Systematic Review and Meta-Analyses of Incidence for Group B *Streptococcus* Disease in Infants and Antimicrobial Resistance, China

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We performed a systematic review and meta-analysis of the incidence, case-fatality rate (CFR), isolate antimicrobial resistance patterns, and serotype and sequence type distributions for invasive group B *Streptococcus* (GBS) disease in infants <1–89 days of age in China. We searched the PubMed/Medline, Embase, Wanfang, and China National Knowledge Infrastructure databases for research published during January 1, 2000–March 16, 2018, and identified 64 studies. Quality of included studies was assessed by using Cochrane tools. Incidence and CFR were estimated by using random-effects meta-analyses. Overall incidence was 0.55 (95% CI 0.35–0.74) cases/1,000 live births, and the CFR was 5% (95% CI 3%–6%). Incidence of GBS in young infants in China was higher than the estimated global incidence (0.49 cases/1,000 live births) and higher than previous estimates for Asia (0.3 cases/1,000 live births). Our findings suggest that implementation of additional GBS prevention efforts in China, including maternal vaccination, could be beneficial.

Group B *Streptococcus* (GBS; *Streptococcus agalactiae*) is a major cause of illness and death in young infants worldwide (*1*–*3*). A recent systematic review reported the global incidence to be 0.49 cases/1,000 live births (*4*). It is estimated that this incidence results in ≈90,000 deaths (uncertainty death range 36,000–169,000) in infants every year (*5*). Furthermore, ≈32% of infants who survive GBS meningitis have neurodevelopmental impairment 18 months after illness, including 18% who have moderate-to-severe neurodevelopmental impairment (*6*). GBS is also a major cause of preterm delivery, stillbirths, and puerperal sepsis (*5*,*7*).

Screening pregnant women for GBS and offering intrapartum antimicrobial drug prophylaxis (IAP) to those who are found to be colonized, or have risk factors, has been widely implemented in many countries (*8*). However, the increased use of antimicrobial drugs has raised concerns regarding the emergence of resistance (*9*). Clindamycin and erythromycin resistance rates have increased greatly in the past 20 years (*10*) but might vary by geographic location (*10*,*11*). Knowledge of local antimicrobial drug resistance of GBS strains can contribute to optimal prophylactic and treatment strategies.

On the basis of the polysaccharide capsule, GBS strains are classified into 10 serotypes (*12*). A global review showed that serotype III was the most frequent isolate from infants who had invasive disease (*4*). Serotyping is of particular relevance to GBS vaccine development because most current candidates include serotype-specific polysaccharide–protein conjugate vaccines (*13*). An effective vaccine will need to prevent most infant disease, avoid the limitations of IAP, and cost-effective. Therefore, knowledge of prevalent serotypes will be relevant to country-specific decisions for vaccine implementation.

Evidence regarding the burden of invasive GBS disease in infants in China is limited. The recent systematic review found only 5 studies from China and estimated an incidence of 0.42 cases/1,000 live births for eastern Asia (*4*). This review was limited because it did not include publications in Mandarin Chinese and might not provide an accurate estimate of the burden of GBS disease in China. Therefore, we performed a systematic review and meta-analysis on

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the incidence, case-fatality rate (CFR), isolate antimicrobial resistance (AMR) patterns, and serotype and sequence type distributions for invasive GBS disease cases in infants <1–89 days of age in China.

Methods

This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (*14*). We focused on infants <1–89 days of age who had invasive GBS disease. We included studies that reported incidence and deaths associated with invasive disease, and antimicrobial drug resistance, serotypes, and multilocus sequence typing (MLST) of GBS isolates. Eligible studies were those published during January 1, 2000–March 16, 2018. The geographic scope of analysis was limited to China and included Taiwan, Hong Kong, and Macau.

Definitions

Invasive GBS disease was defined as a positive GBS culture from any normally sterile site accompanied with signs of clinical disease. Early onset of GBS (EO-GBS) was defined as isolation of GBS from infants ≤1–6 days after birth, and late onset of GBS (LOGBS) was defined as isolation of GBS from infants 7–89 days after birth. Incidence was defined as cases/1,000 live births (invasive GBS disease cases divided by live births at the respective hospital). CFR was defined as number of fatal GBS cases divided by total number of GBS cases. We categorized studies as prospective (data collected for the infant at admission and in hospital) and retrospective (data collected after the infant was discharged from a hospital).

In mainland China, hospitals were classified as primary, secondary, or tertiary institutions. A primary hospital is typically a township hospital that has <100 beds. These hospitals are tasked with providing preventive care, minimal healthcare, and rehabilitation services. Secondary hospitals tend to be affiliated with a medium-size city, county, or district and have >100 but <500 beds. These hospitals are responsible for providing comprehensive health services, as well as medical education and conducting research on a regional basis. Tertiary hospitals are comprehensive or general hospitals at the city, provincial, or national level that have >500 beds. These hospitals provide specialist health services, perform a larger role with regard to medical education and scientific research, and serve as medical hubs providing care to multiple regions.

Search Strategy and Selection Criteria

We searched the PubMed/Medline, Embase, China National Knowledge Infrastructure, and Wanfang med online databases for literature published during January 1, 2000–March 16, 2018. We used the search terms "Streptococcus Group B" or "Group B streptococcal" OR "Streptococcus agalactiae" (medical subject headings) AND "infant," "outcome," "death," "mortality," "case AND fatality AND rate" for English databases. We used search terms "Group B streptococcal" OR "Streptococcus agalactiae" OR "GBS" AND "infant" OR "neonatal" in Chinese for Chinese databases. We limited searches to China, including Taiwan, Hong Kong, and Macau. An additional search for serotype data used the search terms "Streptococcus Group B serotype" or "Group B streptococcal serotype" OR "Streptococcus agalactiae serotype" (medical subject headings) and was performed with the same limits as listed above. We provide the full search strategy (Appendix Tables 1, 2, https://wwwnc.cdc.gov/EID/article/26/11/18-1414-App1.pdf).

We used snowball searches of article reference lists, including reviews, to identify additional studies. Two independent reviewers (Y.D. and Y.H.) critically appraised each paper and discussed discrepancies with a third coauthor (P.H.). We screened titles and abstracts according to specified inclusion and exclusion criteria, and then selected the full texts, followed by the details as described below.

Inclusion and Exclusion Criteria

We included studies with original data on GBS invasive disease in infants <1–89 days of age, which had a population denominator (as the total number of live births at the respective hospital), CFR, serotype, or AMR. We provide full details of inclusion and exclusion criteria (Appendix Table 3).

Data Abstraction and Quality Assessment

Isolates obtained from all normally sterile sites (blood, cerebrospinal fluid [CSF], lung aspirate, and joint specimens) were included for incidence estimates. For AMR, serotype, and MLST data, only isolates obtained from blood or CSF cultures were included. The quality of included studies was assessed in accordance with the Cochrane Handbook (*15*), including 9 items considered essential for good reporting of prevalence studies. Two independent reviewers (Y.D. and Y.H.) critically appraised each study. Disagreements were resolved by discussion with the third reviewer (P.H.).

Statistical Analysis

We performed a meta-analysis by using Stata software version 14.0 (StataCorp, https://www.stata.

com) We estimated overall incidence, EOGBS, LOGBS incidence, and CFR of GBS with random-effects meta-analyses by using the DerSimonian and Laird method. The Q test was performed to test heterogeneity between studies, and the I^2 was used to assess the degree of variation across studies. The level of heterogeneity was defined as low (I^2 = 25%), moderate (I^2 = 50%), and high (I^2 = 75%) (*15*). When heterogeneity was high, we also performed subgroup analysis based on study design (retrospective and prospective), isolate type (blood, CSF, and all sterile sites), and age of onset (EOGBS and LOGBS). Sensitivity analysis was conduct by excluding studies from Taiwan, Hong Kong, and Macau. As we anticipated, different infectious disease patterns, antimicrobial drug resistance, and healthcare systems in these regions might affect the estimates of GBS incidence and CFR. Potential publication bias was assessed by using a funnel plot and the Egger regression test. Descriptive analysis was performed to investigate the distribution of serotype and MLST typing. Antimicrobial drug resistance rates were reported by median with interquartile intervals.

Results

Literature Search and Study Selection

We identified 704 published studies from database searches (407 from China National Knowledge Infrastructure, 139 from Wanfang, 147 from PubMed, and 9 from Embase). Two additional articles were identified from reference lists. A total of 64 articles met our inclusion criteria and search strategy (Figure 1). A total of 14 articles reported incidence, 56 articles reported CFR, 20 articles reported AMR, 4 articles reported serotype, and 2 articles reported MLST. We provide a full list of articles included (Appendix Table 4) and of articles excluded (Appendix Table 5). We provide the publication years of included studies (Appendix Figure 1).

Study Characteristics

Of the 64 studies included, 55 were from mainland China, 7 from Taiwan, 1 from Hong Kong, and 1 from Macau. On the basis of economic divisions, 92.2% (59/64) of studies were from eastern China, 2 each were from western and central China, and 1 was

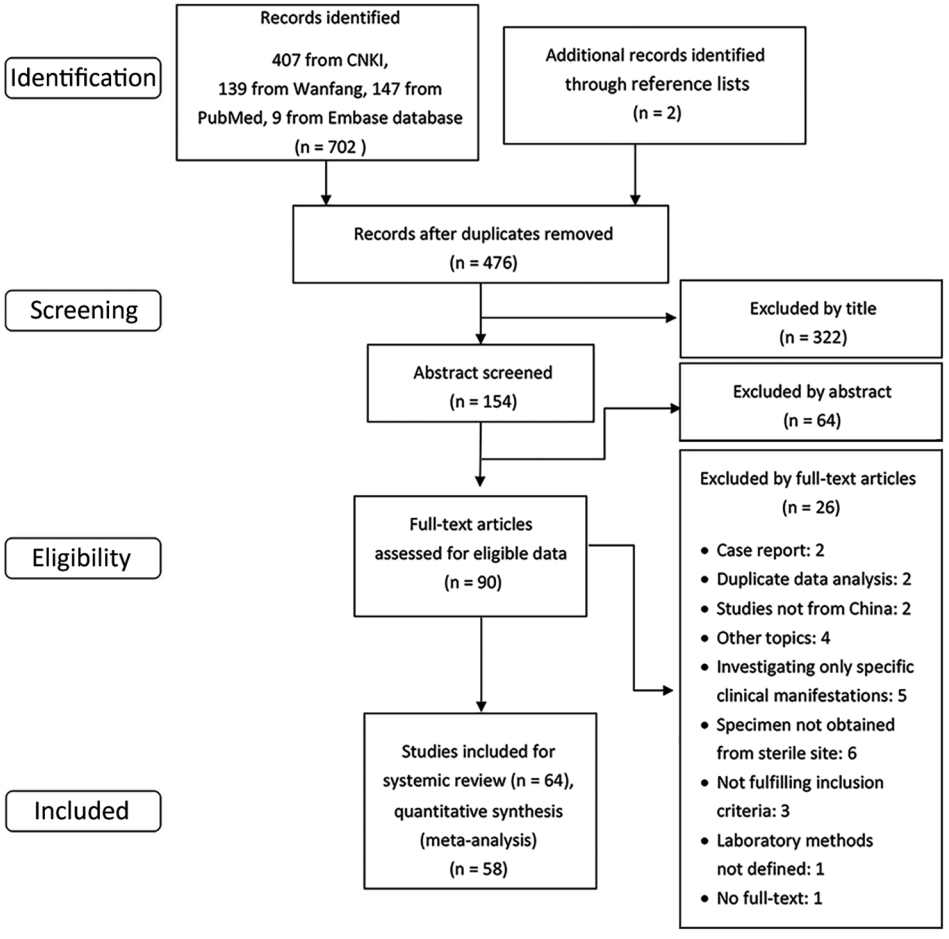

Figure 1. Process of study selection of systematic review and meta-analyses of incidence of group B *Streptococcus* disease in infants and antimicrobial resistance, China. CNKI, China National Knowledge Infrastructure.

from northeastern China. Among the 55 articles from mainland China, 45 were from tertiary hospitals, 9 from secondary hospitals, and 1 from a primary hospital. The 7 articles from Taiwan and the 1 article from Hong Kong were all from teaching hospitals, and the 1 article from Macau was from a general hospital. We provide the distribution of studies of invasive GBS disease reported in China by province (Figure 2).

Among the 14 studies reporting incidence, 13 were from eastern China, and 1 from western China. Six (42.9%) of 14 papers reported use of IAP, all from eastern China; 3 (50%) of 6 IAPs were based on screening. Of the 56 studies that reported CFRs, 52 articles were from eastern China and 2 each were from central and western China. A total of 20 studies reported AMR, 19 papers from eastern China and 1 from northeastern China. Serotypes were available from 4 studies, all of them from eastern China. Only 2 articles included data on MLST. We provide characteristics of included studies and outcome types (Table 1). We also provide the risk for bias of the studies (Appendix Figure 2).

Incidence of Invasive GBS Disease

Of the 14 relevant studies, 13 reported raw data on live births, which enabled a meta-analysis to be performed. Of 424,463 live births, 244 infants had invasive GBS disease at the age of 0–89 days; the pooled estimated incidence was 0.55 cases/1,000 live births (95% CI 0.35–0.74 case/1,000 live births). Significant heterogeneity was observed (p = 0.0001, I^2 = 85.4%) (Figure 3). Subgroup analyses were conducted to

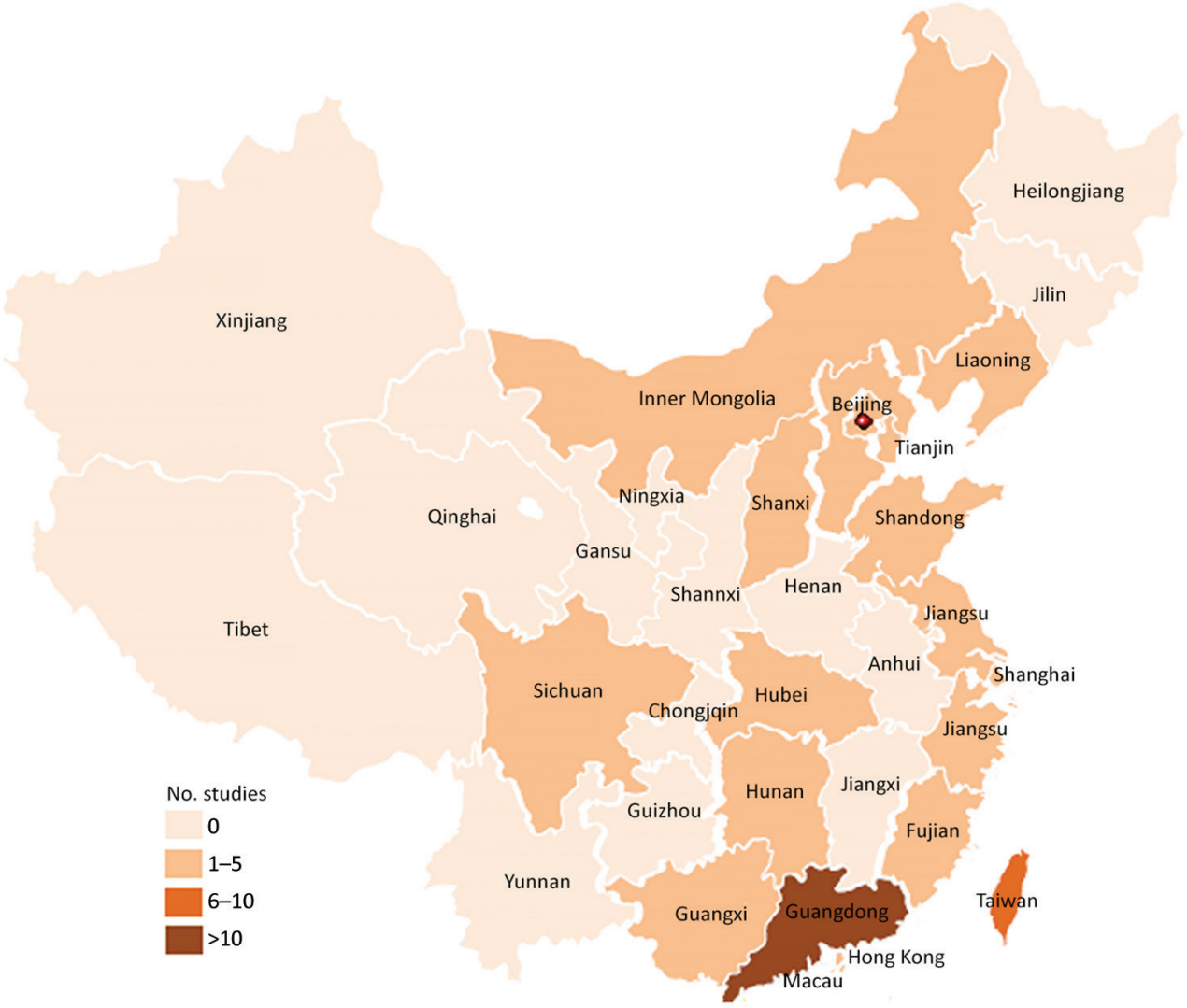

Figure 2. Distribution of study locations in systematic review and meta-analyses of incidence of invasive group B *Streptococcus* disease, by province, China.

