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Group B *Streptococcus* in surgical site and non-invasive bacterial infections worldwide: A systematic review and meta-analysis☆

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ABSTRACT

Objectives: The epidemiology of disease caused by group B *Streptococcus* (GBS; *Streptococcus agalactiae*) outside pregnancy and the neonatal period is poorly characterized. The aim of this study was to quantify the role of GBS as a cause of surgical site and non-invasive infections at all ages.
Methods: A systematic review (PROSPERO CRD42017068914) and meta-analysis of GBS as a proportion (%) of bacterial isolates from surgical site infection (SSI), skin/soft tissue infection (SSTI), urinary tract infection (UTI), and respiratory tract infection (RTI) was conducted.
Results: Seventy-four studies and data sources were included, covering 67 countries. In orthopaedic surgery, GBS accounted for 0.37% (95% confidence interval (CI) 0.08–1.68%), 0.87% (95% CI 0.33–2.28%), and 1.46% (95% CI 0.49–4.29%) of superficial, deep, and organ/space SSI, respectively. GBS played a more significant role as a cause of post-caesarean section SSI, detected in 2.92% (95% CI 1.51–5.55%), 1.93% (95% CI 0.97–3.81%), and 9.69% (95% CI 6.72–13.8%) of superficial, deep, and organ/space SSI. Of the SSTI isolates, 1.89% (95% CI 1.16–3.05%) were GBS. The prevalence of GBS in community and hospital UTI isolates was 1.61% (1.13–2.30%) and 0.73% (0.43–1.23%), respectively. GBS was uncommonly associated with RTI, accounting for 0.35% (95% CI 0.19–0.63%) of community and 0.27% (95% CI 0.15–0.48%) of hospital RTI isolates.
Conclusions: GBS is implicated in a small proportion of surgical site and non-invasive infections, but a substantial proportion of invasive SSI post-caesarean section.

Introduction

Streptococcus agalactiae (group B *Streptococcus*, GBS) is implicated in a range of clinical presentations, including skin and soft tissue infections (SSTI) and urinary tract infections (UTI) (Kerneis et al., 2017; Chaiwarith et al., 2011; Falagas et al., 2006). GBS disease in adults is of growing clinical and public health concern (Bjornsdottir et al., 2016; Lamagni et al., 2013; Skoff et al., 2009), and the increasing prevalence of risk factors for GBS disease including old age and diabetes (Ballard et al., 2016; Camuset et al., 2015; Lefebvre et al., 2007; Huang et al., 2006) implies considerable health and social care costs (Badia et al., 2017; Kennedy et al., 2013; Ciani et al., 2013; Allegranzi et al., 2011). The advent of vaccines to prevent neonatal GBS disease raises the possibility of preventing GBS disease in other patient groups (Kim et al., 2017; Heath et al., 2017; Vekemans et al., 2018). Whilst the worldwide burden of maternal and infant GBS disease has been quantified (Madrid et al., 2017; Le Doare et al., 2017; Russell et al., 2017a; Hall et al., 2017; Tann et al., 2017; Kohli-Lynch et al., 2017; Bianchi-Jassir et al., 2017; Russell et al., 2017b; Seale et al., 2017a; Seale et al., 2017b), the burden of other forms of GBS disease is unknown (Le Doare and Heath, 2013).

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The aim of this systematic review was to quantify the role of GBS as a cause of surgical site, healthcare-associated, and non-invasive bacterial infections. All types of surgical site infection (SSI) were included, namely superficial, deep, and organ/space, along with catheter-associated UTI and ventilator-associated pneumonia (VAP). For other types of infection, 'non-invasive' was defined by excluding infections where GBS was detected at a sterile site. Infections where GBS was detected in urine were included because UTIs are relatively common in the population and the overall proportion attributable to GBS is unquantified.

Methods

This review was registered with PROSPERO (CRD42017068914). Scoping reviews showed that the incidence of GBS has rarely been reported; hence, the primary outcome was GBS as a proportion of the total number of bacterial isolates for each type of infection.

Searches

The types of infection were not pre-specified, but the search strategy aimed to capture epidemiological studies and surveillance sources of surgical site, healthcare-associated, skin/soft tissue/wound, urinary tract, and respiratory tract infections (RTI). The following databases and libraries were searched: MEDLINE, Embase, CINAHL, Scopus, Global Health, and Trip (including DARE and Cochrane). Full search terms are provided as **Supplementary Material**. In brief, medical subject heading (MeSH) search terms for "Bacterial Infections", "Microbial Sensitivity Tests", "Cross Infection", "Soft Tissue Infections", "Urinary Tract Infections", "Respiratory Tract Infections", "Wound Infections", or "*Streptococcus agalactiae*" were used in conjunction with text word terms for healthcare-associated, surgical, or community infection or group B/haemolytic streptococcal infection. Studies with title words indicating a focus on non-surgical invasive infection (bloodstream, endocarditis, meningitis, sepsis, or bacteraemia) were excluded. The search was restricted to publication dates from January 1, 2000 to July 5th 2017 and to studies in humans. There was no language restriction.

Screening and extraction

Citations identified by the search were imported into EndNote (EndNote X8; Clarivate Analytics, Boston, MA, USA) for de-duplication, and then imported into EPPI-Reviewer (EPPI-Reviewer 4; EPPI-Centre Software; Social Science Research Unit, UCL Institute of Education, London, UK) for further de-duplication. One reviewer (SC) conducted a first screen by title and abstract; two reviewers (SC and TL) then conducted a second screen by title and abstract independently and in parallel, and disagreements were resolved with a third reviewer (NS). Full texts of all articles identified in the second screen by title and abstract were retrieved. These were screened for final inclusion by one reviewer (SC) concurrently with data extraction. A second reviewer (TL) independently checked inclusion/exclusion and data extraction from a randomly selected sample (10%) of full texts.

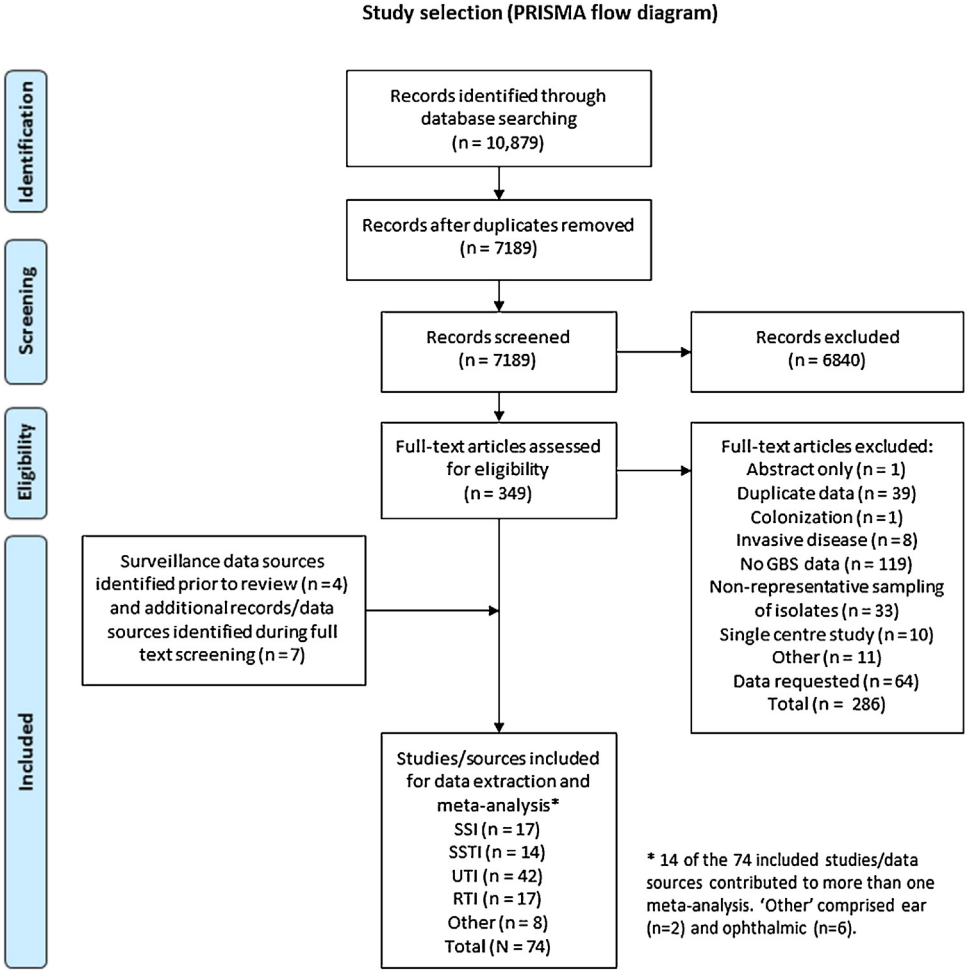

Figure 1. Study selection (PRISMA flow diagram).

