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Drug Utilization Study

Use of Oral Fluoroquinolones in Canada: A Drug Utilization Study Update

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This drug utilization study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

Key Messages

In January 2017, Health Canada issued a risk communication to restrict the use of fluoroquinolone antibiotics due to their potentially persistent and disabling side effects. Updates to the product labels were also made. There is a need to determine if fluoroquinolone utilization patterns have changed since these regulatory actions were implemented.

We conducted an updated study to describe the utilization trends of 4 oral fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) in the outpatient setting from 2008 to 2022 in 6 provinces. We used interrupted time-series analyses to assess the impact of the regulatory actions by estimating the change in the rate of fluoroquinolone dispensations and the percentage of antibiotic dispensations that are fluoroquinolones for 3 specific conditions.

Overall dispensation rates of the 4 oral fluoroquinolones decreased by approximately 50% between 2008 and 2022 across provinces, sexes, and age groups (from 107 to 45 dispensations per 1,000 population). The regulatory actions were followed by reductions in fluoroquinolone dispensation rates, and percentages of antibiotic dispensations that are fluoroquinolones, for urinary tract infections (UTIs) (females), acute exacerbations of chronic obstructive pulmonary disease (COPD) (patients aged ≥ 66 years), and acute bacterial sinusitis, although a decreasing trend was observed prior.

These findings could suggest that Health Canada regulatory actions were followed by reductions in the prescribing of oral fluoroquinolones. However, unmeasured factors, including health care system and patient characteristics, and differences in data characteristics across provinces, including data coding practices, may also affect the study findings.

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Abbreviations

CI	confidence interval
CNODES	Canadian Network for Observational Drug Effect Studies
COPD	chronic obstructive pulmonary disease
EMA	European Medicines Agency
ICD	International Classification of Diseases
RR	relative rate
UTI	urinary tract infection

Introduction and Rationale

Background

Fluoroquinolones, a class of broad-spectrum antibiotics, have been commonly used for a wide range of infections since their introduction in the mid-1980s. Serious adverse effects have been associated with fluoroquinolone use including tendon disorders, aortic aneurysm, retinal detachment, and effects on the central and peripheral nervous system.[1-3] Since 2008, several safety warnings have been issued by regulatory agencies. On May 12, 2016, the US FDA advised that the serious side effects of fluoroquinolones generally outweigh their benefits in infections where other treatment alternatives are available, such as those to treat acute bacterial sinusitis, acute exacerbation of COPD, and uncomplicated UTI.[4] On January 23, 2017 and November 16, 2018, Health Canada and the European Medicines Agency (EMA) similarly recommended restricting fluoroquinolone use due to their potentially persistent and disabling side effects.[5,6] As a result, labelling for all systemic fluoroquinolone products marketed in Canada have been updated with a boxed warning and the indications for fluoroquinolones have been restricted. Further revisions were made to the labels to include information on potential risk of aneurysm and aortic dissection following a safety review conducted by Health Canada in June 2019.[7]

Recently, a drug utilization study commissioned by the EMA evaluated the impact of regulatory actions on fluoroquinolone prescribing patterns in 6 European countries between 2016 and 2021.[8] Although reductions in the use of fluoroquinolones in the primary care setting were observed, they were not temporally related with regulatory actions. These findings resulted in the EMA issuing a reminder on the restricted use of fluoroquinolones in May 2023.[9] In January 2024, the Medicines and Healthcare products Regulatory Agency in the UK published an announcement on further restrictions to limit the use of fluoroquinolones. They recommended that fluoroquinolones should only be used when treatment with other recommended antibiotics have failed, or there is an issue with resistance or when the antibiotic is not safe for patient use.[10] Similarly, drug utilization studies conducted in the US showed that fluoroquinolone use declined in association with the FDA warnings and label changes, but the impact varied by patient and provider characteristics or infection type.[11-14] In Canada, observational studies[15-17] in response to a previous Health Canada query were conducted to assess the appropriate use of fluoroquinolones and compare their clinical outcomes in specific indications in 6 provinces between 2005 and 2015. Study findings showed that fluoroquinolones were commonly used as first-line treatment for uncomplicated UTI and acute exacerbations of COPD, and that their use varied widely across provinces.

Given the uncertainty as to the current trends in fluoroquinolone use in Canada, there is a need to determine if utilization patterns have changed following regulatory actions by Health Canada; specifically risk communication, labelling revisions on the risk of disabling and persistent serious adverse effects and updating restrictions to authorized indications.

Main Take-Aways

Fluoroquinolones, a class of broad-spectrum antibiotics, have been linked with serious adverse events. In January 2017, Health Canada issued a risk communication to restrict their use due to their disabling and potentially persistent side effects. Updates to the product labels were also made. It is unknown if fluoroquinolone utilization patterns have changed since these regulatory actions were implemented.

Purpose of this Report

The findings of this report will inform Health Canada on the need for further regulatory actions.

Policy Issue

Health Canada has requested that the previous drug utilization study[17] conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) be updated to determine the impact of the regulatory actions (risk communication, updates to the labels) applied in 2017 on fluoroquinolone use in Canada. The update is limited to the utilization and indications of 4 oral fluoroquinolones. An analysis of the clinical outcomes (risk of repeat primary care visits, hospitalizations, and subsequent antibiotic dispensations) included in the previous drug utilization study was not required.

Policy Questions

1. What are the current trends of fluoroquinolone use in Canada?
2. Are fluoroquinolones being prescribed for their intended indications?
3. Has drug utilization of fluoroquinolones shifted over time since 2017?
4. How have Health Canada's risk mitigation measures (risk communication, updates to the labels) impacted the use of fluoroquinolones in Canada?

Main Take-Aways

At the request of Health Canada, we updated the previous drug utilization study to determine if further regulatory actions are needed. The overall objective of this study was to describe fluoroquinolone utilization trends from 2008 to 2022 and to assess the impact of the risk minimization measures introduced in 2017.

Objectives

The main objectives of this study were to update our previous study to describe fluoroquinolone utilization trends from 2008 to 2022 and to assess the impact of the risk minimization measures introduced in 2017.

The specific objectives were:

1. To assess utilization patterns and indications of oral fluoroquinolones available in Canada from 2008 to 2022. Specifically:
   a) to describe the annual frequency and rate of use of oral fluoroquinolones in general and the 4 oral fluoroquinolones of interest (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) from 2008 to 2022.
   b) to describe the dosage and duration of use of each oral fluoroquinolone by year from 2008 to 2022
   c) to describe the use of oral fluoroquinolones by prescriber group or specialty
   d) to describe the most common indications for each oral fluoroquinolone by year from 2008 to 2022
   e) to determine the rate and percentage of prescriptions of oral fluoroquinolones as compared with other antibiotics by principal indication (UTI, acute bacterial sinusitis, acute exacerbation of COPD), for adult patients with uncomplicated disease.
2. To assess the impact of the 2017 risk minimization measures (risk communication, updates to the labels) on the use of oral fluoroquinolones over time by estimating change in prescribing rates and percentages of overall antibiotic use.

Research Questions

1. What are the utilization patterns and indications of oral fluoroquinolones in Canada from 2017 to present?
2. How do the current trends of, and indications for, oral fluoroquinolone use compare with those from the previous drug utilization study?
3. How does the drug utilization of fluoroquinolones vary across potential subgroups?

Methods

Population and Setting

This study was conducted by CNODES.[18,19] The study protocol was registered on the HMA-EMA catalogue of real-world data studies (EU PAS number: EUPAS107333). Similar methods to the previous drug utilization study were used.[17] The study population consisted of individuals registered in the provincial administrative databases in 6 provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan) between January 1, 2008, and December 31, 2022 (last year of data available). We selected 2008 as the beginning of the study period as all provinces had complete data as of that year. Due to prescription drug

availability and limited use of fluoroquinolones in children, inclusion was limited to patients aged 18 years and older for Alberta, British Columbia, Manitoba, and Saskatchewan, and patients aged 66 years and older for Nova Scotia and Ontario. As use of fluoroquinolones among children was expected to be very low based on findings in the previous study,[17] patients younger than 18 years were only included in objective 1a (rates of fluoroquinolone dispensations) in the 3 provinces where data were available (British Columbia, Manitoba and Saskatchewan). The study population in each province is described in Appendix 1, Table 1.

Study Design

This is a multicentre retrospective cohort study describing fluoroquinolone utilization trends from 2008 to 2022 and assessing the impact of the risk minimization measures introduced by Health Canada in 2017.

Eligibility Criteria

Overall Fluoroquinolone Utilization

To address objective 1a-d, the study population consisted of all individuals with a dispensation for an oral fluoroquinolone (defined in Exposures) in the outpatient setting between January 1, 2008, and December 31, 2022.

To address objective 1e, we created a separate cohort for each indication of interest (acute bacterial sinusitis, acute exacerbations of COPD, and UTI). In each province, we identified acute sinusitis, COPD, and UTI events in outpatient medical service claims among patients aged 18 years and older (patients aged 66 years and older for Nova Scotia and Ontario) between January 1, 2008, and December 31, 2022. Within each cohort, cohort entry date was defined by the date of the corresponding medical service claim. Specific exclusions were applied to restrict each indication cohort to patients with uncomplicated disease (defined similarly as in the previous study). Patients were eligible to enter the study cohorts multiple times provided they met all the criteria at each inclusion. The list of codes used to define the 3 indication cohorts is available in Appendix 1, Table 2.

Acute Bacterial Sinusitis Cohort Exclusion Criteria

For the acute bacterial sinusitis cohort, we excluded patients with a diagnosis of acute sinusitis in outpatient medical service claims or a hospitalization for any reason in the 30 days before cohort entry date. We excluded acute bacterial sinusitis events occurring less than 5 days before the latest date of data available in each province. We also excluded patients with less than 365 days of health care coverage before the acute bacterial sinusitis event and those with less than 5 days of coverage after the event date.

Acute Exacerbation of COPD Cohort Exclusion Criteria

For the acute exacerbation of COPD cohort, we excluded patients younger than 66 years on the COPD event date. To limit the study cohort to uncomplicated acute exacerbations of COPD, we excluded patients with a COPD event, a hospitalization for any reason, use of oral antibiotics, or use of oral corticosteroids in the prior 90 days. We excluded events occurring less than 5 days before the latest date of data available in each province. We also excluded patients with less than 365 days of health care coverage before the COPD event date. Patients with a history of heart failure or ischemic heart disease in medical service claims

or hospitalization discharge abstracts in the 365 days before or on the COPD event date were excluded as patients with concomitant significant cardiac disease are at higher risk of negative outcomes and are therefore considered to have a complicated disease. Lastly, we excluded patients with less than 5 days of coverage after the event date. We assumed that a visit to a health practitioner for COPD represents an exacerbation especially if accompanied by an antibiotic dispensation, as there is no specific diagnostic code for acute exacerbations of COPD.

Uncomplicated UTI Cohort Exclusion Criteria

For the uncomplicated UTI cohort, we excluded patients with recurrent UTI based on a diagnosis for UTI in outpatient medical service claims or in hospital discharge abstracts in the 90 days before cohort entry date. We excluded events occurring less than 5 days before the latest date of data available in each province. Patients with less than 365 days of health care coverage before the UTI event and less than 5 days of coverage after the event date were excluded. We excluded patients with a hospitalization for any reason in the 30 days before the UTI event. We excluded patients with male or unreported sex (as UTIs in males are usually considered complicated[20]) and with a diagnosis suggesting a complicated UTI in medical service claims or hospitalization discharge abstracts in the 365 days before or on cohort entry. These diagnoses include structural abnormality of urinary tract (including stones), ureteral abnormalities, vesicoureteral reflux, neurogenic bladder, neurologic conditions, pregnancy (in the 270 days prior), or severe diabetes.[21] Lastly, we excluded patients with a history of a kidney or pyelonephritis infection in the 90 days before or on cohort entry, a diagnosis of a sexually transmitted infection within 14 days of the UTI event date, indwelling catheter in the 90 days before or on cohort entry date, and patients in palliative or long-term care at cohort entry date (in provinces where available).

Impact Assessment Analysis

To address objective 2, the study population consisted of all individuals aged 18 years or older with a dispensation of an oral fluoroquinolone in the outpatient setting between January 1, 2008, and December 31, 2022, and for the assessment of the change in prescribing rates. We used the 3 indication cohorts created for objective 1e to assess the change in percentage of overall antibiotic use.

Data Sources

We used administrative health databases from the provinces of Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan. The databases included prescription drug claims, provider registry files (where applicable), medical services claims, hospitalization records, and provincial health insurance registration files in each province. The list of databases used in each province is described in Appendix 1, Table 1.

