High levels of gut carriage of antimicrobial-resistant *Escherichia coli* in community settings in Rio de Janeiro, Brazil

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Abstract
The prevalence and risk factors for gut carriage of antimicrobial-resistant *Escherichia coli* among individuals living in the community in Rio de Janeiro, Brazil, are unknown. The aim of this study was to determine the prevalence of colonization with antimicrobial-resistant *E. coli*, including isolates producing ESBL and harboring plasmid-mediated quinolone resistant (PMQR) genes in this community. We performed a cross-sectional study and analyzed fecal specimens of individuals attending outpatient clinics in the city from January 2015 to July 2019. We investigated susceptibility to antimicrobial agents by disc diffusion tests and used PCR to determine ESBL types, PMQR, and the virulence genes that characterize an isolate as extraintestinal pathogenic *E. coli* (ExPEC). Among the 623 subjects, 212 (34%) carried an isolate resistant to at least one of the tested antimicrobial agents, with the highest frequencies of resistance to ampicillin (26%), trimethoprim-sulfamethoxazole (19%), cefazolin (14%), and ciprofloxacin (CIP, 9%). In addition, 13% (81) of subjects carried a multidrug-resistant-*E. coli* (MDR-E), including 47 (8% of all isolates) ESBL-producing *E. coli* (ESBL-E), mainly of CTX-M-8 (15, 32%) and CTX-M-15 (9, 20%) types. PMQR genes were present in 7% (42) of all isolates, including 60% (32) of the 53 resistant to CIP. Previous use of antimicrobial agents, particularly fluoroquinolones, was a risk factor for colonization with MDR-E (25%, 20/81 vs 13%, 70/542, \(p = 0.01\)), ESBL-E (28%, 13/47, vs 13%, 77/576, \(p = 0.01\)), and resistance to CIP (26%, 14/53, vs 12%, 70/570, \(p = 0.01\)). The most pathogenic phylogroups B2, C, and D were 37% of the MDR-E, 30% of the ESBL-E, 38% of the CIP-resistant, and 31% of PMQR gene carrying *E. coli* isolates. We show that carriage of MDR-E (mostly ESBL-E) reached high levels in the community in Rio de Janeiro, increased by the selection of antimicrobial agents. Much of the resistant *E. coli* isolates are potential pathogenic strains. The widespread use of antimicrobial agents during the COVID-19 pandemic in Brazil may have worsened this picture.

Keywords *Escherichia coli* · Antimicrobial resistance · Carriage · ESBL

Introduction
Infections by *Enterobacterales* isolates usually originate in the gut microbiota. The carriage of multidrug-resistant (MDR) isolates, such as extended-spectrum beta-lactamase (ESBL)-producing gram-negative bacteria, is of concern because of the increased risk of resistant infections. Exposure to antimicrobial agents and travel to high-risk geographic regions [1–3], among other factors [4], are associated with high rates of carriage of MDR bacteria. The increasing prevalence of carriage of ESBL producing *Enterobacterales* worldwide is particularly worrisome because it may severely limit antimicrobial treatment options.
and increase chances of carbapenem use and healthcare costs [5, 6]. CTX-M type is the most common among a broad range of ESBL enzymes [7, 8], with CTX-M-15 as the most widespread variant [9, 10]. Guidelines to control the spread of antimicrobial-resistant pathogens recommend screening for ESBL-producing isolates in high-risk settings, such as during hospital admission of patients previously colonized with MDR bacteria and admission to cancer or intensive care units [11, 12].

Escherichia coli is the most frequent commensal microorganism recovered in the human intestinal microbiota [13]. However, genetic traits carried by E. coli isolates differentiate commensal to pathogenic strains [14], such as extraintestinal pathogenic E. coli (ExPEC) and uropathogenic E. coli (UPEC) [15, 16]. It is expected that, by 2050, infections caused by MDR ExPEC isolates will be responsible for more than three million deaths each year [17]. This outcome will likely be much worse after the current pandemic, because the use of antimicrobial agents should have increased significantly by the (unfound) recommendation of the routine use of antimicrobial agents for COVID-19 patients in certain countries such as Brazil, even for mild or moderate cases [18].