Quality assessment

The methodological quality of included studies was rated by two reviewers (SC 100%, TL 10%) using a nine-item quality assessment tool adapted from the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (see **Supplementary Material**). The adaptation allowed for the assessment of the quality of data from surveillance systems and studies based on routine laboratory data, which comprised the majority of the included data sources. Each source/study was rated as being of 'good', 'fair', or 'poor' quality. Data were not extracted from sources/studies that were rated 'poor'.

Other data sources

If a study did not report data at the level of detail required for the meta-analyses, e.g. pathogens reported solely as '*Streptococcus spp*' or 'Other', or aggregated data for all types of surgical site infection, the authors were contacted to request data. If unpublished data were provided that superseded data reported in retrieved texts, the most relevant or recent reference was retained as the citation or an additional reference was included as 'identified through other sources'. Three institutions that publish routine surveillance data were identified prior to the review as potential sources of data: Public Health England (PHE), the European Centre for Disease Prevention and Control (ECDC), and the US Centers for Disease Control and Prevention (CDC).

Meta-analysis

Binomial-normal random-effects meta-analysis of GBS as a proportion of all isolated microorganisms was performed in Stata Release 13, 2013 (StataCorp., College Station, TX, USA) using 'metaprop_one' (Nyaga et al., 2014). In this approach, the binomial distribution is used to model within-study variability, and the normal distribution is used to model the random effects. Between-study heterogeneity was estimated as τ^2, and evidence of heterogeneity was tested by likelihood ratio (LR) test comparing random- and fixed-effects models. The proportion of overall heterogeneity attributable to between-study variance was quantified using a formulation of the I^2 statistic for binary variables (Zhou and Dendukuri, 2014). Prediction intervals were estimated to show the expected prevalence of GBS taking into account between-study variability (IntHout et al., 2016; Nagashima et al., 2018). Meta-analysis defaulted to fixed-effects if three or fewer studies were included. Subgroup analyses specified a priori were: age group (neonatal, child, adult, elderly); surgical specialty, type of SSI (superficial incisional, deep incisional, or organ/space) (Owens and Stoessel, 2008); and putative origin of infection (community, hospital, device/procedure).

Role of the funding source

The funder of the study (Pfizer Inc.) had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to the data in the study and final responsibility for the decision to submit this paper.

Results

Database searches identified 10 879 references (Figure 1); 349 were retained for full-text review, of which 63 were included for data extraction and meta-analysis. Agreement between the two reviewers at the title/abstract and full-text screening stages was 92% (26/340) and 91% (32/35), respectively. The 63 full-text references included two relating to data sources identified prior to the review, namely CDC (SSI, UTI, and RTI data) (Weiner et al. (2016)) and PHE (SSI data) (Elgohari et al., 2017). ECDC SSI (European Centre for Disease Prevention and Control (ECDC), 2016), ECDC point prevalence survey (PPS) of healthcare-associated infections (HAI) in acute hospitals (European Centre for Disease Prevention and Control (ECDC), 2013), and ECDC intensive care unit (ICU) HAI data (European Centre for Disease Prevention and Control (ECDC), 2017) are summarized in reports, but no published record could be found for PHE UTI data. These four additional data sources (three ECDC, one PHE) were included as 'identified prior to review'; a further seven 'additional records/data sources' were identified during full-text screening (Bouza et al., 2001a; Canadian Antimicrobial Resistance Alliance (CARA), 2016; Lee et al., 2004; Morris et al., 2015; Santé publique France, 2016; Stapleton et al., 2007; Garau et al., 2013) (Figure 1). The total number of included studies and data sources (hereafter referred to as 'sources') was 74 (Table 1, Figure 1), representing 67 countries (Figure 2); 77% (57/74) were rated good quality and 23% (17/74) fair quality (83% agreement) (see **Supplementary Material**).

Types of infection

The six foci of infection that emerged from the review were surgical site (17 sources), skin and soft tissue (14 sources), urinary (42 sources), respiratory (17 sources), ear (two sources), and eye (six sources). SSI were defined in the majority of sources according to

Table 1
Studies/sources contributing data to the meta-analyses for each type of infection.

Type of infection	Number of studies/ data sources[a]	Number of countries	Quality rating			Total number of estimates included[b]	Total number of isolates/ infections	Total number of GBS isolates/ infections
			Good	Fair	Poor			
Surgical site	17	38	14 (82.4%)	3 (17.6%)	0 (0.0%)	87	224 544	2634
Skin and soft tissue	14	60	10 (71.4%)	4 (28.6%)	0 (0.0%)	27	181 575	3842
Urinary	42	45	32 (76.2%)	10 (23.8%)	0 (0.0%)	57	2 820 252	49 609
Respiratory	17	38	12 (70.6%)	5 (27.8%)	0 (0.0%)	23	39 181	171
Ear	2	1	2 (100.0%)	0 (0.0%)	0 (0.0%)	2	264	0
Eye	6	9	3 (50.0%)	3 (50.0%)	0 (0.0%)	6	5981	30

GBS, group B *Streptococcus*.
[a] Fourteen of the 74 sources provided data on more than one type of infection.
[b] Some sources contributed multiple estimates of the prevalence of GBS, e.g. from several settings, cohorts, countries, or time periods.

