·62–1·71)
Intrapartum antibiotic prophylaxis					p=0·968	p=0·112
Any intrapartum antibiotic prophylaxis used	43	13 831 239	8279	0·55 (0·46–0·64)	1	1
No intrapartum antibiotic prophylaxis used	13	596 707	439	0·64 (0·37–0·90)	1·02 (0·50–2·08)	1·81 (0·85–3·85)
Low birthweight*					p=0·014	p=0·005
20–39%	43	12 893 707	7859	0·69 (0·60–0·78)	1	1
<20%	13	1 534 239	859	0·38 (0·28– 0·57)	0·57 (0·36–0·89)	0·51 (0·32–0·81)

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.

***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**

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, 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).

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, 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 by contrast 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 the 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 the 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 birth weight 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.[8,9,37]

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.[37] 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.[37,47]

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,[80] 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[81,82] and vaginal chlorhexidine.[83]

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,[84,85] 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.[86] 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.[87,88]

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.[8,89] 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.[90,91] Group B streptococcus conjugate vaccines are at advanced stages of testing and phase 3 trials will soon begin in Africa.[14,92] Vaccination of pregnant women also has the potential to reduce premature births, stillbirths, and puerperal sepsis caused by group B streptococcus.[6]

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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References

1 Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B Streptococcal and *E coli* disease continues. *Pediatrics* 2011; **127:** 817–26.

2 Remington JS, ed. Infectious disease of the fetus and the newborn infant. 7th edn. Philadephia: Elsevier Saunders, 2011.

3 Colbourn T, Gilbert R. An overview of the natural history of early onset group B streptococcal disease in the UK. *Early Hum Dev* 2007; **83:** 149–56.

4 Guilbert J, Levy C, Cohen R, Delacourt C, Renolleau S, Flamant C. Late and ultra late onset Streptococcus B meningitis: clinical and bacteriological data over 6 years in France. *Acta Paediatr* 2009; **99:** 47–51.

5 Van Dyke MK, Phares CR, Lynfield R, et al. Evaluation of universal antenatal screening for group B streptococcus. *N Engl J Med* 2009; **360:** 2626–36.

6 Heath PT. An update on vaccination against group B streptococcus. *Expert Rev Vaccines* **10:** 685–94.

7 Walsh JA, Hutchins S. Group B streptococcal disease: its importance in the developing world and prospect for prevention with vaccines. *Pediatr Infect Dis J* 1989; **8:** 271–77.

8 Schrag SJ, Zell ER, Lynfield R, et al. A population-based comparison of strategies to prevent early-onset group B streptococcal disease in neonates. *N Engl J Med* 2002; **347:** 233–39.

9 de la Rosa Fraile M, Cabero L, Andreu A, Rao GG. Prevention of group B streptococcal neonatal disease: a plea for a European consensus. *Clin Microbiol Infect* 2001; **7:** 25–27.

10 Colbourn TE, Asseburg C, Bojke L, et al. Preventive strategies for group B streptococcal and other bacterial infections in early infancy: cost effectiveness and value of information analyses. *BMJ* 2007; **335:** 655.

11 Schrag SJ, Zywicki S, Farley MM, et al. Group B streptococcal disease in the era of intrapartum antibiotic prophylaxis. *N Engl J Med* 2000; **342:** 15–20.

12 Madhi SA, Radebe K, Crewe-Brown H, et al. High burden of invasive *Streptococcus agalactiae* disease in South African infants. *Ann Trop Paediatr* 2003; **23:** 15–23.

13 Molyneux E, Walsh A, Phiri A, Molyneux M. Acute bacterial meningitis in children admitted to the Queen Elizabeth Central Hospital, Blantyre, Malawi in 1996–97. *Trop Med Int Health* 1998; **3:** 610–18.

14 Schrag SJ. Group B streptococcal vaccine for resource-poor countries. *Lancet* 2011; **378:** 11–12.

15 WHO. Child Health Epidemiology Reference Group (CHERG). http://www.who.int/child_adolescent_health/data/cherg/en/index.html (accessed May 1, 2011).

