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In vitro susceptibility of urinary *Escherichia coli* isolates to first- and second-line empirically prescribed oral antimicrobials: CANWARD surveillance study results for Canadian outpatients, 2007–2016 ☆

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ABSTRACT

Escherichia coli isolates ($n = 2035$) from urine specimens of outpatients presenting to Canadian medical clinics and hospital emergency departments from 2007–2016 were collected as part of the CANWARD surveillance study. Isolate identification and antimicrobial susceptibility testing (AST) were performed at a central site (Health Sciences Centre, Winnipeg, Canada). AST of first- and second-line oral antimicrobial agents was performed using CLSI methods (M07, 11th ed, 2018); fosfomycin was tested by agar dilution and all other agents by broth microdilution. Minimum inhibitory concentrations (MICs) were interpreted using CLSI M100 (2018) criteria. Fosfomycin (99.2% of isolates susceptible), nitrofurantoin (97.5%) and cefalexin (93.6%) were the most active agents tested; amoxicillin/clavulanic acid (AMC) (85.6%), ciprofloxacin (83.0%) and trimethoprim/sulfamethoxazole (SXT) (77.0%) were less active. Annual percentages of isolates positive for extended-spectrum β-lactamases (ESBLs) or demonstrating multidrug-resistant (MDR) phenotypes increased from 0.8% (2007) to 10.1% (2016), and from 9.7% (2007) to 16.5% (2016), respectively, whilst the annual frequency of AmpC-positive isolates decreased from a high of 3.2% in 2008 to 0.7% in 2016. The most common MDR phenotype of *E. coli* was non-susceptibility to AMC, ciprofloxacin, and SXT, accounting for 12.7% (26/205) of all MDR isolates. Rates of susceptibility were higher for fosfomycin than for the five other oral agents tested against ESBL-positive (96.1% susceptible) and MDR (95.1%) isolates and were equal to nitrofurantoin (96.4%) against AmpC-positive isolates. Prudent use of antimicrobials and close monitoring of antimicrobial susceptibilities of clinical uropathogenic *E. coli* isolates are imperative to help preserve the utility of oral antimicrobials.

1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in humans [1–5]. Uropathogenic *Escherichia coli* cause the majority of UTIs both in outpatients and inpatients [1–8]. Urine culture remains the gold standard for the identification of pathogens causing UTIs in symptomatic patients [1,9]; however, it is not recommended for otherwise healthy, non-pregnant, reproductive-age women presenting with symptomatic acute uncomplicated cystitis as culture results would not alter patient management or outcome in this patient group. Instead, such patients are empirically prescribed oral therapy at their care provider visit. In the majority of these patients, empirical therapy is successful as there is a relatively low likelihood of encountering a resistant uropathogen and the risk of complications with this approach is low [1,5,7]. Urine culture and antimicrobial susceptibility testing (AST) of bacterial pathogens is generally only performed following failure of empirical therapy or in cases of upper UTI (e.g. pyelonephritis), recurrent infection, where there is a risk of infection with antimicrobial-resistant organisms, or for patients with complicated UTI (e.g. urinary obstruction, immunosuppression) given the potential for less common uropathogens, antimicrobial-resistant isolates and higher risk of complications in these patients [5,9]. Treatment of asymptomatic bacteriuria is only indicated for pregnant women and patients undergoing a genitourinary procedure [10,11].

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The Infectious Diseases Society of America (IDSA) currently recommends an empirical regimen of 5 days of nitrofurantoin, a 3-day course of double-strength trimethoprim/sulfamethoxazole (SXT) in settings where the prevalence of SXT resistance is <10–20%, or a 3 g single dose of fosfomycin trometamol for treating acute bacterial cystitis in otherwise healthy, adult, non-pregnant females; fluoroquinolones and oral β-lactams, e.g. amoxicillin/clavulanic acid (AMC) and cefalexin, are second-line therapies [5]. Empirical treatment choices should ideally be based on local cumulative AST data. Fosfomycin and nitrofurantoin are only approved for the treatment of uncomplicated UTIs. Discrepancies between fosfomycin minimum inhibitory concentrations (MICs) determined by the reference agar dilution method [12,13] and by currently available commercial methods have been identified [14,15].