UPEC isolates belong predominantly to phylogenetic groups B2, D/E or F, and commensal E. coli isolates, to groups B1 or A [19, 20]. Further sub-grouping of UPEC isolates by multilocus sequence typing (MLST) has shown that a limited set of E. coli lineages are responsible for a large proportion of extraintestinal infections [21]. Epidemiological studies have shown that lineages ST131, ST73, ST95 and ST69 are the most prevalent ExPEC, especially ST131, the main pandemic clone [22].

In Brazil, MDR E. coli (MDR-E) has already been described in farm animals [23, 24], chicken carcasses [25], wild birds [26], coastal waters [27], and as a cause of infections [28], but not as colonizers among individuals in the community. This information is a useful parameter for empiric antimicrobial therapy and a proxy for the general quality of people’s health. Therefore, the present study aimed to investigate the prevalence and risk factors for antimicrobial resistance among E. coli gut isolates from individuals living in the community in Rio de Janeiro city, the second biggest city of Brazil.

Materials and methods

Patient population and bacterial isolates

From January 2015 to July 2019, we invited outpatients and their companions over 18 years old attending three primary-care medical clinics to participate in the study. Subjects received instructions to self-collect a fecal specimen with an anal swab containing Amies transport media. In our research laboratory, the specimen containing swab tip was transferred to a microtube with 1 mL skim milk, tryptone, glucose, and glycerin (STGG), vortexed for approximately 30 s, and stored at −20 °C. The Ethics Committee approved the study (CAAE: 49,843,315.0.0000.5257).

Microbiological methods

We plated aliquots of specimens containing STGG in three types of culture media as follows. We seeded 10 µL aliquots onto plain MacConkey agar (DifcoTM) to guarantee to obtain isolates from every subject, and onto 2 µg/mL ceftiraxone (Agila®) containing MacConkey agar, to select for ESBL-producing E. coli. In addition, we inoculated a 50 µL aliquot of STGG into 9 mL of trypticase soy broth (TSB) (DifcoTM) containing zinc sulfate (70 µg/mL) and a 10 µg ertapenem (ETP) disc to select for carbapenemase-producing E. coli. Finally, we transferred isolates identified by matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF–MS) (Bruker Daltonics®) as E. coli to a microtube containing 1 mL skim milk (DifcoTM) and glycerol (10%) (Sigma®) and stored at −20 °C. Therefore, we saved a maximum of three isolates (colonies) from each subject. We followed a hierarchical preference to select which isolates to save from each specimen and maximize the chance of detecting antimicrobial resistance: we prioritized colonies grown on MAC agar supplemented with antimicrobial agents. Otherwise, we picked colonies grown on plain MAC agar.

Antimicrobial susceptibility tests

To assess if we could use a single colony from the primary plate of each subject, we ran a small pilot study. We performed antimicrobial susceptibility tests for 12 drugs, by disc diffusion, with three colonies saved from 20 subjects. In just three subjects, we detected one difference in resistance for one drug among the colonies from the same plate. In none of these three cases, the observed difference would cause misclassification of an isolate as MDR [29]. Therefore, we proceeded with testing one isolate from each participant for susceptibility, by disc diffusion according to CLSI 2018 to the following antimicrobial agents: amikacin (AMI), amoxicillin-clavulanate (AMC), ampicillin (AMP), cefazolin (CFZ), cefepime (CPM), cefotaxime (CTX), cefoxitin (CFO), ceftazidime (CAZ), cefuroxime (CRX), ciprofloxacin (CIP), ertapenem (ETP), fosfomycin (FOS), gentamicin (GEN), nitrofurantoin (NIT), and sulfamethoxazole-trimethoprim (SUT). ESBL production was determined with a disc synergy test [30], using CPM, CAZ, CTX, and AMC discs. We classified isolates as MDR as proposed [31]. Accordingly, all ESBL-producing isolates were classified as MDR.
Detection of antimicrobial resistance genes

We screened ESBL-producing isolates for the presence of genes encoding CTX-M, TEM, SHV, and GES type beta-lactamases. The presence of CTX-M-1, CTX-M-2, CTX-M-8, and CTX-M-9 groups and TEM, SHV, and GES genes was detected by multiplex PCR, confirmed in simplex reactions [32], and amplified DNA fragments were sequenced (Macrogen, Seoul, South Korea).