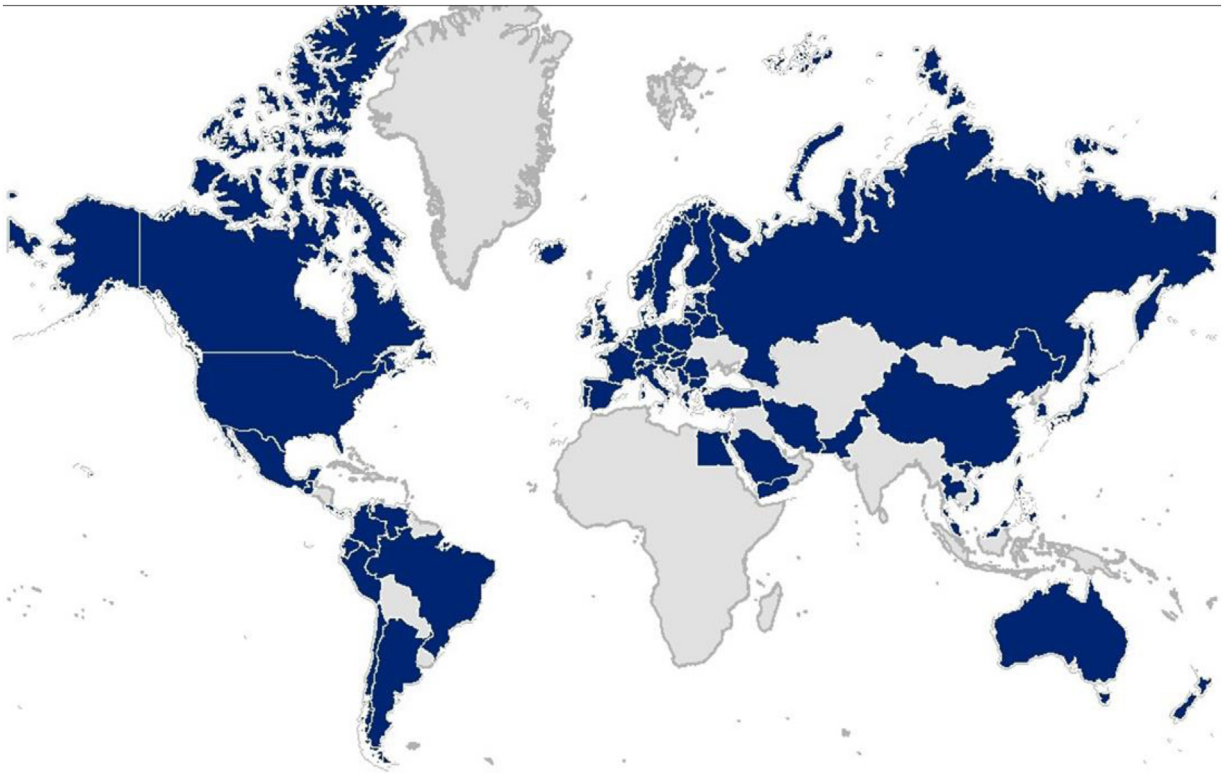

Figure 2. Countries represented in included studies.

CDC/National Healthcare Safety Network (NHSN) criteria, i.e. superficial incisional (involving only skin and subcutaneous tissue of the incision), deep incisional (involving deep soft tissue of the incision, e.g. fascia/muscle), and organ/space (involving any part of the anatomy deeper than the fascial/muscle layers, e.g. organ, breast, spinal or intracranial abscess, bone, joint or bursa, myo-, peri- or endocardium, intra-abdominal, arterial or venous) (Owens and Stoessel, 2008; Horan et al., 2008). UTI case definitions varied more widely, but typically required $>10^5$ CFU/ml or $>10^4$ CFU/ml with symptoms or leukocyturia. Community- vs. healthcare-associated UTI and RTI were differentiated either by time since admission (<48 h for community), specimen source (primary vs. secondary or tertiary care), or if reported as healthcare-associated, e.g. catheter-associated urinary tract infection (CAUTI) and VAP. There was considerable variation across sources of SSTI data: some focused on complicated SSTI (cSSTI), defined as requiring surgical intervention, involving deeper soft tissue or occurring in an immunocompromised patient (Montravers et al., 2013); some included wound and surgical site infection; some included isolates from a range of specimens (including blood). The proportions of studies that accounted for polymicrobial infections, i.e. where the denominator was the total number of isolates, rather than reporting only one isolate per infection, were 88% (15/17) for SSI, 50% (7/14) for SSTI, 60% (25/42) for UTI, and 65% (11/17) for RTI. Fourteen of the 74 sources provided data on more than one type of infection, and some contributed multiple estimates of the prevalence of GBS to each meta-analysis, e.g. from several settings, cohorts, countries, or time periods.

Surgical site infection

Seventeen sources of SSI data were included (Weiner et al., 2016; Elgohari et al., 2017; European Centre for Disease Prevention and Control (ECDC), 2016; Morris et al., 2015; Santé publique France, 2016; Cossin et al., 2015; Deptula et al., 2017; Fong et al., 2015; Jeong et al., 2013; Jodra et al., 2006; Kim et al., 2012; Phu et al., 2016; Rennert-May et al., 2016; Sabra and Abdel-Fattah, 2012; Song et al., 2012; Worth et al., 2015; Mannien et al., 2007), six of which were disaggregated by type of SSI (Elgohari et al., 2017; European Centre for Disease Prevention and Control (ECDC), 2016; Morris et al., 2015; Jodra et al., 2006; Worth et al., 2015; Mannien et al., 2007). GBS represented 0.73% (95% confidence interval (CI) 0.40–1.34%) of SSI isolates from all types of surgery (Table 2). The highest prevalence of GBS was in obstetrics/gynaecology (including caesarean section): GBS represented 3.50% (95% CI 2.14–5.67%) of isolates of any SSI type, 3.87% (95% CI 1.82–8.00%) of superficial SSI isolates, 3.80% (95% CI 1.82–7.76%) of deep incisional isolates, and 10.5% (95% CI 6.86–15.7%) of organ/space isolates (Table 2). For caesarean section, the prevalence of GBS among all SSI isolates was 3.49% (95% CI 1.99–6.06%), increasing from 2.92% (95% CI 1.51–5.55%) for superficial and 1.93% (95% CI 0.97–3.81%) for deep SSI to 9.69% (95% CI 6.72–13.8%) for organ/space SSI (between-subgroups $p < 0.01$) (Figure 3). A similar trend towards a higher prevalence of GBS in invasive compared with superficial SSI was seen for orthopaedic surgery (Figure 4), but not for abdominal or cardiac surgery (Table 2).

GBS accounted for 2.40% (95% CI 1.89–3.05%) of isolates from SSI after vascular surgery, 1.23% (95% CI 0.84–1.79%) of breast surgery SSI isolates, and 1.14% (95% CI 0.51–2.53%) of orthopaedic surgery SSI isolates (Table 2, **Supplementary Material** Figures). For other types of surgery where more than one data source was identified (abdominal, cardiac, neuro/cranial, prostate), the prevalence of GBS was ≤0.25%. Data were available from only a single source (CDC) (Weiner et al., 2016) for kidney, neck, and transplant surgery. Of 18 subgroup meta-analyses by surgical category and SSI type (Table 2), 10 had evidence ($p \leq 0.01$) of between-study heterogeneity, representing 10–25% of variance in prevalence estimates.

Skin and soft tissue infection

Fourteen sources of data on SSTI were included (European Centre for Disease Prevention and Control (ECDC), 2013; Canadian

Table 2
Streptococcus agalactiae as a percentage of surgical site infection (SSI) isolates.