Over the last 20 years, antimicrobial resistance among uropathogens, including uropathogenic *E. coli*, has become increasingly common and is an important consideration in the management of outpatient UTIs [7,16–19]. In the USA, multidrug-resistant (MDR) phenotypes among outpatient urine isolates of *E. coli* increased from 9% in 2001 to 17% in 2010 [17]. Care providers should be cognisant of antimicrobial resistance rates provided in their local antibiogram as well as clinical and epidemiological risk factors associated with MDR infections as treatment options may be limited and the presence of unanticipated resistant or MDR pathogens can lead to ineffective empirical prescribing and subsequently to poor clinical outcomes with low microbiological and clinical cure rates and increased patient morbidity and mortality [7,17,20].

Reports providing antimicrobial susceptibility rates for uropathogens in outpatients receiving initial empirical therapy for community-acquired UTI are very limited because the majority of these patients (i.e. healthy, reproductive-age women presenting with symptomatic acute uncomplicated cystitis) are not requested to submit a urine specimen for culture [5,21]. Therefore, it should be assumed that many reports describing antimicrobial susceptibility of uropathogens in outpatients likely include isolates that are the result of treatment failures, recurrent infection, upper UTI or complicated infection [6,16–18,22–26]. AST surveillance data for uropathogenic *E. coli* isolated from Canadian patients were last published for isolates collected between 2010 and 2013 [22]. In the current study, uropathogenic *E. coli* isolates recovered from outpatients seeking care at medical clinics and hospital emergency departments in Canada from 2007–2016 were tested. The intent was to assess current rates of resistance to all commonly tested and reported empirically prescribed oral first- and second-line antimicrobial agents [5] as well as to document changes in susceptibility to these agents over time.

2. Materials and methods

2.1. Bacterial isolates

The *E. coli* isolates tested in this study ($n = 2035$) were cultured from urine specimens of outpatients attending primary care and specialty medical clinics as well as hospital emergency departments and submitted to the annual CANWARD surveillance study from 2007–2016 [22,27]. If isolate identification at the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada) [28] was not consistent with the identification provided by the submitting laboratory, the isolate was removed from the study. The low number of outpatient urine isolates per year (203–601 isolates/year; mean, 330 isolates/year) (Table 1) collected by the CANWARD surveillance study reflects that these isolates are not the sole focus of the study, however, we believe they are an important source of data to inform on changes in the prevalence of antimicrobial resistance in uropathogenic *E. coli* infecting Canadian outpatients.

2.2. Antimicrobial susceptibility testing (AST)

AST of fosfomycin was performed by the Clinical and Laboratory Standards Institute (CLSI) agar dilution method with Mueller–Hinton agar supplemented with 25 μg/mL glucose-6-phosphate; all other antimicrobial agents were tested in cation-adjusted Mueller–Hinton broth using in-house-prepared 96-well broth microdilution panels prepared according to CLSI guidelines [12,13]. Quality control was performed following CLSI recommendations, and MICs were interpreted using CLSI M100 breakpoints [12]. Cefazolin was tested as a surrogate for cefalexin as permitted by the CLSI M100 standard [12]. Extended-spectrum β-lactamase (ESBL)-producing *E. coli* isolates were screened for and were confirmed phenotypically following the CLSI method [12]. *Escherichia coli* isolates were deemed AmpC β-lactamase-positive if they demonstrated an MIC of ≥1 μg/mL for ceftriaxone and/or ceftazidime (data not shown) and/or aztreonam (data not shown), an MIC of ≥32 μg/mL for cefoxitin (data not shown) and were phenotypically negative for ESBL production [29]. MDR *E. coli* isolates were defined by non-susceptibility to agents from three or more antimicrobial classes according to a published guideline [30].

2.3. Statistical analysis

For the purpose of statistical analysis, isolates were defined as either susceptible or non-susceptible to an antimicrobial agent; isolates testing as intermediate were included in the non-susceptible group. A second-degree factorial multivariate stepwise regression analysis using available variables was performed to identify variables associated with non-susceptibility of *E. coli* isolates in this study. The following variables were included in the model: year of study; patient age; patient sex; and patient location (emergency room or hospital outpatient clinic). Initially, a stepwise regression model was created including all of the variables and second-degree interactions. To exclude variables without a significant impact on the model, variables were excluded from the final model in such a way as to minimise the corrected Akaike Information Criterion. Finally, a regression model was created including only the variables and interactions with a significant impact on resistance to an antimicrobial agent. In the multivariate model, a *P*-value of ≤0.05 was considered statistically significant.

