The Pediatric Infectious Disease Journal Publish Ahead of Print

DOI: 10.1097/INF.0000000000001233

Disease Burden of Group B Streptococcus among Infants in sub-Saharan Africa: A Systematic Literature Review and Meta-Analysis

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Abbreviated title: Group B Streptococcus Disease in Sub-Saharan Africa

Running head: GBS Disease in Sub-Saharan Africa

Conflicts of Interest and Sources of Funding: NH, RSH, and SAM have been in receipt of funding for a GBS vaccine trial from Novartis Vaccines and Diagnostics, Inc. SAM has received honoraria for advisory board participation from Pfizer, Inc. All other authors report no conflict of interest. This study was supported by award OPP1105076 from the Bill and Melinda Gates Foundation.

Key Words: Africa, Group B Streptococcus, neonatal sepsis, neonatal meningitis, global health, meta-analysis

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Background

Group B streptococcus (GBS) is a leading neonatal sepsis pathogen globally. Investment in GBS disease prevention, such as maternal vaccination, requires evidence of disease burden, particularly in high infant mortality regions like sub-Saharan Africa. We aimed to provide such evidence by conducting a systematic literature review and meta-analysis to estimate maternal colonization proportion, GBS disease incidence, and GBS serotype distribution.

Methods

MEDLINE, MEDLINE in process, and Cochrane Library were searched for studies published 1990 – 2014, pertaining to sub-Saharan Africa. Eligible studies were used to estimate the proportion of pregnant women colonized with GBS, early-onset GBS (EOGBS) disease incidence, late-onset GBS (LOGBS) disease incidence, and respective serotype distributions. Random effects meta-analysis was conducted to estimate weighted means and confidence intervals.

Results

We identified 17 studies of colonization, nine of disease incidence, and six of serotype distribution meeting inclusion criteria. 21.8% (95% CI 18.3, 25.5) of expectant women were colonized with GBS. The incidence of EOGBS disease was 1.3 per 1000 births (95% CI 0.81, 1.9), that of LOGBS disease 0.73 per 1000 births (95% CI 0.48, 1.0). The most common disease-causing serotype was 3, followed by 1a. Serotypes 1b, 2 and 5 were next most common in frequency.

Conclusion

Despite methodologic factors leading to under-estimation, GBS disease incidence appears high in sub-Saharan Africa. A small number of GBS serotypes cause almost all disease. GBS disease burden in sub-Saharan Africa suggests that safe, effective, and affordable GBS disease prevention is needed.

Introduction

Streptococcus agalactiae, or group B streptococcus (GBS), is a leading neonatal sepsis pathogen globally and may have a particularly high burden of disease in Africa.(1) Maternal rectovaginal GBS colonization is a risk factor for infant disease. In some high-income countries, intrapartum antibiotic prophylaxis (IAP) that targets pregnant women shown to be colonized with GBS on rectovaginal swabs collected several weeks before delivery has greatly reduced the burden of GBS disease by preventing early-onset cases (EOGBS disease, occurring days 0 – 6 of life).(2) This strategy, however, is unlikely to be feasible in low- and some middle-income countries due to lack of resources. Risk factor-based IAP, which targets women with known risk factors such as intrapartum fever or preterm labor, is less costly than prenatal screening, but nonetheless challenging to implement in resource-poor settings. Moreover, IAP does not prevent late-onset GBS disease (LOGBS disease, occurring days 7 – 90 of life).

A serotype-specific maternal GBS polysaccharide-protein conjugate vaccine to prevent both EOGBS and LOGBS disease in newborns has completed Phase II clinical trials in South Africa and Malawi,(3, 4) Although the trivalent vaccine candidate will not move forward to Phase III trials, planning for the development of a pentavalent vaccine has begun. International health organizations and funders need information on the potential impact of introducing a new vaccine, if encouraging results from clinical trials become available. Such information is also needed for health economic studies, where incidence of GBS disease has been shown to be a leading driver of cost-effectiveness.(5) Thus, disease burden data are key to the evidence base that informs decision-making regarding new vaccine introduction. While global analysis has previously been conducted, relatively few studies from sub-Saharan Africa were included(1) and detailed consideration of sub-Saharan Africa's GBS disease burden is needed to guide policy decisions regarding prevention. We conducted a systematic literature review and evidence synthesis using meta-analysis, focusing on three metrics of GBS disease burden in sub-Saharan Africa: maternal colonization proportion, GBS disease incidence, and GBS serotype distribution.

Methods

Eligibility criteria

Following standard guidelines,(6) we conducted systematic literature reviews and meta-analyses for the following outcomes 1) proportion of pregnant women colonized with GBS; 2) incidence of early-onset and 3) late-onset GBS disease in infants; and 4) proportions of GBS isolate serotypes (Ia, Ib, II, III and V) which would be covered by a potential pentavalent vaccine. Serotype studies were sub-categorized by studies examining maternal colonizing serotypes and infant disease-causing serotypes. Because other candidate vaccines may be developed, we also collected information concerning the contributions of individual serotypes to overall serotype distribution, estimating cumulative serotype coverage sequentially by ordering GBS serotypes by frequency. Information regarding case fatality ratios (CFRs) was also abstracted from incidence studies.

