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ORIGINAL ARTICLE

Intestinal Carriage of Third-Generation Cephalosporin-Resistant and Extended-Spectrum β-Lactamase-Producing *Enterobacteriaceae* in Healthy US Children

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Background. The epidemiology of antibiotic-resistant *Enterobacteriaceae* intestinal carriage in healthy US children has not been well characterized.

Methods. Children between 14 days and 14 years of age were enrolled during well-child visits in Oakland, California, Kansas City, Kansas, and Nashville, Tennessee, between December 2013 and March 2015. Data on recent antibiotic use by the child and travel and hospitalization history of all members of each child's household were obtained with a risk-factor survey. Stool specimens collected from the subjects were screened for extended-spectrum β-lactamase-producing (ESBL-P) bacteria using CHROMagar ESBL medium. Putative ESBL-P *Escherichia coli* and *Klebsiella* colonies underwent phenotypic confirmation by double-disk synergy testing; confirmed third-generation cephalosporin-resistant (3GCR) isolates underwent additional antibiotic-susceptibility testing.

Results. In 519 subjects, the overall 3GCR *Enterobacteriaceae* carriage rate was 4.4% (n = 23) and ranged from 3.4% to 5.1% among the study sites. The ESBL-P *Enterobacteriaceae* carriage rate was 3.5% (n = 18). The rates of 3GCR *Enterobacteriaceae* carriage was highest in 1 to <2 year olds at 6.5%, and was 5.2% in <5 year-olds vs 1.7% in ≥5-year-olds (P = .11). 3GCR and ESBL-P *Enterobacteriaceae* carriage was associated with international travel within the previous year; 11.1% of ESBL-P *Enterobacteriaceae* carriers reported this history compared with 1.6% of noncarriers (P = .004). No other queried factor was found to increase risk. Of the 24 analyzed 3GCR isolates, 58% were multidrug resistant.

Conclusions. The 3GCR *Enterobacteriaceae* carriage rate exceeds 5% in healthy US children <5 years of age. International travel within the previous year increased the risk of 3GCR and ESBL-P *Enterobacteriaceae* carriage. In contrast, we found no differences in the rates of hospitalization or recent antibiotic exposure between carriers and noncarriers. Young children, who have the highest prevalence of colonization, might be a sentinel population to study to gain a better understanding of community sources of antibiotic-resistant *Enterobacteriaceae.*

Keywords. ESBL-producing *Enterobacteriaceae* intestinal carriage; extended-spectrum β-lactamase (ESBL); multidrug-resistant Gram-negative bacteria; third-generation cephalosporin-resistant *Enterobacteriaceae* (3GCR).

Infections caused by extended-spectrum β-lactamase-producing (ESBL-P) *Enterobacteriaceae* and other antibiotic-resistant (AR) Gram-negative bacteria are steadily rising in various healthcare settings [1–3]. This trend includes children; US laboratory surveillance data between 1999 and 2011 revealed a 3- to 5-fold increase in the proportions of pediatric Gram-negative bacterial isolates that were ESBL-P or third-generation cephalosporin resistant (3GCR) (to 0.92% and 3%, respectively) [3]. Although inpatient carriage rates for ESBL-P *Enterobacteriaceae* are the highest and exceed 10% in many intensive care units, individual cases frequently originate in the community and in patients without significant medical comorbidity [3–5]. 3GCR and ESBL-P *Enterobacteriaceae* infections are often multidrug resistant, and management in children can be particularly challenging because of the limited therapeutic options [5].

Asymptomatic intestinal carriage of AR *Enterobacteriaceae* can both follow and precede clinical infection [5–7]. Risk factors for acquisition and colonization of AR *Enterobacteriaceae* in children are not well characterized; the studies that are available identified primarily carriers after an index infection and found underlying neurologic and other medical conditions, along with recent antibiotic intake, to be predisposing factors

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[5–9]. In adults, foreign travel—particularly to certain regions and even after relatively short trips—has been associated with significant rates of new fecal carriage of ESBL-P bacteria [10–13]. Similarly, it has been increasingly recognized that the widespread, global dissemination of ESBLs at the general population level (particularly of the CTX-M enzymes) has resulted in communities with a high prevalence of ESBL carriers [14].

