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Maternal colonization or infection with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in Africa: A systematic review and meta-analysis

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ABSTRACT

Objective: To summarize published studies on the prevalence of and risk factors for maternal bacterial colonization and/or infection with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-E) in pregnant and/or post-partum women in Africa.
Methods: A systematic review was conducted using the PubMed, Scopus, and Google Scholar databases. Bibliographies of included eligible studies were manually searched to identify additional relevant articles. No language restriction was applied. The timeframe of the search included all records from electronic database inception to July 15, 2017. A random-effects meta-analysis was performed to summarize the prevalence and the 95% confidence intervals (CI) of ESBL-E colonization or infection in pregnant or post-partum women in Africa. The meta-analysis was conducted using STATA IC 13.1 software and the metaprop function/plugin.
Results: Ten studies (seven on pregnant women and three on post-partum women) were included, documenting a 17% prevalence of maternal colonization with ESBL-E in Africa (95% CI 10–23%). The prevalence of ESBL-E in community isolates exceeded that in isolates from the hospital setting (22% vs. 14%). The most frequently reported ESBL-encoding gene was CTX-M (cefotaxime hydrolyzing capabilities). Data on risk factors for maternal ESBL-E colonization and infection are very limited.
Conclusions: The prevalence of colonization and/or infection with ESBL-E in pregnant and post-partum women in Africa exceeds that reported from high- and middle-income settings, representing a risk for subsequent neonatal colonization and/or infection with ESBL-E.

Introduction

Antimicrobial resistance (AMR) is a growing threat to human health globally (WHO, 2014; Frieden, 2013). A major mechanism of AMR is the production of extended-spectrum beta-lactamase (ESBL) enzymes, which confer resistance to penicillins, cephalosporins, and monobactams, but not to cephamycins and carbapenems (Paterson and Bonomo, 2005; Pitout et al., 2005), leaving limited therapeutic options for AMR infections. In 2013, the US Centers for Disease Control and Prevention (CDC) identified ESBL-producing *Enterobacteriaceae* (ESBL-E) as a serious threat (Frieden, 2013). In addition, the World Health Organization (WHO) has published a priority pathogens list, and resistant ESBL-E are classified as 'critical', priority number 1 (WHO, 2017).

ESBL- E occur worldwide in both community and hospital settings (Paterson and Bonomo, 2005; Pitout et al., 2005; Sonda et al., 2016; Storberg, 2014; Luvsansharav et al., 2011), and the reported incidence of infections in paediatric and neonatal populations is increasing (Paterson and Bonomo, 2005; Sonda et al., 2016; Storberg, 2014; Flokas et al., 2017; Peirano and Pitout, 2010; Tansarli et al., 2014; Dramowski et al., 2015; Logan et al., 2014). Clinical infections with ESBL-E are associated with increased morbidity (including prolonged hospital stay), increased healthcare costs, and higher mortality rates compared to infections with non-ESBL-E (Blomberg et al., 2005; Zaoutis et al., 2005; Kim et al.,

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2002; Ndir et al., 2016). Among neonates, children, and pregnant/post-partum women, ESBL-E are frequently implicated in urinary tract infections (UTI) (Pitout et al., 2005; Peirano and Pitout, 2010) and bloodstream infections (BSI) (Luvsansharav et al., 2011; Flokas et al., 2017; Dramowski et al., 2015; Zaoutis et al., 2005; Loh and Sivalingam., 2007). Among neonatal ESBL-E infections, *Klebsiella pneumoniae* and *Escherichia coli* are the most frequently isolated species (Flokas et al., 2017; Dramowski et al., 2015; Zaidi et al., 2005).

Well-established risk factors for early-onset neonatal sepsis include maternal infections (e.g. UTIs and chorioamnionitis) and prolonged rupture of the membranes (Chan et al., 2013; Chan et al., 2015). In a well-powered systematic review, additional risk factors identified were maternal bacterial colonization of the vaginal tract (Chan et al., 2013; Chan et al., 2015) and poor antenatal care (defined as less than four antenatal visits per pregnancy) (Mizumoto et al., 2015; Lincetto et al., 2006).

Although ESBL-E are well-documented as important bloodstream pathogens in several African settings (Flokas et al., 2017; Kim et al., 2002; Kang et al., 2004; Schiappa et al., 1996), little is known about the determinants and magnitude of maternal colonization with ESBL-E. Factors contributing to the development of AMR (including ESBL-E) in Africa include socio-economic challenges and health-associated factors (Kariuki and Dougan, 2014) (suboptimal hygiene and sanitation (Toole et al., 1995), weak health systems (Essack et al., 2016), lack of laboratory capacity (Okeke et al., 1999), and misuse of and easy access to antibiotics (Okeke et al., 1999)). A high burden of immunocompromised patients (HIV infection (Emacar et al., 2010) and diabetes (Ntirenganya et al., 2015)), environmental contamination (Dusé, 2005), and inadequate decontamination of medical devices (Dusé, 2005), are other important factors exacerbating AMR pathogen transmission in Africa. The relationship between these factors and maternal colonization or infection with ESBL-E is unclear and requires investigation.

This systematic review and meta-analysis summarizes the magnitude of colonization or infection with ESBL-E among pregnant and post-partum women in Africa and the associated risk factors. Knowledge of the burden and risk factors of maternal colonization or infection with ESBL-E will assist with clinical care, infection prevention, and antibiotic stewardship, and inform the future development of targeted interventions to reduce both maternal and neonatal ESBL-E-associated morbidity and mortality.