16 Global Burden of Diseases, Injuries, and Risk Factors Study. http://www.globalburden.org (accessed May 1, 2011).

17 World Bank. GNI per capita, Atlas method. http://data.worldbank.org/indicator/NY.GNP.PCAP.CD (accessed May 1, 2011).

18 Ansong AK, Smith PB, Benjamin DK, et al. Group B streptococcal meningitis: cerebrospinal fluid parameters in the era of intrapartum antibiotic prophylaxis. *Early Hum Dev* 2009; **85:** S5–7.

19 Bromberger P, Lawrence JM, Braun D, Saunders B, Contreras R, Petitti DB. The influence of intrapartum antibiotics on the clinical spectrum of early-onset group B streptococcal infection in term infants. *Pediatrics* 2000; **106:** 244–50.

20 ACOG Committee Opinion: number 279, December 2002. Prevention of early-onset group B streptococcal disease in newborns. *Obstet Gynecol* 2002; **100**: 1405–12.

21 Strakova L, Motlova J. Active surveillance of early onset disease due to group B streptococci in newborns. *Indian J Med Res* 2004; **119:** 205–07.

22 Andersen J, Christensen R, Hertel J. Clinical features and epidemiology of septicaemia and meningitis in neonates due to *Streptococcus agalactiae* in Copenhagen County, Denmark: a 10 year survey from 1992 to 2001. *Acta Paediatr* 2004; **93**: 1334–39.

23 Ekelund K, Konradsen HB. Invasive group B streptococcal disease in infants: a 19-year nationwide study. Serotype distribution, incidence and recurrent infection. *Epidemiol Infect* 2004; **132:** 1083–90.

24 Kuhn P, Dheu C, Bolender C, et al. Incidence and distribution of pathogens in early-onset neonatal sepsis in the era of antenatal antibiotics. *Paediatr Perinat Epidemiol* 2010; **24:** 479–87.

25 Fluegge K, Siedler A, Heinrich B, Schulte-Moenting J, Moennig MJ, Bartels DB, et al. Incidence and clinical presentation of invasive neonatal group B streptococcal infections in Germany. *Pediatrics* 2006; **117:** e1139–45.

26 Berardi A, Lugli L, Baronciani D, et al. Group B streptococcal infections in a northern region of Italy. *Pediatrics* 2007; **120:** e487–93.

27 Trijbels-Smeulders M, de Jonge GA, Pasker-de Jong PC, et al. Epidemiology of neonatal group B streptococcal disease in the Netherlands before and after introduction of guidelines for prevention. *Arch Dis Child Fetal Neonatal Ed* 2007; **92:** F271–76.

28 van den Hoogen A, Gerards LJ, Verboon-Maciolek MA, Fleer A, Krediet TG. Long-term trends in the epidemiology of neonatal sepsis and antibiotic susceptibility of causative agents. *Neonatology* 2009; **97:** 22–28.

29 Hasseltvedt V, Høiby EA. Systemic streptococcal group B disease in Norway-an increasing health problem. *Euro Surveill* 2001; **5:** 2086.

30 Hajdu A, Blystad H, Hoiby EA, Klouman E, Schimmer B, Nygard K. Unexpected increase in case fatality of invasive group B streptococcal infections in infants in Norway, January–July 2006. *Euro Surveill* 2006; **11:** E060727.2.

31 Neto MT. Group B streptococcal disease in Portuguese infants younger than 90 days. *Arch Dis Child Fetal Neonatal Ed* 2008; **93:** F90–93.

32 Lea J. Screening of hemolytical streptococcus of group B in pregnancy and prevention of infection in newborns. *Ceska Gynekologie* 2004; **69:** 91–94.

33 Carbonell-Estrany X, Figueras-Aloy J, Salcedo-Abizanda S, de la Rosa-Fraile M. Probable early-onset group B streptococcal neonatal sepsis: a serious clinical condition related to intrauterine infection. *Arch Dis Child Fetal Neonatal Ed* 2008; **93:** F85–89.

