

Outpatient prescribing and prophylactic antibiotic use for recurrent urinary tract infections in British Columbia, Canada

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Cite as: Saatchi A, Yoo JW, Marra F. Outpatient prescribing and prophylactic antibiotic use for recurrent urinary tract infections in British Columbia, Canada. *Can Urol Assoc J* 2021 June 22; Epub ahead of print. <http://dx.doi.org/10.5489/cuaj.7162>

Published online June 22, 2021

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Abstract

Introduction: Urinary tract infections (UTI) are one of the most common infections, have frequent recurrences, and may debilitate quality of life. UTI is considered recurrent if there are three individual cases of UTI within 12 months. The objective of this study was to set a baseline for recurrent urinary tract infections (rUTI) in women, and rUTI-associated antibiotic prescribing in the presence of antimicrobial stewardship efforts.

Methods: Data for rUTI in women were organized through a provincial prescription database, physician billing system, and a consolidation file to combine antibiotic prescribing, diagnoses and patient demographics. Rates of rUTI cases and prescriptions were examined, and trends of antibiotics were separated by major anatomical therapeutic chemical classes.

Results: A total of 2 234 903 rUTI-associated prescriptions were dispensed for 674 785 rUTI cases from 2008–2018; 2 205 703 prescriptions were for treatment and 29 310 prescriptions were for prophylaxis of rUTI. The prevalence of rUTI cases declined by 59%, while overall rUTI-associated antibiotic prescribing decreased by 73%. The greatest decrease was seen in quinolones (87%), while nitrofurantoin became the most common rUTI-antibiotic dispensed, accounting for 42% of prescriptions overall.

Conclusions: Implementation of numerous antimicrobial stewardship efforts may have contributed to the decrease in antibiotic prescribing, particularly for quinolones. In line with local antibiograms and guidelines, nitrofurantoin is the most used antibiotic for rUTI by far, distinctly preferred over other antibiotics secondary to the lack of *E. coli* resistance.

Introduction

Urinary tract infections (UTI) are one of the most common bacterial infections, typically caused by *E. coli*, *S. saprophyticus* and other enterobacteriaceae.¹ Women are commonly effected; with more than half experiencing a UTI in their lifetime.² Furthermore, 20-30% of women who encounter one episode of UTI are expected to experience a recurrence (rUTI), defined as three episodes of UTI within 12 months.^{2,3} Repeat occurrences contribute significantly to worldwide healthcare burden, especially in cost. In 2000, the United States relinquished roughly \$2.47 billion to treat UTI in women.⁴ In 2019, Canada expended \$264 billion for healthcare, the same system in which UTI was the 5th most common reason for emergency department visits, and the 8th most common reason for outpatient clinic visits in 2013.^{5,6}

Effective management of rUTI is critical as these infections cause significant discomfort for women and deteriorate quality of life.^{2,7} However, current evidence behind best practices for treating or preventing rUTI has changed with time, with most guidelines suggesting long-term prophylactic antibiotics, yet optimal duration and antibiotic choices are inconclusive.^{7,8} Blind spots in empirical treatment guidelines can contribute to suboptimal, or inconsistent treatment and increase the risk of inappropriate antibiotic use. Antimicrobial resistance (AMR) is a current global health crisis; jeopardizing the long-term efficacy of these essential medications. In Canada, the treatment of drug-resistant infections accounts for \$250 million dollars, annually, in direct medical costs.⁹ As urinary tract infections are amongst both the most common and aggressive forms of resistant infections, the delineation and optimization of their treatment is imperative.¹⁰ Consequences of unchecked AMR encompass increased financial burdens in healthcare, as well as losses in GDP, exponential loss of life, as well as diminished quality. Further, an expert panel determined that resistance effects Canadians disparately, with our most vulnerable groups at highest risk.¹⁰

Recurrent UTI guidelines and community-based antimicrobial stewardship programs, such as Do Bugs Need Drugs? (DBND), have been incorporated into evidence-based practice to help Canadian physicians prescribe appropriately.^{8,11} However, the use of local bacterial resistance patterns is also essential when identifying optimal therapeutic choices.¹²⁻¹⁵

The purpose of this population-based study was to examine the characteristics of adult women in British Columbia (BC), who met the criteria for rUTI, and associated use of antibiotics. Annual trends were analyzed to explore outcomes of interest such as rates of annual rUTI cases, differences in cases between different age groups and rural/urban areas, rates of UTI-associated antibiotic prescribing and comparing the proportion of treatment to prophylactic antibiotic use.