Table 1. Characteristics of included studies and outcome types for systematic review and meta-analyses of incidence of group B *Streptococcus* disease in infants, China*

Characteristic	Type and no. studies					
	Total, 64	Incidence, 14	CFR, 56	AMR, 20	Serotypes, 4	MLST, 2
China						
Eastern	59	13	52	19	4	2
Central	2	0	2	0	0	0
Western	2	1	2	0	0	0
Northeastern	1	0	0	1	0	0
Hospital type						
Mainland China						
Tertiary	45	6	39	18	4	2
Secondary	9	3	9	2	0	0
Primary	1	0	1	0	0	0
Nonmainland China						0
Teaching	8	4	7	0	0	0
General	1	1	0	0	0	0
Study design						
Prospective	4	3	3	0	1	1
Retrospective	60	11	53	20	3	1
Reporting period, days						
Full, 0–89	53	11	46	16	4	2
Full EOGBS <1–6	7	3	6	2	0	0
Full LOGBS 7–89	4	0	4	2	0	0
Specimen type						
Blood only	25	5	18	8	2	0
CSF only	6	0	6	3	0	0
Blood and CSF	23	6	22	9	2	2
All sterile sites	4	3	3	0	0	0
Blood and CSF plus sputum or gastric fluid	6	0	7	0	0	0
IAP						
Any	10	6	9	3	1	1
None	4	0	3	2	0	0
Unknown	50	8	44	15	3	1

*AMR, antimicrobial resistance; CFR, case-fatality rate; CSF, cerebrospinal fluid; EOGBS, early onset group B *Streptococcus*; IAP, intrapartum antimicrobial drug prophylaxis; MLST, multilocus sequence typing; LOGBS, late onset group B *Streptococcus*.

assess heterogeneity by study design, isolate site, and age of onset. Among the 13 studies reporting raw data on live births, 11 studies distinguished early-onset and late-onset cases (n = 3 studies) born in a hospital. There were 133 cases of EOGBS for 352,574 live births, an incidence of 0.38 cases/1,000 live births (95% CI 0.25–0.51 cases/1,000 live births), and 33 cases of LOGBS for 168,849 live births, an incidence of 0.18 cases/1,000 live births (95% CI 0.11–0.25 cases/1,000 live births).We provide results of meta-analysis for LOGBS incidence (Appendix Figure 3), for EOGBA incidence (Appendix Figure 4), and for subgroup analyses (Appendix Table 6).

Sensitivity analysis was conducted to confirm the stability and liability of the meta-analysis by excluding data for Taiwan, Hong Kong, and Macau. This exclusion resulted in a pooled incidence of invasive GBS disease of 0.44 cases/1,000 live births (95% CI 0.25–0.63 cases/1,000 live births) for mainland China (Appendix Figure 5). According to the funnel plot and p value of the Eggers regression test (p = 0.069 [>0.05]), there was no visually apparent publication bias of included studies (Appendix Figure 6).

CFRs for GBS Invasive Disease

A total of 56 papers reported CFR data for infants <1–89 days of age. Of 1,439 infants with GBS invasive disease, 106 died. The overall pooled estimated CFR rate was 5.0% (95% CI 3.0%–6.0%). The EOGBS CFR was 6.0% (4.0%–8.0%), and LOGBS CFR was 4.0% (1.0%–6.0%). We provide results of meta-analysis for overall, EOGBS, and LOGBS CFRs (Appendix Figures 7, 8, and 9, respectively). Sensitivity analysis was conducted to confirm the stability and liability of the meta-analysis by including only studies from mainland China. The pooled estimated CFR was 4.0% (95% CI 2%.0%–6.0%) when data for only mainland China were included (Appendix Figure 5).

Antimicrobial Resistance

A total of 20 articles reported antimicrobial resistance for 598 GBS isolates. The highest prevalence of resistance was reported for tetracycline (median 98.0%, interquartile range [IQR] 80.0%–100%), followed by clindamycin (73.3%m IQR 62.6%–78.7%), erythromycin (64.4%, IQR 56.6%–75%), and ciprofloxacin (25.0%, IQR 9.1%–35.2%). There was no reported resistance to penicillin, ampicillin, vancomycin, or linezolid. For

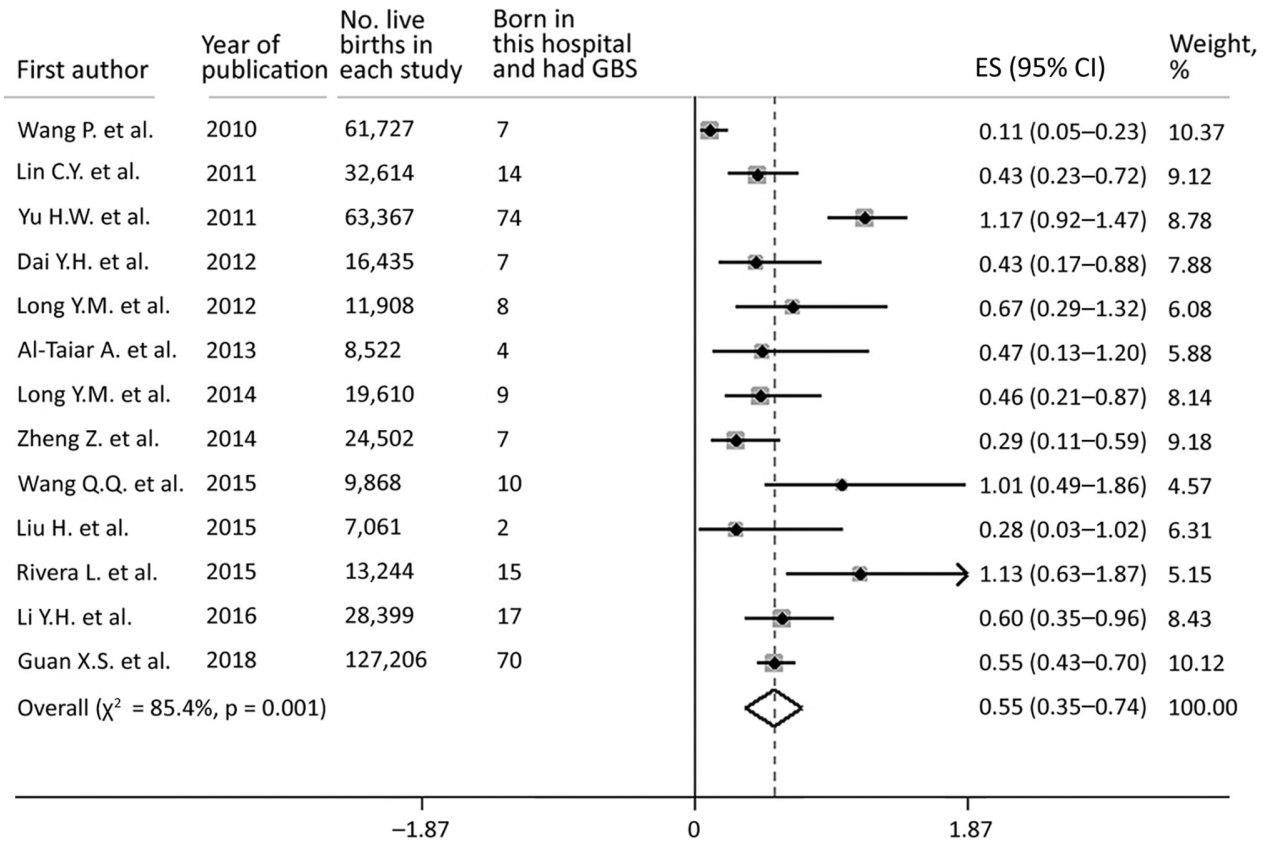

Figure 3. Overall incidence risk per 1,000 live births of invasive GBS disease in 13 infants <1–89 days of age, China. Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Error bars indicate 95% CIs. Reference details are provided in the Appendix (https://wwwnc.cdc.gov/EID/26/11/18-1414-App1.pdf). ES, effect size; GBS, group B *Streptococcus* disease.

ceftriaxone, the median prevalence of resistance was 0% (IQR 0%–60.0%), although 1 study reported 100% prevalence of resistance (1/1 isolates), and 1 study reported 80% resistance (12/15 isolates) (Table 2).

Serotype Distribution

Four studies included data on serotypes for 175 invasive GBS cases. All of these studies were from eastern China. Four serotypes (Ia, Ib, III, and V) accounted for 97% of invasive isolates. Serotype III was the most common (65%, 114/175), followed by Ib (16%, 27/175), Ia (10%, 18/175), and V (6%, 11/175). Two articles distinguished EO and LOGBS serotypes; there were 24 EOGBS isolates and 52 LOGBS isolates. Serotype III predominated in both EO (15/24, 63%) and LOGBS (40/52, 77%) (Appendix Figure 10).

MLST

Only 2 studies reported MLST. Of 76 isolates 15 sequence types (STs) were reported. A total of 89% (68/76) of strains belonged to 6 STs (ST17, ST12, ST23, ST1, ST19, and ST650). More than half (58%, 44/74) of the samples were ST17, followed by ST12 (9%, 7/76) and ST23 (7%, 5/76); ST1, ST19, and ST650 each accounted for 5% (4/76).

Relationship between Serotype and MLST

Only 2/76 papers included data on serotype and MLST. A total of 80% (44/55) of serotype III strains were shown to be ST17, and 54% (7/13) of serotype Ib strains were ST12 (Appendix Table 7).

Discussion

The annual number of births in China ranged from 15.7 million to 17.8 million between 2001 and 2016 (*16*). Thus, with an estimated pooled incidence of 0.55 cases/1,000 live births (95% CI 0.35–0.74 cases/1,000 live births), there is a substantial burden of invasive GBS disease for infants in China. This incidence is also higher than that for all infants in the recent global review (0.49 cases/1,000 live births, 95% CI 0.43–0.56 cases/1,000 live births) and higher than that previously defined for eastern Asia (0.42 cases/1,000 live births) (*4*). Unlike most industrialized countries,

there are no national guidelines for GBS screening and prevention in China, although in 43% of studies from China, IAP was mentioned. However, there are no data on the extent to which IAP is currently used in China. Previous studies suggest that the low incidence of GBS infection for infants in Asia might be related to a lower rate of GBS colonization in pregnant women (*17*). A review of colonization identified 30 studies from China, which included 44,716 women, and showed an overall colonization rate of 11.3%. However, several studies from China reported much higher rates of GBS colonization (31%–36%) (*18*,*19*), suggesting substantial variability.

The CFR in our study (5.0%, 95% CI, 3.0%–6.0%) was lower than that estimated from the global review (8.4%, 95% CI 6.6%–10.2%) (*4*). Most of our data were for level-3 teaching hospitals in which use of antimicrobial drugs and standard of medical care might be higher, which might explain a lower mortality rate. We do not have information on birthweight and gestational age of infants with GBS disease with which we can compare with other settings; the CFR for preterm infants is known to be much higher (*1*).

The prevalence of resistance to clindamycin and erythromycin appear to be high in China. A study in Canada showed the prevalence of resistance to clindamycin was 4.5% and to erythromycin was 8% (*9*). In England and Wales, erythromycin resistance in isolates causing disease in infants was 15% for EO disease and 13% for LO disease (*20*). In South Korea, the prevalence of resistance to erythromycin was 42.9%–51.8% and for clindamycin was 55.4% (*11*,*21*), suggesting that the prevalence might be much higher in Asia. This finding is consistent with a global systematic review (*22*) of GBS isolates causing colonization that reported a pooled prevalence of resistance of 25% for erythromycin and 27% for clindamycin, and notably higher prevalences in Asia (46% for erythromycin and 47% for clindamycin). A study of colonization of pregnant women in China also reported that most isolates were resistant to tetracycline (76.9%), erythromycin (72.1%) and clindamycin (66.4%) (*23*). Macrolide resistance in streptococci is caused mainly by a macrolide–specific efflux mechanism encoded by the *mef* A gene and ribosomal modification by a methylase associated with *erm* (erythromycin ribosome methylase) genes (*24*,*25*). Erythromycin resistance was associated mainly with *ermB* and *mef (A/E)* genes in China (*26*,*27*). The *erm(B)* and *erm(TR/A)* genes were the main macrolide-resistant genes in Spain and Canada (*9*,*25*), and *erm B* and *lnuB* genes were prevalent in South Korea (*28*).

Resistance to erythromycin and clindamycin presents a challenge for treatment and prophylaxis strategies because these antimicrobial drugs are often used for patients in China who are allergic to penicillin.

