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Vaginal-perineal cultures for detecting group B streptococci and extended spectrum β-lactamase producing bacteria in pregnancy

Dorothy J. Huang[a,*], Irene Hösli[a], Sarah Tschudin-Sutter[b], Tabea Pfister[a], Christina Granado[a], Doris Müller-Borer[a], Andreas Schötzau[a], Reno Frei[b,c], Marc Dangel[b], Evelyn A. Huhn[a], Andreas Widmer[b], Danielle Vuichard-Gysin[b]

[a] Department of Obstetrics and Perinatal Medicine, University Hospital Basel, Basel, Switzerland
[b] Department of Infectious Diseases and Hospital Epidemiology, University Hospital Basel, Basel, Switzerland
[c] Division of Clinical Microbiology, University Hospital Basel, Basel, Switzerland

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ABSTRACT

Objective: To compare the detection rates of vaginal-perineal cultures for group B streptococci (GBS) with the standard vaginal and rectal cultures and evaluate the diagnostic yield of vaginal-perineal vs. rectal swabs for extended spectrum β-lactamase producing Enterobacterales (ESBL-E) during the third trimester of pregnancy.

Study design: Vagino-perineal and rectal swabs were collected cross-sectionally from pregnant women between 35–37 weeks gestation and tested for the presence of GBS and ESBL-E. Accuracy of the vagino-perineal swab was compared to the combined vagino-perineal/rectal swab. Risk factors for ESBL carriage were examined. Degrees of pain, discomfort and stress related to the rectal swab were analyzed on visual analogue scales.

Results: 48 out of 250 participants (19.2%) were GBS positive. The vagino-perineal swab was positive in 44 of 48 women (91.7%) yielding a negative predictive value of 98.1%. Agreement (kappa) between the two methods was 0.95. Six out of 190 women with additional ESBL-E screening (3.2%) tested positive by rectal swab. Of these, only two had also a positive vagino-perineal swab. The rectal swab caused overall little subjective discomfort, pain or stress, as indicated by low scores indicated on the visual scales.

Conclusions: The GBS detection rate of the vagino-perineal swab was lower compared to the reference standard. However, agreement between the two screening methods was high and there were no cases of GBS neonatal sepsis in the recruited population, supporting this less invasive screening strategy. In contrast, the vaginal-perineal swab was inferior to the rectal swab for detecting ESBL-E, indicating that this less invasive method for detecting antibiotic resistant bacteria that may be potentially transferred to the neonate during labor and delivery would be inappropriate for ESBL-E screening in pregnant women. The low ESBL-E carriage rate among pregnant women likely reflects the prevalence in the general population.

Introduction

Group B Streptococcus (*Streptococcus agalactiae*, GBS) infection in the newborn can result in significant morbidity and mortality, including neonatal sepsis, pneumonia and meningitis. Prior to implementation of screening tests for maternal GBS colonization and subsequent antibiotic therapy during labor and delivery, vertical transmission to the neonate was reported in 1.8 cases per 1000 live births, with a case fatality rate of up to 50% [1]. Up to 30% of pregnant women worldwide may be colonized with GBS in the genitourinary and/or gastrointestinal tracts [2]. In Europe, the colonization rates are similar and therefore accurate detection of GBS in pregnant women for subsequent antibiotic prophylaxis during delivery is of utmost importance [3].

Recently, the perinatal transmission rate of extended spectrum beta-lactamase producing Enterobacterales (formerly *Enterobacteriaceae*, ESBL-E) from colonized mothers to their infants has been described to be as high as 35%, with mothers colonized or infected with ESBL-E being identified as the most important risk factor for subsequent colonization of their preterm infants [4]. Outcomes of ESBL-E infected neonates are often worse and outbreaks in neonatal intensive care units have been reported [5,6]. ESBL-E

* Corresponding author.
E-mail address: dorothy.huang@usb.ch (D.J. Huang).

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colonization rates in pregnant women vary from 3% to 15% depending on the geographical area [7,8]. Prevalence of ESBL-E carriage in pregnant women in Switzerland and surrounding countries is poorly described. However, these data are important to consider for potential obstetrical screening programs, to determine the potential role of antibiotic prophylaxis during delivery and guide evaluation and treatment of neonatal infection.

