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Original article

Fluoroquinolone use for uncomplicated urinary tract infections in women: a retrospective cohort study

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ABSTRACT

Objectives: The United States Food & Drug Administration released an advisory in 2016 that fluoroquinolones be relegated to second-line agents for uncomplicated urinary tract infections (UTIs) given reports of rare but serious side effects; similar warnings have followed from Health Canada and the European Medicines Agency. The objective was to determine whether alternative non-fluoroquinolone agents are as effective as fluoroquinolones in the treatment of UTIs.
Methods: We conducted a retrospective population-based cohort study using administrative health data from six Canadian provinces. We identified women (n = 1 585 997) receiving antibiotic treatment for episodes of uncomplicated UTIs (n = 2 857 243) between January 1 2005 and December 31 2015. Clinical outcomes within 30 days from the initial antibiotic dispensation were compared among patients treated with a fluoroquinolone versus non-fluoroquinolone agents. High-dimensional propensity score adjustments were used to ensure comparable treatment groups and to minimize residual confounding.
Results: Fluoroquinolone use for UTI declined over the study period in five of six Canadian provinces and accounted for 22.3–48.5% of treatments overall. The pooled effect across the provinces indicated that fluoroquinolones were associated with fewer return outpatient visits (OR 0.89, 95%CI 0.87–0.92), emergency department visits (OR 0.74, 95%CI 0.61–0.89), hospitalizations (OR 0.83, 95%CI 0.77–0.88), and repeat antibiotic dispensations (OR 0.77, 95%CI 0.75–0.80) within 30 days.
Conclusions: Fluoroquinolones are associated with improved clinical outcomes among women with uncomplicated UTIs. This benefit must be weighed against the risk of fluoroquinolone resistance and rare but serious fluoroquinolone side effects when selecting first-line treatment for these patients.
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Introduction

Urinary tract infections (UTIs) are the most frequent bacterial infections prompting healthcare use, and they affect 12% of women per year in North America [1]. Fluoroquinolones are the most common antimicrobial agents used globally in ambulatory care [2–4], and UTIs are the leading indication [5]. However, concern with the rising rate of fluoroquinolone resistance prompted the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) to release joint guidelines for uncomplicated UTIs which relegated fluoroquinolones to second-line agents [6]. Meanwhile, post-marketing surveillance studies have detected a range of rare but serious side effects with fluoroquinolone treatment, including tendon rupture [7], other collagen-associated toxicities [8,9], arrhythmias and nervous system toxicity [10]. In response, the United States Food & Drug Administration (FDA) released an enhanced warning in July 2016 advising that "*the serious side effects associated with fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections who have other treatment options. For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options*" [11]. Similar warnings have been released by Health Canada and the European Medicines Agency (EMA) [12,13]. Alternative agents have therefore been promoted as first-line treatment for uncomplicated UTIs; these include nitrofurantoin, trimethoprim–sulfamethoxazole, and β-lactam antibiotics. However, it is unclear whether these agents are as effective as fluoroquinolones in the contemporary treatment of these infections.

We harnessed population-based data across six Canadian provinces, and sought to determine the comparative effectiveness of fluoroquinolones versus other agents for the treatment of uncomplicated UTIs.

Methods

General study design and data sources

We conducted a retrospective cohort study to examine the comparative effectiveness of fluoroquinolone versus non-fluoroquinolone antibiotic agents in the treatment of women with uncomplicated UTIs. The study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES), a network of investigators and linked databases distributed across the majority of Canadian provinces [14–16]. In each participating province, the universal healthcare system provides well-validated, population-wide, de-identified prescription and healthcare utilization data, linkable at the patient level. The current study spanned from January 1 2005 to the most recently available data in each of the participating provinces: Alberta (to March 31 2015), British Columbia (to December 31 2015), Manitoba (to December 31 2014), Nova Scotia (to March 31 2015), Ontario (to March 31 2015), and Saskatchewan (to March 31 2015). In the CNODES network a common protocol is implemented separately within each of the provinces, and then aggregate results are pooled across provinces; this circumvents the need for sharing of patient-level data across provinces, improves the internal validity of comparisons, and provides a test of robustness of findings across multiple jurisdictions [14].