Methods

Study databases

This study was conducted using three provincial databases containing healthcare-related data on patients in BC.¹⁶⁻¹⁸ PharmaNet is a centralized network connecting pharmacies for all prescriptions filled in the province.¹⁹ This index was used to collect antibiotic dispensing information, as classified by the Anatomical Therapeutic Chemical (ATC) system. The ATC system has been developed and annually updated by the World Health Organization (WHO) and is an integral part of Health Canada drug classification.^{20,21} The Medical Services Plan (MSP) is the public health index for physician billing in BC, documenting information regarding physician visits, including diagnostic codes from the ninth revision of International Classification of Diseases (ICD-9).²² Patient demographics were pulled from a consolidation file.¹⁷ Patient confidentiality was maintained using anonymized studyIDs to link these databases in lieu of personal health numbers. Data was anonymized and made available to researchers by Population Data BC. All inferences, opinions, and conclusions drawn in this study are those of the authors, and do not reflect the opinions or policies of the Data Steward(s).

Study cohort

Data extraction included all records for women who were at least 19 years of age, and residents of BC between January 1, 2008 and December 31, 2018. The definition of a woman with an rUTI required at least 3 individual MSP diagnoses of UTI within a 12-month period. The date of the first UTI-diagnosis was the index date for each UTI event. To rule out ineffective treatment for a single UTI infection, only those physician visits ≥ 30 days apart were counted to identify an event.^{3,23-25} UTI-related diagnoses included: pyelonephritis (590), cystitis (595), and other disorders of urethra and urinary tract (599).²⁶

Antibiotic information was extracted from PharmaNet and linked to relevant UTI diagnoses using an algorithm that matched the date of dispensation to an MSP record, within 5 days. Multiple prescriptions per patient were permitted in the analyses, as patients in the cohort must have received at least 3 UTI diagnoses within a 12-month period to be included. These prescriptions were differentiated by duration; prescriptions with a duration of 14 days or fewer were considered treatment, since this is the maximum period suggested for treatment, while a duration of 28 days or more was considered prophylaxis, based on trials conducted for rUTI.^{8,2} Any rUTI-associated prescription longer than 28 days was considered prophylactic to exclude treatment prescriptions of inappropriate duration, and to include short-term prophylactic prescriptions. Antibiotic classes analyzed included: penicillins [J01C], other beta-lactam antibacterials [J01D], sulfonamides and trimethoprim [J01E], quinolones [J01M], and other antibacterials [J01X].

A postal-code based algorithm was used to determine neighbourhood income quintiles, and rural status was identified by a 0 in the second position of the postal code. These methods standardized by Statistics Canada.²⁷

Study outcomes

All rates were calculated per 1000 population per year, using age and location-specific denominator estimates for the population through statistics BC.²⁸ We first looked at rates of rUTI women per 1000 population across age groups (19-49, 50-64, 65-79, 80+), income quintiles, and rural/urban status, to compare subgroup characteristics and trends.

The overall rate of rUTI associated antibiotic prescriptions, and antibiotic classes and drugs were compared to identify trends and establish the most and least commonly prescribed antibacterials for rUTI. In addition, the ratio of treatment to prophylaxis prescriptions dispensed was analyzed to assess the relative use of prophylaxis in practice, over time. Annual trends of rUTI cases and antibiotic prescribing were measured with generalized linear regression models (Poisson, $\alpha = 0.05$). All analyses were conducted through Excel, SAS 9.4 and R version 4.0.3.

Results

Overall cohort trends

As shown in Table 1, 674,785 women with rUTI were identified, during the study period, with the majority of patients aged between 19-49 years, and living in urban regions; women were equally distributed within the various income quintiles. However, upon applying population denominators, the highest rates of rUTI per 1000 population was concentrated amongst women above 80 years of age, those living in rural regions, and in the lowest income quintile.

Overall, prevalence of rUTI in women decreased by 59% between 2008 and 2018 ($p < 0.05$) as depicted in Figure 1. A decreasing trend of rUTI was identified when women were stratified by age, with the steepest decline occurring in women aged 19 – 49 years (65%) between 2008 and 2018. Although rUTI in the elderly, aged 80 years or older also declined, it was to a lesser degree (45%) during the study period. Women in all income quintiles experienced a decrease in rates of rUTI by 59-61% over the study period, with no significant difference in trends found across quintiles (data not shown). With respect to geographic distributions, the number of women with rUTI decreased by 15% for urban and 17% for rural regions, over the study period (data not shown).