CFO and AMC resistant isolates were screened for genes associated with plasmid AmpC (pAmpC); multiplex PCR was performed for genes encoding MOX-like, CMY-1-like, LAT-like, CMY-2-like, DHA-like, ACC-like, MIR, and ACT beta-lactamases [33].

Multiplex PCR was performed for mcr-1, mcr-2, mcr-3, mcr-4, and mcr-5 genes [34]. We confirmed results obtained by multiplex PCR in simplex reactions and sequenced amplified DNA fragments (Macrogen, Seoul, South Korea).

For each of the genes we screened, we used as control an isolate from our laboratory collection with a positive PCR amplicon confirmed by sequencing.

PMQR gene detection

We investigated the presence of PMQR genes in all isolates by multiplex PCR, as previously described: qnrD, qnr C, and qnr Vc [35], qnrA, qnrS, qnrB [36], aac(6″)-Ib [37], and qepA [38]. For the detection of aac(6″)-Ib-cr, purified aac(6″)-Ib PCR products were sequenced (Macrogen, Seoul, South Korea).

Phylogenetic groups and ExPEC classification

We classified all isolates into phylogenetic groups by multiplex PCR [39–41]. Those belonging to phylogenetic groups B2, D/E, or F were classified as ExPEC based on the presence of two or more defined virulence markers (papAH, sfa/focDE, afa/draBC, iutA, and kpsMT II) [42]. Virulence genes were screened with one multiplex and three simplex PCR tests [43–45].

Statistical analysis

We described numerical data by their median and interquartile range, and categorical data by absolute counts and percentages. Comparisons of distributions of resistance to specific antimicrobial agents was performed with the chi-square test or Fisher’s exact test. Potential statistical associations between the study covariates and the acquisition of MDR-E or ESBL-E were explored in bivariate analyses performed with logistic regression. Statistical significance was defined by a two-sided p-value < 0.05. All analyses were performed with IBM® SPSS v. 23 software.

Results

We recruited 677 volunteers and excluded 54 (8%) because no E. coli isolates were obtained from fecal specimens. Among the 623 participants included in the study, the median age was 42 years (IQR: 31–56), and 67% were female. Most participants had concluded secondary or tertiary school levels (n = 508, 82%), and 188 (30%) reported a comorbid condition (including diabetes, hypertension, and autoimmune diseases). A total of 90 (14%) participants reported the use of antimicrobial agents in the previous 6 months, with the predominance of beta-lactams (n = 54.9%) followed by fluoroquinolones (n = 13.2%). None had an infectious syndrome at the time of sampling.

Antimicrobial resistance, ESBL production, and MDR isolates

Among the 623 participants, 212 (34%) carried an isolate resistant to at least one of the tested drugs. The higher resistance frequencies were for AMP, SUT, and CFZ, as shown in Table 1. Resistance to CIP and the presence of ESBL-E detected by disc synergy tests reached almost 10% each, and MDR-E was detected in 13% of study participants (Table 1). Among ESBL-E isolates, 36% were also resistant to CIP and 30% harbored PMQR genes.

| Antimicrobial agent/resistance phenotype | Number (%) of resistant isolates |
|-----------------------------------------|---------------------------------|
| Ampicillin                               | 164 (26)                        |
| Trimethoprim-sulfamethoxazole            | 120 (19)                        |
| Cefazolin                                | 89 (14)                         |
| Ciprofloxacin                            | 53 (9)                          |
| Cefotaxime                               | 52 (8)                          |
| Cefuroxime                               | 46 (7)                          |
| Cefepime                                 | 39 (6)                          |
| Cefoxitin                                | 25 (4)                          |
| Gentamicin                               | 19 (3)                          |
| Ceftazidime                              | 18 (3)                          |
| Amoxicillin/clavulanate                  | 15 (2)                          |
| Nitrofurantoin                           | 7 (1)                           |
| Fosfomycin                               | 3 (0.5)                         |
| Amikacin                                 | 1 (0.2)                         |
| Ertapenem                                | 0                               |
| ESBL                                     | 47 (8)                          |
| MDR                                      | 81 (13)                         |