Surgical category	Superficial incisional			Deep incisional			Organ/space			All types of SSI		
	Estimates included, *n*	Pooled % prevalence (95% CI)	I^2 (*p*-Value)	Estimates included, *n*	Pooled % prevalence (95% CI)	I^2 (*p*-Value)	Estimates included, *n*	Pooled % prevalence (95% CI)	I^2 (*p*-Value)	Estimates included, *n*	Pooled % prevalence (95% CI)	I^2 (*p*-Value)
Various (not specified)										5	0.74 (0.64–0.86) $\tau^2 = 0.00$	0.0% ($p = 1.00$)
Abdominal[a]	15	0.23 (0.05–1.08) $\tau^2 = 1.92$	11.2% ($p < 0.01$)	12	0.37 (0.08–1.76) $\tau^2 = 1.43$	15.5% ($p < 0.01$)	12	0.19 (0.04–0.84) $\tau^2 = 1.40$	11.7% ($p = 0.01$)	19	0.25 (0.10–0.63) $\tau^2 = 1.03$	16.2% ($p < 0.01$)
Breast										4	1.23 (0.84–1.79) $\tau^2 = 0.00$	0.0% ($p = 1.00$)
Cardiac[b]	11	0.17 (0.07–0.41) $\tau^2 = 0.00$	0.0% ($p = 1.00$)	9	0.18 (0.03–0.96) $\tau^2 = 1.23$	4.1% ($p = 0.10$)	7	0.18 (0.05–0.73) $\tau^2 = 0.00$	0.0% ($p = 1.00$)	12	0.22 (0.07–0.69) $\tau^2 = 1.23$	12.3% ($p < 0.01$)
Obs/Gyn[c]												
Inc. C-section	3	3.87 (1.82–8.00) $\tau^2 = 0.39$	–	2	3.80 (1.82–7.76)	–	3	10.5 (6.86–15.7) $\tau^2 = 0.00$	–	5	3.50 (2.14–5.67) $\tau^2 = 0.30$	85.6% ($p < 0.01$)
Exc. C-section	3	3.12 (1.41–6.78) $\tau^2 = 0.00$	–	2	8.11 (2.64–22.3)	–	2	6.06 (1.52–21.2)	–	3	3.94 (2.30–6.67) $\tau^2 = 0.00$	–
Caesarean section	13	2.92 (1.51–5.55) $\tau^2 = 0.41$	27.6% ($p < 0.01$)	7	1.93 (0.97–3.81) $\tau^2 = 0.00$	0.0% ($p = 1.00$)	7	9.69 (6.72–13.8) $\tau^2 = 0.00$	0.13% ($p = 0.50$)	15	3.49 (1.99–6.06) $\tau^2 = 0.31$	27.2% ($p < 0.01$)
Kidney										1	0.00 (0.00–1.33)	–
Neck[d]										1	0.47 (0.08–2.62)	–
Neuro/cranial[e]										4	0.20 (0.09–0.49) $\tau^2 = 0.00$	0.0% ($p = 1.00$)
Orthopaedic[f]	13	0.37 (0.08–1.68) $\tau^2 = 1.74$	14.3% ($p < 0.01$)	12	0.87 (0.33–2.28) $\tau^2 = 0.78$	25.4% ($p < 0.01$)	11	1.46 (0.49–4.29) $\tau^2 = 1.20$	23.5% ($p < 0.01$)	17	1.14 (0.51–2.53) $\tau^2 = 1.14$	45.3% ($p < 0.01$)
Prostate										2	0.00 (0.00–0.08)	–
Transplant[g]										1	0.25 (0.07–0.89)	–
Vascular[h]										4	2.40 (1.89–3.05) $\tau^2 = 0.00$	0.0% ($p = 1.00$)
All types	52	0.66 (0.31–1.40) $\tau^2 = 0.57$	12.2% ($p < 0.01$)	40	0.66 (0.24–1.84) $\tau^2 = 0.93$	16.2% ($p < 0.01$)	39	1.32 (0.52–3.29) $\tau^2 = 0.86$	25.0% ($p < 0.01$)	87	0.73 (0.40–1.34) $\tau^2 = 0.77$	25.3% ($p < 0.01$)

CI, confidence interval; Inc., including; Exc., excluding.

[a] Abdominal surgery includes appendectomy, bile duct, liver, or pancreatic surgery, gallbladder surgery, colon surgery, gastric surgery, herniorrhaphy, small and large bowel surgery, spleen surgery, and rectal surgery.

[b] Cardiac surgery includes coronary artery bypass graft with chest incision with or without donor incision, pacemaker surgery, and thoracic surgery.

[c] Obstetric and gynaecologic (Obs/Gyn) surgery includes abdominal hysterectomy, ovarian surgery, and vaginal hysterectomy.

[d] Neck surgery includes thyroid and/or parathyroid surgery.

[e] Neurological and cranial surgery includes craniotomy and ventricular shunt.

[f] Orthopaedic surgery includes open reduction of fracture, hip prosthesis, knee prosthesis, limb amputation, spinal fusion, refusion of spine, and laminectomy.

[g] Transplant surgery includes heart, kidney, and liver.

[h] Vascular surgery includes abdominal aortic aneurysm repair, shunt for dialysis, carotid endarterectomy, and peripheral vascular bypass surgery.

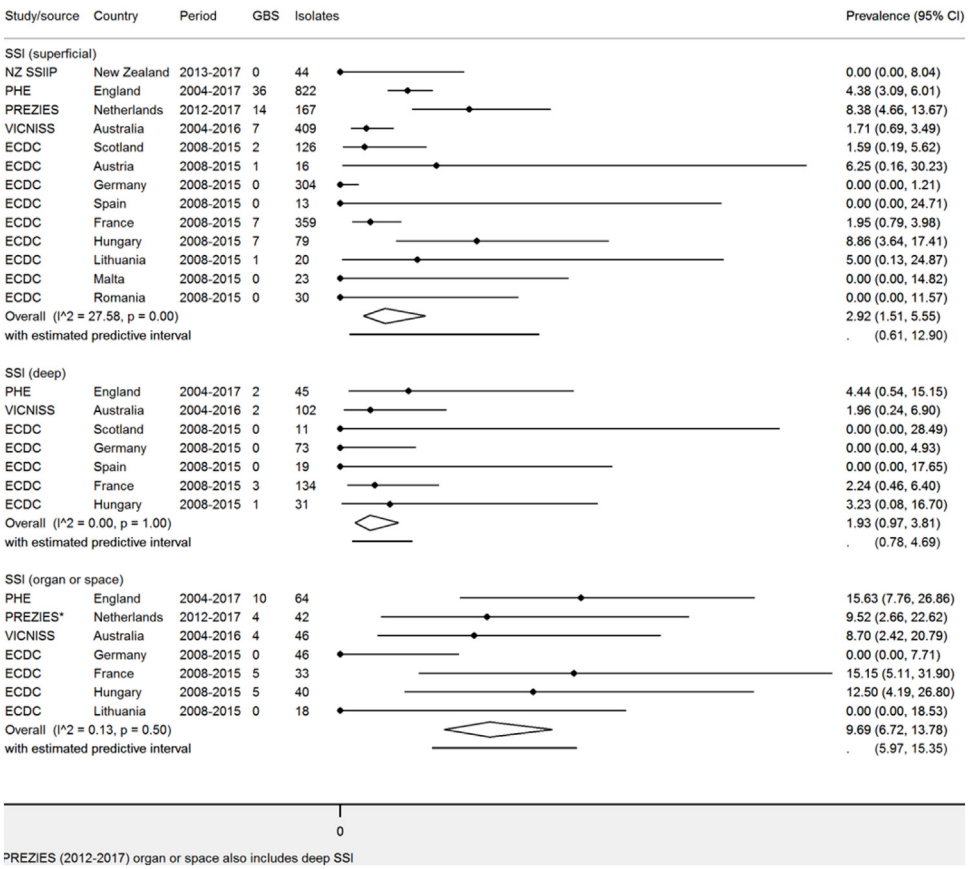

Figure 3. Prevalence of *Streptococcus agalactiae* in isolates from surgical site infection (SSI) after caesarean section (by type of SSI).

Antimicrobial Resistance Alliance (CARA), 2016; Garau et al., 2013; Jodra et al., 2006; Heizmann et al., 2013; Jaaskelainen et al., 2016; Jones et al., 2003; Li et al., 2016; Merritt et al., 2013; Mir et al., 2011; Moet et al., 2007; Ray et al., 2013; Zhanel et al., 2010; Behzadnia et al., 2014). The overall prevalence of GBS in SSTI isolates was 1.89% (95% CI 1.16–3.05%) (Table 3). The pooled prevalence of GBS was lower in cSSTI (1.02%, 95% CI 0.48–2.15%) than in sources that did not focus on cSSTI (3.05%, 95% CI 2.00–4.62%) (between-subgroups $p = 0.01$) (Figure 5). Sources that included SSI in their definition of SSTI yielded a lower prevalence (1.62%, 95% CI 1.00–2.59%) than those that did not include SSI (3.06%, 95% CI 1.58–5.84%), but unsupported statistically ($p = 0.19$). One community-based study of omphalitis in Pakistan reported GBS in 10.1% (95% CI 7.79–12.9%) of 583 isolates from umbilical stump purulent secretions (Mir et al., 2011). There was strong evidence ($p < 0.01$) in each subgroup of between-study heterogeneity, contributing a high proportion ($I^2 = 60–80\%$) of variance in pooled estimates. GBS prevalence in SSTI isolates from children (excluding neonatal omphalitis) was 1.05% (95% CI 0.15–7.09%), compared with 1.68% (95% CI 0.58–4.78%) in studies that included only adults, but this difference was unsupported by evidence of between-subgroup heterogeneity ($p = 0.65$).