Differences between fosfomycin and nitrofurantoin resistance within phenotypic subgroups of *E. coli* were assessed using Fisher's exact test. Significance was defined as $P < 0.05$ with a Bonferroni correction for multiple comparisons. Six phenotype subgroups were assessed (ESBL-positive, MDR, and non-susceptible to ciprofloxacin, SXT, cefalexin or AMC), therefore the *P*-value for significance was corrected to $P < 0.008$ for subgroup analyses. Statistical analysis was performed using JMP 14 software (SAS Institute Inc., Cary, NC).

3. Results

Escherichia coli was the most common urinary pathogen isolated in each year from 2007–2016 accounting for between 56.6% (2015) and 65.8% (2009) of isolates per annum (overall, 61.7%); the second most common pathogen isolated was *Klebsiella pneumoniae*, which accounted for approximately 10% of isolates per year [range, 6.7% (2008) to 12.9% (2013) per annum] (Table 1). Enterobacteriaceae accounted for between 77.2% (2007) and 84.7% (2016) of isolates per annum (overall, 80.4%). Gram-positive cocci (enterococci

Table 1
Annual prevalence of bacterial species isolated from urine specimens of outpatients in Canada, 2007–2016.

Year (total *n*)	*n* (% of annual *n*)							
	Escherichia coli	*Klebsiella* spp.[a]	*Proteus* spp.[b]	*Enterobacter* spp.[c]	Other species of Enterobacteriaceae[d]	*Pseudomonas aeruginosa*	*Enterococcus* spp.[e]	*Staphylococcus* spp.[f]
2016 (215)	139 (64.7)	27 (12.6)	7 (3.3)	6 (2.8)	3 (1.4)	4 (1.9)	15 (7.0)	9 (4.2)
2015 (228)	129 (56.6)	29 (12.7)	10 (4.4)	4 (1.8)	7 (3.1)	3 (1.3)	17 (7.5)	20 (8.8)
2014 (207)	130 (62.8)	19 (9.2)	12 (5.8)	2 (1.0)	4 (1.9)	5 (2.4)	24 (11.6)	6 (2.9)
2013 (255)	146 (57.3)	33 (12.9)	8 (3.1)	11 (4.3)	8 (3.1)	5 (2.0)	24 (9.4)	14 (5.5)
2012 (203)	119 (58.6)	26 (12.8)	9 (4.4)	6 (3.0)	8 (3.9)	5 (2.5)	17 (8.4)	10 (4.9)
2011 (244)	145 (59.4)	27 (11.1)	9 (3.7)	5 (2.0)	9 (3.7)	3 (1.2)	20 (8.2)	15 (6.1)
2010 (441)	271 (61.5)	42 (9.5)	12 (2.7)	12 (2.7)	11 (2.5)	6 (1.4)	55 (12.5)	20 (4.5)
2009 (471)	310 (65.8)	46 (9.8)	15 (3.2)	11 (2.3)	11 (2.3)	5 (1.1)	37 (7.9)	17 (3.6)
2008 (434)	285 (65.7)	29 (6.7)	18 (4.1)	7 (1.6)	13 (3.0)	8 (1.8)	46 (10.6)	20 (4.6)
2007 (601)	361 (60.1)	59 (9.8)	19 (3.2)	6 (1.0)	19 (3.2)	11 (1.8)	70 (11.6)	32 (5.3)
All (3299)	2035 (61.7)	337 (10.2)	119 (3.6)	70 (2.1)	93 (2.8)	55 (1.7)	325 (9.9)	163 (4.9)