Community-based studies of pediatric AR *Enterobacteriaceae* carriage have revealed rates that vary widely, from <3% in young Swedish children (ESBL-P) to 4% to 8% in the Netherlands (3GCR) and >20% in sites in Spain and Africa (ESBL-P) [15–18]. From North America, however, AR bacterial intestinal carriage data at the community level are generally lacking, especially in children [14]. In this investigation, fecal specimens of healthy children from 3 urban US centers were tested for the presence of ESBL-P and 3GCR *Enterobacteriaceae* to determine rates of intestinal carriage. Basic healthcare exposures and travel in household (HH) members were queried and analyzed as risk factors for colonization. In addition, recovered 3GCR *Enterobacteriaceae* isolates were tested for susceptibility to relevant antibiotic classes.

METHODS

Study Design and Participants

This investigation was conducted as a substudy of a larger multicenter study on the epidemiology of pediatric gastroenteritis by the New Vaccine Surveillance Network (NVSN), funded by the US Centers for Disease Control and Prevention. Subjects of this AR *Enterobacteriaceae* colonization study were included after being enrolled as healthy controls in the primary NVSN study. Participating sites in this study were UCSF Benioff Children's Hospital Oakland in Oakland, California (OAK), Children's Mercy Hospital in Kansas City, Missouri, (KC), and Monroe Carrel Jr. Children's Hospital at Vanderbilt in Nashville, Tennessee (NASH).

Children between 14 days and 14 years of age were enrolled during well-child visits at their primary clinic. As healthy controls in the NVSN study, exclusion criteria were being immunocompromised, having had diarrhea or vomiting in the previous 14 days, and having had acute respiratory infection symptoms in the previous 3 days. Participants of this substudy underwent a brief survey that queried antibiotic intake by the child in the previous 3 months and international travel and/or hospitalization in any HH member and foreign visitors to the HH in the previous year (see the questionnaire in Supplementary Appendix).

Specimen Processing, Laboratory Analyses, and Definitions

According to the protocol of the NVSN study, stool specimens from the subject typically were obtained at the time of enrollment; when this was not possible, families were provided a container in which to collect and submit stool within 5 days by either direct drop-off at the study site or a study-arranged courier. After stool receipt, a separate aliquot of approximately 1 g/0.5 ml of stool was prepared in a 1-ml solution of sterile Luria broth with 20% glycerol specifically for this AR *Enterobacteriaceae* colonization study.

For initial screening for the presence of AR *Enterobacteriaceae*, 1 μL of the stool solution described above was streaked directly onto ESBL CHROMagar (CHROMagar, Paris, France) medium plates. The ESBL CHROMagar medium and plates were prepared from a prep powder according to product instructions at each of the 3 sites. Preparation of the stool solution and inoculation onto the ESBL CHROMagar medium plates typically were performed on the day of stool receipt; in the infrequent situation when this process was not possible (eg, specimen received on the weekend or another time when the laboratory coordinator was not available), the prepared stool aliquots were generally maintained at 2 to 8°C and tested within 2 to 3 days.

Inoculated ESBL CHROMagar plates were incubated at 37°C for 18 to 24 hours and then assessed for colony growth. *Klebsiella pneumoniae* (strain ATCC 700603) and *Escherichia coli* (strain ATCC 25922) were used as positive and negative controls, respectively. Non–ESBL-P bacteria are inhibited by ESBL CHROMagar medium; colonies that grow are putative ESBL producers, and different species have distinct colors [19]. Putative ESBL-P *E coli* and *Klebsiella* colonies were subcultured to establish pure colonies, which were placed in Luria broth with 20% glycerol and maintained at −80°C until further analysis. Matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (Bruker Daltonics, Inc, Billerica, MA) was performed on all putative (CHROMagar medium-recovered) ESBL-P *Enterobacteriaceae* colonies for bacteriologic species identification/confirmation.

