ORIGINAL ARTICLE

Antibiotic-resistant *Escherichia coli* in women with acute cystitis in Canada

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BACKGROUND: Trimethoprim-sulfamethoxazole (TMP-SMX) has been a traditional first-line antibiotic treatment for acute cystitis; however, guidelines do not recommend TMP-SMX in regions where *Escherichia coli* resistance exceeds 20%. While resistance is increasing, there are no recent Canadian estimates from a primary care setting to guide prescribing decisions.

METHODS: A total of 330 family physicians assessed 752 women with suspected acute cystitis between 2009 and 2011. Physicians documented clinical features and collected urine for cultures for 430 (57.2%) women. The proportion of resistant isolates of *E coli* and exact binomial 95% CIs were estimated nationally, and compared regionally and demographically. These estimates were compared with those from a 2002 national study.

RESULTS: The proportion of TMP-SMX-resistant *E coli* was 16.0% nationally (95% CI 11.3% to 21.8%). This was not statistically higher than 2002 (10.9% [P=0.14]). TMP-SMX resistance was increased in women ≤50 years of age (21.4%) compared with older women (10.7% [P=0.037]). In women with no antibiotic exposure in the previous three months, TMP-SMX-resistant *E coli* remained more prevalent in younger women (21.8%) compared with older women (4.4% [P=0.003]). The proportion of ciprofloxacin-resistant *E coli* was 5.5% nationally (95% CI 2.7% to 9.9%), and was increased compared with 2002 (1.1% [P=0.036]). Ciprofloxacin resistance was highest in British Columbia (17.7%) compared with other regions (2.7% [P=0.003]), and was increased compared with 2002 levels in this province (0.0% [P=0.025]). Nitrofurantoin-resistant *E coli* levels were low (0.5% [95% CI 0.01% to 2.7%).

DISCUSSION: The proportion of TMP-SMX-resistant *E coli* causing acute cystitis in women in Canada remains below 20% nationally, but may exceed this level in premenopausal women. Ciprofloxacin resistance has increased, notably in British Columbia. Nitrofurantoin resistance levels are low across the country. These observations indicate that TMP-SMX and nitrofurantoin remain appropriate empirical antibiotic agents for treating cystitis in primary care settings in Canada.

Key Words: *Acute cystitis; Antimicrobial resistance;* E coli

L'*Escherichia coli* antibiorésistant chez les femmes ayant une cystite aiguë au Canada

HISTORIQUE : Le triméthoprim-sulfaméthoxazole (TMP-SMX) est un traitement antibiotique de première ligne pour soigner la cystite aiguë, mais les lignes directrices ne le recommandent pas dans les régions ou la résistance à l'*Escherichia coli* dépasse les 20 %. La résistance augmente, mais il n'y a pas d'évaluation canadienne récente en première ligne pour orienter les décisions relatives aux prescriptions.

MÉTHODOLOGIE : Au total, 330 médecins de famille ont évalué 752 femmes ayant eu une cystite aiguë présumée entre 2009 et 2011. Les médecins ont étayé les caractéristiques cliniques et prélevé l'urine de 430 femmes (57,2 %) en vue des cultures. Les chercheurs ont évalué la proportion d'isolats d'*E coli* résistants et les intervalles de confiance (IC) binomiales exactes à 95 % sur la scène nationale et les ont comparés sur la scène régionale et sur le plan démographique. Ils ont ensuite comparé ces évaluations à celles d'une étude nationale menée en 2002.

RÉSULTATS : La proportion d'*E coli* résistant au TMP-SMX s'élevait à 16,0 % sur la scène nationale (95 % IC 11,3 % à 21,8 %). Ce résultat n'était pas statistiquement plus élevé qu'en 2002 (10,9 % [P=0,14]). La résistance au TMP-SMX était plus importante chez les femmes de 50 ans ou moins (21,4 %) que chez les femmes plus âgées (10,7 % [P=0,037]). Chez les femmes n'ayant pas été exposées aux antibiotiques au cours des trois mois précédents, l'*E coli* résistant au TMP-SMX demeurait plus prévalent chez les femmes plus jeunes (21,8 %) que chez les femmes plus âgées (4,4 % [P=0,003]). La proportion d'*E coli* résistant à la ciprofloxacine atteignait 5,5 % sur la scène nationale (95 % IC 2,7 % à 9,9 %), soit un pourcentage plus fort qu'en 2002 (1,1 % [P=0,036]). Dans les régions, la résistance à la ciprofloxacine la plus élevée (17,7 %) s'observait en Colombie-Britannique (2,7 % [P=0,003]), où elle était plus marquée qu'en 2002 (0,0 % [P=0,025]). Le taux d'*E coli* résistant à la nitrofurantoïne était faible (0,5 % [95 % IC 0,01 % à 2,7 %).