The search strategy, inclusion and exclusion criteria are summarized in Table 1. The geographic scope of analysis was limited to sub-Saharan Africa.[*] Only studies published from 1990 to 2014 were included. Published trials and observational studies, including prospective and retrospective cohort, case series, case-control, and cross-sectional studies evaluating maternal colonization, infant GBS disease incidence, and GBS serotypes from expectant mothers or neonates were considered for eligibility. Only English language papers were considered for inclusion.

Sources, search, and study selection

Studies were identified using the databases and search strategies, developed with input from a biomedical reference librarian, shown in Table 1. In addition, the bibliographies of papers selected for inclusion after full text review were searched for additional sources.

[*] Angola, Benin, Botswana, Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Dem. Rep. Congo, Rep. Congo, Côte d'Ivoire, Equatorial Guinea, Eritrea, Ethiopia, Gabon, The Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Namibia, Niger, Nigeria, Rwanda, Senegal, , Sierra Leone, Somalia, South Africa, South Sudan, Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe. The island nations of Cabo Verde, São Tomé and Principe, and Seychelles were excluded.

To mitigate publication bias, an extensive search for unpublished data was conducted. We identified unpublished sources of data in two steps: (1) we searched the online abstract books for 2013 and 2014 for two international congresses (IDWeek and European Society for Paediatric Infectious Diseases). The convening president of a third biannual international congress (World Society for Paediatric Infectious Diseases) held in 2013 was queried regarding relevant abstracts in their abstract book, not available online. The Working Group supporting this project -- investigators working in neonatal sepsis and meningitis in sub-Saharan Africa -- were asked to identify additional sources of abstract-level or unpublished data, either from their own groups or those of colleagues. The review of published literature was conducted in September 2014 and unpublished searches were finalized in January 2015.

Study selection was performed in a standardized manner, applying inclusion and exclusion criteria to titles and abstracts, and then to the full texts of studies. This assessment was performed by a single author (KK) and then reviewed by a second author (AS).

Data collection

Data abstracted described the publication, characterized methods, characterized quality, and summarized outcomes. Detailed data items abstracted from each study are summarized in Table 1.

Data were collected using a data extraction Excel spreadsheet. One author (KK) performed data extraction and a second author (AS) reviewed the extracted data. Uncertainties were resolved by discussion between authors. Summary outcomes were as described under “Eligibility criteria.”

Meta-analysis

Random effects meta-analysis was performed for each outcome,(7) using OpenMetaAnalyst,(8) to estimate weighted means and associated 95% confidence intervals. Because some proportions were close to one, we stabilized variances with a Freeman-Tukey arcsine transformation before pooling. The DerSimonian-Laird method for estimating random-effects, with a correction factor of 0.5 added to zero-valued cells, was implemented to obtain the estimates. Heterogeneity was examined using *Q*, a chi-squared statistic, where a

p-value < 0.05 suggests effects across all studies are not the same, and I^2, a statistic used to quantify inconsistency across studies, with I^2 values >50% representing substantial heterogeneity. (9)

Results

Study selection and study characteristics

The results of the initial literature search and study selection are summarized in Table 2, which concisely summarizes the information that would be included in separate PRISMA charts for each of the four outcomes. Two unpublished studies in progress were identified and included in the systematic literature review.

Tables 3 and 4 summarize study characteristics and provide a description of the studies. In total, nine of 45 sub-Saharan African countries contributed data to at least one of the systematic literature reviews. Five of the ten countries with the largest birth cohorts in sub-Saharan Africa contributed data to at least one of the systematic literature reviews. South Africa predominated as a contributor of data. 4094 (47.4%) observations included in the maternal colonization review were from South Africa; the next two leading contributors were Malawi and Zimbabwe, contributing 1954 (22.6%) and 1491 (17.3%) observations respectively. A similar pattern was observed in the reviews for EOGBS disease incidence, LOGBS disease incidence, maternal serotype distribution, and infant EOGBS/ LOGBS disease serotype distribution. South Africa contributed the largest number of observations of any single country, but 54% of observations in the maternal colonization analysis, 26% of observations contributing to EOGBS disease incidence analysis, 42% contributing to the LOGBS disease incidence analysis, and 43% of observations contributing to any serotype analysis were from low-income countries in sub-Saharan Africa. 21 of 25 studies were performed at urban sites only, while four studies described at least one rural site.

Maternal GBS colonization

Across the region, an average of 21.8% (95% CI 18.3, 25.5) of women included in the studies identified were colonized with GBS either antenatally or during labor. There was heterogeneity across studies in this proportion (Figure 1A), as indicated by a chi-square p value of <0.0001 and I^2 value of 94%. In addition to

possible true population differences, other sources of heterogeneity may have included methodological differences in the collection of specimens and microbiological processing. Four published studies collected only vaginal specimens for culture; eleven studies collected rectovaginal specimens but only seven sampled both lower vagina and rectum, as is recommended to maximize yield.(2) Three published studies did not describe the use of selective enrichment broths, such as Todd-Hewitt or Lim broth, also recommended to maximize yield.(2)

Figure 1B suggests that variability among study results may be related to small study size, with larger studies consistently showing a colonization rate of ~21-22% and smaller studies arrayed symmetrically around this average. In sensitivity analysis, when data from South Africa were removed and data from the remaining countries re-analyzed, the pooled average proportion was 20.7% (15.4, 26.7). When studies were restricted to the seven that sampled both body sites with the highest yield (lower vagina and rectum), the proportion of women colonized with GBS rose to 26.0% (95% CI 17.2, 35.9).