Table 2. Proportion of isolates demonstrating antimicrobial resistance in systematic review and meta-analyses of incidence of group B *Streptococcus* disease in infants, China*

Reference	Publication year	No. isolates	PEN	AMP	CFZ	CAX	VAN	LZD	CHL	ERY	TET	CIP	MXF	LVX	NIT	TGC
Zeng et al.	2013	11	0	0	NT	NT	0	0	NT	NT	100.0	9.1	9.1	9.1	0	0
Luo et al.	2013	15	0	0	NT	0	0	NT	NT	86.7	NT	NT	NT	0	NT	NT
Zheng et al.	2014	12	0	0	NT	NT	0	NT	NT	16.7	66.7	NT	NT	NT	NT	NT
Chen et al.	2014	16	0	0	NT	0	0	NT	NT	62.5	NT	25.0	NT	18.8	NT	NT
Zhu et al.	2014	13	0	10.0	0	100.0	38.5	0	100.0	100.0	NT	33.3	NT	8.3	0	NT
Fan et al.	2014	42	0	0	NT	NT	0	0	NT	69.1	73.8	NT	NT	38.1	NT	0
Wang et al.	2015	15	0	20.0	40.0	80.0	0	0	86.7	100.0	NT	26.7	NT	20.0	0	NT
Zhang et al.	2015	6	0	0	83.3	NT	0	0	NT	NT	NT	NT	NT	NT	NT	NT
Lei et al.	2015	20	NT	0	NT	NT	0	0	25.0	75.0	NT	80.0	NT	70.0	0	NT
Zhang et al.	2015	45	0	2.2	NT	NT	0	0	NT	42.2	93.3	0	0	0	NT	0
Cai et al.	2016	15	0	0	NT	NT	0	0	NT	46.7	100.0	NT	6.7	6.7	13.3	0
Zhao	2016	28	0	0	NT	0	0	3.6	NT	67.9	NT	NT	NT	42.9	NT	NT
Huang et al.	2016	49	NT	NT	NT	NT	NT	NT	NT	63.3	98.0	11.9	12.2	7.7	NT	NT
Liu et al.	2017	15	0	NT	NT	NT	0	NT	NT	NT	NT	NT	NT	NT	NT	NT
Zhang et al.	2017	55	0	0	NT	NT	0	0	NT	56.6	98.1	1.9	NT	NT	NT	NT
Zhang et al.	2017	15	6.7	0	NT	NT	0	0	NT	NT	80.0	73.3	73.3	60.0	0	0
Tan et al.	2017	20	0	0	NT	NT	0	0	NT	NT	100.0	16.7	NT	16.7	NT	0
Zhou et al.	2017	84	4.8	2.4	2.4	0	0	0	4.8	72.6	100.0	35.2	NT	36.9	0	NT
Zhao	2017	45	0	NT	NT	0	0	2.2	NT	64.4	NT	NT	NT	42.2	NT	NT
Guan et al.	2018	68	0	NT	NT	0	0	0	NT	57.4	95.6	NT	NT	5.9	NT	NT
Median	NA	NA	0	0	21.2	0	0	0	55.8	64.4	98.0	25.0	9.1	17.7	0	0
IQI 25%	NA	NA	0	0	0.6	0	0	0	9.8	56.6	80.0	9.1	3.3	6.9	0	0
IQI 75%	NA	NA	0	1.7	72.5	60.0	0	0	96.7	75.0	100	35.2	42.8	41.2	0	0

*Values are percentages. Reference details are provided in the Appendix (https://wwwnc.cdc.gov/EID/26/11/18-1414-App1.pdf). Green indicates a rate of AMR <25%; yellow 25%–50%; red >50%; 25%, and 75% refers to AMR interquartile interval of 25% and 75%. Amp, ampicillin; CFZ, cefazolin; CAX, ceftriaxone, CHL, chloramphenicol; CIP, ciprofloxacin; ERY, erythromycin; IQI, interquartile interval; LZD, linezolid; MXF, moxifloxacin; NA, not applicable; NIT, nitrofurantoin; NT, not tested; PEN, penicillin: TET, tetracycline; TGC, tigecycline; VAN, vancomycin.

However, GBS isolates were susceptible to penicillin, ampicillin, vancomycin, and linezolid, consistent with other reports (*9*,*21*,*22*). The apparent resistance to ceftriaxone is unusual and, as noted, the sample size for these 2 studies was small. Furthermore, because no details were provided on the methods used for testing the isolates, it is essential that this reported resistance is verified.

The serotype and MLST distribution of invasive GBS disease isolates in China is consistent with the global review (*4*); serotype III and ST17 are the most prevalent types (*21*,*29*). Therefore, our data suggest that a conjugate vaccine incorporating 5 serotypes (III, Ia, Ib, II, and V) could cover 97% of invasive GBS disease in infants <3 months of age in China.

Currently, there is limited evidence on the burden of GBS disease for infants in China. Our comprehensive review is a major addition to the literature because it includes a systematic review of studies in the Chinese language, as well as data on incidence, antimicrobial drug susceptibility, and MLST types.

There are several potential limitations to this study. First, major heterogeneity among studies was observed. Although potential sources of heterogeneity were explored by subgroup analyses, none of them sufficiently explain the heterogeneity. Sensitivity analysis suggests that the pooled estimated incidence and CFR was changed when Taiwan, Hong Kong, and Macau were excluded. This finding is plausible and might reflect the differences in healthcare systems compared with those of mainland China. Second, we did not search for unpublished studies, which could result in publication bias. Third, we were not able to assess the time of sample collection or the methods of collection, culture, and antimicrobial drug sensitivity testing. Fourth, there were limited data available on serotypes and MLST types; thus, meta-analysis was not possible. Fifth, for CFRs, we were only able to include patients who died in a hospital; thus, the true CFR might be higher.

The estimated burden of infant GBS disease in China is substantial, suggesting that implementation of additional prevention efforts could be beneficial. Interventions to be considered could include a coordinated national strategy for maternal GBS screening with administration of intrapartum antimicrobial drug prophylaxis, and, when available, maternal vaccination with an effective GBS vaccine. Further research to clarify the noted heterogeneity in infant GBS disease in China, as well as research to assess the acceptability, logistics, and cost-effectiveness of maternal GBS vaccination could help guide these efforts.

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References

1. Heath PT, Balfour G, Weisner AM, Efstratiou A, Lamagni TL, Tighe H, et al.; PHLS Group B Streptococcus Working Group. Group B streptococcal disease in UK and Irish infants younger than 90 days. Lancet. 2004;363:292–4. https://doi.org/10.1016/S0140-6736(03)15389-5
2. Sinha A, Russell LB, Tomczyk S, Verani JR, Schrag SJ, Berkley JA, et al.; GBS Vaccine Cost-Effectiveness Analysis in Sub-Saharan Africa Working Group. Disease burden of group B *Streptococcus* among infants in sub-Saharan Africa: a systematic literature review and meta-analysis. Pediatr Infect Dis J. 2016;35:933–42. https://doi.org/10.1097/INF.0000000000001233
3. Rivera L, Sáez-Llorens X, Feris-Iglesias J, Ip M, Saha S, Adrian PV, et al. Incidence and serotype distribution of invasive group B streptococcal disease in young infants: a multi-country observational study. BMC Pediatr. 2015;15:143. https://doi.org/10.1186/s12887-015-0460-2
4. Madrid L, Seale AC, Kohli-Lynch M, Edmond KM, Lawn JE, Heath PT, et al.; Infant GBS Disease Investigator Group. Infant group B streptococcal disease incidence and serotypes worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S160–72. https://doi.org/10.1093/cid/cix656
5. Seale AC, Bianchi-Jassir F, Russell NJ, Kohli-Lynch M, Tann CJ, Hall J, et al. Estimates of the burden of group B streptococcal disease worldwide for pregnant women, stillbirths, and children. Clin Infect Dis. 2017;65(suppl_2):S200–19. https://doi.org/10.1093/cid/cix664
6. Kohli-Lynch M, Russell NJ, Seale AC, Dangor Z, Tann CJ, Baker CJ, et al. Neurodevelopmental impairment in children after group B streptococcal disease worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S190–9. https://doi.org/10.1093/cid/cix663
7. Heath PT. An update on vaccination against group B streptococcus. Expert Rev Vaccines. 2011;10:685–94. https://doi.org/10.1586/erv.11.61
8. Le Doare K, O'Driscoll M, Turner K, Seedat F, Russell NJ, Seale AC, et al.; GBS Intrapartum Antibiotic Investigator Group. Intrapartum antibiotic chemoprophylaxis policies for the prevention of group B streptococcal disease worldwide: systematic review. Clin Infect Dis. 2017;65(suppl_2):S143–51. https://doi.org/10.1093/cid/cix654
9. de Azavedo JC, McGavin M, Duncan C, Low DE, McGeer A. Prevalence and mechanisms of macrolide

resistance in invasive and noninvasive group B *Streptococcus* isolates from Ontario, Canada. Antimicrob Agents Chemother. 2001;45:3504–8. https://doi.org/10.1128/AAC.45.12.3504-3508.2001
10. Castor ML, Whitney CG, Como-Sabetti K, Facklam RR, Ferrieri P, Bartkus JM, et al. Antibiotic resistance patterns in invasive group B streptococcal isolates. Infect Dis Obstet Gynecol. 2008;2008:727505. https://doi.org/10.1155/2008/727505
11. Yoon IA, Jo DS, Cho EY, Choi EH, Lee HJ, Lee H. Clinical significance of serotype V among infants with invasive group B streptococcal infections in South Korea. Int J Infect Dis. 2015;38:136–40. https://doi.org/10.1016/j.ijid.2015.05.017
12. Le Doare K, Heath PT. An overview of global GBS epidemiology. Vaccine. 2013;31(Suppl 4):D7–12. https://doi.org/10.1016/j.vaccine.2013.01.009
13. Nuccitelli A, Rinaudo CD, Maione D, Group B. Group B *Streptococcus* vaccine: state of the art. Ther Adv Vaccines. 2015;3:76–90. https://doi.org/10.1177/2051013615579869
14. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ. 2009;339:b2700. https://doi.org/10.1136/bmj.b2700
15. Higgins J, Green S. Cochrane handbook for systematic reviews of interventions version 5.1.0. The Cochrane Collaboration; 2011 [cited 2020 Aug 17]. https://handbook-5-1.cochrane.org
16. Su L, Yang X, Bai G, Fenglan L. Spatial inequality and regional difference of population birth rate in China. Journal of Chongqing University of Science and Technology. 2018;32:250–8.
17. Russell NJ, Seale AC, O'Driscoll M, O'Sullivan C, Bianchi-Jassir F, Gonzalez-Guarin J, et al.; GBS Maternal Colonization Investigator Group. Maternal colonization with group B *Streptococcus* and serotype distribution worldwide: systematic review and meta-analyses. Clin Infect Dis. 2017;65(suppl_2):S100–11. https://doi.org/10.1093/cid/cix658
18. Wang Y, He S. Correlation between the colonization of group B *Streptococcus* and the level of defensins in pregnant women in Hanzhong. Xiandai Jianyan Yixue Zazhi. 2013;28:87–9.
19. Wu J, Qian B. Resistance and genotype of B *Streptococcus* infected or colonized in perinatal pregnant woman. Chin Mod Doctor. 2017;55:12–15.
20. Lamagni TL, Keshishian C, Efstratiou A, Guy R, Henderson KL, Broughton K, et al. Emerging trends in the epidemiology of invasive group B streptococcal disease in England and Wales, 1991–2010. Clin Infect Dis. 2013;57:682–8. https://doi.org/10.1093/cid/cit337
21. Kang HM, Lee HJ, Lee H, Jo DS, Lee HS, Kim TS, et al. Genotype characterization of group B *Streptococcus* isolated from infants with invasive dDiseases in South Korea. Pediatr Infect Dis J. 2017;36:e242–7. https://doi.org/10.1097/INF.0000000000001531
22. Huang J, Li S, Li L, Wang X, Yao Z, Ye X. Alarming regional differences in prevalence and antimicrobial susceptibility of group B streptococci in pregnant women: a systematic review and meta-analysis. J Glob Antimicrob Resist. 2016;7:169–77. https://doi.org/10.1016/j.jgar.2016.08.010
23. Wang X, Cao X, Li S, Ou Q, Lin D, Yao Z, et al. Phenotypic and molecular characterization of *Streptococcus agalactiae* colonized in Chinese pregnant women: predominance of ST19/III and ST17/III. Res Microbiol. 2018;169:101–7. https://doi.org/10.1016/j.resmic.2017.12.004
24. Zhong P, Shortridge VD. The role of efflux in macrolide resistance. Drug Resist Updat. 2000;3:325–9. https://doi.org/10.1054/drup.2000.0175
25. Gonzalez JJ, Andreu A; Spanish Group for the Study of Perinatal Infection from the Spanish Society for Clinical Microbiology and Infectious Diseases. Multicenter study of the mechanisms of resistance and clonal relationships of *Streptococcus agalactiae* isolates resistant to macrolides, lincosamides, and ketolides in Spain. Antimicrob Agents Chemother. 2005;49:2525–7. https://doi.org/10.1128/AAC.49.6.2525-2527.2005
26 Yan Y, Hu H, Lu T, Fan H, Hu Y, Li G, et al. Investigation of serotype distribution and resistance genes profile in group B *Streptococcus* isolated from pregnant women: a Chinese multicenter cohort study. APMIS. 2016;124:794–9. https://doi.org/10.1111/apm.12570
27. Lu B, Chen X, Wang J, Wang D, Zeng J, Li Y, et al. Molecular characteristics and antimicrobial resistance in invasive and noninvasive group B *Streptococcus* between 2008 and 2015 in China. Diagn Microbiol Infect Dis. 2016;86:351–7. https://doi.org/10.1016/j.diagmicrobio.2016.08.023
28. Seo YS, Srinivasan U, Oh KY, Shin JH, Chae JD, Kim MY, et al. Changing molecular epidemiology of group B *Streptococcus* in Korea. J Korean Med Sci. 2010;25:817–23. https://doi.org/10.3346/jkms.2010.25.6.817
29. Imperi M, Gherardi G, Berardi A, Baldassarri L, Pataracchia M, Dicuonzo G, et al. Invasive neonatal GBS infections from an area-based surveillance study in Italy. Clin Microbiol Infect. 2011;17:1834–9. https://doi.org/10.1111/j.1469-0691.2011.03479.x

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Systematic Review and Meta-Analyses of Incidence for Group B *Streptococcus* Disease in Infants and Antimicrobial Resistance, China

Appendix

Appendix Table 1. Search terms (for English papers) and search period (January 1, 2000–March 16, 2018) for PubMed/ Medline or Embase (search date: March 17, 2018)*

Search term
Infant
Outcome
Death
Mortality
Case AND Fatality AND rate
Death [MeSH terms]
Mortality [MeSH terms]
Case fatality rate [MeSH terms]
AND
Streptococcal
Streptococcus
Streptococci AND (Group AND B) or agalactiae
Streptococcus agalactiae [MeSH terms]
AND
Streptococcus serotype
Streptococcal serotype
Streptococcus agalactiae serotype [MeSH terms]

*MeSH, medical subject headings

Appendix Table 2. Search terms (for Chinese papers) and search period (January 1, 2000–March 16, 2018) for China National Knowledge Infrastructure or Wanfang med online databases (search date: March 18, 2018)

Search term
族 (Group B Streptococcal)
无乳 (*Streptococcus agalactiae*)
AND
新生儿 (Neonatal)
(Infant)
AND
血清型 (Serotype)

Appendix Table 3. Inclusion and exclusion criteria*

Characteristic	Inclusion criteria	Exclusion criteria
Population	Invasive GBS disease in infants <1–89 days of age at onset of infection	Studies containing only information on high-risk groups
Laboratory	GBS confirmed by blood, CSF, or other sterile site culture	NA
Search	No language restrictions	Foreign language papers for which it was not possible to obtain English or Chinese translations
Study	Study reporting more recent data from country or hospital	Case report, case series, reviews, conference papers; studies from the same country or hospital reporting repeated years or data.

*CSF, cerebrospinal fluid; GBS, group B *Streptococcus*; NA, not applicable.