Methods

Literature search

A systematic review was conducted in PubMed, Scopus, and Google Scholar. The search strategy included the following words, medical subject heading (MeSH) terms, and Boolean operators: "(enterobacteriaceae OR bacteria OR resistant OR resistance OR 'non-susceptible' OR "non susceptible" OR "not susceptible") AND (coloni* OR infect* OR carri*) AND ((Africa OR Algeria OR Angola OR Benin OR Botswana OR Burkina Faso OR Burundi OR Cabo Verde OR Cameroon OR Central African Republic OR Chad OR Comoros OR Democratic Republic of the Congo OR Republic of the Congo OR Cote d'Ivoire OR Djibouti OR Egypt OR Equatorial Guinea OR Eritrea

Table 1
Characteristics of studies included in the review.

Number	Author and year of publication	Country	Study design	Clinical samples	Population	Number of participants colonized with ESBL-E/Total participants (% colonized)	ESBL-E species included (isolate) and proportion	Setting
1	Olufunke et al. (2014)	Nigeria	Cross-sectional	Urine	Pregnant women	69/264 (26.1%)	*Escherichia coli* 69/264	Hospital
2	Onwuezobe (2015)	Nigeria	Cross-sectional	Urine	Pregnant women	16/80 (20%)	*Klebsiella pneumoniae* 8/16 *Escherichia coli* 6/16 *Klebsiella oxytoca* 1/16 *Enterobacter cloacae* 1/16	Community
3	Chereau et al. (2015)	Madagascar	Cross-sectional	Stool	Pregnant women	66/356 (18.6%)	*Escherichia coli* 46/66 *Klebsiella pneumoniae* 11/66 *Enterobacter cloacae* 5/66 *Citrobacter freundii* 3/66 *Morganella morganii* 1/66	Community
4	Nelson et al. (2014)	Tanzania	Cross-sectional	Stool	Post-partum women	16/113 (15%)	*Escherichia coli* 6/20 *Enterobacter spp* 3/20 *Klebsiella pneumoniae* 1/20 *Citrobacter spp* 2/20 *Pantoea spp* 3/20 *Proteus spp* 1/20	Hospital
5	Kaba et al. (2016)	South Africa	Cross-sectional	Stool	Post-partum women	4/90 (4.4%)	*Klebsiella pneumoniae* 2/90 *Escherichia coli* 1/90 *Enterobacter cloacae* 1/90	Community
6	Sáez-lópez et al. (2016)	Mozambique	Cross-sectional	Vaginal swabs	Pregnant women	1/51 (1.9%)	*Escherichia coli* 1/51	Hospital
7	Djuikoue (2016)	Cameroon	Cross-sectional	Stool	Pregnant women	15/26 (57.7%)	*Escherichia coli* 15/26	Community
8	Fortini et al. (2015)	Nigeria	Cross-sectional	Stool	Pregnant women	32/101 (31.7%)	*Escherichia coli* 32/101	Hospital
9	Bebell et al. (2017)	Uganda	Prospective cohort	Urine Blood	Post-partum women	8/174 (4.6%)	*Escherichia coli* 5/174 *Klebsiella pneumoniae* 3/174	Hospital
10	Tito et al. (2017)	Tanzania	Cross-sectional	Urine	Pregnant women	4/49 (8.2%)	*Escherichia coli* 4/49	Hospital

ESBL-E, extended-spectrum beta-lactamase-producing *Enterobacteriaceae*.

OR Ethiopia OR Gabon OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Kenya OR Lesotho OR Liberia OR Libya OR Madagascar OR Malawi OR Mali OR Mauritania OR Mauritius OR Morocco OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR "Sao Tome and Principe" OR Senegal OR Seychelles OR Sierra Leone OR Somalia OR South Africa OR South Sudan OR Sudan OR Swaziland OR Tanzania OR Togo OR Tunisia OR Uganda OR Zambia OR Zimbabwe)) AND (ESBL OR extended-spectrum-beta-lactamase OR extended-spectrum-β-lactamase OR extended spectrum beta lactamase) AND ((pregnant OR pregnancy OR gestation OR post-delivery OR postdelivery OR "post delivery" OR post-part* OR postpartum OR "post partum" OR perinatal OR antenatal OR prenatal OR women))". Bibliographies of eligible studies were manually searched to identify additional relevant articles. It was attempted to contact the authors of relevant studies to obtain specific details. Following the screening of publications, a total of 10 articles were included (Table 1).

Study selection and eligibility criteria

All publications describing colonization and/or infection with ESBL-E in pregnant or post-partum African women in both community and hospital settings were selected, irrespective of the study design. Primary study designs reporting the proportion or prevalence of ESBL-E in pregnant or post-partum women, as well as risk factors, were eligible. No language restriction was applied. The timeframe of the search included all records from electronic database inception to July 15, 2017. The article selection and exclusion process is shown in Figure 1.

Data extraction

A data extraction form was designed to capture the following information: first author and year of publication; country; study design (any type); study setting (community or hospital); study population; number and percentage of women colonized or infected with ESBL-E; total number of women recruited into the study; ESBL-E isolates and their proportions; molecular identification of ESBL-E isolates (if performed); factors associated with ESBL-E colonization or infection in women.