Key Study Measures

Exposures

A detailed list of the codes used to define exposure is included in Appendix 1, Table 3. All dispensations for oral fluoroquinolones in the outpatient setting were examined. Analyses by specific fluoroquinolone molecules were limited to ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin (4 fluoroquinolones of

interest). Oral ofloxacin was not included in analyses by molecules as it is no longer marketed in Canada since 2016.[22] All IV (also used for inhalation) and topical fluoroquinolone formulations were excluded. For objectives 1e and 2 (change in percentage of overall antibiotic use), antibiotic exposure was determined by the first antibiotic dispensation in the outpatient setting of an oral fluoroquinolone of interest (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) or another oral antibiotic within 5 days before and 5 days after the cohort entry date for the indication.

Outcomes of Interest

Overall Fluoroquinolone Utilization

We documented the yearly number and rate of dispensations (per 1,000 population) of all oral fluoroquinolones (i.e., all molecules), the 4 fluoroquinolones of interest combined (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin combined), and each molecule (objective 1a) individually. We reported the duration and daily dosage by year for each of the 4 fluoroquinolones (objective 1b). For objective 1c, the use of fluoroquinolones by prescriber group or specialty was documented by assigning each dispensation of a fluoroquinolone of interest to a prescriber and identifying the prescriber group or specialty. Categories were limited by the data available in each provincial database, but included family physician, specialist physician (as many subcategories as possible), and nonphysician prescribers (as many subcategories as possible, including nurse practitioners and pharmacists if available). In addition, we also documented the percentage of fluoroquinolone dispensations to long-term care residents.

For objective 1d, we documented the common indications associated with fluoroquinolone use. Dispensing dates are not always accurate. For example, a patient may leave hospital with several days supply or delay filling a prescription. To accommodate this uncertainty identifying health service contacts at which fluoroquinolones were prescribed, for each dispensation of a fluoroquinolone of interest, we assessed the medical service claims and hospital discharge abstracts (plus additional relevant data sources where available; Appendix 1, Table 1) within 7 days before and 7 days after the dispensation date to assign an indication. The first (i.e., closest to the day of the dispensation, regardless of whether it was before or after the dispensation date) International Classification of Diseases (ICD), Ninth and Tenth Revisions, code was assigned to the dispensation. For hospital discharge abstracts, the date of admission or discharge date was used as the date of the diagnosis, and this determination was made using additional criteria. If the discharge date occurred on or before the dispensation, then the discharge date was used to determine proximity of the hospitalization to the dispensation. Otherwise (i.e., admission date was after the dispensation date, or dispensation date occurred within the hospitalization), the admission date was used. For hospital discharge abstracts, only the primary (i.e., most responsible) diagnosis was used. In addition, we documented the number and percentage of all dispensations of the 4 fluoroquinolones for which no diagnosis was assigned, overall and by molecule.

For each indication cohort (objective 1e), we documented the annual frequency and percentage of events initially treated with an oral fluoroquinolone. We also documented the percentage of events not treated with an antibiotic and the top 10 most common antibiotic dispensations (based on frequencies) associated with the event.

Impact Assessment Analysis

The outcomes modelled for the impact assessment analysis (objective 2) were the: rate of dispensations for the 4 fluoroquinolones per 1,000 population, and percentage of antibiotic dispensations that were an oral fluoroquinolone of interest.

Covariates of Interest

Fluoroquinolone use was stratified by molecule (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin), age group (patients aged 18 to 65 years and ≥ 66 years) and sex (female or male) (further described in Analyses). Results for children (< 18 years) were included only for objective 1a. For objective 2, we did not stratify by age group or sex, but rather controlled for these covariates to maximize statistical power to detect an effect of the risk minimization measures.

Analyses

Overall Fluoroquinolone Utilization

For objective 1a, crude dispensation rates for all fluoroquinolones, the 4 fluoroquinolones of interest combined, and each molecule individually were estimated yearly (using calendar year) and expressed per 1,000 population (using population estimates from provincial registries). Rates were estimated by age groups (patients aged < 18 years, 18 to 65 years, and ≥ 66 years) and by sex. Age at the time of the prescription was used. Data were presented overall (i.e., aggregated for all provinces) and by province separately.

Duration and daily dosage for each fluoroquinolone dispensation was calculated using the quantity dispensed, medication strength, and days supply (objective 1b). Duration and daily dose were based on treatment episodes defined as all consecutive dispensations of the same molecule with no gap greater than 3 days. The yearly (using calendar year) average, standard deviation, median, and interquartile range (75th percentile minus 25th percentile) of duration and daily dose were reported by province for each fluoroquinolone of interest. Analyses were stratified by age group.

For objective 1c, the yearly (using calendar year) number and percentage of fluoroquinolone dispensations were reported by prescriber group or long-term care status. Results were reported by province.

The yearly (calendar year) most frequent (i.e., the top 10 frequencies) indications for fluoroquinolone prescriptions were documented overall and by molecule (objective 1d). Analyses were stratified by age group and separately by sex. Results were reported by province.

For objective 1e, the percentage of events initially treated with a fluoroquinolone of interest was estimated by calculating the percentage of fluoroquinolone dispensations among all antibiotic dispensations within a year. We estimated the yearly (using calendar year) number and rate of fluoroquinolone dispensations per 1,000 population (using population estimates from provincial registries) for each indication by province. Results were reported by province, overall, and by molecule.

Impact Assessment Analysis

An interrupted time-series analysis was used to assess the impact of the 2017 Health Canada risk minimization measures (risk communication, updates to the labels). To do the before and after comparison, a

segmented regression model was used. The first segment was from January 1, 2008, to December 31, 2016 (prerisk minimization period). The second segment was from January 1, 2017, to February 29, 2020 (postrisk minimization period; pre-COVID-19). The third segment was from March 1, 2020, to December 31, 2022 (postrisk minimization period, COVID-19). The postrisk minimization period was divided into 2 segments to address the potential impact of COVID-19 on fluoroquinolone dispensations.

Two models were fit to the data. In the first model, we estimated the age- and sex-adjusted rate of dispensations (per 1,000 population) for the 4 fluoroquinolones of interest by month for the period between January 1, 2008, and December 31, 2022. We modelled the number of dispensations of an oral fluoroquinolone (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) by age group (using 10-year age groups starting with 18 to 29, 30 to 39, and so on to ≥ 80), sex, month, and segment. The data were modelled using a negative binomial distribution, with the natural logarithm of the population as the model offset. The model covariates were age group, sex, month, and segment; only main effects were included in the model. To account for the dependence in monthly number of dispensations, generalized estimating equations were used, assuming a first-order autoregressive structure, in which correlations were assumed to be highest between adjacent months and systematically decreasing with increasing distance between months, or an exchangeable structure, in which correlations were assumed to be equal between adjacent months. The latter structure was chosen to achieve model convergence in selected provinces because it requires the estimation of fewer parameters (in British Columbia an independent correlation structure was used in selected analyses to achieve model convergence). Season effects were not included in the models because our goal was to estimate the average rate for 1 segment relative to another segment. The model-based, age- and sex-adjusted fluoroquinolone rates (per 1,000 population) by month and segment were estimated. A second model included the main effects for all covariates, as well as the 2-way interaction of month and segment. We used this model to estimate the relative rate (RR) for the second and third segment, using the first segment (before introduction of risk minimization measures) as the reference. We estimated 95% confidence intervals (CIs) for each RR estimate. Within each segment, we estimated the slope (average monthly rate of change) and its 95% CI. In addition, we conducted a sensitivity analysis using a washout period of 6 months after the risk minimization measures were introduced (i.e., segment 2 was defined as the period from July 1, 2017, to February 29, 2020), to account for the time needed to fully implement changes.

Subsequently, we estimated the monthly age- and sex-adjusted percentage of all antibiotic dispensations that were an oral fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin), during the period between January 1, 2008, and December 31, 2022. This analysis was conducted by principal indication (acute bacterial sinusitis, acute exacerbation of COPD, and UTI; using the 3 cohorts created for objective 1e). We calculated the percentages by age group (10-year age groups starting with 18 to 29, 30 to 39, and so on to ≥ 80), sex, month, and segment. For COPD, the age groups were only defined for individuals aged 66 years and older. For the UTI analysis, the cohort was limited to females only, so no sex-adjusted analyses were conducted. The number of fluoroquinolone dispensations divided by the total number of antibiotic dispensations were modelled using a generalized linear model (logistic regression) with a binomial distribution and the logit link function. The model covariates were age group, sex, month, and segment; only main effects were included in the model. Generalized estimating equations with a first-order

autoregressive structure or an exchangeable structure in selected provinces were used to account for dependence in the time-series data. We estimated the model-based age- and sex-adjusted percentages by month and segment for each principal indication. A second model that was fit to the data included the main effects for all covariates, as well as the 2-way interaction of month and segment. The same estimates were produced as for the previous analysis.

Province-specific estimates were pooled using the DerSimonian and Laird random-effects models.[23] The amount of between-province heterogeneity was estimated using the I^2 statistic. Province-specific estimates are also reported. Note that the slope estimates were consistent across all provinces and therefore did not require pooling.

Results

Fluoroquinolone Utilization

Main Take-Aways

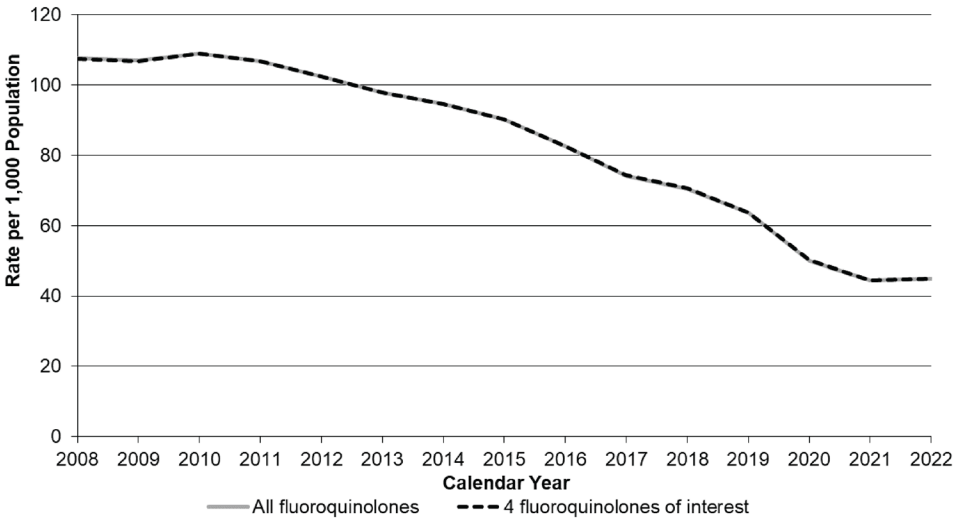
- Overall dispensation rates of the 4 oral fluoroquinolones of interest decreased by approximately 50% across provinces, sexes, and age groups between 2008 and 2022 (from 107 to 45 dispensations per 1,000 population).
- Fluoroquinolone use decreased for the treatment of adults with acute bacterial sinusitis, acute exacerbations of COPD (patients aged ≥ 66 years only), and uncomplicated UTIs (females only).
- Interprovincial variation in the use of fluoroquinolones was noted.

Objective 1a: Rates of Fluoroquinolone Dispensations

The overall crude dispensation rates for all fluoroquinolones and the 4 fluoroquinolones of interest are presented in Figure 1 and Appendix 2, Table 4. The use of fluoroquinolones other than the 4 fluoroquinolones of interest was minimal and decreased to 0 by the end of the study period; therefore, all subsequent results are limited to the 4 molecules of interest (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin). Overall, utilization of the 4 fluoroquinolones decreased by approximately 50% across provinces, both sexes, and age groups from 2008 to 2022. Fluoroquinolone use declined from approximately 107 to 45.0 dispensations per 1,000 population, overall, during the study period.

Figure 2 and Appendix 2, Table 5 present the overall utilization of the 4 fluoroquinolones by age group. Fluoroquinolone use decreased and varied by age group, with crude dispensation rates ranging from 219.8 to 89.0 per 1,000 population among patients aged 66 years and older, and from 78.1 to 27.1 per 1,000 population among patients aged 18 to 65 years. Fluoroquinolones were rarely prescribed among patients younger than 18 years, with crude dispensation rates ranging from 5.1 to 1.2 per 1,000 population and similar use in British Columbia, Manitoba, and Saskatchewan (Figure 3 and Appendix 2, Table 6). Given the limited use in children, all subsequent results include only adults.