[a] The 337 *Klebsiella* spp. isolates comprised *Klebsiella pneumoniae* (*n* = 275), *Klebsiella oxytoca*/*Raoultella* spp. (*n* = 54) and unspeciated *Klebsiella* (*n* = 8).
[b] The 119 *Proteus* spp. isolates comprised *Proteus mirabilis* (*n* = 116) and *Proteus vulgaris* (*n* = 3).
[c] The 70 *Enterobacter* spp. isolates comprised *Enterobacter cloacae* (*n* = 44), *Enterobacter aerogenes* (*n* = 23), *Enterobacter agglomerans* (*n* = 1), *Enterobacter asburiae* (*n* = 1) and unspeciated *Enterobacter* (*n* = 1).
[d] The 93 other species of Enterobacteriaceae comprised *Citrobacter freundii* (*n* = 27), *Morganella morganii* (*n* = 20), *Citrobacter koseri* (*n* = 15), *Serratia marcescens* (*n* = 9), *Citrobacter amalonaticus* (*n* = 5), *Providencia stuartii* (*n* = 5), *Citrobacter braakii* (*n* = 2), unspeciated *Citrobacter* (*n* = 2), *Hafnia alvei* (*n* = 2), *Providencia rettgeri* (*n* = 2), *Citrobacter diversus* (*n* = 1), *Lelliottia amnigena* (*n* = 1), *Salmonella enterica* (*n* = 1) and *Serratia fonticola* (*n* = 1).
[e] The 325 *Enterococcus* spp. isolates comprised *Enterococcus faecalis* (*n* = 164), unspeciated *Enterococcus* (*n* = 152), *Enterococcus faecium* (*n* = 7), *Enterococcus avium* (*n* = 1) and *Enterococcus casseliflavus* (*n* = 1).
[f] The 163 *Staphylococcus* spp. isolates comprised *Staphylococcus aureus* (*n* = 75), unspeciated coagulase-negative staphylococci (*n* = 48), *Staphylococcus saprophyticus* (*n* = 33), *Staphylococcus epidermidis* (*n* = 6) and *Staphylococcus hominis* (*n* = 1).

Table 2
Annual rates of in vitro susceptibility of first- and second-line empirically prescribed oral antimicrobial agents for outpatient urine isolates of *Escherichia coli* in Canada, 2007–2016.

Year (*n*)	MIC_{90} (μg/mL)/% susceptible					
	AMC	LEX[a]	CIP	FOS	NIT	SXT
2016 (139)	16/79.1	>128/88.5	>16/79.9	4/99.3	16/97.8	>8/77.7
2015 (129)	16/83.7	16/92.2	>16/77.5	2/99.2	16/97.7	>8/73.6
2014 (130)	16/83.7	>128/87.6	>16/78.3	2/100	16/98.5	>8/71.3
2013 (146)	16/86.3	8/94.5	16/84.2	4/100	32/97.9	>8/80.1
2012 (119)	16/79.0	8/94.1	>16/83.2	4/99.2	32/96.6	>8/77.3
2011 (145)	16/86.8	64/88.3	>16/73.8	2/99.3	32/97.2	>8/70.8
2010 (271)	16/82.3	4/97.0	>16/83.0	4/99.6	32/96.7	>8/75.6
2009 (310)	8/94.8	8/95.8	>16/85.8	4/99.4	16/98.7	>8/74.2
2008 (285)	8/97.5	8/91.9	>16/83.5	4/97.2	32/96.5	>8/76.8
2007 (361)	16/75.8	8/96.4	>16/88.1	2/99.4	32/97.5	>8/84.5
All (2035)	16/85.6	8/93.6	>16/83.0	4/99.2	32/97.5	>8/77.0

MIC_{90}, minimum inhibitory concentration required to inhibit 90% of the isolates; AMC, amoxicillin/clavulanic acid; LEX, cefalexin; CIP, ciprofloxacin; FOS, fosfomycin; NIT, nitrofurantoin; SXT, trimethoprim/sulfamethoxazole.
[a] LEX susceptibility was predicted by cefazolin minimum inhibitory concentration (MIC) ≤16 μg/mL [12].

and staphylococci) accounted for between 11.2% (2016) and 17.0% (both 2007 and 2010) of isolates per annum (overall, 14.8%).

Overall from 2007–2016, fosfomycin (99.2% of isolates susceptible), nitrofurantoin (97.5%) and cefalexin (93.6%) were the most active agents against urinary *E. coli* isolates (Table 2); AMC (85.6% of isolates susceptible), ciprofloxacin (83.0%) and SXT (77.0%) were less active. Of the six antimicrobial agents tested against *E. coli*, a trend of decreasing susceptibility was observed for SXT ($P = 0.0435$), cefalexin ($P = 0.0004$) and ciprofloxacin ($P = 0.0001$) but did not reach significance for AMC ($P = 0.0881$) (Table 2). In the most recent year of data (2016), in vitro susceptibilities of urinary *E. coli* isolates to SXT (77.7%), AMC (79.1%) and ciprofloxacin (79.9%) were <80% and were compromised in comparison with fosfomycin (99.3%) and nitrofurantoin (97.8%).