Data synthesis

A random-effects meta-analysis was performed to summarize the proportions and the 95% confidence intervals (CI) of ESBL-E in pregnant or post-partum women in Africa. To ensure proportionate weight distribution to studies presenting extreme prevalence (near 0 or 1), the Freeman–Tukey arcsine methodology was applied (Nyaga et al., 2014). The between-study heterogeneity was assessed using the I^2 statistic (which quantifies the percentage of variation across studies due to heterogeneity rather than to chance): I^2 <75% was considered as moderate heterogeneity (Higgins and Thompson, 2002) and >75% reflected high heterogeneity, in which case subset analyses were performed. The random-effects model was chosen based on the anticipated assumption that studies reporting on the magnitude of ESBL-E in pregnant and post-partum women used different laboratory methods, were conducted in different settings (hospital and community), or had other unknown factors influencing the magnitude of ESBL-E in

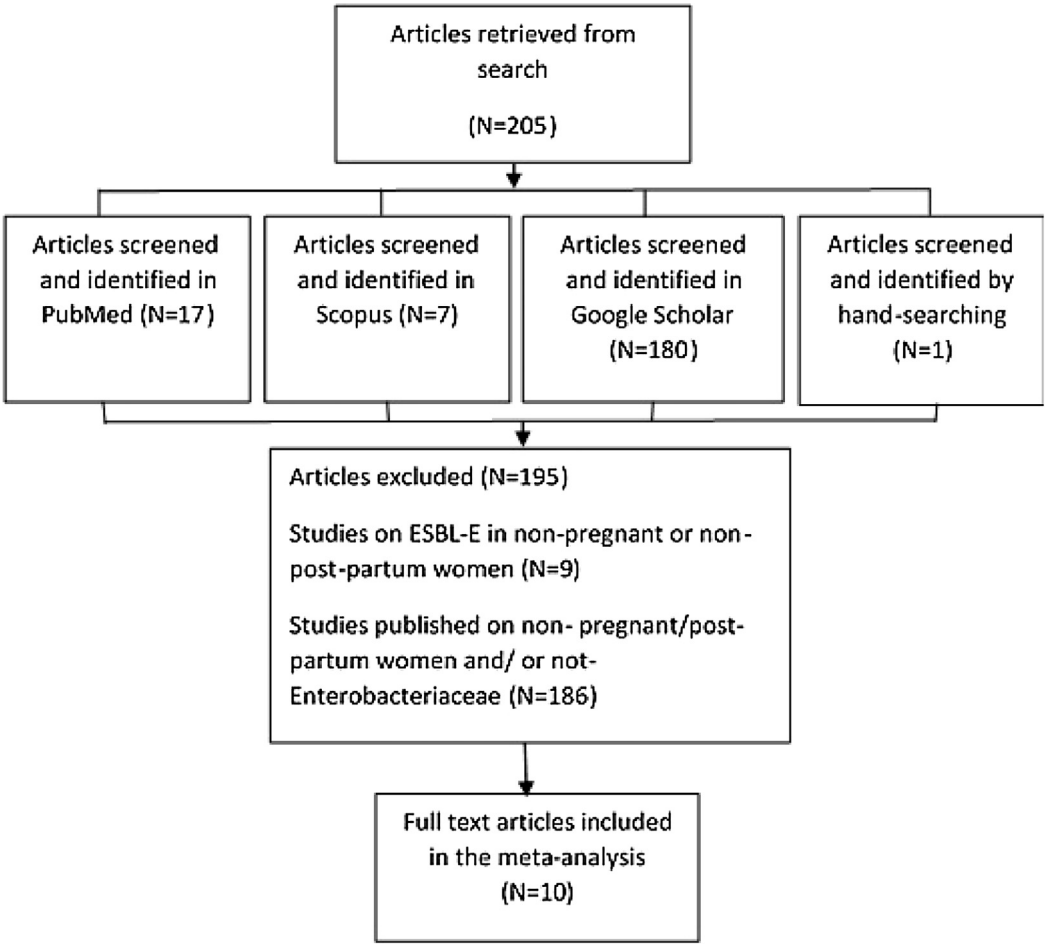

Figure 1. Flow diagram of study selection.

pregnant and post-partum women in Africa. The meta-analysis was performed using STATA IC version 13.1 software and the metaprop function/plugin, which is a specific STATA program designed for the meta-analysis of binomial data, allowing pooling of proportions (Nyaga et al., 2014). A total of 1304 participants were pooled from the studies included (927 pregnant women and 377 post-partum women).

Reporting of the meta-analysis of observational studies

This meta-analysis of observational studies is reported in compliance with the MOOSE statement and checklist (Stroup et al., 2000) (Meta-analysis of Observational Studies in Epidemiology).

Assessment of bias

The Newcastle–Ottawa Scale (Herzog et al., 2013) adapted for cross-sectional studies (see below) was used to assess the risk of bias for each selected study. This scale includes an evaluation of participant selection, comparability, and outcome; each section has a maximum number of 'stars' that can be awarded as a score (5, 2, and 3, respectively). For the overall quality assessment, the maximum score is 10 stars. Studies with a minimum score of 3 were considered of acceptable methodological quality for inclusion in the meta-analysis (Table 2).

