

Early-Onset Infection Caused by *Escherichia coli* Sequence Type 1193 in Late Preterm and Full-Term Neonates

Célie Malaure,¹ Guillaume Geslain,¹ André Birgy, Philippe Bidet, Isabelle Poilane, Margaux Allain, Mathilde Liberge, Nizar Khattat, Paola Sikias, Stéphane Bonacorsi



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Learning Objectives

Upon completion of this activity, participants will be able to:

- Assess the prevalence and complications of early-onset neonatal sepsis (EOS)
- Compare characteristics of *Escherichia coli* isolates from EOS and healthy vaginal carriage in the current study
- Analyze characteristics of sequence type 1193 EOS in the current study
- Evaluate similarities and differences in *E. coli* EOS among preterm and term infants in the current study

CME Editor

Tony Pearson-Clarke, MS, Technical Writer/Editor, Emerging Infectious Diseases. *Disclosure: Tony Pearson-Clarke, MS, has no relevant financial relationships.*

CME Author

Charles P. Vega, MD, Health Sciences Clinical Professor of Family Medicine, University of California, Irvine School of Medicine, Irvine, California. *Disclosure: Charles P. Vega, MD, has the following relevant financial relationships: served as an advisor or consultant for Boehringer Ingelheim; GlaxoSmithKline; Johnson & Johnson Services, Inc.*

Authors

Célie Malaure, PharmD; Guillaume Geslai, MD; André Birgy, PharmD, PhD; Philippe Bidet, MD, PhD; Isabelle Poilane, PharmD; Margaux Allain, PharmD; Mathilde Liberge, PharmD; Nizar Khattat, MD; Paola Sikias, MD; Stéphane Bonacorsi, MD, PhD.

Using whole-genome sequencing, we characterized *Escherichia coli* strains causing early-onset sepsis (EOS) in 32 neonatal cases from a 2019–2021 prospective multicenter study in France and compared them to *E. coli* strains collected from vaginal swab specimens from women in third-trimester gestation. We observed no major differences in phylogenetic groups or virulence profiles between the 2 collections. However, sequence type (ST) analysis showed the presence of 6/32 (19%) ST1193 strains causing EOS, the same frequency as in the highly virulent clonal group ST95. Three ST1193 strains caused meningitis, and 3 harbored extended-spectrum β -lactamase. No ST1193 strains were isolated from vaginal swab specimens. Emerging ST1193 appears to be highly prevalent, virulent, and antimicrobial resistant in neonates. However, the physiopathology of EOS caused by ST1193 has not yet been elucidated. Clinicians should be aware of the possible presence of *E. coli* ST1193 in prenatal and neonatal contexts and provide appropriate monitoring and treatment.

Extraintestinal pathogenic *Escherichia coli* and *Streptococcus agalactiae* are bacterial pathogens that commonly cause early-onset neonatal sepsis (EOS) in industrialized countries. EOS is confirmed by a blood or cerebrospinal fluid culture positive for the causative pathogen ≤ 72 hours after birth. EOS incidence is $\approx 1/1,000$ live births (1,2); 10% of cases are complicated by meningitis, which can lead to neurologic sequelae in up to 50% and death in 10% of cases in industrialized countries (3).

EOS caused by *S. agalactiae* can be prevented by peripartum antimicrobial prophylaxis but not EOS caused by *E. coli*. *E. coli* strains that cause neonatal meningitis have been well characterized, but *E. coli* strains that cause EOS less so (4,5). Neonatal meningitis *E. coli* strains belong mainly to phylogenetic group B2/sequence type complex (STc) 95 (6) and are frequently O18:K1, O1:K1, O83:K1, or O45_{S88}:K1 serotypes (7,8). Most STc95 strains are distributed worldwide and still largely susceptible to antimicrobials (9). However, other strains that can cause EOS, notably in preterm

neonates, might be resistant to probabilistic antimicrobial therapy. In a recent study in Israel (10), maternal carriage rates of extended-spectrum β -lactamase (ESBL)-producing *E. coli* were 17.5% for mothers and 12.9% for preterm neonates; in China, ESBL accounted for up to 48% of *E. coli* infections in neonates (11).

Characterizing *E. coli* strains that cause EOS would constitute a critical first step towards better understanding the pathophysiology of this condition and developing potential preventive strategies. We conducted a prospective study covering a large area in France to estimate annual incidence and pathogen distribution of EOS in neonates born at ≥ 34 weeks of gestation during 2019–2021 (12). In total, we recorded 107 cases of bacteremia including 35 caused by *E. coli*, 15 (incidence 0.89/1,000 births) in late-preterm and 20 (0.06/1,000 births) in full-term infants. We prospectively recorded data on maternal and infant demographics, maternal antimicrobial therapy, peripartum antimicrobial prophylaxis, and outcomes (12). We aimed to use whole-genome sequencing (WGS) to characterize *E. coli* strains that caused EOS in cases from this prospective study and stratify results according to these data. In addition, we determined to compare those strains to *E. coli* strains obtained from cultures from vaginal swabs collected to screen for *S. agalactiae* carriage at 34–38 weeks of gestation from woman with newborns who had no history of EOS. The ethics committee institutional review board (Ramsay Santé Recherche & Enseignement, IRB00010835) authorized the study (12).

Methods

Bacterial Strains

We recorded 35 cases of EOS caused by *E. coli* during a prospective study in 81 maternity wards of the Ile de France area during 2019–2021 (12). Thirty-two *E. coli* isolates were sent to the National Reference Center in Robert-Debré Hospital to be further characterized. For comparison with the isolates from the

Author affiliations: *Escherichia coli* National Reference Center, Robert-Debré University Hospital, Assistance Publique–Hôpitaux de Paris, Paris, France (C. Malaure, A. Birgy, P. Bidet, S. Bonacorsi); Paediatric Intensive Care Unit, Robert-Debré University Hospital, Assistance Publique–Hôpitaux de Paris, Paris (G. Geslain); Paris Cité University, Paris (G. Geslain, A. Birgy, P. Bidet, S. Bonacorsi); Avicenne University Hospital, Assistance Publique–Hôpitaux de Paris, Bobigny, France (I. Poilane); Louis Mourier University Hospital, Assistance Publique–Hôpitaux de

Paris, Colombes, France (M. Allain); Saint Louis University Hospital, Assistance Publique–Hôpitaux de Paris, Paris (M. Liberge); Neonatal Care Unit, Robert-Debré University Hospital, Assistance Publique–Hôpitaux de Paris, Paris (N. Khattat); Hôpital Privé d'Antony, Ramsay Santé, Antony, France (P. Sikias)

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[†]These authors contributed equally to this article.

