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Impact of risk mitigation measures on oral fluoroquinolone prescribing: a multi-site population-based Canadian cohort study

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Abstract

Background Use of fluoroquinolones (FQs), broad-spectrum antibiotics, has been linked to adverse health outcomes and resulted in safety warnings by regulatory agencies worldwide. We tested the effect of Canadian risk mitigation measures (RMMs) introduced in January 2017 on FQ prescription rates.

Methods We conducted a retrospective multi-site cohort study using administrative data from six Canadian provinces. The cohort included adults (18 + years) with outpatient prescriptions for four oral systemic FQs (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin) between 2008 and 2022. Overall FQ prescription rates and percentage of FQ prescriptions for three antibiotic indications (acute bacterial sinusitis [ABS], acute exacerbation of chronic obstructive pulmonary disease [AECOPD], urinary tract infection [UTI]) were assessed before and after RMMs were introduced. Segmented generalized linear models were applied to monthly prescription rates and percentages for: (1) pre-RMM (January 2008-December 2016; reference), (2) post-RMM pre-COVID (January 2017-Feburary 2020), and (3) post-RMM within-COVID (March 2020-December 2022) segments. We estimated province-specific relative rates (RR) for the post-RMM segments and slope coefficients for pre- and post-RMM segments and their 95% confidence intervals (CIs) and pooled them using random-effects models.

Results Crude annual FQ prescription rates decreased from 107.5 to 45.0 per 1,000 population over the study period; in the pre-RMM segment, age- and sex-adjusted rates decreased an average of 0.30 per 1,000 population per month (95% CI: 0.19–0.41); province-specific estimates of decrease ranged from 0.16 to 0.48. The pooled RR for the post-RMM pre-COVID segment was 0.50 (95% CI: 0.43–0.59); the post-RMM within-COVID segment pooled RR was similar (RR = 0.38; 95% CI: 0.29–0.50). The decline in percentage of FQ prescriptions post-RMM pre-COVID was largest for UTI (pooled RR = 0.32, 95% CI: 0.25–0.41), followed by ABS (RR = 0.41, 95% CI: 0.34–0.51) and AECOPD (RR = 0.51, 95% CI: 0.37–0.69), although there was variation across provinces.

Conclusions Canadian RMMs for FQ use were associated with a decrease in prescription rates overall and for three indications, although rates had begun to decline before RMMs were introduced and the magnitude of decrease

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varied across provinces. Safety warnings tailored to specific indications and regional practices may be needed to address variation in FQ prescribing.

Trial registration HMA-EMA catalogue of real-world data studies (Study ID: 108,049).

Keywords Prescription medication use, Safety outcomes, Observational study, Administrative health data, Time series

Text box 1. Contributions to the literature

- Adds to international literature about the impact of regulatory actions on the use of fluoroquinolones, one of the most commonly prescribed classes of antibiotics, a topic of importance to regulatory agencies and healthcare providers
- Describes the use of fluroquinolones in real-world settings before and after introduction of regulatory actions
- Reveals regional variation in decreasing trends in fluoroquinolone use
- Identifies that multiple factors may contribute to reducing the risks associated with fluoroquinolones and that both regulatory action and wider action in healthcare systems is needed

Background

Fluoroquinolones (FQs), broad-spectrum antibiotics used to treat a wide range of infections, have been linked to adverse effects, including musculoskeletal issues such as tendon damage and mental disorders such as depression [1]. Consequently, FQ safety warnings have been issued by regulatory agencies in several countries and regions [2–6]. In 2016 the United States Food and Drug Administration (FDA) advised that serious side effects of FQs outweigh their benefits for treating infections when alternative antibiotics are available, including for the treatment of acute bacterial sinusitis (ABS), acute exacerbations of chronic obstructive pulmonary disease (AECOPD), and uncomplicated urinary tract infections (UTI) [6]. Health Canada made a similar recommendation in January 2017, and produced safety warnings in communications targeted at both patients and healthcare providers, including an information update and letter to healthcare professionals [7, 8]. Updates to product labels were also made. In 2018, the European Medicines Agency (EMA) also recommended restricting FQ use due to their side effects and produced revised indications and warning about FQ use [9, 10]. In addition, direct communications to healthcare professionals, including media campaigns and communications from professional societies were initiated. Subsequent safety warning updates were published as a consequence of continued high use of FQs and variations in FQ use across different healthcare systems, healthcare providers, and antibiotic indications [11, 12].

Information about the impact of risk mitigation measures (RMMs) on FQ prescribing practices can aid in refining or revising RMMs and targeting risk messages to specific populations, providers, or geographies [5, 13]. Investigations using electronic health data are particularly valuable for monitoring the impact of RMMs, because they provide a population-based perspective on medication safety and enable objective assessments of variations in medication prescribing across populations and regions [14]. A multi-country study commissioned by the EMA used electronic health data to evaluate the impact of regulatory actions on FQ use in six European countries between 2016 and 2021; an overall reduction in prescribing was observed. However, there was substantial heterogeneity across countries and inconsistent evidence that the reductions were temporally related to RMMs [13]. US research also demonstrated that FQ use decreased in association with the FDA warnings and label changes, but that the magnitude of the decrease was variable when examined by patient and provider characteristics and infection type [15].

COVID-19 has been shown to impact the use of healthcare in many settings, including antibiotic medications [16]. The pandemic influenced FQ use [17–19], although studies about the effect of RMM during the pandemic are limited. One multi-site study that investigated RMM effects alongside pandemic effects, which was conducted in the UK and the Netherlands, found a small effect of the pandemic on FQ prescribing following the introduction of RMMs. However, further investigation is warranted to explore the potential impact of the pandemic following RMMs in other geographic locations [5].

Within Canada, variation in FQ prescribing has been described over time and across different populations, but not after RMMs were introduced in 2017 [20]. Previous research about FQ use as a first-line treatment for AECOPD and uncomplicated UTI found wide variation across several provinces [20], but did not investigate the impact of RMMs on this variation. The impact of the pandemic on antibiotic use has been investigated, but not for FQs [16].

Our purpose was to assess the impact of FQ RMMs, which included communications to healthcare professionals and patients, and updates to product labels to include safety information, that were introduced in Canada in January 2017. The objectives were to: (1) describe FQ prescribing before and after introduction of the RMMs across provinces, and (2) test the impact of the RMMs overall and for specific antibiotic indications.

Methods

Study design and data sources

A multi-site retrospective cohort study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES), a pan-Canadian network that examines questions of drug safety and effectiveness at the request of government stakeholders [21, 22]. Databases from six Canadian provinces were used, including Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan, representing more than two-thirds of the total Canadian population. The study period was from January 1, 2008, which was selected to provide a historical perspective on FQ prescribing, to December 31, 2022, the last date that data were available at the time of the study. A common study protocol was implemented in each province and pre-registered in the HMA-EMA catalogue of real-world data studies (Study ID: 108,049).

The source population comprised all adults (≥ 18 years for Alberta, British Columbia, Manitoba, and Saskatchewan; ≥ 66 years for Nova Scotia and Ontario due to age exclusions based on prescription drug data availability) with a dispensation for an oral systemic FQ in the outpatient setting during the study period. Individuals were included at the date of the first FQ dispensation from a community pharmacy.

Study data from each province included health insurance registrations, prescription drug dispensation records, medical service claims, and hospitalization records (Table 1). Other ambulatory (i.e., outpatient) datasets were used in provinces (Alberta, Ontario, and Saskatchewan) where they were available, to achieve a comprehensive picture of FQ prescribing and study outcomes. Within each province, data sources were linked at the individual level using anonymized personal health numbers. All provinces have universal health care programs, which means that virtually the entire population of each province is captured in the study databases, with the exceptions noted.

Health insurance registration files capture start and end dates of health insurance coverage, including the date of loss of coverage due to death or migration; demographic and residence location information is also maintained in these files. Prescription drug dispensation records capture medications dispensed by community pharmacies; in-hospital medication dispensations are not included. Medical service claims contain information about ambulatory services provided by specialists and general practitioners, including type of service, date of service, and at least one diagnosis code associated with the reason for the service; the latter are recorded using the 8th (Ontario only) and 9th revisions of the International Classification of Diseases (i.e., ICD-8 and ICD-9). Hospitalization records contain information for each patient during the hospital stay, including up to 25 diagnoses codes recorded using ICD-10-CA (i.e., 10th revision, enhanced Canadian version).