Urinary tract infection

Forty-two sources reporting GBS in UTI were included (Weiner et al., 2016; European Centre for Disease Prevention and Control (ECDC), 2013; European Centre for Disease Prevention and Control (ECDC), 2017; Bouza et al., 2001a; Lee et al., 2004; Jodra et al., 2006; Phu et al., 2016; Sabra and Abdel-Fattah, 2012; Zhanel et al., 2010; Behzadnia et al., 2014; Agodi et al., 2013; Alvarez Lerma et al., 2005; Andreu et al., 2005; Bauserman et al., 2013; Bouza et al., 2001b; Brabazon et al., 2012; Choi et al., 2016; Greenhow et al., 2014; Guerreiro et al., 2012; Hanna-Wakim et al., 2015; Hayami et al., 2013; Hedin et al., 2002; Hooton et al., 2013; Karlowsky et al., 2011; Kazemier et al., 2014; Kiffer et al., 2007; Kronenberg et al., 2011; Laupland et al., 2007; Lee et al., 2011; Magliano et al., 2012; Malmartel and Ghasarossian, 2016; Matsumoto et al., 2011; Monsen et al., 2014; Moulton et al., 2017; Rodriguez et al., 2005; Sorlozano et al., 2014; Zajac-Spychala et al., 2016; Naber et al., 2008). GBS was found in 1.09% (95% CI 0.77–1.54%) of UTI isolates, with a higher prevalence for community (1.61%, 95% CI 1.13–2.30%) than hospital UTI (0.72%, 95% CI 0.43–1.22%) (between-subgroups $p = 0.01$) (Table 4, Figure 6). The prevalence was no higher in female-only community cohorts (1.51%, 95% CI 0.87–2.62%) than for both sexes combined (Table 4). GBS accounted for a low proportion of CAUTI isolates (0.26%, 95% CI 0.24–0.29%) (Figure 7). The one study that reported a high prevalence of GBS in CAUTI isolates (8.33%, 95% CI 1.03–27.0%) was in a cohort of women who had undergone caesarean section (Moulton et al., 2017). Between-study heterogeneity represented a moderate-to-high proportion of overall variance ($I^2 = 40–80\%$, $p < 0.01$) for all meta-analyses except CAUTI (0%).

Respiratory tract infection

Seventeen sources of respiratory tract infection data were included (Weiner et al., 2016; European Centre for Disease Prevention and Control (ECDC), 2013; Canadian Antimicrobial Resistance Alliance (CARA), 2016; Jodra et al., 2006; Phu et al., 2016; Sabra and Abdel-Fattah, 2012; Zhanel et al., 2010; Behzadnia et al., 2014; Agodi et al., 2013; Alvarez Lerma et al., 2005; Choi et al., 2016; El-Kholy et al., 2012; Nizami et al., 2006; Varotto et al., 2001; Ba-Saddik et al., 2014; Hanna et al., 2006). The prevalence of GBS in

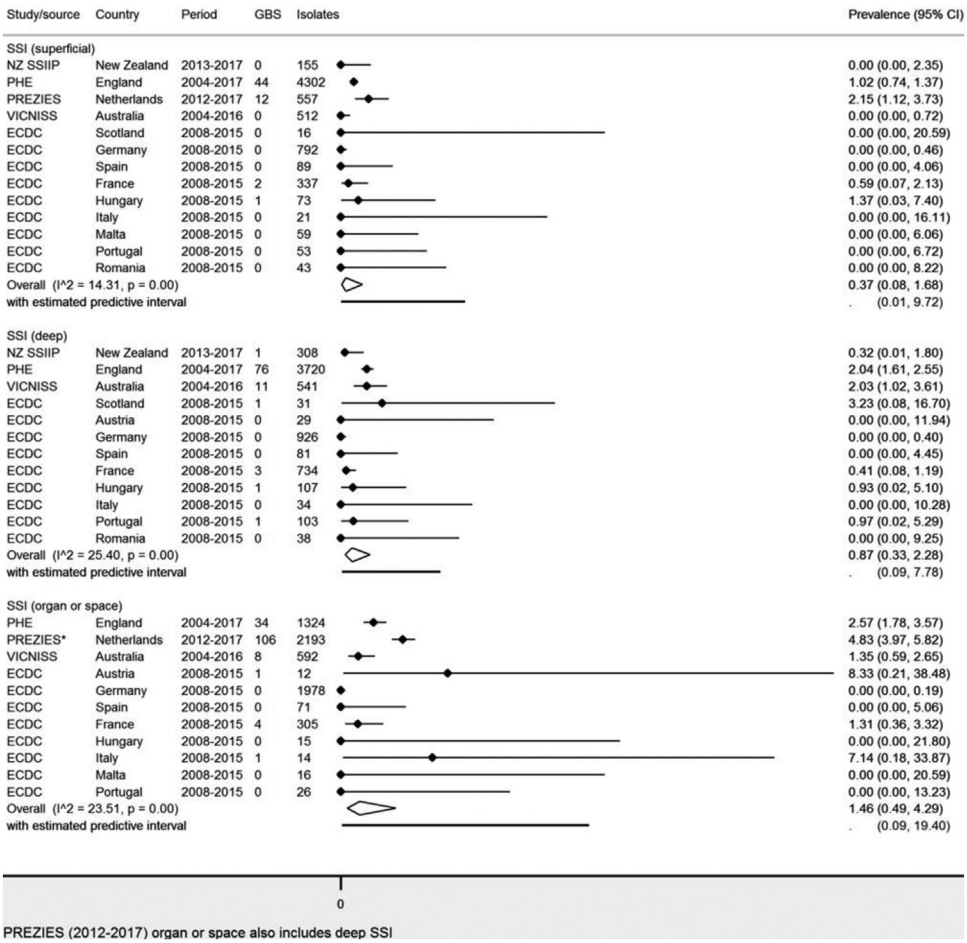

Figure 4. Prevalence of *Streptococcus agalactiae* in surgical site infection (SSI) isolates after orthopaedic surgery (by type of SSI).

Table 3
Streptococcus agalactiae as a percentage of skin and soft tissue infection (SSTI) isolates.

SSTI definition	Number of estimates included	Pooled % prevalence estimate (95% CI)	I^2 (p-value)
All types	27	1.89 (1.16–3.05); $\tau^2 = 0.76$	70.4% ($p < 0.01$)
Complicated vs. non-specific[a]			
Complicated SSTI (cSSTI)	13	1.02 (0.48–2.15); $\tau^2 = 0.72$	57.4% ($p < 0.01$)
Not focusing on cSSTI	14	3.05 (2.00–4.62); $\tau^2 = 0.32$	65.1% ($p < 0.01$)
Including vs. excluding surgical site infection (SSI)			
Including SSI	17	1.62 (1.00–2.59); $\tau^2 = 0.37$	60.6% ($p < 0.01$)
Excluding SSI	7	3.06 (1.58–5.84); $\tau^2 = 0.57$	78.3% ($p < 0.01$)

CI, confidence interval.
[a] Skin and soft tissue infections are typically defined as complicated when a surgical intervention is required and/or the infection is suspected or confirmed to involve deeper soft tissue such as the fascia and/or muscle layers. SSTI may also be considered complicated when it occurs in an immunocompromised patient or with a complicating comorbidity such as diabetes mellitus, peripheral vascular disease, or peripheral neuropathy.

RTI isolates from community and hospital sources (including VAP) was 0.30% (95% CI 0.17–0.52%) (Table 5, Figure 8). Prevalence was similar for community (0.35%, 95% CI 0.19–0.63%) and hospital RTI (0.27%, 95% CI 0.15–0.48%) (between-subgroups $p = 0.57$). There was evidence of low between-study heterogeneity ($I^2 = 12$–14%) for all subgroups.