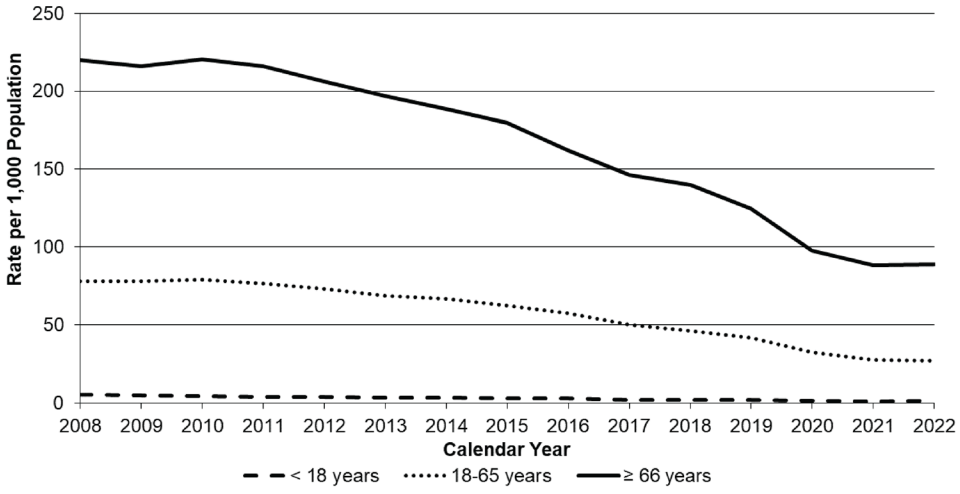
Figure 1: Overall Crude Dispensation Rates (per 1,000 Population) for All Fluoroquinolones and the 4 Fluoroquinolones of Interest by Calendar Year



Note: Data aggregated for all 6 provinces (all ages and both sexes combined). Data available in Alberta for patients aged ≥ 18 years, and in Nova Scotia and Ontario for patients aged ≥ 66 years.

All fluoroquinolones (all molecules) and 4 fluoroquinolones of interest (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin).

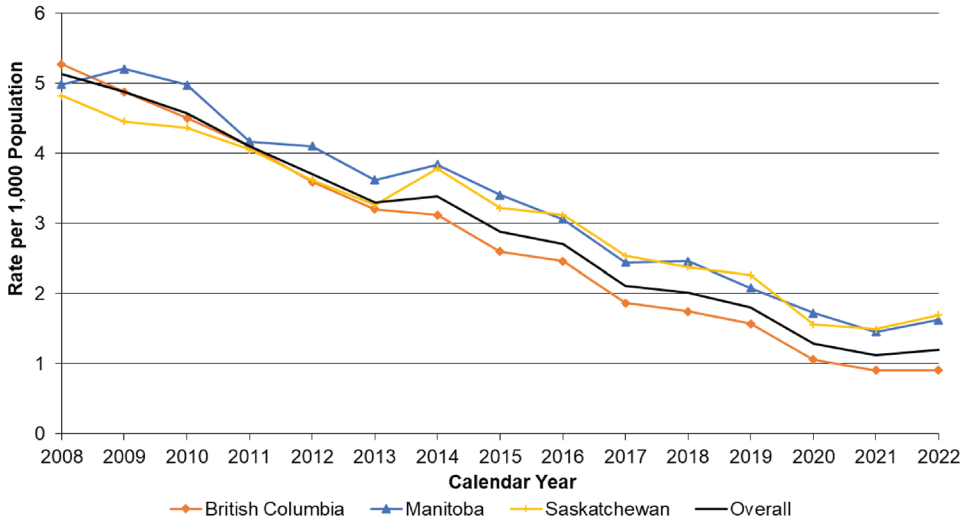
Figure 2: Overall Crude Dispensation Rates (per 1,000 Population) for the 4 Fluoroquinolones by Age and Calendar Year



Note: Data aggregated for all 6 provinces. Data available in Alberta for patients aged ≥ 18 years, and in Nova Scotia and Ontario for patients aged ≥ 66 years.

The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

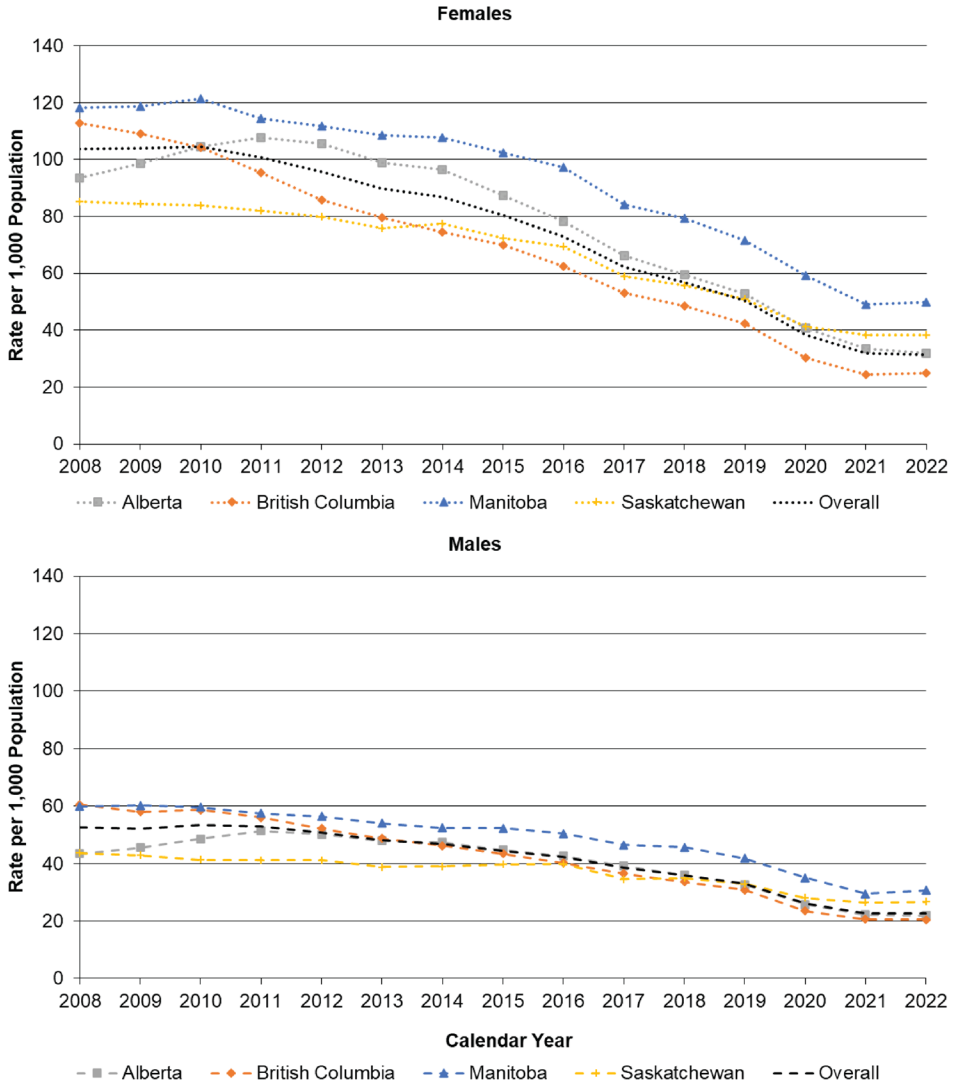
Figure 3: Crude Dispensation Rates (per 1,000 Population) for the 4 Fluoroquinolones Among Patients Aged < 18 Years by Calendar Year, Overall, and by Province



Note: Overall represents data aggregated for all 3 provinces. Data not available in Alberta, Nova Scotia, and Ontario.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

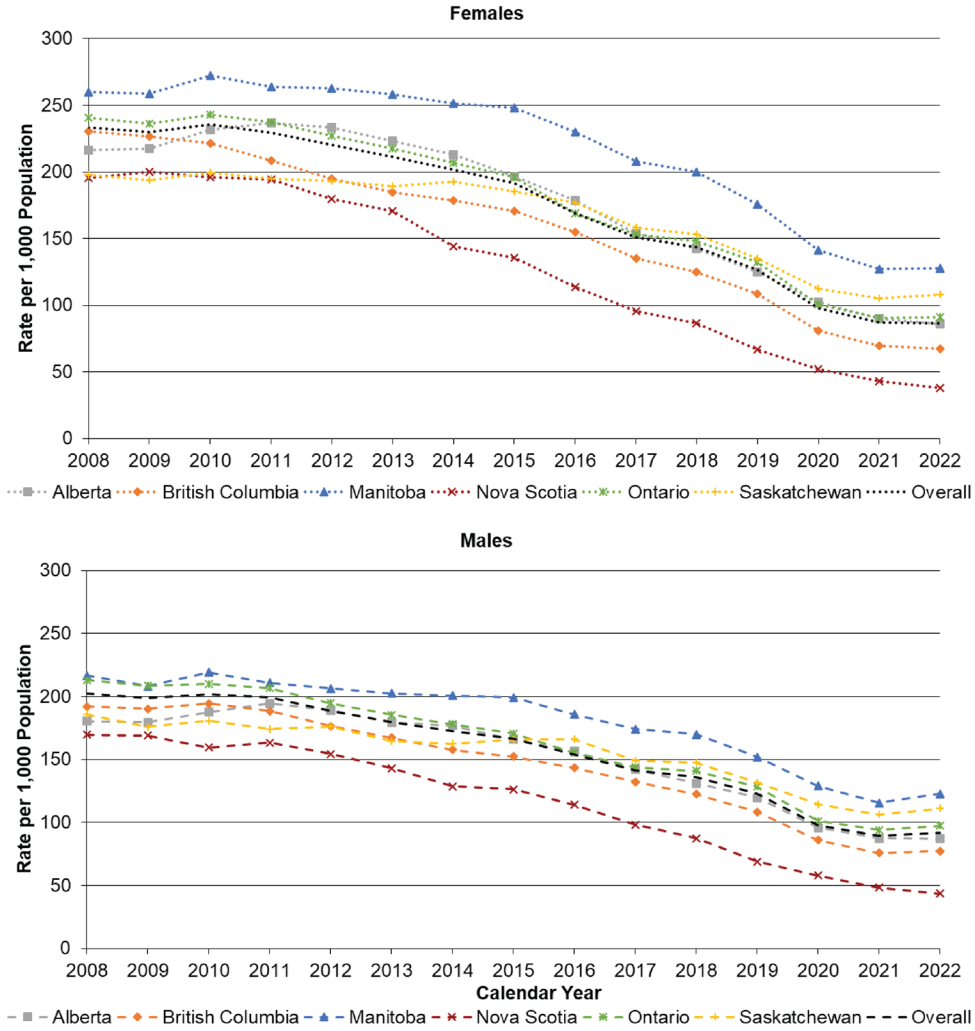
Utilization of the 4 fluoroquinolones among adults by age group and sex, overall, and by province is presented in Figures 4 and 5 and Appendix 2, Table 7. Fluoroquinolone use was highest among females compared with males regardless of age, with use declining overall and across provinces. Among patients aged 18 to 65 years from 2008 to 2022, overall use decreased from 103.8 to 31.5 and 52.6 to 22.7 dispensations per 1,000 population for females and males, respectively. The difference between sexes was less in patients aged 66 years and older, with overall use decreasing from 233.4 to 86.3 and 202.5 to 92.0 dispensations per 1,000 population for females and males, respectively. There were some differences in utilization across provinces, with higher dispensation rates observed in Manitoba, Alberta, and Ontario and lower rates in Saskatchewan, British Columbia, and Nova Scotia.

Figure 4: Crude Dispensation Rates (per 1,000 Population) for the 4 Fluoroquinolones Among Patients Aged 18 to 65 Years by Sex and Calendar Year, Overall, and by Province



Note: Overall represents data aggregated for all 4 provinces. Data not available in Nova Scotia and Ontario.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

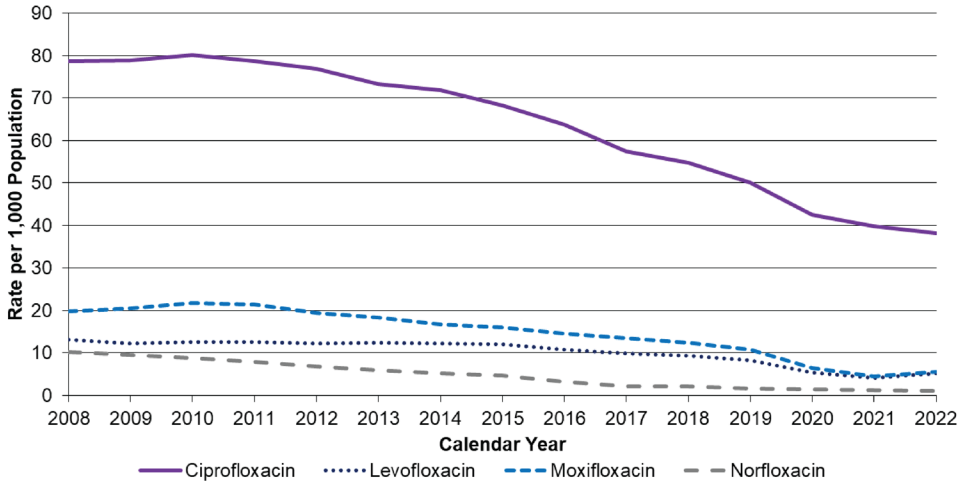
Figure 5: Crude Dispensation Rates (per 1,000 Population) for the 4 Fluoroquinolones Among Patients Aged ≥ 66 Years by Sex and Calendar Year, Overall, and by Province



Note: Overall represents data aggregated for all 6 provinces.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