Table 1 Study population and databases used in each province

Province	Study population	Database				
		Prescription drug claims[a]	Medical service claims	Hospitalization records	Health insurance registration file	Other
Alberta	≥ 18 years	Pharmaceutical Information Network (all)	Practitioner Claims	CIHI Discharge Abstract Database	Provincial Registry	Alberta Continuing Care Information System (ACCIS)
British Columbia	≥ 18 years	BC PharmaNet (all)[b]	BC Medical Services Plan	CIHI Discharge Abstract Database	BC Ministry of Health Client Roster	NA
Manitoba	≥ 18 years	Drug Program Information Network (all)	Medical Claims/Medical Services	CIHI Discharge Abstract/Manitoba Hospital Abstracts	Manitoba Health Insurance Registry	NA
Nova Scotia	≥ 66 years	Seniors' Pharmacare (public)	Medical Services Insurance Physician Billings	CIHI Discharge Abstract Database	Insured Patient Registry	Licensed Provider Registry Eligibility Group
Ontario	≥ 66 years	Ontario Drug Benefit Claims (public)	Ontario Health Insurance Plan Claims Database	CIHI Discharge Abstract Database	Ontario Health Insurance Plan Registered Person's Database	ICES Physician Database Continuing Care Reporting System
Saskatchewan	≥ 18 years	Prescription Drug Plan Historical Claims (all)	Medical Services Branch	CIHI Discharge Abstract Database	Person Health Registration System	NACRS[c]

BC British Columbia, *CIHI* Canadian Institute for Health Information, *NA* Not applicable, *NACRS* National Ambulatory Care Reporting System

[a]Indicates whether dispensations captured are those reimbursed by public or private drug plans or all (including out-of-pocket)

[b]Excludes patients who are federally insured and beneficiaries of the First Nations Health Benefits plan

[c]Emergency department data available from 2012 onward

FQ prescription rates

The World Health Organization's Anatomic, Therapeutic, Chemical (ATC) Classification codes were used to identify prescriptions for four commonly used oral systemic FQs available for use in Canada: ciprofloxacin (J01MA02), levofloxacin (J01MA12), moxifloxacin (J01MA14), and norfloxacin (J01MA06) from the prescription drug dispensation records in each province. Age and sex at the time of the prescription dispensation was determined from the provincial health insurance registry.

Overall prescription rates were calculated. The numerator was the total number of prescription dispensations for the four FQs. The denominator was the number of eligible individuals from the provincial health insurance registry, ascertained at either midpoint (i.e., June 30) or end of the year. The number of eligible individuals was assumed constant for all months in the year when calculating monthly FQ rates.

Table 2 Diagnosis, medication, and procedure codes to define the antibiotic indication cohorts

Indication	Codes to define inclusion criteria	Codes to define exclusion criteria
ABS	ICD-9-CM: 461.x ICD-10-CA: J01.x	–
AECOPD	ICD-9-CM: 490.x, 491.x, 492.x, 496.x ICD-10-CA: J40.x-J44.x	Oral antibiotics: ATC: J01 Oral corticosteroids: ATC: H02AB Heart failure or ischemic heart disease: ICD-9-CM: 410.x-414.x, 428.x ICD-10-CA: I24.x, I25.x, I50.x
UTI	ICD-9-CM: 595.x, 599.x ICD-10-CA: N30.x, N39.x	Stones: ICD-9-CM: 592.x, 594.x ICD-10-CA: N20.x, N21.x Ureteral abnormalities/vesicoureteral reflux: ICD-9-CM: 593.x ICD-10-CA: N13.x, N28.x, R80.x Neurogenic bladder: ICD-9-CM: 344.x, 596.x ICD-10-CA: N32.x Neurologic condition: ICD-9-CM: 323.x, 336.x, 337.x, 340.x, 341.x, 342.x, 343.x, 344.x, 952.x ICD-10-CA: G04.x, G05.x, G35.x, G36.x, G37.x, G80.x, G82.x, G83.x, G90.x, G92.x, G95.x, S14.x Pregnancy: ICD-9-CM: V22.x, V23.x ICD-10-CA: Z33.x, Z34.x, Z35.x Severe diabetes: ATC: A10 Infection of the kidney/pyelonephritis: ICD-9-CM: 590, 590.1, 590.2, 590.8, 590.9 ICD-10-CA: N10, N12, N15.1, N16.x Sexually transmitted disease: ICD-9-CM: 090.x-099.x ICD-10-CA: A50.x-A64.x Indwelling of urinary catheter: ICD-9-CM: V53.6, 996.64, 996.76, 996.31 ICD-9-CM procedure code: 57.94 CCP procedure code: 69.94 ICD-10-CA: T83.0x, Y84.6, Z46.6, Z96.0 CCI procedure code: 1.PM.52.CA-TS

ABS Acute bacterial sinusitis, *AECOPD* Acute exacerbation of chronic obstructive pulmonary disease, *ATC* Anatomical Therapeutic Chemical Classification System, *CCI* Canadian Classification of Health Interventions, *CCP* Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures, *ICD* International Classification of Diseases 9th revision with clinical modification (ICD-9-CM) or 10th revision with Canadian enhancements (ICD-10-CA), *UTI* Urinary tract infection

Antibiotic prescribing indications

In each province, we adopted established methods to identify all individuals with one or more ABS, AECOPD, and UTI events using outpatient medical service claims. We then constructed three separate indication cohorts (Table 2) [20, 23]. Inclusion criteria for each indication cohort were based on ICD-9-CM diagnosis codes. Exclusion criteria, which were based on diagnosis, medication, and procedure codes, were applied primarily to restrict each indication cohort to patients with uncomplicated conditions.

The entry date into an indication cohort was determined by the date of the corresponding medical service claim. Individuals could enter more than one indication cohort. Individuals were also eligible to enter each indication cohort multiple times, provided they met all the criteria at each entry date. We selected the closest dispensation date for which the physician number on the entry date matched the prescribing physician number on the prescription dispensation record. Where the physician number did not match, we selected the closest dispensation within five days before or after the cohort entry date. Antibiotic exposure was determined by the first antibiotic dispensation in the outpatient setting within the period from five days before to five days after the cohort entry date for the indication of interest [6].

For each indication, we calculated the prescription rate, where the numerator was the number of FQ prescription dispensations in the indication cohort and the denominator was the number of eligible cohort members from the provincial health insurance registry. For each indication, we also calculated the percentage of antibiotic prescriptions that were for a FQ and the percentage of events for which there was no antibiotic prescription.

Statistical analysis

We estimated crude and age- and sex-standardized overall FQ prescription rates by month and year. For each antibiotic indication cohort (e.g., ABS, AECOPD, UTI)

we estimated the age- and sex-standardized percentage of antibiotic prescriptions that were FQs by month and year. For the former, we modeled the number of dispensations using a generalized linear model and a negative binomial distribution with the natural logarithm of the population as the model offset. For the latter, we adopted a binomial distribution. The negative binomial model was defined as $\log(\mu_i) = X_i\beta + \log(N_i)$, where u_i is the number of dispensations, X_i is the vector of model covariates, β is the vector of model parameters, and N_i is the population total (i.e., offset) in the ith age group-sex-month-year strata. The variance for the negative binomial is var $(\mu_i) = \mu_i + \kappa\mu_i$, where κ is the dispersion parameter. The binomial model was $\text{logit}(\mu_i) = X_i\beta$ and $\text{var}(\mu_i) = \mu_i$ $(1—\mu_i)$. Categorical covariates in both models were age group (10-year groups starting with 18–29, 30–39, and so on to ≥ 80 years; 18–29 years reference group), sex (male reference group), month (January reference month), and year (2008 reference year). For the AECOPD indication cohort, the age groups were defined for individuals ≥ 66 years. For the UTI indication cohort, males were excluded so the model did not include sex as a covariate. To account for dependence in the monthly number/percentage of prescription dispensations, generalized estimating equations (GEEs) were used [24]. In most provinces we adopted a first-order autoregressive structure [25], however, an exchangeable or independent structure was adopted to achieve model convergence in some provinces. FQ prescription rates were expressed per 1,000 population.