Table 1. Characteristics of mothers and their newborns with early-onset sepsis caused by *Escherichia coli* strains, France*

Case ID	Birth city†	Pregnancy term, wk	Prepartum antimicrobial‡	Meningitis§	Serotypes¶	FimH type	ST (STc)#	ESBL
APIMF52	Pontoise	37	–	–	O18:K1	fimH15	95	–
APIMF53	Antony	38	–	–	O13:K1	fimH21	357	–
APIMF54	Paris (Robert Debre)	35	+	–	O7:K5	fimH27	93 (168)	–
APIMF56	Orsay	41	+	–	O84	fimH38	2040	–
APIMF57	Clamart	40	+	–	O8	fimH32	58 (155)	–
APIMF58	Clichy	36	+	–	O18:K5	fimH27	14	–
APIMF59	Paris (Necker)	36	–	–	O25:K5	fimH30	131	+
APIMF60	Paris (Clinique Bleuets)	37	+	+	O75:K1	fimH64	1193 (14)	+
APIMF63	Quincy Sous Senart	39	–	–	O2:K1	fimH34	10	–
APIMF67	Mantes-La-Jolie	39	–	–	O18:K1	fimH107	95	–
APIMF68	Paris (Pitie)	40	–	–	O2:K1	fimH27	95	–
APIMF69	Saint Cloud	35	–	–	O18:K1	fimH15	95	–
APIMF70	Saint Denis	40	–	–	O25:K1	fimH41	59	–
APIMF71	Paris (Trousseau)	37	–	–	O7:K1	fimH1	80 (568)	–
APIMF72	Aulnay	36	–	–	O1:K1	fimH41	95	–
APIMF73	Villeneuve Saint-Georges	34	+	–	O75:K1	fimH64	1193 (14)	+
APIMF76	Colombes	41	–	–	O75:K1	fimH64	1193 (14)	–
APIMF77	Nogent Sur Marne	41	–	–	O17/O77:K52	Unknown	394	–
APIMF78	Coulommiers	41	–	+	O75:K1	fimH64	1193 (14)	–
APIMF79	Longjumeau	38	–	–	O6:K23	fimH103	73	–
APIMF80	Eaubonne	38	–	–	O4:K96	fimH5	12	–
APIMF81	Jossigny	34	–	–	O75:K5	fimH27	14	–
APIMF82	Meaux	34	+	–	O25:K5	fimH28	2279 (131)	–
APIMF83	Saint-Maurice	39	+	–	O8	fimH29	58 (155)	–
APIMF84	Creteil	39	+	–	O15:K96	fimH30	69	–
APIMF85	Arpajon	41	–	–	O4:Ku	fimH8-like	12	–
APIMF87	Paris (Trousseau)	35	–	+	O7:K1	fimH44	62	–
APIMF88	Marne La Vallee	36	+	+	O7:K1	fimH44	62	–
APIMF89	Creteil	36	+	+	O75:K1	fimH64	1193 (14)	+
APIMF90	Levallois Perret	36	+	–	O75:K1	fimH64	1193 (14)	–
APIMF91	Melun	34	–	–	O1:K1	fimH41	59	–
APIMF92	Beaumont Sur Oise	40	+	+	O18:K1	fimH15	95	–

*ESBL, extended spectrum β -lactamase; FimH, type 1 fimbriae D-mannose specific adhesin; ID, identification; Ku, unknown serogroup capsular; +, positive for condition; –, negative for condition.

†For Paris birthplaces, name of hospital where born is indicated in parentheses.

‡Amoxicillin was the only antimicrobial prescribed within 3 days before labor.

§Early onset neonatal meningitis.

¶O antigen predicted with SerotypeFinder 2.0 and serogroup capsular predicted by the Center for Genomic Epidemiology (<https://genomicpidemiology.org>).

#Sequence type complex (STc) indicated in parentheses if different from ST number.

Ile de France study, we included 50 *E. coli* isolates obtained from cultures from vaginal swabs collected from 4 maternity wards to screen pregnant woman for *S. agalactiae* carriage at 34–38 weeks of gestation. We found healthy vaginal carriage (HVC) among all; that is, none of the infants of the pregnant

women from the *S. agalactiae* screening developed EOS caused by *E. coli*.

Antimicrobial Susceptibility Testing and Phenotypic Characterization

We determined antimicrobial susceptibility of the *E. coli* strains using disk diffusion on Mueller-Hinton agar plates (bioMérieux, <https://www.biomerieux.com>), as recommended by Comité de l'Antibiogramme de la Société Française de Microbiologie (<https://www.sfm-microbiologie.org>) guidelines. We defined ESBL production by synergy between clavulanic acid and ≥ 1 extended-spectrum cephalosporin or aztreonam.

Molecular Characterization

We performed WGS on 82 isolates, 32 described elsewhere (12) and 50 from the HVC/*S. agalactiae* screening. We extracted bacterial genomic DNA using the DNeasy UltraClean Microbial Kit

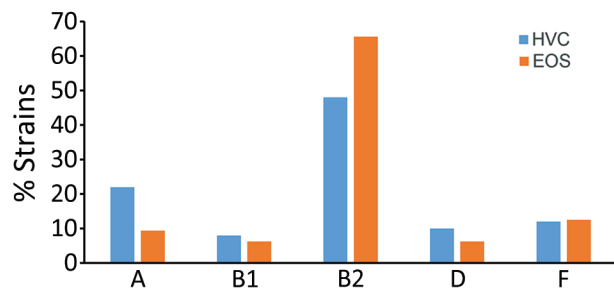


Figure 1. Phylogroup distribution among 32 EOS *Escherichia coli* strains from neonates and 50 HVC strains, France. No significant difference was observed in each group. EOS, early-onset neonatal sepsis; HVC, healthy vaginal carriage.

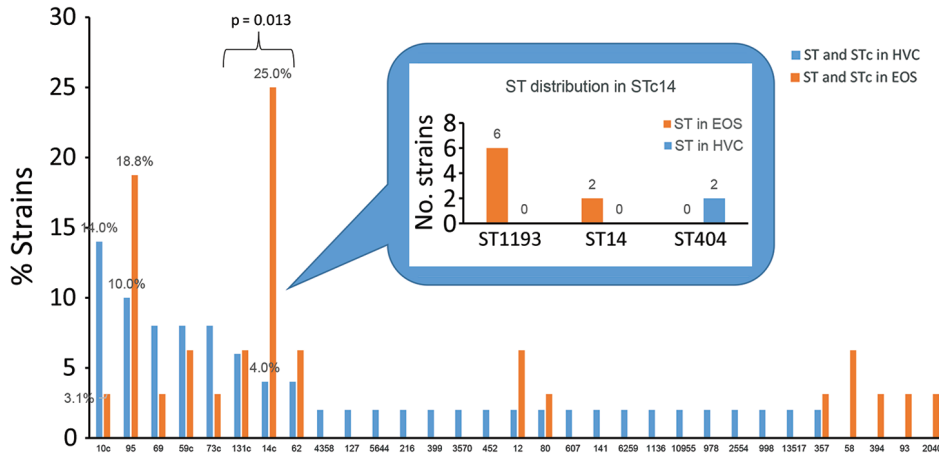


Figure 2. ST and STc distributions of EOS neonate and HVC *Escherichia coli* strains, France. STc14 distribution is detailed. STc10 includes ST10, ST13795, ST6826, and ST13957; STc59 includes ST59, ST415, and ST13796; STc11 includes ST73 and ST355; STc131 includes ST131 and ST2279. EOS, early-onset neonatal sepsis; HVC, healthy vaginal carriage; ST, sequence type; STc, ST complex.