Annual ESBL rates among isolates of *E. coli* were variable but increased significantly from 0.8% in 2007 to 10.1% in 2016 ($P < 0.0001$) (Table 3). MDR frequencies were also variable but increased significantly from 9.7% in 2007 to 16.5% in 2016 ($P = 0.0009$), whilst AmpC-positive annual frequencies decreased non-significantly from 3.2% in 2008 to 0.7% in 2016 ($P = 0.8005$).

The overall percent susceptible rate to fosfomycin was approximately 10% higher than to nitrofurantoin for ESBL-positive isolates (96.1% vs. 87.0% susceptible; $P = 0.0393$) and MDR isolates (95.1% vs. 86.8% susceptible; $P = 0.0026$) of *E. coli* (Table 4). The percent susceptible rate to fosfomycin was approximately 5–6% higher than to nitrofurantoin for *E. coli* isolates that were non-susceptible to SXT (98.3% vs. 94.0% susceptible; $P = 0.0004$), cefalexin (96.2% vs. 90.8% susceptible; non-significant, $P = 0.0652$), AMC (99.3% vs. 94.9% susceptible; $P = 0.0001$) and ciprofloxacin (97.1% vs. 91.6% susceptible; $P = 0.0013$).

Of the 2035 *E. coli* isolates, 1674 (82.3%) were from female patients and 539 (26.5%) were from female patients aged 18–45 years. Increasing age was significantly associated with non-susceptibility to cefalexin ($P = 0.0024$), ciprofloxacin ($P < 0.0001$) and nitrofurantoin ($P = 0.0001$) as well as being associated with isolation of ESBL-positive ($P = 0.0021$) and MDR ($P < 0.0001$) isolates. *Escherichia coli* isolates with MDR (13.0% vs. 9.4%), ESBL-positive (5.3% vs. 3.5%) and AmpC-positive (1.9% vs. 1.3%) phenotypes were more commonly isolated from male patients than from female patients, however these differences did not reach

Table 3
Annual rates of multidrug-resistant (MDR), extended-spectrum β-lactamase (ESBL)-positive and AmpC-positive isolates among outpatient urine isolates of *Escherichia coli* in Canada, 2007–2016.

Year (*n*)	% of annual *n*		
	% MDR[a,b]	% ESBL	% AmpC
2016 (139)	16.5	10.1	0.7
2015 (129)	12.4	5.4	0.8
2014 (130)	16.9	10.8	0.8
2013 (146)	7.5	3.4	2.1
2012 (119)	9.2	1.7	1.7
2011 (145)	13.1	9.0	2.1
2010 (271)	8.5	1.8	1.1
2009 (310)	6.5	1.6	1.6
2008 (285)	8.8	3.2	3.2
2007 (361)	9.7	0.8	NA
Mean (2035)	10.1	3.8	1.4

SXT, trimethoprim/sulfamethoxazole; AMC, amoxicillin/clavulanic acid.

[a] A MDR isolate was defined by a phenotype that was non-susceptible to agents from three or more antimicrobial classes [30]. The agents used to define *E. coli* isolates as MDR were gentamicin (aminoglycoside), piperacillin/tazobactam (antipseudomonal penicillin + β-lactamase inhibitor), meropenem (carbapenem) and cefazolin [non-extended-spectrum cephalosporin; a cefazolin minimum inhibitory concentration (MIC) of ≥32 μg/mL was used to predict non-susceptibility to cefalexin], ceftriaxone (extended-spectrum cephalosporin), ciprofloxacin (fluoroquinolone), SXT (folate pathway inhibitor), tigecycline (glycylcycline), AMC (penicillin + β-lactamase inhibitor), fosfomycin (phosphonic acid) and nitrofurantoin (nitrofuran) [30].

[b] The five most common MDR phenotypes were: isolates non-susceptible to AMC, ciprofloxacin and SXT ($n = 26$; 12.7% of MDR isolates); isolates non-susceptible to ciprofloxacin, gentamicin and SXT ($n = 25$; 12.2% of MDR isolates); isolates non-susceptible to AMC, ciprofloxacin, gentamicin and SXT ($n = 11$; 5.4% of MDR isolates); isolates non-susceptible to cefazolin, ceftriaxone, ciprofloxacin, gentamicin and SXT ($n = 11$; 5.4% of MDR isolates); and isolates non-susceptible to cefazolin, ceftriaxone, ciprofloxacin and SXT ($n = 10$; 4.9% of MDR isolates).

statistical significance in the multifactorial regression model because age was identified as a confounding variable that had a greater effect on non-susceptibility of isolates from males (median age 60 years) than females (median age 46 years) (Table 5). However, *E. coli* isolates non-susceptible to ciprofloxacin were significantly more common in males (24.1%) than in females (15.5%) independent of age ($P = 0.0014$).

