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Antibiotic resistance pattern of extended-spectrum-beta lactamases-producing *Escherichia coli* isolated from pregnant women and their new born

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Historic

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Abstract

The incidence of healthy pregnant women carrying CTX-M-type extended-spectrum beta-lactamase (ESBL)-producing *E. coli* and their transmission to neonates is increasing worldwide. ESBL-*E coli* and especially the carriage of CTX-M-type causes early or late onset of neonatal sepsis, resulting in increased morbidity and mortality rates. Although maternal carriage and maternal-neonatal transmissions of ESBL-E have been reported in several countries, the prevalence of CTX-M-type ESBL-producing *E. coli* in pregnant women and its transmission to newborns at birth in Cameroon has not been reported yet. We describe here the carriage of CTX-M-type ESBL-producing *E. coli* pregnant women in neonatal ward of the Yaoundé gyneco-obstetric and pediatric hospital and their transmission to newborns. Among the 102 pregnant women and their newborns present in the ward, 88 (86.3%) and 75 (73.5%) *E. coli* strains were detected in rectal colonization, respectively. Antibiotic susceptibility testing of *E. coli* isolated from the mothers indicated a higher resistance rate to antibiotics of the β-lactams and sulfamide families, while the resistances to other antibiotic families (aminosides, quinolones and fluoroquinolones) were low. Comparatively, only cefotaxime (100%) showed a higher resistance rate to *E. coli* isolated from newborns. This may suggest a different source of contamination between mothers and newborns. Moreover, the rate of carriage of CTX-M-type ESBL-producing *E. coli* in pregnant mother and their newborns were 30.7 % and 14.7 %, respectively. This suggests that newborns had other colonization sources than the mothers. Indeed, multiple regression analysis indicated that newborns were exposed to CTX-M-type ESBL-producing *E. coli* from mothers and that from the hospital environment (eg. caregivers). Overall, the current investigation may provide insight on establishing an efficient therapeutic strategy against materno-neonatal and nosocomial transmission of CTX-M-type ESBL-producing *E. coli*.

1. Introduction

Antibiotic resistance is one of the greatest threats to global public health [1] (WHO, 2015). It is a natural phenomenon, but is accelerated by the inappropriate prescription of antibiotics, poor infection control practices in humans and inadequate use of antibiotics in agriculture and livestock [2]. The main characteristic of resistance is that it reduces the ability to treat common bacterial infections, leading to an increased duration of infection, an increased risk of complications and case fatality. Because of ineffective treatment due to resistance, patients remain contagious for longer, and are therefore likely to transmit infections to other individuals. Antibiotic resistance may jeopardize the progress made in the treatment of infections since the discovery of antibiotics and the contribution of these drugs to improving child survival, especially newborns in developing, low or middle income countries where more than 80% of the world population lives [3].

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It is well documented that extended-spectrum beta-lactamases (ESBL)-producing bacteria occur worldwide both at community and hospital levels [4, 5, 6]. Published data suggest that the infection incidence in pediatrics and neonatal populations is increasing [4, 7, 8, 9, 10, 11]. The consequences of the infections by ESBL-producing bacteria in pediatric are the increased morbidity (including prolonged hospital stay), increased healthcare costs, and higher mortality rates compared to non-ESBL-producing bacteria [12, 13, 14, 15]. In addition, pathologies developed upon infection with ESBL-producing bacteria among neonates, children, and pregnant/post-partum women are frequently urinary tract infections [5, 7] and bloodstream infections [6, 11, 10, 14, 16]. Among neonatal ESBL-producing bacterial infections, the most frequently isolated species are *Klebsiella pneumoniae* and *Escherichia coli* (*E. coli*) [11, 10, 17].

E. coli is a facultative aero-anaerobic bacterium commensal to the intestines of humans and other mammals [18]. Among the bacteria developing resistance to antibiotics upon infection, Enterobacteriaceae such as *E. coli* producing to β-lactamines and fluoroquinolones are particularly concerned [19]. ESBLs are enzymes produced by Enterobacteriaceae with the characteristic

of resisting to penicillin's, cephalosporin's and aztreonam but not carbapenems [20]. These enzymes are divided into several main groups [e.g., sulphydryl variable (SHV), temoneira (TEM) and cefotaximases (CTX-M)] [21, 7]. In Africa, an overall prevalence of 17% of CTX-M-type ESBL-producing-Enterobacteriaceae is observed in pregnant women, of which 5.1% are CTX-M-type ESBL-producing *E. coli* [22, 23]. The prevalence of CTX-M-type ESBL-producing *E. coli* rise from 34.7% in Ibadan, Nigeria [24] to 69.6% in Madagascar [25] among pregnant women. In Cameroon, a prevalence of 66.3 % of CTX-M type ESBL-producing *E. coli* among pregnant women has already been reported in Yaoundé [26].