The current US Centers for Disease Control and Prevention (CDC) guidelines from 2010 recommend obtaining a vaginal and rectal swab to test for GBS between 35–37 weeks` gestation [9]. However, relatively small studies have shown that a vaginal-perineal specimen allows similar detection of GBS colonization with less patient discomfort. Jamie et al. found no difference in GBS detection rates between vagino-perineal and vagino-rectal swabs in a study of 200 pregnant women in the third trimester [10] and Trappe et al. showed a high agreement between vagino-perineal and a vagino-rectal swabs for the detection of GBS-colonization in 193 pregnant women [11]. Based on these studies, the Swiss Society of Gynecologists and Obstetricians (SGGG) no longer supports performance of an additional rectal swab that is still recommended by the CDC to avoid subjecting women to the unnecessary discomfort [12].

As potential pain arising from a rectal swab is usually considered mild, further justification is needed for implementing a test that may be less sensitive than the gold standard. In addition, it remains largely unknown whether this simplified screening method would suffice to detect ESLB-E carriage. So far, the optimal screening site for ESBL-E in pregnant women has not been evaluated and previous studies in pregnant women screening for ESBL-E used inconsistent approaches, including evaluation of urine samples, vaginal, perineal or rectal swabs, thereby challenging the comparability of detection rates [7,8,13]. To the best of our knowledge, there are no studies comparing two different screening sites for ESBL-E carriage in pregnant women.

Our study compared the diagnostic accuracy of the vaginal-perineal swab with the gold standard method recommended by the CDC for GBS detection. We hypothesized that the additional rectal swab does not improve the GBS detection rate justifying the SGGG recommendations. We further compared the ESBL-E detection rate of a vaginal-perineal swab to the standard rectal swab, and determined the prevalence of ESBL-E in pregnant women. As pain may be influenced by different factors including ethnicity and culture [14], we evaluated the acceptance and tolerance of the rectal swab.

Study methods

Study population

This was a cross-sectional study conducted from November 2014 to November 2016 at the outpatient obstetrics clinic of the University Hospital of Basel, a tertiary care center with approximately 2600 deliveries per year. We prospectively enrolled women attending their routine prenatal visit at 35–37 weeks of gestation and for whom screening for GBS was planned. Women who did not qualify for GBS screening according to internationally accepted guidelines (including having GBS-positive urine cultures or a previous child with neonatal GBS-sepsis) were excluded from this study. Women with preterm delivery before 37 weeks, evidence of other current urogenital infections, inability to understand the nature and execution of the study and antibiotic therapy within the last two weeks were also excluded. This study was approved by the local ethics committee of north-west Switzerland (Ethikkommission Nordwest Schweiz, EKNZ, No. 2014-087).

Women who agreed to participate were asked to read a detailed information sheet, which was available in English and German, and to sign a consent to participate form. These women were also asked about optional participation in a simultaneous study to test for colonization with ESBL-E using the same samples. Demographics and clinical data were entered into a standardized case report form.

Sample collection and microbiological analyses

Midwives and physicians were trained to correctly obtain the two swabs (Copan eSwab™ collection and transport system). For every woman, the vaginal-perineal swab was taken first, followed directly by the rectal sampling obtained with a second swab. The first swab was inserted approximately 1–2 cm past the vaginal introitus, removed again and then swabbed over the perineum. The second swab was obtained by inserting it 2–3 cm intraanally, turning it 2–3 times, and then removing it again. The specimens were sent for analysis in separate transport media.

Both the vaginal-perineal and rectal specimen were analysed for the presence of GBS. Cultures were grown in Todd-Hewitt-Broth for 24 h according to CDC guidelines for the culture of GBS, then further subcultured onto a selective chromogenic agar medium for GBS for an additional 24 h (CHROMID® Strepto B, bioMérieux, Marcy-l'Etoile, France) [9]. In the women who agreed to the additional study on ESBL-E carriage, the vagino-perineal and rectal swab specimens were further processed and incubated overnight at 37 °C in an enrichment broth (trypticase soy broth with 0.5% sodium chloride) [15], followed by inoculation onto a selective chromogenic medium for the detection of third-generation cephalosporin resistant organisms (chromID® ESBL, bioMérieux). Colony growth was identified by matrix-assisted laser desorption/ionization - time of flight mass spectrometry (MALDI Biotyper, Bruker Daltonics, Bremen, Germany). Screening for and confirmation of ESBL-E were performed using the Vitek 2® system (bioMérieux, Hazelwood, Mo, USA) and the combination disk method according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance, version 1.0, December 2013, www.eucast.org) Further details can be found in a previous publication [16].