(QIAGEN, <https://www.qiagen.com>) and prepared libraries using Nextera Flex/DNA Prep library kits (Illumina, <https://www.illumina.com>) as specified by the manufacturers. We performed sequencing using 2 × 150 bp MiniSeq technology (Illumina) and assembled models using SPAdes (<https://github.com/ablab/spades>). We estimated quality of sequencing data using standard metrics, including N50 and mean coverage (Appendix, <https://wwwnc.cdc.gov/EID/article/30/1/23-0851-App1.pdf>). We determined phylogenetic groups, serotypes, fimH type, sequence type (ST), and STcs (which regroup all STs of ≤1 allele difference), whole-genome multilocus sequence typing (MLST), and hierarchical clustering of core genome MLST using Enterobase (<https://enterobase.warwick.ac.uk>) (13). We used the Center for Genomic Epidemiology website (<https://genomicepidemiology.org>) to search for resistance and virulence genes. We also used a local BLAST with a collection of virulence genes as described elsewhere (14). We used Fisher exact analysis for statistical comparisons among groups.

Results

Bacterial Collection and Demographic and Clinical Features of Patients

We studied 82 *E. coli* isolates. Birth locations of the neonates within Ile de France were diverse (30 different locations among 32 EOS case-patients). Babies were delivered at full term (≥37 weeks of gestation) in 59% (19/32) and preterm (<37 weeks of gestation) in 41% (13/32) of cases. In 6 (31%) cases from the full-term group and 7 cases (54%) from the preterm group, mothers received antimicrobial treatment ≤3 days before labor. We observed 6 cases of meningitis, 3 each from the full-term and preterm neonate groups (Table 1).

Diversity and Phylogenetics of EOS and HVC

***E. coli* Strain Collections**

Five of 7 major *E. coli* phylogroups—A, B1, B2, D, and F, but not C or E—were represented in similar proportions in both the Ile de France study and vaginal swab collections (p>0.05). The exceptions to this trend were phylogroup A being more common in vaginal swab (22%) than EOS (9.4%) isolates and group B2 more common in EOS (65.6%) than vaginal swab (48%) isolates (Figure 1). Among the 3 most frequent ST/STc variants in our study, STc10 (phylogroup A) was present in more HVC strains, whereas ST95 and STc14 (phylogroup B2) were more common in EOS strains. The imbalance was striking for STc14, which was present in 25% of EOS strains but only 4% of HVC strains (p = 0.01) (Figure 2). STc14 isolates included 6 ST1193, 2 ST14, and 2 ST404. Of note, the 6 ST1193 isolates were found exclusively in the EOS collection.

Virulence and Antimicrobial Resistance

We observed no significant difference in distribution of virulence factors between the EOS and HVC strain

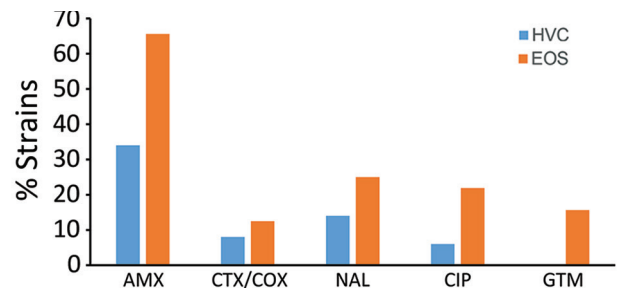


Figure 3. Antibiotic resistance rates among EOS neonate and HVC *Escherichia coli* strains, France. AMX, amoxicillin; CIP, ciprofloxacin; CTX/COX, cefotaxime/ceftriaxone; EOS, early-onset neonatal sepsis; GTM, gentamicin; HVC, healthy vaginal carriage; NAL, nalidixic acid.

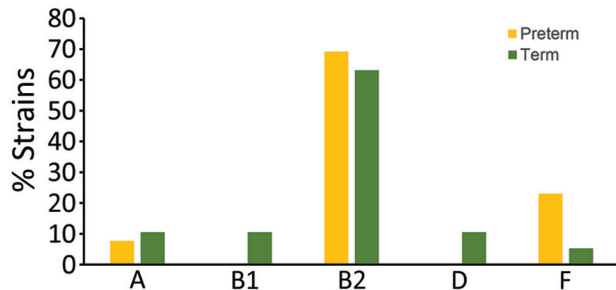


Figure 4. Phylogroup distributions according to birth term among 32 neonates with early-onset sepsis, France. EOS, early-onset neonatal sepsis.

collections, except for genes encoding the K1 capsule, which were present significantly more in the EOS collection (Appendix Table 1). In contrast, antimicrobial resistance differed markedly between collections (Figure 3). Aminopenicillin resistance was ≈ 2 times higher among EOS (65.6%) than HVC (34%) collection strains ($p = 0.007$); ESBL was present in 12.5% of EOS and 8% of HVC strains ($p > 0.05$). Resistance to fluoroquinolone and gentamicin were also more common among EOS strains (Figure 3).

We examined the distribution of phylogenetic groups and ST/STc frequency among EOS strains stratified by gestational term of newborns. Differences in rates of B2 phylogroup strains in the 2 subpopulations (69% in preterm, 63% in full-term neonates) were not statistically significant (Figure 4). STc14 (ST14/ST1193) was > 2 times as frequent in the preterm (38.5%) as the full-term subpopulation (15.8%), but the difference was not statistically significant ($p > 0.05$). Distribution of ST95, the second most frequent ST, was similar between preterm (15.4%) and full-term (21.1%) subpopulations (Figure 5). There were more mothers with STc14 *E. coli* isolates (5/13 [38.5%]) among those who received antimicrobial therapy ≤ 3 days before delivery than those who did

not (3/19 [15.8%]) ($p > 0.05$) (Figure 6). In contrast, there were fewer ST95 isolates among mothers receiving prenatal antimicrobial therapy (1/13 [7.69%]) than those receiving no therapy (5/19 [26.32%]) ($p > 0.05$).

Main Features of EOS Caused by ST1193 *E. coli* and Characterization of Isolates

All 6 ST1193 EOS strains were isolated from different maternity hospitals. Half (3/6) of neonates with ST1193 EOS were born at full term. Three neonates had meningitis, 2 full-term and 1 preterm. Four (67%) mothers with ST1193 strains received prenatal antimicrobial therapy compared with nine (35%) for the non-ST1193 strains ($p > 0.05$) (Table 1; Figure 6). All strains were resistant to fluoroquinolones, 3 were resistant to azithromycin, and 3 others harbored an ESBL phenotype (Table 2). All strains were lactose nonfermenters (data not shown).