Appendix Table 4. Characteristics of included studies for infant invasive group B *Streptococcus* (GBS) disease in children*

Reference	Region of China	Year of publication	Year of data collection	Incidence	CFR	AMR	Serotype	MLST	IAP	Reporting period, y	Study design
Chang CJ et al. (*1*)	Taiwan	2003	1986.1–2001.12	N	Y	N	N	N	U	<1–89	R
Chung MY et al. (*2*)	Taiwan	2004	1996.1.1–2002.12.31	Y	Y	N	N	N	U	<1–89	R
Jiang JH et al. (*3*)	Taiwan	2004	1992.1–2001.12	N	Y	N	N	N	N	<1–89	R
Wu JH et al. (*4*)	Taiwan	2009	2001.1–2006.12	N	Y	N	N	N	U	<1–89	P
Wang P et al. (*5*)	Beijing	2010	2005–2009	Y	Y	N	N	N	U	<1–6	R
Liu ZW et al. (6)	Shang Hai	2011	1999.1–2008.12	N	Y	N	N	N	U	<1–89	R
Lin CY et al. (7)	Taiwan	2011	2001.1–2008.11	Y	N	N	N	N	Y	<1–6	R
Yu HW et al. (*8*)	Taiwan	2011	2002.1–2005.6	Y	Y	N	N	N	Y	<1–89	R
Wu MF (*9*)	Guang Dong	2012	2008.1–2012.1	N	Y	N	N	N	U	<1–89	R
Dai YH et al. (*10*)	Guang Dong	2012	2008.6–2011.4	Y	Y	N	N	N	U	<1–89	R
Long YM et al. (*11*)	Guang Dong	2012	2009.7–2011.6	Y	Y	N	N	N	U	<1–89	R
Zeng SJ et al. (*12*)	Guang Dong	2013	2012.1–2012.12	N	Y	Y	N	N	U	<1–89	R
Luo J et al. (*13*)	Guang Dong	2013	2007.1–2011.12	N	Y	Y	N	N	U	7–89	R
Chen L et al. (*14*)	Guang Dong	2013	2010–2012	N	Y	N	N	N	U	<1–89	R
Al-Taiar A et al. (*15*)	Macau	2013	2006.1.1–2009.12.31	Y	N	N	N	N	U	<1–89	P
Wu YY (*16*)	Guang Dong	2014	2010–2013	N	Y	N	N	N	U	<1–89	R
Fan WH et al. (*17*)	Beijing	2014	2011.1–2013.9	N	N	Y	N	N	U	<1–89	R
Zheng Z et al. (*18*)	Fujian	2014	2011.10–2013.4	Y	Y	Y	N	N	Y	<1–6	R
Chen Y et al. (*19*)	Guang Dong	2014	2011.1–2013.10	N	Y	Y	N	N	U	<1–6	R
Wei CP et al. (*20*)	Shan Dong	2014	2012–2014	N	Y	N	N	N	U	<1–89	R
Huang HJ et al. (*21*)	Guang Dong	2014	2011.1–2012.12	N	Y	N	N	N	U	<1–89	R
Long YM et al. (*22*)	Guang Dong	2014	2011.1–2013.12	Y	Y	N	N	N	U	<1–89	R

Reference	Region of China	Year of publication	Year of data collection	Incidence	CFR	AMR	Serotype	MLST	IAP	Reporting period, y	Study design
Zhu ML et al. (23)	Zhe Jiang	2014	2005.1–2013.5	N	Y	Y	N	N	Y	<1–89	R
Liu X et al. (*24*)	Jiang Su	2015	2013.3–2015.3	N	Y	N	N	N	U	<1–89	R
Zhang S et al. (*25*)	Guang Dong	2015	2013.1–2014.3	N	Y	Y	N	N	U	7–89	R
Zeng SJ et al. (*26*)	Guang Dong	2015	2012–2014	N	N	N	Y	N	U	<1–89	R
Li K et al. (*27*)	Guang Dong	2015	2011.3–2014.2	N	Y	N	N	N	U	<1–89	R
Wang QQ et al. (*28*)	Zhe Jiang	2015	2010.4–2014.4	Y	Y	Y	N	N	Y	<1–89	R
Wang YC et al. (*29*)	Jiang Su	2015	2013.1–2013.12	N	Y	N	N	N	Y	<1–89	R
Luo MJ et al. (*30*)	Guang Dong	2015	2010–2012	N	Y	N	N	N	U	<1–6	R
Zhao N et al. (*31*)	Guang Dong	2015	2011.11–2014.4	N	Y	N	N	N	U	<1–89	R
Lei MF et al. (*32*)	Tianjin	2015	2006.12.-2014.09	N	Y	Y	N	N	U	<1–89	R
Liu H et al. (*33*)	Guang Dong, Hunan	2015	2013.09–2014.09	Y	Y	N	Y	Y	Y	<1–89	P
Rivera L et al. (*34*)	Hong Kong	2015	U	Y	Y	N	N	N	Y	<1–89	P
Zhang JS et al. (*35*)	Guang Dong	2015	2010–2014	N	Y	Y	N	N	U	<1–89	R
Liu ZY et al. (*36*)	Fu jian	2016	2011.3–2014.10	N	Y	N	N	N	U	<1–89	R
Zhang XH et al. (*37*)	Shan Xi (Tai Yuan)	2016	2013.1–2015.11	N	Y	N	N	N	U	<1–89	R
Li L et al. (*38*)	Guang Dong	2016	2008.1–2014.8	N	Y	N	N	N	U	<1–89	R
Li YH et al. (*39*)	Nei Menggu	2016	2013.6–2016.6	Y	Y	N	N	N	U	<1–89	R
Yang HH et al. (*40*)	Shang Hai	2016	2012.1–2015.5	N	Y	N	N	N	N	<1–89	R
Shen YH et al. (*41*)	Beijing	2016	2008.1–2014.1	N	Y	N	N	N	U	<1–89	R
Cai YF et al. (*42*)	Guang Dong	2016	2011.1–2014.10	N	Y	Y	N	N	U	<1–89	R
Lai JD et al. (*43*)	Fu Jian	2016	2010.1–2015.2	N	Y	N	N	N	U	<1–6	R
Zhao L (*44*)	Jiang Su	2016	2014.4–2016.4	N	Y	Y	N	N	U	<1–89	R
Ju HQ et al. (*45*)	Shang Hai	2016	2010.3–2015.2	N	Y	N	N	N	U	<1–89	R
Huang LF et al. (*46*)	Guang Dong	2016	2010.11–2014.2	N	N	Y	N	N	U	<1–89	R

Reference	Region of China	Year of publication	Year of data collection	Incidence	CFR	AMR	Serotype	MLST	IAP	Reporting period, y	Study design
Yue D (*47*)	Hu Bei	2017	2014.1–2016.1	N	Y	N	N	N	U	<1–89	R
Qiao LY et al. (*48*)	Shan Dong	2017	2012.1–2016.1	N	Y	N	N	N	U	7–89	R
Guan XS et al. (*49*)	Guang Dong	2017	2012.1–2015.12	N	Y	N	N	N	U	<1–89	R
Liu WW et al. (*50*)	Guang Dong	2017	2012.1–2015.12	N	Y	Y	N	N	U	<1–89	R
Lv CH (*51*)	Shan Dong	2017	2014.1–2015.12	N	Y	N	N	N	U	<1–89	R
Zhou YZ et al. (*52*)	Zhe Jiang	2017	2008.2–2016.11	N	N	Y	Y	N	U	<1–89	R
Zhang JS et al. (*53*)	Guang Dong	2017	2010.1.1–2015.21.31	N	Y	Y	N	N	U	<1–89	R
Zhang N et al. (*54*)	Shan Dong	2017	2013.1–2016.5	N	Y	Y	N	N	N	<1–89	R
Wang YJ et al. (*55*)	Guang Dong	2017	2011.4–2015.4	N	Y	N	N	N	U	7–89	R
Shenzhen GBS study group (*56*)	Guang Dong	2017	2010.1–2016.6	N	Y	N	N	N	Y	<1–89	R
Zhang S et al. (*57*)	Beijing	2017	2010–2014	N	Y	N	N	N	U	<1–89	R
Tan KH et al. (*58*)	Guang Dong	2017	2012.3–2016.3	N	N	Y	N	N	N	<1–89	R
Zhao TL (*59*)	Liaoning	2017	2015.1–2016.2	N	N	Y	N	N	U	<1–89	R
Ma HL et al. (*60*)	Si Chuan	2017	2014.1–2016.2	N	Y	N	N	N	U	<1–6	R
Huang W et al. (*61*)	Gong Dong, Guang Xi	2017	2013.1–2015.2	N	Y	N	N	N	U	<1–89	R
Chen IL et al. (*62*)	Taiwan	2017	2008.1–2013.12	N	Y	N	N	N	U	<1–89	R
Chen HY et al. (*63*)	Zhe Jiang	2018	2014.6.1–2017.6.31	N	Y	N	N	N	Y	<1–89	R
Guan XS et al. (*64*)	Guang Dong	2018	2011.1–2014.12	Y	Y	Y	Y	Y	U	<1–89	R

*AMR, antimicrobial drug resistance; CFR, case-fatality rate; GBS, group B *Streptococcus*; IAP, intrapartum antimicrobial drug prophylaxis; MLST, multilocus sequence typing; N, no; P, prospective study; R, retrospective study; U, unknown (information not available); Y, yes.

Appendix Table 5. Studies with reasons for exclusions

Reference	Year of publication	Year of data collection	Reasons for exclusion
Resiner DP et al. (*65*)	2000	1994.2–1997.1	Studies not from China
Chang C et al. (*66*)	2000	1984–1997	Investigating only specific clinical manifestations
Zhong Y et al. (*67*)	2002	1998.11–1999.7	Not fulfilling inclusion criteria
Liao CH et al. (*68*)	2002	1980.1–2000.3	No full text
Tiskumara R et al. (*69*)	2009	2005.1.1–2005.12.31	Studies not from China
Lin MC et al. (*70*)	2012	1984–2008	Investigating only specific clinical manifestations
Ye F et al. (*71*)	2013	2009–2011	Other topics
Zhang J et al. (*72*)	2013	2010.1–2011.1	Case report
Lin Z et al. (*73*)	2013	2009.1–2013.5	Investigating only specific clinical manifestations
Tan JF et al. (*74*)	2014	2011.8–2012.8	Other topics
Chu SM et al. (*75*)	2014	20014.1–2011.12	Other topics
Zhang J et al. (*76*)	2015	2009.1–2012.12	Duplicate data analysis
Li L et al. (*77*)	2015	2008.1–2014.8	Not fulfilling inclusion criteria
Mu L et al. (*78*)	2015	2011.7.2014.7	Specimen not obtained from sterile site
Zhong H et al. (*79*)	2015	2011–2014	Specimen not obtained from sterile site
Zhong H et al. (*80*)	2015	2011.1–2014.5	Duplicate data analysis
Wang P et al. (*81*)	2015	2008–2013	Not defined laboratory methods
Li L et al. (*82*)	2016	2008.1–2014.8	Not fulfilling inclusion criteria
Wang Y et al. (*83*)	2016	2013.9–2015.9	Specimen not obtained from sterile site
Geng H et al. (*84*)	2016	2010–2015	Other topics
Huang J et al. (*85*)	2016	2011.11–2015.9	Specimen not obtained from sterile site
Hua CZ et al. (*86*)	2016	2011.1–2015.12	Investigating only specific clinical manifestations
Ding Y et al. (*87*)	2017	2008–2015	Case report
Wang Y et al. (*88*)	2017	2015.10–2016.12	Specimen not obtained from sterile site
Jing L et al. (*89*)	2017	2009.1–2015.2	Specimen not obtained from sterile site
Wu IH et al. (*90*)	2017	2006.1–2013.12	Investigating only specific clinical manifestations

Appendix Table 6. Results of subgroup analysis of total incidence of GBS invasive disease*

Subgroup	No. studies	Incidence (95% CI)	Heterogeneity test	
			I2, %	Q test p value
Study design				
Retrospective	10	0.54 (0.32–0.75)	88.20	0.001
Prospective	3	0.60 (0.12–1.08)	56.80	0.10
Isolate type				
Blood	5	0.37 (0.14–0.60)	69.70	0.01
All sterile sites	1	1.17 (0.89–1.44)		
Blood plus CSF	7	0.52 (0.35–0.69)	46.00	0.09
Age of onset, y				
EOGBS	11	0.38 (0.25–0.51)	65.40	0.001
LOGBS	3	0.18 (0.11–0.25)	0.0	0.45

*CSF, cerebrospinal fluid; EOGBS; early-onset group B *Streptococcus*; LOGBS, late-onset group B *Streptococcus.*

Appendix Table 7. Relationship between group B *Streptococcus* serotypes and MLST results*

Author	No samples	Serotype	ST17	ST12	ST23	ST10	ST1	New 17-like
Liu H et al.	2	III	1	0	0	0	0	1
	3	Ib	0	2	0	1	0	0
	2	Ia	0	0	2	0	0	0
	1	V	0	0	0	0	1	0
Guan XS et al.	53	III	43	0	0	0	0	0
	10	Ib	0	5	1	1	0	0
	2	Ia	0		2	0	0	0
	3	V	0	0	0	0	3	0

*MLST, multilocus sequence typing; ST, sequence type.

References

1. Chang CJ, Chang WN, Huang LT, Huang SC, Chang YC, Hung PL, et al. Neonatal bacterial meningitis in southern Taiwan. Pediatr Neurol. 2003;29:288–94. PubMed https://doi.org/10.1016/S0887-8994(03)00273-X

2. Chung MY, Ko DJ, Chen CC, Huang CB, Chung CH, Chen FS, et al. Neonatal group B streptococcal infection: a 7-year experience. Chang Gung Med J. 2004;27:501–8. PubMed

3. Jiang JH, Chiu NC, Huang FY, Kao HA, Hsu CH, Hung HY, et al. Neonatal sepsis in the neonatal intensive care unit: characteristics of early versus late onset. J Microbiol Immunol Infect. 2004;37:301–6. PubMed

4. Wu JH, Chen CY, Tsao PN, Hsieh WS, Chou HC. Neonatal sepsis: a 6-year analysis in a neonatal care unit in Taiwan. Pediatr Neonatol. 2009;50:88–95. PubMed https://doi.org/10.1016/S1875-9572(09)60042-5

5. Wang P, Ma J, Wang Y, Wen C, Li H, Zhuang T, et al. Perinatal clinical features of early-onset neonatal septicemia caused by group B streptococcus. Clin J Neonatol. 2010;25:219–22.

6. Liu Z, Tang Z, Ding Y, Huang X. Study of early-onset and late-onset neonatal sepsis. J Clin Pediatr. 2011;29:446–9.

7. Lin CY, Hsu CH, Huang FY, Chang JH, Hung HY, Kao HA, et al. The changing face of early-onset neonatal sepsis after the implementation of a maternal group B *Streptococcus* screening and intrapartum prophylaxis policy: a study in one medical center. Pediatr Neonatol. 2011;52:78–84. PubMed https://doi.org/10.1016/j.pedneo.2011.02.001

8. Yu HW, Lin HC, Yang PH, Hsu CH, Hsieh WS, Tsao LY, et al. Group B streptococcal infection in Taiwan: maternal colonization and neonatal infection. Pediatr Neonatol. 2011;52:190–5. PubMed https://doi.org/10.1016/j.pedneo.2011.05.008

9. Wu M. Clinical analysis of 20 cases of neonatal group B streptococcal septicaemia. Contemp Med. 2012;18:70–1.

10. Dai Y, Zeng L, Gao P. Clinical analysis of 14 cases of neonatal group B streptococcal septicaemia. Clin J Neonatol. 2012;27:44–6.