Evaluation of perceptions during rectal sampling

Immediately after the examination, the women were asked to mark on visual analog scales the level of stress, discomfort or pain arising from the rectal swab sampling. The scales ranged from 0 to 10. We considered a score of 0 to represent no discomfort, pain or stress; scores of 0.5–3.4 were regarded as minimal discomfort, pain or stress; scores of 3.5–6.4 were considered as moderate, 6.5–9.4 as strong, and 9.5–10 as maximal discomfort, pain or stress.

Follow-up

Women who tested negative for GBS in both swabs were considered GBS negative and routine pregnancy care was continued. Women who tested positive for GBS in one or both swabs were considered as GBS positive and were given antibiotic therapy during labor and delivery according to standard guidelines. Neonates of ESBL-E positive mothers underwent screening for ESBL-E from stool culture on a case-by-case basis.

Statistical analysis

Data were entered by three persons (CG, DM and TP) into standardized case report forms (CRFs). Each CRF had a unique identifier to prevent duplicates. Data from the CRFs were automatically extracted and entered into an Excel spreadsheet

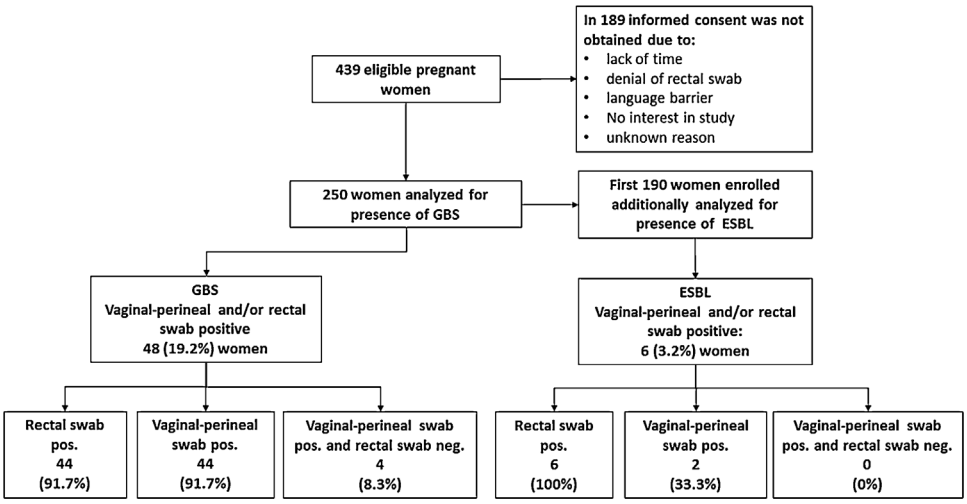

Fig. 1. Study flow chart indicating recruitment pattern and results of GBS and ESBL testing according to sampling location (rectal, vaginal-perineal, or both vaginal-perineal and rectal). As two swabs per woman were obtained, the number of culture positive swabs is not exactly equal to the total number of women testing positive (some women tested positive in both swabs).

using TeleForm software. MD and DV scrutinized the spreadsheet for outliers by visual inspection and means of descriptive analyses. Data outside reasonable limits were double-checked with the person who filled in the specific CRF and corrections were made if indicated.

We based the sample size calculation on our primary endpoint. With the assumption of a GBS prevalence of 20% in pregnant women, a two-sided type I error probability alpha of 5% and a statistical power of 80%, we calculated that between 350 and 720 patients would be necessary for a relative risk range between 0.65 and 0.75 for GBS detection with the new method [17]. Taking into account our total resources, we aimed for a total sample size of 450 women. The accuracy of the vagino-perineal swab compared to the combined vagino-perineal and rectal swab was expressed as positive and negative predicted values, as well as sensitivity and specificity along with the exact 95% confidence interval (CI). We applied Cohen's *kappa* to measure agreement between the vagino-perineal swab and the reference standard. We used absolute numbers and percentages to express the women's different perceptions as measured on analog scales. We used Fisher's exact test to compare differences in proportions and means, respectively. A p-value < 0.05 was considered as statistically significant. Analyses were performed using Excel for Windows and SPSS Version 23.