A segmented generalized linear model was applied to assess the impact of the 2017 RMMs (i.e., communications to health professionals, updates to product labels) on overall FQ prescription rates and percentage of FQ prescriptions in each antibiotic indication cohort [26]. Three segments were defined: January 1, 2008 to December 31, 2016 (pre-RMM), January 1, 2017 to February 29, 2020 (post-RMM pre-COVID), and March 1, 2020 to December 31, 2022 (post-RMM within-COVID). We created two segments in the post-RMM period to address the potential impact of the COVID-19 pandemic on prescription rates [27]. The generalized linear models fit to the data had the following covariates: age group, sex, month, segment. In addition, the two-way interaction of month and segment was included. We adopted a negative binomial distribution for prescription rates and a binomial distribution for modeling the percentage data. From these models, we estimated the relative rate (RR) for the second and third segments, using the first segment (pre-RMM) as the reference, along with 95% confidence intervals (CIs). Within each segment, we estimated the slope (average monthly rate of change) and 95% CI.

We conducted a sensitivity analysis using a washout period of 6 months after the RMMs were introduced (i.e., the post-RMM pre-COVID segment was defined from July 1, 2017 to February 29, 2020), to account for the time potentially needed to fully implement or adopt new prescribing policies in each province.

Province-specific RR and slope estimates were pooled using the DerSimonian and Laird random-effects models [28]. Differences in pooled estimates between segments were assessed using their 95% CIs. The magnitude of between-province heterogeneity was estimated using the I^2 statistic, the percentage of the variability in effect estimates due to heterogeneity [29]. For this statistic, a value of 0% indicates no observed between-province heterogeneity in the estimates and larger values indicate greater between-province heterogeneity in the estimates.

Results

Overall FQ prescription rates

The overall annual crude prescription rate for the four FQs decreased from 107.5 per 1,000 population in 2008 to 45.0 per 1,000 population in 2022. There was a levelling off of the prescription rate in the post-RMM within-COVID segment (Fig. 1). The use of FQs other than these four FQs was minimal during the study period. Ciprofloxacin was most frequently prescribed of these four FQs, followed by moxifloxacin, levofloxacin, and norfloxacin.

Figure 2 shows age- and sex-standardized monthly FQ prescription rates for each province. There was substantial variation across provinces, although the highest rate was consistently observed for the province of Ontario during the study period. The pooled slope estimates revealed an overall average monthly decrease of 0.27 prescriptions per 1,000 population in the pre-RMM segment (95% CI: 0.13 – 0.40), a higher average monthly rate of decrease of 0.87 prescriptions per 1,000 population in the post-RMM pre-COVID segment (95% CI: 0.56 – 1.17), and a similar average monthly decrease of 0.74 prescriptions per 1,000 population in the post-RMM within-COVID segment (95% CI: 0.19 – 1.29). The I^2 statistics were greater than 95% for each model, indicating substantial heterogeneity across provinces.

The pooled RR estimate in the post-RMM pre-COVID segment (Fig. 3a) was 0.50 (95% CI: 0.43 – 0.59), indicating an average 50% reduction in the overall FQ prescription rate when compared to the pre-RMM segment. The pooled RR estimate for the post-RMM within-COVID segment (Fig. 3b) was 0.38 (95% CI: 0.29 – 0.50), indicating a 62% reduction for this segment when compared to the pre-RMM segment. The unweighted average monthly prescription rate was 6.75 per 1,000 population in the post-RMM pre-COVID segment and 4.33 per 1,000 population in the post-RMM post-COVID period. Province-specific RR estimates ranged from 0.35 to 0.63 in the post-RMM pre-COVID segment, and from 0.22 to 0.58 in the post-RMM within-COVID segment (Table 3).

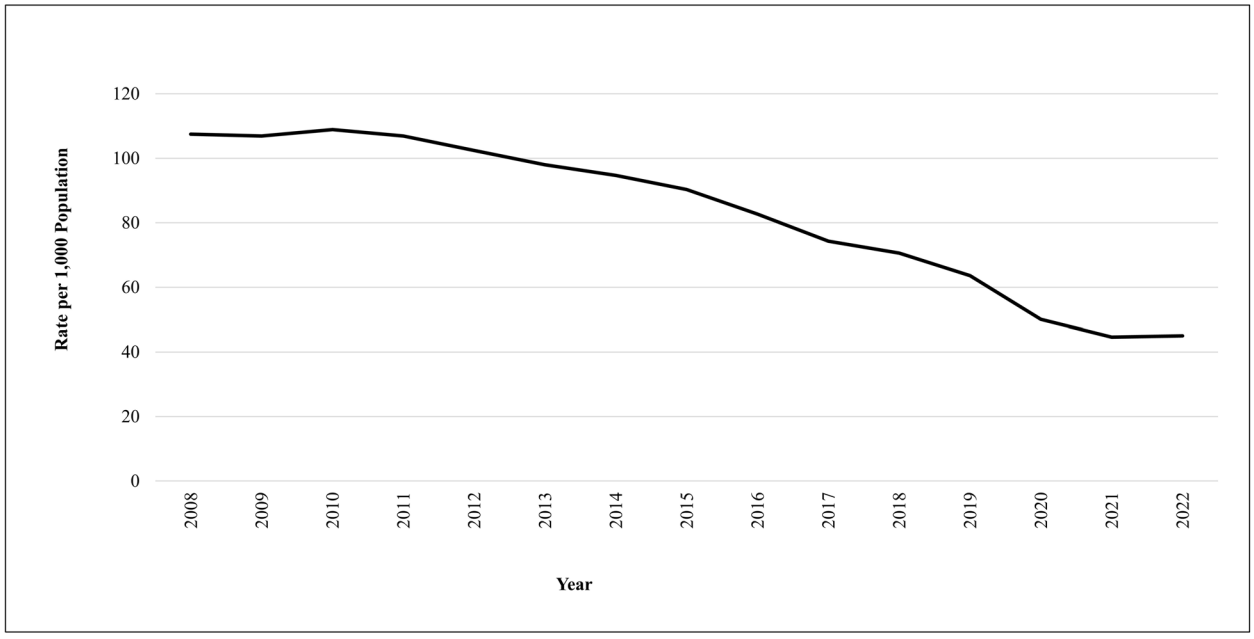

Fig. 1 Annual crude fluoroquinolone prescription rates per 1,000 population. Note: Data available in Nova Scotia and Ontario for ≥ 66 years, and in other provinces for ≥ 18 years. Rates are for four fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin

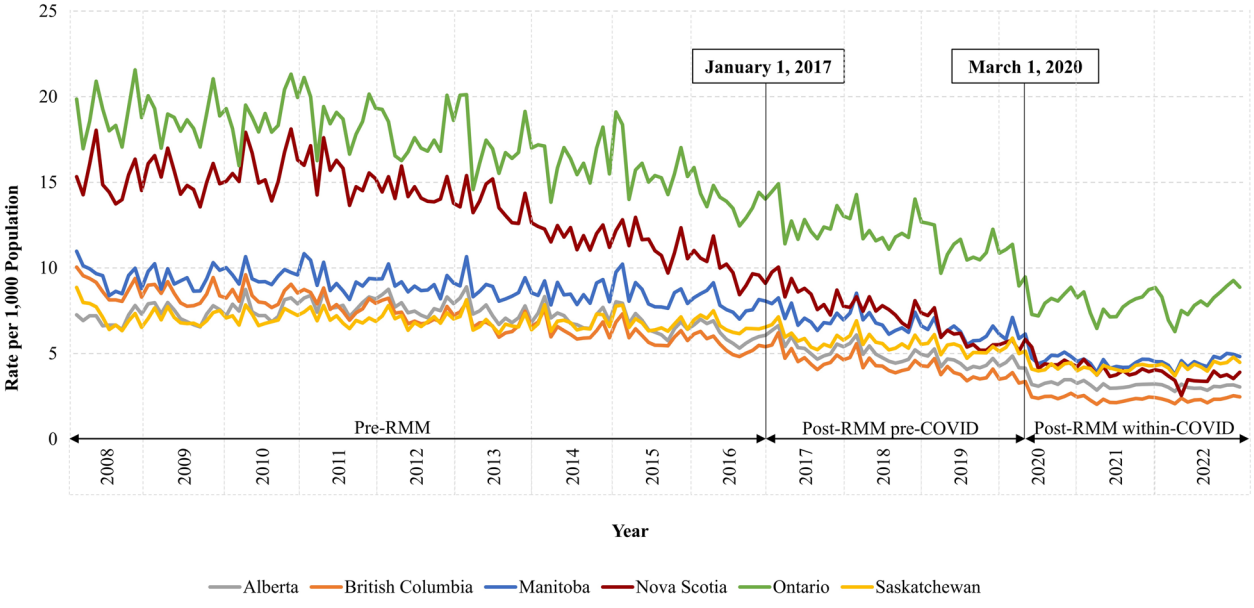

Fig. 2 Monthly age- and sex-standardized fluoroquinolone prescription rates by province and RMM segment. Note: Data available in Nova Scotia and Ontario for ≥ 66 years, and in other provinces for ≥ 18 years. Rates are for four fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
RMM Risk mitigation measure

The I^2 statistics for both models were greater than 95%, indicating substantial heterogeneity across provinces. In the sensitivity analysis with a six-month RMM washout period, the RR estimates and I^2 statistics for the two post-RMM segments were almost identical to those obtained when no washout period was used (Additional File 1).

Antibiotic indications

Trends in the three antibiotic indications are shown in Fig. 1 of Additional File 3. They reveal the largest decrease in the percent for events with a FQ prescription for UTI, followed by AECOPD.

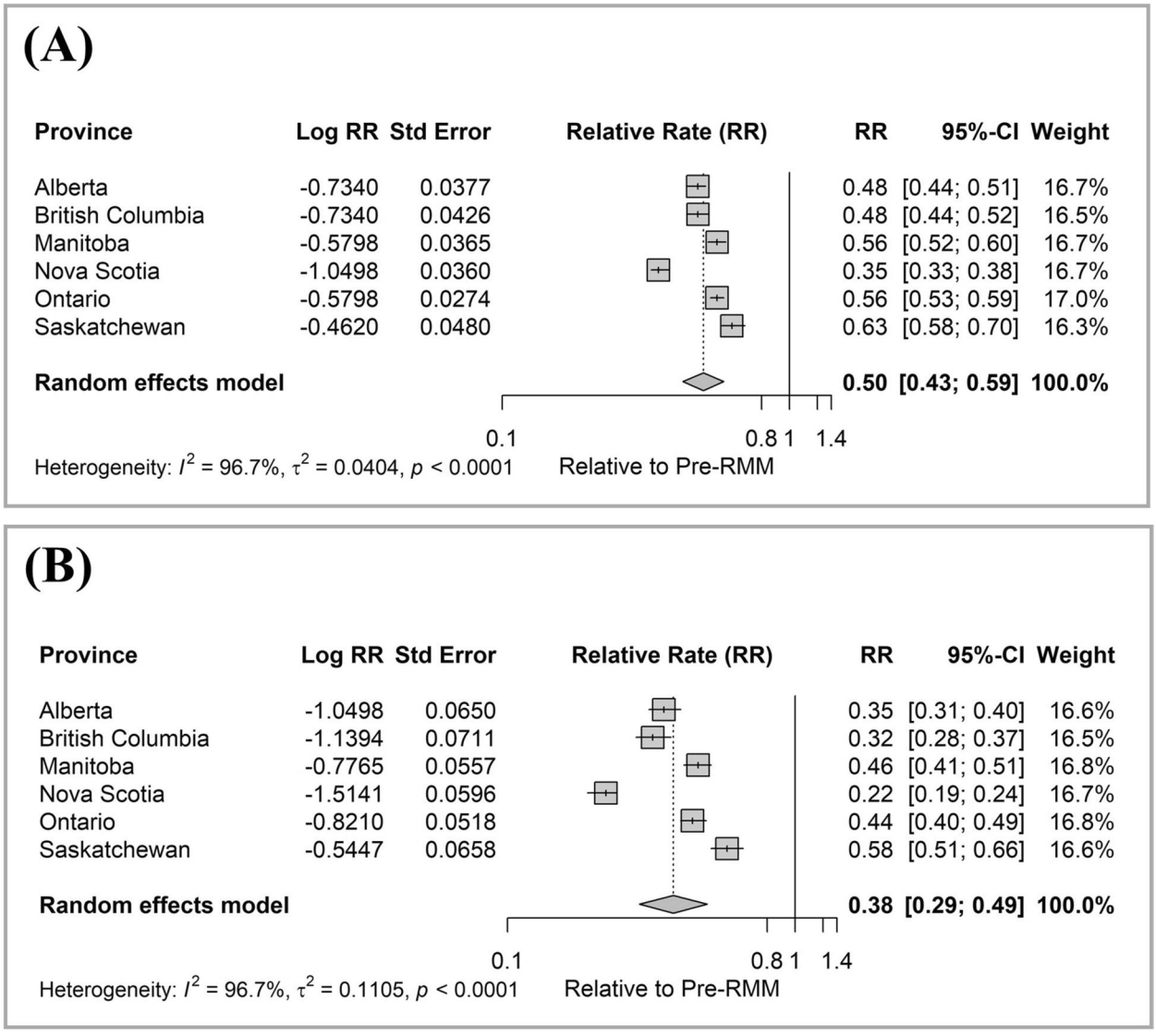

Fig. 3 Forest plot of province-specific and pooled fluoroquinolone prescription relative rates by RMM segment. Note: Panel (**A**) corresponds to post-RMM pre-COVID segment (January 1, 2017 to February 29, 2020). Panel (**B**) corresponds to post-RMM within-COVID segment (March 1, 2020 to December 31, 2022). The reference is the pre-RMM segment (January 1, 2008 to December 31, 2016). Data available in Nova Scotia and Ontario for ≥ 66 years, and for ≥ 18 years for all other provinces. Rates are for four fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin *ABS* Acute bacterial sinusitis, *CI* Confidence interval, *RMM* Risk mitigation measure

ABS

More than 5 million ABS events were identified amongst 2.7 million individuals in the six provinces during the study period (Additional File 2, Fig. 1). At the beginning of the period (data not shown), no antibiotic prescriptions were identified for 20.2% (Manitoba) to 45.6% (Alberta) of ABS events; at the end of the study period in 2022, these percentages were similar, ranging from 20.5% (Saskatchewan) to 34.1% (Ontario).

While FQs were not commonly prescribed for ABS, their use still declined over time (Additional File 3, Fig. 2). The pooled slope estimates (Table 4) revealed an overall average monthly rate of decrease of 0.74% in the events with a FQ prescription in the pre-RMM segment (95% CI: 0.57 – 0.90), and a similar decrease of 0.70% in the post-RMM pre-COVID segment (95% CI: 0.46 – 0.94). In the post-RMM within-COVID segment, the rate of decrease was much higher (1.57%; 95% CI: 1.18 – 1.97). The overall pooled RR of all antibiotic prescriptions for ABS that were FQs for the post-RMM pre-COVID segment was 0.42 (95% CI: 0.34 – 0.51) and for the post-RMM within-COVID segment it was 0.26 (95% CI: 0.18 – 0.38), relative to the pre-RMM segment (Fig. 4). The unweighted average monthly percentage of ABS events with a FQ prescription was 3.32 in the post-RMM pre-COVID segment and 2.77 in the post-RMM within-COVID period.