The study protocol was approved by the institutional review boards at all participating sites.

Inclusion/exclusion criteria

Within each province we included women dispensed an outpatient antibiotic prescription for treatment of a UTI, with the age criteria for accrual determined by the availability of universal drug coverage which enables capture of antibiotic prescriptions. In British Columbia, Saskatchewan, and Manitoba drug data are available for the full population; in Alberta the population was limited to those over the age of 18; and in Ontario and Nova Scotia the population was limited to those over the age of 65. Urinary tract infections were detected during an outpatient visit via International Classification of Diseases 9th revision (ICD-9) codes of 595. x and 599. x, or 10th revision (ICD-10) codes of N30. x or N39. x, and patients were required to have received an antibiotic prescription within 5 days of the UTI diagnosis.

We excluded males and patients with prior health conditions suggesting the possibility of complicated UTI, including kidney stones, ureteral abnormalities, vesicoureteral reflux, neurogenic bladder, neurological conditions or pregnancy (from diagnoses in healthcare databases in the year preceding the UTI event date). We also excluded patients with a prior UTI event in the preceding 90 days, and those with recent hospitalization (in the preceding 30 days). Finally, we excluded patients with insufficient baseline health data (<365 days of continuous coverage prior to the UTI event) or insufficient follow-up data (<35 days from index prescription). (Supplementary material Fig. S1 displays the study cohort creation.).

Antimicrobial exposures

The initial antibiotic exposure was determined on the basis of the first antibiotic dispensed within 5 days from the uncomplicated UTI diagnosis. If a patient received both a non-fluoroquinolone and a fluoroquinolone antibiotic on the same day, they were classified in the fluoroquinolone group.

Outcomes

Patients were followed 30 days from the incident antibiotic prescription to analyse for the presence of each of the four co-primary outcomes of interest: repeat outpatient visits for UTI, emergency department visits for UTI, hospitalizations for UTI, and repeat antibiotic dispensations. The codes used to define UTIs included both those associated with cystitis (ICD-9(CM) 595. x and 599. x, ICD-10 N30. x or N39. x) and those signifying pyelonephritis (ICD-9(CM) 590. x, ICD-10-CA N10, N11, N12, N15.9, N16.0). Although physician claim and hospitalization databases are available in all provinces, emergency department visits could be measured in only two provinces (Alberta and Ontario).

Statistical analysis

To account for differences in potential confounders between subjects receiving fluoroquinolone versus non-fluoroquinolone antibiotics, we generated high-dimensional propensity scores based on: (a) hospital diagnoses, (b) hospital procedures, (c) ambulatory physician diagnoses, (d) ambulatory physician visit fee items, and (e) prescription drug dispensations in the 365 days prior to cohort entry [17]. This process identified empirical candidate covariates in each dimension, calculated potential bias for each covariate, and then selected the top 500 covariates across all dimensions based on highest multiplicative bias. Age and calendar year were also forced into a logistic regression model along with these covariates to generate propensity scores for fluoroquinolone use. We estimated the inverse probability of treatment weights (IPTWs) to account for differences between the fluoroquinolone and non-fluoroquinolone recipients; in this approach, patients received greater weight if they had a higher propensity to be in the other treatment group [18].

Parallel analyses were conducted within each province according to the confidentiality safeguards in place at each province [14].

For each province we reported the odds ratio (OR) and 95% confidence interval (CI) for each of the primary outcomes. Aggregate results within each province were then pooled across provinces, weighted by the inverse of the standard error of the estimate, using a random effects model. Heterogeneity across provinces was determined via I^2 statistic [19,20].