34 Lopez Sastre JB, Fernandez Colomer B, Coto Cotallo GD, Ramos Aparicio A. Trends in the epidemiology of neonatal sepsis of vertical transmission in the era of group B streptococcal prevention. *Acta Paediatr* 2005; **94:** 451–57.

35 Andreu A, Sanfeliu I, Vinas L, et al. [Decreasing incidence of perinatal group B streptococcal disease (Barcelona 1994-2002). Relation with hospital prevention policies]. *Enferm Infecc Microbiol Clin* 2003; **21:** 174–79.

36 Persson E, Berg S, Trollfors B, et al. Serotypes and clinical manifestations of invasive group B streptococcal infections in western Sweden 1998–2001. *Clin Microbiol Infect* 2004; **10:** 791–96.

37 Heath PT, Balfour G, Weisner AM, et al. Group B streptococcal disease in UK and Irish infants younger than 90 days. *Lancet* 2004; **363:** 292–94.

38 Oddie S, Embleton ND. Risk factors for early onset neonatal group B streptococcal sepsis: case-control study. *BMJ* 2002; **325:** 308.

39 Weisner AM, Johnson AP, Lamagni TL, et al. Characterization of group B streptococci recovered from infants with invasive disease in England and Wales. *Clin Infect Dis* 2004; **38:** 1203–08.

40 Vergnano S, Menson E, Kennea N, et al. Neonatal infections in England: the NeonIN surveillance network. *Arch Dis Child Fetal Neonatal Ed* 2010; **96:** F9–14.

41 Martin TC, Adamson J, Dickson T, DiGiantomasso E, Nesbitt C. Does group B streptococcal infection contribute significantly to neonatal sepsis in Antigua and Barbuda? *West Indian Med J* 2007; **56:** 498–501.

42 Vaciloto E, Richtmann R, de Paula Fiod Costa H, Kusano EJ, de Ameida MF, Amaro ER. A survey of the incidence of neonatal sepsis by group B streptococcus during a decade in a Brazilian maternity hospital. *Braz J Infect Dis* 2002; **6:** 55–62.

43 Bell Y, Barton M, Thane M, Nicholson A, Trotman H. Neonatal sepsis in Jamaican neonates. *Ann Trop Paediatr* 2005; **25:** 293–96.

44 Trotman H, Bell Y. Neonatal group B streptococcal infection at the University Hospital of the West Indies, Jamaica: a 10-year experience. *Ann Trop Paediatr* 2006; **26:** 53–57.

45 Castrodale L, Gessner B, Hammitt L, Chimonas MA, Hennessy T. Invasive early-onset neonatal group B streptococcal cases—Alaska, 2000–2004. *Matern Child Health J* 2007; **11:** 91–95.

46 Chen KT, Puopolo KM, Eichenwald EC, Onderdonk AB, Lieberman E. No increase in rates of early-onset neonatal sepsis by antibiotic-resistant group B Streptococcus in the era of intrapartum antibiotic prophylaxis. *Am J Obstet Gynecol* 2005; **192:** 1167–71.

47 Hyde TB, Hilger TM, Reingold A, Farley MM, O'Brien KL, Schuchat A. Trends in incidence and antimicrobial resistance of early-onset sepsis: population-based surveillance in San Francisco and Atlanta. *Pediatrics* 2002; **110:** 690–95.

48 Mayor-Lynn K, Gonzalez-Quintero VH, O'Sullivan MJ, Hartstein AI, Roger S, Tamayo M. Comparison of early-onset neonatal sepsis caused by Escherichia coli and group B Streptococcus. *Am J Obstet Gynecol* 2005; **192:** 1437–39.

49 Phares CR, Lynfield R, Farley MM, et al. Epidemiology of invasive group B streptococcal disease in the United States, 1999–2005. *JAMA* 2008; **299:** 2056–65.

50 Puopolo KM, Madoff LC, Eichenwald EC. Early-onset group B streptococcal disease in the era of maternal screening. *Pediatrics* 2005; **115:** 1240–46.

51 Perinatal group B streptococcal disease after universal screening recommendations—United States, 2003–2005. *MMWR Morb Mortal Wkly Rep* 2007; **56:** 701–05.