Table 3 Province-specific and pooled average monthly decrease (95% CI) in fluoroquinolone prescription rates and age- and sex-adjusted prescription rates by RMM segment

Province and Segment	Average Monthly Decrease	Prescription Rate (per 1,000 Population) at Start of Segment	Prescription Rate (per 1,000 Population) at End of Segment
Alberta			
Pre-RMM	0.19 (0.15, 0.23)	7.26	6.35
Post-RMM Pre-COVID	1.62 (1.49, 1.75)	6.63	4.16
Post-RMM Within-COVID	0.84 (0.64, 1.03)	4.14	3.04
British Columbia			
Pre-RMM	0.48 (0.39, 0.57)	10.05	5.50
Post-RMM Pre-COVID	0.88 (0.80, 0.96)	6.21	3.28
Post-RMM Within-COVID	0.32 (0.23, 0.42)	3.36	2.47
Manitoba			
Pre-RMM	0.23 (0.17, 0.30)	10.97	7.92
Post-RMM Pre-COVID	1.15 (1.01, 1.30)	8.26	5.88
Post-RMM Within-COVID	0.59 (0.47, 0.72)	6.14	4.82
Nova Scotia			
Pre-RMM	0.45 (0.39, 0.52)	15.33	9.76
Post-RMM Pre-COVID	1.57 (1.44, 1.71)	10.05	5.14
Post-RMM Within-COVID	1.08 (0.92, 1.25)	5.83	3.90
Ontario			
Pre-RMM	0.30 (0.26, 0.34)	19.85	14.46
Post-RMM Pre-COVID	0.80 (0.65, 0.94)	14.92	8.95
Post-RMM Within-COVID	0.08 (−0.08, 0.24)	9.47	8.87
Saskatchewan			
Pre-RMM	0.16 (0.09, 0.23)	8.86	6.68
Post-RMM Pre-COVID	1.00 (0.83, 1.18)	7.14	5.00
Post-RMM Within-COVID	0.27 (0.14, 0.39)	5.14	4.48
Pooled Estimate/I^2 Statistic			
Pre-RMM	0.27 (0.13, 0.40)/ 96.3%	–	–
Post-RMM Pre-COVID	0.87 (0.56, 1.17)/ 96.3%	–	–
Post-RMM Within-COVID	0.74 (0.19, 1.29)/ 95.7%	–	–

Data available in Nova Scotia and Ontario for ≥ 66 years, and for ≥ 18 years for all other provinces

RMM Risk mitigation measure, *CI* Confidence interval

There was substantial heterogeneity in the site-specific estimates; the I^2 statistics had values of 97% for each of the post-RMM segments. Province-specific RR estimates for the percentage of events with a FQ prescription in the post-RMM pre-COVID segment ranged from 0.25 to 0.62, and in the post-RMM within-COVID period they ranged from 0.11 to 0.50.

AECOPD

More than 2.0 million AECOPD events were identified amongst 784,916 patients aged 66 years and older (Additional File 2; Fig. 2). A large percentage of AECOPD events were not associated with an antibiotic prescription, but this percentage varied across provinces. For example, in the largest province of Ontario, this percentage was 86.0% in 2008 and 87.5% in 2022. In Saskatchewan, a smaller province, this percentage was 61.3% in 2008 and 80.0% in 2022 (data not shown).

The percent of all antibiotic prescriptions that were FQs for AECOPD events (Additional File 3, Fig. 3) in the first month of the study period ranged from 34.7% in Ontario to 10.4% in Nova Scotia. Pooled slope estimates (Table 4) indicated a much greater monthly rate of decrease in the percent of antibiotic prescriptions that were FQs for AECOPD events in the post-RMM pre-COVID segment (0.94%; 95% CI: 0.56 – 1.32) and in the post-RMM within-COVID segment (1.28%; 95% CI: 0.11 – 1.40) than in the pre-RMM segment (0.31%; 95% CI: 0.21 – 0.41). The pooled RR estimate for the post-RMM pre-COVID segment was 0.51 (95% CI: 0.37 – 0.69) and for the post-RMM within-COVID segment it was 0.38 (95% CI: 0.30 – 0.48), indicating a lower average percent in both post-RMM segments when compared to the pre-RMM segment (Fig. 5). The unweighted average monthly percentage of AECOPD events with a FQ prescription was 11.85 in the post-RMM pre-COVID segment and 9.94 in

Table 4 Province-specific average monthly decrease (95% CI) in percent of antibiotic prescriptions for fluoroquinolones by RMM segment and indication

Province and Segment	ABS	AECOPD	UTI
Alberta			
Pre-RMM	0.78 (0.74, 0.81)	0.27 (0.17, 0.36)	0.99 (0.94, 1.03)
Post-RMM Pre-COVID	0.94 (0.84, 1.03)	1.17 (0.84, 1.50)	1.43 (1.34, 1.53)
Post-RMM Within-COVID	1.92 (1.60, 2.23)	1.50 (1.02, 1.99)	1.05 (0.88, 1.22)
British Columbia			
Pre-RMM	0.80 (0.74, 0.86)	0.26 (0.20, 0.32)	1.31 (1.24, 1.37)
Post-RMM Pre-COVID	0.60 (0.38, 0.82)	0.79 (0.53, 1.05)	1.22 (1.08, 1.36)
Post-RMM Within-COVID	1.58 (1.34, 1.82)	1.19 (0.89, 1.49)	1.15 (0.95, 1.35)
Manitoba			
Pre-RMM	0.90 (0.80, 1.01)	0.13 (−0.03, 0.29)	0.35 (0.31, 0.40)
Post-RMM Pre-COVID	0.68 (0.41, 0.95)	0.77 (0.20, 1.33)	1.23 (1.06, 1.40)
Post-RMM Within-COVID	2.18 (1.65, 2.70)	1.52 (1.01, 2.02)	0.76 (0.61, 0.91)
Nova Scotia			
Pre-RMM	1.01 (0.77, 1.25)	0.53 (0.37, 0.68)	0.57 (0.47, 0.67)
Post-RMM Pre-COVID	2.15 (0.94, 3.34)	1.65 (0.96, 2.33)	1.88 (1.69, 2.07)
Post-RMM Within-COVID	1.10 (−2.19, 4.27)	0.64 (−1.10, 2.36)	1.00 (0.30, 1.71)
Ontario			
Pre-RMM	0.58 (0.55, 0.62)	0.40 (0.35, 0.44)	0.78 (0.70, 0.86)
Post-RMM Pre-COVID	0.49 (0.25, 0.72)	1.20 (1.10, 1.31)	0.71 (0.56, 0.86)
Post-RMM Within-COVID	1.14 (0.95, 1.33)	1.22 (0.97, 1.46)	0.54 (0.49, 0.58)
Saskatchewan			
Pre-RMM	0.42 (0.35, 0.49)	0.24 (0.15, 0.34)	0.27 (0.12, 0.42)
Post-RMM Pre-COVID	0.46 (0.15, 0.77)	0.10 (−0.41, 0.61)	0.60 (0.49, 0.72)
Post-RMM Within-COVID	0.99 (0.18, 1.79)	1.63 (0.24, 3.00)	0.18 (−0.06, 0.41)
Pooled Estimate/I^2 Statistic			
Pre-RMM	0.74 (0.57, 0.90)/ 96.8%	0.31 (0.21, 0.41) 84.3%	0.71 (0.40, 1.03) 99.3%
Post-RMM Pre-COVID	0.70 (0.46, 0.94)/ 82.4%	0.94 (0.56, 1.32) 82.0%	1.18 (0.80, 1.55) 97.6%
Post-RMM Within-COVID	1.57 (1.18, 1.97)/ 82.5%	1.28 (0.11, 1.40) 0.0%	0.76 (0.46, 1.07) 93.8%

Data available in Nova Scotia and Ontario for ≥ 66 years, and for ≥ 18 years for all other provinces

ABS Acute bacterial sinusitis, *AECOPD* Acute exacerbation of chronic obstructive pulmonary disease, *CI* Confidence interval, *RMM* Risk mitigation measure, *UTI* Urinary tract infection

the post-RMM within-COVID period. In the post-RMM pre-COVID segment, province-specific estimates ranged from 0.30 to 0.89; in the post-RMM within-COVID segment, province-specific estimates ranged from 0.25 to 0.57.