Results

Geographic distribution of articles describing ESBL-E in women in Africa

Ten observational studies were included for quantitative analysis. These were from Nigeria ($n = 3$), Tanzania ($n = 2$), Madagascar ($n = 1$), South Africa ($n = 1$), Mozambique ($n = 1$), Uganda ($n = 1$), and Cameroon ($n = 1$). Six studies reported on pregnant women and four on post-partum women. Three studies reported ESBL-E isolates from urine, five others from stool, one from vaginal swabs, and one from both urine and blood.

Table 2
Risk of bias assessment for studies included in the quantitative synthesis (all observational studies).[a]

Author and year of publication	Selection		Comparability	Exposure	Overall quality assessment score (out of a maximum of 10)
	Representativeness of the sample	Ascertainment of exposure	Comparability of the groups on the basis of design or analysis	Assessment of outcome	
Olufunke et al. (2014)	*Truly representative of average pregnant women with ESBL *Enterobacteriaceae*	*Pregnant women diagnosed with clinical isolates producing ESBL – DDST	Study did not control for other factors	*Independent blind assessment	4
Onwuezobe (2015)	*Truly representative of average pregnant women with ESBL *Enterobacteriaceae*	**Pregnant women diagnosed with clinical isolates producing ESBL – DDST	Study did not control for other factors	*Independent blind assessment	4
Kaba et al. (2016)	*Truly representative of post-partum women with ESBL *Enterobacteriaceae* in the community	**ESBL production was confirmed using the combination disc test	Study did not control for other factors	*Independent blind assessment	4
Chereau et al. (2015)	*Truly representative of pregnant women with ESBL *Enterobacteriaceae* in the community	**Production of ESBL in ESC-resistant *Enterobacteriaceae* was confirmed by DDST (CASFM)	*Study controlled for other factors, multivariate analysis	*Independent blind assessment	5
Nelson et al. (2014)	*Truly representative of post-partum women with ESBL *Enterobacteriaceae* in the hospital	*Rectal swabs plated onto MacConkey agar (OXOID, Basingstoke, UK) supplemented with cefotaxime 2 mg/l for preliminary screening of ESBL bacterial isolates	Study did not control for other factors	*Independent blind assessment	3
Sáez-lópez et al. (2016)	No description of participant selection	**ESBL producers were identified by DDST using CTX, AMC and CAZ	Study did not control for other factors	*Independent blind assessment	3
Djuikoue et al. (2016a,b)	*Truly representative of outpatient women consulting for a suspicion of UTI, during the study period	**The presence of ESBL was determined using the double disc diffusion phenotypic method	*Study controlled for other factors, multivariate analysis	*Independent blind assessment	5
Fortini et al. (2015)	*Truly representative of healthy pregnant women on the day of admission to hospital in Ibadan (Nigeria)	**Phenotypic and genotypic characterization of ESBL production	Study did not control for other factors	*Independent blind assessment	4
Tito et al. (2017)	*Truly representative of HIV-positive pregnant women attending the PMTCT clinics; all consenting HIV-positive pregnant women were included during the study period	**ESBL production was concomitantly tested on the same Mueller–Hinton agar plate, using the DDST method	*Study controlled for other factors, multivariate analysis	*Independent blind assessment	5
Bebell et al. (2017)	*Truly representative of febrile, hypothermic, or normothermic post-partum women in the hospital	**ESBL phenotype if synergy was observed between AMC and CAZ or CTX	The study design allowed a 4:1 ratio of normothermic to febrile/hypothermic post-partum women, but did not control for other factors	**Record linkage and the statistical test used clearly described and appropriate; *p*-value presented	5

AMC, amoxicillin–clavulanic acid; CASFM, Committé Antibiogramme – Société Française de Microbiologie; CAZ, ceftazidime; CTX, cefotaxime; DDST, double disc synergy test; ESBL, extended-spectrum beta-lactamase-producing; ESC, extended-spectrum cephalosporin; PMTCT, prevention of mother to child transmission; UTI, urinary tract infection.

[a] Stars (*) represent the number of points awarded for the category; * = 1, ** = 2.