ESBL, extended-spectrum beta-lactamase producing isolate; MDR, multidrug-resistant isolate
genes. Considering two study periods (2015–2016 and 2017–2019), carriage of MDR-E increased from 11% (39/341) to 15% (42/282, \( p = 0.23 \)), ESBL-E from 6% (20/341) to 10% (27/270, \( p = 0.09 \)), and resistance to CIP from 6% (22/319) to 11% (31/251, \( p = 0.06 \)).

### Presence of PMQR genes

Among the study isolates, 42 (7%) carried a PMQR gene, including 17 susceptible to CIP, as shown in Table 2.

| PMQR | Number (%) of isolates | \( p \) |
|------|------------------------|-------|
| total | \( N = 623 \) |       |
| CIP R | \( N = 53 \) |       |
| CIP S | \( N = 570 \) |       |
| \( qnrB \) | 23 (4) | 9 (17) | 14 (2) | \( < 0.01 \) |
| \( qnrS \) | 9 (1) | 3 (6) | 6 (1) | 0.06 |
| \( aac(6')-Ib-cr \) | 7 (1) | 4 (8) | 3 (0.5) | \( < 0.01 \) |
| \( qepA \) | 2 (0.3) | 1 (2) | 1 (0.2) | 0.3 |
| \( qnrB + aac(6')-Ib-cr \) | 1 (0.2) | 0 | 1 (0.2) | 0.9 |
| total | 42 (7) | 17 (32) | 25 (4) | \( < 0.01 \) |

PMQR, plasmid-mediated quinolone resistance genes; CIP R, ciprofloxacin resistant isolates; CIP S, ciprofloxacin susceptible isolates. \( p \) values < 0.05 are shown in bold.

### Bivariate analysis of variables associated with antimicrobial resistance phenotypes and the presence of PMQR genes

The potential associations of study variables with carriage of MDR-E, ESBL-E, and resistance to CIP are described in Table 3. We found no correlation between age, gender, and education level with any of the three outcomes. Previous antimicrobial use, particularly CIP, was associated with colonization with carriage of MDR-E, ESBL-E, and resistance to CIP (\( p = 0.01 \)).

### ESBL types

Almost all ESBL types were CTX-M, more than half CTX-M8 or CTX-M-15, as shown in Table 4. We did not detect any isolate suspect of carbapenemase-producing, nor pAmpC or \( mcr \) carrying isolates.

### Pathogenic phylogenetic groups and ExPEC

Among all \( E. coli \) isolates, 204 (33%) belonged to phylogenetic groups B2, D/E, or F, including 37% of the MDR-E, 31% of the ESBL producing, 31% of the PMQR-carrying, and 38% of the CIP resistant isolates. Of the B2, D/E, or F isolates, 120 (59%) were classified as ExPEC based on the presence of virulence markers.

| Variable | Number and (% of subjects) |
|----------|-----------------------------|
| Female sex | 49 (61) 371 (68) \( p = 0.16 \) 27 (57) 393 (68) \( p = 0.14 \) 17 (32) 191 (34) \( p = 0.88 \) |
| Secondary or tertiary level education | 62 (77) 447 (82) \( p = 0.26 \) 36 (77) 472 (82) \( p = 0.46 \) 43 (81) 465 (82) \( p = 1.00 \) |
| Comorbidity present | 12 (15) 71 (13) \( p = 0.71 \) 8 (17) 75 (13) \( p = 0.32 \) 19 (36) 169 (30) \( p = 0.35 \) |
| Study period | 2015–2016 39 (48) 302 (56) \( p = 0.23 \) 20 (43) 321 (56) \( p = 0.09 \) 22 (42) 319 (56) \( p = 0.06 \) |
| 2017–2019 | 42 (52) 240 (44) \( p = 0.27 \) 27 (57) 255 (44) \( p = 0.31 \) 58 (25) 251 (44) |
| Used antimicrobial agent | 20 (25) 70 (13) \( p = 0.01 \) 13 (28) 77 (13) \( p = 0.02 \) 14 (26) 70 (12) \( p = 0.01 \) |
| Fluoroquinolone (\( N = 13 \)) | 5 (39) 8 (6) \( p = 0.01 \) 4 (9) 9 (1) \( p = 0.01 \) 4 (8) 9 (2) \( p = 0.01 \) |
| Other classes (\( N = 77 \))* | 15 (20) 62 (19) \( p = 0.01 \) 9 (19) 68 (12) \( p = 0.01 \) 10 (18) 67 (12) |
| No use | 61 (11) 472 (75) \( p = 0.01 \) 34 (72) 499 (87) \( p = 0.01 \) 39 (74) 494 (86) |

