Review

Colonisation with extended-spectrum β-lactamase-producing Enterobacteriaceae in pregnant/post-partum women: Systematic review and meta-analysis

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ABSTRACT

Objectives: Maternal colonisation with extended-spectrum β-lactamase (ESBL)-producing micro-organisms can lead to transmission of such pathogens to neonates, resulting in considerable morbidity. The aim of this study was to determine the global prevalence of maternal colonisation with ESBL-producing Enterobacteriaceae (ESBL-E).

Methods: A systematic review of PubMed, Embase, Scopus, Web of Science and ProQuest databases as well as the grey literature was performed. Studies reporting the prevalence of ESBL-E colonisation during pregnancy or postpartum period were included. Prevalence data were grouped by geographic region. The pooled prevalence and 95% confidence interval (CI) was estimated by meta-analysis using a random-effects model.

Results: Nineteen studies with reports from 16 countries (seven studies from Africa, one study from South America, two studies from Asia and nine studies from Europe) reporting data for 7352 pregnant/postpartum women were included. The pooled prevalence of ESBL-E colonisation was 8% (95% CI 5–10%). Prevalence estimates were 15% (95% CI 5–24%) in Africa, 6% (95% CI 4–10%) in South America, 5% (95% CI 4–6%) in Asia and 4% (95% CI 2–5%) in Europe. The pooled prevalence was higher in studies with low risk of bias (10%; 95% CI 7–13%) compared with those with high risk of bias (3%; 95% CI 2–3%).

Conclusion: There was heterogeneity regarding ESBL-E colonisation rates in different continents. The pooled prevalence rate was higher in Africa compared with other areas. Given that the highest rate was observed in Africa, implementing screening efforts for ESBL-E colonisation during pregnancy may be justified.

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1. Introduction

Extended-spectrum β-lactamases (ESBLs) are β-lactamase enzymes produced mainly by Enterobacteriaceae, a large family of Gram-negative bacteria. ESBLs have been detected in *Escherichia coli*, *Klebsiella pneumoniae* and *Acinetobacter*, among others [1]. ESBLs confer resistance to most β-lactam antibiotics, including third-generation cephalosporins and the monobactam aztreonam [2]. Production of ESBLs is considered the most common mechanism of resistance to cephalosporins among Enterobacteriaceae [3]. ESBL-producing Enterobacteriaceae (ESBL-E) can colonise various body parts, in particular the urinary and gastrointestinal tracts [4].

Undoubtedly, one of the major groups of patients affected by antimicrobial resistance and its consequences is pregnant women. ESBL-E colonisation in this particular group poses several threats both to maternal and fetal/neonatal health [1]. In addition to complicated maternal infections, especially urinary tract infections (UTIs) and pyelonephritis, the contribution of ESBL-E to obstetric complications (e.g. preterm labour), colonisation of very low birth weight (VLBW) infants [5] as well as perinatal transmission and consequent neonatal infection [6] highlights the necessity to ascertain the global prevalence of maternal ESBL-E colonisation and its geographic distribution.

Whether there are true differences in terms of the prevalence of maternal ESBL-E colonisation in different geographic areas is unknown, and knowledge regarding this issue is clinically important. Some authors have stated the requirement for ESBL-E screening in mothers who give birth to preterm infants [7]. Whether such recommendations can be translated into applicable actions requires a true understanding of the epidemiology of ESBL-E.

Two previous meta-analyses regarding the prevalence of ESBL-E in paediatric patients reported a pooled prevalence of 14% in paediatric UTI combining data from 16 primary studies [8] and a pooled prevalence of 9% in paediatric bloodstream infections using data from 23 primary studies [9]. Two separate meta-analyses regarding gastrointestinal colonisation with such organisms reported a similar pooled prevalence of 18% in solid-organ transplant patients [10] and residents of long-term care facilities [11]. A previous study in the UK focusing on women of reproductive age reported that 20% of subjects were ESBL-E carriers [12]. We identified only a single recent review confined to 10 studies from Africa [13], which estimated the maternal ESBL-E colonisation/infection rate as 17%. Therefore, providing a more comprehensive estimate of the prevalence of maternal ESBL-E colonisation and its distribution in broader geographic regions appears necessary. In addition, several authors have asserted that the prevalence of ESBL carriage is increasing in the community. For example, it was demonstrated that in the period 2002–2011, the community carriage rate of ESBL-E in Europe increased significantly by 0.5% per year [14]. However, little is known about a possible similar trend in pregnant women. Difficulties in the development of novel antimicrobials to treat infected patients highlight the importance of recognising colonised patients in order to find preventive ways to avoid the spread of multidrug-resistant Gram-negative bacteria, although at present no reliable decolonisation methods exist for such organisms [12].

The objectives of this review were to estimate the prevalence of maternal colonisation with ESBL-producing bacteria globally and to determine the heterogeneity of prevalence measures in different geographical areas as well as the methodological quality of the primary studies. In our opinion, the findings of this review would represent contemporary estimates regarding the epidemiology of ESBL-E in pregnancy/postpartum period and will have implications for clinicians, researchers and infection control programmes. Furthermore, geographical areas with limited or no prevalence data will be identified.

2. Methods

This systematic review and meta-analysis was prepared according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 checklist [15].

2.1. Eligibility criteria

All cross-sectional studies (descriptive or descriptive-analytical) reporting the prevalence of laboratory-confirmed ESBL-E colonisation among women during pregnancy or postpartum period (within 6 weeks after delivery) as well as the culture technique used identify ESBL-E were eligible for inclusion in the meta-analysis. ESBL-E colonisation was defined as isolation of ESBL-E through culture from vaginal, rectal or perianal samples. No age limit was imposed.

Exclusion criteria were studies that reported UTIs, asymptomatic bacteriuria or specific populations of women, including women with genital infection, human immunodeficiency virus (HIV) infection, gestational diabetes mellitus, those admitted to the intensive care unit (ICU) and those with any obstetric/neonatal complications (i.e. preterm labour, VLBW infants, and mothers of neonates who required neonatal ICU admission). Case reports, case series, outbreak reports (to avoid overestimation) and review articles were excluded. Studies without clear reporting of the prevalence or extractable figures to calculate the prevalence of ESBL-E (i.e. number of colonised patients with ESBL-producing pathogens divided by total number of patients tested), despite contact with the authors, were also excluded.

No language restriction was imposed. Studies reported in languages other than English were translated to English using Google Translation service and consultation with an official translation centre, if required. Published reports in journals (original articles and letters) as well as abstracts presented at conferences/meetings and unpublished data were eligible. If studies were reported both at a conference and as full-text in a journal, only the full-text was included.