All putative ESBL-P *E coli* and *Klebsiella* colonies underwent standard double-disk synergy testing on Muller-Hinton agar (BD Difco, Sparks, MD) following Clinical Laboratory Standards Institute (CLSI) guidelines [20]. Briefly, bacterial colonies were tested with the third-generation cephalosporins cefotaxime (30 μg) and ceftazidime (30 μg) alone and in combination with clavulanic acid (10 μg); the ESBL phenotype was defined as a ≥5-mm increase in the zone of inhibition with the combination of a third-generation cephalosporin with clavulanic acid when compared to the third-generation cephalosporin alone. Third-generation cephalosporin resistance was defined as nonsusceptibility (intermediate susceptibility or resistance) to either cefotaxime or ceftazidime (nonsusceptible zones of inhibition: cefotaxime, <23 mm; ceftazidime, <18 mm).

All confirmed 3GCR and ESBL-P *E coli* and *Klebsiella* isolates underwent additional antibiotic testing on Muller-Hinton agar with disks of amoxicillin-clavulanic acid, piperacillin-tazobactam, trimethoprim-sulfamethoxazole, aztreonam, nalidixic acid, meropenem, ampicillin, cephalothin, ceftriaxone and

cefepime (BD BBL, Franklin Lakes, NJ) and ciprofloxacin, tetracycline, cefaclor, gentamicin, amikacin, and imipenem (Hardy Diagnostics, Santa Maria, CA). Antimicrobial zones of inhibition were interpreted according to CLSI guideline breakpoints [20]. Multidrug resistance was defined as nonsusceptibility to ≥1 agent in ≥3 antimicrobial classes.

Statistics

Sample sizes for analysis and subject enrollment targets were governed primarily by feasibility considerations and what was anticipated to be achievable during a remaining year of the main NVSN surveillance study. Also, an absence of baseline data on AR *Enterobacteriaceae* carriage in healthy US children, along with uncertainties in the distribution of hypothesized risk factors (eg, proportion of subjects with foreign travel in HH members), challenged power calculations. A target of approximately 500 healthy controls who had submitted stool specimens was set and divided nearly evenly among the 3 participating sites.

Intestinal carriage was defined as having the presence of at least 1 colony of the specific AR *Enterobacteriaceae* in the subject's stool specimen. Descriptive statistics for intestinal 3GCR and ESBL-P *Enterobacteriaceae* carriage for various demographic groups were generated. 3GCR and ESBL-P *Enterobacteriaceae* carriers were compared with noncarriers for association with potential risk factors by χ^2 testing; statistical significance was set at a P value of <.05. The small sample of identified AR *Enterobacteriaceae* carriers, and subject subgroups (eg, according to age or reporting HH international travel), challenged the reliability of multivariable methods; thus, these methods were not performed. Statistical analysis was performed within the RedCAP 6.13.3 database system (Vanderbilt University) and with MedCalc 16.4.3 (MedCalc, Ostend, Belgium).

Ethics

The protocol was approved by the institutional review board/ethics committee at each participating site and the Centers for Disease Control and Prevention. Informed consent for performing the risk-factor survey and stool specimen laboratory testing was obtained from the legal guardians of each participant (all ≤14 years of age).

RESULTS

Between December 2013 and March 2015, a total of 761 subjects from the 3 sites were enrolled, and 519 (68.2%) submitted a stool specimen. The median age of the subjects with a stool specimen was 18 months; 51.1% were female.

Twenty-three analyzed subjects harbored 3GCR *Enterobacteriaceae* in their stool, for an overall intestinal carriage rate of 4.4%. Site-specific rates varied from 3.4% at OAK to 5.1% at KC (Table 1). Of the 3GCR intestinal carriers, 60.9% were female (P = .36). Of the 3GCR isolates, 78% (n = 18) were confirmed ESBL-P, and the overall ESBL-P *Enterobacteriaceae* carriage rate was 3.5%. The carriage rates for 3GCR and ESBL-P *Enterobacteriaceae* in 1- to <2-year-old children were 6.5% and 5.7%, respectively (Table 2). The carriage rates for 3GCR *Enterobacteriaceae* were 5.2% for <5-year-olds and 1.7% for ≥5-year-olds (P = .11).