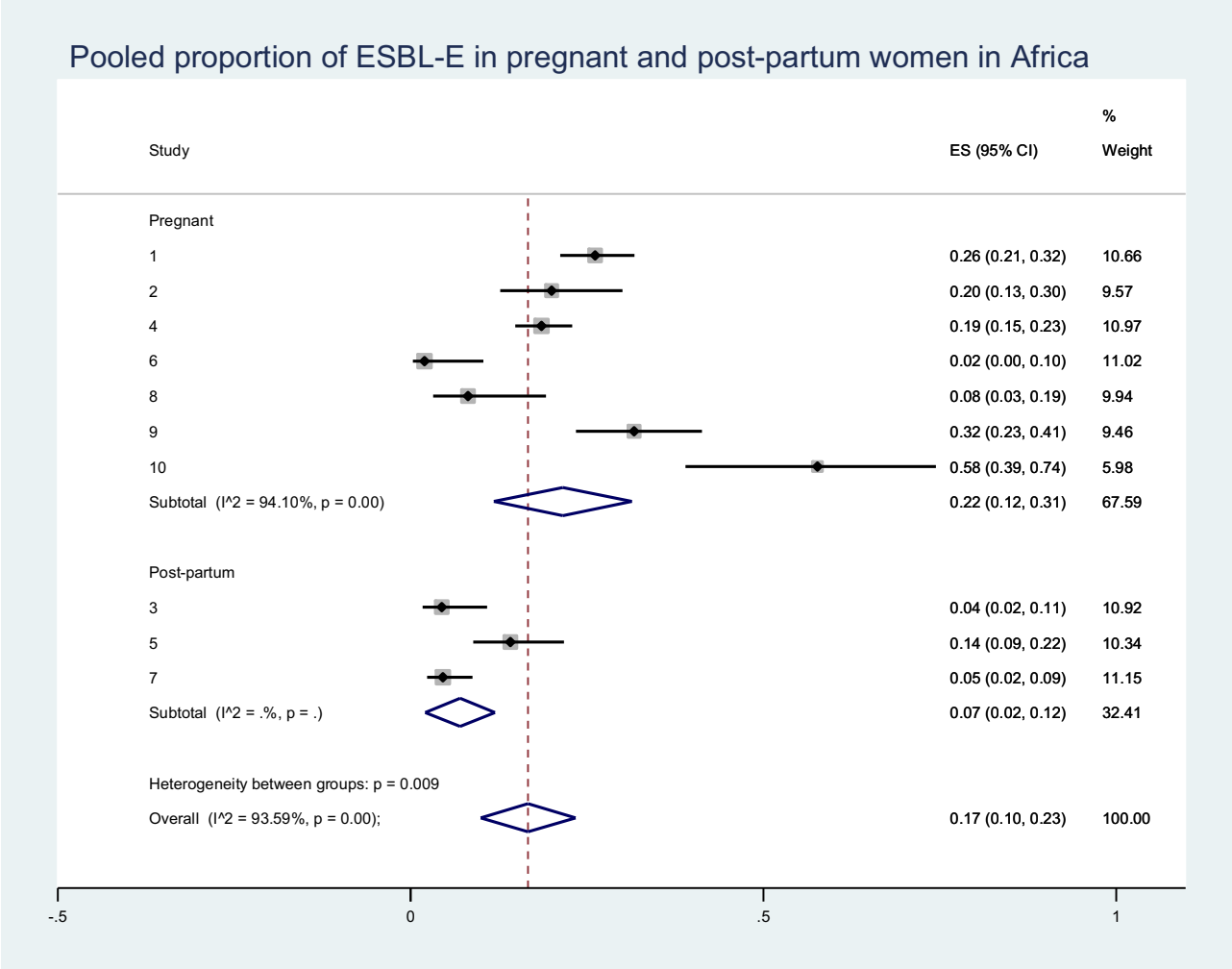

Figure 2. Pooled proportion of ESBL-E in pregnant and post-partum women in Africa.

Proportion estimates of ESBL-E in pregnant and post-partum women in Africa

Through meta-analysis of the eligible studies, the overall pooled estimate of the ESBL-E proportion in pregnant and post-partum women in Africa was determined to be 0.17 (95% CI 0.10–0.23) or 17% (95% CI 10–23%) (Figure 2). The heterogeneity was high ($I^2 = 93.6\%$, $p < 0.001$).

The pooled proportion of ESBL-E in pregnant women was 0.22 (95% CI 0.12–0.31) (Figure 2) and that of ESBL-E in post-partum women was 0.07 (95% CI 0.02–0.12). The pooled proportion of ESBL-E in hospital settings was 0.14 (95% CI 0.05–0.23) compared to 0.22 (95% CI 0.09–0.34) in community settings (Figure 3).

The pooled proportion of ESBL-E infections was 0.13 (95% CI 0.01–0.27) compared to 0.19 (95% CI 0.01–0.27) for ESBL-E colonized pregnant and post-partum women (Figure 4).

Molecular epidemiology of ESBL-E colonization/infection

Chereau et al. (2015) (Madagascar) identified 66 ESBL-producing isolates in pregnant women, including *E. coli* ($n = 46$), *Klebsiella spp* ($n = 11$), *Enterobacter cloacae* ($n = 5$), *Citrobacter freundii* ($n = 3$), and *Morganella morganii* ($n = 1$). Forty-five isolates carried a $bla_{CTX\text{-}M}$ gene, 15 carried bla_{SHV} and $bla_{CTX\text{-}M}$ genes, and two carried a bla_{SHV} gene alone. No bla_{ESBL} gene and no cefoxitin resistance was detected in four ESBL-producing *E. coli* isolates. Sáez-lópez et al. (2016) identified one ESBL-E isolate and it carried the CTX-M-15 gene. Kaba et al. (2016) reported that one mother–infant pair was ESBL-positive at birth with SHV-5-producing *E. cloacae*. Djuikoue et al. (2016a) reported that among 15 *E. coli* ESBL, all were CTX-M group 1 ($n = 15$). Fortini et al. (2015) found *E. coli* ($n = 32$) producing CTX-M-15.

Detection and confirmation of ESBL in the laboratory: what methods were used?

Five studies (Nelson et al., 2014; Olufunke et al., 2014; Aljabri et al., 2010; Bebell et al., 2017; Tito et al., 2017), detected ESBL production using the double disc synergy test (DDST). Chereau et al. (2015), Djuikoue et al. (2016b), and Kaba et al. (2016) utilized both synergy testing and molecular identification of ESBL (PCR sequencing). Sáez-lópez et al. (2016) and Fortini et al. (2015) used molecular identification of ESBL.