4. Discussion

Recent studies describing the antimicrobial susceptibilities of urinary *E. coli* isolates in North America and elsewhere have frequently reported rates of resistance to SXT and fluoroquinolones of >20% and rates of susceptibility to fosfomycin and nitrofurantoin in excess of 97% and 99%, respectively [6,16–18,22–26]. In addition, 10–20% of urinary *E. coli* isolates have been reported to harbour ESBLs [6,16,23,31,32] that inactivate penicillins and cephalosporins. The spread of *E. coli* sequence type 131 (ST131), which possesses a plasmid-mediated ESBL (CTX-M-14 or CTX-M-15) and chromosomal fluoroquinolone resistance-conferring mutations (in *gyrA*/*gyrB* genes), underlies the majority of increases in resistance noted for these two antimicrobial classes in patients both with community-onset and healthcare-associated diseases [6,16,23,31,32].

In the current study, the *E. coli* isolates tested likely represented at least partially a selected population given that only 61.7% of outpatient urinary isolates were *E. coli*, a percentage well below the expected prevalence of 75–95% [1–8]. However, these data do represent real-world isolates that can be expected to be grown from outpatient urine specimens submitted to clinical microbiology laboratories for culture and AST. We accept that the data may somewhat overestimate the prevalence of resistance, ESBLs, AmpC β-lactamases and MDR isolates among uropathogenic *E. coli* in outpatients in Canada. Regardless of these caveats, fosfomycin (99.2% susceptible) and nitrofurantoin (97.5% susceptible) were both very active in vitro against the *E. coli* isolates tested. Current (2016) in vitro susceptibilities of urinary isolates of *E. coli* to SXT (77.7%) and ciprofloxacin (79.9%), two frequently prescribed empirical agents for outpatient UTIs, appear compromised compared with fosfomycin and nitrofurantoin. Of note, when comparing fosfomycin and nitrofurantoin, susceptibility to fosfomycin was ≥10% higher than to nitrofurantoin both for ESBL-positive and MDR isolates of *E. coli*, and susceptibility to fosfomycin was ≥5% higher than to nitrofurantoin for isolates of *E. coli* non-susceptible to SXT, cefalexin, AMC and ciprofloxacin.

In the current study, fosfomycin (99.2% of isolates susceptible), nitrofurantoin (97.5%) and cefalexin (93.6%) were observed to be the most active oral agents; AMC (85.6%), ciprofloxacin (83.0%) and SXT (77.0%) were less active. ESBL rates among isolates of *E. coli* increased from 0.8% in 2007 to 10.1% in 2016 and MDR rates increased from 9.7% in 2007 to 16.5% in 2016, whilst the annual frequency of AmpC-positive isolates decreased from a high of 3.2% in 2008 to 0.7% in 2016. Rates of susceptibility were higher for fosfomycin than for the other agents tested against ESBL-positive (96.1% susceptible) and MDR isolates (95.1% susceptible) and were equal to nitrofurantoin (96.4%) against AmpC-positive isolates. Several studies have shown that older patient age, male sex, recent hospitalisation, prior use of antimicrobials and specific geographical locations are risk factors associated with increased resistance rates to SXT, fluoroquinolones and penicillins as well as elevated rates of ESBL-producing and MDR isolates of uropathogenic *E. coli* both in community and hospitalised patients, whilst carbapenems, fosfomycin and nitrofurantoin remain effective treatments in patients with these risk factors [6,18,22–26].

This study has a few limitations that are important to identify. First, because urine specimens are not recommended to be collected from patients with uncomplicated UTI, we acknowledge that the rates of resistance calculated may overestimate the actual resistance rates in outpatients, as patients with complicated UTIs, co-morbidities or recent antimicrobial exposure, or healthcare-related infections may be present in the data set [33]. Second, we cannot account for the possible inclusion of isolates representing asymptomatic bacteriuria in the collection, which also may have had an impact on the resistance rates reported. Lastly, although we tried to restrict isolates to those that represented outpatient infections, it is possible that some isolates were from patients who had been hospitalised shortly before sample collection. Also, some of these outpatients may have received antimicrobial agents in the weeks prior to their current UTI, which potentially may have increased the isolation of resistant bacterial pathogens reported.