11. Long Y, Zhang Z, Chen X. Clinical analysis of 13 cases of neonatal group B streptococcal septicaemia. China Health Care and Nutrition. 2012;9.

12. Zeng S, Qiu H. Clinical analysis of 11 cases of neonatal *Streptococcus agalactiae* sepsis. Zhongguo Fuyou Baojian. 2012;28:3290–1.

13. Luo J, Ma L, Xu F, Lu G, Feng Z. Clinical characteristics and prognosis of late-onset group B streptococcal sepsis in NICU. J Clin Pediatr. 2013;3:805–8.

14. Chen L, Wu B, Cheng H, Tang Y, Wu J, Yan X, et al. Group B Streptococcal septicemia combined with purulent meningitis: clinical analysis of five cases. Chin Gen Pract. 2013;16:2750–2.

15. Al-Taiar A, Hammoud MS, Cuiqing L, Lee JK, Lui KM, Nakwan N, et al. Neonatal infections in China, Malaysia, Hong Kong and Thailand. Arch Dis Child Fetal Neonatal Ed. 2013;98:F249–55. PubMed https://doi.org/10.1136/archdischild-2012-301767

16. Wu Y. Clinical analysis of 88 cases of neonatal group B hemolytic streptococcal infection. J Frontier Med. 2014;17:280–1.

17. Fan W, Zhao M, Liu J. Antimicrobial resistance in 42 cases of neonate septicemia caused by *Streptococcus agalactiae* infection. Int J Lab Med. 2014;35:2309–10.

18. Zheng Z, Huang J. Clinical analysis of 12 cases of early-onset B group streptococci sepsis in neonates. Clin Pediatr Emerg Med. 2014;21:161–3.

19. Chen Y, Chen R, Wu Z, Lu G. Clinical analysis of 16 cases of neonatal early-onset group B *Streptococcus* sepsis. J Pediatr Pharm. 2014;2011:13–6.

20. Wei C, Li M. Clinical analysis of neonatal group B streptococcal septicemia of eight cases and literature review. Medical Innovation of China. 2014;11:147–50.

21. Huang H, Yu Z, Yang H, Feng J, Liu X. Clinical analysis of neonatal group B streptococcal sepsis. Clin Pediatr Emerg Med. 2014;21:39–40.

22. Long Y, Lai Y, Li Y. Clinical analysis of 16 cases of neonatal group B streptococcal septicaemia. Clin Pediatr Emerg Med. 2014;21:447–8.

23. Zhu M, Zhu J, Li H, Liu P, Lin Z. [Clinical analysis and follow-up of neonatal purulent meningitis caused by group B *streptococcus.*]. Zhonghua Er Ke Za Zhi. 2014;52:133–6. PubMed

24. Liu X, Zhou Q, Shang E, Cheng Y. Analysis of clinical characteristics in neonatal septicemia patients with *Streptococcus agalactiae* and its clinical medication. Anti Infect Pharm. 2015;12:835–7.

25. Zhang S, Luo X, Zhou T, Fu S, Zhu J. Clinical features and therapeutic strategies of late-onset *Streptococcus agalactiae* meningitis. Chin Gen Pract. 2015;18:3633–5.

26. Zeng S, Zhao W, Wang H, Qiu H, Tang X, Feng Z. Study on the serotype of *Streptococcus agalactiae* in neonatal sepsis. Zhongguo Fuyou Baojian. 2015;30:6028–30.

27. Li K, Zhang Y, Du L, Yue W. Clinical analysis and follow-up of 27 cases of neonatal group B streptococcal septicaemia. Shenzhen J Integr Tradit Chin West Med. 2015;15:103–5.

28. Wang Q, Su W. Clinical analysis of 15 cases of neonatal group B streptococcal septicaemia. Zhejiang JITCWM. 2015;2.

29. Wang Y, Lu W, Zhou L. The study of risk factors for neonatal *Streptococcus agalactiae* infection and sensitivity analysis of antibacterials. Int J Lab Med. 2015;36:1065–7.

30. Luo M, Zhang Y, Weng Z, Ou Q, Xiao X. Clinical features of early-onset neonatal septicaemia caused by group B *Streptococcus.* Guangzhou Med J. 2015;46:36–9.

31. Zhao N, Wang P, Lu W, He J, Gu R, Jiang C. Clinical analysis of neonatal purulent meningitis caused by group B *Streptococcus.* Clin Pediatr Emerg Med. 2015;22:177–9.

32. Lei M, Zhang Y, Guo J. Clinical analysis of purulent meningitis related to *Streptococcus agalactiae* in 22 newborn and infants. Zhongguo Shiyong Erke Zazhi. 2015;30:696–700.

33. Liu H, Zeng H, Wang W, Deng Q, Margarit I, Rinaudo CD, et al. Estimating the burden of invasive Group B Streptococcal disease in young infants in southern mainland China: an observational study. Int J Clin Exp Med. 2015;8:13699–707. PubMed

34. Rivera L, Sáez-Llorens X, Feris-Iglesias J, Ip M, Saha S, Adrian PV, et al. Incidence and serotype distribution of invasive group B streptococcal disease in young infants: a multi-country observational study. BMC Pediatr. 2015;15:1–9. PubMed https://doi.org/10.1186/s12887-015-0460-2

35. Zhang J, Zhao R, Dong Y, Zheng Y. Invasive group B streptococcal infection in infants in Shenzhen, China. Int J Clin Exp Med. 2015;8:2939–43. PubMed

36. Liu Z, Xu J, Wang R, Wu L, Chen D. Clinical analysis of 33 cases of neonatal group B Streptococcal sepsis. Clin Pediatr Emerg Med. 2016;23:248–51.

37. Zhang X, Liu K, Wang C. Wu f, Guan H. Clinical analysis of 11 cases of neonatal group B Streptococcal infection. Chin Remed Clin. 2016;9:1360–2.

38. Li L, Wu W, Wu B, Wang S. The relevance of genotype and clinical manifestations of group B *Streptococcus* invasion infection in neonates. Clin J Neonatol. 2016;31:272–5.

39. Li Y, Du F. Clinical analysis of neonatal GBS infection in the third staff hospital of Baogang group. Journal of Inner Mongolia University for Nationalities. 2016;31:525–6.

40. Yang H, Li J. Clinical and prognostic analysis of sepsis caused by *Streptococcus agalactiae* combined with purulent meningitis in 12 neonates J. Clin Pediatr. 2016;34:181–4.

41. Shen Y, Liu H, Qi Y, Dong S, Jin F, Weng J, et al. Retrospective study of group B haemolytic streptococci sepsis in newborn. J Shanxi Med Univ. 2016;47:1041–5.

42. Cai Y, Lin N, Fang X. Study on 15 cases of neonatal group B *Streptococcus* sepsis. Chin J School Doctor. 2016;30:386–8.

43. Lai J, Zheng Z, Lin X, Zhu Y, Lin Y. Clinical analysis of 36 cases of neonatal early onset B *Streptococcus* infection. J Frontier Med. 2016;6:78–9.

44. Zhao L. Clinical characteristics and medication analysis of neonatal *Streptococcus agalactiae* sepsis. Chin Mod Doctor. 2016;54:56–8.

45. Ju H, Bei F, Sun J. Clinical analyses of 16 neonatal group B *Streptococcus* meningitis cases. Clin J Neonatol. 2016;31:178–81.

46. Huang L, Liu H, Huang Y, Guan X, Zhong H, Xie Y, et al. Drug sensitivity analysis of neonatal sepsis and meningitis group B *Streptococcus* isolates in Guangzhou. Guangdong Med J. 2016;37:1873–6.

47. Yue D. Analysis of infection status of neonatal β-hemolytic streptococcus. Chin J Clinical Rational Drug Use. 2017;10:151–2.

48. Qiao L, Ma S, Li D, Yu H, Sun Y. Analysis of 24 cases of infants with late-onset group B streptococci purulent meningitis. Shandong Yiyao. 2017;57:80–2.

49. Guan X, Mu X, Huang Y, Zhong H, Deng Q, Liu H. Epidemiological characteristics of invasive group B streptococcal disease of young infants. Guangzhou Med J. 2017;48:11–4.

50. Liu W, Li H. Clinical analysis of 15 cases of neonatal group B streptococcal septicaemia. Chin J Woman Child Health Research. 2017;28:600–2.

51. Lv C. Clinical Observation on Neonatal *Streptococcus agalactiae* Septicemia complicated with meningitis. China Continuing Medical Education. 2017;9:71–2.

52. Zhou Y, Wang L, Fang Y. Research on the serum type and drug resistance of newborn bloodstream infection caused by group B *Streptococcus.* Chin J Health Lab Tec. 2017;27:1190–3.

53. Zhang J, Deng J, Dong Y, Zhang L, Zhang R, Jia C. Clinical analysis of 55 infants with group B *Streptococcus* bloodstream infection. Chin J Infect Dis. 2017;35:214–7.

54. Zhang N, Yang N, Qu N, Li Z. Clinical analysis of purulent meningitis caused by *Streptococcus agalactiae* in young infants. Zhonghua Shiyong Erke Linchuang Zazhi. 2017;32:1571–4.

55. Wang Y, Li J, Ye S, Li H, Li W. Clinical characteristics of neonatal meningitis caused by *Streptococcus agalactiae.* Pract Clin Med. 2017;18:76–8.

56. Shenzhen NGIRCGi. The clinical study on the early onset and late onset B group haemolytic *Streptococcus* infection in neonates. Clin J Neonatol. 2017;32:241–4.

57. Zhang Sheng ZL, Qiuping L, Xiujuan W, Jie X, Yupei Z, Zhichuan F. Clinical distribution and antimicrobial resistance of *Streptococcus agalactiae* in neonatal intensive care unit. Can J Infect Control. 2017;16:804–6.

58. Tan K, Lu Y, Zhang N. Clinical analysis of 20 cases of neonatal group B streptococcal septicaemia. Guangdong Yixue. 2017;S1:176–8.

59. Zhao T. Study on drug resistance of neonatal *Streptococcus agalactiae sepsis.* Med J Chinese People's Health. 2017;29:27–8.

60. Ma H, Wang Y, Huang Z, Ran M, Tan S, Huang J. Perinatal clinical features of early-onset neonates with group B streptococcal septicemia. J Frontier Med. 2017;7:177–8.

61. Huang W, Lin G, Liu G, Wei Q. Clinical analysis of 30 cases of neonatal group B streptococcal sepsis. Zhonghua Shiyong Erke Linchuang Zazhi. 2017;32:1721–4.

62. Chen IL, Chiu NC, Chi H, Hsu CH, Chang JH, Huang DT, et al. Changing of bloodstream infections in a medical center neonatal intensive care unit. J Microbiol Immunol Infect. 2017;50:514–20. PubMed https://doi.org/10.1016/j.jmii.2015.08.023

63. Chen H, Hu Y, Zhang H, Yang J, Lin M, Zheng J. Clinical features of neonatal group B *Streptococcus* for septicaemia and its risk factors analysis. Chin J Health Lab Tec. 2018;28:300–2.

64. Guan X, Mu X, Ji W, Yuan C, He P, Zhang L, et al. Epidemiology of invasive group B streptococcal disease in infants from urban area of South China, 2011–2014. BMC Infect Dis. 2018;18:14. PubMed https://doi.org/10.1186/s12879-017-2811-0

65. Reisner DP, Haas MJ, Zingheim RW, Williams MA, Luthy DA. Performance of a group B streptococcal prophylaxis protocol combining high-risk treatment and low-risk screening. Am J Obstet Gynecol. 2000;182:1335–43. PubMed https://doi.org/10.1067/mob.2000.106246

66. Chang Chien HY, Chiu NC, Li WC, Huang FY. Characteristics of neonatal bacterial meningitis in a teaching hospital in Taiwan from 1984-1997. J Microbiol Immunol Infect. 2000;33:100–4. PubMed

67. Zhong Y, Wu M, Tong Y, Shen A, Yang Y. A study of neonatal group B streptococcal infection. Chin J Perinat Med. 2002;5:38–41.

68. Liao CH, Huang LM, Lu CY, Lee CY, Hsueh PR, Tsao PN, et al. Group B *streptococcus* infection in infancy: 21-year experience. Acta Paediatr Taiwan. 2002;43:326–9. PubMed

69. Tiskumara R, Fakharee SH, Liu CQ, Nuntnarumit P, Lui KM, Hammoud M, et al.; Asia-Pacific Neonatal Infections Study. Neonatal infections in Asia. Arch Dis Child Fetal Neonatal Ed. 2009;94:F144–8. PubMed https://doi.org/10.1136/adc.2008.139865

70. Lin MC, Chi H, Chiu NC, Huang FY, Ho CS. Factors for poor prognosis of neonatal bacterial meningitis in a medical center in Northern Taiwan. J Microbiol Immunol Infect. 2012;45:442–7. PubMed https://doi.org/10.1016/j.jmii.2011.12.034

71. Ye F, Chang H. Pathogen distribution and antimicrobial resistance of 43 cases of early onset neonatal septicaemia. Clin J Neonatol. 2013;28:85–7.

72. Zhang J, Li B, Dong Y. 5 cases of infantile *Streptococcus agalactiae* septicaemia. J Chin Pediatr. 2013;31:189–90.

73. Lin Z, Wang J. Clinical analysis of 22 cases of neonatal B group hemolytic streptococcal infection. J Chin Physician. 2013;15:1718–9.

74. Tan J, Zhu X, Zhou Y, Mao L. Clinical treatment exploration of 60 cases of neonatal group B streptpcoccal meningitis. Zhongguo Fuyou Baojian. 2014;29:65–7.

75. Chu SM, Hsu JF, Lee CW, Lien R, Huang HR, Chiang MC, et al. Neurological complications after neonatal bacteremia: the clinical characteristics, risk factors, and outcomes. PLoS One. 2014;9:e105294. PubMed https://doi.org/10.1371/journal.pone.0105294

76. Zhang J, Dong Y, Zhao R, Zheng Y. Infant with Group B streptococcal infection: a retrospective analysis of 35 cases. Zhongguo Shiyong Erke Zazhi. 2015;30:215–8.

77. Li L, Wu W, Wu B, Wang S. The relevance between serotypes and clinical characteristics of neonatal infection due to Group B streptococcus and antibiotic sensitivity of serotypes isolated from these infants. Clin J Neonatol. 2015;30:339–42.

78. Mu L, Kuang L, Zhou W, Su M, Jiang Y. Clinical characteristics and antimicrobial resistance analysis of neonatal streptococci infection. Guizhou Med J. 2015;39:644–5.

79. Zhong H, Guan X, Xie Y, Huang L, Wu X. Distribution of serotypes and drug sensitivity analysis of group B *Streptococcus* among infants in Guangzhou area. Zhongguo Fuyou Baojian. 2015;30:6261–3.