Factors associated with ESBL-E in pregnant women in Africa

Three studies included a multivariate analysis of risk factors for ESBL-E colonization/infection among pregnant women. Chereau et al. (2015) identified private indoor access to drinking water (odds ratio (OR) 3.8, 95% CI 1.2–11.6) and living in an individual house (OR 2.2, 95% CI 1.0–4.8) as independent risk factors for ESBL-E colonization among Malagasy women (after adjusting for

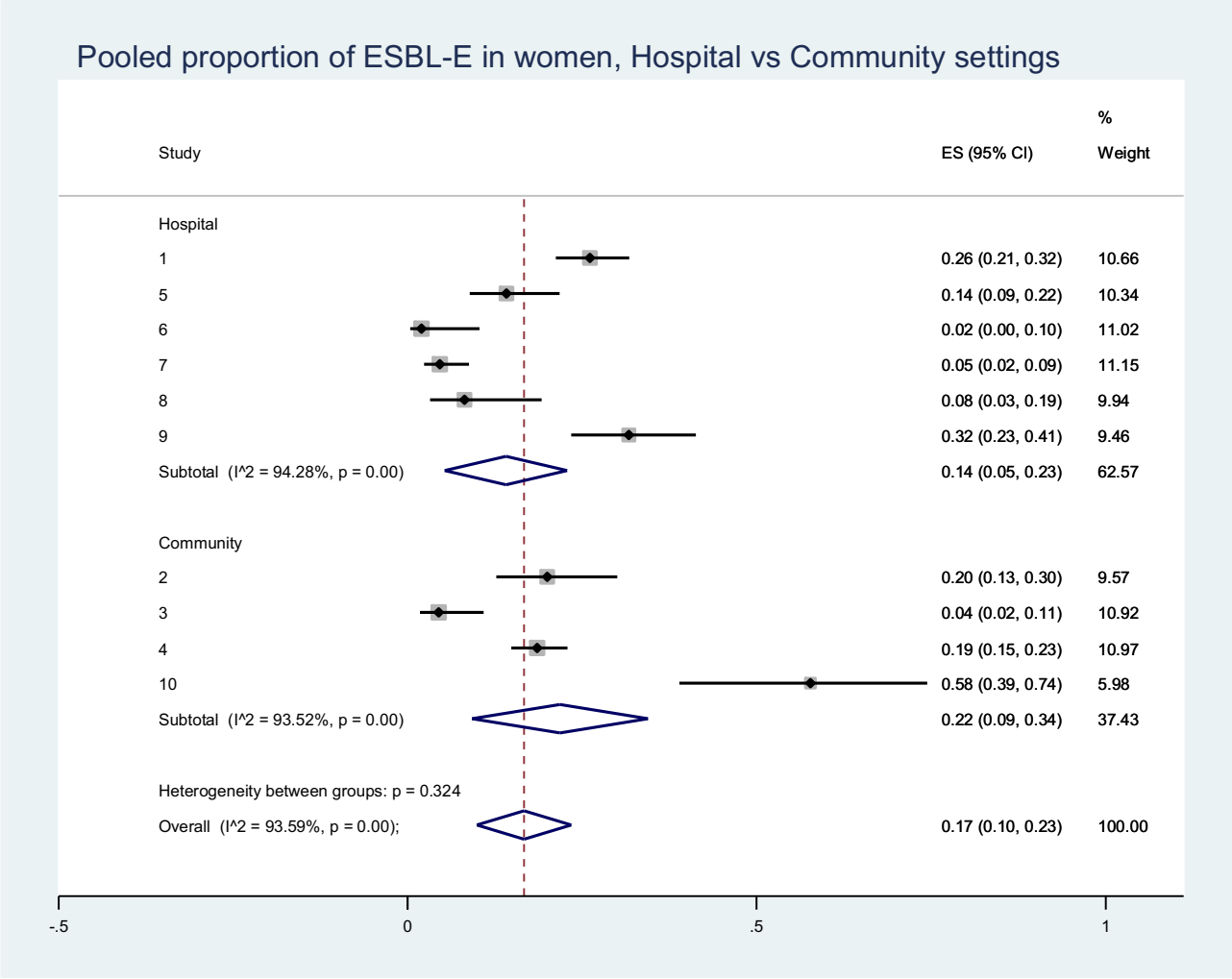

Figure 3. Pooled proportion of ESBL-E in women, Hospital vs Community settings.

delivery period and study area). Djuikoue et al. (2016b)) found that the detection of antimicrobial activity in the stool sample was the only independent risk factor associated with ESBL *E. coli* carriage in Cameroonian women (OR 5.4, 95% CI 2.0–14.7). Bebell et al. (2017)) identified single marital status (OR 2.6, 95% CI 1.1–6.1, $p = 0.026$), low CD4+ count of $<200/\mu l$ (OR 2.9, 95% CI 1.1–7.7, $p = 0.031$), and current UTI symptoms (OR 2.5, 95% CI 1.1–6.0, $p = 0.03$) as independent predictors of ESBL-E infection.

The following elements were not found to be significantly associated with ESBL-E colonization/infection in these three studies: being employed or being a housewife (Tito et al. 2017), drinking water supply from a spring or a well (Chereau et al., 2015), and hospitalization in the last 3 months (Djuikoue et al. 2016a,b).

Discussion

The close relationship of the mother–infant pair represents a potential risk for cross-transmission of maternal pathogens leading to neonatal colonization or infection. Several studies have confirmed the role of maternal colonization in the subsequent development of neonatal sepsis (particularly for group B Streptococcus, but also for ESBL-E) (Chan et al., 2013; Kaba et al., 2016; Denkel et al., 2014; Rettedal et al., 2015).