EXPOSÉ : La proportion d'*E coli* résistant au TMP-SMX responsable d'une cystite aiguë chez les femmes du Canada demeure sous les 20 % au pays, mais peut dépasser ce pourcentage chez les femmes préménopausées. La résistance à la ciprofloxacine a augmenté, notamment en Colombie-Britannique. Les taux de résistance à la nitrofurantoïne sont faibles au pays. D'après ces observations, le TMP-SMX et la nitrofurantoïne demeurent des agents antibiotiques empiriques pertinents pour traiter la cystite en première ligne au Canada.

Acute bacterial cystitis is a common reason to prescribe antibiotics to women in the community. It is caused by *Escherichia coli* in 75% to 95% of cases (1). Over time, antibiotic-resistant *E coli* have become more prevalent (2); however, the prevalence of resistance reported in different geographical areas varies widely (2-4). One reason may be differences in the populations studied. Some studies have included men and children (3) while others have studied tertiary care outpatient populations (5). Still others have used routinely submitted urine cultures without information regarding age, sex, type of infection or previous antibiotic exposure (6,7). Furthermore, urine cultures are not always obtained because empirical antibiotic treatment is widely recommended (8-10). These factors may introduce bias into estimates of antimicrobial resistance when applied to women with uncomplicated cystitis in the community.

A recent international guideline, sponsored by the Infectious Diseases Society of America (IDSA) and endorsed by Canadian and European organizations, recommended that trimethoprim-sulfamethoxazole (TMP-SMX) not be prescribed if *E coli* resistance to TMP-SMX in an area exceeded 20% (10). TMP-SMX has been a commonly recommended first-line empirical antibiotic treatment in North America (8,11). In Canada, *E coli* resistance to TMP-SMX has been estimated to be as low as 10.8% (12) and as high as 18.9% for the

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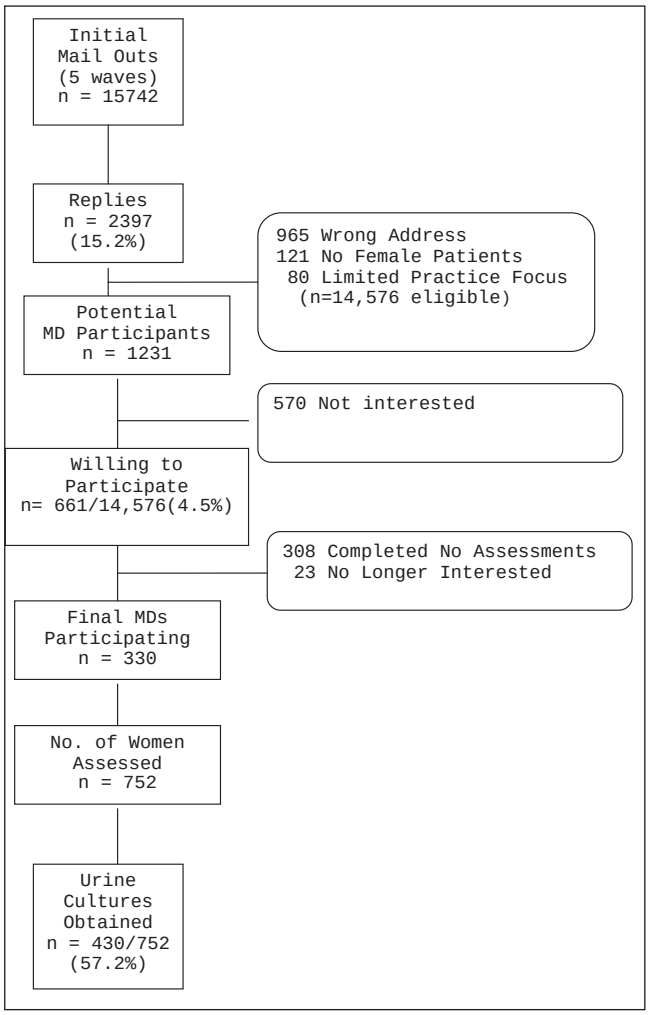