80. Zhong H, Guan X, Xie Y, Huang L, Huang Y, Liu H. Infection distribution and drug sensitivity analysis of *Streptococcus agalactiae* in infants and young children. Int J Lab Med. 2015;36:2907–9.

81. Wang P, Ma Z, Tong J, Zhao R, Shi W, Yu S, et al. Serotype distribution, antimicrobial resistance, and molecular characterization of invasive group B *Streptococcus* isolates recovered from Chinese neonates. Int J Infect Dis. 2015;37:115–8. PubMed https://doi.org/10.1016/j.ijid.2015.06.019

82. Li L, Wu W, Wu B, Wang S. The relevance of genotypes and clinical manifestations of group B streptococcus invasion infection in neonates. Clin J Neonatol. 2016;31:272–5.

83. Wang Y. Clinical features of early onset and late onset sepsis in neonates. Chin J Mod Drug Appl. 2016;6.

84. Geng H, Yang B, Zhu X. Clinical analysis of 53 cases of neonatal meningitis and the characteristics of *Streptococcus agalactiae* meningitis. Zhonghua Linchuang Yishi Zazhi. 2016;10:751–4.

85. Huang J. Analysis on the antimicrobial resistance of *Streptococcus agalactiae* in Department of Neonatology. Chin J Clinical Rational Drug Use. 2016;9:21–2.

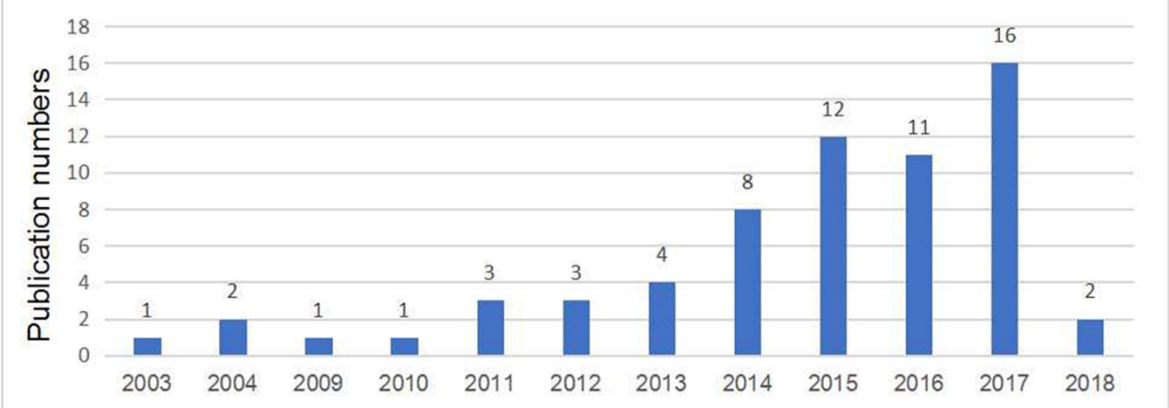
86. Hua CZ, Yu H, Zhuang JQ, Li XL, Xu HM, Luo QE, et al. An analysis of 181 cases with blood stream infection caused by *Streptococcus agalactiae* in children from 2011 to 2015: a multi-center retrospective study. Zhonghua Er Ke Za Zhi. 2016;54:577–81. PubMed

87. Ding Y, Chen Z, Li R, Lu Y. 10 cases of clinical analysis on group B haemolytic *Streptococcus* meningitis of neonates. Chin Med Pharm. 2017;7:254–6.

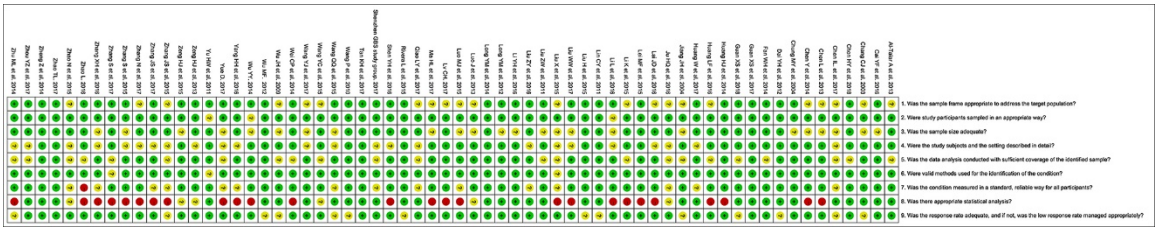
88. Wang Y, Chen J, Wei B, Jiang Y, Fu J. Epidemiological survey of neonatal group B hemolytic *Streptococcus.* Zhongguo Fuyou Baojian. 2017;32:2440–2.

89. Jing L, Li Y, Meng D, Wei Q. Multivariate regression analysis of risk factors for neonatal early-onset group B hemolytic streptococcus infection. Chin Mod Doctor. 2017;55:49–51.

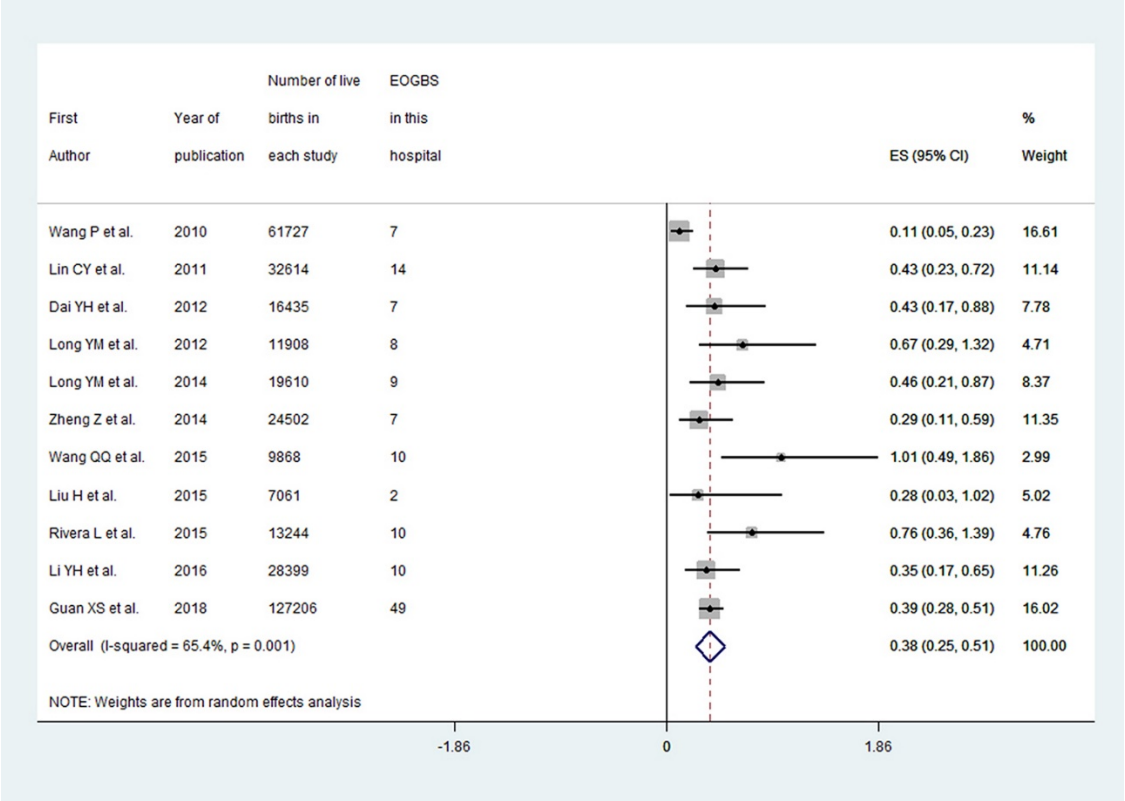
90. Wu IH, Tsai MH, Lai MY, Hsu LF, Chiang MC, Lien R, et al. Incidence, clinical features, and implications on outcomes of neonatal late-onset sepsis with concurrent infectious focus. BMC Infect Dis. 2017;17:465. PubMed https://doi.org/10.1186/s12879-017-2574-7



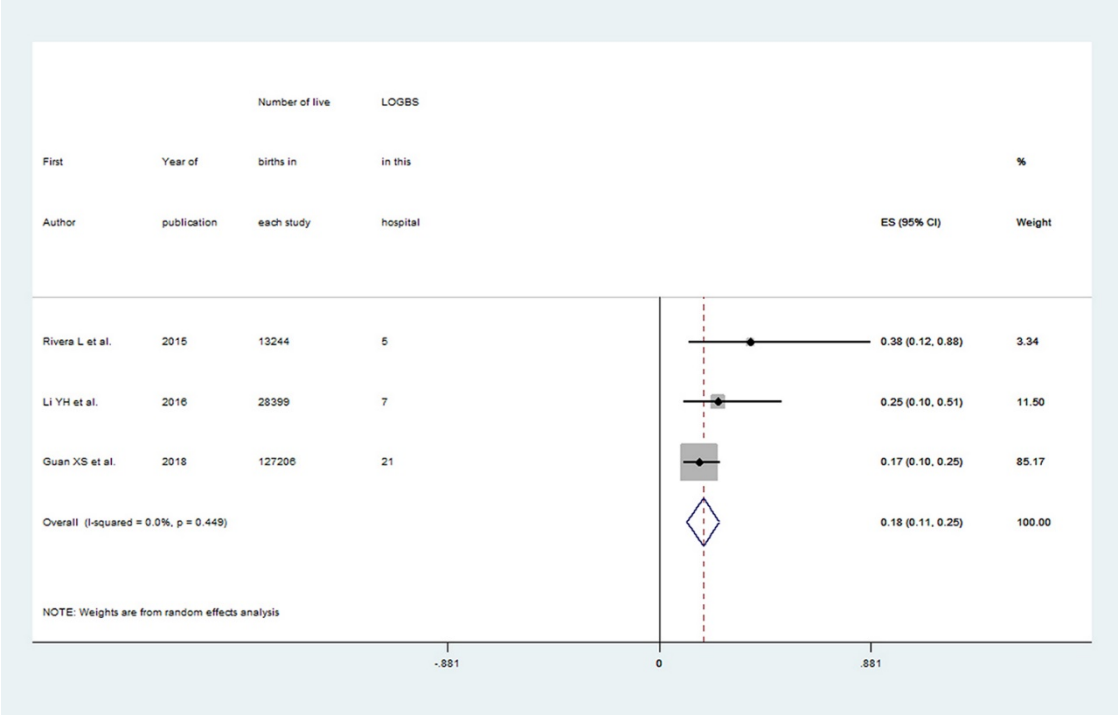
Appendix Figure 1. Publication year of included studies of infants invasive group B *Streptococcus* disease (n = 64) In 2018, we only searched articles published before March16, 2018.



Appendix Figure 2. Risk for bias in the studies. Colored circles indicate different risks. Green, low risk; yellow, unknown risk; red, high risk.

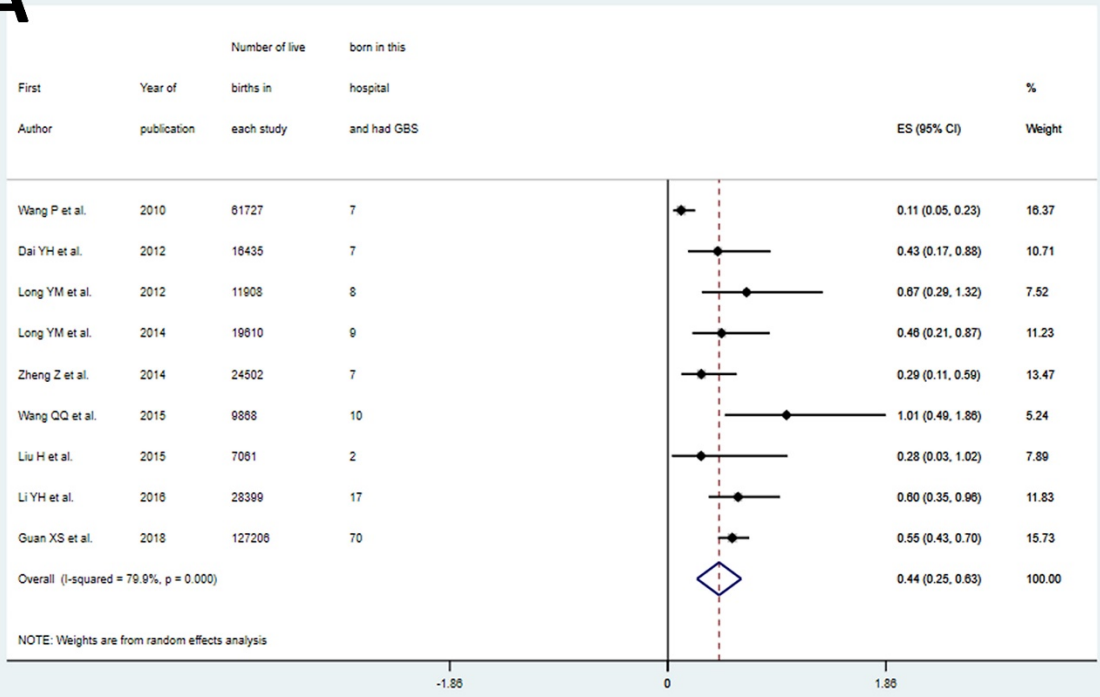


Appendix Figure 3. Incidence risk for early-onset group B *Streptococcus* (EOGBS) disease (n = 11). Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Error bars indicate 95% CI. ES, effect size; GBS, group B *Streptococcus* disease.

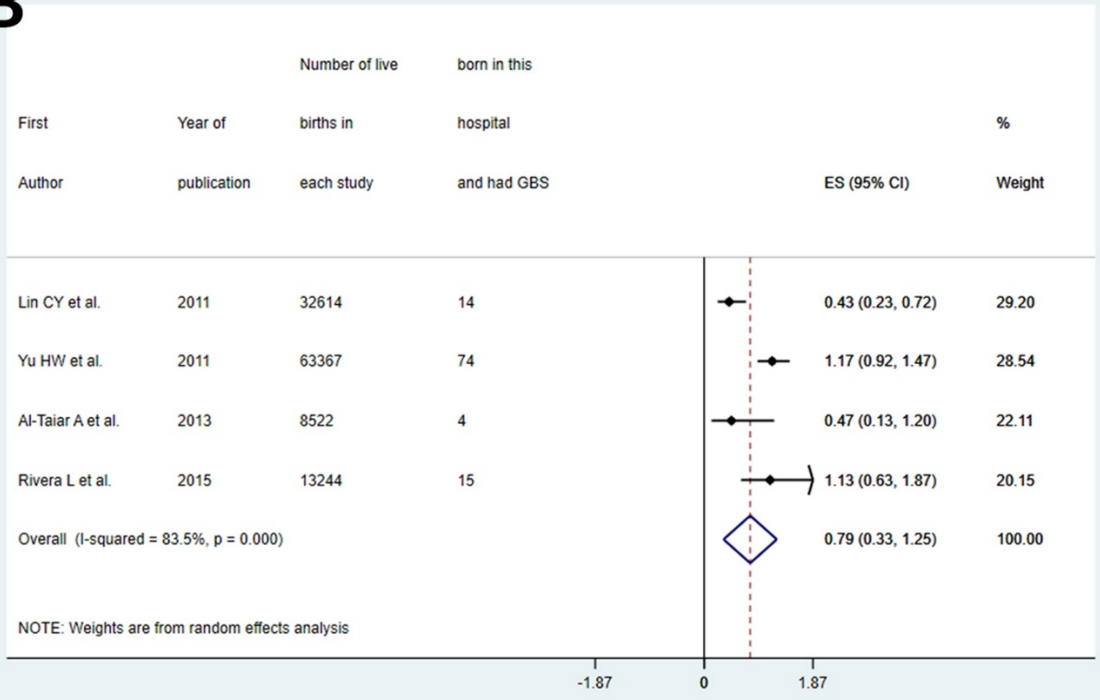


Appendix Figure 4. Incidence risk for late-onset **(**age 7–89 days) group B *Streptococcus* (LOGBS) disease (n = 3). Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Shaded areas indicate relative weight that each individual study contributes to the overall pooled effect. Error bars indicate 95% CI. ES, effect size.