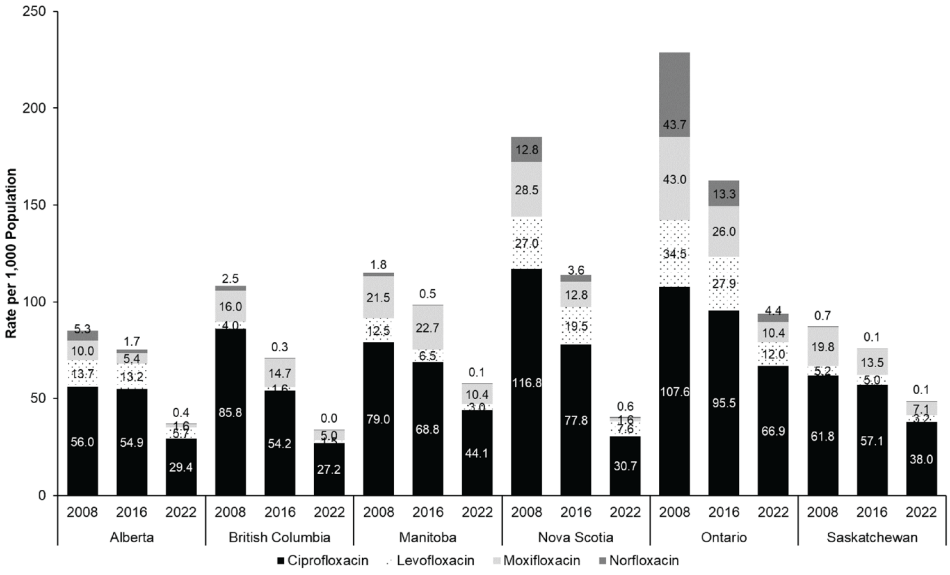
Figure 6 represents overall utilization for each fluoroquinolone for all provinces combined. Overall, utilization of each molecule declined between 2008 and 2022. Ciprofloxacin was the most frequently prescribed fluoroquinolone molecule (78.7 to 38.1 dispensations per 1,000 population), followed by moxifloxacin (19.9 to 5.6 dispensations per 1,000 population) and levofloxacin (13.1 to 5.2 dispensations per 1,000 population), whereas norfloxacin was less prescribed (10.3 to 1.1 dispensations per 1,000 population). Crude dispensation rates by province in 2008, 2016, and 2022 are presented in Figure 7. In all provinces, use of each molecule declined over the study period but some differences in use were observed between provinces.

Figure 6: Overall Crude Dispensation Rates (per 1,000 Population) for Each Molecule by Calendar Year



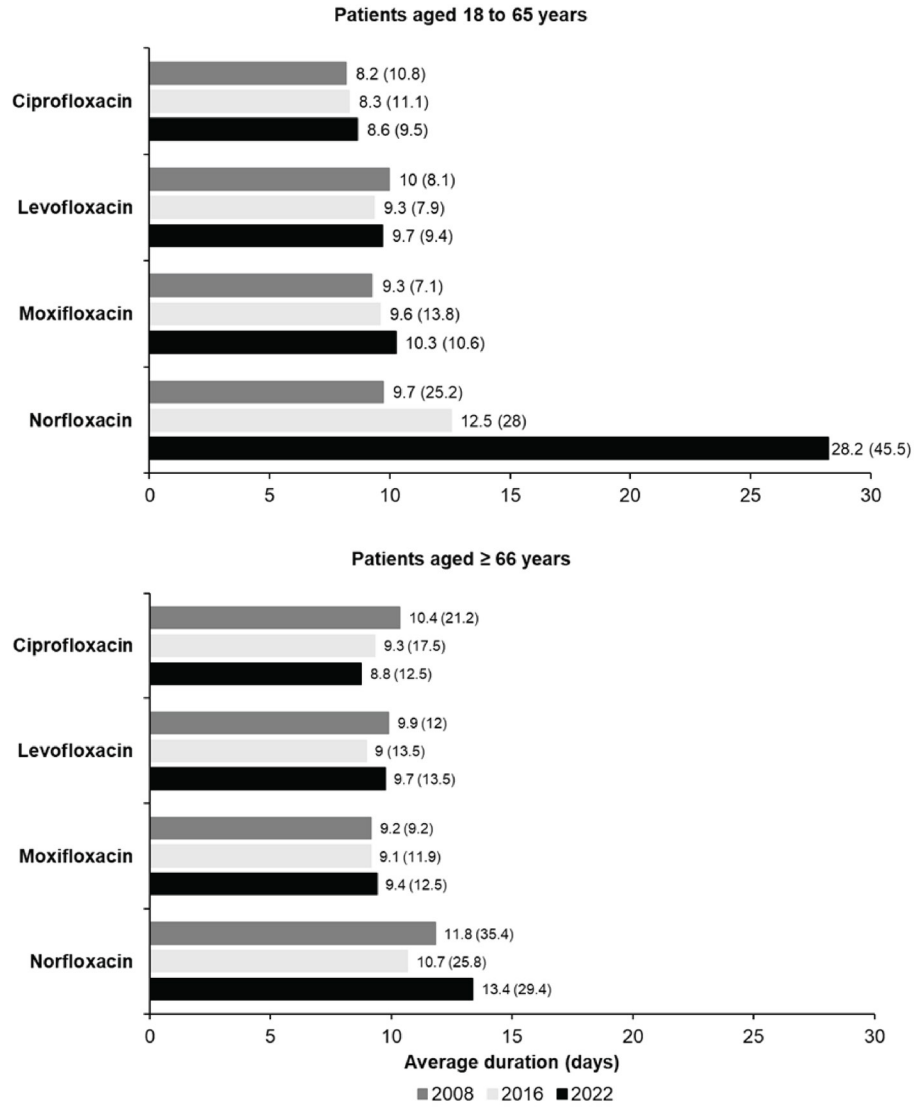
Note: Data aggregated for all 6 provinces (all patients aged ≥ 18 years and both sexes combined).

Figure 7: Crude Dispensation Rates (per 1,000 Population) for Each Fluoroquinolone by Province in 2008, 2016, and 2022



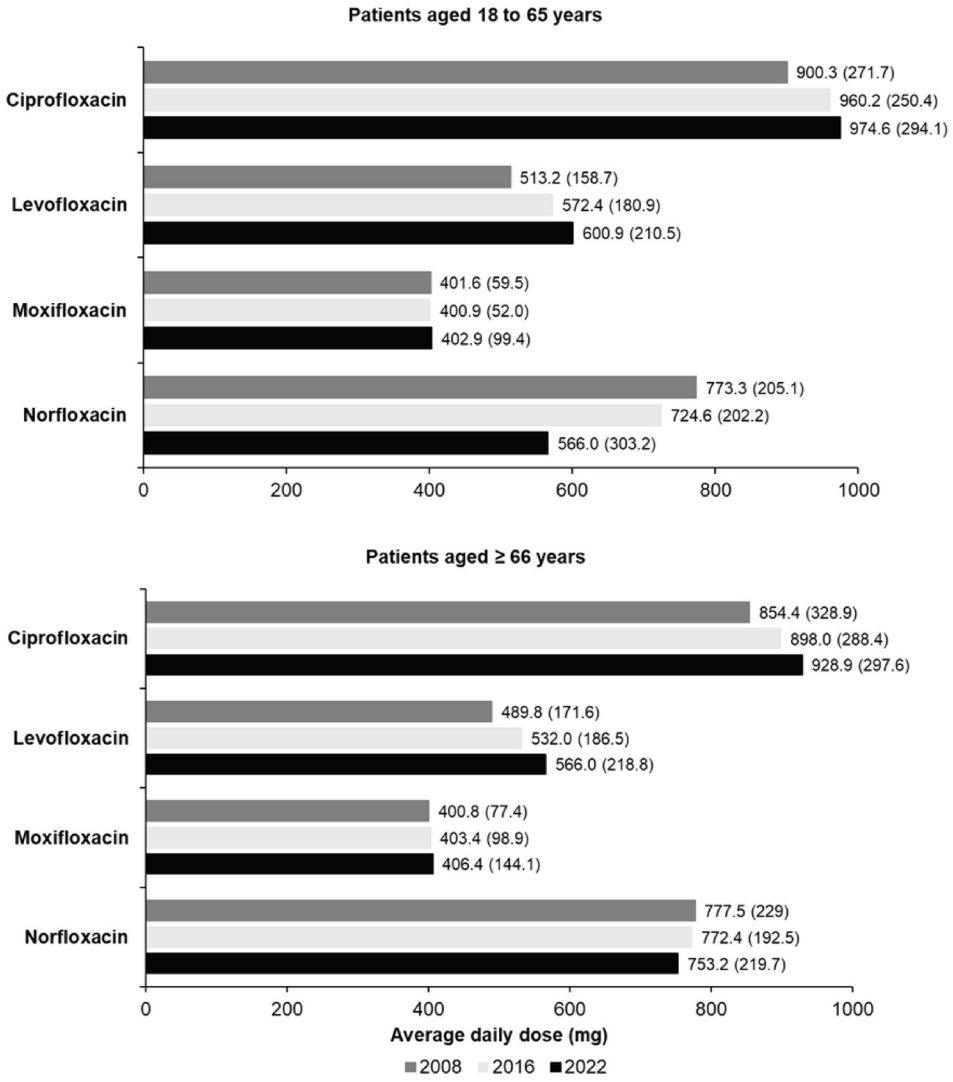
Note: Data presented by province (for all patients aged ≥ 18 years and sexes combined). Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

Figure 8: Average Duration of Use for Each Fluoroquinolone by Age Group in 2008, 2016, and 2022



Note: Data aggregated for all 6 provinces and presented as mean (standard deviation). Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

Figure 9: Average Daily Dose for Each Fluoroquinolone by Age Group in 2008, 2016, and 2022



Note: Data aggregated for all 6 provinces and presented as mean (standard deviation). Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

Objective 1b: Use of Fluoroquinolones by Dosage and Duration

The average duration of use for each fluoroquinolone is presented by age group in 2008, 2016, and 2022 in Figure 8. Duration of use remained relatively similar among patients aged 18 to 65 years and patients aged 66 years and older for all molecules during the study period, except norfloxacin. For norfloxacin, the average duration of use increased to about 30 days among patients aged 18 to 65 years at the end of the study period. This is likely a reflection of the gradual limitation of use of this antibiotic to patients with a chronic indication, usually for prevention of recurrent UTIs.

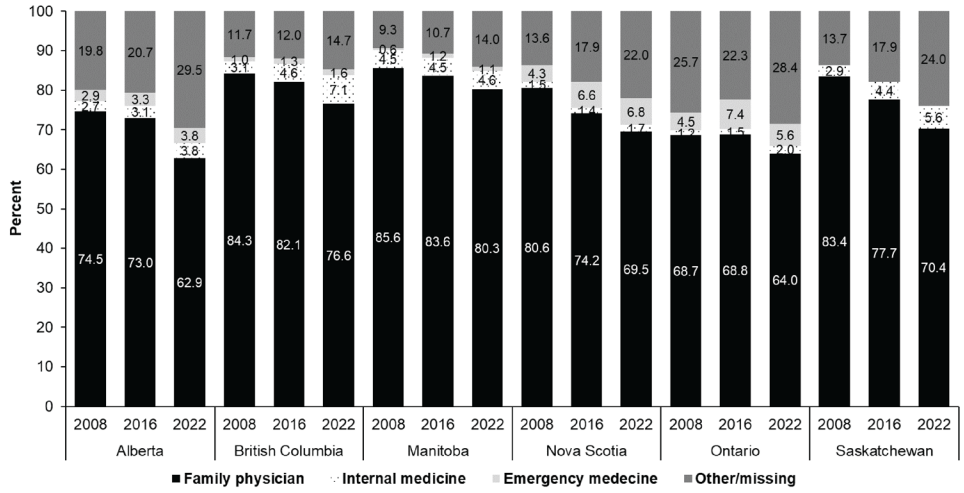
Figure 9 depicts the average daily dose (mg) for each fluoroquinolone by age group in 2008, 2016, and 2022. The average daily doses remained relatively similar across age groups for all molecules during the study period. The average daily doses for ciprofloxacin and levofloxacin among patients aged 66 years and older tended to be lower than among patients aged 18 to 65 years as per treatment guidelines. The recommended dosage for each molecule is: ciprofloxacin 250 to 750 mg twice per day, levofloxacin 250 to 750 mg per day, moxifloxacin 400 mg per day, and norfloxacin 400 mg twice per day.