According to the estimation made by Liu et al. [27], 5.9 million children under 5 die annually worldwide, of which 45.1% during the neonatal period as a result of infections due to ESBL-producing Enterobacteriaceae. The relevance of this study is justified by the fact that children shares 40% antibiotic resistance genes and 37% of the mobile genetic elements contained in his gut with their mother [28]. Thus, the digestive carriage of CTX-M-type ESBL-Enterobacteriaceae by pregnant women constitutes a major risk factor for the transmission to newborns during childbirth [29]. In order to fight against the emergence and transmission of bacterial resistances, we carried out a phenotypic characterization of CTX-M-type ESBL-producing *E coli* both in pregnant women and their newborns. In addition, we determined the transmission route to neonatal colonization and the risk factors.

2. Materials and methods

2.1 Ethical consideration

This study was approved by the "Université des Montagnes" Ethics Committee (2020/028 / UdM / PR / CIE). In addition, authorization to collect data and analyze samples from eligible patients was issued by the Yaoundé Gyneco-Obstetrics and Pediatric Hospital (YGOPH) (911 / CIERSH / DM / 2019). Before starting our study, an information letter on the objectives and progress of the investigation was given to the guarantors of women in labor and newborns. All eligible participants had given their free and informed consent and assent with signature of the guarantors. The confidentiality of the research results was respected by using a unique identification code for each participant.

2.2 Study setting and population

We carried out a cross-sectional and descriptive study between October 2019 and March 2020 at the Gyneco-Obstetrics and Pediatric Hospital in Yaoundé, the capital of Cameroon. The study population consisted of pregnant women (n=102) and their newborns from the maternity and neonatal units of the YGOPH. Sampling was consecutive and women in labor who gave their free and informed consent as well as for their newborns were included in the study. A standardized questionnaire was performed for collection of demographic information on mothers and neonates (age of the mother, age of the newborn, employment status, newborns gender).

2.3 Sample collection and bacterial isolation

Freshly emitted stools from pregnant mothers were collected in sterile co-proculture pots, while newborns first stool (meconium) emitted in a diaper was collected with a sterile spatula and both sample were stored in icebox and transported to the laboratory. At the laboratory, stools samples from mother and newborn were diluted in brain heart infusion broth (Oxoid Ltd, England). Aliquots (100 µL) of the neat sample and 10^{-2} and 10^{-4} dilutions were inoculated on to quality controlled Eosine Methylene Blue (EMB) agars (Becton Dickinson, Heidelberg, Germany) supplemented with a 1 mg/L cefotaxime and incubated at 37 °C for 24-36 hours. Each colony growing on EMB agar was subcultured on nutrient agar and then identified using the Api 20 E kit.

2.4 Biochemical identification of the bacterial isolates

The Biochemical identification was carried out on gallery Api 20E according to the recommendations of the manufacturer (Biomérieux, Marcy l'Etoile, France), which constitutes a standardized system of the identification of Enterobacteriaceae.

2.5 Antimicrobial Susceptibility testing

Antibiotic Sensitivity Testing using the disc diffusion method was performed for the identified *E. coli* isolates. This test was conducted on 18 to 24 hours bacterial pure culture obtained by streaking *E. coli* isolates on fresh nutrient agar and allowing for an overnight aerobic incubation at 37°C. From the resulting *E. coli* population, a suspension to the density of a McFarland 0.5 turbidity standard prepared in 0.9% saline was adjusted to the final opacity recommended for susceptibility tests by agar diffusion technique on Mueller Hinton. Test procedures and interpretations were done according to the standard guidelines recommended by the "Comité de l'Antibiogramme de la Société Française de Microbiologie" [30]. We used 30µg of each antibiotic disc (Oxoid Ltd, England) that included *Amoxicillin*, ticarcillin, amoxicillin + clavulanic acid, cefoxitin, cefotaxime, ceftazidin, cefepime, meropenem, gentamycin, amykacin, kanamycin, ofloxoxacin, ciprofloxacin, co-trimoxazole, nalidixic acid, and fosfomycin. *Escherichia coli* ATCC25922 from American Type Culture Collection (Manassas, Virginia, USA) was used as reference for quality control.