52 Stoll BJ, Hansen N, Fanaroff AA, et al. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. *N Engl J Med* 2002; **347:** 240–47.

53 Trends in perinatal group B streptococcal disease—United States, 2000–2006. *MMWR Morb Mortal Wkly Rep* 2009; **58:** 109–12.

54 Early-onset and late-onset neonatal group B streptococcal disease—United States, 1996–2004. *MMWR Morb Mortal Wkly Rep* 2005; **54:** 1205–08.

55 Cordero L, Rau R, Taylor D, Ayers LW. Enteric gram-negative bacilli bloodstream infections: 17 years' experience in a neonatal intensive care unit. *Am J Infect Control* 2004; **32:** 189–95.

56 Jordan HT, Farley MM, Craig A, et al. Revisiting the need for vaccine prevention of late-onset neonatal group B streptococcal disease: a multistate, population-based analysis. *Pediatr Infect Dis J* 2008; **27:** 1057–64.

57 Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med* 2005; **352:** 39–47.

58 Gray KJ, Bennett SL, French N, Phiri AJ, Graham SM. Invasive group B streptococcal infection in infants, Malawi. *Emerg Infect Dis* 2007; **13:** 223–29.

59 Ojukwu JU, Abonyi LE, Ugwu J, Orji IK. Neonatal septicemia in high risk babies in South-Eastern Nigeria. *J Perinat Med* 2005; **34:** 166–72.

60 Cutland CL, Madhi SA, Zell ER, et al. Chlorhexidine maternal-vaginal and neonate body wipes in sepsis and vertical transmission of pathogenic bacteria in South Africa: a randomised, controlled trial. *Lancet* 2009; **374:** 1909–16.

61 Al-Zwaini EJ. Neonatal septicaemia in the neonatal care unit, Al-Anbar governorate, Iraq. *East Mediterr Health J* 2002; **8:** 509–14.

62 Tiskumara R, Fakharee SH, Liu CQ, et al. Neonatal infections in Asia. *Arch Dis Child Fetal Neonatal Ed* 2009; **94:** F144–48.

63 El-Said MF, Bessisso MS, Janahi MA, Habob LH, El-Shafie SS. Epidemiology of neonatal meningitis in Qatar. *Saudi Med J* 2002; **23:** 789–92.

64 Ben Hamida Nouaili E, Harouni M, Chaouachi S, Sfar R, Marrakchi Z. [Early-onset neonatal bacterial infections: a retrospective series of 144 cases]. *Tunis Med* 2008; **86:** 136–39.

65 Angstetra D, Ferguson J, Giles WB. Institution of universal screening for Group B streptococcus (GBS) from a risk management protocol results in reduction of early-onset GBS disease in a tertiary obstetric unit. *Aust N Z J Obstet Gynaecol* 2007; **47:** 378–82.

66 Daley AJ, Isaacs D. Ten-year study on the effect of intrapartum antibiotic prophylaxis on early onset group B streptococcal and Escherichia coli neonatal sepsis in Australasia. *Pediatr Infect Dis J* 2004; **23:** 630–34.

67 May M, Daley AJ, Donath S, Isaacs D. Early onset neonatal meningitis in Australia and New Zealand, 1992–2002. *Arch Dis Child Fetal Neonatal Ed* 2005; **90:** F324–27.

68 Kim JS, Jang YT, Kim JD, et al. Incidence of *Haemophilus influenzae* type b and other invasive diseases in South Korean children. *Vaccine* 2004; **22:** 3952–62.

69 Niduvaje K, Amutha C, Roy J. Early neonatal streptococcal infection. *Indian J Pediatr* 2006; **73:** 573–76.

70 Darmstadt GL, Saha SK, Choi Y, et al. Population-based incidence and etiology of community-acquired neonatal bacteremia in Mirzapur, Bangladesh: an observational study. *J Infect Dis* 2009; **200:** 906–15.

71 Sundaram V, Kumar P, Dutta S, et al. Blood culture confirmed bacterial sepsis in neonates in a North Indian tertiary care center: changes over the last decade. *Jpn J Infect Dis* 2009; **62:** 46–50.