Objective 1c: Use of Fluoroquinolones by Prescriber Group or Specialty

Figure 10 presents the percentage of dispensations for the 4 fluoroquinolones by prescriber group or specialty by province in 2008, 2016, and 2022. In all provinces, fluoroquinolones were mostly prescribed by family physicians, with percentage of dispensations ranging from 68.7% (Ontario) to 85.6% (Manitoba) in 2008, and 62.9% (Alberta) to 80.3% (Manitoba) in 2022. Internal medicine accounted for 1.2% (Ontario) to 4.5% (Manitoba) of dispensations at the beginning of the study period, and 1.7% (Nova Scotia) to 7.1% (British Columbia) at the end of the study period. In Nova Scotia and Ontario, emergency medicine accounted for a higher percentage of fluoroquinolone dispensations (ranging from 4.3% in 2008 to 6.8% in 2022) compared with Alberta, British Columbia, and Manitoba (ranging from 0.6% in 2008 to 3.8% in 2022). Other common specialties included urology in Alberta, British Columbia, Nova Scotia, and Ontario (ranging from 3.1% in 2008 to 10.3% in 2022), surgery in Manitoba and Saskatchewan (ranging from 4.1% in 2008 to 8.0% in 2022), and respirology in Alberta and Ontario (ranging from 0.6% in 2008 to 1.9% in 2022). Between 9.3% in 2008 and 29.5% in 2022 of dispensations had another or missing prescriber group or specialty. Data on other prescribers were limited across provinces (data not shown). Fluoroquinolones were rarely prescribed by pharmacists in Alberta, British Columbia, and Nova Scotia between 2008 and 2022 (< 1%). Prescriptions by nurse practitioners accounted for less than 0.3% to 6.6% of fluoroquinolone dispensations in British Columbia, Nova Scotia, and Saskatchewan throughout the study period, whereas this was rare in Alberta (< 0.3%).

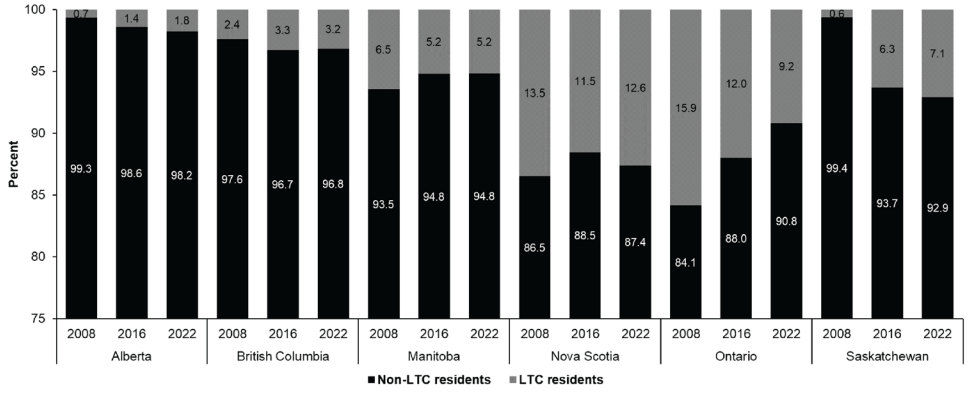
The percentages of dispensations for the 4 fluoroquinolones by long-term care status by province in 2008, 2016, and 2022 are presented in Figure 11. A higher proportion of fluoroquinolones were prescribed to patients residing in long-term care facilities in Nova Scotia and Ontario compared with other provinces (ranging from 9.2% to 15.9% versus 0.6% to 7.1% throughout the study period), which is expected given that the study population is limited to patients aged 66 years and older in these 2 provinces.

Figure 10: Percentage of Dispensations for the 4 Fluoroquinolones by Prescriber Group or Specialty by Province in 2008, 2016, and 2022



Note: Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin. Emergency medicine not available in Saskatchewan.

Figure 11: Percentage of Dispensations for the 4 Fluoroquinolones by Long-Term Care Status by Province in 2008, 2016, and 2022



LTC = long-term care.
Notes: Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Objective 1d: Common Indications Associated With Fluoroquinolone Use

The top 3 most common indications associated with the 4 fluoroquinolones are reported by province in 2008, 2016, and 2022 by age group and sex separately in Appendix 2, Tables 8 to 11. The proportion of dispensations with a missing indication ranged between approximately 5% to 20% across provinces. In general, the top 3 indications remained relatively similar across years in all provinces and both sexes and age groups. The most common indication for fluoroquinolones were for genitourinary tract or respiratory infections. Common indications by molecule were relatively similar across provinces and age groups and sex

(data not shown). Principal indications for ciprofloxacin were disorders of the genitourinary tract and digestive systems. The principal indications for levofloxacin and moxifloxacin were disorders of the respiratory system, and for norfloxacin, the genitourinary tract system. Interprovincial variations in the most common indications associated with fluoroquinolone use were noted, in part due to differences in coding practices across provinces.

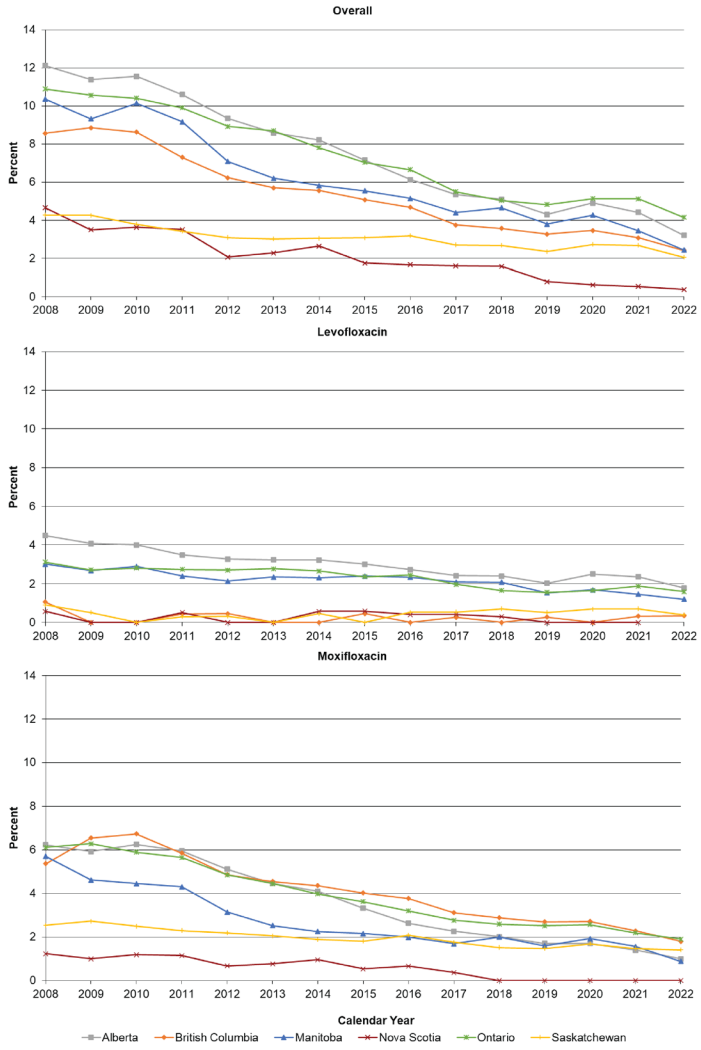
Objective 1e: Antibiotics for Acute Bacterial Sinusitis, Acute Exacerbations of COPD, and UTI

Acute Bacterial Sinusitis

A total of 5,151,456 acute bacterial sinusitis events among 2,699,047 patients in 6 provinces were identified between 2008 and 2022 (Appendix 2, Figure 28). At the beginning of the study period, no antibiotic dispensations were found for 20.2% (Manitoba) to 45.6% (Alberta) of events, and in 20.5% (Saskatchewan) to 34.1% (Ontario) at the end of the study period (Appendix 2, Table 12). In all provinces, fluoroquinolones were not commonly prescribed for acute bacterial sinusitis, and their use declined over time (Figure 12). Fluoroquinolone use varied from 4.3% (Saskatchewan) to 12.1% (Alberta) of all antibiotic prescriptions in 2008, and from 0.4% (Nova Scotia) to 4.1% (Ontario) in 2022. Moxifloxacin represented between 1.2% (Nova Scotia) and 6.2% (Alberta) of all treated episodes of acute bacterial sinusitis in 2008 and 0.0% (Nova Scotia) and 1.9% (Ontario) in 2022. At the beginning of the study period, levofloxacin represented between 0.6% (Nova Scotia) and 4.5% (Alberta) of all treated episodes and less than 0.4% (British Columbia, Nova Scotia, and Saskatchewan) and 1.8% (Alberta) at the end of the study period. When presented per 1,000 population, use of fluoroquinolones for acute bacterial sinusitis declined over the study period and was highest in Alberta (crude dispensation rates: 3.2 to 0.6 in 2008 and 2022), followed by British Columbia (2.7 to 0.4), Manitoba (2.1 to 0.4), Ontario (1.9 to 0.5), Saskatchewan (1.2 to 0.4), and Nova Scotia (0.6 to < 0.1) (Figure 13).

Among acute bacterial sinusitis events treated with an antibiotic, amoxicillin was the most prescribed molecule in all provinces over the study period followed by macrolides (azithromycin, clarithromycin), amoxicillin-clavulanate, and doxycycline (Appendix 2, Table 12). Fluoroquinolones were not commonly used, with moxifloxacin being the most commonly prescribed antibiotic (fourth or fifth molecule) in Alberta, British Columbia, Manitoba, and Ontario, followed by levofloxacin (fifth to eighth molecule, except in British Columbia where it was not in the top 10) and ciprofloxacin (sixth to 10th molecule, except in Alberta where it was not in the top 10). In Nova Scotia and Saskatchewan, fluoroquinolones were not in the top 5 most common antibiotics prescribed for acute bacterial sinusitis.

Figure 12: Percentage of Fluoroquinolone Dispensations Associated With Incident Acute Bacterial Sinusitis Events Treated With Antibiotics by Province, Overall, and by Specific Molecule

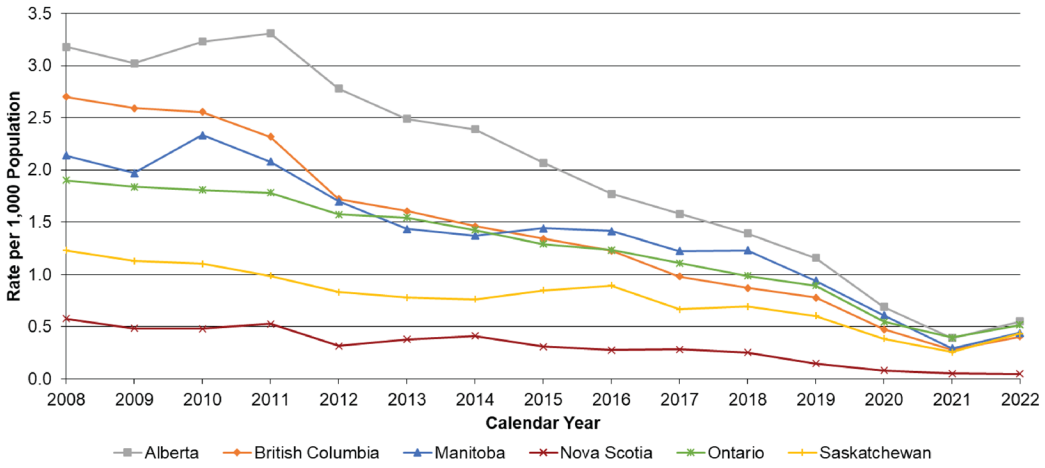


Note: Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Values between 1 and 5 inclusively were suppressed due to privacy restrictions for British Columbia in 2009, 2010, 2013, 2014, 2016, 2018, 2020, for Nova Scotia in 2009, 2010, 2012, 2013, 2019 to 2022, and for Saskatchewan in 2010, 2013, and 2015 for levofloxacin. Values were suppressed for Nova Scotia in 2018 to 2020 for moxifloxacin.