Table 1. 3GCR, ESBL-P, and MDR *Eb* Carriage

Site (Total No. of Subjects Tested)	*Eb* Carriage Rate (% [Total No. of Carriers])		
	3GCR	ESBL-P	MDR
Oakland (176)	3.4 (6)	3.4 (6)	3.4 (6)
Kansas City (177)	5.1 (9)	3.4 (6)	1.7 (3)
Nashville (166)	4.8 (8)	3.6 (6)	2.4 (4)
Total (519)	4.4 (23)	3.5 (18)	2.5 (13)

Abbreviations: 3GCR, third-generation cephalosporin resistant; *Eb, Enterobacteriaceae*; ESBL-P, extended-spectrum β-lactamase producing (confirmed by double-disk diffusion testing); MDR, multidrug resistant (defined as nonsusceptible to ≥1 agent in ≥3 antimicrobial classes).

Completed risk-factor questionnaires from all 3GCR and ESBL-P *Enterobacteriaceae* carriers and 489 (98.6%) of 496 noncarriers were available; the associations of 3GCR and ESBL-P *Enterobacteriaceae* carriage with queried risk factors are presented in Table 3. 3GCR and ESBL-P *Enterobacteriaceae* carriage was associated with HH member foreign travel within the preceding year; for ESBL-P *Enterobacteriaceae*, 11.1% of carriers versus 1.6% of noncarriers (P = .004) had personal travel abroad. At OAK, where travel rates were highest among the 3 sites, 50% (3 of 6) of 3GCR and ESBL-P *Enterobacteriaceae* carriers had a HH travel history versus 11.2% of the noncarriers (P = .005). The countries that 3GCR and ESBL-P *Enterobacteriaceae* carriers and their HH members visited were Mexico, Nepal, the Dominican Republic, and Vietnam. Rates of hospitalization in the previous year and of having had any antibiotic exposure in the previous 3 months did not differ between carriers and noncarriers (for both 3GCR and ESBL-P *Enterobacteriaceae*).

Two distinct 3GCR *Enterobacteriaceae* isolates were analyzed from a single carrier; of the 24 analyzed isolates, 23 were 3GCR *E*

Table 2. 3GCR and ESBL-P *Eb* Carriage According to Age

Age Group (Total No. of Subjects)	*Eb* Carriage Rate (% [Total No. of Carriers])	
	3GCR	ESBL-P
0 to <1 y (178)	4.5 (8)	2.2 (4)
1 to <2 y (123)	6.5 (8)	5.7 (7)
2 to <3 y (60)	5.0 (3)	5.0 (3)
3 to <4 y (20)	5.0 (1)	5.0 (1)
4 to <5 y (23)	4.3 (1)	4.3 (1)
5 to <6 y (33)	0 (0)	0 (0)
6 to <7 y (19)	5.3 (1)	5.3 (1)
7 to 14 y (63)	1.6 (1)	1.6 (1)

Abbreviations: 3GCR, third-generation cephalosporin resistant; *Eb, Enterobacteriaceae*; ESBL-P, extended-spectrum β-lactamase producing (confirmed by double-disk diffusion testing).

Table 3. Risk Factors for 3GCR and ESBL-P *Eb* Carriage

	3GCR *Eb* (%)			ESBL-P *Eb* (%)		
Risk Factor	Carriers	Noncarriers	*P*[a]	Carriers	Noncarriers	*P*[a]
Any antibiotic in previous 3 mo	8.7	8.6	.99	11.1	8.5	.7
Child hospitalized[b]	4.3	4.3	1.0	5.6	4.3	.8
Any HH member hospitalized[b]	21.7	12.9	.22	22.2	12.8	.25
Any HH member admitted to ICU[b]	4.3	2.2	.51	5.6	2.2	.35
Foreign travel[b] by child[c]	8.7	1.6	**.02**	**11.1**	**1.6**	**.004**
Foreign travel[b] by HH member and not child	8.7	4.5	.35	11.1	4.5	.2
Foreign travel[b] by any HH member	17.4	6.1	**.03**	22.2	6.1	**.007**
Foreign visitors[b]	0	8.0	.16	0	7.9	.22