In a sensitivity analysis we repeated all measurements limited to a single, randomly selected UTI episode from each unique patient. We then repeated all comparisons limiting fluoroquinolone recipients to only those who received the most common fluoroquinolone agent (ciprofloxacin), and then comparing separately to recipients of each of the most common alternative agents.

Results

UTI episodes and treatments

After applying exclusion criteria (Supplementary material Fig. S1), the study population included 2 857 243 episodes of uncomplicated UTI, occurring among 1 585 997 unique women, including 537 354 UTI episodes in Alberta, 1 206 892 in British Columbia, 311 692 in Manitoba, 47 067 in Nova Scotia, 478 088 in Ontario, and 276 150 in Saskatchewan.

Of these uncomplicated UTI episodes, 1 023 576 (35.8%) were initially treated with fluoroquinolone agents, including 883 863 (86.4%) with ciprofloxacin, 126 979 (12.4%) with norfloxacin, 8548 (0.8%) with levofloxacin, 2928 (0.3%) with moxifloxacin, and 545 (0.05%) with ofloxacin. Of the prescriptions for non-fluoroquinolones, nitrofurantoin (1 001 822, 54.6%), sulfamethoxazole/trimethoprim (570 081, 31.0%), amoxicillin (107 052, 5.8%) and cephalexin (53 135, 2.9%) were used most commonly. Only a small minority of patients (4.7%) received initial prescriptions for multiple antibiotics. Most of the prescriptions for ciprofloxacin were for more than 3 days of therapy (80.2%) with 6–7 days (37.9%) being the most common duration of therapy. The median (IQR) duration of other commonly used antibiotics (median IQR) included 7 (5–7) days for sulfamethoxazole/trimethoprim, 7 (7–7) days for nitrofurantoin, 7 (7–10) days for amoxicillin, 7 (7–10) days for cephalexin, and 7 (5–7) days for norfloxacin. The proportion of UTI episodes treated with fluoroquinolones varied across the provinces: Alberta (48.5%), Manitoba (39.3%), Ontario (35.1%), British Columbia (33.4%), Nova Scotia (23.2%) and Saskatchewan (22.3%). The percentage of UTI episodes treated with fluoroquinolones declined over the study period in five of six provinces.

Clinical outcomes among patients receiving fluoroquinolone and non-fluoroquinolone agents

In five of six provinces, the crude rates of return outpatient visits were lower among patients treated with fluoroquinolones as compared to alternative antibiotic agents (Table 1). The crude rates of emergency department visits were lower among patients with fluoroquinolone treatments in the two provinces assessed. The rate of hospitalization for urinary tract infection was lower among fluoroquinolone recipients in four of six provinces. In all six provinces, repeat antibiotic dispensations were less common among those initially treated with fluoroquinolones (Table 1).

Adjusted risk of clinical outcomes among fluoroquinolone and non-fluoroquinolone recipients

After accounting for potential confounding bias with high dimensional propensity scores and inverse probability of treatment weighting, all clinical sequelae were less common among fluoroquinolone recipients. Repeat primary care visits were less common among fluoroquinolone recipients in all six provinces, with a pooled OR of 0.89 (95%CI 0.87–0.92) (Fig. 1). Subsequent emergency department visits were less common among fluoroquinolone recipients in the two provinces with this outcome, and the pooled OR was 0.74 (95%CI 0.61–0.89) (Fig. 2). Hospitalizations for UTI were less common in recipients of fluoroquinolone in five of six provinces, and the pooled OR was 0.83 (95%CI 0.77–0.88) (Fig. 3). Finally, repeat antibiotic dispensations were less common among recipients of fluoroquinolone in all six provinces, and the pooled OR was 0.77 (95%CI 0.75–0.80) (Fig. 4).