In conclusion, *E. coli* was the most common bacterial pathogen isolated from urine specimens of Canadian outpatients when culture was performed. The annual prevalence of Enterobacteriaceae, *P. aeruginosa* and Gram-positive cocci among urine specimens from Canadian outpatients was consistent from 2007–2016. In vitro susceptibility of urine isolates of *E. coli* to SXT was <80% for 8 of the 10 years between 2007 and 2016, and its use as empirical therapy should be reviewed based upon local antibiograms. Fosfomycin (99.2% of isolates susceptible) and nitrofurantoin (97.5% of isolates susceptible) were the most active antimicrobial agents in vitro against *E. coli* isolated from Canadian outpatients from 2007–2016. Based on these data as well as recent data generated by other investigators and expert reviews of the available literature [7,21,22,25], the activity of fosfomycin and nitrofurantoin remains high for most cases of *E. coli* UTI, including infections caused by MDR *E. coli* isolates.

Table 4
Cumulative in vitro activities of first- and second-line empirically prescribed oral antimicrobial agents against outpatient urine isolates of *Escherichia coli* in Canada, 2007–2016, stratified by resistance profile.

Phenotype (*n*)	Antimicrobial agent	MIC (μg/mL)			CLSI M100 MIC interpretation		
		MIC_{50}	MIC_{90}	Range	%S	%I	%R
All isolates (2035)	AMC	4	16	≤0.06 to >32	85.6	10.5	3.9
	Cefalexin	2	8	≤0.5 to >128	93.6	NA[a]	6.4
	Ciprofloxacin	≤0.06	>16	≤0.06 to >16	83.0	0.1	16.9
	Fosfomycin	≤1	4	≤1 to >512	99.2	0.7	0.1
	Nitrofurantoin	16	32	≤1–256	97.5	1.6	0.9
	SXT	≤0.12	>8	≤0.12 to >8	77.0	NA	23.0
SXT-non-susceptible (468)	AMC	8	16	1 to >32	71.4	22.8	5.8
	Cefalexin	4	>128	≤0.5 to >128	85.3	NA	14.7
	Ciprofloxacin	0.25	>16	≤0.06 to >16	56.6	0.5	42.9
	Fosfomycin	≤1	4	≤1–128	98.3	1.7	0
	Nitrofurantoin	16	32	≤1–256	94.0	3.4	2.6
	SXT	>8	>8	4 to >8	0	NA	100
Nitrofurantoin-non-susceptible (51)	AMC	8	16	1–32	70.6	23.5	5.9
	Cefalexin	4	>128	1 to >128	76.5	NA	23.5
	Ciprofloxacin	16	>16	≤0.06 to >16	43.1	0	56.9
	Fosfomycin	2	16	≤1–128	96.0	4.0	0
	Nitrofurantoin	64	128	64–256	0	62.7	37.3
	SXT	>8	>8	≤0.12 to >8	45.1	NA	54.9
Fosfomycin-non-susceptible (17)	AMC	4	16	2–32	88.2	5.9	5.9
	Cefalexin	2	>128	1 to >128	70.6	NA	29.4
	Ciprofloxacin	16	>16	≤0.06 to >16	41.2	0	58.8
	Fosfomycin	128	128	128 to >512	0	94.1	5.9
	Nitrofurantoin	16	64	4–64	88.2	11.8	0
	SXT	0.5	>8	≤0.12 to >8	52.9	NA	47.1
Cefalexin-non-susceptible (131)	AMC	16	>32	≤0.06 to >32	47.3	26.0	26.7
	Cefalexin	>128	>128	32 to >128	0	NA	100
	Ciprofloxacin	>16	>16	≤0.06 to >16	38.2	0	61.8
	Fosfomycin	2	4	≤1 to >512	96.2	3.0	0.8
	Nitrofurantoin	16	32	≤1–256	90.8	5.4	3.8
	SXT	>8	>8	≤0.12 to >8	47.3	NA	52.7
AMC-non-susceptible (293)	AMC	16	32	16 to >32	0	73.0	27.0
	Cefalexin	8	>128	1 to >128	76.5	NA	23.5
	Ciprofloxacin	≤0.06	>16	≤0.06 to >16	64.5	0	35.5
	Fosfomycin	≤1	4	≤1–128	99.3	0.7	0
	Nitrofurantoin	16	32	≤1–256	94.9	3.4	1.7
	SXT	0.5	>8	≤0.12 to >8	54.3	NA	45.7
Ciprofloxacin-non-susceptible (346)	AMC	8	16	1 to >32	69.9	24.3	5.8
	Cefalexin	4	>128	1 to >128	76.6	NA	23.4
	Ciprofloxacin	>16	>16	2 to >16	0	0.6	99.4
	Fosfomycin	2	4	≤1 to >512	97.1	2.6	0.3
	Nitrofurantoin	16	32	≤1–256	91.6	5.5	2.9
	SXT	>8	>8	≤0.12 to >8	41.3	NA	58.7
MDR[b] (205)	AMC	16	32	1 to >32	40.5	39.0	20.5
	Cefalexin	32	>128	1 to >128	47.8	NA	52.2
	Ciprofloxacin	>16	>16	≤0.06 to >16	20.5	0	79.5
	Fosfomycin	2	4	≤1 to >512	95.1	4.4	0.5
	Nitrofurantoin	16	64	≤1–256	86.8	8.8	4.4
	SXT	>8	>8	≤0.12 to >8	22.4	NA	77.6
ESBL-positive (77)	AMC	8	16	4 to >32	59.7	32.5	7.8
	Cefalexin	>128	>128	16 to >128	1.3	NA	98.7
	Ciprofloxacin	>16	>16	≤0.06 to >16	18.2	0	81.8
	Fosfomycin	2	4	≤1–128	96.1	3.9	0
	Nitrofurantoin	16	64	≤1–256	87.0	9.1	3.9
	SXT	>8	>8	≤0.12 to >8	33.8	NA	66.2
AmpC-positive (28)	AMC	32	>32	1 to >32	25.0	21.4	53.6
	Cefalexin	64	>128	≤0.5 to >128	35.7	NA	64.3
	Ciprofloxacin	0.12	>16	≤0.06 to >16	57.1	0	42.9
	Fosfomycin	2	8	≤1 to >512	96.4	0	3.6
	Nitrofurantoin	16	32	4–256	96.4	0	3.6
	SXT	0.25	>8	≤0.12 to >8	64.3	NA	35.7