Treatment and prophylaxis dispensing

Over the study period, the dispensation of treatment antibiotics (N=2,205,703) dominated over prophylactic antibiotics (N=29,310) (Table 2). Treatment antibiotic dispensing decreased by 73%, from 186 prescriptions per 1000 population in 2008, to 50 prescriptions by 2018. Prophylactic antibiotic dispensing saw a comparable 70% reduction during the study period

(2000: 2 per 1000; 2018: 0.7 per 1000). (Table 2) In a comparison of treatment:prophylaxis antibiotic dispensing, there was a decrease of 9% over the study period (Table 2).

Drug and drug class specific trends

Over 2,234,903 prescriptions for oral antibiotics were dispensed for recurrent urinary tract infections during the 11-year study period (Table 1).

Figure 2 details the rUTI-associated prescriptions dispensed, by major ATC class. Overall, rUTI-associated antibiotic utilization decreased from 188 prescriptions per 1000 population to only 51 by the end of the study period ($p < 0.05$) (Table 2). Quinolones (J01M), the most frequently dispensed rUTI associated antibiotic class until 2011, had the greatest decrease (87%) from 84 to 11 prescriptions per 1000 women over the study period ($p < 0.05$), and this was related to an 86% decrease in ciprofloxacin dispensing (Table 3). In contrast, other quinolones including: ofloxacin, levofloxacin, moxifloxacin and particularly norfloxacin, with 4 prescriptions dispensed per 1000 women in 2008, are rarely used at the end of the study period (Table 3).

The decline in the quinolone class was followed by an 84% reduction in the class of sulfonamides and trimethoprim (J01E), from 33 to 5 prescriptions per 1000 women over the study period ($p < 0.05$); attributed to an 85% decrease in sulfamethoxazole and trimethoprim (SMX/TMP) dispensing (Table 3).

Penicillin (J01C) dispensing decreased by 69% over the study period ($p < 0.05$). Although use of most penicillin antibiotics decreased between 78-95%, amoxicillin with an enzyme inhibitor increased by 28%. (Table 3) Cephalosporins (J01D) remained consistent with only a 7% decrease over the study period ($p < 0.05$), but within this antibiotic class, cephalexin and cefuroxime use decreased by 66% and 70% respectively, while cefixime dispensing increased four-fold from 1.2 to 4.7 prescriptions per 1000 women per year over the study period. In 2008, penicillin and cephalosporins were the two antibiotic classes least likely to be dispensed for rUTI, and this remained true for 2018 as well.

The utilization of J01X drugs decreased by 54% from 56 to 26 prescriptions per 1000 women over the study period ($p < 0.05$), related to a decrease of 61% in use of nitrofurantoin, but fosfomycin use increased from 0.02 to 1.64 prescriptions per 1000 women. (Figure 2 and 3) In 2008, ciprofloxacin was the most utilized antibiotic with 79.2 prescriptions dispensed per 1000 women however its use was overtaken by nitrofurantoin from 2010 onward, and in 2018 nitrofurantoin persisted as the most dispensed rUTI-associated antibiotic, with 21.5 prescriptions dispensed per 1000 women in 2018. (Table 3) However, ciprofloxacin remains frequently used, and was the second most dispensed antibiotic for rUTI at the end of the study period with 11 prescriptions per 1000 women in 2018.

Nitrofurantoin was dispensed the most for both treatment and prophylaxis. (Supplemental Fig.1,2) Its dispensation decreased by 61% from 52.8 to 20.8 treatment prescriptions per 1000 women, and 72% from 1.25 to 0.35 prophylactic prescriptions per 1000 women over the study

period. Prophylactic prescriptions for ciprofloxacin and SMX/TMP were few in comparison; and dispensation decreased for both antibiotics by approximately 70%, with prophylactic ciprofloxacin dispensing decreasing by 73% from 0.24 to 0.06 prescriptions per 1000 women, and prophylactic SMX/TMP dispensing decreasing by 72% from 0.38 to 0.15 prescriptions per 1000 women.