Figure 1) *Recruitment of physicians and women, and urine culture reports obtained. MD Medical doctor; No Number*

same time period (5). More recently, a study of Canadian tertiary care centres estimated 22.1% of *E coli* isolates were TMP-SMX-resistant (7). However, this study included midstream and catheter specimens from outpatients and inpatients, both male and female. The IDSA guideline acknowledged that the prevalence of resistance in women with uncomplicated community-acquired infection may be lower than in hospital-associated populations (10). They recommended studies using unbiased surveillance of uropathogens at the local practice level to best inform treatment decisions. We conducted a national, community-based study of clinically documented cases of acute uncomplicated cystitis in which all women submitted urine for culture, to provide updated and unbiased estimates of uropathogen antibiotic resistance in Canada.

METHODS

The present study was a pragmatic cross-sectional, observational prevalence analysis of urine samples collected from women visiting family physicians with symptoms of cystitis. Between April 2009 and March 2011, 15,742 family physicians and general practitioners from across Canada were contacted. Physicians identified as family physicians or general practitioners from the 2008 *Scott's Canadian Medical Directory* (Business Information Group, Toronto) were eligible. A random sample of physicians was selected from each province proportional to the total number of physicians in each province in the directory. Physicians were ineligible if they did not provide primary care to adult women or their practice was limited to emergency medicine, palliative care, sports medicine, outpatient clinics or hospitalist care. Materials were available in both French and English.

Women ≥16 years of age with new urinary symptoms suggestive of acute uncomplicated cystitis were eligible. Children, men, pregnant women, nursing home residents, women with dementia or unable to understand French or English, were ineligible for the study. Physicians assessed up to four women chosen at their discretion. Clinical and other factors were documented using a standardized form. Urine strips to test for the presence of nitrites and leukocyte esterase (Siemens Multistix 8 SG, Siemens Healthcare Diagnostics Inc, USA) were provided, and a urine culture was requested for all women. The study paid for cultures that the physician indicated they would not normally have ordered.

Assessed characteristics included age, symptoms, previous urinary tract infections (UTIs), complicating factors including diabetes, neurogenic bladder, catheter use, recent urinary tract procedures, antibiotic use within three months, hospitalization within one month and anatomical problems predisposing to infection (listed as 'eg, polycystic kidney disease, recurrent kidney stones, other'). Women were provided with an information sheet and those agreeing to participate were given an anonymized package that included a survey of risk factors for resistance and a consent form to release a copy of the urine culture result.

Urine culture results were obtained from the physician's chart once consent was obtained. Cultures were processed by the local laboratory normally used by the physician. No attempt was made to standardize the methods of testing or reporting. Urine cultures in these symptomatic women were considered to be positive if a known uropathogen was identified with a colony count as low as 10^5 colony-forming units/L as per the IDSA guidelines for symptomatic women (8). All culture reports were reviewed by a microbiologist (TM) and assigned to one of three categories: positive, negative or contaminated.

The sample size was based on estimating the proportion of TMP-SMX-resistant *E coli* isolates to rule out that current levels were >20%, using an expected proportion of 15% resistance based on a previous national study (13). An intraclass correlation coefficient of 0.15 was incorporated to account for the clustering of cases by physician (14), resulting in 352 *E coli* isolates needed. In a previous study (12), 60% of women with cystitis had positive cultures, and 80% of the cultures grew *E coli*. Thus, 365 physicians completing two encounters each were needed. Based on a physician participation rate of 20% (12), and allowing for incorrect addresses and not all women consenting, 4000 family physicians were initially contacted. Additional mailings of randomly selected physicians were performed as needed.

All data were double entered and discrepancies were corrected. Variables were described using frequencies and means as appropriate. Pearson's χ^2 test, or Fisher's exact test and nonparametric Wilcoxon rank sum tests were used for unadjusted comparisons. Proportions and exact binomial 95% CIs were produced for main resistance estimates. Unadjusted comparisons between 2002 (12) and 2009 to 2011 resistance estimates were performed. Multivariate adjustments for differences in characteristics of compared populations were performed using multiple logistic regression. Because generalized estimating equation analyses incorporating clustering of cases within physicians did not change the significance of any results, only the unadjusted analyses are presented. All analyses were completed using SAS version 9.3 (SAS Corporation, USA). The Research Ethics Board of the Mount Sinai Hospital (Toronto, Ontario) provided approval for the study.