Results

During the study period, 439 eligible women were asked to participate in this study, of which 250 consented (Fig. 1). Reasons for declining to participate mainly included fear of pain and discomfort arising from the rectal sampling as well as language and comprehension barriers. The baseline characteristics of the participants are summarized in Table 1.

Overall, the prevalence of GBS was 19.2%, corresponding to 48 women detected as GBS positive in either or both swabs. The detection rate by vaginal-perineal swab alone was 17.6%. Four women with a positive vagino-perineal swab had a negative rectal swab (Table 2). The sensitivity of the simplified vagino-perineal swab compared to the combined swab for detecting GBS was 91.7% (95% CI 79.1–97.3) and specificity was 100% (95% CI 97.7–100.0). Agreement between the two methods was 0.95. The positive and negative predictive values of the vagino-perineal swab were 100% and 98.1%, respectively. All 48 women with a positive GBS swab received intrapartum antibiotic therapy. Postpartum follow-up showed that none of their newborns developed early onset GBS sepsis.

Of the 190 women consenting for the ESBL-E screening, six (3.2%) women were positive for ESBL-producing *Escherichia coli* in the rectal swab (Table 2). In the univariable analysis, none of the ESBL-E negative women had been exposed to quinolones, while one of six ESBL-E positive women had taken a quinolone antibiotic within the six months prior to study enrollment ($p = 0.032$) (Table 3). Of the six ESBL-E positive women, two (33%) also had a positive vagino-perineal swab. Sensitivity and specificity (95% CI) of the vagino-perineal swab were 33% (6–76) and 100% (97–100), respectively, compared to the rectal swab (Fig. 1). Four of six neonates of ESBL-positive mothers were tested for the presence of ESBL-E. Of these, two neonates were colonized with ESBL-E as determined by stool culture or rectal swab. Neither of them developed consecutive infection.

Evaluation of the patients` perceptions regarding the rectal swab showed that the rectal swab was well-tolerated and caused little subjective discomfort, pain or stress. The scales were filled out by nearly all study participants. Of the 246 women who filled

Table 1
Baseline characteristics of study participants (n = 250).

Age in years, mean (SD)	32.7 (4.6)
Gravidity, mean (SD)	2 (1)
Parity, mean (SD)	1 (1)
BMI before pregnancy, mean (SD)	22.5 (3.5)
Weight gain (kg) during pregnancy, mean (SD)	14.9 (7.9)
Gestational diabetes, n (%)	10 (4.0)
Arterial hypertension, n (%)	7 (2.8)
Immunosuppression, n (%)	3 (1.2)
(Sub)continent of origin, n (%)	
Europe	195 (78.0)
India/Indian subcontinent	13 (5.2)
Asia other than India	13 (5.2)
North America	5 (2.0)
Africa	5 (2.0)
Middle East	5 (2.0)
South America	4 (1.6)
Unknown	10 (4.0)
Any systemic antibiotic treatment within the last 6 months before enrollment n (%)	34 (13.6)
Amoxicillin clavulanate	16 (6.4)
Other antibiotic compound	9 (3.6)
Antibiotic compound unknown	9 (3.6)

Table 2
Overview of the women tested positive or negative for either GBS and/or ESBL-E in at least one of the two specimens.