Abbreviations: 3GCR, third-generation cephalosporin resistant; *Eb*, *Enterobacteriaceae*; ESBL-P, extended-spectrum β-lactamase producing (confirmed by double-disk diffusion testing); HH, household; ICU, intensive care unit.
[a]According to "N-1" χ^2 test.
[b]Within the previous year.
[c]All subjects/children who travelled internationally had done so with a HH member (for AR *Eb* carriers and noncarriers).

coli, and 1 was *Klebsiella pneumoniae*. Antibiotic-susceptibility testing results are presented in Table 4. Seventy-nine percent of the isolates were resistant to trimethoprim-sulfamethoxazole, and 58% were resistant to ciprofloxacin. One (4%) isolate was meropenem intermediate. The proportion of 3GCR isolates that were multidrug resistant was 58% overall, but it varied substantially among the study sites (KC, 33%; OAK, 100%; NASH, 56%). All (6) 3GCR *Enterobacteriaceae* isolates from OAK were ESBL-P and were multidrug resistant.

DISCUSSION

In this analysis of 519 healthy children in Oakland, Nashville, and Kansas City, 4.4% were carriers of intestinal *Enterobacteriaceae*

Table 4. 3GCR *Enterobacteriaceae* Antibiotic Susceptibilities

3GCR Isolate	Identification	Cipro	TMP-SMX	Gent	Cefepime	Pip-Tazo	Mero	ESBL	MDR
OAK1	*E coli*	R	R	R	S	S	S	Y	Y
OAK2	*E coli*	R	R	R	I	I	S	Y	Y
OAK3	*E coli*	R	R	R	S	S	S	Y	Y
OAK4	*E coli*	R	R	S	S	S	S	Y	Y
OAK5	*E coli*	R	R	S	S	S	S	Y	Y
OAK6	*E coli*	R	R	S	S	S	S	Y	Y
KC1	*E coli*	S	S	S	S	R	S	N	N
KC2	*E coli*	S	R	S	S	S	S	N	N
KC3	*E coli*	S	S	S	S	S	S	Y	N
KC4	*E coli*	R	R	S	S	S	S	N	Y
KC5	*E coli*	S	R	S	S	S	S	Y	N
KC6	*E coli*	S	R	R	I	I	S	Y	Y
KC7	*E coli*	R	R	S	I	S	S	Y	Y
KC8	*E coli*	S	R	S	S	S	S	Y	N
KC9	*E coli*	R	S	S	S	S	S	Y	N
NASH1	*E coli*	R	S	R	I	S	S	Y	Y
NASH2	*E coli*	S	S	S	S	I	S	N	N
NASH3a[a]	*E coli*	R	R	R	S	I	S	Y	Y
NASH3b[a]	*E coli*	R	R	R	I	S	I	Y	Y
NASH4	*E coli*	R	R	S	S	S	S	Y	Y
NASH5	*E coli*	S	R	S	I	S	S	Y	N
NASH6	*E coli*	S	R	S	I	S	S	Y	N
NASH7	*E coli*	R	R	R	I	I	S	Y	Y
NASH8	*K pneumoniae*	S	R	S	R	S	S	N	N
Nonsusceptible, ESBL-P, or MDR rate (%)		58	79	33	38	25	4	79	58

Abbreviations: 3GCR, third-generation cephalosporin resistant; Cipro, ciprofloxacin; ESBL-P, extended-spectrum β-lactamase producing (confirmed by double-disk diffusion testing); Gent, gentamicin; I, intermediate; KC, Kansas City; MDR, multidrug resistant (defined as nonsusceptible to ≥1 agent in ≥3 antimicrobial classes); Mero, meropenem; N, no; NASH, Nashville; OAK, Oakland; Pip-Tazo, piperacillin-tazobactam; R, resistant; S, susceptible; TMP-SMX, trimethoprim-sulfamethoxazole; Y, yes.
[a]From the same subject.

resistant to third-generation cephalosporins; 3.5% specifically harbored ESBLs. This study is the largest community-based characterization of AR *Enterobacteriaceae* colonization in healthy children from North America to date. It is also 1 of very few pediatric studies to have examined international travel as a risk factor for either AR *Enterobacteriaceae* colonization or infection [21].