RESULTS

There were 2397 replies from 15,742 physicians contacted (Figure 1). Of 14,576 eligible family physicians, 661 (4.5%) agreed to participate. Of these, 330 (49.9%) physicians completed at least one clinical assessment form or a survey was received for 752 women from 167 towns and cities across Canada. Urine culture reports were obtained for 430 (57.2%) women.

TABLE 1
Demographic and clinical characteristics of 430 community-dwelling Canadian women with symptoms of acute cystitis seen by family physicians, 2009 to 2011

Characteristic	n (%)
Age group, years	
16 to 50	208 (48.4)
≥51	222 (51.6)
Province*	
Newfoundland and Labrador	17 (4.0)
Prince Edward Island	8 (1.9)
Nova Scotia	10 (2.3)
New Brunswick	9 (2.1)
Quebec	27 (6.3)
Ontario	222 (51.6)
Manitoba	13 (3.0)
Saskatchewan	8 (1.9)
Alberta	49 (11.4)
British Columbia	67 (15.6)
Symptoms (n=409)	
Dysuria	346 (84.6)
Frequency	360 (88.0)
Urgency	325 (79.5)
History of fever	14 (3.4)
Comorbidities (n=409)	
Diabetes	23 (5.6)
Neurogenic bladder	8 (2.0)
Predisposing anatomical factors	13 (3.2)
Catheter use	3 (0.7)
Immunosuppressed state	15 (3.7)
Hospitalized within one month	7 (1.7)
Recent urinary tract procedure	10 (2.4)
Antibiotic use within three months	127 (31.1)
Urine culture result	
Positive	263 (61.2)
Negative	167 (38.8)

**Some percentage totals >100% due to rounding*

TABLE 2
Organisms isolated from adult women presenting to family physicians with symptoms of acute cystitis from across Canada (n=263 positive cultures)

Organism	n (%)
Escherichia coli	208 (79.1)
Klebsiella pneumoniae	10 (3.8)
Proteus mirabilis	10 (3.8)
Staphylococcus saprophyticus	6 (2.3)
Group B streptococcus	6 (2.3)
Enterococcus	5 (1.9)
Other*	18 (6.8)

**Includes* Citrobacter koseri *(n=2);* Citrobacter braakii *(n=1);* Citrobacter youngae *(n=1); Coagulase-negative staphylococcus (n=2); Enteric Gram-negative bacilli (n=2);* Klebsiella oxytoca *(n=2);* Klebsiella *species (n=2); Lactose-fermenting organisms (n=1);* Pseudomonas aeruginosa *(n=1);* Streptococcus *species (n=2); Lactose-negative coliform (n=1);* Staphylococcus aureus *(n=1)*

The mean (± SD) age of the study subjects was 51.0±18.7 years and ranged from 16 to 93 years (Table 1). There were similar proportions of women ≤50 years of age and >50 years of age. For the present analysis, the younger group was considered to be premenopausal. Each province was represented, although only a few culture reports were received from some provinces. Clinical presentations were consistent with acute cystitis, with 374 of 409 (91.4%) women with complete information having at least two of the symptoms of dysuria, frequency or urgency and 3.4% indicating a history of fever. At least one complicating factor was present in 164 of 409 (40.1%) women, and was most often reported antibiotic use within the previous three months (31.1%). Compared with the 2011 Canadian census (15), there was a higher proportion of older women in the study (26.0% were ≥65 years of age versus 18.9% in the Canadian female population) and underrepresentation from Quebec (6.3% versus 23.4% Canada; Appendix 1).

The characteristics of women from whom a urine culture report was obtained (n=430) were compared with women with no culture report (n=322, Appendix 2). There were no statistically significant differences in provincial representation, symptoms, history of UTIs, comorbidities or whether physicians would have ordered a culture. Women without a culture report tended to be younger (P<0.001) and less likely to have had antibiotics recently (P=0.04).

The prevalence of positive urine cultures was 263 of 430 (61.2%). *E coli* was the most frequent pathogen isolated (Table 2), in both premenopausal women (104 of 133 [78.2%]) and older women (104 of 130 [80.0%]; P=0.72). Pathogens other than *E coli* accounted for 20.9% of isolates.