Incidence of EOGBS and LOGBS disease

The estimated average incidence of EOGBS disease was 1.3 cases per 1,000 births (Figure 2A). The estimated incidence of LOGBS disease was 0.73 per 1,000 births (Figure 2B), roughly 1/2 the EOGBS disease incidence. As with maternal colonization, there was substantial heterogeneity across studies reporting EOGBS (LOGBS) incidence with chi-square p-values <0.0001 for both outcomes and I^2 values of 90% (59%). Of note, 2 of 8 published studies reported intrapartum antibiotic use in the study population; the remainder did not provide this information.

In addition to any true population differences, methodological differences may also have contributed to heterogeneity. Studies differed in the method of case ascertainment: Five of the published studies were prospective; three of the studies were retrospective; two collected blood only for culture, as opposed to five that collected both blood and/ or cerebrospinal fluid for culture. It is likely that clinician thresholds for drawing sterile site cultures and the ability to capture infants on the day of birth varied across studies, although this information was difficult to abstract from published reports. Studies also varied in setting, with

the majority of studies conducted in urban settings. All studies appeared facility-based but varied in whether facilities were outpatient (health centers and clinics) or inpatient.

All studies undergoing abstract review for EOGBS or LOGBS incidence were also screened for information concerning CFRs. All incidence studies also presented information on CFRs. However, they reported CFRs after sub-categorizing EOGBS and LOGBS disease in different ways and using different patient age cut-offs, making meta-analysis impractical because CFRs were defined using different numerators and denominators. For example, a study from Malawi(10) defined EOGBS and LOGBS disease as GBS isolated from blood or CSF sample from patients from birth to six days of age and from seven to ninety days of age, respectively. It reported a CFR of 38% (95% CI 20, 56) for EOGBS disease and a CFR of 29% (95% CI 12, 45) for LOGBS disease. A large study from South Africa(11) also defined EOGBS and LOGBS disease as positive blood or CSF sample from patients from birth to six days old and from seven to ninety days, respectively; it reported a CFR of 20% (95% CI 13, 27) for EOGBS disease and 14% (95% CI 5, 22) for LOGBS disease. A second study from Malawi(12) and a study from Mozambique(13) reported CFRs for all GBS septicemia and meningitis occurring between the ages of 0 to 30 days of 21% and 26% respectively (insufficient information to calculate 95% CI). By comparison, a much lower CFR for all GBS disease occurring between 0 and 30 days (12%) was reported in a study in progress in Mozambique (95% CI 1, 23). [Betuel Sigauque, personal communication]

GBS serotype distribution

967 maternal colonizing samples from five studies were included in the meta-analysis of the proportion of maternal colonizing serotypes that would be covered by a pentavalent vaccine (Ia, Ib, II, III, and V). The average proportion of vaccine-covered maternal colonizing serotypes was 83.9% (95% CI 75.3, 91.0; Figure 3a). These studies comprise a subset of those included in the maternal colonization analysis and as a result, significant heterogeneity was present with a p value < 0.001 and I^2 value of 84%.

A total of 237 serotyped infant samples from three studies conducted in Malawi and South Africa were included in the meta-analysis of the proportion EOGBS disease-causing serotypes covered by a pentavalent vaccine; for LOGBS disease-causing isolates, 173 samples and 3 studies were analyzed. The average proportion of EOGBS isolates that were vaccine-covered serotypes was 97.4% (95% CI 93.7, 99.6;

Figure 3b), while for LOGBS the proportion was 97.7 (95% CI 90.5, 100; Figure 3c). Heterogeneity was not found in the analysis of EOGBS disease-causing isolates but was found in the analysis of LOGBS disease-causing isolates (p-value=0.045, I^2 = 68%).

Figure 4 shows individual serotype contributions. Serotypes Ia, Ib, II, III and V were dominant strains, with serotype III alone contributing 54% to the overall serotype distribution for EOGBS disease and 79% to the overall distribution for LOGBS disease. The same serotypes were the most common maternal colonizing strains, although serotype III was a less dominant contributor.

Discussion

The estimated incidence in sub-Saharan Africa of EOGBS disease, 1.3 cases per 1,000 live births, and LOGBS disease, 0.7 cases per 1,000 live births, suggest a burden of disease at least comparable to that found in high income settings prior to the use of intrapartum antibiotics.(14) For example, in early 1990s in the U.S. EOGBS incidence was 1.3 – 1.7 cases per 1,000 live births. However, these estimated incidences for sub-Saharan Africa are likely to be under-estimates of the true rates due to factors typical of health systems in low-income countries that make it difficult to identify GBS disease accurately. Such factors include access to care, availability of microbiologic laboratories, many febrile infants at risk for sepsis and/or meningitis not receiving blood and cerebrospinal fluid (CSF) sampling, antibiotic use prior to blood and CSF sampling, early mortality prior to clinical care, and home births. In addition, the limited sensitivity of blood and CSF culture for disease even when properly performed(15) contributes to underestimating disease incidence.