2.6 Detection of the ESBL-producing *E. coli* and CTX-M phenotype.

The presence of extended spectrum β-lactamases was determined by the double synergy test as recommended by the "Comité de l'Antibiogramme de la Société Française de Microbiologie" [30]. Briefly, Discs of cefotaxime, cefepime, and ceftazidime were placed around an amoxicillin/clavulanic acid (20/10 µg) disc at a distance of 30 mm (center to center). The plate was incubated at 37 °C for 18 to 24 hours and the synergy between clavulanic acid and at least one of these molecules was monitored. When synergy was observed between clavulanic acid and cefotaxime, the strain was said to produce CTX-M type ESBLs.

2.7 Data management and statistical analysis

Extracted data were recorded in Microsoft Excel 2016 spreadsheet and the variables calculated were presented as percentage. The statistical analysis of all data was done using the STATVIEW Statistical Package version 5 (SAS University Edition, SAS Institute Inc., Cary, USA). The antibiotic susceptibility and rate of carriage of ESBL-producing *E. coli* by neonates and mothers was reported as the number of infections per 100 positive patients. Multivariate analysis was performed using logistic regression in order to identify risk factors associated with intestinal colonization of

neonates and mother with ESBL-producing *E. coli*. In addition, logistic regression was used to determine the risk factors for maternal-neonatal transmission of *E. coli* strains. The multivariate results were reported using unadjusted odds ratios (ORs) and 95% confidence interval (95% CI), and the logistic regression results expressed as adjusted odds ratios (aORs) and 95% CI. The significance level was set at a P-value less than or equal to 0.05.

3. Results

3.1 Demographic Characteristics and bacterial isolates

All of the 102 pregnant women included in this study were living in different Yaoundé neighborhood, indicating that HGOPY is the most requested hospital structure in the city of Yaoundé for childbirth. More than half of these women were unemployed (n=62, 60.8%) while 40 (39.2%) had a job. The average age of the pregnant women was 28 with a minimum age of 17 years and a maximum age of 45 years. None of the mother gave birth to more than one baby; therefore the number of newborns was identical to that of mother (102 newborn). Our population of newborns was mainly made up of females (n=54; 52.9%), with 48 males (47.1%) giving a sex ratio of 0.88. The average age of the newborns was 6 hours with a minimum of 2 hours and a maximum of 14 hours.

The screening of the fecal flora of 102 pregnant women resulted in 102 positive culture, indicating the presence of one bacteria strain per stool examined. In total, bacteria susceptibility to cefotaxime allowed the isolation of 102 strains. The biochemical identification test using the Api 20 E gallery showed that of 102 bacterial strains isolated in pregnant women, 88 (86,3%) were *E. coli*. Moreover, the other bacteria strain identified bacteria were *Klebsiella oxytoca* (n=12, 11,8%) and *Salmonella* spp. (n=2, 1.9%) (Table 1).

Table 1 : Microbiological profile of the bacterial isolates

Bacteria isolates	Pregnant women n (%)	Newborns n (%)
Escherichia coli	88 (86,3)	75 (73,5)
Klebsiella oxytoca	12 (11,8)	16 (15,7)
Salmonella spp.	02 (1,9)	0 (0)
Serratia liquefaciens	0 (0)	08 (7,8)
Colobacter kosei	0 (0)	03 (2,9)

The bacterial susceptibility to cefotaxime allowed the isolation of 99 (97%) bacterial isolates out of 102 rectal swabs tested. In newborns rectal swabs tested, biochemical identification of bacterial isolates indicated that they were colonized by *E. coli* (n=75, 73.5%), *Klebsiella oxytoca* (n=16, 15.7%), *Serratia liquefaciens* (n=8, 7.8%) and *Colobacter kosei* (n=3, 2.9%).