The pattern of *E coli* resistance is shown in Table 3. Adjacent provinces were grouped into regions where culture reports were few. Ampicillin resistance among *E coli* isolates was 31.6% nationally. The proportion of *E coli* isolates resistant to TMP-SMX was 16.0% nationally (95% CI 11.3% to 21.8%), with no significant differences according to region. Ciprofloxacin resistance was substantially lower (5.5% [95% CI 2.7% to 9.9%]), as was nitrofurantoin resistance (0.5% [95% CI 0.01% to 2.7%]). Regionally, there was a higher proportion of ciprofloxacin-resistant *E coli* in British Columbia (17.7% [95% CI 6.8% to 34.5%]) compared with other regions combined (four of 148; 2.7% [P=0.003]). A comparison of women from British Columbia with women from other regions did not identify differences in age (P=0.36), complicating factors (P=0.36), antibiotic exposure (P=0.18) or fluoroquinolone exposure in the previous three months (P=0.80, Appendix 3).

There were no differences in TMP-SMX or ciprofloxacin resistance according to year, or the presence or absence of complicating factors (Table 3). TMP-SMX-resistant *E coli* were more common among premenopausal women (21.4%) compared with older women (10.7% [P=0.037]), but there were no age differences for ampicillin or ciprofloxacin resistance. TMP-SMX resistance was increased with antibiotic exposure in the previous three months (26.0% versus 13.7% [P=0.045]). The higher proportion of TMP-SMX-resistant *E coli* in premenopausal women was not explained by previous antibiotic exposure; 21.8% of premenopausal women with no antibiotic exposure in the previous three months had TMP-SMX-resistant *E coli* compared with 4.4% (P=0.003) of older women.

Resistance estimates from the present study were compared with a previous national study also involving family physicians (Table 4) (12). There was no statistical difference in the TMP-SMX resistance estimate from 2002 (10.9%) and 2009 to 2011 (16.0% [P=0.14]), and there were no regional increases in resistance. TMP-SMX resistance increased over this time period in premenopausal women (10.7% versus 21.4% [P=0.03]). Ciprofloxacin resistance increased significantly between 2002 (1.1%) and 2009 to 2011 (5.5% [P=0.036]). The increase in ciprofloxacin resistance was greatest in British Columbia (0.0% versus 17.7%) and in premenopausal women (0.0% versus 4.8%). After controlling for differences in age and regional representation between the two studies, the adjusted OR for *E coli* TMP-SMX resistance in 2009 to 2011 compared with 2002 was 1.54 (95% CI 0.83 to 2.86) and for ciprofloxacin resistance (age adjusted only) it was 4.58 (95% CI 0.98 to 21.4); these values were not statistically significant.

The proportion of nitrofurantoin-resistant *E coli* remained low between 2002 (two of 187 [1.1%]) and 2009 to 2011 (0.5% [P= 0.61]). There was a trend toward increased resistance among non-*E coli*

TABLE 3
Variations in antibiotic-resistant *Escherichia coli* isolated from Canadian women with acute cystitis, 2009 to 2011 (n=208)

	Antibiotic resistance, n/n (%)			
Factor	**Ampicillin**	**TMP-SMX**	**Ciprofloxacin**	**Nitrofurantoin**
Canada	65/206 (31.6)*	33/206 (16.0)	10/182 (5.5)	1/205 (0.5)
Region				
British Columbia	10/34 (29.4)	7/34 (20.6)	6/34 (17.7)	–
Prairies†	15/38 (39.5)	8/38 (21.1)	0/20 (0.0)	–
Ontario	23/98 (23.5)	12/98 (12.2)	2/93 (2.2)	–
Quebec, Maritimes‡	17/36 (47.2)	6/36 (16.7)	2/35 (5.7)	–
	(P=0.04)	(P=0.51)	(P=0.008)§	
Year				
2009	34/104 (32.7)	19/104 (18.3)	6/91 (6.6)	–
2010	21/67 (31.3)	8/67 (11.9)	2/61 (3.3)	–
2011	10/35 (28.6)	6/35 (17.1)	2/30 (6.7)	–
	(P=0.90)	(P=0.53)	(P=0.67)§	
Age group, years				
16 to 50	38/102 (37.3)	22/103 (21.4)	4/84 (4.8)	–
≥51	27/104 (26.0)	11/103 (10.7)	6/98 (6.1)	–
	(P=0.08)	(P=0.037)	(P=0.75)§	
Comorbidity¶				
None	35/128 (27.3)	18/128 (14.1)	5/113 (4.4)	–
≥1	27/68 (39.7)	15/68 (22.1)	5/61 (8.2)	–
	(P=0.08)	(P=0.15)	(P=0.32)	
Antibiotics in previous three months				
No	42/146 (28.8)	20/146 (13.7)	6/129 (4.7)	–
Yes	20/50 (40.0)	13/50 (26.0)	4/45 (8.9)	–
	(P=0.14)	(P=0.045)	(P=0.29)§	
Age group, years (stratified according to antibiotic exposure in the previous three months)				
No antibiotic				
16 to 50	–	17/78 (21.8)	–	–
≥51	–	3/68 (4.4)	–	–
		(P=0.003)§	–	–
Antibiotics				
16 to 50	–	5/20 (25.0)	–	–
≥51	–	8/30 (26.7)	–	–
		(P=1.00)	–	–