However, the scarcity of research on determinants of maternal colonization in Africa is worrisome. This meta-analysis of eligible published studies determined an overall pooled prevalence of colonization or infection with ESBL-E in pregnant and post-partum women in Africa of 17% (95% CI 10–23%). This rate of colonization or infection with ESBL-E is in line with a well-powered systematic review conducted in Africa by Tansarli et al. (2014), who reported proportions varying from 1.5% to 22.8% (pooled from 13 studies with isolates from clinical urine samples) among patients either infected or colonized with *Enterobacteriaceae*. However, these proportions were not for pregnant and post-partum women as specific groups. The pooled ESBL-E rate documented herein is substantially higher than the rates found in high- and middle-income countries, e.g., Norway (2.9%) (Rettedal et al., 2015) and Argentina (5.4%) (Villar et al., 2013). Possible explanations for increased ESBL-E carriage among African populations (both in community (Pitout et al., 2005; Pallecchi et al., 2004) and hospital settings) include poverty, suboptimal hygiene, contamination of drinking water (faeces (Bain et al., 2014), antibiotics), water sewage, communal toilets, easy access to antibiotics among pregnant and post-partum women in Africa, and possibly also increased use of antibiotics in livestock in Africa (Kariuki and Dougan, 2014). Another possible explanation is that the lack of trained healthcare workers (Kimang'a, 2012) and weak laboratory and infection control capacity (Petti et al., 2006) may contribute to healthcare-associated transmission of ESBL-E to pregnant and post-partum women.

Another important finding is that the pooled proportion of ESBL-E in community settings exceeded that in hospital settings

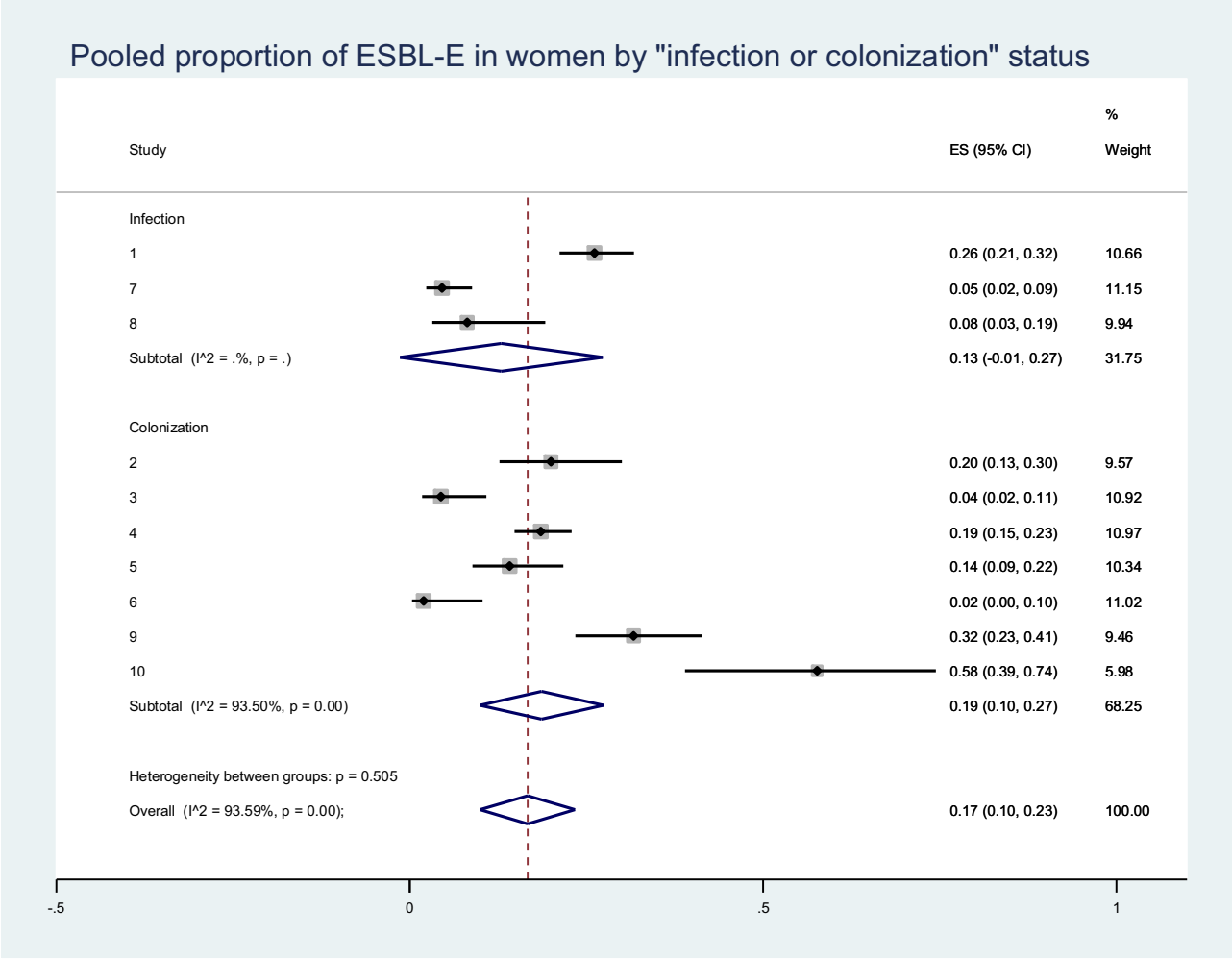

Figure 4. Pooled proportion of ESBL-E in women by "infection or colonization" status.