Figure 13: Crude Dispensation Rates for the 4 Fluoroquinolones (per 1,000 population) Associated With Incident Acute Bacterial Sinusitis Events, by Province and Year



Note: Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

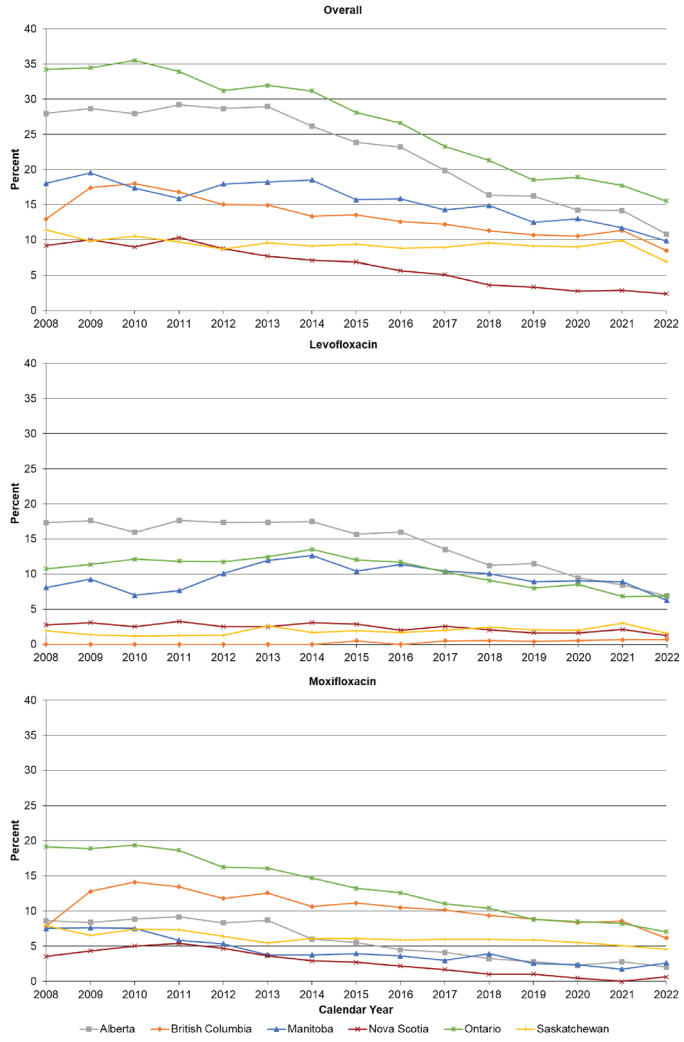
Acute Exacerbations of COPD

We identified 2,006,900 acute exacerbations of COPD events among 784,916 patients aged 66 years and older (Appendix 2, Figure 29). Between 60.4% (Manitoba) to 86.0% (Ontario) of events had no antibiotic dispensation in 2008, and 73.1% (Manitoba) to 90.3% (British Columbia) in 2022 (Appendix 2, Table 13). The high percentage without antibiotics likely results from limitations in coding; we used the codes for COPD in general as there are no specific codes for acute exacerbations of COPD. Figure 14 presents the percentage of fluoroquinolone dispensations by province. Fluoroquinolone use varied across provinces, with highest use at the beginning of the study period and declining around 2016 and 2018. Fluoroquinolone dispensations for treated acute exacerbations of COPD ranged from 9.2% (Nova Scotia) to 34.2% (Ontario) in 2008, and 2.4% (Nova Scotia) to 15.5% (Ontario) in 2022. Levofloxacin was used for between 1.9% (Saskatchewan) and 17.3% (Alberta) of all treated episodes in 2008 and between 1.2% (Nova Scotia) and 6.9% (Alberta and Ontario) in 2022. Levofloxacin was not commonly used in British Columbia throughout the study period (< 0.7%). Moxifloxacin represented between 3.6% (Nova Scotia) and 19.2% (Ontario) of exacerbations treated with an antibiotic in 2008 and 0.6% (Nova Scotia) and 7.1% (Ontario) in 2022. Expressed per 1,000 population, use of fluoroquinolones declined over the study period and was highest in Manitoba (crude dispensation rates: 3.4 to 0.8 per 1,000 population in 2008 and 2022), followed by Nova Scotia (3.2 to 0.3), Saskatchewan (2.3 to 0.6), Alberta (2.2 to 0.4), British Columbia (1.6 to 0.4), and Ontario (1.3 to 0.4) (Figure 15).

Over the study period, macrolides (azithromycin, clarithromycin), amoxicillin, and doxycycline were among the top 3 most common antibiotics dispensed for acute exacerbations of COPD in most provinces (Appendix 2, Table 13). In all provinces, levofloxacin and moxifloxacin were the most dispensed fluoroquinolones (second to fifth molecule in Alberta, Manitoba, and Ontario, and fourth or fifth molecule in

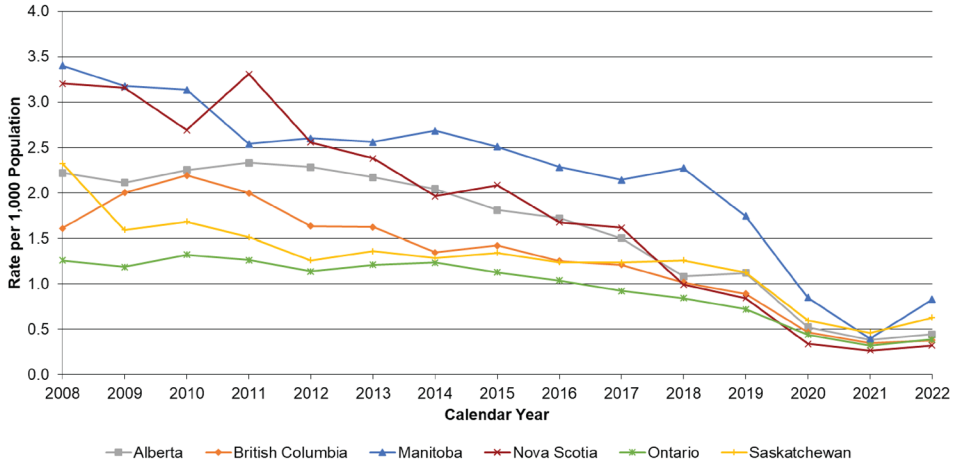
British Columbia and Saskatchewan). In Nova Scotia, fluoroquinolones were not in the top 5 most common antibiotics prescribed at any time.

Figure 14: Percentage of Fluoroquinolone Dispensations Associated With Incident Acute Exacerbations of COPD Events Treated With Antibiotics, Overall and by Specific Molecule



Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions for British Columbia in 2008 to 2014 and 2016 for levofloxacin. Values suppressed for Nova Scotia in 2021 for moxifloxacin.

Figure 15: Crude Dispensation Rates of 4 Fluoroquinolones (per 1,000 population) Associated With Incident Acute Exacerbations of COPD Events, by Province and Year



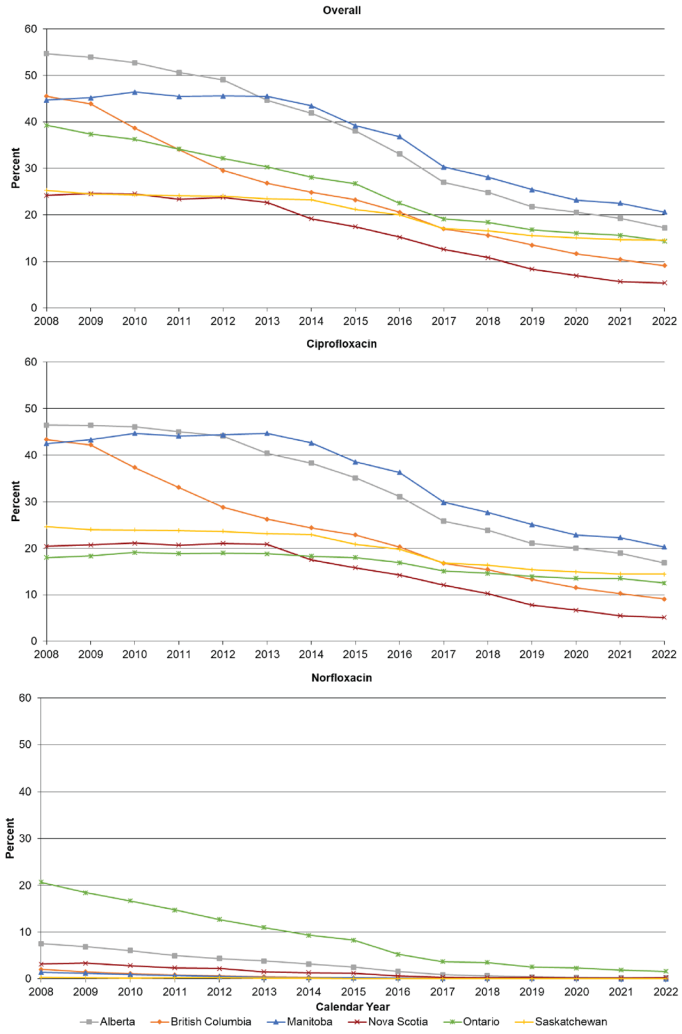
Note: The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

UTI

Over the study period, 7,354,365 uncomplicated UTI events were identified among 3,031,914 females (Appendix 2, Figure 30). No antibiotic dispensations were found for 24.1% (Manitoba) to 45.2% (Alberta) of events in 2008, and 23.9% (Manitoba) to 37.2% (Ontario) in 2022 (Appendix 2, Table 14). In all provinces, fluoroquinolones were frequently dispensed for UTI, with highest use at the beginning of the study period and declining gradually between 2013 and 2022 (Figure 16). Their use varied across provinces, ranging from 24.2% (Nova Scotia) to 54.7% (Alberta) in 2008, and from 5.4% (Nova Scotia) to 20.6% (Manitoba) in 2022. Ciprofloxacin was the most dispensed fluoroquinolone, representing between 18.0% (Ontario) and 46.5% (Alberta) of events treated with an antibiotic in 2008 and 5.1% (Nova Scotia) and 20.3% (Manitoba) in 2022. Norfloxacin use declined over the study period and was more commonly used in Ontario (20.7% to 1.6% in 2008 and 2022) and Alberta (7.5% to 0.2%) during the study period, whereas use was limited in Nova Scotia (< 3.3%), British Columbia (< 2.0%), Manitoba (< 1.4%), and Saskatchewan (< 0.3%). When presented per 1,000 population, use of fluoroquinolones declined over the study period and was highest in Manitoba (crude dispensation rates: 25.2 to 11.8 in 2008 and 2022), followed by Alberta (23.4 to 7.6), Ontario (22.5 to 8.4), Saskatchewan (20.4 to 8.5), British Columbia (17.2 to 2.9), and Nova Scotia (11.7 to 1.9) (Figure 17).

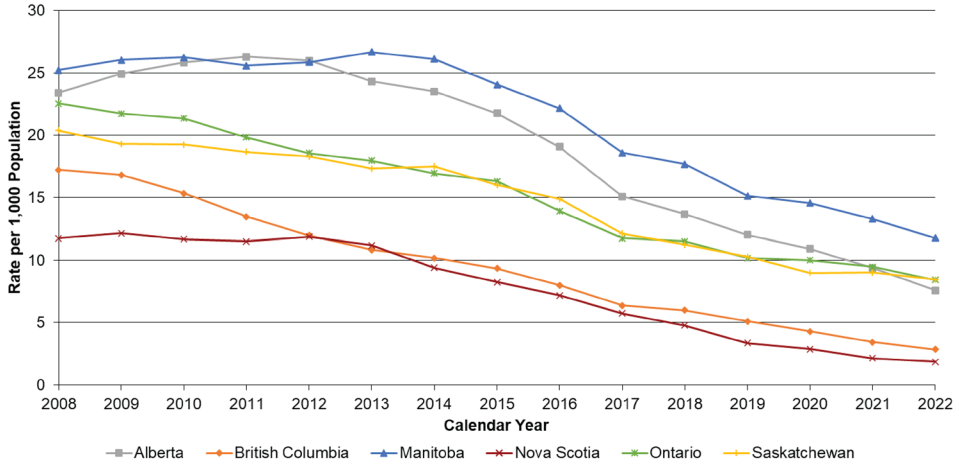
Over the study period, nitrofurantoin was the most common antibiotic dispensed for uncomplicated UTIs in females in all provinces, except Manitoba where it was the top 1 molecule at the end of the study period (Appendix 2, Table 14). Among fluoroquinolones, ciprofloxacin was the most dispensed molecule in all provinces (in the top 3 molecules in all provinces; except in Nova Scotia at the end of the study period). Norfloxacin was commonly dispensed in Ontario (second or fifth molecule in 2008 and 2016) and less frequently in other provinces (fourth to 10th molecule in Alberta, British Columbia, Manitoba, and Nova Scotia; not in top 10 in Saskatchewan). It declined in rank over the years and was not commonly dispensed for UTI in all provinces by 2022 (seventh molecule in Ontario and not in top 10 in other provinces).

Figure 16: Percentage of Fluoroquinolone Dispensations Associated With Incident Uncomplicated UTI Events Treated With Antibiotics, Overall, and by Specific Molecule



Note: Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
Values between 1 and 5 inclusively were suppressed due to privacy restrictions for Saskatchewan in 2019 to 2022 for norfloxacin.

