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Seasonal variation in antimicrobial resistance rates of community-acquired *Escherichia coli* bloodstream isolates ☆

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ABSTRACT

Seasonal variation in community antimicrobial consumption has been demonstrated, with the lowest utilisation rates during summer months. This retrospective cohort study examined seasonality in antimicrobial resistance (AMR) rates of community-acquired *Escherichia coli* bloodstream isolates. *Escherichia coli* bloodstream isolates (2010–2015) were identified through the central Palmetto Health microbiology laboratory database. Multivariate logistic regression was used to examine seasonal variation in AMR. Poisson regression was used to evaluate the association between proportion of multidrug-resistant (MDR) isolates and bimonthly ambulatory antimicrobial prescription rates. Among 339 unique patients with community-acquired *E. coli* bloodstream infection [median age 65 years; 205 (60.5%) female], AMR rates were lower during summer (June–September) than the rest of the year for amoxicillin/clavulanic acid (17% vs. 29%; aOR = 0.53, 95% CI 0.30–0.92; $P = 0.02$), cefazolin (6% vs. 19%; aOR = 0.26, 95% CI 0.10–0.58; $P < 0.001$), ceftriaxone (2% vs. 6%; aOR = 0.25, 95% CI 0.04–0.93; $P = 0.04$) and trimethoprim/sulfamethoxazole (9% vs. 27%; aOR = 0.27, 95% CI 0.13–0.53; $P < 0.001$). The proportion of MDR *E. coli* declined from 31–36% during peak antimicrobial prescription to 11–14% in summer months; a 6.8% decline per interval decrease in antimicrobial prescription rates of 10/100 person-years ($P = 0.01$). There is significant seasonal variation in AMR rates of *E. coli* bloodstream isolates to four agents from frequently utilised antimicrobial classes in the community. Examination of seasonal variation in dominant serotypes of community-acquired *E. coli* bloodstream isolates in future will be valuable.

1. Introduction

Escherichia coli is the most common bacterium causing bloodstream infections (BSIs) in population-based settings [1–3]. Increasing antimicrobial resistance (AMR) rates of *E. coli* bloodstream isolates has limited the potential treatment options [4,5]. AMR in the community is often multifactorial, including dynamic interactions between hosts and the environment, person-to-person transmission and antimicrobial selection pressure. AMR of *E. coli* bloodstream isolates has been associated with recent use of antimicrobial agents, with the highest risk of resistance within 3 months of exposure [6–8].

Seasonal variation in antimicrobial consumption in the community has been previously demonstrated, with the highest rates of antimicrobial use during the winter and the lowest during summer months [9,10]. This seasonal variation was apparent for multiple antimicrobial classes, in particular penicillins and cephalosporins [9]. Moreover, there was an association between an increase in antimicrobial prescription rates and the peak of the influenza season [11]. This suggests that many antimicrobials may have been prescribed for viral upper respiratory tract infections in patients without clinical criteria for secondary bacterial infections [12]. A recent study estimated that at least one-third of ambulatory antimicrobials were prescribed for inappropriate indications [13]. The association between ambulatory antimicrobial use and resistance has been described mostly in children with otitis media and respiratory infections due to *Streptococcus pneumoniae* [14–16]. However,

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the impact of ambulatory antimicrobial consumption on potentially life-threatening community-acquired infections such as *E. coli* BSI remains undefined.

The aims of this retrospective cohort study were (i) to examine the seasonality of AMR rates of community-acquired *E. coli* bloodstream isolates to various agents and (ii) to evaluate the seasonality of multidrug-resistant (MDR) *E. coli* and the association between the proportion of MDR *E. coli* and community antimicrobial consumption.

2. Materials and methods

2.1. Settings

This retrospective cohort study was conducted at Palmetto Health inpatient and ambulatory facilities in Richland County, SC, USA. This included three community hospitals with a combined capacity of >1000 licensed beds, three emergency rooms, several affiliated urgent treatment centres and ambulatory care clinics. Palmetto Health provides medical care for over one-half of the population of Richland County. The Institutional Review Board at Palmetto Health approved the study and waived informed consent.

2.2. Definitions

Escherichia coli BSI was defined as monomicrobial growth of *E. coli* in a blood culture. A BSI was considered community-acquired if it occurred outside of the hospital or within 48 h of hospitalisation in the absence of healthcare-associated criteria such as recent hospitalisation or residence in a skilled nursing facility [17]. The primary source of BSI was determined based on the US Centers for Disease Control and Prevention (CDC) criteria [18]. An *E. coli* isolate was considered MDR if it was non-susceptible to at least three classes of antimicrobial agents [19].