Discussion

Across 11 years, over 2 million prescriptions for rUTI-associated antibiotics were dispensed to women aged 19 and older. The prevalence of women with rUTI diminished by 59%, and rUTI-associated prescribing declined by 73% over the study period. Nitrofurantoin accounted for 42% of prescriptions, whereas ciprofloxacin was dispensed in 31% of prescriptions. A potential confounder is that a decrease in the diagnosis of rUTI itself would likely decrease the rates of prescribing. However, there was a 34% decrease in overall prescriptions versus cases of rUTI, suggesting a decrease in antibiotic use, independent of rates of rUTI.

Variability in decreasing rates of rUTI across age groups can be attributed to advances in the clinical characterizations of various urinary tract infections, which may have previously been misdiagnosed as rUTI. For younger women aged 19 – 49 years, the 65% decrease observed may be linked, in part, to an increased awareness of interstitial cystitis/bladder pain syndrome, which can present similarly to recurrent urinary tract infections, but does not require antibiotic treatment.^{29, 30} In 2016, Canadian guidelines were released to clarify the diagnosis and subsequent treatment of interstitial cystitis/bladder pain syndrome, which correlate temporally with a decrease in observed cases of rUTI in our study population.³¹ Stewardship efforts to address the issue of inappropriate prescribing for asymptomatic bacteriuria may account for the observed decrease of rUTI in women aged 80 years and above.³²⁻³⁴ As this condition does not necessitate antimicrobial use, its proper diagnosis and management is imperative as suboptimal use of antibiotic treatment, and prophylaxis, in elderly populations has been associated with increased risk for adverse outcomes.^{35,36}

Another promising finding in our study is the low level of prophylactic antibiotics dispensed. The utilization of prophylactic antibiotics is associated with increased resistance, likely from the constant use of antibiotics over time.³⁷ In addition, there is a lack of evidence in the optimal duration and antibiotic choices for prophylaxis, and UTI is known to recur after the termination of prophylaxis.⁷ Infrequent prophylaxis use reflects recommendations to curtail resistance.³⁷ However, other factors such as frequency of infections or recurrence, as well as the sequelae of infections may also play an integral role in low prophylactic use.

The steep decline in ciprofloxacin use, an 86% decrease over the study period, is an achievement of significance. Ciprofloxacin, while superior to non-quinolone antibiotics in clinical outcomes when treating uncomplicated UTI in women, is a broad-spectrum antibiotic with severe consequences of resistance and adverse drug events.^{38,39} In addition, an alarming increase in ciprofloxacin resistant *E. coli*, the most common pathogen in UTI, has been noted

across the globe, including British Columbia.³⁹ To combat antibiotic resistance and enhance appropriate drug use, the community antimicrobial stewardship program, Do Bugs Need Drugs (DBND), had a clinician education program cautioning against fluoroquinolone use but promoting the use of nitrofurantoin, which at the time had only 2.1% of *E. coli* resistant isolates to nitrofurantoin in 2014.⁴¹⁻⁴³

While the dispensation of most antibiotics declined over the study period, amoxicillin-clavulanate, cefixime, and fosfomycin dispensing increased which may be explained by local beta-lactam susceptibility patterns.⁴⁴ In 2016, 41% of British Columbia's *E. coli* isolates were resistant to monotherapy ampicillin, while only 24% were resistant to amoxicillin/clavulanate and 11% were resistant to third-generation oral cephalosporin, cefixime.⁴¹ With superior activity against resistant uropathogens, amoxicillin/clavulanate and cefixime would be preferred. Fosfomycin, on the other hand, has been recommended to be used as a first-line UTI antibiotic in the ESMID/IDSA guidelines of 2011, studied to be as effective as nitrofurantoin in treating UTI.⁴⁵ However, the use of these antibiotics for rUTI are a mere fraction compared to the use of nitrofurantoin or ciprofloxacin. BC specific guidelines released in 2016 for UTI suggest reserving amoxicillin/clavulanate and cefixime for conditions where there is a possibility of increased resistance found in uropathogens.⁴⁶ In addition, ESMID/IDSA guidelines suggest reserving fosfomycin for its efficacy against multi-drug resistant isolates, electing to use nitrofurantoin or SMX/TMP instead.⁴⁵ The findings of our study are in line with guideline recommendations, and indicate appropriate prescribing for rUTI in BC.