3.2 Characterization of *E. coli* isolates from pregnant women and newborns

All *E. coli* isolates whether from pregnant mothers (n=88) or from newborns (n=74) were characterized by the disc diffusion method using 8 antibiotics of the ß-lactam family (three penicillin's, four cephalosporin's and one carbapenems) (Table 2). The results highlight a higher resistance rate of *E. coli* isolated from pregnant women to antibiotics (amoxicillin, 84.1%; Amoxicilline + acide clavulanique, 71.5%; Ticarcilline, 100%) of the penicillin family. In contrast, *E. coli* isolated from newborns showed a mild resistance rate to the same antibiotics (amoxicillin, 34.7%; Amoxicilline + acide clavulanique, 36%; Ticarcilline, 38.7%). Likewise, *E. coli* isolated from pregnant women also displayed a higher resistance rate to the antibiotics of the cephalosporin's family. In newborns, a higher resistance rate to the antibiotics of the cephalosporin's family was only observed with cefotaxime (100%), which is a third generation cephalosporin. *E. coli* strains isolated from pregnant women also showed a higher resistance rate to meropenem (67%), the only carbapenem tested in this study, In contrast, *E. coli* isolated from newborns showed a very low resistance rate (6.7%) to meropenem (Table 2).

We also tested the susceptibility of *E. coli* isolated from both pregnant women and newborns feces to other antibiotic families (Table 3). Results of these tests indicated that the *E. coli* strains from pregnant women were highly resistant to the antibiotic of the sulfamides (Cotrimoxazole, 83.1%), quinolones (nalidixic acid, 67%) and fluoroquinolones (Ciprofloxacin, 60.2; Ofloxacin, 60.2%) families. In addition, *E. coli* from pregnant women showed resistance to only one (Gentamycin, 67%) out of the 3 antibiotics of the aminosides family (Table 3). In contrast, *E coli* from newborns showed an extremely mild resistance rate to antibiotics of the sulfamides, quinolones, fluoroquinolones, and aminosides families (Table 3). Moreover, when *E coli* from pregnant mothers and newborns were tested for antibiotic susceptibility using a novel class of antibacterial drugs (Fosfomycin) with a chemical structure unrelated to other known antibiotics, both showed a mild resistance rate (Table 3).

3.3 Frequency of CTX-M type ESBLs among maternal and neonates *E. coli* isolates

To further characterize the maternal and newborn strains of *E. coli* isolates obtained in this study, we decide to determine the frequency of CTX-M-type ESBLs phenotype. Therefore, we used the disc diffusion test and a panel of antibiotics for this purpose. Of the 88 maternal *E. coli* isolates obtained in the course of this study, 27 were identified as CTX-M type ESBLs giving a frequency of 30.7%. Likewise, we identified 11 CTX-M type ESBLs in a total of 75 newborn *E. coli* isolates yielding a carriage rate of 14.7%.

3.4 Risk factors for maternal carriage of CTX-M type ESBLs *E. coli*

To determine the risk factors associated to maternal carriage of CTX-M type ESBLs E. coli, parameters such as being employee, primiparous, breeding at home, Farming, and Intrapartum antibiotic therapy were considered. These parameters were added into the multiple logistic regression analysis and the results revealed that being employee and primiparous, as well as practicing agriculture (farming) was not a risk factor for maternal carriage of CTX-M-type ESBLs *E. coli*. In contrast, having a small breeding (OR = 8.03; 95% CI= 2.05-31.47; p= 0.002) and intrapartum antibiotic therapy (OR = 3,72; 95% CI= 1,02-24,17; p= 0.012) were main risk factors for CTX-M-type ESBLs *E. coli* Carriage (Table 4).

Table 2 : Susceptibility of maternal and newborn *E. coli* isolates to antibiotics of ß-lactams family

Antibiotics Family	Antibiotics	Maternal resistance n (%)	Newborn resistance n (%)
Penicillin	Amoxicillin	74 (84,1)	26 (34,7)
	Ticarcillin	88 (100)	29 (38,7)
	Amoxicillin + clavulanate	63 (71.6)	27 (36)
Cephalosporin	Cefoxitin	47 (53.4)	05 (6.7)
	Cefotaxime	88 (100)	75 (100)
	Ceftazidime	74 (84.1)	35 (46.7)
	Cefepime	66 (75)	19 (25.3)
Carbapenem	Ertapenem	59 (67)	05 (6,7)