Figure 17: Crude Dispensation Rates of 4 Fluoroquinolones (per 1,000 population) Associated With Incident Uncomplicated UTI Events, by Province and Year



Note: Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The fluoroquinolones of interest are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Impact Assessment Analysis

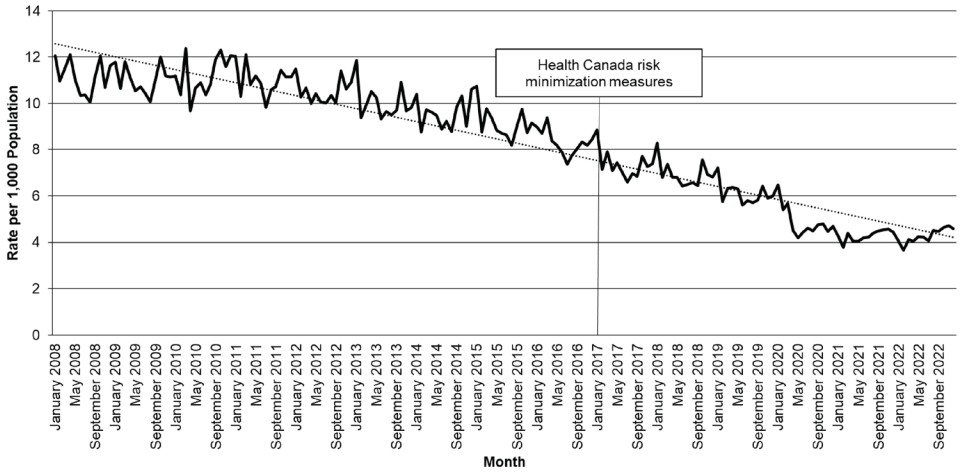
Main Take-Aways

- The reduction in the rates of fluoroquinolone dispensations was 50% from January 1, 2017, to February 29, 2020 (segment 2) and 62% from March 1, 2020, to December 31, 2022 (segment 3) relative to segment 1 (January 1, 2008, to December 31, 2016; before introduction of risk minimization measures).
- Similarly, reductions in the percentages of antibiotic dispensations for fluoroquinolones were observed for the 3 selected conditions: uncomplicated UTIs (females only), acute exacerbations of COPD (patients aged ≥ 66 years only), and acute bacterial sinusitis.
- There were variations across provinces in the magnitude of the reductions in the rates of fluoroquinolone dispensations and the percentage of antibiotic dispensations that were fluoroquinolones.

Rate of Dispensations for the 4 Fluoroquinolones

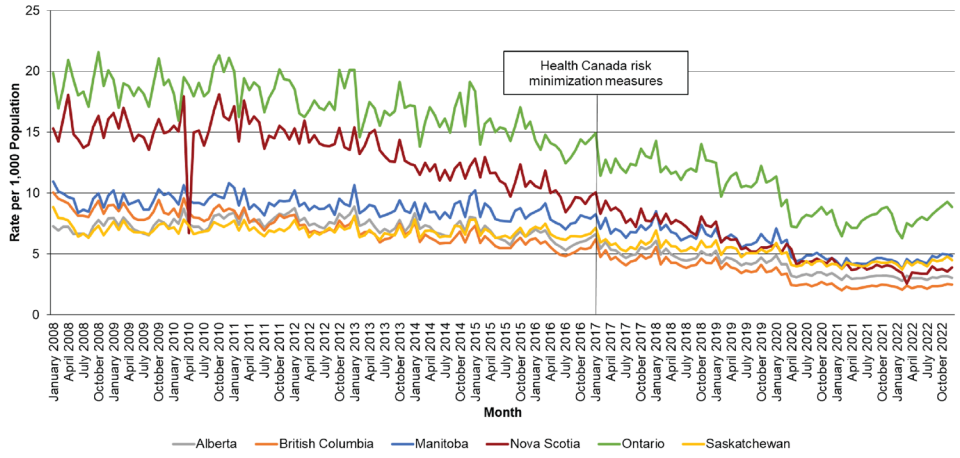
Figure 18 presents the unweighted average monthly age- and sex-adjusted dispensation rate for the 4 fluoroquinolones. The rates by province are presented in Figure 19. These figures demonstrate the substantial decline in rates across the months of the study period, even before the risk minimization measures were introduced in 2017. The estimated slope for the trend line from 2008 to 2022 is −0.47, indicating an average reduction of 4.7% in the average unweighted monthly rate for the 4 fluoroquinolones of interest. The decline was evident in all provinces, although substantial variation exists in the monthly rates, in part due to small numbers of fluoroquinolone dispensations in individual provinces.

Figure 18: Unweighted Average Monthly Dispensation Rates for the 4 Fluoroquinolones With Linear Trend Line



Note: Aggregated data for all provinces. Monthly average rates are age- and sex-adjusted.
Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Figure 19: Monthly Dispensation Rates for the 4 Fluoroquinolones by Province



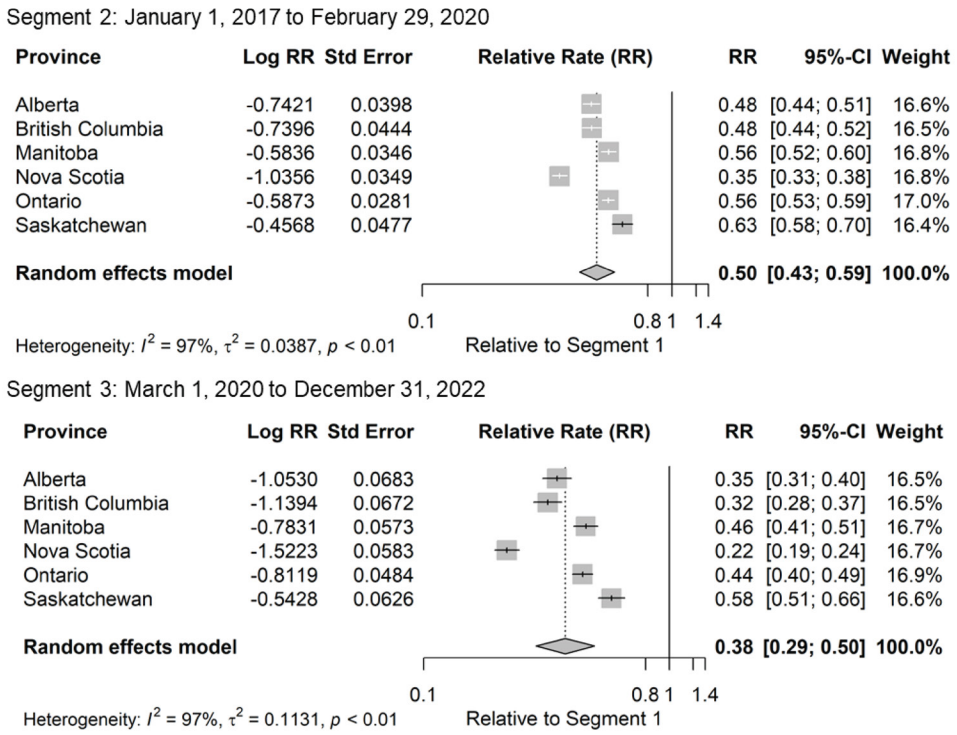
Note: Monthly rates are age- and sex-adjusted.
Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The fluoroquinolones of interest are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

The pooled rates for the primary analysis and sensitivity analysis using a 6-month washout period are presented in Figures 20 and 21, respectively. Site-specific results for the slope estimates in each period are available in Appendix 3, Tables 15 and 16. The slope estimates were consistently less than 1, indicating a decreasing rate in all provinces.

The results in Figure 20 show that the pooled RR for segment 2 was estimated to be 0.50 (95% CI, 0.43 to 0.59), indicating an estimated 50% reduction in the average age- and sex-adjusted rate for the second segment from January 1, 2017, to February 29, 2020, relative to the first segment of time from January 1, 2008, to December 31, 2016. These results in Figure 20 also show that the pooled estimated RR for segment 3 was 0.38 (95% CI, 0.29 to 0.50), indicating an estimated 62% reduction in the average age- and sex-adjusted rate for this segment from March 1, 2020, to December 31, 2022, relative to the first segment before introduction of the risk minimization measures. The results in Figure 20 also show substantial heterogeneity in the site-specific estimates, with an I^2 statistic of 97% for segments 2 and 3. Site-specific estimates ranged between 0.35 and 0.63 in segment 2, and 0.22 and 0.58 in segment 3.

The results in Figure 21, in which data associated with the 6-month period from January 1 to June 30, 2017, were removed from the regression model before estimating the fluoroquinolone RRs (i.e., the washout period), are consistent with those from Figure 20. Specifically, the RR estimates for Segment 2 and Segment 3 were almost identical to those obtained when data associated with the 6-month washout period from January 1 to June 30, 2017, were not removed. Estimates of heterogeneity in site-specific rates were similar for both sets of models.

Figure 20: Relative Rate of All Dispensations for the 4 Fluoroquinolones by Study Segment



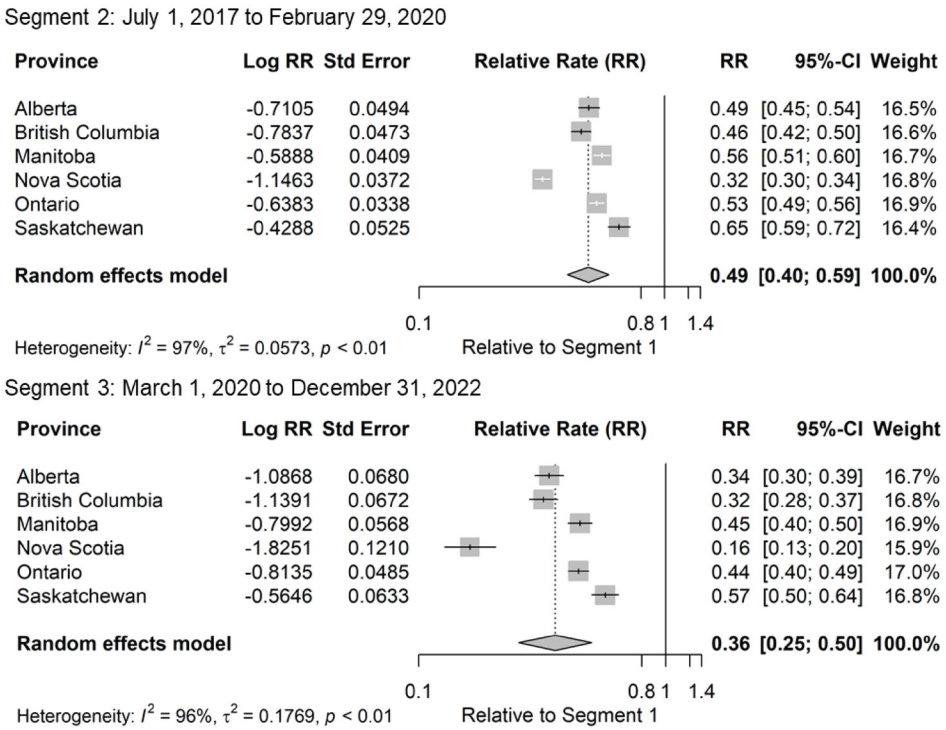
CI = confidence interval; RR = relative rate; Std = standard.

Note: Age- and sex-adjusted dispensation rate (per 1,000 population) in segment 2 and 3, using segment 1 (January 1, 2008 to December 31, 2016) as the reference.

Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Figure 21: Relative Rate of All Dispensations for the 4 Fluoroquinolones by Study Segment, With 6-Month Washout Period for Implementation of Risk Minimization Measures



CI = confidence interval; RR = relative rate; Std = standard.

Note: Age- and sex-adjusted dispensation rate (per 1,000 population) in segment 2 and 3, using segment 1 (January 1, 2008, to December 31, 2016) as the reference.

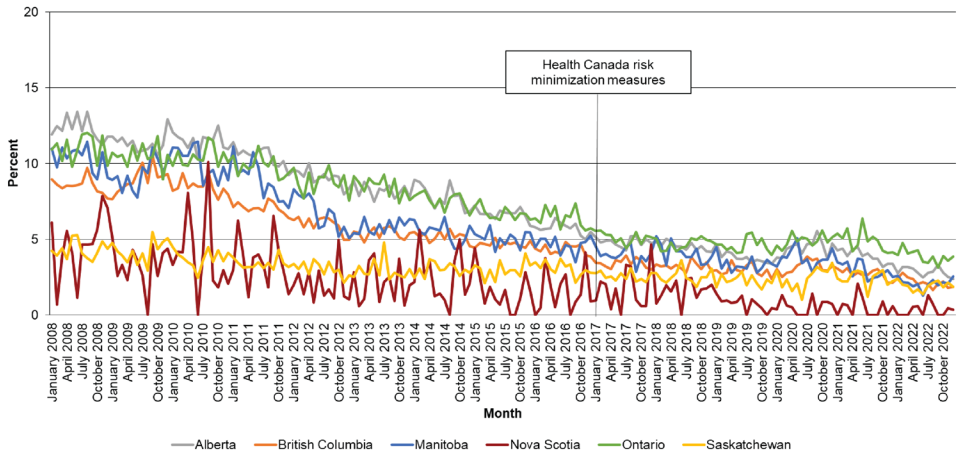
Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Percentage of All Antibiotic Dispensations That Are an Oral Fluoroquinolone