MIC, minimum inhibitory concentration; $MIC_{50/90}$, MIC required to inhibit 50% and 90% of the isolates, respectively; CLSI, Clinical and Laboratory Standards Institute; S, susceptible; I, intermediate; R, resistant; AMC, amoxicillin/clavulanic acid; SXT, trimethoprim/sulfamethoxazole' MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase.

[a] NA, not available (intermediate MIC interpretative breakpoints are not published by the CLSI for this antimicrobial agent) [12].

[b] A MDR isolate was defined by a phenotype that was non-susceptible to agents from three or more antimicrobial classes [30]. See footnote '[b]' under Table 3 for a detailed description of the most common MDR isolates identified in this study.

Table 5
Sex and age group analysis of *Escherichia coli* isolates cultured from urine specimens of outpatients in Canada, 2007–2016.

Sex (*n*)/age group (*n*)	% of sex total	MDR		ESBL		AmpC	
		n	% of sex/age group isolates	*n*	% of sex/age group isolates	*n*	% of sex/age group isolates
Female							
0–17 years (297)	17.7	17	5.7	8	2.7	2	0.7
18–45 years (539)	32.2	42	7.8	17	3.2	6	1.1
46–64 years (301)	18.0	30	10.0	12	4.0	6	2.0
≥65 years (537)	32.1	69	12.8	21	3.9	7	1.3
Total (1674)	100	158	9.4	58	3.5	21	1.3
Male							
0–17 years (76)	21.1	3	3.9	0	0	1	1.3
18–45 years (42)	11.6	8	19.0	3	7.1	0	0
46–64 years (95)	26.3	12	12.6	4	4.2	1	1.1
≥65 years (148)	41.0	24	16.2	12	8.1	5	3.4
Total (361)	100	47	13.0	19	5.3	7	1.9
Grand total		205		77		28	

MDR, multidrug-resistant; ESBL, extended-spectrum β-lactamase.

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Competing interests

None declared.

Ethical approval

The CANWARD study receives annual approval by the University of Manitoba Research Ethics Board [H2009:059].

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