72 Yossuck P, Preedisripipat K. Neonatal group B streptococcal infection: incidence and clinical manifestation in Siriraj Hospital. *J Med Assoc Thai* 2002; **85** (suppl 2)**:** S479–87.

73 Milledge J, Calis JC, Graham SM. Aetiology of neonatal sepsis in Blantyre, Malawi: 1996–2001. *Ann Trop Paediatr* 2005; **25:** 101–10.

74 Sigauque B, Roca A, Mandomando I, et al. Community-acquired bacteremia among children admitted to a rural hospital in Mozambique. *Pediatr Infect Dis J* 2009; **28:** 108–13.

75 Matsubara K, Yamamoto G. Invasive group B streptococcal infections in a tertiary care hospital between 1998 and 2007 in Japan. *Int J Infect Dis* 2009; **13:** 679–84.

76 Park KH, Kim KH, Kang JH, et al. Current status and clinical presentations of invasive neonatal Group B streptococcal infections in Korea. *Pediatr Int* 2010; **53:** 236–39.

77 Cho HK, Lee H, Kang JH, et al. The causative organisms of bacterial meningitis in Korean children in 1996–2005. *J Korean Med Sci* 2010; **25:** 895–99.

78 Chang CJ, Chang WN, Huang LT, et al. Neonatal bacterial meningitis in southern Taiwan. *Pediatr Neurol* 2003; **29:** 288–94.

79 Jiang JH, Chiu NC, Huang FY, et al. Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset. *J Microbiol Immunol Infect* 2004; **37:** 301–06.

80 Epalza C, Goetghebuer T, Hainaut M, et al. High incidence of invasive group B streptococcal infections in HIV-exposed uninfected infants. *Pediatrics* 2010; **126:** e631–38.

81 Ohlsson A, Shah VS. Intrapartum antibiotics for known maternal Group B streptococcal colonization. *Cochrane Database Syst Rev* 2009: **3:** CD007467.

82 Woodgate P, Flenady V, Steer P. Intramuscular penicillin for the prevention of early onset group B streptococcal infection in newborn infants. *Cochrane Database Syst Rev* 2004; **3:** CD003667.

83 Stade B, Shah V, Ohlsson A. Vaginal chlorhexidine during labour to prevent early-onset neonatal group B streptococcal infection. *Cochrane Database Syst Rev* 2004; **3:** CD003520.

84 Edmond K, Zaidi A. New approaches to preventing, diagnosing, and treating neonatal sepsis. *PLoS Med* 2010; **7:** e1000213.

85 Zaidi AK, Huskins WC, Thaver D, Bhutta ZA, Abbas Z, Goldmann DA. Hospital-acquired neonatal infections in developing countries. *Lancet* 2005; **365:** 1175–88.

86 Edmond KM, Quigley MA, Zandoh C, et al. Aetiology of stillbirths and neonatal deaths in rural Ghana: implications for health programming in developing countries. *Paediatr Perinat Epidemiol* 2008; **22:** 430–37.

87 Conclusions from the WHO multicenter study of serious infections in young infants. The WHO Young Infants Study Group. *Pediatr Infect Dis J* 1999; **18** (10 suppl)**:** S32–34.

88 Stoll BJ. The global impact of neonatal infection. *Clin Perinatol* 1997; **24:** 1–21.

89 Stoll BJ, Hansen NI, Sanchez PJ, et al. Early onset neonatal sepsis: the burden of group B streptococcal and *E. coli* Disease Continues. *Pediatrics* 2011; **127:** 817–26.

90 O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. *Lancet* 2009; **374:** 893–902.

91 Trotter CL, McVernon J, Ramsay ME, et al. Optimising the use of conjugate vaccines to prevent disease caused by *Haemophilus influenzae* type b, *Neisseria meningitidis* and *Streptococcus pneumoniae*. *Vaccine* 2008; **26:** 4434–45.

92 DEVANI. Vaccine against neonatal infections: design of a vaccine to immunize neonates against GBS infections through a durable maternal immune response. Oct 5, 2010. http://www.devaniproject.org (accessed May 1, 2011).