We assessed presence of putative virulence factors among the 6 ST1193 isolates (Table 2; Appendix Table 2) and identified presence of factors with a significant difference ($p < 0.05$) among ST1193 compared with non-ST1193 strains: adherence protein *Iha*, colicin Ia immunity protein *Imm*, major pilin subunit *PapA_F43*, plasmid-encoded enterotoxin *SenB*, serine protease *Sat*, vacuolating autotransporter toxin *Vat*, and Type 1 fimbrin D-mannose specific adhesion 64.

Three strains harbored ESBL phenotypes contained the β -lactamase-encoding genes *bla*_{CTX-M-15} and *bla*_{OXA-1} associated with the *aac(6')-Ib-cr* genes, and 3/6 strains harbored the *mph(A)* gene (macrolide 2'-phosphotransferase), which inactivates macrolides, reinforcing observed phenotypic resistance to azithromycin. None of the non-ST1193 strains carried that gene. One strain was resistant only to fluoroquinolones (Table 2). All strains had different hierarchical cluster 10 (HC10) but the same HC20 (571), whereas ribosomal MLST (rMLST) split the strains into 2 main populations:

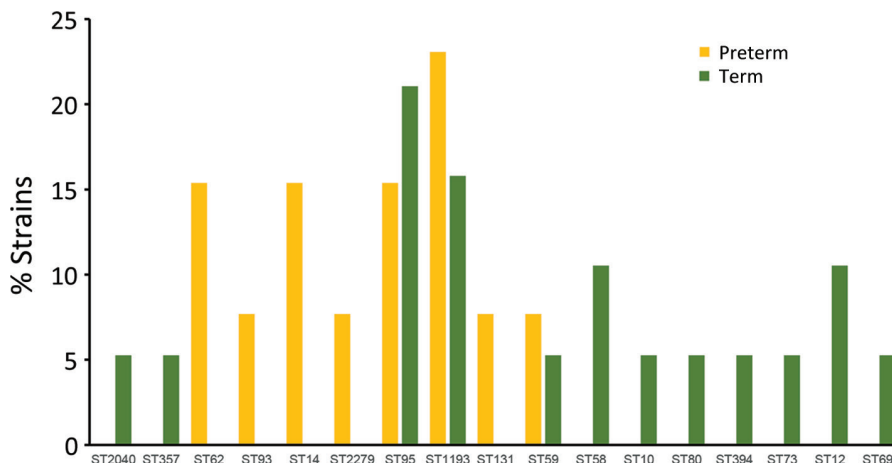


Figure 5. ST distributions according to birth term among 32 neonates with early-onset neonatal sepsis. ST, sequence type.

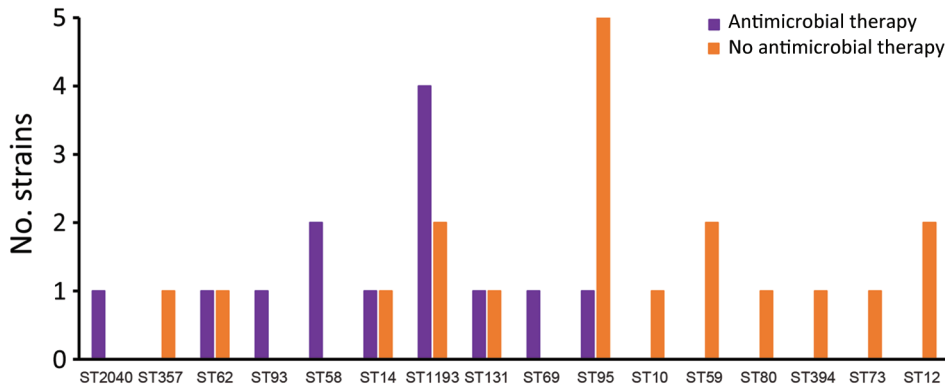


Figure 6. Distribution of maternal antimicrobial therapy within 3 days before delivery according to *Escherichia coli* ST among 32 neonates with early-onset neonatal sepsis, France. ST, sequence type.

rMLST 33503, which regroups the 3 ESBL-producing strains, and rMLST 1674, which contains 2 less-resistant isolates.

Discussion

In our study, we used WGS to characterize *E. coli* strains causing EOS from a prospective multicenter study in France (12) and compared them to *E. coli* strains obtained from vaginal samples from pregnant women at 34–38 weeks of gestation. Although we observed no major differences between the EOS study and vaginal sample collections in distribution of phylogroups or virulence factors except the K1 antigen, we identified emerging ST1193 strains as major causes of EOS. Three isolates of the ST1193 clonal group caused meningitis, and half harbored an ESBL. *E. coli* ST1193 thus appears to be the most virulent and antimicrobial-resistant *E. coli* group that causes EOS.

Among major phylogroups, B2 and, to a lesser extent, D are associated with extraintestinal infections, whereas A and B1 are most associated with commensal strains or intestinal infections (15). We also observed predominance of B2 strains in our EOS population, regardless of the term of birth of the newborns. Although the proportion of phylogroup A strains was higher in the HVC than the EOS population, B2 strains largely predominated in the HVC collection, as reported in previous studies (16,17). However, sequence typing enabled a finer comparison between the 2 collections. Among the HVC strains, phylogroup A/STc10 (ST10, ST13795, ST6826, and ST13957) was predominant but was rarely observed among the EOS patients, in which ST95 and STc14 (notably ST14 and ST1193) were largely predominant. The high frequency of ST95 was expected because of its virulence in neonates, notably those with neonatal meningitis, which is well known worldwide (6,18). Of note, ST95 was second most common among HVC strains, suggesting its capacity to colonize the vagina, at least temporarily. Five of 6 mothers with EOS caused by ST95 received no prepartum antimicrobials.

In contrast, ST14 and ST1193 strains were frequently associated with women receiving prepartum antimicrobials (5/8), and those strains were not present among HVC patients, suggesting the vaginal environment might inhibit the presence of ST14 and ST1193 strains. Of note, STc14 but not ST95 was more prevalent among preterm neonates with EOS, and 3/6 infections caused by ST1193 strains occurred in preterm newborns. It might be that ST1193 strains are less virulent than ST95 strains commonly found in full-term neonates. However, almost all women with preterm newborns received antimicrobial drugs, which might favor the selection of resistant strains, such as ST1193.