Previous reports on AR *Enterobacteriaceae* colonization in healthy children examined mainly ESBL-P (rather than 3GCR) *Enterobacteriaceae* and were primarily from discrete sites in Europe, with few from other regions. Although pediatric rates from earlier studies in other northern European countries were consistently <7% [15, 22–24], a recent analysis of 125 well 8- to 16-month-old children in northern Spain found a surprising 24% overall prevalence of ESBL-P *Enterobacteriaceae* colonization [17]. Data from children in Africa and Asia, which might inform community-level colonization, are limited but have consistently indicated high prevalences; children screened on presentation to medical facilities in Niger and Guinea-Bissau had ESBL-P *Enterobacteriaceae* rates of 32.6% and 31%, respectively [17, 25], and in nearly 400 healthy <6-year-olds attending childcare centers in Laos (2011), the ESBL-P *Enterobacteriaceae* carriage rate was 23% [26]. Existing data from adults in North America itself are minimal, and ESBL community carriage (based on travelers before departure [12], healthy military personnel [27], and vegetarians living in the Midwest [28]) might be best estimated to be ~2% [29]. In this context, ESBL-P *Enterobacteriaceae* rates found in this study (3.5% overall and 5.7% in children aged 1 to <2 years) are higher than ever reported in healthy Americans and are generally comparable to those in European countries.

In various case-control analyses [30, 31] and in studies that examined fecal carriage of travelers before and after trips abroad [10, 13], international travel was found to be a risk factor for ESBL-P *Enterobacteriaceae* colonization and infection in adults. Investigations of stool from Scandinavian travelers found that >20% acquire ESBL-P *Enterobacteriaceae* after time abroad (trips typically ~2 weeks); the rates were highest for those who visited destinations in Asia and were up to 80% for those who had diarrhea and took antibiotics during their journey [10, 13]. A recent comprehensive meta-analysis found that international travel conferred a higher risk for ESBL colonization than any other factor (relative risk, >4) [29]. A separate systematic review in which available community carriage and population census data were used estimated there are >1.1 billion ESBL-P *Enterobacteriaceae* carriers in southeast Asia [14]; these and other authors have described what has become a globalization of the CTX-M ESBL enzyme (in particular), with international travel and migration being key drivers [14, 31]. The findings of our analysis reflect the existing literature in adults; children with a personal history of foreign travel were 5 times more likely to be 3GCR *Enterobacteriaceae* carriers that those without such as history (20% [2 of 10] vs 4.1% [21 of 509], respectively; $P = .015$)

In our study, 3GCR and ESBL-P *Enterobacteriaceae* carriers and noncarriers had antibiotic exposure within the previous 3 months in nearly equal proportions. Although recent antibiotic use has been associated with increased risk of ESBL-P *Enterobacteriaceae* colonization in adults [28] and of ESBL infections in children [7–9, 32], previous pediatric studies did not show a consistent association of antibiotic intake with fecal ESBL-P *Enterobacteriaceae* carriage [16, 20, 24, 26, 33]. In addition, a history of hospitalization in our subjects or in their HH members was not a definitive risk factor for 3GCR or ESBL-P *Enterobacteriaceae* colonization, which also is consistent with data from adults [29]. The factors underlying new and sustained fecal carriage of AR bacteria are complex and not fully characterized, but they seem to involve gastrointestinal disruption and selective antibiotic pressure along with exogenous exposure to AR *Enterobacteriaceae* [6, 13, 34].