Maternal rectovaginal colonization with GBS is an important risk factor for EOGBS disease, with a relative risk of approximately 30.(14) Similar to the U.S., the proportion of expectant mothers colonized with GBS was 21-22% and this was true when studies from South Africa, a large contributor to the data, were excluded. Also similar to the U.S., serotypes Ia and Ib, II, III, and V were predominant in both colonizing and disease-causing GBS isolates. Of note, when considering a potential pentavalent vaccine covering these five serotypes, the serotype coverages for both EOGBS and LOGBS disease were higher than serotype

coverage for maternal colonization; the most important contributor to the difference between colonizing and disease-causing serotypes was serotype III, which has been associated with higher invasiveness potential in other studies.(16)

As have other investigators,(17) we found substantial heterogeneity across studies concerning maternal GBS colonization and EOGBS/LOGBS disease incidence. For maternal colonization, the number of studies was large, and we could best examine patterns between study characteristics and study outcome. Our results suggested that small sample sizes and unstable estimates for some smaller studies might have contributed to variability in results. In addition, only seven studies collected specimens from both rectal and lower vaginal swabs, as is recommended to maximize yield during antepartum screening. Finally, some studies did not use selective enrichment broths and the failure to do so can result in a 50% false-negative rate.(2) For EOGBS and LOGBS incidence, as well as serotype distribution, the number of studies was smaller but reasons for heterogeneity could include different approaches to case ascertainment, denominators used and sites of microbiological culture taken.

The EOGBS incidence for sub-Saharan Africa estimated in this analysis was roughly double that found by other investigators for the sub-Saharan Africa region in a global systematic literature review by Edmond et al.(1) This may be due to our inclusion of four studies, published in 1990,(18) 1991,(19) 2001,(20) and 2003,(11) that did not meet the date range criteria of the global review, in addition to including a study from Mozambique currently in progress. Our choice to use a longer time window, 1990 to 2014, was informed by the knowledge that data from sub-Saharan Africa are relatively sparse, and the longer time window enabled the analysis to capture four large studies (cumulative subjects = 122,908) that would not otherwise have been included. This difference between the two systematic reviews had less impact on estimation of LOGBS, where our finding (0.7 per 1000 births) was similar to that of the global review by Edmond et al. Serotype distribution estimates were similar with both studies finding upwards of 85% of disease-causing isolates to be covered by the trivalent candidate vaccine that is no longer in trials. A potential pentavalent vaccine was not considered by the earlier analysis. We find that a pentavalent vaccine including serotypes Ia, Ib, II, III, and V would cover over 95% of isolates.

Limitations to this study include lack of consideration of maternal risk factors, such as maternal fever, preterm versus term delivery, and prolonged rupture of membranes. We were unable to include consideration of these risk factors due to variable reporting practice. Different distributions of these risk factors for GBS disease across studies could also have contributed to the heterogeneity observed. In addition, consideration of HIV-exposure could also have been important. For example, a recent study from South Africa, published after completion of these analyses, found that HIV-exposed infants may have a 64% higher risk of disease, compared with HIV-non-exposed infants (4.46 GBS cases versus 2.72 cases per 1000 live births).(21) Of note, with an incidence of 2.72 per 1000 live births, this study also documented a significant disease burden in non-HIV-exposed infants. Because the literature review was confined to English, publications from French-speaking West Africa may have been excluded.

Regional data were dominated by the contribution of South Africa, highlighting the need for research investment and information on disease burden from low-income countries within the region. As an example, information on disease-causing serotypes was only available from one low-income country, Malawi. Serotype data will be important to understanding the effectiveness of prevention through maternal vaccination. Information on death due to EOGBS and LOGBS disease was reported in a variable fashion, making estimation of regional GBS mortality burden difficult. Importantly, our analysis did not include the pathogen's contributions to maternal puerperal sepsis, stillbirth and potentially preterm delivery, all of which may be part of its disease burden.(22) Additional investments to estimate disease burden should include the contributions of these syndromes, as the full estimation of GBS disease burden will be a key driver in understanding the value of GBS-targeted prevention efforts.(5)

Despite these gaps, the data reviewed in this analysis suggest a substantial disease burden, a finding that is supported by broader evidence syntheses documenting the important contribution of sepsis to neonatal mortality.(23) An existing set of antepartum, intrapartum and postpartum strategies to prevent neonatal sepsis and meningitis and its consequences are available.(24) Other strategies, including the development of effective maternal GBS vaccines, are in development. If supported by further disease burden data and

cost-effectiveness analyses, investments in these strategies may have the potential to avert cases and save newborn lives in the short- and long-term.

Acknowledgements

The authors would like to thank Kim Klingler for expert technical assistance. This work was supported by award OPP1105076 from the Bill and Melinda Gates Foundation.

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Figure Legends

Figure 1. Studies of maternal GBS colonization in sub-Saharan Africa. (A) Forest plot from random-effects meta-analysis of proportion of pregnant women colonized with GBS in sub-Saharan Africa. Studies in which a swab for culture was collected from women antepartum or in labor were included. (25-39), (Musa Mohammed, personal communication) **(B) Proportion (%) of women colonized by the number of women cultured in each study.** Larger studies consistently showed a colonization rate of ~21-22% and smaller studies are arrayed symmetrically around this average.