UTI

In total, more than 7.3 million uncomplicated UTI events were identified among more than 3 million women (Additional File 2, Fig. 3) in the study period. No antibiotic prescription dispensations were observed for 24.1% (Manitoba) to 45.2% (Alberta) of UTI events in 2008, and 23.9% (Manitoba) to 37.2% (Ontario) in 2022 (data not shown).

The percent of antibiotic prescriptions that were FQs for treating uncomplicated UTIs (Additional File 3, Fig. 4) ranged from 56.0% in Alberta to 20.8% in Nova Scotia in the first month of the study period. The pooled average monthly rate of decline was 0.71% in the pre-RMM segment (95% CI: 0.40 – 1.03), 1.18% in the post-RMM pre-COVID segment (95% CI: 0.80 – 1.55), and 0.76% (95% CI: 0.46 – 1.07) in the post-RMM within-COVID segment (Table 4). The pooled RR for the post-RMM pre-COVID segment (RR 0.32; 95% CI: 0.25 – 0.41) was lower than for the pre-RMM segment (Fig. 6a). The same was true for the post-RMM within-COVID segment (Fig. 6b; RR 0.24; 95% CI: 0.17 – 0.35). The unweighted average monthly percentage of UTI events with a FQ prescription was 13.49 in the post-RMM pre-COVID segment and 9.79 in the post-RMM within-COVID period. The I^2 statistics were very large for both models, indicating substantial between-province heterogeneity.

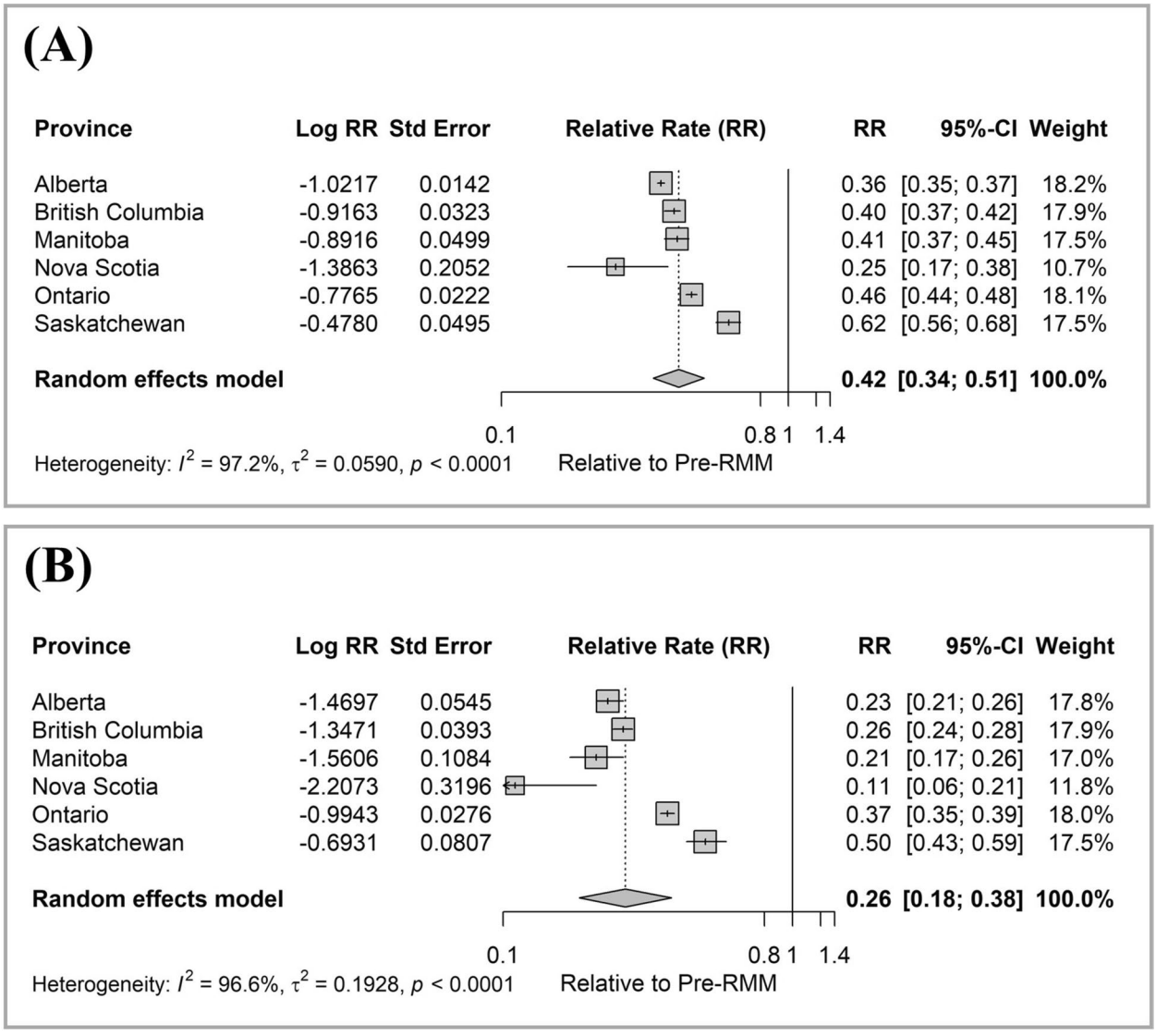

Fig. 4 Forest plot of province-specific and pooled fluoroquinolone prescription relative rates for ABS indication by RMM segment. Note: Panel (**A**) corresponds to post-RMM pre-COVID segment (January 1, 2017 to February 29, 2020). Panel (**B**) corresponds to post-RMM within-COVID segment (March 1, 2020 to December 31, 2022). The reference is the pre-RMM segment (January 1, 2008 to December 31, 2016). Data available in Nova Scotia and Ontario for ≥ 66 years, and for ≥ 18 years for all other provinces. Rates are for four fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin *ABS* Acute bacterial sinusitis,CIConfidence interval, *RMM* Risk mitigation measure

Discussion

We investigated prescribing of four oral systemic FQs before and after implementation of Health Canada RMMs (i.e., risk communications, updates to product labels) in 2017 overall and in six of 10 Canadian provinces for whom population-based administrative health data were available for the study. To our knowledge, this is the first study about the impact of the RMMs on FQ prescribing in the outpatient setting in Canada. A substantial decline in FQ prescription rates was observed between 2008 and 2022, with this decline occurring even before RMM was introduced. This finding is consistent with that observed elsewhere (e.g., in European countries) and suggests that the RMMs were not solely responsible for declines in use [13]. However, we found that the 2017 regulatory actions were followed by greater reductions in the rate of FQ prescriptions overall and the percentages of antibiotic prescriptions that were FQs for the three investigated indications of ABS, AECOPD in older adults, and uncomplicated UTI in women, than before the regulatory actions.

We also found differences for the within-COVID and pre-COVID periods of the post-RMM segment for some, but not all indications. Specifically, for ABS the rate of decrease was much larger in the within-COVID period than in the pre-COVID period. The pandemic likely had