ST1193 was identified within STc14 approximately 25 years ago; its prevalence in extraintestinal infections could become a public health burden (19–21). One study observed an increased rate of ST1193 causing bloodstream infections, mostly in elderly patients in Canada during 2016–2018 (22). In an analysis of the population structure of 218 ESBL-producing *E. coli* in urinary tract infections in febrile children in France during 2014–2017, we noted prevalence of ST1193 rose from 0% to 9% (23). Large epidemiologic studies of ST1193 prevalence in neonatal infection have only recently been conducted. In 2 studies, ST1193 was shown to be a major cause of neonatal sepsis; however, because the definition of EOS in those studies differed from ours, data are difficult to compare (11,24). The finding of a worrying percentage of ST1193 among EOS patients (19%) in our study population indicates that in the future that ST should be closely monitored using microbiologic detection.

One epidemiologic study of intracranial infections in neonates caused by *E. coli* (25) found ST1193 to be the most prevalent ST (28%). All 8 ST1193 isolates caused late-onset infections, although none caused EOS. Only 1 recent case of early-onset meningitis caused by *E. coli* ST1193 has been reported, but cases of meningitis caused by ST1193 occurring >72 hours after birth were described in another study (24,26).

RESEARCH

Table 2. Characteristics of newborns with early onset sepsis caused by ST1193 *Escherichia coli* and genetic and phenotypic features of the isolates*

APIMF case ID	EOS clinical features		Genetic and phenotypic characteristic of <i>E. coli</i> strains ST1193					
	Term wk†	Antimicrobial prepartum‡	Virulence genes§	Antimicrobial resistance genes§	Phenotypic AMR	HC10¶	HC20¶	rMLST#
60**	37	Amoxicillin	<i>aslA, chuA, csgA, fdeC, fimH, fyuA, gad, iha, irp2, iucC, iutA, kpsE, kpsMII_K1, neuC, nlpI, ompT, papA_F43, sat, senB, shiA, sitA, terC, tia, usp, vat, yehA, yehB, yehC, yehD, yfcV</i>	<i>dfrA17, aph(6)-IId, aac(6)-Ib-cr, aac(3)-IIa, aph(3'')-Ib, sul2, catB3, mph(A), sitABCD, tet(B), bla_{CTX-M-15}, bla_{TEM-1B}, bla_{OXA-1}</i>	AMX, CTX, CIP, SXT, GTM, AZI, TET, CMP, ESBL	132,558	571	33,503
73	34	Amoxicillin	<i>aslA, chuA, csgA, fdeC, fimH, fyuA, gad, iha, irp2, iucC, iutA, kpsE, kpsMII_K1, neuC, nlpI, ompT, papA_F43, sat, senB, sitA, terC, usp, vat, yehA, yehB, yehC, yehD, yfcV</i>	<i>catB3, tet(B), bla_{CTX-M-15}, bla_{OXA-1}, aph(6)-IId, aac(3)-IIa, aph(3'')-Ib, aac(6)-Ib-cr, sul2, aac(6)-Ib-cr, qnrB19, dfrA17</i>	AMX, CTX, CIP, SXT, GTM, TET, ESBL	148,092	571	33,503
76	41	None	<i>aslA, ccl, chuA, clbB, csgA, fdeC, fimH, fyuA, gad, iha, irp2, iucC, iutA, kpsE, kpsMII_K1, neuC, nlpI, ompT, papA_F43, sat, senB, sitA, terC, usp, vat, yehA, yehB, yehC, yehD, yfcV</i>	None	CIP	227,323	571	1,674
78**	41	None	<i>AslA, chuA, csgA, fdeC, fimH, fyuA, gad, iha, irp2, iucC, iutA, kpsE, kpsMII_K1, neuC, nlpI, ompT, papA_F43, sat, senB, sitA, terC, usp, vat, yehA, yehB, yehC, yehD, yfcV</i>	<i>aadA5, dfrA17, mph(A)</i>	CIP, AZI, SXT	11,740	571	1,674
89**	36	Amoxicillin/gentamicin	<i>AslA, astA, chuA, colE7, csgA, fdeC, fimH, fyuA, gad, iha, irp2, iucC, iutA, kpsE, kpsMII_K1, neuC, nlpI, ompT, papA_F43, sat, senB, shiA, sitA, terC, tia, usp, vat, yehA, yehB, yehC, yehD, yfcV</i>	<i>aac(3)-IIa, aac(6)-Ib-cr, bla_{CTX-M-15}, bla_{OXA-1}, catB3</i>	AMX, CTX, CIP, GTM, CMP, ESBL	4,073	571	33,503
90	36	Amoxicillin	<i>AslA, chuA, csgA, fdeC, fimH, fyuA, gad, iha, irp2, iucC, iutA, kpsE, kpsMII_K1, neuC, nlpI, ompT, papA_F43, sat, senB, sitA, terC, usp, vat, yehA, yehB, yehC, yehD, yfcV</i>	<i>bla_{TEM-1B}, dfrA17, mph(A), aph(6)-IId, aph(3'')-Ib, sul2, tet(B)</i>	AMX, CIP, SXT, AZI, TET	227,336	571	New

*AMR, antimicrobial resistance; AMX, amoxicillin; AZI, azithromycin; cgMLST, core genome multilocus sequence typing; CIP, ciprofloxacin; CMP, chloramphenicol; CTX, cefotaxime; EOS, early-onset neonatal sepsis; ESBL, extended spectrum β-lactamase; GTM, gentamicin; HC, human chromosome; ID, identification; rMLST, ribosomal multilocus sequence typing; ST, sequence type; SXT, trimethoprim/sulfamethoxazole; TET, tetracycline.

†Term of pregnancy at birth in weeks.

‡Antimicrobial treatment within 3 days before labor began.

§Search for antimicrobial resistance genes and replicon/plasmid sequence types run using Center for Genomic Epidemiology website

(<https://genomicepidemiology.org>) and local BLAST.

¶Hierarchical clustering of distances between genomes calculated using 10 (HC10) or 20 (HC20) shared core genome MLST alleles and genomes linked on a single-linkage clustering criteria.

#Approach that indexes variation of the 53 genes encoding the bacterial ribosome protein subunits.

**Early-onset neonatal sepsis with meningitis.

The recent case occurred in a late-preterm neonate with a history of prolonged rupture of the membrane with prepartum and peripartum antimicrobial drugs administered, as in most of our cases.

Given that 3/6 ST1193 strains caused neonatal meningitis, such strains were shown to have high invasive disease potential in newborns. Several virulence factors and genetic determinants have been shown to be involved in the pathophysiology of neonatal meningitis, such as capsule K1, siderophore salmochelin, plasmid *pS88*, and invasin *IbeA*

(27). Of note, among these determinants, only the K1 capsule was present in the ST1193 strains. Several virulence factors (*Iha*, Imm, plasmid-encoded enterotoxin *SenB*, *Sat*) were present in all ST1193 strains, with a significant p value ($p < 0.05$) compared with non-ST1193 (Appendix Table 2) strains, and were present in >85% of ST1193 strains in the large collection of 1 study (28). Therefore, without in vivo study, it is difficult to determine the specific roles of these key factors in the invasiveness of ST1193 in cerebrospinal fluid.