Figure 2. Incidence of GBS disease in sub-Saharan infants. (A) Forest plot of the incidence of early-onset GBS disease for sub-Saharan infants. Studies with infants <7 days old with GBS-positive blood or cerebrospinal fluid test were included. **(11, 19, 20, 26, 40-43)** (Betuel Sigauque, personal communication) (**B) Forest plot of the incidence of late-onset GBS disease for sub-Saharan infants.** Studies with infants 7-90 days old with GBS-positive blood or cerebrospinal fluid culture were included. **(11, 19, 26, 40-43)**

Figure 3. Proportion of GBS serotypes in a pentavalent vaccine (Ia, Ib, II, III, and V). (A) Forest plot of GBS serotype proportion covered for maternal colonization. Studies in which women received swab for culture antepartum or in labor were included. (25, 31, 34, 44) (Musa Mohammed, personal communication) **(B) Forest plot of GBS serotype proportion covered for early-onset GBS disease**. Studies with infants < 7 days old with GBS-positive blood or cerebrospinal fluid culture were included. (11, 25, 44) **C) Forest plot of GBS serotype proportion covered for late-onset GBS disease.** Studies with infants 8-90 days old with GBS-positive blood or cerebrospinal fluid culture were included. (11, 25, 44)

Figure 4. Distribution of GBS serotypes in sub-Saharan mothers and infants. (A) Maternal colonization (n =1073 isolates), (B) EOGBS disease (n = 237 isolates) and (C) LOGBS disease (n = 173 isolates). Error bars indicate the 95% confidence intervals. The line plot indicates the cumulative proportion of GBS serotypes. (11, 25, 31, 34, 44) (Musa Mohammed, personal communication)

Table 1. Literature review methods and data abstracted: maternal GBS colonization, EOGBS disease incidence, LOGBS disease incidence, and GBS serotype distribution. * Studies that approximated these intervals were also included in the analysis.

	Maternal GBS colonization	Incidence		GBS serotype distribution	
		EOGBS	***LOGBS***	***Maternal***	***Infant***
Databases searched	Medline, Medline In-Progress, Cochrane Library				
Unpublished data sources	Expert query, online abstracts for 2013 and 2014 international congresses, hand search of paper bibliographies				
Search terms	("Streptococcus agalactiae" [Mesh] OR "Streptococcus Group B" OR "Group B Streptococcal") AND ("Africa" [Mesh] OR "developing countries" OR "low income countries")				
Outcome of interest	Proportion rectovaginal swab (+) for GBS	Sterile site (blood, cerebrospinal fluid) culture (+) for GBS	Sterile site (blood, cerebrospinal fluid) culture (+) for GBS	Serotype results for rectovaginal swab (+) for GBS	Serotype results for sterile site culture (+) for GBS
Types of participants	Expectant women	Infants aged 0 to 6 days	Infants aged 7 to 89 days old	Expectant women in their last trimester	Infants 90 days old or less
Study time frame	1990 to present				
Other inclusion/ exclusion criteria	Time of screening: antepartum or intrapartum, otherwise exclude	Time of illness onset: approximately 0 – 6 days after birth, otherwise exclude*	Time of illness onset: approximately 7 - 90 days after birth, otherwise exclude*	Time of screening: antepartum or intrapartum Only studies in which serotyping was performed were included.	Sterile site cultures only (blood or cerebrospinal fluid), otherwise exclude. Infant colonization studies excluded
Summary outcomes	Proportion of women colonized with GBS	Cases per 1,000 live births of EOGBS disease	Cases per 1,000 live births of LOGBS disease	Proportion covered by potential candidate vaccine	Proportion covered by potential candidate vaccine

Table 2. Systematic literature review results. The table concisely summarizes systematic literature review results typically depicted using PRISMA flow charts.(6) Supplementary Figure S1 (available online) shows analogous results for the review of conference abstracts. * See Table 3 for references.

	Maternal GBS colonization	Incidence		GBS serotype distribution	
		EOGBS	*LOGBS*	*Maternal*	*Infant*
Number of non-duplicate citations identified, published literature	86	51	51	16	9
Number of papers screened at abstract level	86	51	51	16	9
Exclusions after abstract review	38	41	41	10	5
Reasons for exclusion	No maternal colonization information (13) Year (13) Not human (5) Not GBS (3) Not sub-Saharan Africa (3) Not pregnant (1)	Not EOGBS (24) No denominator (6) Not English (3) Review article (3) Not human (2) No blood or CSF test (1) Not sub-Saharan Africa (1) Secondary analysis of an included article (1)	Not EOGBS (24) No denominator (6) Not English (3) Review article (3) Not human (2) No blood or CSF test (1) Not sub-Saharan Africa (1) Secondary analysis of an included article (1)	No serotype information (10)	No serotype information (5)
Number of full text papers, retrieved and reviewed	48	10	10	6	4
Number of unpublished data sources identified	0	0	0	0	0

	Maternal GBS colonization	Incidence		GBS serotype distribution	
		EOGBS	***LOGBS***	***Maternal***	***Infant***
Exclusions after review	32	1	2	1	1
Reasons for exclusion	Review article (13) Second analysis of an included article (5) Not sub-Saharan Africa (3) Year (2) Not maternal colonization (2) Specimen collection method unspecified (1) Not English (1) Not GBS (1) Not pregnant (1) Not recto-vaginal swab (1) Post labor (1) Unavailable (1)	Review article (1)	Review article (1) Not LOGBS (1)	Insufficient information on serotype (1)	Method of sample collection unclear (1)
Number of unpublished sources included in meta-analysis	0	0	0	0	0
Number of studies included in quantitative synthesis*	16	9	8	5	3