There were no international studies identified that observed the prevalence of women with rUTI and associated prescriptions against which to compare our results. However, a similar Canadian study conducted by Daneman et al. examined the use of fluoroquinolones for uncomplicated UTI in women from six Canadian provinces between 2005 and 2015; the provinces examined were BC, Alberta, Saskatchewan, Manitoba, Ontario, and Nova Scotia.³⁸ Although they did not evaluate recurrent urinary tract infections per se, our findings corroborated Daneman et al., as fluoroquinolones account for approximately one-third of UTI prescriptions, and their use was noted to have diminished over the study period in five of the provinces.³⁸ Similarly, a study conducted by Mulder et al. in the Netherlands between 1996-2014 detailed the effects of guideline implementations in 2005 on female UTI prescribing.⁴⁷ They found that nitrofurantoin use significantly increased, and SMX/TMP use significantly decreased.⁴⁷ However, as the Netherlands' guidelines had excluded quinolones from first-line treatment since 1989, quinolone usage was significantly lower than nitrofurantoin usage throughout their study period.⁴⁷ In contrast, the United States relies heavily on quinolones. A study comparing UTI-associated prescribing between 2002-2011 found that quinolones are used more frequently than SMX/TMP or nitrofurantoin for UTI, indicating widespread inappropriate use of antibiotics.⁴⁸ These suggestions are corroborated by Wattengel et al., who found that between 2005-2018 in

the US, 68% of outpatients were treated inappropriately for UTI with suboptimal regimens, dose, durations, and drug choice.⁴⁹

Stewardship efforts to combat the crisis of AMR within British Columbia were formalized provincially with the introduction of the Do Bugs Need Drugs campaign in late 2005.¹¹ With heavy, early emphases on handwashing and judicious antimicrobial use for respiratory tract infections. The program has since been attributed to curtailing the overuse of antibiotics related to upper and lower respiratory tract infections, as well as optimizing their prescribing.⁵⁰ Around 2009, the focus of the program turned towards stewardship for UTI prescribing; international and local guidelines, as well as various stewardship materials were disseminated regarding the judicious use of antibiotics for UTIs.^{45,51-52} Our study period reviews a decade of antimicrobial prescribing in BC and trends reported are reflective of the provincial efforts to optimize UTI prescribing.

However, our analyses do not include rates prior to 2008, and as such reported trends do not encompass the increasing trends in antibiotic use observed provincially, prior to the introduction of the DBND program.^{44,53} The absence of additional years of data results in the reported declines seen in 2008, with more modest changes thereafter. Additional study limitations are relevant to all retrospective studies conducted using administrative data, which is reliant on accurate coding by billing physicians. Our antibiotics data was obtained through linking PharmaNet dispensing and MSP billing within 5 days of each other, which may exclude self-administered treatment with refills, as they would not visit a clinic, therefore the data may be an underestimation of the true number of prescriptions dispensed. In addition, as only dispensing data is available, levels of compliance are unknown and unfilled prescriptions are missed. The inclusion of ICD-9 code: 599 (other disorders of urethra and urinary tract) may have led to an overestimation of associated-antibiotic prescriptions, as this code could be attributed to diagnoses including, but not limited to, urinary tract infections. However, because our definition for rUTI necessitated at least 3 physician visits within a year we found it necessary to include this code alongside 590 (pyelonephritis) and 595 (cystitis) in order to ensure maximum case capture—in the absence of well-established definitions for recurrent urinary tract infection. Further, as lab data was not available to confirm presence of infection and comorbidity data were unavailable to delineate higher risk populations, our use of ICD-9 codes may be subject to misclassification bias.

Future research should use this baseline data to further optimize rUTI-associated prescribing, ensuring continued efficacy and safety of medications used, and directing stewardship efforts. Furthermore, an examination of patient outcomes in tandem to decreasing rates of prescribing is imperative to ensure that reduced antibiotic use is not associated with increased adverse events, like emergency department visits or hospitalizations. Although low levels of prophylactic prescribing are promising, further analyses to delineate associated sequelae are also integral factors to understanding appropriateness in antibiotic use. With increasing rates

of antimicrobial resistance and stewardship, this study offers insight as one of the first delineations of rUTI-associated antibiotic utilization.