2.3. Case ascertainment

All patients aged ≥18 years with a first episode of *E. coli* BSI were identified through the central Palmetto Health microbiology laboratory database from 1 January 2010 to 31 December 2015 ($n = 664$). Patients with hospital-onset ($n = 97$) and healthcare-associated ($n = 228$) *E. coli* BSIs were excluded since resistance in these isolates might be influenced by antimicrobial use in hospitals or skilled nursing facilities rather than the community. The remaining 339 patients with community-acquired *E. coli* BSI were included in the analysis.

Blood cultures were processed using standard microbiology techniques according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Identification of bloodstream isolates was performed using a VITEK®2 microbial identification system (bioMérieux, Marcy-l'Étoile, France) throughout the study period. Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) was added as a second method of identification after 1 January 2014. Antimicrobial susceptibility testing was performed using a VITEK®2 system with CLSI susceptibility breakpoints according to document M100-S20 throughout the study period.

2.4. Community antimicrobial use

Medicaid and State Employee Health Plan pharmacy claims for ambulatory oral antimicrobials were used for estimation of community antimicrobial prescription rates in South Carolina. Aggregated rate data were available from 1 January 2012 through 31 December 2015. Medicaid and State Employee Health Plan beneficiaries were estimated to represent 28% of South Carolina residents.

2.5. Statistical analysis

The primary aim of this retrospective cohort study was to examine the difference in AMR rates of *E. coli* bloodstream isolates during summer months (June–September) compared with the rest of the year, allowing a comparison of AMR rates between months with the lowest antimicrobial consumption and those with the highest antimicrobial consumption in the community, including the subsequent 3 months when the impact of antimicrobial exposure may still persist. Seasonal variation in AMR rates of *E. coli* bloodstream isolates to ampicillin, amoxicillin/clavulanic acid (AMC), cefazolin, ceftriaxone, ciprofloxacin and trimethoprim/sulfamethoxazole (TMP-SMX) were evaluated. To simplify statistical analysis, *E. coli* isolates that were non-susceptible to an antimicrobial agent were considered resistant. Logistic regression was used to examine the difference in AMR between the summer months and the rest of the year. A multivariate model determined whether seasonality in AMR was independent of calendar year, demographics (age, sex and ethnicity) and baseline clinical characteristics (diabetes mellitus, end-stage renal disease, liver cirrhosis, cancer and immunocompromised status, and source of BSI). Variables that demonstrated an association with AMR in the univariate analysis with a *P*-value of <0.10 were included in the respective multivariate model using backward selection criteria. The adjusted odds ratio (aOR) and 95% confidence interval (CI) was reported to demonstrate the strength of association between each variable and AMR.

The second aim of this study was to examine the seasonality of MDR *E. coli* bloodstream isolates. First, the proportion of MDR *E. coli* during the summer months was compared with the rest of the year using multivariate logistic regression as above. Second, the monthly proportions of MDR *E. coli* were plotted against time to visually demonstrate the seasonal variation in AMR throughout the 6-year study period. Third, Poisson regression was used to examine the association between community antimicrobial consumption in South Carolina and the proportion of MDR *E. coli* bloodstream isolates. Since antimicrobial use data were available from 1 January 2012 through to 31 December 2015, this analysis included only *E. coli* BSI during the respective 4 years of the study. Both antimicrobial use and proportion of MDR *E. coli* bloodstream isolates were divided into 2-month intervals to allow a stable and meaningful number of *E. coli* isolates in each interval for statistical analysis.

All study definitions and statistical analyses were determined a priori. JMP Pro v.12.1 (SAS Institute Inc., Cary, NC) was used for statistical analysis. The level of significance for statistical testing was defined as $P < 0.05$ (two-sided) unless otherwise specified.

3. Results

3.1. Antimicrobial resistance of Escherichia coli bloodstream isolates

During the 6-year study period, 339 *E. coli* bloodstream isolates were identified from 339 unique patients with a first episode of community-acquired *E. coli* BSI. The demographic and clinical characteristics of the cohort are given in Table 1. Overall in vitro antimicrobial susceptibility testing results of the *E. coli* bloodstream isolates are shown in Table 2.