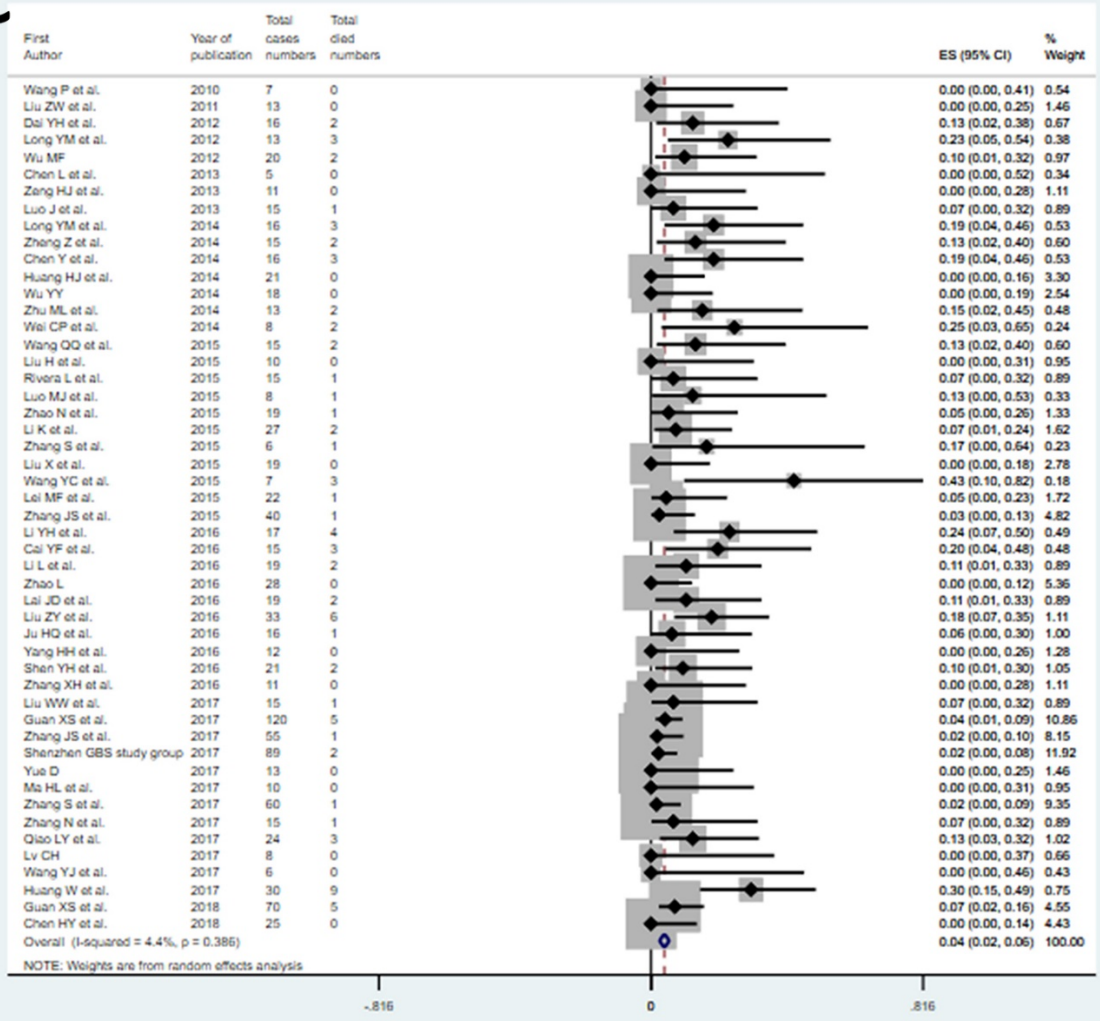
A

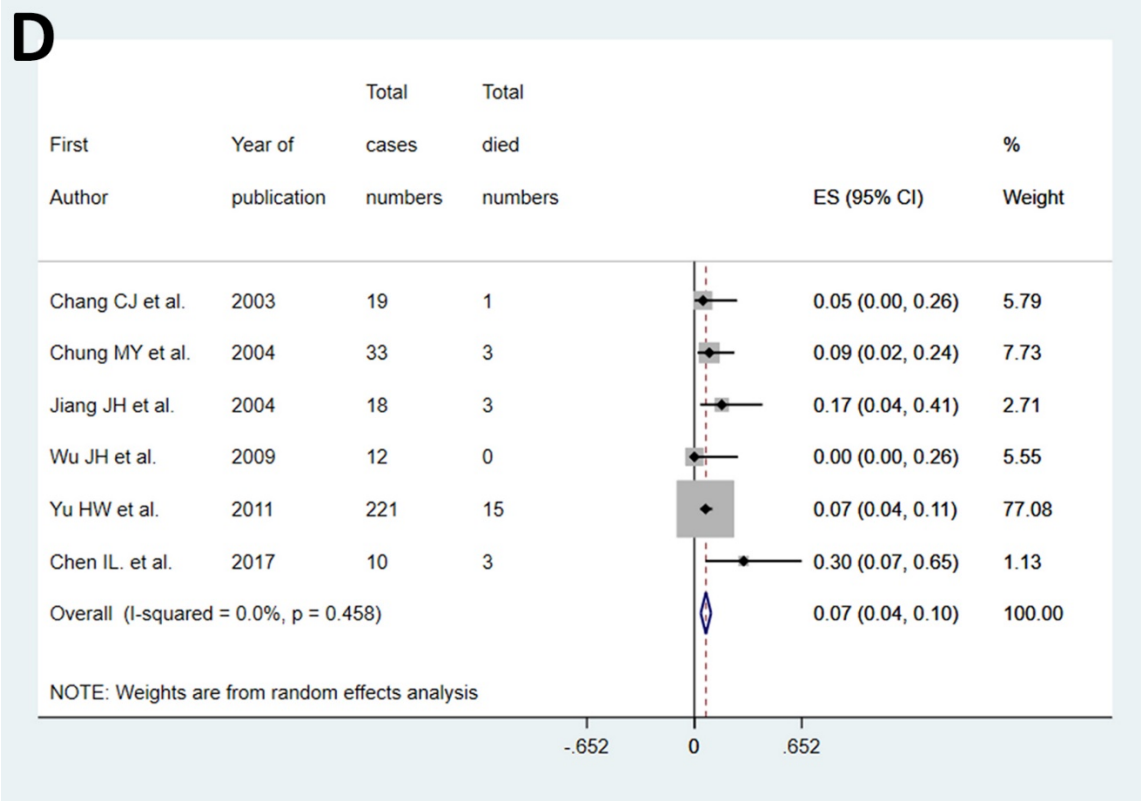

First Author
Year of publication
Number of live births in each study
born in this hospital and had GBS
ES (95% CI)
%
Weight
Wang P et al. 2010 61727 7 0.11 (0.05, 0.23) 16.37
Dai YH et al. 2012 16435 7 0.43 (0.17, 0.88) 10.71
Long YM et al. 2012 11908 8 0.67 (0.29, 1.32) 7.52
Long YM et al. 2014 19610 9 0.46 (0.21, 0.87) 11.23
Zheng Z et al. 2014 24502 7 0.29 (0.11, 0.59) 13.47
Wang QQ et al. 2015 9868 10 1.01 (0.49, 1.86) 5.24
Liu H et al. 2015 7061 2 0.28 (0.03, 1.02) 7.89
Li YH et al. 2016 28399 17 0.60 (0.35, 0.96) 11.83
Guan XS et al. 2018 127206 70 0.55 (0.43, 0.70) 15.73
Overall (I-squared = 79.9%, p = 0.000) 0.44 (0.25, 0.63) 100.00
NOTE: Weights are from random effects analysis
-1.86
0
1.86

B

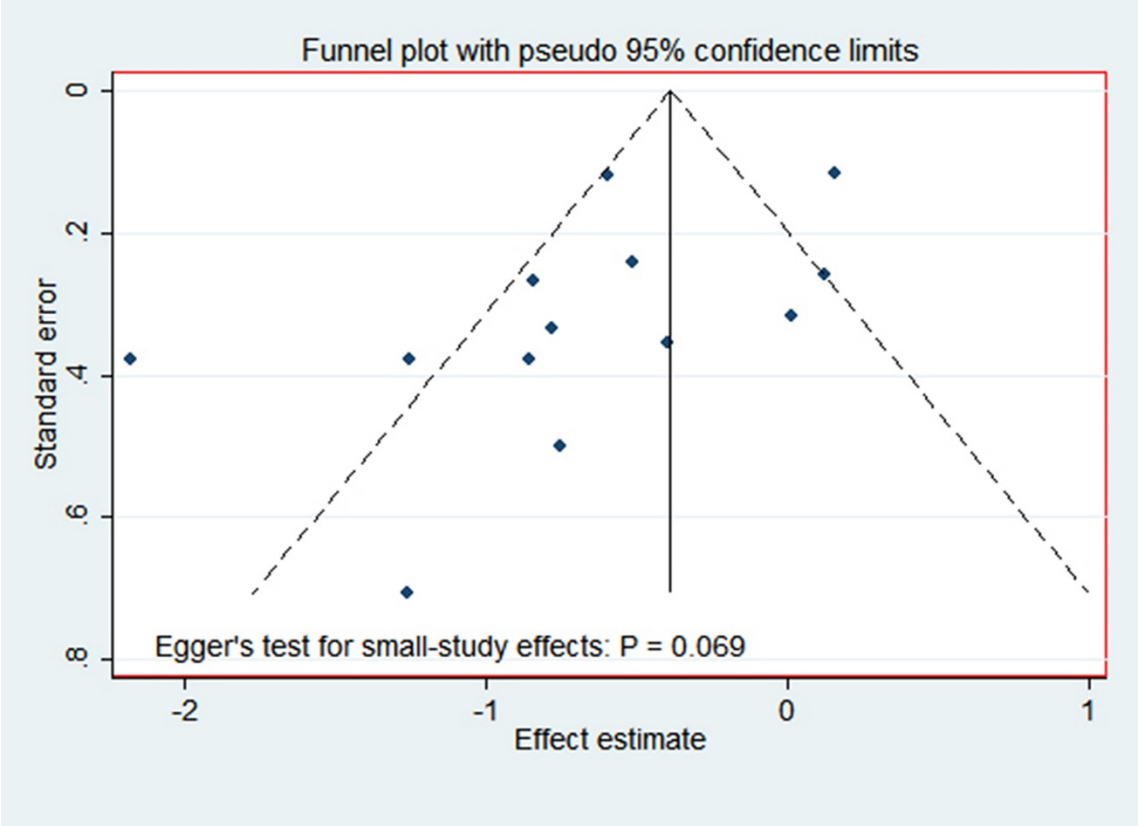

First Author
Year of publication
Number of live births in each study
born in this hospital and had GBS
ES (95% CI)
%
Weight
Lin CY et al. 2011 32614 14 0.43 (0.23, 0.72) 29.20
Yu HW et al. 2011 63367 74 1.17 (0.92, 1.47) 28.54
Al-Taiar A et al. 2013 8522 4 0.47 (0.13, 1.20) 22.11
Rivera L et al. 2015 13244 15 1.13 (0.63, 1.87) 20.15
Overall (I-squared = 83.5%, p = 0.000) 0.79 (0.33, 1.25) 100.00
NOTE: Weights are from random effects analysis
-1.87
0
1.87