2.2. Information sources

Studies were identified by searching electronic databases as well as hand-searching of pertinent articles between 10 October 2008 and 10 October 2018. For the electronic bibliographic database search, the PubMed, Embase, Scopus, Web of Science and ProQuest databases were

searched. In addition, LILACS (Latin American and Caribbean Health Sciences Literature Database), abstracts of European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) meetings [via the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) eLibrary] [16], International Congress on Infectious Diseases (ICID) abstracts (via International Journal of Infectious Diseases) [17], the US Centers for Disease Control and Prevention (CDC) website and Goggle Scholar were searched using key words.

2.3. Search

The electronic databases were searched (1 October 2018) both using controlled vocabulary [Medical Subject Headings (MeSH) for PubMed and Emtree for Embase] and free-text words without any language restriction. Appendix 1 presents the search strategy for

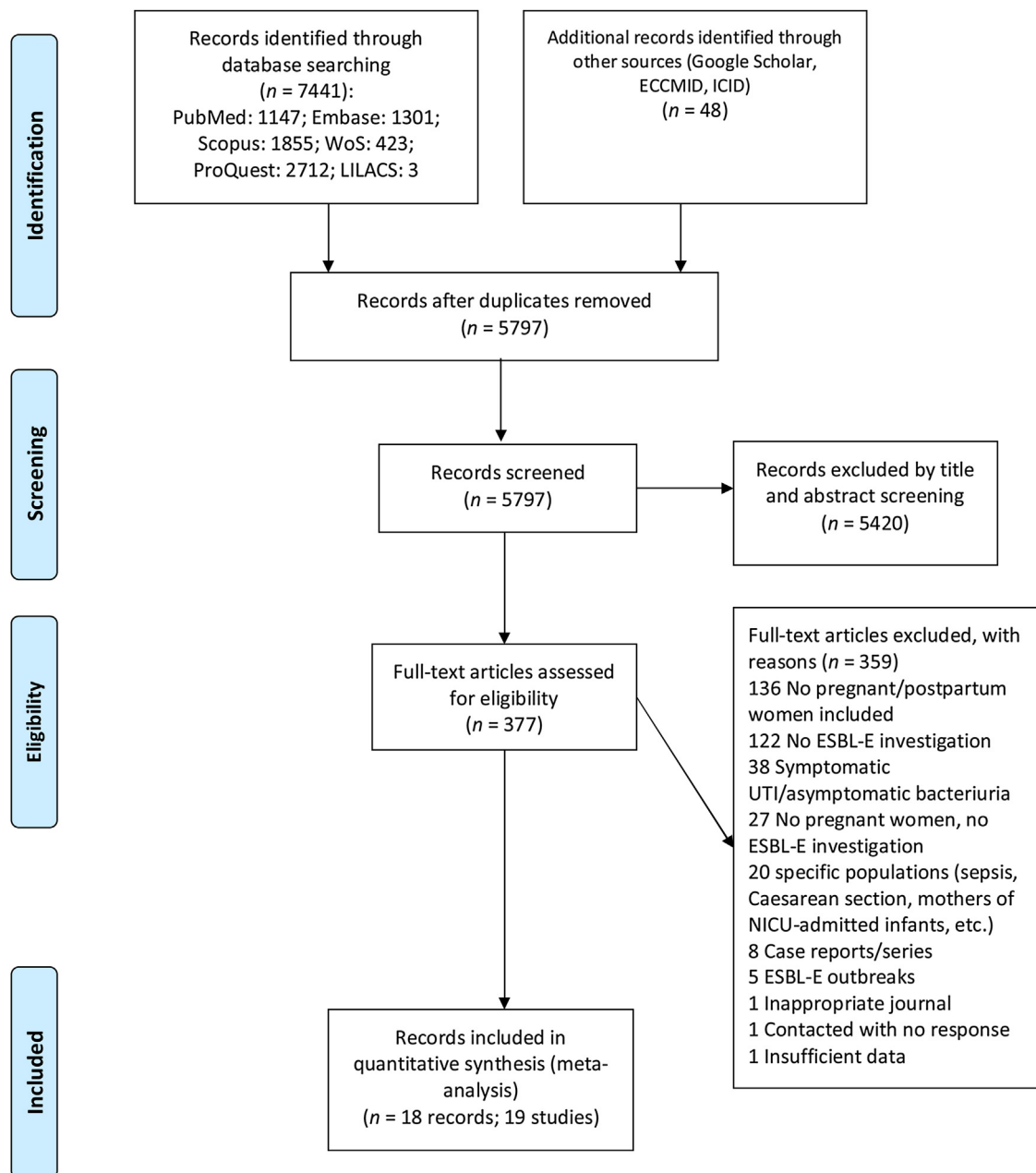**Fig. 1.** Flow diagram of selection of studies reporting the prevalence of colonisation by extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) during pregnancy/postpartum period. WoS, Web of Science; ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; ICID, International Congress on Infectious Diseases; UTI, urinary tract infection; NICU, neonatal intensive care unit.

Table 1

Characteristics of the included studies reporting the prevalence of colonisation with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) among pregnant/postpartum women in countries grouped by United Nations region.