AMR rates of community-acquired *E. coli* bloodstream isolates were significantly lower during the summer months compared with the rest of the year for AMC, cefazolin, ceftriaxone and TMP-SMX (Fig. 1). The proportions of *E. coli* bloodstream isolates demonstrating resistance to AMC, cefazolin, ceftriaxone and TMP-SMX during each 2-month interval of the study period are shown in Fig. 2.

Univariate logistic regression models demonstrated a lower risk of AMR among *E. coli* bloodstream isolates to AMC, cefazolin,

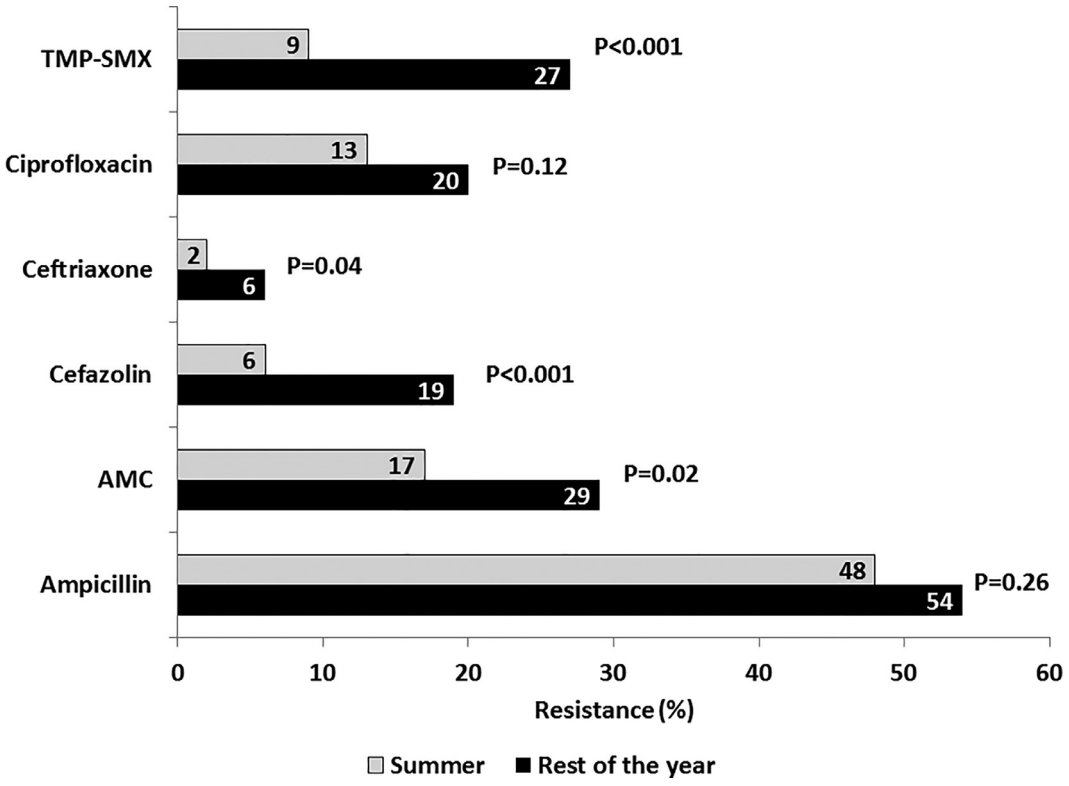

Fig. 1. Antimicrobial resistance rates of *Escherichia coli* bloodstream isolates during summer (June–September) compared with the rest of the year. AMC, amoxicillin/clavulanic acid; TMP-SMX, trimethoprim/sulfamethoxazole.