Sensitivity analyses

A sensitivity analysis limited to one randomly selected UTI episode per unique patient yielded results comparable to the main analysis (Supplementary material Fig. S2). In a sensitivity analysis limited to patients receiving ciprofloxacin or nitrofurantoin, ciprofloxacin was associated with a significant reduction in each outcome in each individual province (Supplementary material Fig. S3). A comparison of ciprofloxacin versus trimethoprim/sulfamethoxazole recipients also favoured ciprofloxacin, aside from equivocal results in Saskatchewan (Supplementary material Fig. S4). As compared to recipients of amoxicillin or cephalexin, ciprofloxacin was associated with reductions in repeat outpatient visits, emergency department visits and repeat antibiotic dispensations, but there was no detectable difference in hospitalization rates (Supplementary material Fig. S5).

To examine the impact of a potential change in resistance over 10 years, the outcomes were examined separately for a 3-year period at the start of the study period (2005–2007) and a 3-year period at the end of the study period (2012–2014) in the four provinces where complete data were available (BC,MB,NS,ON). There was no indication in the pooled analysis that the results differed appreciably in the two time periods (primary care visits 2005–2007 0.89 95%CI 0.87–0.91, 2012–2014 0.90 95%CI 0.85–0.95; hospitalizations 2005–2007 0.63 95%CI 0.65–0.96, 2012–2014 0.86 95%CI 0.76–0.97, prescriptions 2005–2007 0.77 95%CI 0.74–0.81, 2012–2014 0.79 95%CI 0.74–0.84). ED visits were analysed only for Ontario but these results were also similar in the two periods (2005–2007 0.61 95%CI 0.54–0.69, 2012–2014 0.74 95% 0.67–0.82).

Table 1
Outcome events (percentages) among women with uncomplicated urinary tract infections (UTI) treated with fluoroquinolone (FQ) and non-fluoroquinolone (non-FQ) antibiotic agents

Outcome percentage	British Columbia		Alberta		Saskatchewan		Manitoba		Ontario		Nova Scotia	
	FQ	Non-FQ	FQ	Non-FQ	FQ	Non-FQ	FQ	Non-FQ	FQ	Non-FQ	FQ	Non-FQ
Repeat outpatient visit for UTI	16.6	17.4	13.3	15.0	18.2	16.9	13.8	14.4	16.9	18.8	18.8	19.5
Emergency department visit for UTI	–	–	1.62	1.94	–	–	–	–	0.87	1.30	–	–
Hospitalization for UTI	0.35	0.36	0.29	0.34	0.56	0.49	0.23	0.24	0.38	0.54	0.96	0.81
Repeat antibiotic dispensation	17.4	19.6	15.9	19.6	18.1	19.7	16.8	19.3	21.6	26.6	20.9	23.8

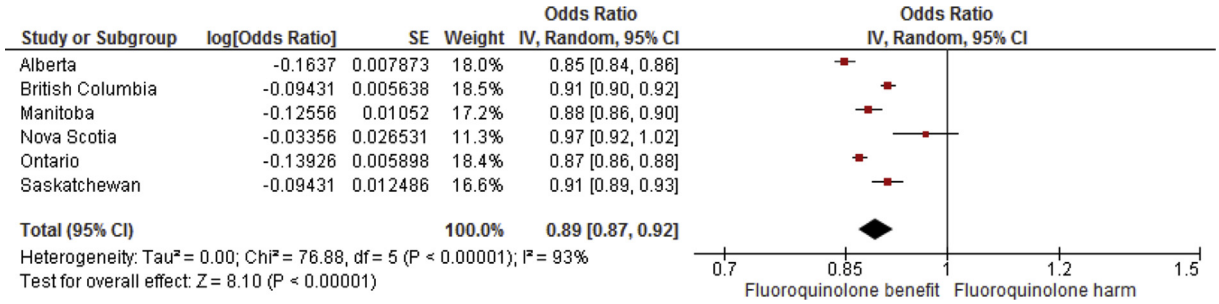

Fig. 1. Forest plot of repeat outpatient visits among women with uncomplicated urinary tract infections (UTIs) treated with fluoroquinolone versus non-fluoroquinolone agents.