	GBS detection		ESBL-E detection	
Case No.	vagino-perineal	rectal	vagino-perineal	rectal
1	+	+	neg.	neg.
2	+	+	neg.	neg.
3	+	+	neg.	neg.
4	+	+	neg.	neg.
5	+	+	neg.	neg.
6	+	+	neg.	neg.
7	neg.	neg.	+	+
8	neg.	+	neg.	neg.
9	+	+	neg.	neg.
10	+	+	neg.	neg.
11	+	+	neg.	neg.
12	+	+	neg.	neg.
13	+	+	neg.	neg.
14	+	+	neg.	neg.
15	+	+	neg.	neg.
16	+	+	neg.	neg.
17	+	+	neg.	neg.
18	neg.	neg.	+	+
19	+	+	neg.	neg.
20	+	neg.	neg.	neg.
21	+	+	neg.	neg.
22	neg.	neg.	neg.	+
23	neg.	+	neg.	+
24	+	+	neg.	neg.
25	neg.	neg.	neg.	+
26	+	+	neg.	neg.
27	+	+	neg.	neg.
28	+	+	neg.	neg.
29	+	+	neg.	neg.
30	+	+	neg.	neg.
31	+	+	neg.	neg.
32	+	+	neg.	neg.
33	+	+	neg.	neg.
34	+	neg.	neg.	neg.
35	+	+	neg.	neg.
36	+	+	neg.	neg.
37	+	+	neg.	neg.
38	neg.	+	neg.	neg.
39	+	+	Consent denial	
40	+	+	neg.	neg.
41	+	+	neg.	+
42	+	+	n.a.	
43	+	neg.	n.a.	
44	+	neg.	n.a.	
45	+	+	n.a.	
46	+	+	n.a.	
47	+	+	n.a.	
48	neg.	+	n.a.	
49	+	+	n.a.	
50	+	+	n.a.	
51	+	+	n.a.	
52	+	+	n.a.	

Annotation: GBS = Group B streptococci; ESBL-E = Extended Spectrum Beta-Lactamase producing Enterobacterales (formerly Enterobacteriaceae); n.a. = not applicable, those women were not asked to participate in the ESBL-E substudy.

out the scale for discomfort, 166 women (67.5%) rated discomfort arising from the rectal sampling as minimal or none (scores 0–3.4). Overall scores for stress and pain were even lower, with 88.7% (220/248) of women reporting no or minimal stress and 89.5% (221/247) reporting no or minimal pain. Only two women (0.8%) reported maximal discomfort (score 9.5–10) and none reported maximal stress or pain (Fig. 2).

Discussion

In our cohort, which had a similar GBS prevalence to that reported in the literature, the sensitivity of the vagino-perineal swab alone to detect GBS was high (91.7%) with 100% specificity. Our results are in line with the results from previous studies [10,11], thus providing additional support for the use of the modified GBS screening method as a reasonable alternative to the CDC-recommended vaginal and rectal swab [9].

In contrary, the low sensitivity of the vaginal-perineal swab to detect ESBL-E suggests that this method is inappropriate for screening pregnant women for ESBL-E. The rectal carriage rate for *E. coli* ESBL of 3.2% found in this study among healthy pregnant women is in accordance with other reported ESBL *E. coli* prevalence data from healthy Swiss travelers (2.8%), community-acquired urinary tract infections (2.2%) and clinical isolates from outpatients (5.0%) [16,18,19]. In contrast, a previous study evaluating ESBL-E carriage rates during pregnancy from perineal swabs [8] yielded a markedly lower value of 5.4% than the prevalence of 18.9% found in the corresponding general population as determined by fecal specimens [20].

The impact of routine screening for ESBL-E in a low prevalence country remains to be determined and, in view of more recent data, may rather be limited to mothers of preterm infants due to the increased risk of developing sepsis compared to term infants [4]. Such a strategy is supported by our finding of a high probability of ESBL-E detection in neonates born from colonized mothers.

Overall, post-examination scoring of subjective experiences with the rectal swab showed that the majority of women found it not to be excessively painful, stressful or uncomfortable. Few women reported strong to maximal discomfort and even fewer reported strong to maximal pain or stress. The reasoning for not performing the gold standard rectal / vaginal swab should therefore not be based solely on the belief that the rectal swab is excessively uncomfortable, painful or stressful, as our results show that it is quite well tolerated. This is in accordance with other study results [21]. This result may, however, be subjected to selection bias as fear of pain/stress was a common reason for not consenting to participate in this study. Thus, adapting a screening strategy without rectal swabs may result in higher overall acceptance rates and facilitate broader implementation, as studies have shown that the perianal swab is still less uncomfortable/painful than the rectal swab, and the agreement between the two methods is high [11].

Strengths of our study were the prospective, systematic approach with dual screening of pregnant women including the gold standards for GBS and ESBL-E detection and the standardized evaluation of mental and physical perception of the rectal swab using a widely applied scale, as well as the complete follow up of the cohort.