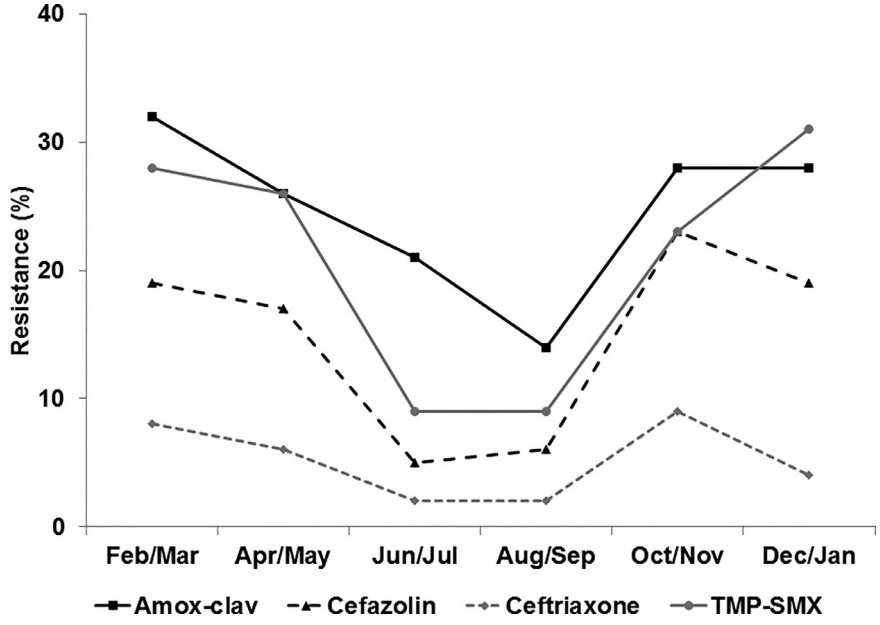

Fig. 2. Proportion of antimicrobial-resistant *Escherichia coli* bloodstream isolates by 2-month intervals, 2010–2015. Amox-clav, amoxicillin/clavulanic acid; TMP-SMX, trimethoprim/sulfamethoxazole.

ceftriaxone and TMP-SMX during summer months compared with the rest of the year (Supplementary Table S1). Notably, there were trends of declining AMR rates of *E. coli* isolates to AMC and TMP-SMX throughout the study period.

Following adjustments for calendar year, demographics and clinical variables in the respective multivariate models, the summer months remained independently associated with a significant decrease in AMR to AMC (aOR = 0.53, 95% CI 0.30–0.92; $P = 0.02$), cefazolin (aOR = 0.26, 95% CI 0.10–0.58; $P < 0.001$), ceftriaxone (aOR = 0.25, 95% CI 0.04–0.93; $P = 0.04$) and TMP-SMX (aOR = 0.27, 95% CI 0.13–0.53; $P < 0.001$).

3.2. Multidrug-resistant Escherichia coli

Overall, 82 (24.2%) of the *E. coli* bloodstream isolates were MDR. There was no significant temporal change in the proportion of MDR *E. coli* bloodstream isolates between 2010 and 2015 ($P = 0.25$). The proportion of MDR *E. coli* bloodstream isolates declined

Table 1
Demographic and clinical characteristics of patients with community-acquired *Escherichia coli* bloodstream infection ($n = 339$).

Characteristic	n (%)[a]
Age (years) [median (IQR)]	65 (52–76)
Female sex	205 (60.5)
Ethnicity	
African–American	172 (50.7)
White	152 (44.8)
Other	15 (4.4)
Diabetes mellitus	124 (36.6)
Liver cirrhosis	12 (3.5)
Cancer	38 (11.2)
Immunocompromised	27 (8.0)
Source of infection	
Urinary tract	265 (78.2)
Biliary tract	18 (5.3)
Gastrointestinal tract	18 (5.3)
Skin and soft tissue	6 (1.8)
Respiratory tract	5 (1.5)
Other	2 (0.6)
Unknown	25 (7.4)

IQR, interquartile range.
[a] Data are n (%) unless otherwise stated.

Table 2
In vitro antimicrobial susceptibility testing results of *Escherichia coli* bloodstream isolates ($n = 339$).

Antimicrobial agent	Susceptibility [n (%)]		
	S	I	R
Ampicillin	164 (48.4)	6 (1.8)	169 (49.9)
Amoxicillin/clavulanic acid	256 (75.5)	36 (10.6)	47 (13.9)
Cefazolin	290 (85.5)	8 (2.4)	41 (12.1)
Ceftriaxone	323 (95.3)	1 (0.3)	15 (4.4)
Ertapenem	339 (100)	0 (0)	0 (0)
Ciprofloxacin[a]	278 (82.5)	1 (0.3)	58 (17.2)
Gentamicin	312 (92.0)	0 (0)	27 (8.0)
Trimethoprim/sulfamethoxazole	269 (79.4)	0 (0)	70 (20.6)

S, susceptible; I, intermediate; R, resistant.
[a] Only 337 isolates were tested.