Conclusions

The achievements of antimicrobial stewardship are reflected through rUTI-associated prescribing in BC: a decrease in overall prescribing and particularly quinolones, while relatively increasing the overall usage of nitrofurantoin instead, a first-line agent in accordance with guidelines for common types of rUTI. Amoxicillin with enzyme inhibitor, cefixime and fosfomycin usage have increased, but remain reserved for specific indications with preference to other agents for most rUTI cases. Prophylactic antibiotic use is rare in comparison to treatment. This suggests improvements in prescribing through the use of local antibiograms and guidelines to ensure optimal efficacy and minimize resistance.

DRAFT

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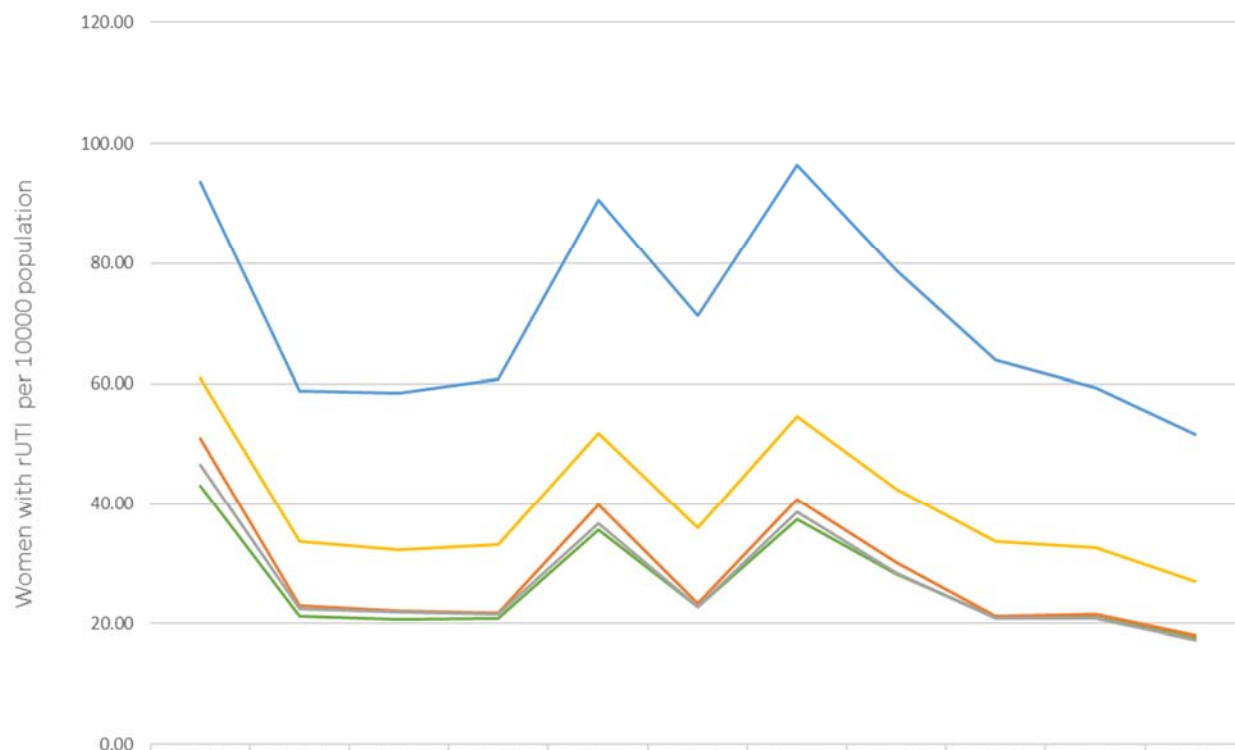
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Figures and Tables

Fig. 1. Rate of recurrent urinary tract infections in women by age, 2008–2018

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
TOTAL	42.95	21.27	20.69	20.77	35.57	22.77	37.31	28.30	21.08	20.96	17.61
19 - 49 YEARS	50.83	23.00	22.04	21.73	39.82	23.23	40.70	30.13	21.20	21.61	17.99
50 - 64 YEARS	46.49	22.40	21.97	21.59	36.64	22.70	38.52	28.32	20.76	20.78	17.29
65 - 79 YEARS	60.85	33.62	32.27	33.15	51.82	36.00	54.63	42.46	33.74	32.65	26.97
≥80 YEARS	93.60	58.79	58.51	60.74	90.53	71.21	96.47	78.92	63.83	59.33	51.61