Other types of infection

Two sources reported zero GBS isolates from ear infections: paediatric conjunctivitis–otitis syndrome (COS), 0/86 middle ear fluid samples (Bingen et al., 2005); infant otitis media, 0/178 (Husson et al., 2001). Eye infection data were obtained from six studies (Stapleton et al., 2007; Bingen et al., 2005; Goh et al., 2010; Miller, 2017; Morrissey et al., 2004; Truong et al., 2016). Two studies of keratitis reported zero GBS isolates (out of 59 and 241 isolates) (Stapleton et al., 2007; Truong et al., 2016), as did one study of corneal ulcer isolates (0/34) (Goh et al., 2010). Two studies of mixed ocular infections reported GBS prevalence of 0.62% (29/4649) (Miller, 2017) and 0.19% (1/532) (Morrissey et al., 2004). The paediatric COS study found no GBS in 466 conjunctival exudate isolates (Bingen et al., 2005). Based on the five eye-only sources (Stapleton et al., 2007; Goh et al., 2010; Miller, 2017; Morrissey et al., 2004; Truong et al., 2016), the prevalence of GBS in ocular isolates was 0.16% (95% CI 0.04–0.34%); including COS reduced this to 0.03% (95% CI 0.00–0.30%).

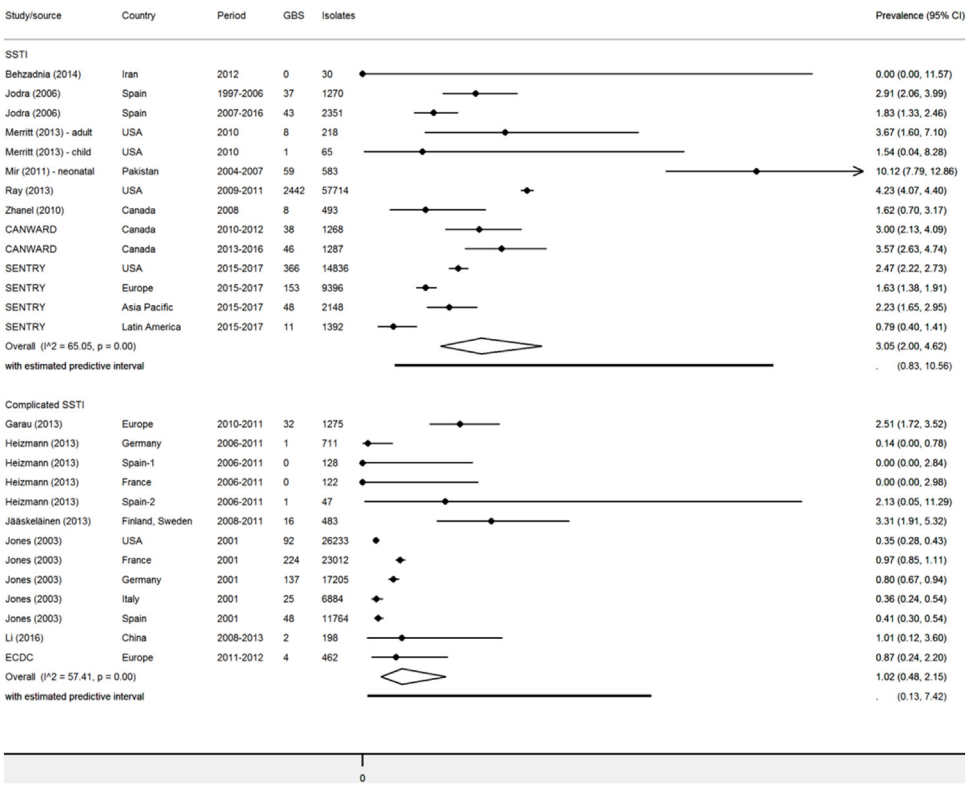

Figure 5. Prevalence of *Streptococcus agalactiae* in isolates from skin and soft tissue infections (SSTI).

Table 4
Streptococcus agalactiae as a percentage of urinary tract infection (UTI) isolates.

Setting[a]	Age group	Number of estimates included	Pooled % prevalence estimate (95% CI)	I^2 (p-value)
Community + hospital	All ages combined	57	1.09 (0.77–1.54); $\tau^2 = 0.94$	60.1% ($p < 0.01$)
Community (both sexes)	Overall (all ages combined)	30	1.61 (1.13–2.30); $\tau^2 = 0.64$	79.5% ($p < 0.01$)
	Infants (<4 months)	2	0.61 (0.38–1.00)	–
	Child	2	0.91 (0.86–0.96)	–
	Adult (all ages)	12	1.86 (1.05–3.25); $\tau^2 = 0.74$	78.7% ($p < 0.01$)
	Adult (elderly)[b]	4	1.63 (0.72–3.64); $\tau^2 = 0.35$	48.3% ($p < 0.01$)
Community (female)	All ages	12	1.51 (0.87–2.62); $\tau^2 = 0.75$	68.9% ($p < 0.01$)
	Adult (all ages)	8	1.66 (0.87–3.15); $\tau^2 = 0.56$	74.6% ($p < 0.01$)
	Adult (elderly)[b]	1	6.82 (1.43–18.9)	–
Hospital (non-specific + CAUTI)	All ages	27	0.73 (0.43–1.23); $\tau^2 = 1.04$	39.7% ($p < 0.01$)
Hospital (non-specific)	Overall (all ages combined)	19	0.99 (0.58–1.68); $\tau^2 = 0.74$	53.2% ($p < 0.01$)
	Infants (<4 months)	3	1.23 (0.72–2.12); $\tau^2 = 0.13$	–
	Child	4	1.09 (0.47–2.51); $\tau^2 = 0.47$	41.8% ($p < 0.01$)
	Adult	2	2.15 (2.12–2.18)	–
Hospital (CAUTI)	All ages	8	0.26 (0.24–0.29); $\tau^2 = 0.00$	0.0% ($p = 1.00$)

CI, confidence interval; CAUTI, catheter-associated UTI.
[a] Community UTI specimens either from GP/primary care/outpatient clinic or a hospital inpatient specimen within 48 h of admission; hospital (non-specific) UTI do not specifically exclude CAUTI; 3/6 CAUTI sources were intensive care units (ICU).
[b] Three quarters of community elderly adult settings were long-term care facilities (LTCF), including the setting for community female elderly adult UTIs.

Discussion

This study generated global estimates for the potential role of *S. agalactiae* (GBS) as a causative agent of a wide range of community and healthcare-associated infections. Overall, GBS was isolated from a small proportion (1%) of SSI and UTI, and a very small proportion (<0.5%) of RTI. However, GBS was implicated in noticeably higher proportions of SSI following caesarean section (3.5% overall, 9.7% of organ/space SSI), vascular surgery SSI (2.4%), SSTI (1.9%), and community UTI (1.6% overall). GBS also accounted for slightly higher proportions of SSI after orthopaedic (1.1%) and breast surgery (1.2%), which is of concern given current and projected volumes of these procedures (Kummerow et al., 2015; Kurtz et al., 2007) and the potential seriousness of prosthetic joint infections (Gundtoft et al., 2017). Estimates based on a small number of studies for eye and ear infections indicated a very low proportion of GBS among ocular infection isolates, and no GBS isolated from ear infections.

The relatively high proportion of caesarean section organ/space SSI attributable to GBS reflects the role of GBS as an important pathogen in maternal sepsis, causing 15–25% of bacteraemia in pregnancy and postpartum (Blanco et al., 1981; Drew et al., 2015; Knowles et al., 2015; Surgers et al., 2013). Studies of post-caesarean SSI suggest that up to 10% of caesarean sections had a subsequent SSI (Wilson et al., 2013; Aulakh et al., 2018; Griffiths et al., 2005).