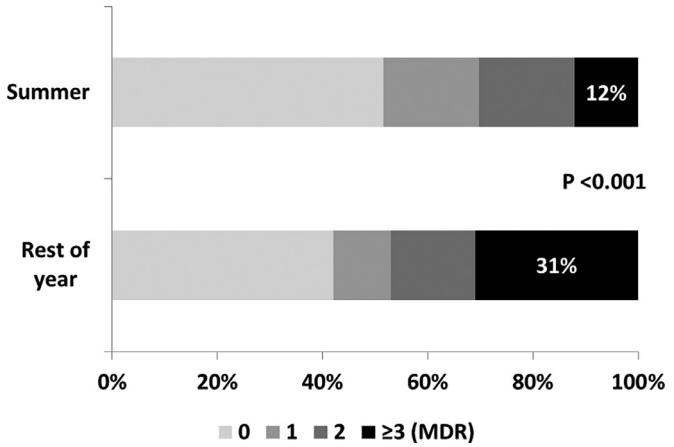

Fig. 3. Proportion of *Escherichia coli* bloodstream isolates by number of classes of antimicrobial resistance during summer months compared with rest of the year. MDR, multidrug-resistant.

during the summer months compared with the rest of the year (Fig. 3). Only 12% of *E. coli* isolates were MDR during summer months (June–September) compared with 31% during the rest of the year ($P < 0.001$). After adjustments in multivariate logistic regression, *E. coli* bloodstream isolates were less likely to be MDR during the summer than rest of the year (aOR = 0.32, 95% CI 0.17–0.59; $P < 0.001$). When plotted against time, the proportion of MDR *E. coli* peaked in the winter and declined during the summer months every year throughout the study period (Fig. 4).

3.3. Ambulatory antimicrobial use

There was seasonal variation in ambulatory antimicrobial consumption in South Carolina. The mean antimicrobial prescription rate was 69 per 100 person-years during the summer and 91 per 100 person-years during the rest of the year in 2012–2015 ($P < 0.001$) (Fig. 5). There was a significant association between the proportion of community-acquired MDR *E. coli* bloodstream isolates and ambulatory antimicrobial consumption in South Carolina ($P = 0.01$). The proportion of MDR *E. coli* declined by 6.8% (95% CI 2.3–11.2%) for each interval decrease in the rate of ambulatory antimicrobial prescription of 10/100 person-years.

4. Discussion

4.1. Seasonality of antimicrobial and multidrug resistance

Seasonal variation in the incidence rate of *E. coli* BSI has been demonstrated in population-based settings [20–22]. An increase in the incidence rate of gastrointestinal infections due to *E. coli* O157 in summer months compared with the rest of the year has also been previously described [23]. To our knowledge, this is the first study to report seasonal variation in AMR of community-acquired *E. coli* bloodstream isolates. AMR rates to four different agents and the proportion of MDR *E. coli* were lower during summer months compared with the rest of the year. This study also demonstrates a temporal association between the proportion of MDR *E. coli* and ambulatory antimicrobial consumption.

Penicillins and cephalosporins are among the most frequently prescribed oral antimicrobials in the community, with seasonal variation in ambulatory prescriptions in the USA [9,10]. It is likely that high consumption of oral penicillins and cephalosporins mostly for upper respiratory tract infections during the cold and flu season contribute to colonisation and subsequent infection with antimicrobial-resistant *E. coli* isolates [11]. This likely explains the seasonal variation in AMR of community-acquired *E. coli* bloodstream isolates to AMC, cefazolin and ceftriaxone. The seasonal variation in AMC and cefazolin resistance is consistent with the results of previous investigations of *E. coli* urinary isolates in Australia and community-acquired *E. coli* isolates from various sources in Spain [24,25]. It is speculated that the lack of significant seasonality in ampicillin resistance in the current study is likely due to the higher overall prevalence of ampicillin resistance among *E. coli* isolates throughout the calendar years 2010—2015 in comparison with earlier studies [24,26]. To our knowledge, this is the first study to describe seasonal variation in *E. coli* resistance rates to third-generation cephalosporins.