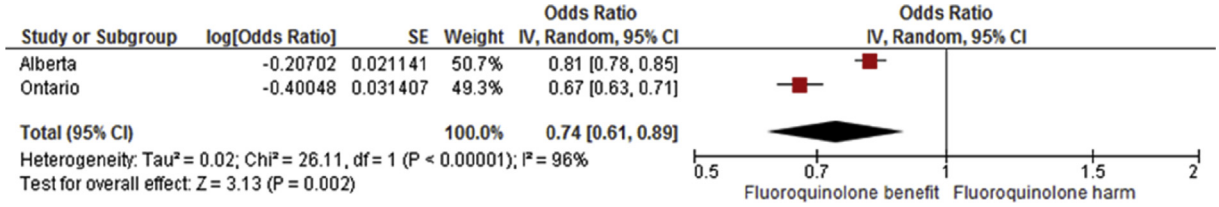

Fig. 2. Forest plot of emergency department visits among women with uncomplicated urinary tract infections (UTIs) treated with fluoroquinolone versus non-fluoroquinolone agents.

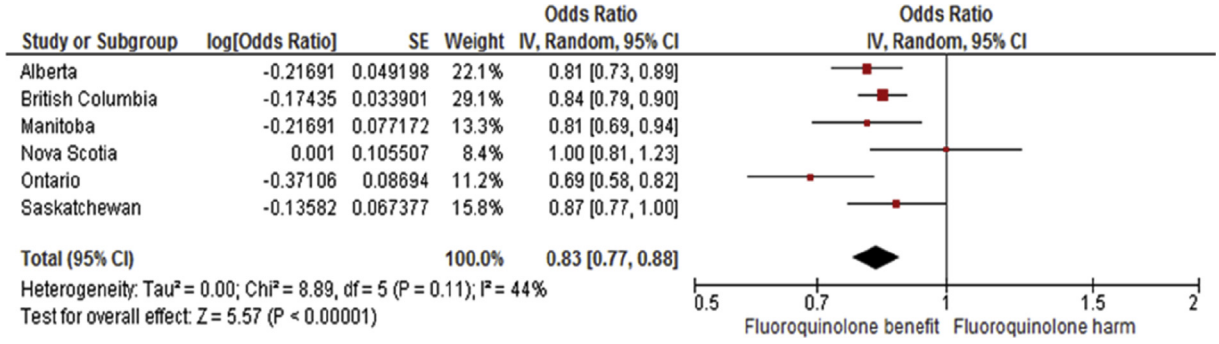

Fig. 3. Forest plot of hospitalizations among women with uncomplicated uncomplicated urinary tract infections (UTIs) treated with fluoroquinolone versus non-fluoroquinolone agents.

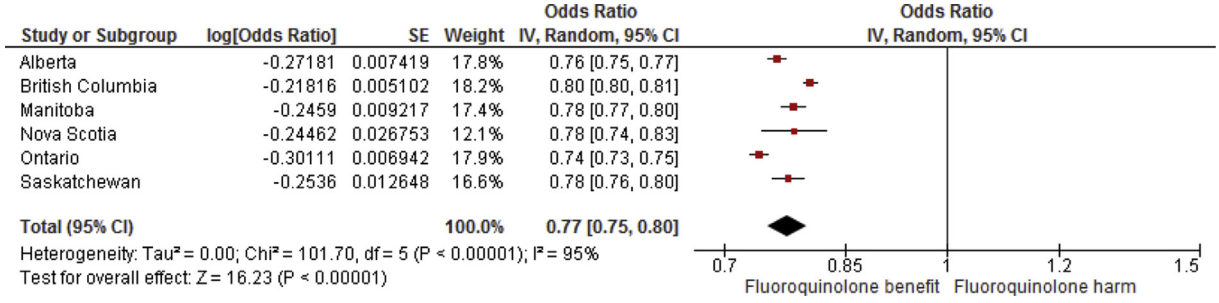

Fig. 4. Forest plot of repeat antibiotic dispensations among women with uncomplicated urinary tract infections (UTIs) treated with fluoroquinolone versus non-fluoroquinolone agents.