First author	Study date	Country	Sample	Studied population	Total population	Colonised patients [n (%)]	Specific organism distribution (n)	ESBL-E confirmation test
Africa (n = 7 studies)								
Chereau [24]	2013 [a]	Madagascar	Stools	All pregnant women living in study areas	356	66 (18.5)	*Escherichia coli* (46), *Klebsiella* spp. (11), *Enterobacter cloacae* (5), *Citrobacter freundii* (3), *Morganella morganii* (1)	DDST, CA-SFM guidelines
Herindrainy [25]	2016 [a]	Madagascar	Stools and endorectal swabs	All pregnant women living in study areas	275	54 (19.6)	NR	DDST, CA-SFM guidelines
Sáez-López [23]	2013	Morocco	Vagina	Asymptomatic pregnant women during antenatal control or at delivery in maternity hospital	320	0	–	DDST, CLSI guidelines
Sáez-López [23]	2014	Mozambique	Vagina	Asymptomatic pregnant women during antenatal control or at delivery in hospital	200	1 (0.5)	*E. coli* (1)	DDST, CLSI guidelines
Fortini [26]	2011	Nigeria	Stools	Healthy pregnant women admitted to hospital	101	32 (31.7)	*E. coli* (32)	Disk diffusion and genotyping, EUCAST guidelines
Kaba [27]	2016	South Africa	Stools	Asymptomatic pregnant women living in three subdistrict locations near Cape Town	90	4 (4.4)	NR	CDT
Nelson [28]	2013	Tanzania	Rectal	Postpartum women at a medical centre	113	17 (15.0)	20 isolates in 17 patients: *E. coli* (6), *Enterobacter* spp. (4), *Pantoea* spp. (3), *Acinetobacter* spp. (3), *Citrobacter* spp. (2), *Klebsiella pneumoniae* (1), *Proteus* sp. (1)	DDST, CLSI guidelines
South America (n = 1 study)								
Villar [29]	2012	Argentina	Rectal	Perianal swabs of asymptomatic pregnant women at a laboratory	259	16 (6.2)	*E. coli* (14), *E. cloacae* (1), *Citrobacter koseri* (1)	CDT, CLSI guidelines
Asia (n = 2 studies)								
Pathak [30]	2008 [a]	India	Perianal	Asymptomatic pregnant women attending for routine antenatal care at teaching and non-teaching hospital outpatient clinics	710	109 (15.4)	*E. coli* (109)	CDT, CLSI guidelines
Nanayakkara [31]	2015 [a]	Sri Lanka	Vagina	Asymptomatic mothers admitted for delivery at a teaching hospital	250	4 (1.6)	*E. coli* (2), *Klebsiella* spp. (2)	DDST, CLSI guidelines
Europe (n = 9 studies)								
Zamfir [32]	2014 [a]	Germany	Perianal	Asymptomatic pregnant women with a planned vaginal delivery upon admission at two clinics	763	20 (2.6)	*E. coli* (20)	CDT, EUCAST guidelines
Patyi [33]	2014 [a]	Hungary	Stools/anorectal	Pregnant women at delivery in hospital	751	19 (2.5)	NR	NR
Knowles [34]	2015	Ireland	Rectal	Rectal swabs received for GBS screening in a maternity hospital	123	2 (1.6)	3 isolates in 2 patients: *E. coli* (2), *Proteus mirabilis* (1)	CDT, EUCAST guidelines
Rettedal [35]	2012	Norway	Rectal	Asymptomatic pregnant women attending pre-delivery consultation at a teaching hospital	901	26 (2.9)	27 isolates in 26 patients: *E. coli* (26), *K. pneumoniae* (1)	CDT, EUCAST guidelines
Kaczmarek [36]	2008	Poland	Rectovaginal	Isolates of asymptomatic pregnant women at an academic microbiology department	100	0	–	DDST
Jiménez-Rámila [37]	2015 [a]	Spain	Rectovaginal		815	55 (6.7)	58 isolates: *E. coli* (56), *K. pneumoniae* (1), *Klebsiella oxytoca* (1)	CDT, CLSI
López-Cerero [38]	2013	Spain	Rectovaginal	Asymptomatic pregnant women giving birth at an academic centre	406	39 (9.6)	*E. coli* (33), *K. pneumoniae* (5), *K. oxytoca* (1)	DDST, CLSI guidelines
Sáez-López [39]	2012 [a]	Spain	Vagina	Asymptomatic pregnant women at antenatal visits at maternity department of a hospital (603 with normal gestation and 35 with preterm labour/premature membrane rupture)	638	0	–	DDST, CLSI guidelines
Gysin [40]	2015 [a]	Switzerland	Vagina/perineum/rectal	Asymptomatic pregnant women at routine follow-up visit at a university hospital	181	5 (2.8)	*E. coli* (5)	NR

DDST, double-disk synergy test; CA-SFM, Antibiogram Committee of the French Society of Microbiology; NR, not reported; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; CDT, combined disk test; GBS, group B *Streptococcus*.
Note: All studies reported community-acquired ESBL-E colonisation.
[a] Midyear of the study period.

PubMed, and Appendix 2 shows the search strategy for Embase. The search results from all sources were entered into EndNote program.

2.4. Study selection

Two authors (MK and SA) independently screened the titles and abstracts of the search results for eligibility. The number of retained articles was compared and any disagreement was solved by discussion, reviewing the full-text of the articles and, if required, comments of a third author (AN). In the next stage, the full-texts of the articles were reviewed and, if eligibility criteria were met, the required data were extracted.

2.5. Data extraction

A data-gathering checklist was developed considering the required variables. The included full-text articles were reviewed independently by two authors (NJ and AN) and the required data were extracted. Any disagreement or unclear data were resolved by trying to contact the authors of the report. The authors were also contacted for further information if required. The gathered variables included: last name of first author; year of sampling; year of publication; country; continent; sample analysed in the laboratory (stool, rectal, vaginal); studied population; total number of subjects; number of subjects recognised as colonised with ESBL-E; responsible organism; frequency of organisms; and ESBL-E confirmatory diagnosis method used.

2.6. Assessing the risk of bias in primary studies

To determine the risk of bias in each study separately, the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for

Prevalence Studies was used [18]. This checklist consists of nine items addressing issues related to prevalence studies such as sampling frame, adequate sample size, appropriate statistical analyses and valid methods to describe the condition. For each item, four possible answers are available: 'yes', 'no', 'unclear' and 'not available'. The studies were first reviewed separately by two authors (MK and NJ) and then, through discussion and comments by a third author (AN) if required, the final critical appraisal was completed. To categorise the studies, a total score was calculated for each study as follows: 'yes' to any of the 9 items scored 1; and 'no', 'unclear' or 'not available' responses scored 0. Studies with total scores of 8 or 9 were considered as having a low risk of bias and lower scores ($\leq$7) were regarded as having a high risk of bias.

2.7. Synthesis of results

Prevalence data were grouped by geographical region based on the classification proposed by the United Nations Statistics Division, which includes Africa, Americas, Asia, Europe and Oceania [19]. The heterogeneity of prevalence measures was determined by the I^2 statistic and a value >75% indicated a high level of heterogeneity. To estimate the pooled prevalence and 95% confidence interval (CI), meta-analysis was performed using a random-effects model and 'metaprop' command [20]. Since some studies reported a prevalence rate of <5%, 'binomial exact method' [via cimethod(exact) option] was applied in the meta-analysis. Analysis was carried out using Stata Statistical Software: Release 12 (StataCorp LP, College Station, TX, USA).

2.8. Assessing publication or reporting bias

Publication bias was checked by inspecting the funnel plot of the prevalence rates and performing Begg's test and Egger's test

Table 2
Quality assessment of the included studies using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for studies reporting prevalence data.

First author	Was the sample frame appropriate to address the target population?	Were study participants sampled in an appropriate way?	Was the sample size adequate?	Were the study subjects and the setting described in detail?	Was the data analysis conducted with sufficient coverage of the identified sample?	Were valid methods used for identification of the condition?	Was the condition measured in a standard, reliable way for all participants?	Was there appropriate statistical analysis?	Was the response rate adequate and, if not, was the low response rate managed appropriately?
Africa (n = 7 studies)									
Chereau [24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Herindrainy [25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sáez-López, Morocco [23]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sáez-López, Mozambique [23]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Fortini [26]	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Kaba [27]	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes
Nelson [28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
South America (n = 1 study)									
Villar [29]	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Asia (n = 2 studies)									
Pathak [30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nanayakkara [31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Europe (n = 9 studies)									
Zamfir [32]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Patyi [33]	No	Unclear	Yes	No	Yes	Unclear	Unclear	Yes	Yes
Knowles [34]	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rettedal [35]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kaczmarek [36]	No	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jiménez-Rámila [37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
López-Cerero [38]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sáez-López [39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Gysin [40]	Yes	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes

[21]. Based on the Egger's or Begg's test, when the publication bias was non-ignorable (Begg's or Egger's tests *P*-value < 0.05), the trim-and-fill method was used to adjust for publication bias [22].