Table 3 : Susceptibility of maternal and newborn *E. coli* isolates to other antibiotic family

Antibiotic family	Antibiotis	Maternal resistance n (%)	Newborn resistance n (%)
Aminosides	Gentamycin	59 (67)	19 (25.3)
	Kanamycin	41 (46.6)	11 (14.7)
	Amikacin	29 (33.1)	05 (6.7)
Quinolones	Nalidixic acid	59 (67)	05 (6.7)
Fluoroquinolones	Ciprofloxacin	53 (60.2)	16 (21.3)
	Ofloxacin	53 (60.2)	16 (21.3)
Sulfamides	Cotrimoxazole	73 (83.1)	08 (10.7)
New antibiotic class	Fosfomycin	30 (34.1)	13 (17.3)

Table 4 : Multiple regression logistic analysis for risk factors associated with intestinal carriage of CT-M-type ESBLs *E. coli* by pregnant women

Variables	Size/Percentage N= 102 (100%)	CT-M type ESBLs *E. coli* in pregnant women		P-value
		OR	95% CI	
Employee				
No	62 (60,8)	1		
Yes	40 (39,2)	3,35	[0,82 ; 13,62]	0,09
Primiparous				
No	59 (57,8)	1		
Yes	43 (42,2)	0,42	[0,02 ; 9,59]	0,58
Small breeding				
No	72 (70,6)	1		
Yes	30 (29,4)	8,03	[2,05 ; 31,47]	**0,002****
Farming				
No	65 (63,7)	1		
Yes	37 (36,3)	0,78	[0,16 ; 3,84]	0,76
Intrapartum antibiotic therapy				
No	93 (91,2)	1		
Yes	09 (8,8)	3,72	[1,02 ; 24,17]	**0,012****

OR: Odd ratio; 95 % IC: 95% confidence interval. **Significant.

3.5 Risk factors associated with ESBL-producing *E. coli* isolates

To determine the risk factors associated to the transmission of CTX-M type ESBLs *E coli* from mother to newborn, parameters such as maternal intestinal carriage of CTX-M type ESBLs *E. coli*; previous hospitalization, cesarean, and newborn gender were first examined in an univariate analysis for selection (Table 5). The parameters were all selected for a further analysis in a multiple regression logistic analysis, since each had a *p*-value equal or less than 0.2 (Table 6). These selected parameters analyzed in a multiple logistic regression setting revealed that newborn gender parameter was not a risk factor for materno-neonate transmission of CTX-M type ESBL *E. coli*. In contrast, parameters such as maternal carriage of CTX-M type ESBL *E. coli* (OR = 6,45; 95% CI= 1,09-37,98; *p*= 0.04) and cesarean (OR = 5,69; 95% CI= 2,06-44,43; *p*= 0.03) were significant risks factors associated with the materno-neonate transmission of CTX-M type ESBL-producing *E. coli*.

Table 5: Univariate analysis of parameters for materno-neonate transmission of CTX-M-type ESBL E. coli strains

	Total number of sample	Presence of CTX-M-type ESBL *E. coli* in newborn meconium		P-value
	N=102 (100%)	Yes, n (%)	No, n (%)	
Digestive presence of ESBL CTX-M E. coli in the parturient				
No	61(69,3)	2(3,3)	59(96,7)	
Yes	27(30,7)	5(18,5)	22(81,5)	0,01
Delivery route				
Normal delivery	98(96,1)	7(7,2)	91(92,9)	
Caesarean	04(3,9)	1(25)	3(75)	0,001
Gender				
Male	48(47,1)	1(2,6)	47(97,9)	
Female	54(52,9)	5(9,3)	49(90,7)	0,21

Table 6: Determination of risk factors for materno-neonate transmission of CTX-M-type ESBL-producing E. coli by multiple regression analysis.