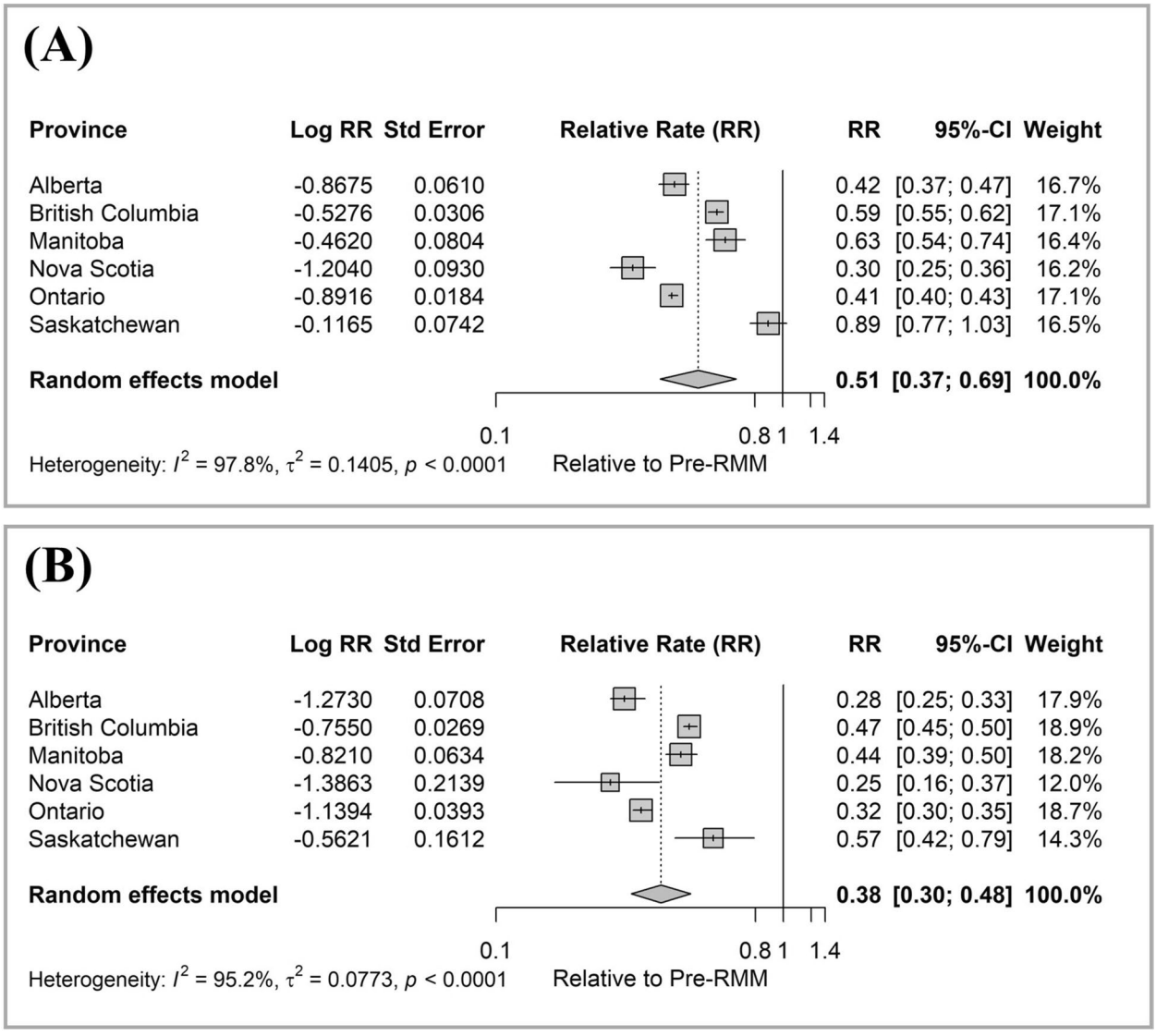

Fig. 5 Forest plot of province-specific and pooled fluoroquinolone prescription relative rates for AECOPD indication by RMM segment. Note: Panel (**A**) corresponds to post-RMM pre-COVID segment (January 1, 2017 to February 29, 2020). Panel (**B**) corresponds to post-RMM within-COVID segment (March 1, 2020 to December 31, 2022). The reference is the pre-RMM segment (January 1, 2008 to December 31, 2016). Data available in all provinces for ≥ 66 years. Rates are for four fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin *AECOPD* Acute exacerbation of chronic obstructive pulmonary disease, *CI* Confidence interval, *RMM* Risk mitigation measure

a significant impact on prescribing of some antibiotics due to reductions in healthcare seeking of patients during the earliest months of the pandemic as well as changes in healthcare provider perceptions of preventative measures [30]. However, our finding of a continual decrease in FQ use during the within-COVID period for all three indications is not consistent with global studies about antibiotic consumption based on sales data, which revealed a decreasing trend after the implementation of population movement restrictions followed by an increasing trend after lifting these restrictions in some countries, including Canada [31, 32].

We observed a decrease in the use of FQs for these three indications in all provinces. This finding is consistent with studies that examined utilization after the FDA warnings were released [6, 33]. The results indicate that FQs are no longer being used as the first-line treatment of AECOPD and UTI, which is consistent with guideline recommendations and the 2017 Health Canada risk communication [23, 34]. The use of FQs for the treatment of ABS was generally low throughout the study period.

There was substantial interprovincial variation in FQ use and decreases in use over time. These variations are consistent with international findings [13], and are likely not due to any one factor but can be explained by

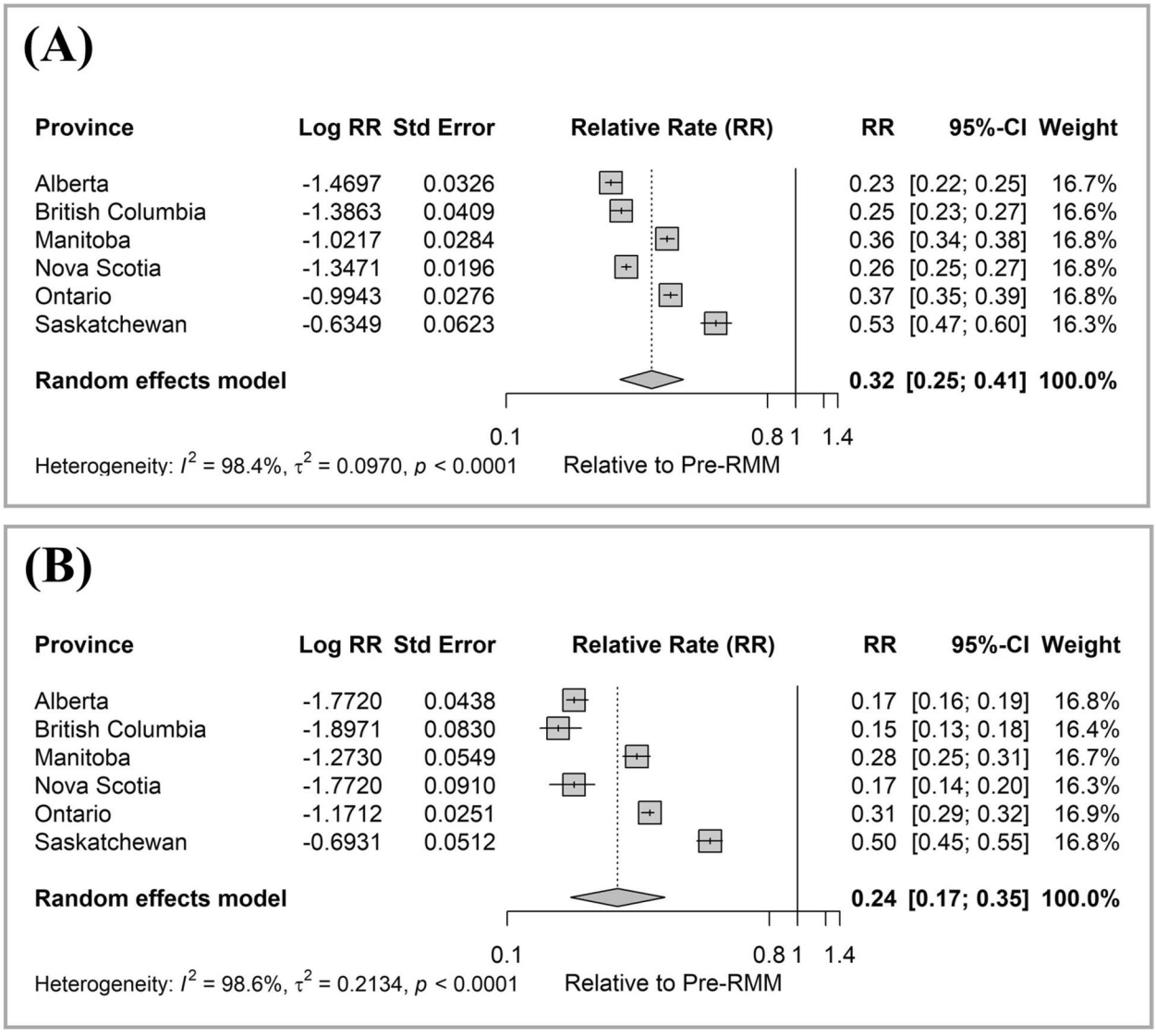

Fig. 6 Forest plot of province-specific and pooled fluoroquinolone prescription relative rates for UTI indication by RMM segment. Note: Panel (**A**) corresponds to post-RMM pre-COVID segment (January 1, 2017 to February 29, 2020). Panel (**B**) corresponds to post-RMM within-COVID segment (March 1, 2020 to December 31, 2022). The reference is the pre-RMM segment (January 1, 2008 to December 31, 2016). Data available in Nova Scotia and Ontario for ≥ 66 years, and for ≥ 18 years for all other provinces. Data are for women only. Rates are for four fluoroquinolones: ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin *CI* Confidence interval, *RMM* Risk mitigation measure; *UTI* Urinary tract infection