(22% vs. 14%) (Figure 3). This finding may have been influenced by the high prevalence of ESBL-E in community isolates (58%) in the Cameroonian study. However, another explanation may be the effect of high-level ESBL-E contamination of community water and food sources, lack of sanitation, and possibly overuse of antibiotics. The apparent difference in ESBL-E proportions between community and hospital settings could also be explained by the fact that all included studies from the community only studied ESBL-E colonization. In this meta-analysis, the proportion of ESBL-E colonization was found to be greater than ESBL-E infection.

The detection of ESBL-E in samples from hospitalized pregnant women with short lengths of stay may represent community-acquired colonization and/or infection with ESBL-E. Because ESBL-E stool carriage persists for a variable length of time (Ahmed et al., 2014), the study population may have acquired ESBL-E during pregnancy that then persisted up to delivery and the post-partum period, reflecting community-acquired antimicrobial resistance genes rather than healthcare-associated acquisition.

The pooled proportion of ESBL-E was higher among pregnant women than post-partum women (22% vs. 7%) (Figure 2). This difference may be explained by a greater probability of UTIs with ESBL-E during pregnancy than in the post-partum period (Sáez-lópez et al., 2016). It may also possibly represent differences in asymptomatic bacteriuria during pregnancy, differences in antibiotic prescribing practices, and different decision-making when choosing to send samples from pregnant vs. post-partum women for culture.

The clinical significance of increased ESBL-E-associated UTI during pregnancy is the potential for adverse pregnancy and neonatal outcomes, including intrauterine growth restriction, low birth weight, premature rupture of the membranes, foetal death, and neonatal infections (Loh and Sivalingam., 2007; Romero et al., 1989; Ovalle and Levancini, 2001; Matuszkiewicz-Rowińska et al., 2015).

In this systematic review and meta-analysis, a few studies attempted to report on factors associated with ESBL-E colonization in women in Africa; however, the risk factors analysed varied from one study to another and their pooled estimates could not be produced. The molecular epidemiology of the ESBL-E enzymes identified in the Madagascar (Chereau et al., 2015), Nigeria (Fortini et al., 2015), Cameroon (Djuikoue et al., 2016b), and Mozambique (Sáez-lópez et al., 2016) studies was in keeping with the global predominance of the CTX-M clone, which is also widely reported in community-acquired UTI (Pitout et al., 2005; Peirano and Pitout, 2010; Pallecchi et al., 2004; Livermore et al., 2007).

This systematic review has several strengths. A comprehensive search of several electronic databases was performed, in addition to manual searches and attempts to contact authors of relevant studies to obtain specific details. The authors made an effort to search the 'grey literature' by using Google Scholar, as many African publications are not listed in PubMed or Scopus. This appears to be the first systematic review and meta-analysis on ESBL-E colonization and/or infection focusing on pregnant and post-partum women in Africa. This group is of particular

importance for vertical transmission and subsequent neonatal colonization and/or infection. Each study was thoroughly assessed for risk of bias.

While informative, this systematic review and meta-analysis has a number of limitations. The number of eligible studies was small, demonstrating the apparent lack of studies on ESBL-E colonization and infection in this population group: pregnant and post-partum women in Africa. Given the limited sample size, the findings of this systematic review and meta-analysis may not be generalizable to all pregnant and/or post-partum women in Africa. The publications retrieved and included in the meta-analysis were all observational studies, a study type that is prone to many biases, including selection and information biases (Archer and Horn, 2006).

More robust studies are needed to understand how frequently pregnant and/or post-partum women become colonized or infected with ESBL-E in Africa, as well as the related risk factors in both community and hospital settings, to inform future interventions to reduce their rates. Interventions could include improved sanitation and water supplies, education of mothers on personal hygiene, restriction of antibiotic use during pregnancy, and strengthening of infection prevention in healthcare facilities.

Plain language summary

The level of colonization and/or infection with ESBL-E in pregnant and post-partum women in Africa is higher than that reported from high- and middle -income settings. In African pregnant and post-partum women, the prevalence of ESBL-E in community isolates exceeds that in hospital isolates. Maternal ESBL-E colonization/infection represents a risk for mother to child pathogen transmission with the potential for subsequent neonatal colonization and/or infection.

Key recommendation

Further studies are needed to establish ESBL-E colonization and infection rates amongst pregnant and post-partum women and their determinants in all African regions. Interventions to reduce ESBL-E colonization and carriage in Africa should focus on preventing both community- and healthcare-associated ESBL-E acquisition. Potential interventions could include the provision of safe sanitation and clean water supplies, education of mothers on personal hygiene, restricted use of antibiotics in pregnancy, and strengthening of infection prevention efforts in healthcare facilities (hand hygiene and appropriate disinfection of obstetric equipment and the environment).

Research gaps

It is not well understood how frequently pregnant and post-partum women become colonized and infected with ESBL-E, which risk factors promote ESBL-E colonization/infection, and how this could be prevented or managed, both in community and hospital settings in Africa. In addition, health systems research is needed to increase the understanding of the problem of antimicrobial resistance in maternal and neonatal infections at the macro (leadership or governance), meso (healthcare facilities and programmes), and micro (pregnant women or service consumers) levels.

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None.

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