There was no significant seasonal variation in ciprofloxacin resistance of *E. coli* bloodstream isolates in the current study. This was also consistent with previous studies of *E. coli* urinary isolates in Australia and all-source ambulatory *E. coli* isolates in the USA [24,26]. This may be due to the uniqueness of the fluoroquinolone class. Whereas respiratory fluoroquinolones (e.g. levofloxacin and moxifloxacin) may be more frequently prescribed during the winter for respiratory tract infections, higher ciprofloxacin use during the summer predominantly for urinary tract infections may mask the seasonality of fluoroquinolone resistance [10,20]. Moreover, the long-term impact of fluoroquinolones on the microbiome may also explain the lack of significant seasonal variation in fluoroquinolone resistance among *E. coli* isolates. Although the highest risk of fluoroquinolone resistance was observed within 3 months from exposure, patients who received prior fluoroquinolones continued to

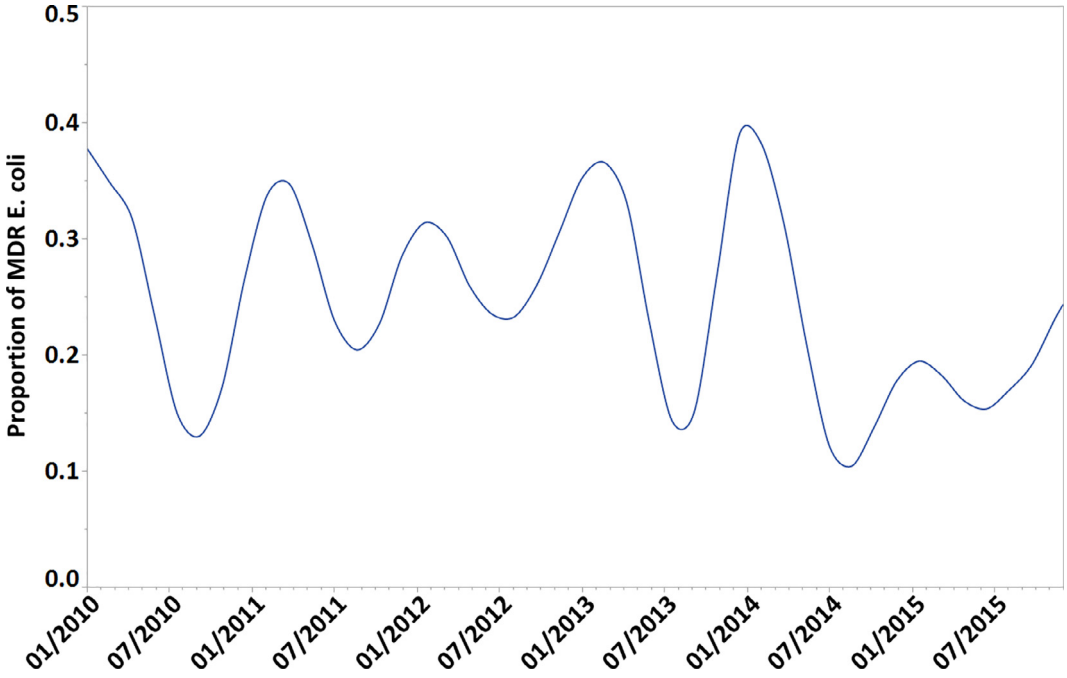

Fig. 4. Seasonal variation in multidrug-resistant (MDR) *Escherichia coli* bloodstream isolates.

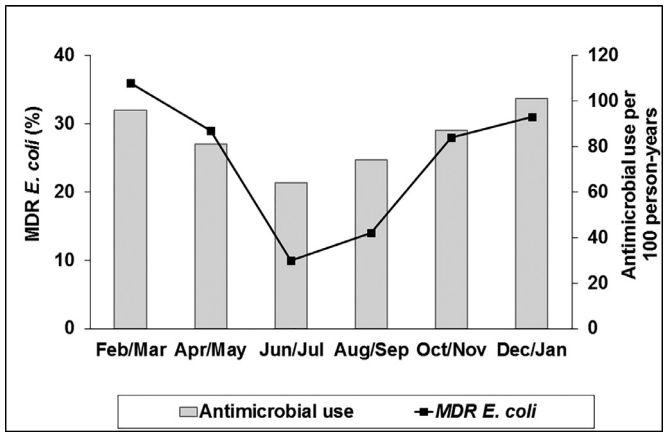

Fig. 5. Association between proportion of multidrug-resistant (MDR) *Escherichia coli* bloodstream isolates and ambulatory antimicrobial prescription rates in 2012–2015.

have a higher risk of resistance than those without prior fluoroquinolone use up to 1 year from the index fluoroquinolone course [27].