Table 3. Characteristics of studies included for meta-analysis

	Maternal GBS colonization (25-39)	**Incidence**		**GBS serotype distribution**	
		EOGBS (11, 19, 20, 26, 40-43)	***LOGBS*** (11, 19, 26, 40-43)	***Maternal*** (25, 31, 34, 44)	***Infant*** (11, 25, 44)
Countries	Ethiopia (2), Gambia, Kenya, Malawi (2), Mozambique (2), Nigeria, South Africa (2), Tanzania (1), Zimbabwe (4)	Kenya, Malawi, Mozambique Nigeria, South Africa (4), Zimbabwe	Kenya, Malawi, Mozambique Nigeria, South Africa (3), Zimbabwe	Ethiopia, Kenya, Malawi, South Africa, Zimbabwe	Malawi, South Africa (2)
Study design	Case control (2), cross-sectional (13), longitudinal cohort (1)	Case control (1), cross-sectional (5), retrospective (3)	Case control (1), cross-sectional (5), retrospective (2)	cross-sectional (5)	cross-sectional (3)
Study population	Antepartum women (11), intrapartum women (5)	0-2 days (2), 0-5 days (1), 0-6 days (4), 0-7 days (2)	<5 days (1), 2-28 days (2), 8-28 days (1), 7-90 days (4)	Antepartum women (3), intrapartum women (2)	7-90 days (3)
Ascertainment of endpoints	Vaginal culture only (4), vaginal and rectal culture (12)	blood culture only (3), blood and CSF culture (6)	blood culture only (3), blood and CSF culture (5)	Vaginal culture only (3), vaginal and rectal culture (2)	blood culture only (1), blood and CSF culture (2)
Notes	Timing of culture during antepartum period varied between 20 – 37+ weeks gestation				

Table 4. Description of studies included in meta-analyses. *Personal communications from first authors. **Contributed to serotype distribution analysis only.

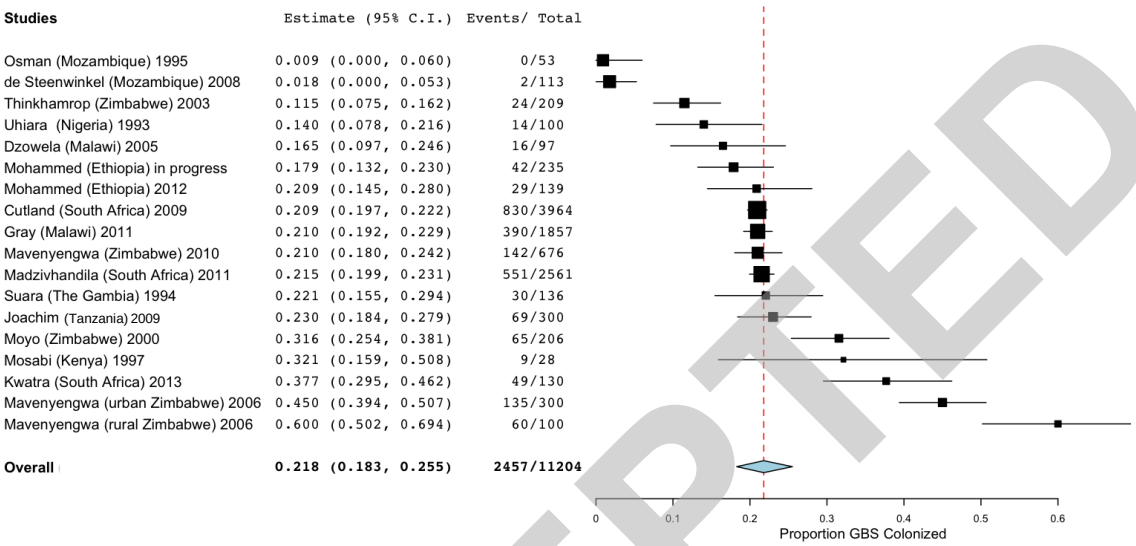
Country	First Author (Reference)	Year published	N	Study design	Case ascertainment	Rural/ Urban	Serotypes reported?
Colonization							
Nigeria	Uhiara(36)	1993	100	cross-sectional, hospital-based	in labor, high vaginal + rectal swabs	Urban	No
Gambia	Suara(33)	1994	136	cross-sectional, health center-based	in labor, vaginal + rectal swab	Rural	No
Mozambique	Osman(28)	1995	53	case-control, hospital-based	25-36 weeks gestation, posterior vaginal fornix swab	Urban	No
Kenya	Mosabi(34)	1997	28	cross-sectional, hospital-based	hospital-associated antenatal or postnatal clinic, high vaginal swab	Urban	Yes
Zimbabwe	Moyo(31)	2000	206	cross-sectional, hospital-based	all pregnant women, high vaginal + rectal swabs	Urban	Yes
Zimbabwe	Thinkhamrop(32)	2003	209	cross-sectional, hospital-based	20-32 weeks gestation, cervix + lower vagina	Urban	No
Malawi	Dzowela(37)	2005	97	cross-sectional, hospital-based	> 34 weeks gestation, lower vaginal and rectal swabs	Urban	No
Zimbabwe	Mavenyengwa(39)	2006	400	cross-sectional, clinic- and hospital-based	20-30 weeks gestation, lower vaginal and rectal swabs	Both	No
Mozambique	de Steenwinkel(27)	2008	113	cross-sectional, health center-based	35-37 weeks gestation, rectovaginal swabs	Urban	No
Tanzania	Joachim(35)	2009	300	cross-sectional, hospital-based	37 weeks of gestation, high vaginal + rectal swabs	Urban	No