	OR	IC à 95%	*p*-value
Digestive carriage of ESBL CTX-M *E. coli* by the mother during childbirth			
No	Ref.		
Yes	6,45	[1,09; 37,98]	0.04
Newborn gender			
Female	Ref.		
Male	0,2	[0,02; 2,06]	0.18
Delivery route			
Normal delivery	Ref.		
Caesarian	5,69	[2,06; 44,43]	0,03

4. Discussion

The current study aimed to determine the frequency of intestinal carriage of CTX-M-type ESBL-producing *E. coli* strains in pregnant women and their newborns and identify risk factors associated with the carriage of these bacteria and determine possible risk factors for the neonatal colonization. We found that *E. coli* was the main bacteria strain present in both mother and newborns feces. This is in agreement with the data published by Ebongue *et al.* [31], who found that *E coli* was the most abundant bacteria that are found in patient's intestine. We also found that *E. coli* isolated from the mother's feces were highly resistant to antibiotics of the β-lactams family in addition to antibiotics of the sulfamides, quinolones and fluoroquinolones families. In fact, β-lactams are among the drugs that are the most prescribed in hospitals to pregnant patients and are easily available from street pharmacies. In contrast to mothers, *E coli* from neonate's feces showed a very low resistance rate to all antibiotic families tested, except cefotaxime. The difference in the resistance between *E. coli* from mothers and newborns may indicate that the mother is not the only source of contamination for newborns, rather the hospital environment may also contribute to the contamination.

In this study, the prevalence of CTX-M-type ESBL-producing *E. coli* carriage by mothers was higher (30.7%), which is consistent with the results of other reports in Niger [32] and Senegal [33], but was very low compared to the one reported in Ngaoundéré, Cameroon [34]. However, 14.7% of ESBL-producing *E. coli* strains isolated from newborns were CTX-M type, which is lower compared to the rate observed in the population of mothers. The difference in

the resistance rate between CTX-M-type ESBL-producing *E. coli* from mothers and newborns indicates that the mother is not the only contamination source for newborns. Therefore, others sources of contamination like the hospital environment may be considered since caregivers are the first to have contact with newborns at birth. Anyway, the better understanding of the sources of newborns contamination during childbirths is critical to establishing effective control measures to limiting infection and the spread of infectious diseases. Hence, to understand the dynamics of newborns infection by CTX-M-type ESBL-producing *E. coli* and estimate the part of newborns colonization that may be attributed to mother-to-child transmission, it is necessary to eliminate other possible transmission sources such as the hospital environment and family members of newborns

This study demonstrates that drug resistant *E. coli* exists as colonizers in the digestive tract of pregnant women. Multiple logistic regression analysis showed that small breeding practice by pregnant women and the intrapartum antibiotic therapy were the main risk factors for carriage of CTX-M-type ESBL-producing *E. coli*; which is in agreement with other findings [35, 36, 37].

Multivariate logistic regression confirmed that the digestive carriage of CTX-M-type ESBLs *E coli* by the mother in the delivery room represents a risk factor for digestive carriage of CTX-M-type ESBLs *E coli* for her newborn. These findings are similar to those made by Chan et al. [38] who found that maternal colonization by ESBL-producing Enterobacteriaceae is likely to play an important role in colonization and/or infection of newborns during childbirth. In addition, other investigations also claim that during childbirth, there is a massive colonization of the newborn with bacteria due to exposure to maternal microbiota (vaginal, rectal and skin) [39, 40, 41]. The composition and development of the newborn's microbiota is therefore influenced by its mother's microbiota but also by the hospital and community environment. Moreover, we also found Caesarean section as risk factor for newborn infection by CTX-M-type ESBL-producing *E. coli*. In this condition, the newborn is more likely to be infected by *E. coli* from the hospital environment (caregivers), rather than the mother microbiota. It is important to indicate that it has already been shown that cesarean birth deprives newborns of exposure to maternal flora (vaginal and intestinal) and this could influence the development of the newborn's microbiota [42, 43].

Conclusion

In summary, we show that both mothers and their newborns are colonized by *E. coli* and other bacteria species. Moreover, the resistance rate of E. coli isolated from mother is completely different from that isolated from newborn. This was also true when comparing the rate of CTX-M-type ESBL-producing *E. coli* isolates of mothers and their newborns. We therefore concluded from those results that the sources of newborns bacterial colonization are not uniquely the mother's microbiota, but also the hospital environment. We also found that farming and intrapartum use of antibiotics were major parameters that influence carriage of CTX-M-type ESBL-producing *E. coli* by pregnant women. In addition, major risk factors for colonization of newborn during delivery were the mother microbiota and practicing farming by mothers. The actual data may be used to establishing an efficient therapeutic strategy against newborns infections during delivery

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