Except for consistency of fluoroquinolone resistance and carrying the fimH64 allele, which characterized all ST1193 *E. coli* strains described in previous studies, multiple plasmid-borne resistance genes have been reported but are inconsistently associated with ST1193 (19,28,29). No isolates harbored the same phenotypic antimicrobial resistance pattern, highlighting their diversity. The co-occurrence of *bla*_{CTX-M-15}/*bla*_{OXA-1}/*aac(6)-Ib-cr*, which we observed in 3/6 of EOS strains, has been frequently described, initially in ST131 but also more recently in emerging lineages of ST1193 (30). Half of our strains, similar to findings from other studies (28), carried the *mphA* resistance gene and had a high azithromycin MIC (>32 mg/L) (data not shown), which might have contributed to the emergence of ST1193 given that azithromycin is among the most-prescribed antimicrobial drugs worldwide among adult outpatients (31).

As of May 2023, sequences of 2,031 *E. coli* ST1193 strains from all over the world are available in Enterobase (13). Of those, 80% belong to HC20 571, as did our strains, and most (82%) harbor rMLST 1674, whereas rMLST 33503 is found in only 8%. Hierarchical clustering analysis did not suggest the presence of a particular clone in our collection. Distribution of rMLSTs was notably different: half of our ST1193 strains belonged to rMLST 33503. Whether this subgroup is emerging or has specific invasive disease potential in neonates has yet to be determined.

Among its strengths, our prospective epidemiologic study, conducted in a large area of France, estimated annual incidence and pathogen distribution in EOS patients (12) and documented the unique molecular and phenotypic characteristics of the strains in our study. We were limited by the small number of patients; results, especially implication of ST1193 in infections in very preterm neonates, need to be confirmed in larger study populations.

In conclusion, our findings suggest that ST1193 is emerging as a major *E. coli* pathogen that can cause EOS and early-onset neonatal meningitis in full-term and late-preterm newborns and might surpass ST95 in incidence and causing illness because of its potential virulence combined with its resistance to multiple antimicrobials. Pediatricians and microbiologists should be aware of the public health threat from *E. coli* ST1193 and the benefits of prepartum/peripartum EOS treatment with effective antimicrobials. Isolating ST1193 *E. coli* strains in the neonatal context (from mother, newborn, or both) will require careful, sustained clinical monitoring of newborns. It might also require implementing measures to limit spread, especially in neonatal wards. On the basis of microbiologic evidence, ST1193 should be suspected when 3 properties are all present: high

resistance to ciprofloxacin, K1 capsule, and non-lactose-fermenting colonies, each of which can easily be tested for in a microbiology laboratory. Further studies should help to define the genetic determinants of ST1193 virulence in neonates and confirm and subsequently explain its inability or weak ability to colonize the vagina. Clinicians need to be aware of the possible presence of *E. coli* ST1193 in prenatal and neonatal contexts and provide appropriate monitoring and treatment.

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About the Author

Dr. Malaure is a medical resident in clinical microbiology at Robert Debré Hospital, Université Paris Cité, Paris, France. Her main research interests are bacterial pathogens, molecular typing, and bacterial resistance.

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Address for correspondence: Stéphane Bonacorsi, Service de Microbiologie, Hôpital Universitaire Robert-Debré, AP-HP, 48 Boulevard Sérurier 75019 Paris, France; email: stephane.bonacorsi@aphp.fr

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Early-Onset Infection in Late Preterm and Full-Term Neonates Caused by *Escherichia coli* Sequence Type 1193

Appendix

Appendix Table 1. Genes encoding virulence or putative virulence factors among *E. coli* strains in EOS (n = 32) or HVC (n = 50) collections*

Genes†	EOS, n (%)	HVC, n (%)
AsIA (Putative sulfatase AsIA)	29 (91)	43 (86)
aamR:FN554766	4 (13)	12 (24)
afaA (Putative transcriptional regulator AfaA-VIII)	1 (3)	7 (14)
afaB (Chaperone protein AfaB)	1 (3)	6 (12)
afaC (Outer membrane usher protein AfaC)	1 (3)	7 (14)
afaD (aggregative adherence fimbria - Afimbrial adhesion)	2 (6)	10 (20)
afaE (aggregative adherence fimbria - Adhesin protein)	1 (3)	5 (10)
air (Enteragggregative immunoglobulin repeat protein Air)	6 (19)	10 (20)
anr (Transcriptional activator protein anr)	15 (47)	16 (32)
capU (Hexosyltransferase homologue protein CapU)	7 (22)	12 (24)
Cea (Colicin E1)	8 (25)	16 (32)
chuA (Hemin receptor)	27 (84)	35 (70)
Cia (Colicin Ia)	4 (13)	7 (14)
clbB (Colibactin biosynthesis protein ClbB)	12 (38)	13 (26)
cnf1 (Cytotoxic Necrotizing Factor 1 (CNF1))	5 (16)	6 (12)
csgA (Major curlin subunit)	32 (100)	50 (100)
cvaC (Colicin V precursor)	8 (25)	5 (10)
cvi (Colicin V immunity protein)‡	8 (25)	8 (16)
dhaK (dihydroxyacetone kinase)	7 (22)	6 (12)
eilA (Salmonella HilA activator homologue)	6 (19)	11 (22)
espY2:000868321	4 (13)	7 (14)
etsC (Putative type I secretion outer membrane protein EtsC)	8 (25)	9 (18)
fdeC (factor adherence)	32 (100)	45 (90)
fimH (Type 1 fimbria D-mannose specific adhesin)	31 (97)	48 (96)
focC (S fimbrial/F1C minor subunit)	4 (13)	3 (6)
focCsfAe (S fimbrial/F1C minor subunit)	4 (13)	4 (8)
fyuA (Yersiniabactin siderophore receptor)	31 (97)	42 (84)
Gad (Glutamate decarboxylase (acid resistance))	27 (84)	47 (94)
Hha (Hemolysin expression-modulating protein Hha)	13 (41)	33 (66)
hlyA (Hemolysin A)	7 (22)	8 (16)
HlyE (Hemolysin E)	11 (34)	25 (50)
HlyF (Hemolysin F)	8 (25)	7 (14)
hra (Heat-resistant agglutinin)	6 (19)	12 (24)
ibeA (Invasin IbeA)	7 (22)	6 (12)
Iha (Adherence protein Iha)	17 (53)	27 (54)
Imm (Colicin Ia immunity protein)‡	18 (56)	25 (50)
ireA (Iron-regulated outer membrane virulence protein)	9 (28)	14 (28)
iroN (Salmochelin siderophore receptor IroN)	14 (44)	17 (34)
irp2 (Yersiniabactin siderophore biosynthesis protein Irp2)	31 (97)	42 (84)
iss (Increased serum survival protein)	21 (66)	35 (70)
iucC (Aerobactin siderophore biosynthesis protein IucC)	22 (69)	31 (62)
iutA (Aerobactin siderophore receptor IutA)	22 (69)	31 (62)
kpsE (Capsule polysaccharide export inner membrane protein)	29 (91)	39 (78)
kpsMII (Polysialic acid transport protein)	1 (3)	8 (16)