ESBL, extended-spectrum beta-lactamase producing \( E. coli \) isolates; MDR, multidrug-resistant \( E. coli \) isolate; CIP-R, ciprofloxacin resistant isolates.

*54 (70%) subjects took a betalactam drug; **included among MDR isolates. \( p \) values < 0.05 are shown in bold.
isolated reports [47].

Community and hospital isolates, which is much higher than all estimates a prevalence of almost 60%, including commute-Asia and Africa (22%) [4, 48, 49]. The WHO report on the highest levels in countries of West Pacific (46%) and different parts of the world, which vary from 2 to 46%, with the lower side of that reported by many studies in different parts of the world, which vary from 2 to 46%, with the highest levels in countries of West Pacific (46%) and Asia and Africa (22%) [4, 48, 49]. The WHO report on third-generation cephalosporin resistance from GLASS estimates a prevalence of almost 60%, including community and hospital isolates, which is much higher than all isolated reports [47].

We observed a worrying trend of increased resistance of gut colonizers over time. Such an upsurge is reported around the world [48, 49] with an annual increasing rate of approximately 5% [48], which may be related to high levels of antimicrobial consumption in the community, as described by others [5, 48]. In fact, in the present study, the only factor with a significant association with the carriage of MDR-E or ESBL-E was the previous use of antimicrobial agents, as reported by others [50–54]. It would be interesting to reassess such levels late in the year 2021, after the establishment of Brazil as one epicenter of the COVID-19 pandemic, certainly driving a substantial increment of antimicrobial consumption. Traveling abroad was reported only by few subjects, and we found no correlation between other factors such as age, gender, educational level, and comorbid conditions, and carriage of MDR-E or ESBL-E. Antimicrobial use, specifically CIP, was associated with colonization with MDR-E or ESBL-E. The use of a fluoroquinolone has been previously associated with an increased chance of colonization with E. coli resistant to the drug [55] and with ESBL producing isolates [56]. This association may be related to the frequent presence of quinolone resistance determinants within ESBL gene-carrying plasmids [57].

Several of the E. coli isolates of the present study, including a significant portion of those resistant to CIP, carrying PMQR genes and producing ESBL, belong to phylogenetic groups B2, D/E, or F which comprise more virulent strains, and thus more likely to cause UTI. Indeed, most of such isolates were ExPEC, including among MDR-E and ESBL-E. Studies showing that a specific resistant and virulent colonizing strain causes an infection are rare [58]. However, epidemiologic data show an association between risk factors for acquisition of MDR isolates and infection with such microorganisms [52]. The genome plasticity of E. coli and other Enterobacterales is well known and the transfer of genes from gut-colonizers to pathogenic isolates causing infection has been already demonstrated [58]. Therefore, subjects colonized with a virulent strain that has also increased resistance are at higher risk for developing an infection with treatment failure, extended hospital stay, and increased mortality [52].