3. Results

3.1. Study selection

A total of 7489 records were identified, of which 1692 were duplicates. A further 5420 citations were excluded during screening of the titles and abstracts. Of the remaining 377 records, 359 were excluded for various reasons, such as not reporting ESBL-E colonisation, ESBL-E colonisation reported but no pregnant women investigated, and pregnant women with symptoms of genitourinary infection. Finally, 18 records met the inclusion criteria and were included the review [23–40]. One article [23] included data from two distinct geographic areas in Africa and the data were entered as two distinct studies. This translated to a total of 19 studies from 16 countries (Fig. 1). The included studies comprised seven studies from Africa [23–28], one from South America [29], two studies from Asia [30,31] and nine studies from Europe [32–40]. We tried to contact the authors of seven studies. The authors of three studies did not reply [41–43]. In one study the author confirmed that no pregnant women were included [44]. One study was performed purely on laboratory specimens (urine and sputum) without further clinical variables [45], and in another study the required data to calculate the prevalence was not available [46]. The author of the last study provided the necessary information (i.e. total number of pregnant women), resulting in inclusion of the study in the meta-analysis [23].

3.2. Study characteristics

Table 1 summarises the characteristics of the included studies by continent. For studies that lasted for longer than 12 months, the midyear of the study period that actual sampling and laboratory evaluation was done was determined as the study date.

3.3. Risk of bias within studies

Table 2 presents the quality assessment for risk of bias in each study. Of the 19 included studies, 14 studies [23–26,28–32,35,37–39] were of 'high quality' and a low risk of bias and 5 studies [27,33,34,36,40] were categorised as high risk of bias.

3.4. Synthesis of the results

Overall, the 19 included studies [23–40] reported data for 7352 women. The pooled prevalence of ESBL-E colonisation was 8% (95% CI 5–10%). The pooled prevalence rates of ESBL-E colonisation were 15% (95% CI 5–24%) in Africa, 6% (95% CI 4–10%) in South America, 5% (95% CI 4–6%) in Asia and 4% (95% CI 2–5%) in Europe (Fig. 2). Three studies
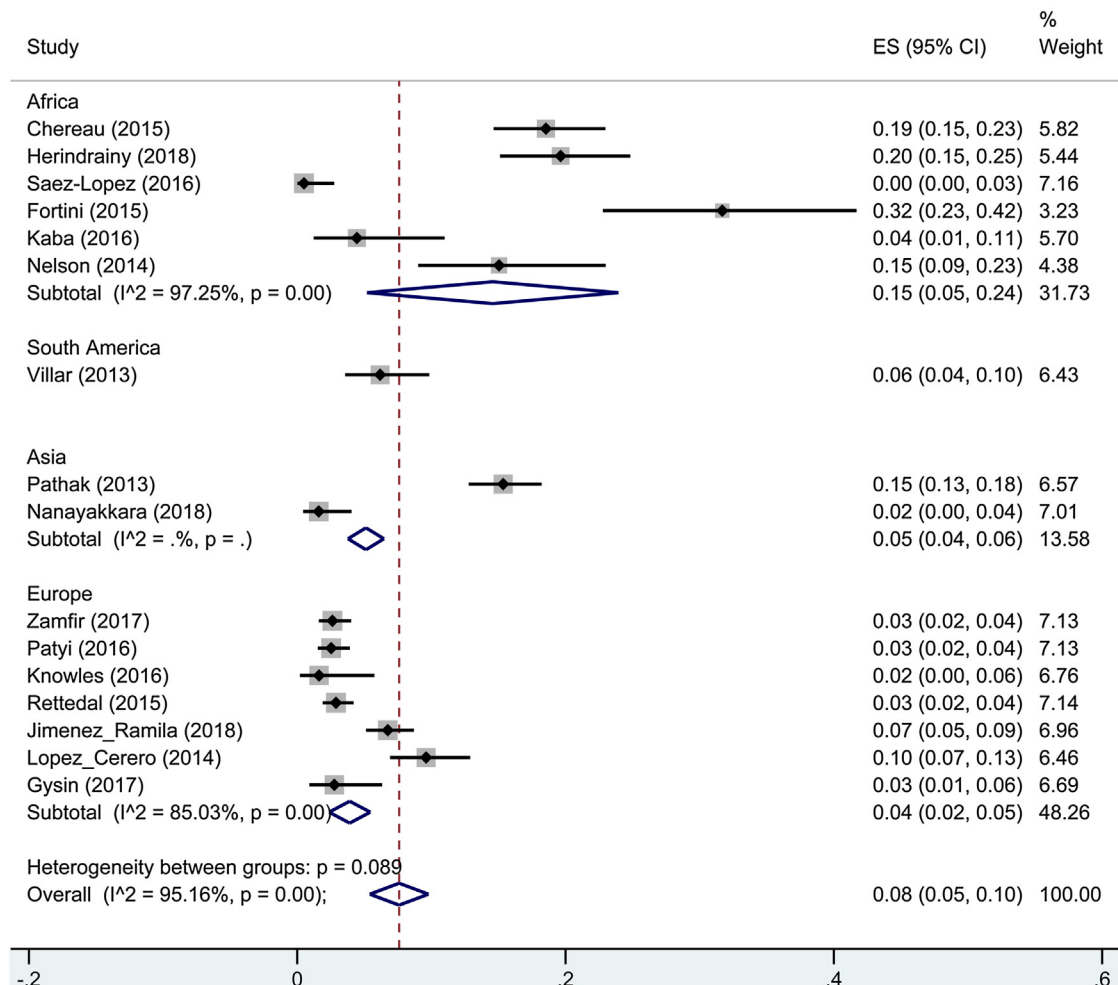

Fig. 2. Forest plot showing the prevalence of colonisation by extended-spectrum β-lactamase-producing Enterobacteriaceae in pregnant/postpartum women by geographical area. Three studies [23,36,39] that did not find any resistant organisms were not included. ES, effect size; CI, confidence interval.

did not report any ESBL-E colonisation among the investigated subjects [23,36,39]. There was high heterogeneity (I^2 = 95.16%).

The pooled prevalence of ESBL-E colonisation was 10% (95% CI 7–13%) in the studies with low risk of bias and 3% (95% CI 2–3%) in those studies with high risk of bias (Fig. 3).

Three studies did not report specific isolates recognised as ESBL-producers [25,27,33]. The remaining 13 studies reported various organisms cultured and identified as ESBL-producers. The most commonly reported organism was *E. coli*, with a pooled prevalence of 78% (95% CI 65–90%).