**Denominators vary because not all laboratories tested the sensitivity of the isolated* E coli *to all antibiotics; †Alberta, Manitoba, Saskatchewan; ‡New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island; §Fisher's exact test; ¶See text for complete list. TMP-SMX Trimethoprim-sulfamethoxazole*

organisms comparing 2002 (five of 35 [14.3%]) and 2009 to 2011 (14 of 42; 33.3% [P=0.054]). One *E coli* isolate (one of 208 [0.5%]) from this community sample was extended spectrum beta-lactamase (ESBL) positive. This occurred in a premenopausal woman with a history of two previous UTIs and treatment with norfloxacin in the previous three months. The isolate was resistant to ampicillin, cephalosporins, TMP-SMX and ciprofloxacin, and sensitive to nitrofurantoin, gentamicin, fosfomycin and meropenem.

DISCUSSION

The prevalence of antibiotic-resistant *E coli* causing acute cystitis in adult women in the community has remained relatively stable over the past decade in Canada, but some regional and demographic increases in resistance have occurred.

The present study found 16.0% of *E coli* isolates nationally to be resistant to TMP-SMX compared with 10.9% in 2002 for a similar group of women. While these estimates were not statistically different, this may have been an issue of study power. A recent and larger European study comparing resistance rates between 2000 and 2008 in women with acute uncomplicated cystitis (16) reported similar estimates for TMP-SMX resistance, but the observed increase was statistically significant. The *E coli* TMP-SMX resistance rate in Europe was 12.3% in 2000 and 16.7% in 2008 (P<0.05).

The current study demonstrates the importance of unbiased sampling in determining uropathogen resistance estimates on which to base antibiotic prescribing recommendations in primary care. A national study from Canadian tertiary care outpatient settings in 2008 reported 22.1% of urinary *E coli* isolates were TMP-SMX resistant (7). This is above the guideline-recommended threshold for not using TMP-SMX as a first-line empirical antibiotic for acute cystitis (10). The current estimate of 16% resistance utilizing sampling from primary care settings is below this threshold and indicates TMP-SMX remains an appropriate empirical antibiotic choice to manage acute cystitis in Canadian primary care. However, these primary care-derived estimates should not guide prescribing decisions in other settings where resistance may be higher.

The recent international guideline on antibiotic treatment of acute cystitis (10) addressed premenopausal women only and recommended the use of nitrofurantoin, TMP-SMX or fosfomycin as first-line antibiotic choices for empirical treatment. However, TMP-SMX was not recommended in regions where the prevalence of TMP-SMX-resistant *E coli* exceeded 20%. Lower rates of microbiological cure (17), longer time to symptom resolution (18) and higher reconsultation rates (19) have been found in acute cystitis when resistance is present. In premenopausal women, the proportion of TMP-SMX-resistant *E coli* was 21.4% and was significantly higher than in 2002 (10.7%) (12). These

TABLE 4
Comparison of trimethoprim-sulfamethoxazole (TMP-SMX) and ciprofloxacin antibiotic-resistant *Escherichia coli* in adult women with acute cystitis in Canada between 2002 and 2009 to 2011

Comparison	2002	2009 to 2011	P
TMP-SMX resistance			
Canada overall	20/183 (10.9)	33/206 (16.0)	0.14
Region			
British Columbia	4/31 (12.9)	7/34 (20.6)	0.52*
Prairies†	5/18 (27.8)	8/38 (21.1)	0.74
Ontario	11/118 (9.3)	12/98 (12.2)	0.49
Quebec, Maritimes‡	0/6 (0.0)	6/36 (16.7)	0.16*
Age group, years			
16 to 50	13/121 (10.7)	22/103 (21.4)	0.03
≥51	7/62 (11.3)	11/103 (10.7)	0.90
Ciprofloxacin resistance			
Canada overall	2/178 (1.1)	10/182 (5.5)	0.036*
Region			
British Columbia	0/32 (0.0)	6/34 (17.7)	0.025*
Prairies†	0/20 (0.0)	0/20 (0.0)	–
Ontario	1/113 (0.9)	2/93 (2.2)	0.59*
Quebec, Maritimes	1/13 (7.7)	2/35 (5.7)	1.00*
Age group, years			
16 to 50	0/112 (0.0)	4/84 (4.8)	0.032*
≥51	2/66 (3.0)	6/98 (6.1)	0.48*