Genes†	EOS, n (%)	HVC, n (%)
kpsMII_K1 (Polysialic acid transport protein)§	19 (59)	16 (32)
kpsMII_K5 (Polysialic acid transport protein)	5 (16)	9 (18)
mcbA (Bacteriocin microcin B17)	2 (6)	6 (12)
mchB (Microcin H47)	5 (16)	10 (20)
mchC (Microcin H47)	5 (16)	10 (20)
mchF (Transporter protein MchF)	11 (34)	16 (32)
mcmA (Microcin M part of colicin H)	5 (16)	9 (18)
mig14 (Mig-14 protein)‡	7 (22)	5 (10)
neuC (K1 capsule synthesis UDP-N-acetylglucosamine 2-epimerase)§	19 (59)	18 (36)
ompT (Outer membrane protease (protein protease 7)	30 (94)	39(78)
omptp (Outer membrane protease (plasmidic))‡	7 (22)	5 (10)
Pic (Serine protease pic autotransporter)	2 (6)	8 (16)
papA_F43 (Major pilin subunit)	13 (41)	11 (22)
papC (Pyelonephritis associated pili Outer membrane usher protein PapC)	11 (34)	18 (36)
papGII (Pyelonephritis associated pili class II adhesin)‡	7 (22)	13 (26)
sat (Serine protease autotransporters of Enterobacteriaceae (SPATE) Sat)	15 (47)	21(42)
senB (Plasmid-encoded enterotoxin)	17 (53)	19 (38)
sfaD (S fimbrial/F1C minor subunit)	8 (25)	8 (16)
sfaS (S-fimbriae minor subunit)	4 (13)	2 (4)
shiA (Shikimate transporter)	8 (25)	7 (14)
shiB	8 (25)	17 (34)
sitA (Iron transport protein SitA)	31 (97)	41 (82)
tcpC (toll/interleukin-1 receptor domain-containing protein)	4 (13)	6 (12)
terC (Tellurium ion resistance protein)	32 (100)	50 (100)
tia	12 (38)	15 (30)
traJ (Relaxosome protein)	12 (38)	15 (30)
traT (Outer membrane protein complement resistance)	20 (63)	32 (64)
tsh ((SPATE) Temperature-sensitive hemagglutinin)	4 (13)	1 (2)
usp (Uropathogenic-specific protein)	23 (72)	28 (56)
vat ((SPATE) Vacuolating autotransporter toxin)	18 (56)	20 (40)
yehA (Uncharacterized fimbrial-like protein YehA)	31 (97)	49 (98)
yehB (Outer membrane usher protein YehB)	29 (91)	47 (94)
yehC (Probable fimbrial chaperone YehC)	28 (88)	47 (94)
yehD (Uncharacterized fimbrial-like protein YehD)	29 (91)	46 (92)
yfcV (Fimbrial protein)	25 (78)	30 (60)

*EOS, early onset neonatal sepsis; HVC, healthy vaginal carriage

†Only virulence genes with a prevalence of ≥ 10 in one of the collections are listed.

‡Virulence genes detected by local BLAST (see methods)

§Indicate a significant difference of genes prevalence ($p < 0.05$) between the 2 collections

Appendix Table 2. Genes encoding virulence or putative virulence factors among *E. coli* strains in EOS ST1193 (n = 6) or EOS non-ST1193 (n = 26) collections*

Genes†	ST1193, n (%)	Non-ST1193, n (%)	p-value§
AsIA (Putative sulfatase AsIA)	6 (100)	23 (88)	>0.05
aamR:FN554766	0 (0)	4 (15)	>0.05
air (Enteroaggregative immunoglobulin repeat protein Air)	0 (0)	6 (23)	>0.05
anr (Transcriptional activator protein anr)	0 (0)	15 (58)	0.02
astA (Arginine N-succinyltransferase)	1 (17)	2 (8)	>0.05
capU (Hexosyltransferase homologue protein CapU)	0 (0)	7 (27)	>0.05
cea (Colicin E1)	0 (0)	8 (31)	>0.05
ccl (cloacin)	1 (17)	1 (4)	>0.05
chuA (Hemin receptor)	6 (100)	21 (81)	>0.05
cia (Colicin Ia)	0 (0)	4 (15)	>0.05
clbB (Colibactin biosynthesis protein ClbB)	1 (17)	11 (42)	>0.05
cnf1 (Cytotoxic Necrotizing Factor 1 (CNF1))	0 (0)	5 (19)	>0.05
colE7 (Colicin-E7)	1 (17)	0 (0)	>0.05
csgA (Major curlin subunit)	6 (100)	26 (100)	>0.05
cvaC (Colicin V precursor)	0 (0)	8 (31)	>0.05
dhaK (dihydroxyacetone kinase)	0 (0)	7 (27)	>0.05
eilA (Salmonella HilA activator homologue)	0 (0)	6 (23)	>0.05
espY2:000868321	0 (0)	4 (15)	>0.05
etsC (Putative type I secretion outer membrane protein EtsC)	0 (0)	8 (31)	>0.05
fdeC (factor adherence)	6 (100)	26 (100)	>0.05
any fimH (Type 1 fimbria D-mannose specific adhesin)	6 (100)	25 (96)	>0.05
fimH 64 (Type 1 fimbria D-mannose specific adhesion 64)	6 (100)	0 (0)	<0.001
focC (S fimbrial/F1C minor subunit)	0 (0)	4 (15)	>0.05
focCsfAe (S fimbrial/F1C minor subunit)	0 (0)	4 (15)	>0.05