3.5. Publication bias

Results of the Begg's test showed a z-value of 1.04 (P = 0.3) and Egger's test showed publication bias of –4.96 (P = 0.03). The trim-and-fill method did not estimate any missing studies and did not adjust the random-effect estimate (Fig. 4). Considering these findings, it can be assumed that publication bias was ignorable.

4. Discussion

4.1. Summary of the evidence

The pooled prevalence of maternal ESBL-E colonisation was 8%, with the highest rate found in African studies (15%). Not all sampled women were positive for ESBL-producing bacteria, as in three studies (Morocco [23], Poland [36] and Spain [39]) no colonised mothers were reported. Although several guidelines such as those from the Clinical and Laboratory Standards Institute (CLSI), the European Committee on Antimicrobial Susceptibility
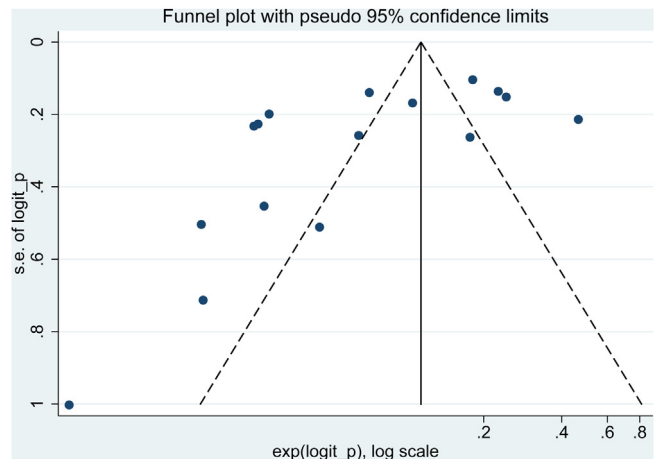

Fig. 4. Funnel plot for publication bias.

Testing (EUCAST) and the Antibiogram Committee of the French Society of Microbiology (CA-SFM) as well as methods (double-disk synergy test, combined disk test) were described by the authors to identify ESBL-producing organisms, the inclusion criteria were not limited to any specific guideline or laboratory method. This was primarily decided in order to obtain as much data as possible for a more accurate and comprehensive estimation of colonisation.

The highest rate of maternal colonisation with ESBL-producing bacteria was seen in Africa. This rate was higher than the rate reported from Asian studies, although only two reports from Asia were available
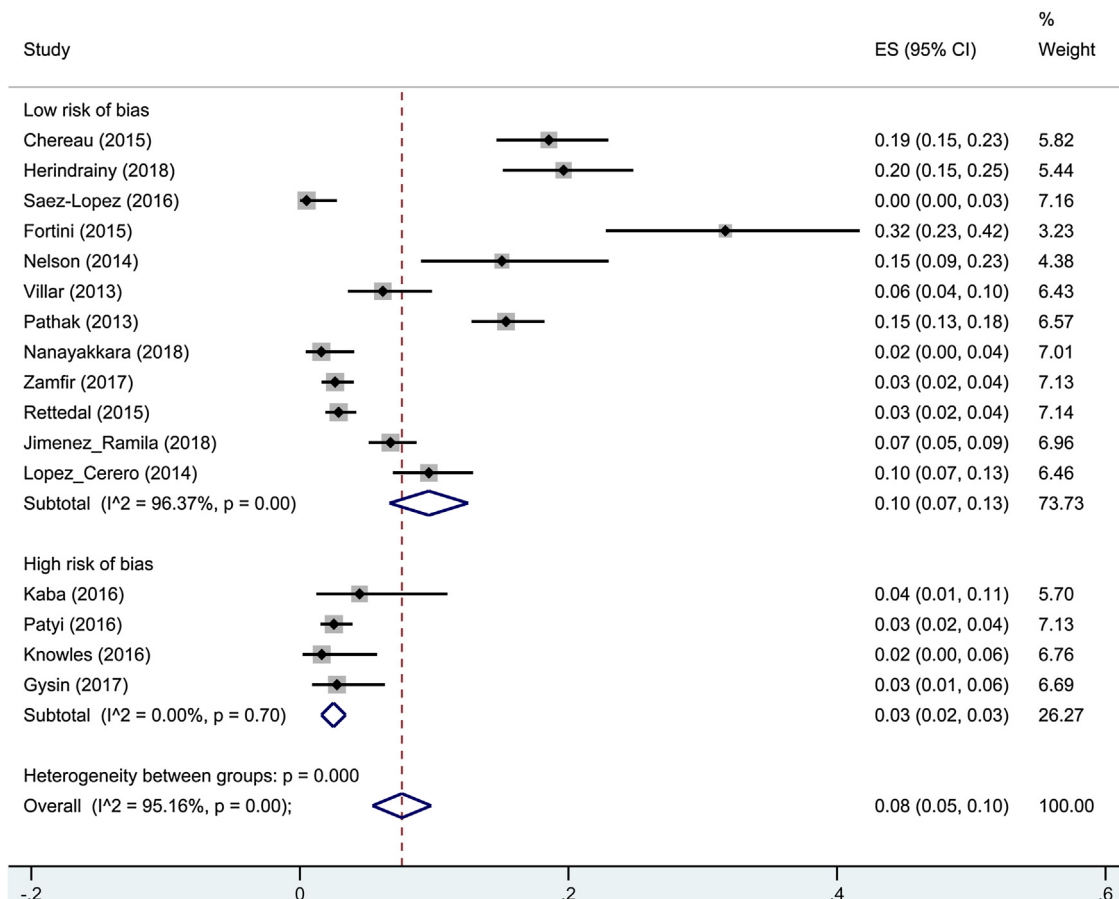

Fig. 3. Forest plot of studies reporting the prevalence of colonisation by extended-spectrum β-lactamase-producing Enterobacteriaceae in pregnant/postpartum women by risk of bias. Three studies [23,36,39] that did not find any resistant organism were not included. ES, effect size; CI, confidence interval.

with high heterogeneity. This finding is similar to a previous meta-analysis that demonstrated the highest global prevalence of maternal colonisation with group B *Streptococcus* in Africa [47]. The high rate of maternal colonisation in Africa may be explained by several factors, such as extensive antimicrobial use and challenges in implementing antimicrobial resistance surveillance action plans [48], that have been linked to a high prevalence of antimicrobial resistance. With respect to the quality of the primary studies, African studies had a low risk of bias. Therefore, the heterogeneity seen regarding the difference in pooled prevalence rates between studies with low risk and high risk of bias may be factitious due to geographical variation in maternal colonisation. Substantial variations existed within some regions. For instance, in Africa one study reported no mother with ESBL-E colonisation in Morocco [23], but two other studies reported high prevalence rates from Nigeria (31%) [26] and Madagascar (18%) [24]. In Europe, for example, although one study in Spain did not find laboratory evidence of ESBL-E colonisation from vaginal samples of 638 women in a hospital in Barcelona [39], another study reported a prevalence of 9.6% from rectovaginal samples of mothers in a university hospital located in Seville [38]. Most studies recruited laboratory samples at hospitals or mothers who presented for routine antenatal care or delivery at larger hospitals. This can potentially bias the estimated prevalence towards urban settings and underestimate the true prevalence in rural areas or smaller local health centres with probably poorer socioeconomic status. Only two studies [24,25] were true population-based studies.