The seasonality in *E. coli* resistance to TMP-SMX is intriguing. First, TMP-SMX is not commonly used for the treatment of respiratory tract infections and does not demonstrate seasonal variation in prescription patterns [9,24,26]. However, a decline in TMP-SMX resistance was demonstrated during the summer months compared with rest of the year among *E. coli* bloodstream isolates in the current study as well as in *E. coli* isolates from urinary and other sources in two prior studies [24,26]. Future studies are warranted to further examine and explain the seasonality of AMR to TMP-SMX.

4.2. Potential explanations and implications

MDR *E. coli*, particularly ST131, emerged at the turn of the century as a dominant clone in the community in the USA [28]. BSIs due to MDR *E. coli* have a heavy burden both on patients and the healthcare system owing to higher mortality and longer hospital length of stay than BSIs due to susceptible isolates [29,30]. It is alarming that 24.2% of community-acquired *E. coli* bloodstream isolates in the current study overall were MDR and 36% during the peak of antimicrobial prescription season in the winter. The predominance of viral aetiology among respiratory tract infections (e.g. acute sinusitis, bronchitis, etc.) in the winter implies there is a huge room for improvement in ambulatory antimicrobial prescription [11,13]. Although patients with secondary bacterial infections may benefit from antimicrobial therapy, these patients may be identified based on established clinical criteria [12,31]. It has been estimated that up to 50% of ambulatory antimicrobials prescribed for respiratory conditions in the USA are unnecessary [32]. This emphasises the importance of ambulatory antimicrobial stewardship efforts to reduce inappropriate and unnecessary antimicrobial use in the community.

Although antimicrobial prescription rates in the community may provide an explanation for the seasonal variation in AMR of *E. coli* bloodstream isolates, it is surprising that changes in antimicrobial prescription over a relatively short period of time during the year may impact AMR rates at such a magnitude. Current observations may also be due to the cyclic emergence of antimicrobial-resistant *E. coli* clones in the environment during the winter for unexplained reasons [33]. Moreover, *E. coli* represents a broad range of bacterial strains. The current results may reflect different epidemics with various *E. coli* strains observed during the year. On a global scale, improving sanitation and reducing opportunities for transmission of antimicrobial-resistant bacteria in the environment and community may have more impact on AMR rates than simply reducing antimicrobial utilisation [33]. The current study also highlights the importance of national and international surveillance systems devoted to monitoring AMR profiles in bacterial species of particular clinical interest.

4.3. Strengths and limitations

Examination of seasonal variation in MDR *E. coli* and the association between the proportion of MDR *E. coli* and ambulatory antimicrobial prescription rates are unique features of the current

study. Moreover, focusing on AMR of *E. coli* bloodstream isolates adds clinical relevance to the current work given the heavy burden of BSIs on the general population owing to relatively high morbidity and mortality [34]. The current study has limitations. First, it demonstrated a temporal association between *E. coli* resistance rates in Richland County (South Carolina, USA) and antimicrobial prescription rates in a proportion of the state population using available data. However, overall antimicrobial utilisation rates in the current study are consistent with 2015 multisource data in South Carolina as reported by the CDC [35]. In addition, seasonal variation in antimicrobial prescription rates in South Carolina is consistent with national trends [9,10]. Second, AMR is often multifactorial involving various interactions between the host and the environment. Transmission of AMR in hospitals, intensive care units and other healthcare settings includes much more complex dynamics than the community [36,37]. Third, the study examined *E. coli* bloodstream isolates from one large healthcare system. Multicentre studies from various geographical locations may provide more diverse populations and AMR patterns. Finally, additional testing was not performed to determine the group or serotype of *E. coli* bloodstream isolates.

5. Conclusion

There is significant seasonal variation in AMR rates of community-acquired *E. coli* bloodstream isolates. This includes lower AMR rates to four tested agents and a smaller proportion of MDR *E. coli* during summer months than the rest of the year. This reduction in the proportion of MDR *E. coli* has been temporally associated with lower antimicrobial prescription rates during the summer in South Carolina. Future population-based studies should examine the seasonal variation in the most dominant serotypes of community-acquired *E. coli* bloodstream isolates.

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None.

Competing interests

PBB is an advisory board member for CutisPharma and has participated on a speaker's bureau for Melinta Therapeutics. All other authors declare no competing interests.

Ethical approval

The study was approved by the Institutional Review Board of Palmetto Health (Columbia, SC).

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2019.03.010.

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