Lastly, we examined all-cause ED visits and hospitalizations in an attempt to generate a net measure to account for both effectiveness and harms of antimicrobial treatment for uncomplicated UTI. While all-cause ED visits remained lower for fluoroquinolones (pooled OR 0.91 95%CI 0.85–0.98), there was not a net benefit in all-cause hospitalizations (pooled OR 1.00 95%CI 0.82–1.08).

Numbers needed to treat (NNT)

Among women with uncomplicated UTIs across all six provinces, the crude results indicated that fluoroquinolone treatment was associated with a 1.33% absolute risk reduction (ARR) in repeat outpatient visits, a reduction in ED visits of 0.28%, a reduction in hospitalizations of 0.05%, and a reduction in subsequent antibiotic

dispensations of 3.12%. To account for potential confounders and to more accurately reflect the impact of fluoroquinolones compared to other antibiotics, we used the adjusted values from the pooled analyses presented in Figs. 1–4 to calculate NNT for the four outcomes. For repeat outpatient visits the estimated NNT was 63 (95% CI 53–88), for ED visits the NNT was 242 (95%CI 161–574), for hospitalizations the NNT was 1807 (95%CI 1488–2301), and for subsequent antibiotic dispensations the NNT was 25 (95%CI 23–29).

Discussion

In this Canadian multi-provincial retrospective cohort study of more than 2.8 million episodes of uncomplicated UTI among more than 1.5 million women, fluoroquinolone treatment was associated with improved clinical outcomes as compared with non-fluoroquinolone antibiotic agents. Perhaps in response to guideline recommendations, safety concerns and concerns about antimicrobial resistance, the use of fluoroquinolones for uncomplicated UTI declined in most provinces. However, the superiority of fluoroquinolones was consistent across multiple clinical outcomes: repeat clinic visits, emergency department visits, hospitalizations and repeat antibiotic dispensations; it was consistent across six different jurisdictions; and it was robust across a number of sensitivity analyses, including single drug comparisons between ciprofloxacin and each of the most common alternative agents (nitrofurantoin, trimethoprim/sulfamethoxazole and amoxicillin and/or cephalexin). However, when net benefit was assessed with all-cause ED visits and hospitalizations, the superiority of fluoroquinolones was evident only for ED visits.

Recent literature has emphasized the rare but serious adverse effects that have been detected with fluoroquinolones, including tendon rupture [7], other collagen-related toxicities [8,9], and nervous system toxicity [10]. These concerns have prompted the United States FDA to recommend against fluoroquinolone use for uncomplicated UTIs [11]. However, there may be efficacy trade-offs in recommending alternative agents for these patients. A prior Cochrane review of randomized clinical trials, including 6016 patients across 21 studies, suggested that other therapies should be as effective as fluoroquinolones for women with uncomplicated UTI. Trimethoprim/sulfamethoxazole was non-inferior to fluoroquinolones for clinical cure (RR 1.00, 95%CI 0.97–1.03), and in-turn β-lactam drugs and nitrofurantoin were determined to be non-inferior to trimethoprim/sulfamethoxazole [21]. The only signal of superiority for fluoroquinolones was in comparisons to β-lactams on the outcome of microbiological cure (RR 1.22, 95%CI 1.13–1.31) [21]. Our findings differ from this prior systematic review in that fluoroquinolone outcomes were superior to those of trimethoprim/sulfamethoxazole. This could relate to residual confounding in our observational study design. However, it could also relate to issues in the design of the prior RCTs. For example, two of the largest RCTs compared different durations of antibiotics, with the ciprofloxacin arm limited to 3 days of treatment and the trimethoprim/sulfamethoxazole arm extended to 7 days [22,23]. In contrast, over 75% of the fluoroquinolone dispensations in the provincial databases included in our analyses were for 6 days or more. Moreover, at least one of the trials indicated higher 1-month urine eradication rates for ciprofloxacin [22]. The numbers needed to treat with fluoroquinolones are large to prevent the more severe outcomes, and so could explain why benefits of fluoroquinolones were not detected in smaller RCTs.