There is evidence of intestinal carriers of ESBL-producing pathogens both in inpatient and outpatients [49]. As there is evidence that maternal colonisation is a major factor for transmission of such organisms to neonates who developed sepsis with ESBL-E [50], it seems essential to have an accurate understanding of the epidemiology of this condition. Thus, we decided to determine the prevalence of ESBL-producing bacteria among pregnant women, not among Enterobacteriaceae. It is likely that reporting the estimated prevalence rates among subjects will yield more practical findings for epidemiological purposes addressing pregnant women. Currently, there is no guideline or international consensus regarding routine screening of pregnant women for ESBL-producing bacterial colonisation. The current findings may have implications for programmers to consider screening methods, at least in areas with higher ESBL-E colonisation rates. A recent review from Africa including 10 studies reported an estimated prevalence of ESBL-E colonisation of 17% during pregnancy/postpartum period [13]. The prevalence estimate of 15% in Africa calculated in the current analysis is close to the abovementioned study, although differences in the inclusion criteria should be noted. Here we carried out the review by including those records that only reported colonisation rates among asymptomatic pregnant women. Those citations that reported pregnant patients for whom clinical infection (UTI, obstetric infection, sepsis, etc.) had been diagnosed were not included. However, the previous African review presented prevalence rates combining both colonised and infected patients. The approach to colonised versus infected patients may be different in clinical practice. Moreover, the messages conveyed to physicians or programmers regarding each of these states are different. Hence, we decided to report only the estimated colonisation rate.

4.2. Limitations

Some gaps were noticed regarding published results from broader geographic areas. No reports were found from North America or Oceania (Australia and New Zealand). Moreover, due to insufficient data in most studies, ascertaining potential risk factors for maternal ESBL-E colonisation was not feasible. Most studies recruited mothers from maternity hospitals or antenatal care facilities. This translates to the fact that further high-quality and preferably population-based studies are required, in particular from countries with no/limited data on maternal ESBL-E carriage.

5. Conclusions

There was heterogeneity regarding ESBL-E colonisation rates in different continents. The pooled prevalence rate was higher in Africa compared with South America, Asia and Europe. More population-based and high-quality studies, in particular from regions with limited reported data, are required for more accurate estimations. High rates in Africa may justify considering implementing screening efforts for ESBL-E colonisation during pregnancy.

Appendix 1. PubMed search strategy

#1 beta-lactamases
#2 "beta lactamase*"[tiab] OR
#3 beta-lactamase*[tiab] OR
#4 "beta lactamase*"[tiab]
#5 "extended-spectrum beta-lactamase*"[tiab]
#6 "extended-spectrum β-lactamase*"[tiab]
#7 "extended spectrum beta-lactamase*"[tiab]
#8 "extended spectrum β-lactamase*"[tiab]
#9 "extended spectrum b-lactamase"[tiab]
#10 "extended-spectrum beta-lactamase-producing"[tiab]
#11 ESBL*[tiab]
#12 "drug resistance, microbial"[Mesh]
#13 (drug resistance AND microbial)
#14 "antimicrobial drug resistance"[tiab]
#15 "antimicrobial drug resistances"[tiab]
#16 ("antibiotic resistance" AND microbial[tiab])
#17 "antibiotic resistance"[tiab]
#18 (resistance AND antibiotic[tiab])
#19 "antimicrobial resistance"[tiab]
#20 "drug resistance, bacterial"[Mesh]
#21 ("drug resistance" AND bacterial)
#22 "antibacterial drug resistance"[tiab]
#23 ("antibiotic resistance" AND bacterial[tiab])
#24 "bacterial drug resistance"[tiab]
#25 Enterobacteriaceae[tiab])
#26 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
#27 (pregnancy OR pregnancies[tiab]

#28 gestation[tiab]
#29 "pregnant women"
#30 "pregnant woman"[tiab]
#31 pregnant[tiab]
#32 "postpartum period"
#33 "post-partum period"[tiab]
#34 (period AND postpartum[tiab])
#35 postpartum[tiab]
#36 post-partum[tiab]
#37 "postpartum women"[tiab]
#38 (women AND postpartum[tiab])
#39 puerperium[tiab]
#40 mothers
#41 mother*[tiab]
#42 maternal[tiab])
#43 #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
#44 2008/10/10:2018/10/10[dp]
#45 #26 AND #43 AND #44

Appendix 2. Embase search strategy

#1 'beta lactamase'/exp
#2 'beta-lactamase':ti,ab
#3 'extended spectrum beta lactamase'/exp
#4 'extended spectrum beta lactamase producing Enterobacteriaceae'/exp
#5 ESBL:ti,ab
#6 'antibiotic resistance'/exp
#7 'antimicrobial drug resistance':ti,ab
#8 'antimicrobial resistance':ti,ab
#9 'antibacterial drug resistance':ti,ab
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 'pregnancy'/exp
#12 'pregnancies':ti,ab
#13 'pregnant women':ti,ab
#14 'pregnant woman':ti,ab
#15 'pregnant':ti,ab
#16 'postpartum period':ti,ab
#17 'post-partum period':ti,ab
#18 'postpartum':ti,ab
#19 'post-partum':ti,ab
#20 'postpartum women':ti,ab
#21 'puerperium'/exp
#22 'mother'/exp
#23 'mothers':ti,ab
#24 'maternal':ti,ab
#25 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24
#26 [2008-2018]/py
#27 #10 AND #25 AND #26

References

[1] Eppes CS, Clark SL. Extended-spectrum β-lactamase infections during pregnancy: a growing threat. Am J Obstet Gynecol 2015;213:650–2, doi:http://dx.doi.org/10.1016/j.ajog.2015.03.020.

[2] Curello J, MacDougall C. Beyond susceptible and resistant, part II: treatment of infections due to Gram-negative organisms producing extended-spectrum β-lactamases. J Pediatr Pharmacol Ther 2014;19:156–64, doi:http://dx.doi.org/10.5863/1551-6776-19.3.156.

[3] Bailey JK, Pinyon JL, Anantham S, Hall RM. Commensal Escherichia coli of healthy humans: a reservoir for antibiotic-resistance determinants. J Med Microbiol 2010;59:1331–9, doi:http://dx.doi.org/10.1099/jmm.0.022475-0.

[4] Biehl LM, Schmidt-Hieber M, Liss B, Cornely OA, Vehreschild MJ. Colonization and infection with extended spectrum β-lactamase producing Enterobacteriaceae in high-risk patients—review of the literature from a clinical perspective. Crit Rev Microbiol 2016;42:1–16, doi:http://dx.doi.org/10.3109/1040841x.2013.875515.