Country	First Author (Reference)	Year published	N	Study design	Case ascertainment	Rural/ Urban	Serotypes reported?
South Africa	Cutland(26)	2009	3964	prospective randomized clinical trial, hospital-based	in labor, lower vagina	Urban	No
Zimbabwe	Mavenyengwa(30)	2010	676	prospective cohort, clinic- and hospital-based	~26 weeks gestation and in labor, lower vaginal + rectal swab	Both	No
South Africa*	Madzivhandila(44)	2011	2561	prospective case series, hospital-based	in labor, vaginal swab	Urban	Yes
Malawi	Gray(25)	2011	1857	cross-sectional, hospital-based	in labor, low vagina + rectal swab	Urban	Yes
Ethiopia	Mohammed(38)	2012	139	cross-sectional, health center-based	35-37 weeks gestation, lower 1/3 of vagina + anal region	Urban	No
South Africa	Kwatra(17)	2013	130	cross-sectional, community clinic-based	20+ weeks gestation, lower vaginal and rectal swabs	Urban	No
Ethiopia	Mohammed*	in progress	235	cross-sectional, hospital-based	before delivery	Urban	Yes
EOGBS and LOGBS disease							
Zimbabwe	Nathoo(18)	1990	12917	prospective, hospital-based	Ages EOGBS < 48 hrs, 48 hrs – 28 days; blood culture	Urban	No
South Africa	Haffejee(19)	1991	14340	retrospective, hospital	Ages EOGBS 0-5 days, LOGBS >5 days; blood and/or CSF culture	Urban	No
South Africa	Bomela(20)	2001	28424	retrospective and prospective cohort, hospital-based	Ages EOGBS 0-6 days; blood and CSF culture	Urban	No
South Africa	Madhi(11)	2003	6722	retrospective	Ages EOGBS	Urban	Yes

Country	First Author (Reference)	Year published	N	Study design	Case ascertainment	Rural/ Urban	Serotypes reported?
			7	cohort, hospital-based	0-6 days, LOGBS 7 – 90 days; blood and CSF culture		
Kenya	Berkley(40)	2005	27284	prospective cohort, hospital-based	Ages EOGBS 0-7 days, 8 – 90 days; blood culture	Rural	No
Nigeria	Ojukwu(43)	2006	4135	prospective cohort, hospital-based	Ages EOGBS 0-6 days, LOGBS 7 – 90 days; blood and CSF culture	Urban	No
Malawi	Gray(41)	2007	31458	prospective cohort, hospital-based	Ages EOGBS 0-6 days, LOGBS 7- 90 days; blood and CSF culture	Urban	Yes
South Africa	Cutland(26)	2009	8129	prospective randomized clinical trial, hospital-based	Ages EOGBS 0-2 days, LOGBS 3-28 days; blood and/or CSF culture	Urban	No
South Africa	Madzivhandila(44)**	2011	2542	prospective case series, hospital-based	Ages EOGBS 0-6 days, LOGBS 7-90 days; blood and/or CSF culture	Urban	Yes
Mozambique	Sigauque*	in progress	10072	cross-sectional, hospital-based	Ages EOGBS 0-7 days, LOGBS 8 – 28 days; blood and/or CSF culture	Urban	No

Figure 1.

A.



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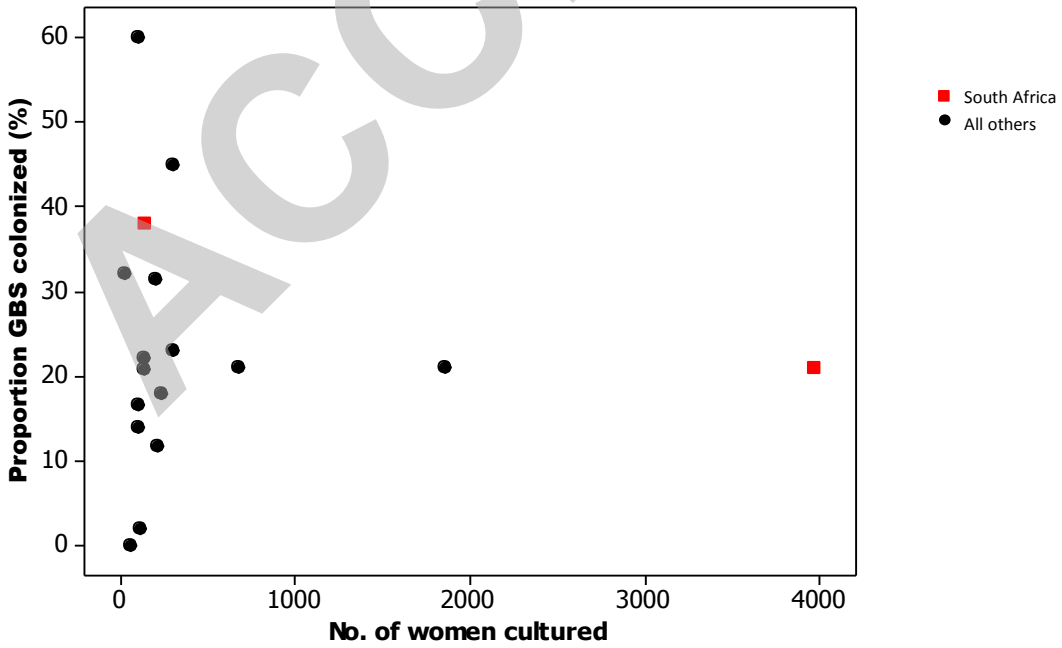

Figure 2.