ESBL produced by isolates were mostly of CTX-M type, mainly CTX-M-8 and CTX-M-15. A blaCTX-M-type gene harboring plasmid usually carries additional genes encoding fluoroquinolone resistance, pAmpC, carbapenemases, and aminoglycoside inactivating enzymes. This way, the use of several antimicrobial agents would give an advantage to isolates with a blaCTX-M-type gene [57]. Carbapenemase producers and pAmpC or mcr gene carriers were not detected in the present population. Resistance to carbapenems has been largely related to hospital-associated infections in Brazil. pAmpC is still a rare

### Table 4 Frequency of ESBL encoding genes detected among 623 study isolates

| ESBL type (N=46.98%) | ESBL encoding gene | Number and (%) of isolates |
|----------------------|---------------------|-----------------------------|
| CTX-M                | blaCTX-M8           | 15 (32)                     |
|                      | blaCTX-M15          | 9 (20)                      |
|                      | blaCTX-M2           | 6 (13)                      |
|                      | blaCTX-M127         | 5 (11)                      |
|                      | blaCTX-M14          | 3 (6)                       |
|                      | blaCTX-M55          | 3 (6)                       |
|                      | blaCTX-M27          | 3 (6)                       |
|                      | blaCTX-M65          | 3 (6)                       |
|                      | blaCTX-M1           | 1 (2)                       |
| SHV (N=1.2%)         | blashv-28           | 1 (2)                       |

**ESBL**, extended-spectrum beta-lactamase

### Discussion

In the present study, we determined the prevalence of human carriage of antimicrobial-resistant E. coli in a community in Rio de Janeiro city. A small number of subjects were excluded because no E. coli was obtained from the rectal specimen, probably related to insufficient yield due to self-sampling.

Resistance frequencies for the top five drugs were high, including SUT and CIP, two of the leading choices for treatment of UTI until recently. The presence of resistant isolates in these high frequencies compromises the microbiota of people in the city. UTI usually starts from the ascending route, with gut microorganisms reaching the bladder [46]. Therefore, one expects a correlation between isolates that colonize the gut and UPEC. In fact, the resistance prevalences among colonizing-isolates of the present study are lower than we observed in a series of ~500 UPEC isolates obtained from individuals living in the same region in 2015 [28]. These rates, in turn, are lower than observed around the world among community UTI E. coli isolates, according to the global antimicrobial resistance and the use surveillance system (GLASS) report of WHO [47]. Otherwise, in the present study, we detected ESBL-E from almost 10% of individuals, similar to the prevalence we observed among UPEC isolates in the city in 2015 (8%) [28]. However, this prevalence is in the lower side of that reported by many studies in different parts of the world, which vary from 2 to 46%, with the highest levels in countries of West Pacific (46%) and Asia and Africa (22%) [4, 48, 49]. The WHO report on third-generation cephalosporin resistance from GLASS estimates a prevalence of almost 60%, including community and hospital isolates, which is much higher than all isolated reports [47].
beta-lactamase, found in less than 1% of UPEC isolates from community-associated infections in Rio de Janeiro [28].

A limitation of the present study was the use of a swab for collecting fecal specimens, which may have provided a smaller expected yield compared with fecal specimens; resistance rates could have been even higher. In addition, self-collection of specimens might have led to the use of suboptimal sampling procedures. However, we believe that this approach was a critical facilitator making the study feasible. Another limitation of the present study was the lack of strain typing, specially MLST. This information could have led to the description of the presence of pandemic clones as colonizers in the community.

In conclusion, we show that subjects in our community may carry MDR-E and ESBL-E around 10% of the time. The use of antimicrobial agents, particularly fluoroquinolones [53], is a significant risk factor for the carriage of a resistant isolate, indicating the importance of stewardship programs that must be extensive to outpatients.

**Author contribution** Káris Maria de Pinho Rodrigues made substantial contributions to the conception or design of the work; analysis, or interpretation of data; drafted the work, approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Beatriz Meurer Moreira made substantial contributions to the conception or design of the work; drafted the work, revised it critically for important intellectual content, approved the version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Michelle Pessanha Pinto was responsible for data acquisition, and made substantial contribution to the analysis or interpretation of data, and approved the version to be published.

Daniele Ferreira de Rezende made substantial contribution the analysis and interpretation of data, and approved the version to be published.

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**Code availability** Not applicable.

**Data availability** All data can be made available by the authors.

**Declarations**

**Conflict of interest** The authors declare no competing interests.

**Ethics approval** The study was approved by the Ethics Committee of the University registered at CAAE: 49843315.0.0000.5257. Consent to participate and consent for publication. All participants filled an informed consent to participate and to allow the publication of data.

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