*Data presented as n/n (%) unless otherwise indicated. *Fishers exact test; †Alberta, Manitoba, Saskatchewan; ‡New Brunswick, Newfoundland and Labrador, Nova Scotia, Prince Edward Island*

observations require confirmation because they suggest TMP-SMX may no longer have a role as a first-line empirical antibiotic treatment for acute cystitis in premenopausal women in Canada.

The proportion of ciprofloxacin-resistant *E coli* in Canada remains below 10%, but increased fivefold between 2002 and 2009 to 2011. This increase was most marked in British Columbia and, to a lesser degree, in premenopausal women. While these could be chance findings due to multiple comparisons, a higher rate of ciprofloxacin-resistant *E coli* in British Columbia was reported in another national study, but using routine culture reports (13). In addition, a 2010 BC Centre for Disease Control report noted ciprofloxacin-resistant *E coli* increased 10-fold between 1998 and 2010 (20). However, these estimates were also based on routinely submitted urine samples without clinical information. The current study included women visiting family physicians in the community with clinically documented acute cystitis. Nonetheless, an increase in ciprofloxacin-resistant *E coli* was also observed in British Columbia compared with other areas in Canada.

Nitrofurantoin resistance remains low in isolates of *E coli* from women with acute cystitis in Canada. However, resistance may be increasing in non-*E coli* organisms, which comprised 20% of the cystitis isolates in the present study. It is also contraindicated if the creatinine clearance is less than 60 mL/min, which may limit its use in older post-menopausal women (21). The IDSA treatment recommendations were limited to premenopausal women without comorbidities such as diabetes or urological abnormalities (10). However, more than 50% of women that these family physicians treated were >50 years of age and 40% had diabetes or another factor that were exclusions in the IDSA guidelines. The rate of TMP-SMX resistance in older women was 10.7% and did not change over time. However, TMP-SMX side effects are possible with concomitant spironolactone use (22) or severe renal impairment, both of which may be more prevalent in elderly patients. With antibiotic exposure in the previous three months, TMP-SMX resistance was 26.0%. Recent antibiotic use has been found to a risk factor for resistance in some (23,24), but not all, studies (25).

One *E coli* isolate (0.5%) in the present community-based sample of women was ESBL positive, similar to a recent European estimate of 0.6% (six of 903) in women with community-acquired acute cystitis (16). A cross-Canada study found most ESBL cases were from UTIs in the community, but it was not clear whether these were women with uncomplicated cystitis (26). A Spanish study reported 60% of ESBL cases were cystitis related, but whether these were in primary care settings was unclear (27). As the epidemiology of ESBL-containing organisms continues to evolve in the community, this may significantly impact treatment choices, including for women with acute cystitis (28,29).

A limitation of the present study was the small sample size and wide CIs around resistance estimates. This occurred because not all women provided consent to allow for a copy of the culture report. As a result, the study power was reduced for some comparisons. Physicians also enrolled women at their discretion to facilitate physician participation, but it is unclear whether this introduced any selection bias. Future studies could assess the feasibility of a more random process in selecting which women to enroll. However, there was broad representation of women from across the country, and their symptoms indicate these were presentations typical of acute cystitis. Thus, the present study represents the most recent community-based sample of clinically documented cases of uncomplicated cystitis in women from whom urine cultures were obtained in all cases. Finally, while significance levels were not adjusted for multiple comparisons, the increased ciprofloxacin resistance in British Columbia reported in other studies (13,20) suggests these are not chance findings.

The prevalence of TMP-SMX-resistant *E coli* causing acute cystitis in Canadian women in primary care settings remains below 20% nationally, but may be increasing, particularly in premenopausal women. Ciprofloxacin-resistant *E coli* have increased, most notably in British Columbia. Nitrofurantoin resistance remains low in *E coli* causing cystitis. Ongoing surveillance of these trends is necessary, using sampling from the appropriate setting. However, TMP-SMX and nitrofurantoin remain appropriate first-line empirical antibiotic treatments for the management of acute cystitis in Canadian primary care.