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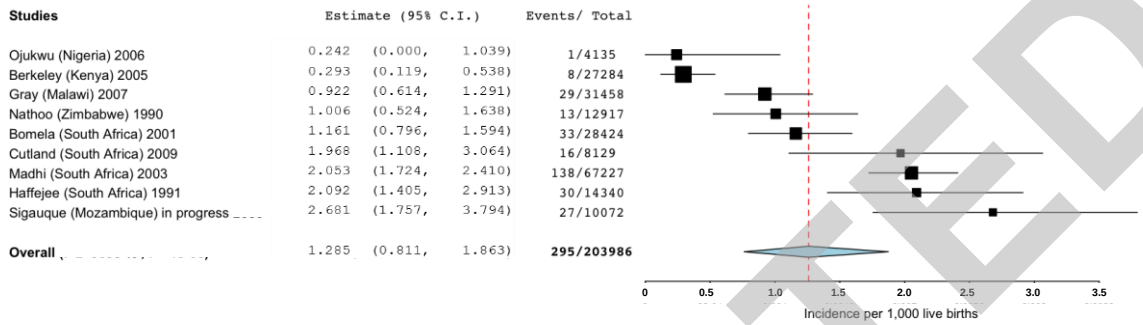

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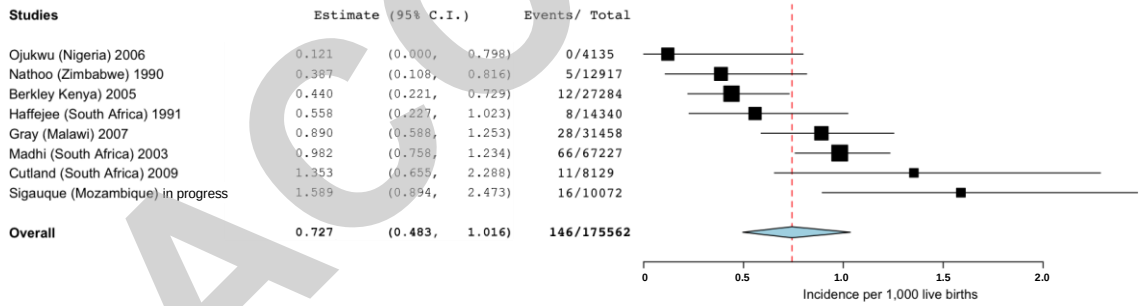
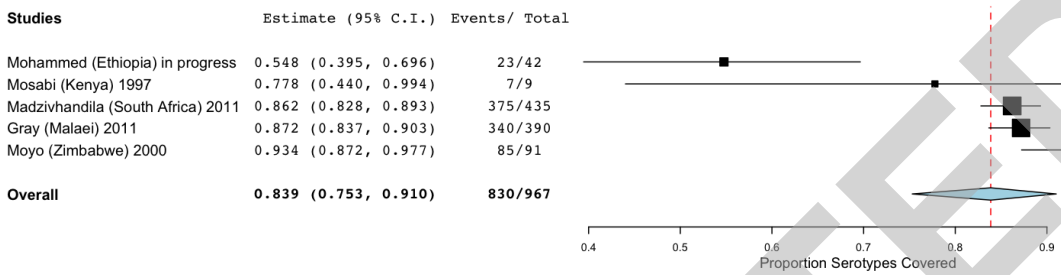


Figure 3.

A.



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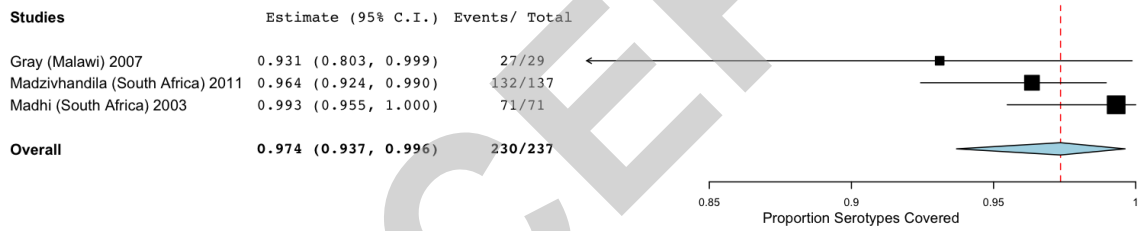

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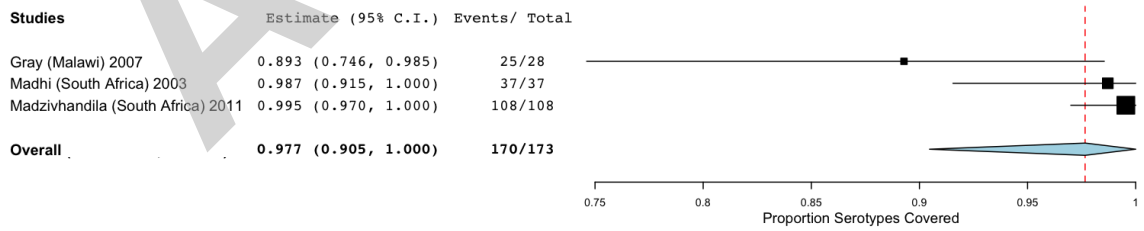

Figure 4.