a combination of differences or changes in institutional or regional practice patterns, adherence to treatment guidelines, antibiotic resistance rates within populations or institutions, antimicrobial stewardship efforts, and provincial formulary criteria that determine which medications are covered by provincial health insurance programs and under what conditions. For example, the Public Health Agency of Canada's *Tackling Antimicrobial Resistance and Antimicrobial Use: A Pan-Canadian Framework for Action,* which was introduced in 2017 [35], examines strategies for surveillance, infection prevention and control, anti-microbial stewardship, and research might impact FQ use. Moreover, the Pan-Canadian Action Plan on Antimicrobial Resistance, introduced in 2023 to define potential professional and health system activities to prevent antimicrobial resistance, might further impact FQ prescribing in subsequent years [36]. Also there is the potential that awareness of potential adverse effects was increasing or changing over time, given that Health Canada has published other warnings about FQs both before and after the 2017 RMMs [20].

Our study has some limitations. First, the study data is restricted to antibiotics dispensed in community (i.e., outpatient) pharmacies and cannot be generalized to other settings of care, such as inpatient settings. As well, dispensations represent only one measure of FQ use. It

is not known whether dispensed medications are consumed. Information on FQ sales might provide a different picture of use. The event definitions for the three indications of interest are based on diagnosis codes and do not include clinical characteristics or laboratory values. Therefore, there is the potential for misclassification of individuals in each of the indication cohorts due to diagnostic uncertainty. Although antibiotic exposure was defined as the first antibiotic dispensed within five days of the event, it is not possible to be certain that the antibiotic was actually prescribed for the indication listed as the diagnosis associated with the physician visit. In addition, exposure was defined using prescription dispensation records; it is not possible to know if a medication is actually consumed. There may have been changes in treatment guidelines or clinical practice around the time of introduction of the 2017 RMM that we did not have information on. There are also differences in the data available across the provinces. In Nova Scotia and Ontario, data are limited to patients aged 66 years and older and prescription drug data capture dispensations reimbursed by the public drug plans only, whereas all dispensations, regardless of payer, are captured in the other provinces included in this study. Lastly, our study is limited to six Canadian provinces and the findings may not generalize to other provinces and territories.

Conclusions

In our multicenter retrospective cohort study, we observed a decline in the use of the four most commonly used oral systemic FQs in the outpatient setting in six Canadian provinces between 2008 and 2022. Overall prescription rates decreased by approximatively 50% over the study period; rates had begun to decline even before the 2017 regulatory actions were introduced. While substantial variation in rates of decline by region and indication were observed there was no consistent pattern of decrease in utilization across the provinces or for three common indications for antibiotics.

A recent systematic review [37] explored factors that influence antibiotic prescription practices and variation in practices, including physician-related, patient-related, and healthcare system-related factors; the authors suggested that variation is likely due to a complex combination of these factors. Systematic exploration of these factors cannot be conducted entirely with administrative health data, as they lack the granularity and types of information to investigate such factors as the attitudes of physicians towards risk communication messages, diagnostic uncertainty, and the effects of medical education and training. At the same time, administrative data can be used to explore the effect of RMMs in specific patient populations, for defined indications, or amongst specific groups of providers or types of facilities. Thus, there is opportunity for future research to explore factors associated with variations in prescribing rates across provinces.

Abbreviations

ABS	Acute bacterial sinusitis
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ATC	Anatomical Therapeutic Chemical
CNODES	Canadian Network for Observational Drug Effect Studies
CI	Confidence interval
EMA	European Medicines Agency
FDA	Food and Drug Administration
FQ	Fluoroquinolones
GEE	Generalized estimating equations
ICD	International Classification of Diseases
RR	Relative rate
RMM	Risk mitigation measure
UTI	Urinary tract infection

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

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by the Saskatchewan Ministry of Health and eHealth Saskatchewan. The interpretation and conclusions contained herein do not necessarily represent those of the Government of Saskatchewan, the Saskatchewan Ministry of Health, or eHealth Saskatchewan. CNODES is led by the https://CNODES steering committee and comprises many researchers who have provided significant support to this project. The opinions, results, and conclusions contained in this manuscript are those of the authors. No endorsement by Health Canada, Canada's Drug Agency, the provinces, the Government of Alberta, Alberta Health or Alberta Health Services, the Manitoba Centre for Health Policy or Manitoba Health, ICES, data stewards, the participating research centers, or CIHI is intended or should be inferred. We acknowledge the support of CNODES Investigators: Robert W. Platt (Executive), Samy Suissa (Executive); Colin R. Dormuth (British Columbia); Paul E. Ronksley (Alberta); Donica Janzen (Saskatchewan); Alan Katz and Matt Dahl (Manitoba); J. Michael Paterson (Ontario); Daniel J. Dutton (Atlantic); Pierre Ernst and Kristian B. Filion (UK Clinical Practice Research Datalink [CPRD]); Lisa M. Lix (Database Development Team); and Ingrid S. Sketris (Knowledge Translation Team).

Authors' contributions

All authors participated in the study design, analysis, and interpretation of results. LML drafted the manuscript. All authors reviewed and approved the final manuscript before submission.

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Data availability

This study was conducted by CNODES using administrative health data obtained through data-sharing agreements between its member research centers and their respective provincial data stewards. Data availability thus differs by site. ***Alberta:*** The authors cannot make the dataset used in this study available to other researchers due to their contractual arrangements with the provincial health ministry (Alberta Health), who is the data custodian. Researchers may make requests to obtain a similar dataset at (https://absporu.ca/research-services/service-application). ***British Columbia:*** The authors do not have permission to share data from this study. The data that support the findings of this study are available from Population Data BC (https://www.popdata.bc.ca), but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. ***Manitoba:*** Data used in this article were derived from administrative health and social data as a secondary source. The data were provided under specific data-sharing agreements only for approved use at Manitoba Centre for Health Policy (MCHP). The original source data are not owned by the researchers or MCHP and as such cannot be provided to a public repository. The original data source and approval for use have been noted in the acknowledgments of the article. Where necessary, source data specific to this article or project may be reviewed at MCHP with the consent of the original data providers, along with the required privacy and ethical review bodies. ***Nova Scotia:*** De-identified data in this study were obtained from Health Data Nova Scotia of Dalhousie University. These data can be acquired by researchers with an academic affiliation who submit a research protocol that is approved by a Data Access Committee and Research Ethics Board. ***Ontario:*** The data set from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., health organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at (https://www.ices.on.ca/DAS) (email: [das@ices.on.ca]). ***Saskatchewan:*** This study is based in-part on de-identified data provided by the Saskatchewan Ministry of Health. Restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data may be available from the authors upon reasonable request and with permission of the Saskatchewan Ministry of Health.

Declarations

Ethics approval and consent to participate

Research ethics board approvals were obtained at each participating institution: the Conjoint Health Research Ethics Board at the University of Calgary (Alberta); the Clinical Research Ethics Board at the University of British Columbia (British Columbia); the Health Research Ethics Board at the University of Manitoba (Manitoba); the Health Sciences Research Ethics Board at Dalhousie University (Nova Scotia); and the Biomedical Research Ethics Board at the University of Saskatchewan (Saskatchewan), except at ICES in Ontario, where research ethics board approval was not legally required. Informed consent was not required because this study used anonymized administrative data. All methods were carried out in accordance with relevant guidelines and regulations.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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