It should be noted that the majority (57% [13 of 23]) of 3GCR *Enterobacteriaceae*–colonized children lacked all the considered risk factors of HH international travel, recent personal antibiotic exposure, and HH hospitalization history. These findings support the idea that AR *Enterobacteriaceae* are truly present at the community level and that potential sources, including the food supply and general environment, might be widespread and common [14, 29, 33, 35].

Children have a unique place in the transmission dynamics (both acquisition and transfer) of AR bacteria. Infants in particular might have intimate contact with several adult caregivers and, by nature, are incontinent, have limited hygiene, and frequently touch materials in their environment. The immature neonatal/infant intestine seems particularly vulnerable to AR *Enterobacteriaceae* acquisition; the results of recent studies highlighted the fact that the infant microbiome is unstable and frequently populated with AR genes [36, 37]. Young children also appear prone to protracted carriage: studies employing molecular techniques of ESBL *Enterobacteriaceae* carrying infants discharged from neonatal intensive care units (NICU) [38, 39] and in international adoptees [40] have demonstrated duration of colonization of up to 2 years. AR *Enterobacteriaceae* strains can be regularly spread and then sustained within HH and daycare settings; in 1 longitudinal investigation, the intrafamilial transmission rate from colonized post–neonatal intensive care unit infants was 32% [39].

In addition, young children might have higher risk related to AR *Enterobacteriaceae* carriage itself; ~5% of children have at least 1 community-onset urinary tract infection by the age of 5 years (the pathogens of which, in healthy individuals, are presumed to be from their own intestinal flora). This risk is reflected in US clinical laboratory-based surveillance data; approximately half of 3GCR and ESBL-P pediatric isolates are from 1- to 5-year-olds, and the majority are from urine specimens [3].

Our study has important limitations. As a subinvestigation of a larger study, questions added to assess exposures associated

with AR *Enterobacteriaceae* carriage were few and simplistic; as a result, the evaluation of potential risk factors is incomplete. In particular, mainly to avoid recall bias, antibiotic exposure was gauged only in the binary fashion of having any or none within the previous 3 months; data on specific agent(s) and total duration of exposure and more distant antibiotic use, all of which can significantly affect intestinal *Enterobacteriaceae* composition, were not captured. Also, other possible contributors to AR *Enterobacteriaceae* carriage, such as diet, acid-suppressing drugs, and outpatient medical exposures, were not queried at all. Regarding international travel, children who visited abroad all did so with other HH members, which challenges determining the relative contribution of personal versus close-contact foreign travel on pediatric AR *Enterobacteriaceae* carriage. The relatively small number of subjects who reported HH member international travel limited closer consideration of destination and timing of travel in relation to carriage. Likewise, the small number of 3GCR (n = 23) and ESBL-P (n = 18) *Enterobacteriaceae* carriers limited our study power and did not allow for reliable comparisons of some possibly important strata, such as age and geographic site. Lastly, our initial specimen screening on a commercial medium and phenotypic (rather than genotypic) methods for AR bacterial detection might have failed to capture certain 3GCR or ESBL-P *Enterobacteriaceae*, which in turn would lead to an underestimation of carriage prevalence.

In conclusion, the current 3GCR and ESBL-P *Enterobacteriaceae* colonization rate in healthy US children is appreciable and >5% in specific locations and age groups. Acquisition and dissemination are most likely in the HH and community setting and might be unrelated to healthcare exposures. In our analysis, pediatric carriers of 3GCR and ESBL-P *Enterobacteriaceae* reported 5- to 7-fold-higher rates of international travel than noncarriers, which was the only significant risk factor. Young children have distinct risks related to 3GCR and ESBL-P *Enterobacteriaceae*, with what seem to be higher rates of acquisition and prolonged carriage, and might serve as an ideal population for additional study. With ESBL carriage recently estimated to be rising 5% per year globally [29], the issue is a serious public health concern with broad-ranging implications related to optimal empiric management of community-onset infections, transnational antibiotic stewardship, and infection control.

Supplementary Data

Supplementary materials are available at Journal of *the Pediatric Infectious Diseases Society* online.

Notes

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