Genes†	ST1193, n (%)	Non-ST1193, n (%)	p-value§
fyuA (Yersiniabactin siderophore receptor)	6 (100)	25 (96)	>0.05
gad (Glutamate decarboxylase (acid resistance))	6 (100)	21 (81)	>0.05
Hha (Hemolysin expression-modulating protein Hha)	0 (0)	13 (50)	>0.05
hlyA (Hemolysin A)	0 (0)	7 (27)	>0.05
HlyE (Hemolysin E)	0 (0)	11 (42)	>0.05
HlyF (Hemolysin F)	0 (0)	8 (31)	>0.05
hra (Heat-resistant agglutinin)	0 (0)	6 (23)	>0.05
ibeA (Invasin IbeA)	0 (0)	7 (27)	>0.05
lha (Adherence protein lha)	6 (100)	11 (42)	0.019
Imm (Colicin Ia immunity protein)**	6 (100)	12 (46)	0.024
ireA (Iron-regulated outer membrane virulence protein)	0 (0)	9 (35)	>0.05
iroN (Salmochelin siderophore receptor IroN)	0 (0)	14 (54)	>0.05
irp2 (Yersiniabactin siderophore biosynthesis protein Irp2)	6 (100)	25 (96)	>0.05
iss (Increased serum survival protein)	0 (0)	21 (81)	<0.001
iucC (Aerobactin siderophore biosynthesis protein IucC)	6 (100)	16 (62)	>0.05
iutA (Aerobactin siderophore receptor IutA)	6 (100)	16 (62)	>0.05
kpsE (Capsule polysaccharide export inner membrane protein)	6 (100)	23 (88)	>0.05
kpsMII_K1 (Polysialic acid transport protein)	6 (100)	13 (50)	>0.05
kpsMII_K5 (Polysialic acid transport protein)	0 (0)	5 (19)	>0.05
mig14 (Mig-14 protein)**	0 (0)	7 (27)	>0.05
mchB (Microcin H47)	0 (0)	5 (19)	>0.05
mchC (Microcin H47)	0 (0)	5 (19)	>0.05
mchF (Transporter protein MchF)	0 (0)	11 (42)	>0.05
mcmA (Microcin M part of colicin H)	0 (0)	5 (19)	>0.05
neuC (K1 capsule synthesis UDP-N-acetylglucosamine 2-epimerase)	6 (100)	13 (50)	>0.05
ompT (Outer membrane protease (protein protease 7))	6 (100)	24 (92)	>0.05
omptp (Outer membrane protease (plasmidic))**	0 (0)	7 (27)	>0.05
papA_F43 (Major pilin subunit)	6 (100)	7 (27)	0.0019
papA_feiA_F8	0 (0)	3 (12)	>0.05
papC (Pyelonephritis associated pili Outer membrane usher protein PapC)	0 (0)	11 (42)	>0.05
papGII (Pyelonephritis associated pili class II adhesin)**	0 (0)	7 (27)	>0.05
sat (Serine protease autotransporters of Enterobacteriaceae (SPATE) Sat)	6 (100)	9 (35)	0.006
senB (Plasmid-encoded enterotoxin)	6 (100)	11 (42)	0.019
sfaD (S fimbrial/F1C minor subunit)	0 (0)	8 (31)	>0.05
sfaS (S-fimbriae minor subunit)	0 (0)	4 (15)	>0.05
shiA (Shikimate transporter)	2 (33)	6 (23)	>0.05
shiB	0 (0)	8 (31)	>0.05
sitA (Iron transport protein SitA)	6 (100)	25 (96)	>0.05
tcpC (toll/interleukin-1 receptor domain-containing protein)	0 (0)	4 (15)	>0.05
terC (Tellurium ion resistance protein)	6 (100)	26 (100)	>0.05
tia	2 (33)	10 (38)	>0.05
• traJ (Relaxosome protein)	0 (0)	12 (46)	>0.05
traT (Outer membrane protein complement resistance)	0 (0)	20 (77)	0.001
Tsh (Temperature-sensitive hemagglutinin)	0 (0)	4 (15)	>0.05
usp (Uropathogenic-specific protein)	6 (100)	17 (65)	>0.05
vat (Vacuolating autotransporter toxin)	6 (100)	12 (46)	0.024
yehA (Uncharacterized fimbrial-like protein YehA)	6 (100)	25 (96)	>0.05
yehB (Outer membrane usher protein YehB)	6 (100)	23 (88)	>0.05
yehC (Probable fimbrial chaperone YehC)	6 (100)	22 (85)	>0.05
yehD (Uncharacterized fimbrial-like protein YehD)	6 (100)	23 (88)	>0.05
yfcV (Fimbrial protein)	6 (100)	19 (73)	>0.05

*ST, sequence type

†Only virulence genes with a prevalence of ≥ 10 in one of the collections are listed.

‡Virulence genes detected by local BLAST

§p value calculated with Fisher exact analysis, threshold for significance: <0.05.

Appendix Table 3. Healthy vaginal colonization *E. coli*

Isolates	N50	Coverage
21660147MF_S24	244667	169
21670134KC_S29	59409	79
21680051BM_S28	108785	96
21680077DG_S25	355528	122
21680084BFK_S27	104814	95
21680097DM_S26	245687	152
21710028CP_S30	177894	79
21710041BE_S31	300298	113
21710098-BB_S20	219523	65
21720121-SN_S21	117586	67
21730098-SS_S22	101344	68
21740131-BS_S23	217515	95
21820063-RMH_S25	106321	57
21870051-DM_S24	59348	67
21960106-DK_S26	108429	91
21990114-RA_S27	57564	106
22010042-BA_S28	275248	109
22010109-WA_S29	240556	49
AVC1RV_S1	263633	93
AVC2MJ_S2	127932	125
AVC3BA_S3	177581	147
AVC4CR_S4	127841	110
AVC5LA_S5	228082	121
AVC6VE_S6	86987	68
AVC7AK_S7	287923	153
AVC8DD_S8	111095	114
AVC-9-a.m._S30	259573	85
AVC11GA_S10	203351	86
LMR1EL_S11	191062	99
LMR2CK_S12	544568	106
LMR4DM_S14	77856	34
LMR6MC_S16	388705	57
LMR7BD_S17	95117	120
LMR8MR_S18	212470	103
LMR9PO_S19	122371	82
LMR10AS_S20	58328	113
AVC-10-CM	203897	136
21540126-BH	259845	140
21610097-KH	261749	164
LMR3-BL	93255	141
LMR5-ES	60504	118
LRB1	94759	117
LRB3	305009	200
LRB4	377622	188
LRB5	191824	97
LRB6	179883	128
LRB7	240768	113
LRB8	99769	116
LRB10	269065	87
LRB11	78259	88
Maximum	544568	200
Minimum	57564	34
Median	185472.5	106

Appendix Table 4. Early onset neonatal sepsis *E. coli*

Isolates	N50	Coverage
APIMF52	333512	154
APIMF53	298766	140
APIMF54	79272	90
APIMF56	168482	133
APIMF57	109201	159
APIMF58	246576	66
APIMF59	223171	126
APIMF60	210541	114
APIMF63	104989	106
APIMF67	341395	152
APIMF68	178169	78
APIMF69	419368	74
APIMF70	66787	102
APIMF71	551760	117
APIMF72	563762	88
APIMF73	215239	114
APIMF76	210541	71
APIMF77	204129	85
APIMF78	274362	99
APIMF79	171995	86
APIMF80	211242	90
APIMF81	196353	89
APIMF82	237021	68
APIMF83	134788	106
APIMF84	223226	85
APIMF85	341964	55
APIMF87	94828	73
APIMF88	111031	86
APIMF89	209517	97
APIMF90	216134	88
APIMF91	61362	74
APIMF92	204007	130
Maximum	563762	159
Minimum	61362	55
Median	210541	90