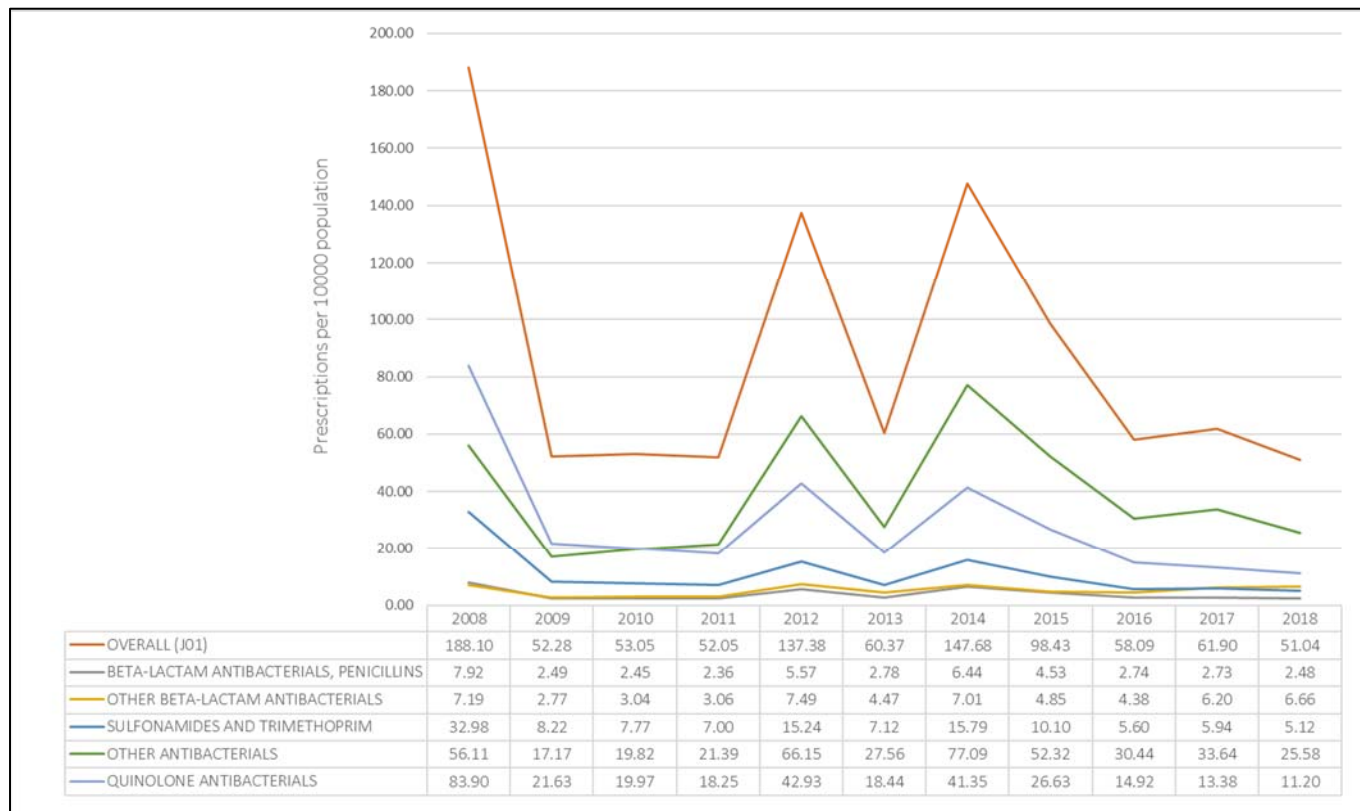
Fig. 2. Rates of antibiotic prescribing by major anatomical therapeutic chemical (ATC) class for women with recurrent urinary tract infections, 2008–201

Table 1. Cohort characteristics	
Cohort characteristics (n)	Overall (2008–2018)
Total number of UTI patients	3 307 765
Mean UTI diagnoses per patient	8.24
Number of rUTI patients	674 785
Number of rUTI patients by age	
19–49	309 145
50–64	149 115
65–79	124 054
80+	92 471
Number of rUTI patients by income quintile ¹	
Quintile 1 (lowest)	138 196
Quintile 2	135 949
Quintile 3	133 785
Quintile 4	134 828
Quintile 5 (highest)	123 925
Missing ³	8102
Number of rUTI patients by rural/urban status ²	
Rural	96 341
Urban	552 518
Missing ³	25 926
rUTI-associated antibiotic prescriptions	2 234 903

¹Population Data BC determined neighborhood income quintile (i.e., household size-adjusted measure of household income) using a postal code-based algorithm standardized by Statistics Canada. ²Rural status represents local population of 1000 to 29 999; urban status represents local population ≥30 000. ³Missing represents absent or not applicable patient demographic information. rUTI: recurrent urinary tract infection.