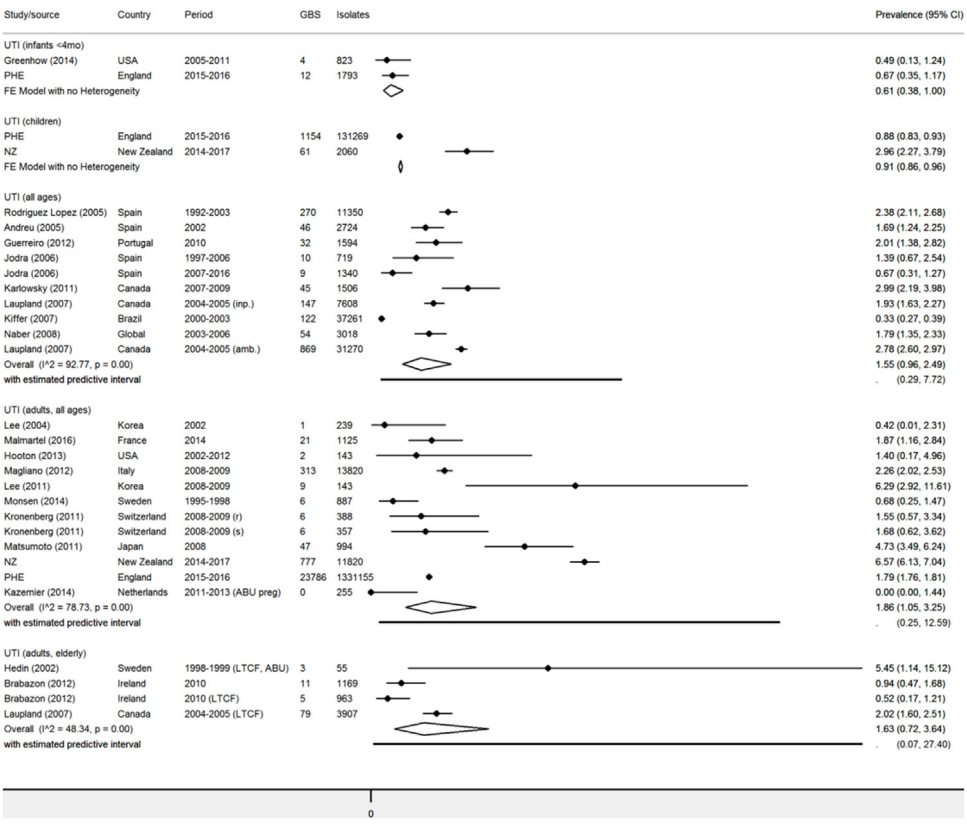

Figure 6. Prevalence of *Streptococcus agalactiae* in isolates from community urinary tract infections (UTI).

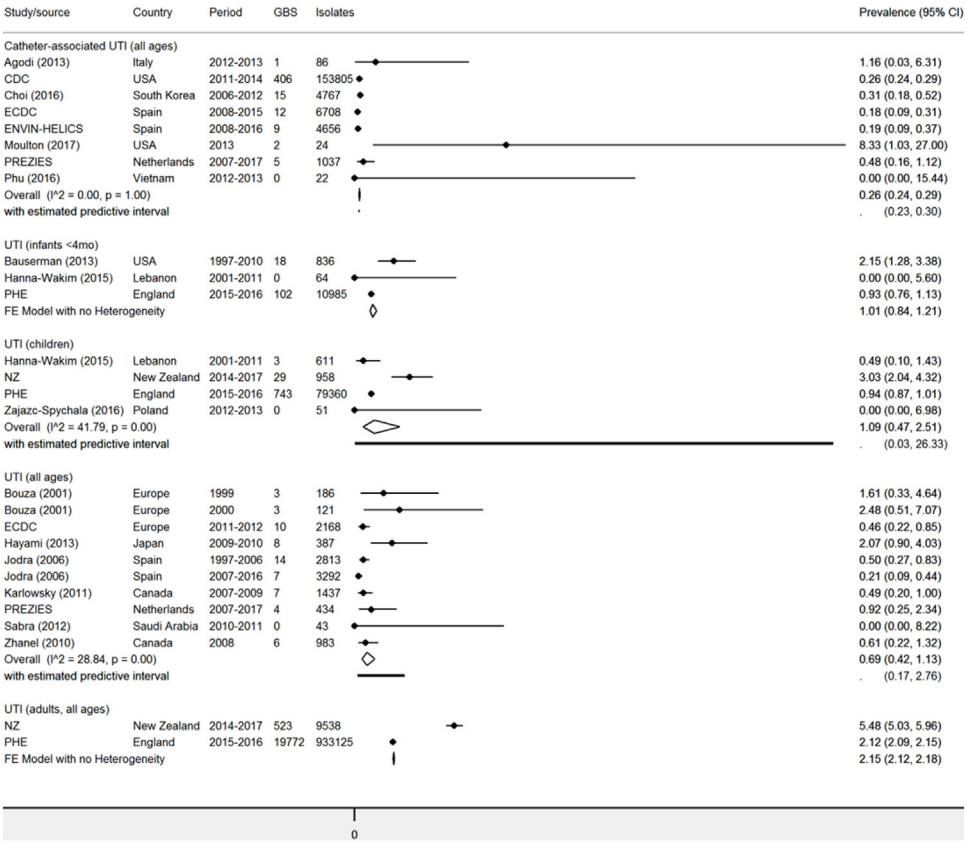

Figure 7. Prevalence of *Streptococcus agalactiae* in isolates from healthcare-associated urinary tract infections (UTI).

Table 5
Streptococcus agalactiae as a percentage of respiratory tract infection (RTI) isolates.

Setting[a]	Age group	Number of estimates included	Pooled % prevalence estimate (95% CI)	I^2 (p-value)
Community + hospital	All ages combined	23	0.30 (0.17–0.52); $\tau^2 = 0.65$	17.1% ($p < 0.01$)
	Child	3	0.19 (0.03–1.32); $\tau^2 = 0.00$	–
	Adult (all ages)	1	0.00 (0.00–0.63)	–
Community	All ages combined	4	0.35 (0.19–0.63); $\tau^2 = 0.00$	0.00% ($p = 1.00$)
	Child	2	0.19 (0.03–1.36)	–
Hospital (non-specific + VAP)	All ages combined	17	0.27 (0.15–0.48); $\tau^2 = 0.59$	12.5% ($p < 0.01$)
Hospital (non-specific)	All ages combined	10	0.45 (0.23–0.88); $\tau^2 = 0.44$	11.6% ($p < 0.01$)
	Child	1	0.00 (0.00–24.7)	–
Hospital (VAP)	All ages combined	7	0.17 (0.07–0.39); $\tau^2 = 0.43$	13.9% ($p < 0.01$)
	Adult (all ages)	1	0.00 (0.00–0.63)	–

CI, confidence interval; VAP, ventilator-associated pneumonia.
[a] Community RTI specimens either from GP/primary care/outpatient clinic or a hospital inpatient specimen within 48 h of admission; hospital (non-specific) RTI do not specifically exclude VAP; 5/7 VAP settings were intensive care units (ICU).