[5] Denkel LA, Schwab F, Kola A, Leistner R, Garten L, von Weizsacker K, et al. The mother as most important risk factor for colonization of very low birth weight (VLBW) infants with extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E). J Antimicrob Chemother 2014;69:2230–7, doi:http://dx.doi.org/10.1093/jac/dku097.

[6] Nakamura K, Kaneko M, Abe Y, Yamamoto N, Mori H, Yoshida A, et al. Outbreak of extended-spectrum β-lactamase-producing Escherichia coli transmitted through breast milk sharing in a neonatal intensive care unit. J Hosp Infect 2016;92:42–6, doi:http://dx.doi.org/10.1016/j.jhin.2015.05.002.

[7] Denkel LA, Gastmeier P, Piening B. To screen or not to screen mothers of preterm infants for extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E). J Perinatol 2015;35:893–4, doi:http://dx.doi.org/10.1038/jp.2015.100.

[8] Flokas ME, Detsis M, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing Enterobacteriaceae in paediatric urinary tract infections: a systematic review and meta-analysis. J Infect 2016;73:547–57, doi:http://dx.doi.org/10.1016/j.jinf.2016.07.014.

[9] Flokas ME, Karanika S, Alevizakos M, Mylonakis E. Prevalence of ESBL-producing Enterobacteriaceae in pediatric bloodstream infections: a systematic review and meta-analysis. PLoS One 2017;12:e0171216, doi:http://dx.doi.org/10.1371/journal.pone.0171216.

[10] Alevizakos M, Kallias A, Flokas ME, Mylonakis E. Colonization with extended-spectrum β-lactamase-producing Enterobacteriaceae in solid organ transplantation: a meta-analysis and review. Transpl Infect Dis 2017;19:e12718, doi:http://dx.doi.org/10.1111/tid.12718.

[11] Flokas ME, Alevizakos M, Shehadeh F, Andreatos N, Mylonakis E. Extended-spectrum β-lactamase-producing Enterobacteriaceae colonisation in long-term care facilities: a systematic review and meta-analysis. Int J Antimicrob Agents 2017;50:649–56, doi:http://dx.doi.org/10.1016/j.ijantimicag.2017.08.003.

[12] Seale J, Millar M. Perinatal vertical transmission of antibiotic-resistant bacteria: a systematic review and proposed research strategy. BJOG 2014;121:923–8, doi:http://dx.doi.org/10.1111/1471-0528.12746.

[13] Bulabula ANH, Dramowski A, Mehtar S. Maternal colonization or infection with extended-spectrum β-lactamase-producing Enterobacteriaceae in Africa: a systematic review and meta-analysis. Int J Infect Dis 2017;64:58–66, doi:http://dx.doi.org/10.1016/j.ijid.2017.08.015.

[14] Woerther PL, Burdet C, Chachaty E, Andremont A. Trends in human fecal carriage of extended-spectrum β-lactamases in the community: toward the globalization of CTX-M. Clin Microbiol Rev 2013;26:744–58, doi:http://dx.doi.org/10.1128/cmr.00023-13.

[15] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097, doi:http://dx.doi.org/10.1371/journal.pmed.1000097.

[16] European Society of Clinical Microbiology and Infectious Diseases (ESCMID). ESCMID library. https://www.escmid.org/escmid_publications/escmid_elibrary/. [Accessed 1 October 2018].

[17] International Journal of Infectious Diseases. International Congress on Infectious Diseases (ICID). https://www.journals.elsevier.com/international-journal-of-infectious-diseases/special-issues. [Accessed 1 October 2018].

[18] Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 2015;13:147–53, doi:http://dx.doi.org/10.1097/xeb.0000000000000054.

[19] United Nations Statistics Division. Standard country or area codes for statistical use (M49). https://unstats.un.org/unsd/methodology/m49/. [Accessed 1 October 2018].

[20] Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 2014;72:39, doi:http://dx.doi.org/10.1186/2049-3258-72-39.

[21] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[22] Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.

[23] Sáez-López E, Cossa A, Benmessaoud R, Madrid L, Moraleda C, Villanueva S, et al. Characterization of vaginal Escherichia coli isolated from pregnant women in two different African sites. PLoS One 2016;11:e0158695, doi:http://dx.doi.org/10.1371/journal.pone.0158695.

[24] Chereau F, Herindrainy P, Garin B, Huynh BT, Randrianirina F, Padget M, et al. Colonization of extended-spectrum-β-lactamase- and NDM-1-producing Enterobacteriaceae among pregnant women in the community in a low-income country: a potential reservoir for transmission of multiresistant Enterobacteriaceae to neonates. Antimicrob Agents Chemother 2015;59:3652–5, doi:http://dx.doi.org/10.1128/aac.00029-15.

[25] Herindrainy P, Rabenandrasana MAN, Andrianirina ZZ, Rakotoarimanana FMJ, Padget M, de Lauzanne A, et al. Acquisition of extended spectrum β-lactamase-producing Enterobacteriaceae in neonates: a community based cohort in Madagascar. PLoS One 2018;13:e0193325, doi:http://dx.doi.org/10.1371/journal.pone.0193325.

[26] Fortini D, Fashae K, Villa L, Feudi C, Garcia-Fernandez A, Carattoli A. A novel plasmid carrying bla$_{CTX-M-15}$ identified in commensal Escherichia coli from healthy pregnant women in Ibadan, Nigeria. J Glob Antimicrob Resist 2015;3:9–12, doi:http://dx.doi.org/10.1016/j.jgar.2014.12.002.

[27] Kaba M, Manenzhe R, Moodley C, Zar H, Nicol M. Epidemiology of extended-spectrum β-lactamase- and carbapenemase-producing bacteria in stool from apparently healthy children, South Africa. Int J Infect Dis 2016;45(Suppl. 1):96, doi:http://dx.doi.org/10.1016/j.ijid.2016.02.254.

[28] Nelson E, Kayega J, Seni J, Mushi MF, Kidenya BR, Hokororo A, et al. Evaluation of existence and transmission of extended spectrum β lactamase producing bacteria from post-delivery women to neonates at Bugando Medical Center, Mwanza-Tanzania. BMC Res Notes 2014;7:279, doi:http://dx.doi.org/10.1186/1756-0500-7-279.

[29] Villar HE, Aubert V, Baserni MN, Jugo MB. Maternal carriage of extended-spectrum β-lactamase-producing Escherichia coli isolates in Argentina. J Chemother 2013;25:324–7, doi:http://dx.doi.org/10.1179/1973947813y.0000000081.

[30] Pathak A, Chandran SP, Mahadik K, Macaden R, Lundborg CS. Frequency and factors associated with carriage of multi-drug resistant commensal Escherichia coli among women attending antenatal clinics in central India. BMC Infect Dis 2013;13:199, doi:http://dx.doi.org/10.1186/1471-2334-13-199.