It is possible that superior outcomes with fluoroquinolones could be related to changing susceptibility profiles among top UTI-causing pathogens. However, similar results were found early in the study period (2005–2007) and late in the study period (2012–2014). The 2013–2014 data of antimicrobial resistance indicate that among outpatient *Escherichia coli* isolates in Canada, ciprofloxacin susceptibility (75%) was similar to susceptibility to cephalexin (75%) and trimethoprim/sulfamethoxazole (74%), and lower than susceptibility to nitrofurantoin (93%) [24]. Only amoxicillin had a substantially lower rate of susceptibility (46%) than ciprofloxacin. However, these estimates of outpatient resistance prevalence would include isolates from both complicated and uncomplicated UTIs, and so the role of antimicrobial resistance cannot be ruled out as an explanation for our findings.

It is possible that the improved outcomes with fluoroquinolones could relate to other pharmacokinetic or pharmacodynamic properties of these agents. For example, fluoroquinolones have been demonstrated to eradicate uropathogens from the rectal and vaginal flora, whereas β-lactam antibiotics may promote vaginal colonization with uropathogens and thereby predispose to higher rates of relapse [25]. Clinical failures among patients with nitrofurantoin could relate to coexisting unrecognized bacteraemia or upper tract infection, since nitrofurantoin achieves blood levels (C_{max} of 1 μg/mL) that are 100-fold lower than urine levels, and far below the susceptibility breakpoint for this antibiotic (32 μg/mL) [26]; alternatively, nitrofurantoin failures could relate to the pharmacodynamics of this agent, and the need for longer treatment courses.

Our study is subject to the limitations inherent in retrospective design and the use of administrative datasets, in which diagnostic codes may have imperfect sensitivity and specificity. However, we required that patients have both a diagnostic code for urinary tract infection and concurrent antibiotic treatment which increases the specificity of our definition of uncomplicated UTI. In addition, the provincial pharmacy databases are accurate and well validated; for example, the Ontario database has an accuracy exceeding 99% as compared to pharmacy chart abstraction [27]. Some of the dispensed antibiotics may not have been taken by the patients, because of issues of lack of adherence or planned delayed prescriptions, but we would expect rates to be similar among fluoroquinolone and non-fluoroquinolone prescriptions. We are unable to link patient-level data between provinces, but conducting each analysis within the individual provinces may actually enhance internal generalizability of our findings whilst the reproducible results across all six provinces enhances external generalizability. Microbiology data are not available for linkage, and so we are unable to determine whether the differential outcome among fluoroquinolone versus non-fluoroquinolone treatment is driven by pathogens or resistance patterns. Finally, there could be residual confounding-by-indication among fluoroquinolone-versus non-fluoroquinolone-treated patients despite our use of high dimensional propensity scores. However, we would have expected the indication bias to be against fluoroquinolones which are perceived as more potent and potentially reserved for sicker patients.

In summary, our large observational study of women with uncomplicated UTIs found better outcomes with fluoroquinolone treatment; these results were consistent across all six provinces studied, across all four outcome measures, and across multiple sensitivity analyses. If fluoroquinolones are indeed more effective than other agents in the treatment of this common infection, then this must be weighed against the rare but severe fluoroquinolone side effects when clinicians select empirical and definitive treatment for women with uncomplicated UTIs.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2019.10.016.

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