C

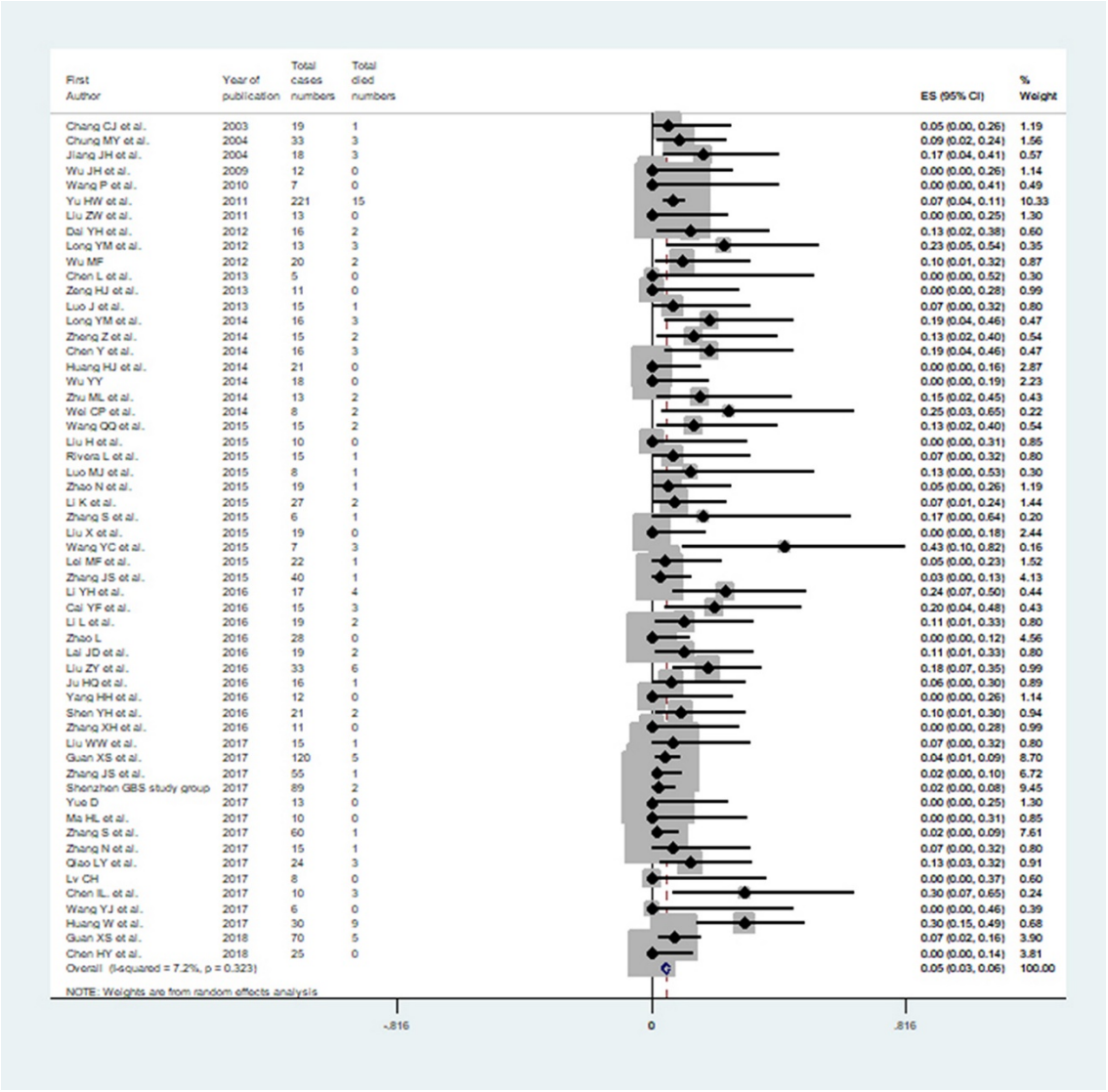

First Author
Year of publication
Total cases numbers
Total died numbers
ES (95% CI)
% Weight
Wang P et al. 2010 7 0 0.00 (0.00, 0.41) 0.54
Liu ZW et al. 2011 13 0 0.00 (0.00, 0.25) 1.46
Dai YH et al. 2012 16 2 0.13 (0.02, 0.38) 0.67
Long YM et al. 2012 13 3 0.23 (0.05, 0.54) 0.38
Wu MF 2012 20 2 0.10 (0.01, 0.32) 0.97
Chen L et al. 2013 5 0 0.00 (0.00, 0.52) 0.34
Zeng HJ et al. 2013 11 0 0.00 (0.00, 0.28) 1.11
Luo J et al. 2013 15 1 0.07 (0.00, 0.32) 0.89
Long YM et al. 2014 16 3 0.19 (0.04, 0.46) 0.53
Zhang Z et al. 2014 15 2 0.13 (0.02, 0.40) 0.60
Chen Y et al. 2014 16 3 0.19 (0.04, 0.46) 0.53
Huang HJ et al. 2014 21 0 0.00 (0.00, 0.16) 3.30
Wu YY 2014 18 0 0.00 (0.00, 0.19) 2.54
Zhu ML et al. 2014 13 2 0.15 (0.02, 0.45) 0.48
Wei CP et al. 2014 8 2 0.25 (0.03, 0.65) 0.24
Wang QQ et al. 2015 15 2 0.13 (0.02, 0.40) 0.60
Liu H et al. 2015 10 0 0.00 (0.00, 0.31) 0.95
Rivera L et al. 2015 15 1 0.07 (0.00, 0.32) 0.89
Luo MJ et al. 2015 8 1 0.13 (0.00, 0.53) 0.33
Zhao N et al. 2015 19 1 0.05 (0.00, 0.26) 1.33
Li K et al. 2015 27 2 0.07 (0.01, 0.24) 1.62
Zhang S et al. 2015 6 1 0.17 (0.00, 0.64) 0.23
Liu X et al. 2015 19 0 0.00 (0.00, 0.18) 2.78
Wang YC et al. 2015 7 3 0.43 (0.10, 0.82) 0.18
Lei MF et al. 2015 22 1 0.05 (0.00, 0.23) 1.72
Zhang JS et al. 2015 40 1 0.03 (0.00, 0.13) 4.82
Li YH et al. 2016 17 4 0.24 (0.07, 0.50) 0.49
Cai YF et al. 2016 15 3 0.20 (0.04, 0.48) 0.48
Li L et al. 2016 19 2 0.11 (0.01, 0.33) 0.89
Zhao L 2016 28 0 0.00 (0.00, 0.12) 5.36
Lai JD et al. 2016 19 2 0.11 (0.01, 0.33) 0.89
Liu ZY et al. 2016 33 6 0.18 (0.07, 0.35) 1.11
Ju HQ et al. 2016 16 1 0.06 (0.00, 0.30) 1.00
Yang HH et al. 2016 12 0 0.00 (0.00, 0.26) 1.28
Shen YH et al. 2016 21 2 0.10 (0.01, 0.30) 1.05
Zhang XH et al. 2016 11 0 0.00 (0.00, 0.28) 1.11
Liu WW et al. 2017 15 1 0.07 (0.00, 0.32) 0.89
Guan XS et al. 2017 120 5 0.04 (0.01, 0.09) 10.86
Zhang JS et al. 2017 55 1 0.02 (0.00, 0.10) 8.15
Shenzhen GBS study group 2017 89 2 0.02 (0.00, 0.08) 11.92
Yue D 2017 13 0 0.00 (0.00, 0.25) 1.46
Ma HL et al. 2017 10 0 0.00 (0.00, 0.31) 0.95
Zhang S et al. 2017 60 1 0.02 (0.00, 0.09) 9.35
Zhang N et al. 2017 15 1 0.07 (0.00, 0.32) 0.89
Qiao LY et al. 2017 24 3 0.13 (0.03, 0.32) 1.02
Lv CH 2017 8 0 0.00 (0.00, 0.37) 0.66
Wang YJ et al. 2017 6 0 0.00 (0.00, 0.46) 0.43
Huang W et al. 2017 30 9 0.30 (0.15, 0.49) 0.75
Guan XS et al. 2018 70 5 0.07 (0.02, 0.16) 4.55
Chen HY et al. 2018 25 0 0.00 (0.00, 0.14) 4.43
Overall (I-squared = 4.4%, p = 0.386) 0.04 (0.02, 0.06) 100.00
NOTE: Weights are from random effects analysis
-.816
0
.816



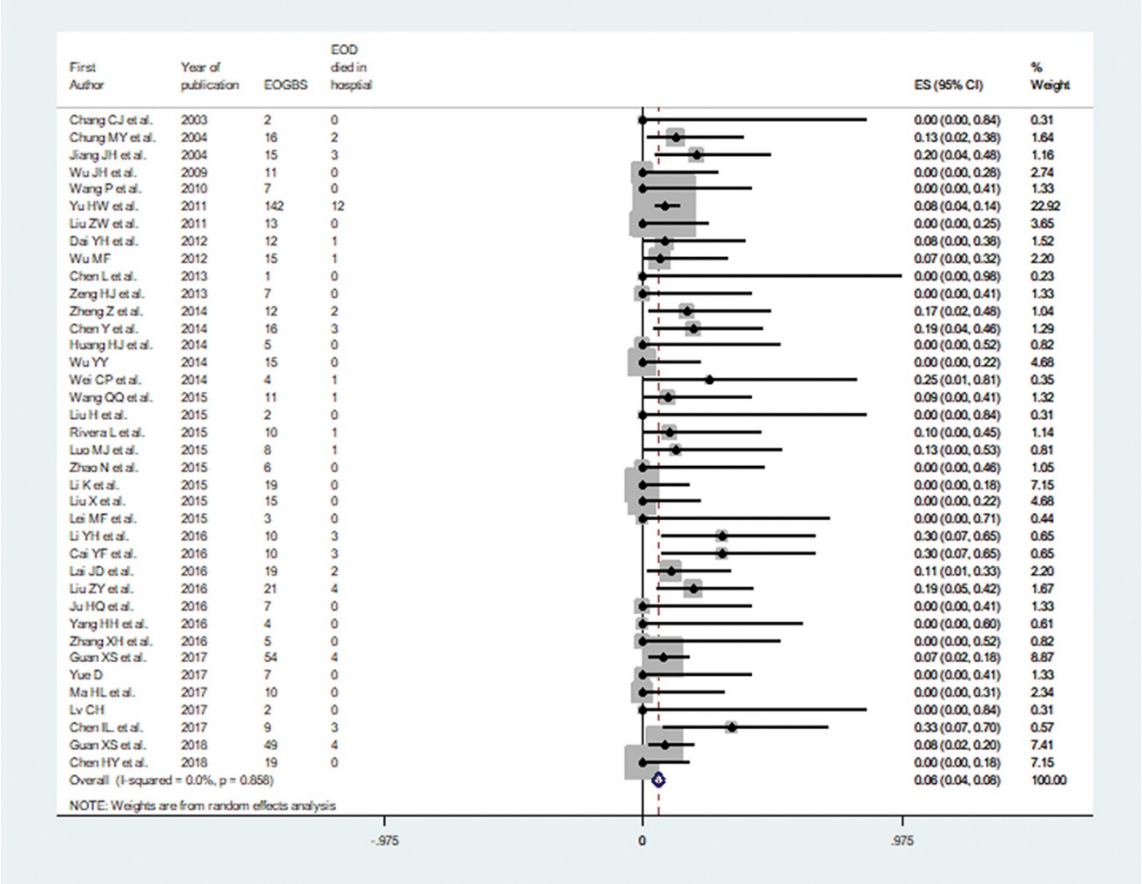
Appendix Figure 5. Sensitivity analysis of GBS invasive diseases incidence studies. A) Total incidence of GBS invasive disease in Mainland China; B) total incidence of GBS invasive disease in Taiwan, Hong Kong, and Macau; C) total CFR of GBS invasive disease in Mainland China; D) total CFR of GBS invasive disease in Taiwan, Hong Kong, and Macau. Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Shaded areas indicate relative weight that each individual study contributes to the overall pooled effect. ES, effect size; GBS, group B *Streptococcus* disease.



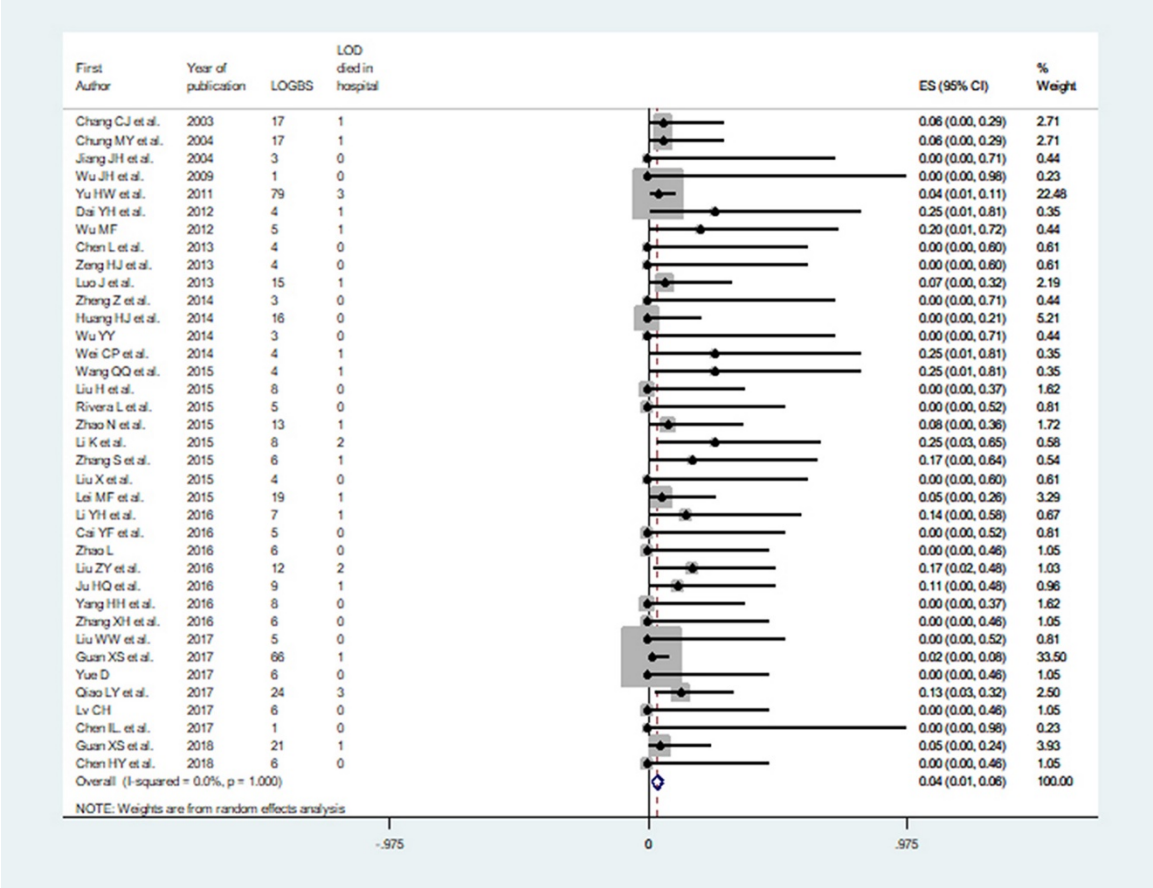
Appendix Figure 6. Funnel plot showing publication bias for group B *Streptococcus* disease.



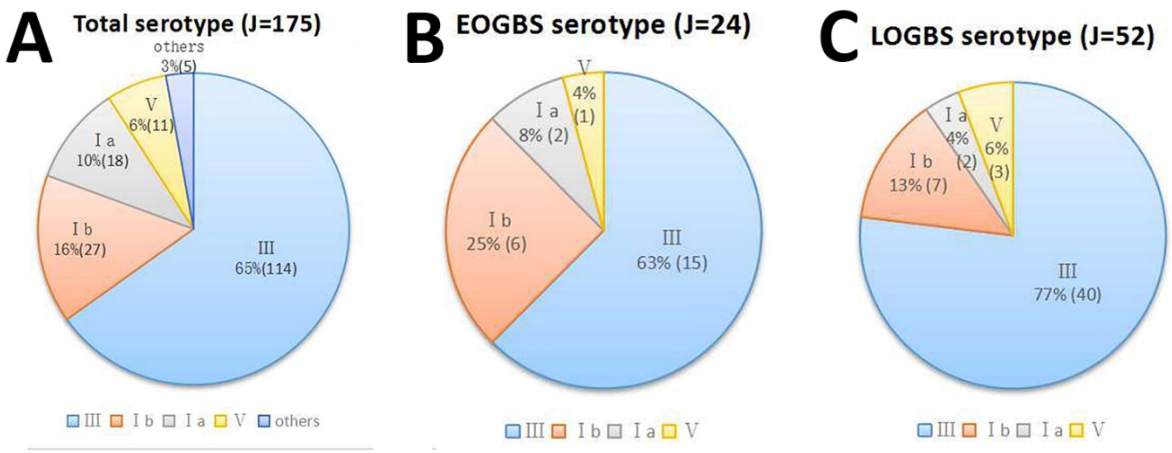
Appendix Figure 7. Case-fatality rate of group B *Streptococcus* (GBS) disease in infants <1–89 days of age (n = 56). Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Shaded areas indicate relative weight that each individual study contributes to the overall pooled effect. CFR, case-fatality rate; ES, effect size; GBS, group B *Streptococcus* disease.



Appendix Figure 8. Case-fatality rate (CFR) of early-onset group B *Streptococcus* (EOGBS) disease (n = 38). Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Shaded areas indicate relative weight that each individual study contributes to the overall pooled effect. EOD, patient died in the hospital; ES, effect size.



Appendix Figure 9. Case fatality rate (CFR) of late-onset group B *Streptococcus* (LOGBS) disease in children 7–89 days of age (n = 37). Vertical dashed line indicates a visual assessment of heterogeneity of the studies. If the vertical line can be drawn, forest plots indicate that all studies are similar enough to be included for meta-analysis. Shaded areas indicate relative weight that each individual study contributes to the overall pooled effect. LOD, patient died in the hospital; ES, effect size.



Appendix Figure 10. Serotype distribution of group B *Streptococcus* (GBS) in infants <1–89 days of age with invasive disease. A) Overall serotype distribution of GBS; B) distribution of early-onset GBS disease; C) distribution of late-onset GBS disease. EOGBS, early-onset GBS disease; LOGBS, late-onset GBS disease.