[31] Nanayakkara D, Liyanapathirana V, Kandauda C, Gihan C, Ekanayake A, Adasooriya D. Maternal vaginal colonization with selected potential pathogens of neonatal sepsis in the era of antimicrobial resistance, a single center experience from Sri Lanka. BMC Infect Dis 2018;18:351, doi:http://dx.doi.org/10.1186/s12879-018-3262-y.

[32] Zamfir M, Adler AC, Kolb S, Dammeyer A, Nasri L, Schomacher L, et al. Evaluation of sampling locations in pregnant women and newborns for the detection of colonisation with antibiotic-resistant bacteria. Eur J Clin Microbiol Infect Dis 2017;36:1819–26, doi:http://dx.doi.org/10.1007/s10096-017-2997-5.

[33] Patyi M, Tóth Z, Kelemen E, Tálosi G. Examination of maternal extended spectrum β-lactamase bacterial colonization and follow-up of newborns requiring neonatal intensive care unit admission [in Hungarian]. Orv Hetil 2016;157:1353–6, doi:http://dx.doi.org/10.1556/650.2016.30514.

[34] Knowles SJ, Jacob AM, O'Dea G. Prevalence of multi-drug-resistant organism carriage in pregnant women. J Hosp Infect 2016;93:68–9, doi:http://dx.doi.org/10.1016/j.jhin.2016.02.005.

[35] Rettedal S, Lohr IH, Bernhoff E, Natas OB, Sundsfjord A, Oymar K. Extended-spectrum β-lactamase-producing Enterobacteriaceae among pregnant women in Norway: prevalence and maternal–neonatal transmission. J Perinatol 2015;35:907–12, doi:http://dx.doi.org/10.1038/jp.2015.82.

[36] Kaczmarek A, Skowron K, Budzynska A, Gospodarek-Komkowska E. Virulence-associated genes and antibiotic susceptibility among vaginal and rectal Escherichia coli isolates from healthy pregnant women in Poland. Folia Microbiol (Praha) 2018;63:637–43, doi:http://dx.doi.org/10.1007/s12223-018-0598-z.

[37] Jiménez-Rámila C, López-Cerero L, Aguilar Martín MV, Vera Martín C, Serrano L, Pascual Á, et al. Vagino-rectal colonization and maternal–neonatal transmission of Enterobacteriaceae producing extended-spectrum β-lactamases or carbapenemases: a cross-sectional study. J Hosp Infect 2019;101:167–74, doi:http://dx.doi.org/10.1016/j.jhin.2018.09.010.

[38] López-Cerero L, Jiménez C, Luna S, Vera C, Rodríguez-Baño J, Pascual A. Prevalence of ESBL-producing Enterobacteriaceae mother colonization and mother-to-neonate transmission. 24th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). [poster P0554].

[39] Sáez-López E, Guiral E, Fernández-Orth D, Villanueva S, Goncé A, López M, et al. Vaginal versus obstetric infection Escherichia coli isolates among pregnant women: antimicrobial resistance and genetic virulence profile. PLoS One 2016;11:e0146531, doi:http://dx.doi.org/10.1371/journal.pone.0146531.

[40] Gysin D, Tschudin-Sutter S, Huang D, Nogarth D, Dangel M, Hoesli I, et al. Extended-spectrum β-lactamase producing Enterobacteriaceae among healthy pregnant women in Switzerland: preliminary results of an ongoing cross-sectional study. 27th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID). [poster].

[41] Rashki A. Cervico-vaginopathogenic Escherichia coli in Iran: serogroup distributions, virulence factors and antimicrobial resistance properties. Microb Pathog 2014;75:29–34, doi:http://dx.doi.org/10.1016/j.micpath.2014.08.004.

[42] Birgy A, Mariani-Kurkdjian P, Bidet P, Doit C, Genel N, Courroux C, et al. Characterization of extended-spectrum-β-lactamase-producing Escherichia coli strains involved in maternal–fetal colonization: prevalence of E. coli ST131. J Clin Microbiol 2013;51:1727–32, doi:http://dx.doi.org/10.1128/jcm.03255-12.

[43] Chitnis S, Chitnis V, Chitnis D. Emergence of multidrugresistant Gram negative bacilli and enterococci from rectal swabs of newborn and their mothers from Central India. Int J Infect Dis 2010;14(Suppl. 1):e40–1, doi:http://dx.doi.org/10.1016/j.ijid.2010.02.1577.

[44] Li B, Lu Y, Lan F, He Q, Li C, Cao Y. Prevalence and characteristics of ST131 clone among unselected clinical Escherichia coli in a Chinese university hospital. Antimicrob Resist Infect Control 2017;6:118, doi:http://dx.doi.org/10.1186/s13756-017-0274-0.

[45] Miao Z, Li S, Wang L, Song W, Zhou Y. Antimicrobial resistance and molecular epidemiology of ESBL-producing Escherichia coli isolated from outpatients in town hospitals of Shandong Province, China. Front Microbiol 2017;8:63, doi:http://dx.doi.org/10.3389/fmicb.2017.00063.

[46] Chaintarli K, Lenglet A, Beauzile BD, Senat-Delva R, Mabou MM, Martino C, et al. High prevalence of ESBL-positive bacteria in an obstetrics emergency hospital and neonatal care unit—Haiti, 2016. Infect Control Hosp Epidemiol 2018;39:1381–3, doi:http://dx.doi.org/10.1017/ice.2018.213.

[47] Kwatra G, Cunnington MC, Merrall E, Adrian PV, Ip M, Klugman KP, et al. Prevalence of maternal colonisation with group B Streptococcus: a systematic review and meta-analysis. Lancet Infect Dis 2016;16:1076–84, doi:http://dx.doi.org/10.1016/S1473-3099(16)30055-X.

[48] Essack SY, Desta AT, Abotsi RE, Agoba EE. Antimicrobial resistance in the WHO African region: current status and roadmap for action. J Public Health (Oxf) 2017;39:8–13, doi:http://dx.doi.org/10.1093/pubmed/fdw015.

[49] Djuikoue IC, Woerther PL, Toukam M, Burdet C, Ruppé E, Gonsu KH, et al. Intestinal carriage of extended spectrum β-lactamase producing E. coli in women with urinary tract infections, Cameroon. J Infect Dev Ctries 2016;10:1135–9, doi:http://dx.doi.org/10.3855/jidc.7616.

[50] Marando R, Seni J, Mirambo MM, Falgenhauer L, Moremi N, Mushi MF, et al. Predictors of the extended-spectrum-β lactamases producing Enterobacteriaceae neonatal sepsis at a tertiary hospital, Tanzania. Int J Med Microbiol 2018;308:803–11, doi:http://dx.doi.org/10.1016/j.ijmm.2018.06.012.