Table 2. Rate of rUTI-associated antibiotic use over time by prescription type											
	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
rUTI-associated prescriptions¹	188.10	52.28	53.05	52.05	137.38	60.37	147.68	98.43	58.09	61.90	51.04
Treatment	185.84	51.14	51.95	51.01	135.86	59.50	146.18	97.56	57.36	61.06	50.34
Prophylactic	2.27	1.01	1.00	0.92	1.61	0.84	1.63	1.16	0.73	0.79	0.67
Ratio ²	82.0	50.7	52.0	55.4	84.4	70.8	89.7	83.9	78.7	77.1	74.9

¹Rates calculated as prescriptions per 1000 population. ²Ratio of treatment:prophylactic use. rUTI: recurrent urinary tract infection.

Fig. 3. Heatmap of antibiotic use (%) over time, by medications of interest

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Beta-lactam (J01C)											
Phenoxymethylpenicillin	0.09%	0.16%	0.14%	0.10%	0.08%	0.07%	0.06%	0.08%	0.09%	0.06%	0.06%
Amoxicillin	3.47%	3.64%	3.53%	3.23%	2.95%	3.25%	2.86%	2.87%	2.89%	2.60%	2.76%
Ampicillin	0.20%	0.23%	0.18%	0.15%	0.11%	0.16%	0.10%	0.13%	0.15%	0.09%	0.10%
Cloxacillin	0.04%	0.04%	0.04%	0.05%	0.04%	0.02%	0.02%	0.02%	0.01%	0.03%	0.01%
Amoxicillin with enzyme inhibitor	0.40%	0.70%	0.69%	0.98%	0.86%	1.09%	1.31%	1.50%	1.57%	1.63%	1.90%
Other beta-lactams (J01D)											
Cephalexin	2.67%	3.43%	3.29%	2.92%	2.49%	2.80%	2.46%	2.42%	2.43%	2.73%	3.30%
Cefuroxime	0.48%	0.60%	0.62%	0.71%	0.61%	0.73%	0.73%	0.64%	0.69%	0.62%	0.54%
Cefixime	0.62%	1.16%	1.79%	2.25%	2.35%	3.87%	1.55%	1.87%	4.42%	6.67%	9.20%
Sulfonamides & trimethoprim (J01E)											
Trimethoprim	0.24%	0.32%	0.34%	0.28%	0.19%	0.22%	0.21%	0.16%	0.20%	0.22%	0.21%
Sulfamethoxazole & trimethoprim	17.31%	15.44%	14.32%	13.17%	10.91%	11.58%	10.49%	10.11%	9.46%	9.38%	9.82%
Quinolones (J01M)											
Ciprofloxacin	42.17%	39.52%	36.24%	33.87%	30.31%	29.83%	27.51%	26.68%	25.33%	21.28%	21.69%
Ofloxacin	0.05%	0.02%	0.01%	0.01%	0.01%	0.00%	0.01%	0.00%	0.00%	0.00%	0.00%
Levofloxacin	0.19%	0.22%	0.21%	0.18%	0.16%	0.16%	0.09%	0.09%	0.11%	0.12%	0.11%
Norfloxacin	2.12%	1.53%	0.99%	0.84%	0.62%	0.42%	0.29%	0.15%	0.14%	0.10%	0.06%
Moxifloxacin	0.13%	0.19%	0.25%	0.20%	0.16%	0.16%	0.13%	0.15%	0.12%	0.13%	0.11%
Other antibacterial (J01X)											
Nitrofurantoin	29.28%	32.09%	36.72%	40.46%	47.45%	44.15%	49.50%	49.37%	46.59%	47.33%	42.16%
Fosfomycin	0.01%	0.08%	0.05%	0.00%	0.04%	0.81%	2.03%	3.13%	5.14%	6.35%	7.21%
Metronidazole	0.52%	0.63%	0.57%	0.60%	0.67%	0.69%	0.67%	0.63%	0.66%	0.66%	0.75%

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