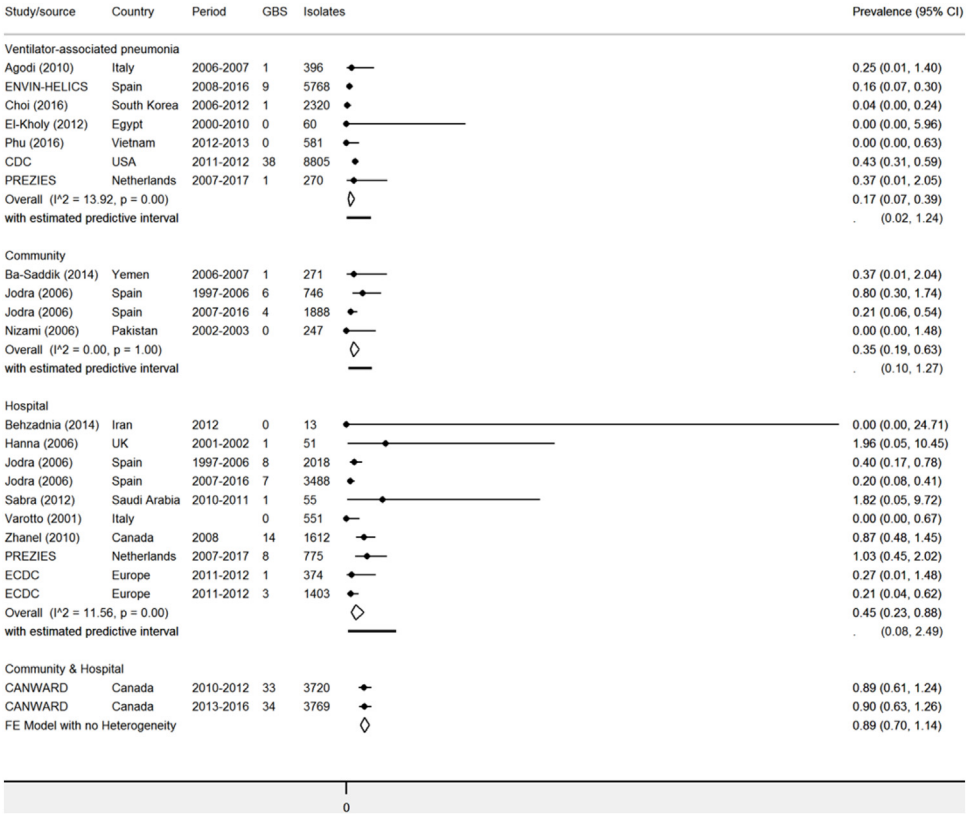

Figure 8. Prevalence of *Streptococcus agalactiae* in isolates from respiratory tract infection.

PHE data implicated GBS in 5% of caesarean section SSI, corresponding to national estimates of approximately 850 cases (including 170 organ/space SSI) after 170 000 annual operations. It was also noted that the one study that reported a high prevalence of GBS in CAUTI isolates (8.33%, 95% CI 1.03–27.0%) was in a cohort of women who had undergone caesarean section (Moulton et al., 2017). The extent to which a common underlying mechanism of infection, such as epithelial exfoliation (Vornhagen et al., 2018), explains ascending infection leading to invasive GBS disease in pregnancy and also serious postpartum SSI and UTI remains to be determined. Commonly used and endorsed prophylaxis regimens (e.g. cefazolin) are generally effective against GBS, and it may be that utility of and compliance with recommendations needs be evaluated, including optimal timing of antibiotic administration. In future, measures to prevent neonatal GBS disease could have the additional clinical and cost benefit of preventing a significant proportion of maternal GBS disease (Kim et al., 2017; Vekemans et al., 2018).

A trend towards a higher prevalence of GBS by degree of invasiveness (from superficial to deep to organ/space) was also evident for orthopaedic, but not abdominal or cardiac SSI, the latter including donor site incisions. Reasons for these discrepancies, and for the relatively high prevalence of GBS in breast and vascular SSI, are unclear. Breast cancer as a risk factor for invasive GBS disease has been described in two population studies, but as an underlying disease rather than in relation to surgery (Farley et al., 1993; Jackson et al., 1995). GBS represented a smaller proportion of SSTI isolates in studies that focused on cSSTI (1.0%) compared with studies that did not focus on cSSTI (3.1%). This is the opposite of what might be expected given an increased risk of invasive GBS infection in patients with chronic underlying conditions (Sendi et al., 2008), and if GBS has a proclivity for invasive infection.

The mains strengths of this systematic review are its wide geographic scope and the inclusion of data from several large surveillance systems. Also, for SSI, common case definitions (based on CDC/NHSN criteria) were used by all but one of the included studies. The main limitations are heterogeneity in case definitions for the other types of infections, and heterogeneity and bias in sampling and laboratory methods. For example, in community and primary care settings, GBS is more likely to be implicated in the types of infection, e.g. cystitis, that are treated empirically, with testing reserved for recalcitrant, e.g. antimicrobial-resistant, infections that are less likely to be caused by GBS. Or, in settings where all urine samples are routinely tested, generic culture methods may not favour the identification of GBS. Both of these factors would underestimate the prevalence of GBS in UTIs. For wound and SSI we would expect GBS to be detected by routinely used non-selective culture methods, although the use of non-selective media could fail to detect GBS in wound infections such as perineal or groin or peri-anal abscesses where competing microflora can inhibit the growth of GBS in culture (El Aila et al., 2010; Gupta and Briski, 2004). An example of heterogeneity between studies is in the healthcare-associated UTI in children subgroup, where the higher prevalence of GBS in data from New Zealand may be related to the Auckland District Health Board providing most of the complex healthcare for New Zealand, including national paediatric care, meaning that this source of UTI data will encompass children with high dependency and significant co-morbidities.

Hooton et al. reported that the detection of GBS in midstream urine samples has poor positive predictive value for acute cystitis (using paired midstream-catheter urine samples from healthy premenopausal women) regardless of colony count threshold, although the number of GBS cystitis cases was very small (Hooton et al., 2013). Given that the majority of UTI studies reported on midstream urine samples, contamination by colonizing GBS would inflate the prevalence of GBS as a causative agent of UTI in the present meta-analysis. The misattribution of clinical infection to colonizing GBS would be more of an issue for superficial incisional, skin, respiratory, throat, and eye infections than for deep/organ/space infections, and correcting this bias would reduce GBS prevalence estimates for these types of infection towards zero.

Where the frequency of GBS was not originally reported in a published study, the authors' responses indicated that the actual frequency was zero vs. non-zero in similar proportions (10/22 zero vs. 12/22 non-zero). This suggests that the meta-analyses will not be biased towards over-reporting the prevalence of GBS. Publication bias is unlikely to affect the study findings because much of the data originated from surveillance systems and were purely descriptive. Some sources did not account for polymicrobial infections in their denominators, but this would not affect GBS as a proportion of the total number of isolates unless there was preferential reporting of particular microorganisms or if GBS in polymicrobial flora were more likely to be colonizing rather than infecting; no differences in GBS prevalence by type of denominator were detected. Some of the surgical categories encompassed a wide range of procedures within which GBS may have represented a varying proportion of SSI, e.g. colorectal and bowel operations within the abdominal surgery category, and coronary artery bypass graft with or without donor incision surveillance in the cardiac surgery category. Overall, superficial SSIs are less likely to be captured by surveillance systems owing to inconsistent use of community post-discharge surveillance, whereas deep and organ-space infections frequently result in re-admission to hospital.

In conclusion, although GBS accounts for a relatively small proportion of SSI and UTI, the absolute numbers of patients with infections due to GBS will be large. Accurate estimates of GBS prevalence, particularly for infections such as UTI, which are often treated empirically, require studies designed specifically to detect GBS, using selective media in unbiased samples of clinical cases. The relatively high prevalence of GBS in caesarean section SSI suggests a need for further research with a view to evaluating current practices concerning surgical antibiotic prophylaxis administration (choice, timing of delivery of agents) and the assessment of treatment regimens to ensure use of an agent that covers GBS.

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Ethical approval

Not required.

Conflict of interest

The authors declare no competing interests.

One-sentence summary

Worldwide, group B *Streptococcus* is implicated in a small proportion (1–2%) of surgical site, skin and soft tissue, and urinary tract infections, a very small proportion (<0.5%) of respiratory tract infections, but a substantial proportion (10%) of invasive surgical site infections following caesarean section.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.04.017.

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