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APPENDIX 1
Age and provincial distribution of community-dwelling Canadian women with symptoms of acute cystitis in the present study compared with the 2011 Canadian population of women ≥15 years of age

Characteristic	Community-dwelling Canadian women (n=430)	2011 Canadian population*
Age group, years		
15 to 64	318 (74.0)	11,833.7 (81.1)
≥65	112 (26.0)	2755.7 (18.9)
Province		
Newfoundland and Labrador	17 (4.0)	223.3 (1.5)
Prince Edward Island	8 (1.9)	63.0 (0.4)
Nova Scotia	10 (2.3)	418.1 (2.9)
New Brunswick	9 (2.1)	329.5 (2.3)
Quebec	27 (6.3)	3415.4 (23.4)
Ontario	222 (51.6)	5703.9 (39.1)
Manitoba	13 (3.0)	513.5 (3.5)
Saskatchewan	8 (1.9)	432.6 (3.0)
Alberta	49 (11.4)	1515.3 (10.4)
British Columbia	67 (15.6)	1975.0 (13.5)

*Data presented as n (%). *Statistics Canada, Canadian Socioecononic Information Management, table 051-001; figures are for woman 15 to 64 years of age and older (thousands) excluding population of the Yukon, Northwest Territories and Nunavut*

APPENDIX 2
Characteristics of women from whom a urine culture report was obtained compared with women with no urine culture report

Characteristic*	Urine culture report Yes	Urine culture report No	P
All women (n=752)	430 (57.2)	322 (42.8)	–
Mean age, years (n=743)	51.0	43.9	<0.001
Age group, years (n=743)			
16 to 50	208 (48.4)	199 (63.6)	
≥51	222 (51.6)	114 (36.4)	<0.001
Province/region (n=752)			
British Columbia	67 (15.6)	43 (13.4)	
Prairies†	70 (16.3)	49 (15.2)	
Ontario	222 (51.6)	152 (47.2)	
Quebec	27 (6.3)	28 (8.7)	
Maritimes	44 (10.2)	50 (15.5)	0.13
History of ≥2 urinary tract infections (n=712)	263 (64.3)	189 (60.4)	0.22
Comorbidity (n=722)			
Diabetes	23 (5.6)	17 (5.4)	0.91
Neurogenic bladder	8 (2.0)	2 (0.6)	0.20‡
Hospitalized in past month	7 (1.7)	4 (1.3)	0.76
Recent urinary tract procedure	10 (2.4)	6 (1.9)	0.63
Uses a catheter	3 (0.7)	4 (1.3)	0.47‡
Renal/urinary anatomical issues	13 (3.2)	10 (3.2)	0.99
Physician would culture (n=719)	361 (88.7)	275 (88.1)	0.82
Antibiotics in the past 3 months (n=722)	127 (31.1)	75 (24.0)	0.04
Symptoms (n=722)			
Dysuria	346 (84.6)	262 (83.7)	0.75
Frequency	360 (88.0)	276 (88.2)	0.95
Urgency	325 (79.5)	233 (74.4)	0.11
Flank discomfort	72 (17.6)	57 (18.2)	0.83
History of fever	14 (3.4)	12 (3.8)	0.77

*Data presented as n (%) unless otherwise indicated. *Denominators vary due to incomplete data for some variables; †Alberta, Saskatchewan, Manitoba; ‡Fishers exact test*

APPENDIX 3
Comparison of characteristics of women in British Columbia compared with women in other regions combined (n=430)

Characteristic	British Columbia	Other Canadian provinces	P
Age group, years			
≤50	29 (43.3)	179 (49.3)	
>50	38 (56.7)	184 (50.7)	0.36
Complicating factors (n=409)*			
None	41 (65.1)	204 (59.0)	
Any	22 (34.9)	142 (41.0)	0.36
Any antibiotics in preceding 3 months (n=409)			
No	48 (76.2)	234 (67.6)	
Yes	15 (23.8)	112 (32.4)	0.18
Quinolone antibiotic in preceding 3 months (n=409)			
No	59 (93.7)	316 (91.3)	
Yes	4 (6.3)	30 (8.7)	0.80†

*Data presented as n (%) unless otherwise indicated. *Denominators vary due to incomplete data for some variables; †Fishers exact test*

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