Our study has several limitations. First, language or comprehensive difficulties in our multicultural and often immigrant population were a significant barrier to recruitment. The Basel region, as well as Switzerland in general, has an increasingly diverse population due to high levels of immigration in recent decades. Furthermore, many women who were approached to participate in this study rejected participation due to fears of pain and discomfort resulting from the rectal swab. It may be that the women who declined to participate were generally more pain-sensitive, stressed or fearful to start with. Thus, our findings may have been influenced through a partially self-selected population.

Secondly, although the low sensitivity for ESBL-E detection of the vaginal-perineal swab is informative, the low number of ESBL-E positive women precluded us from reliably identifying determinants for maternal colonization or assessing mother-to-child transmission rates. This is, however, of relevance, since antibiotic resistance rates in the general population are on the rise and current recommendations for perinatal management regarding prevention of infection in the neonate may need to be reconsidered.

Table 3
Univariable analysis of potential risk factors for ESBL-E carriage in pregnancy.

	ESBL negative (n = 184)	ESBL positive (n = 6)	p-value
Age in years, mean (SD)	32.6 (5.0)	33.3 (6.5)	0.631
Non-European, n/total* (%)	30/177 (16.9)	3/6 (50.0)	0.073
History of recurrent UTI, n/total* (%)	12/184 (6.5)	0/6 (0.0)	1.0
Diarrheal illness during travelling, n/total* (%)	22/163 (13.5)	0/6 (0.0)	1.0
Hospital stay in foreign country, n/total* (%)	9/169 (5.3)	0/6 (0)	1.0
>1 antibiotic course during pregnancy, n/total* (%)	5/184 (2.7)	0/6 (0.0)	1.0
Quinolone treatment within the last 6 months, n/total* (%)	0/184 (0.0)	1/6 (16.7)	0.032
Amoxicillin clavulanate treatment within the last 6 months, n/total* (%)	13/184 (7.1)	0/6 (0.0)	1.0

* The total number indicates the number of women who completed the specific question.

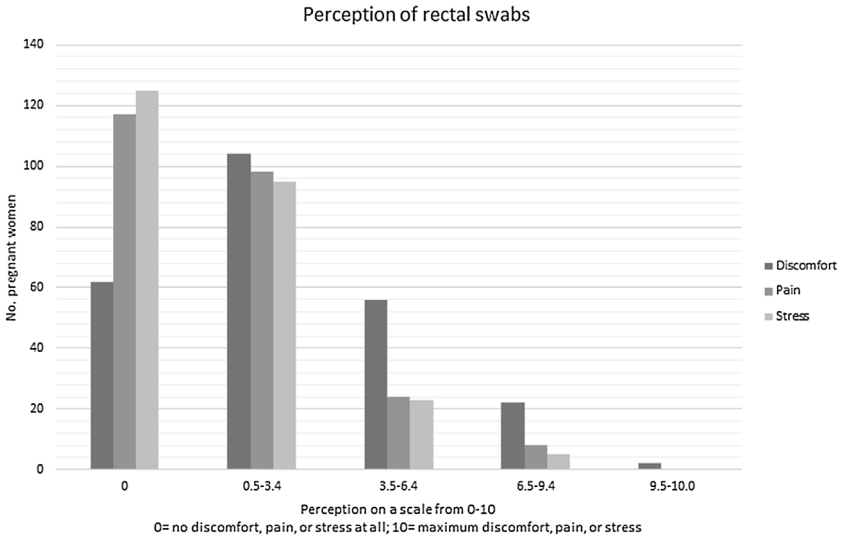

Fig. 2. Rectal swab perceptions directly following sampling. Values on a scale of 0–10 are depicted regarding discomfort (dark gray), pain (gray) and stress (light gray).

Adequate screening for GBS during pregnancy is important and colonization of the mother with GBS can have significant implications for the neonate. The diagnostic performance of the vagino-perineal swab was sufficient to safely rule out GBS carriage in pregnant women at term. We therefore conclude that this less invasive screening test, which may be generally more acceptable for women reluctant to have a rectal examination, can be continued to be used in our patient population. On the contrary, the perianal swab is inadequate for detecting ESBL-E carriage in pregnant women and therefore we would recommend using rectal swabs to evaluate for ESBL-E when testing is necessary. As antibiotic resistance is increasing and detection of resistant strains is of increasing importance, it remains to be determined in which settings prenatal screening for ESBL-E should be recommended.

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