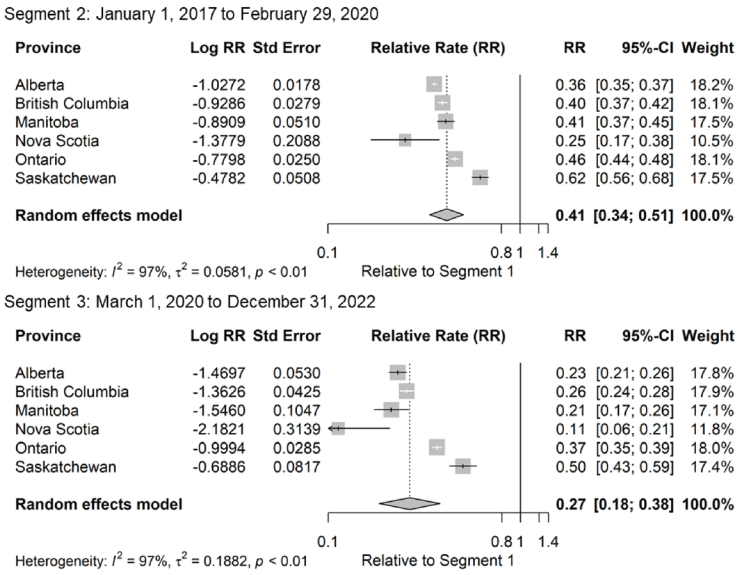
The percentage of antibiotic dispensations that are an oral fluoroquinolone for the acute bacterial sinusitis indication is presented by province in Figure 22. Figure 23 presents the pooled RR estimates. There was a decline in the monthly percentage of antibiotic dispensations that are fluoroquinolones in all provinces over the study period, even before risk minimization measures were introduced. The pooled RR for segment 2 was 0.41 (95% CI, 0.34 to 0.51), indicating an estimated 59% reduction in the average age- and sex-adjusted percentage for the segment from January 1, 2017, to February 29, 2020, relative to the first segment from January 1, 2008, to December 31, 2016. The reduction in the average age- and sex-adjusted percentage was estimated to be 73% for the third segment from March 1, 2020, to December 31, 2022, relative to the first segment (pooled RR: 0.27; 95% CI, 0.18 to 0.38). There was substantial heterogeneity in the site-specific estimates, with an I^2 statistic of 97% for segment 2 (site-specific estimates ranged from 0.25 to 0.62) and 97% for segment 3 (site-specific estimates ranged from 0.11 to 0.50). Site-specific results for the slope estimates are available in Appendix 3, Table 17. The slope estimates were less than 1, indicating a decrease in rates for all provinces.

Figure 22: Monthly Percentage of Antibiotic Dispensations That Are a Fluoroquinolone for the Acute Bacterial Sinusitis Indication, by Province



Notes: Monthly percentages are age- and sex-adjusted. Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The 4 fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Figure 23: Relative Rate of Antibiotic Dispensations That Are a Fluoroquinolone by Study Segment, Acute Bacterial Sinusitis Indication

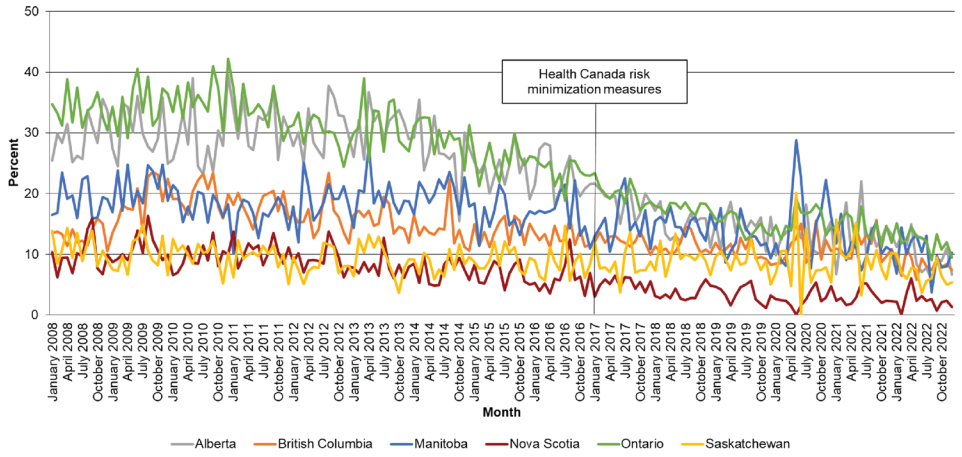


CI = confidence interval; RR = relative rate; Std = standard.
Note: Age- and sex-adjusted percentage of dispensations in segment 2 and 3, using segment 1 (January 1, 2008, to December 31, 2016) as the reference.
Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.
The 4 fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Figure 24 and Figure 25 report the results for the acute exacerbations of COPD indication among patients aged 66 years and older. Over the study period, the percentage of antibiotic dispensations that

are fluoroquinolones declined substantially in all provinces, even before the introduction of the 2017 risk minimization measures. The reduction in the average age- and sex-adjusted percentage was estimated at 49% for the second segment relative to the first segment (pooled RR: 0.51; 95% CI, 0.37 to 0.69). The pooled RR for segment 3 was 0.38 (95% CI, 0.30 to 0.48), indicating an estimated 62% reduction relative to the first segment. Heterogeneity in the site-specific estimates was observed, with an I^2 statistic of 98% for segment 2 (site-specific estimates ranged from 0.30 to 0.89) and 95% for segment 3 (site-specific estimates ranged from 0.25 to 0.57). Site-specific results for the slope estimates are presented in Appendix 3, Table 17. The slope estimates were less than 1, indicating a decreasing trend in all provinces.

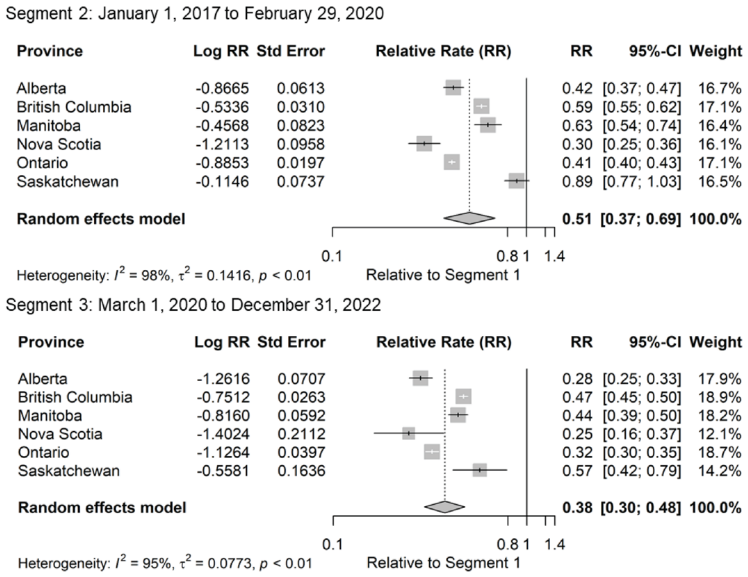
Figure 24: Monthly Percentage of Antibiotic Dispensations That Are a Fluoroquinolone for the Acute Exacerbations of COPD Indication Among People Aged ≥ 66 Years, by Province



Note: Monthly percentages are age- and sex-adjusted.
The 4 fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

The results for the uncomplicated UTI indication among females are reported in Figures 26 and 27. The percentage of antibiotic dispensations that are fluoroquinolones declined substantially over the study period, even before the 2017 risk minimization measures were introduced. The decline was evident in all provinces, although interprovincial variations were observed. The pooled RR for segment 2 was 0.32 (95% CI, 0.25 to 0.41), indicating an estimated 68% reduction in the average age-adjusted percentage for the second segment relative to the first segment. The reduction in the third segment was estimated at 76% relative to the first segment (pooled RR: 0.24; 95% CI, 0.17 to 0.35). There was substantial heterogeneity in the site-specific estimates (0.23 to 0.53 for segment 2; 0.15 to 0.50 for segment 3), with an I^2 statistic of 98% for segment 2 and 98% for segment 3. Site-specific results for the slope estimates are available in Appendix 3, Table 17. The slope estimates were less than 1 (i.e., decreasing slope) in all provinces.

Figure 25: Relative Rate of Antibiotic Dispensations That Are a Fluoroquinolone by Study Segment, Acute Exacerbations of COPD Indication Among People Aged ≥ 66 Years

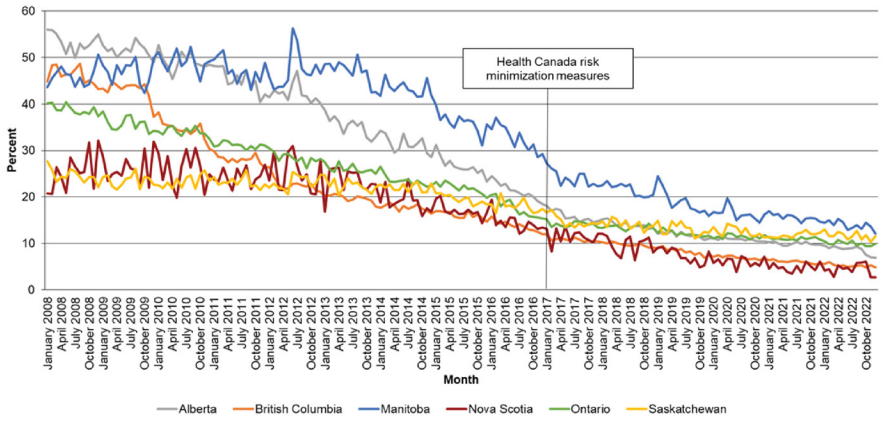


CI = confidence interval; RR = relative rate; Std = standard.

Note: Age- and sex-adjusted percentage of dispensations in segment 2 and 3, using segment 1 (January 1, 2008, to December 31, 2016) as the reference.

The 4 fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Figure 26: Monthly Percentage of Antibiotic Dispensations That Are a Fluoroquinolone for the UTI Indication Among Females, by Province

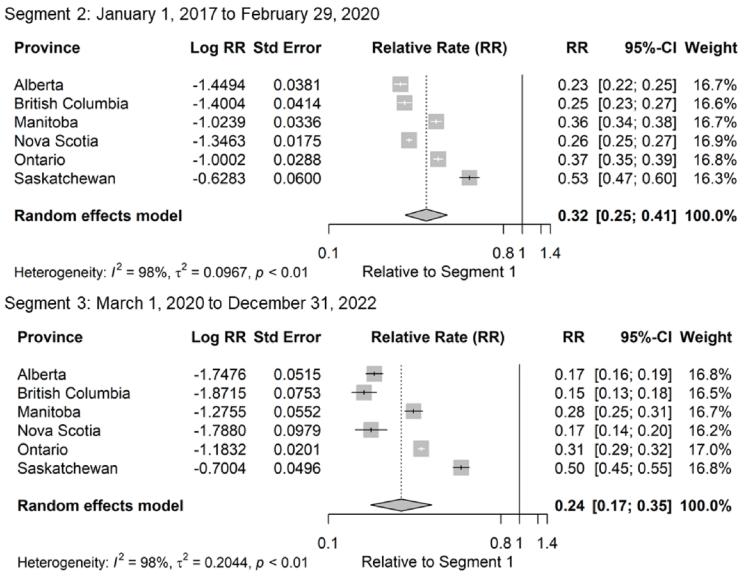


Note: Monthly percentages are age- and sex-adjusted.

Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

The 4 fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Figure 27: Relative Rate of Antibiotic Dispensations That Are a Fluoroquinolone by Study Segment, Uncomplicated UTI Indication Among Females



CI = confidence interval; RR = relative rate; Std = standard.

Note: Age- and sex-adjusted percentage of dispensations in segment 2 and 3, using segment 1 (January 1, 2008, to December 31, 2016) as the reference.

Data available in Nova Scotia and Ontario for patients aged ≥ 66 years.

The 4 fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Strengths and Limitations

To our knowledge, this represents the first study to review the dispensation of oral fluoroquinolones after the implementation of the 2017 Health Canada risk minimization measures. Our results provide an important update on the utilization patterns and indications for fluoroquinolones since our previous study which ended in 2015.

Our study has potential limitations. First, our data are limited to antibiotics dispensed in outpatient pharmacies and cannot be generalized to other settings of care. Second, event definitions for the 3 indications of interest are based on diagnosis codes and do not include clinical characteristics or laboratory values. Although antibiotic exposure is defined as the first antibiotic dispensed within 5 days of the event, we cannot be certain the antibiotic was prescribed for the indication listed as the diagnosis associated with the medical visit. In addition, exposure is defined by a drug dispensation, which may not represent actual consumption of the drug. Third, we are unable to document all influences on prescribing rates such as changes in local practice patterns, adherence to treatment guidelines, antibiotic resistance rates, antibiotic stewardship programs, or provincial formulary status or inclusion, and prescribing criteria (Appendix 4) that may have varied over the study period. These unmeasured factors could influence the interrupted time-series analysis. There may have been changes in treatment guidelines or clinical practice around the time

of introduction of the 2017 Health Canada risk minimization measures. In addition, the COVID-19 pandemic had an impact on community-level antibiotic use in Canada, with reductions in antibiotic use overall and especially for respiratory antibiotics.[24] Fourth, another limitation is the data availability in each province, with Nova Scotia and Ontario limited to patients aged 66 years and older. In addition, there are differences in the type of dispensations captured in the prescription drug databases across provinces. All dispensations are captured in Alberta, British Columbia, Manitoba, and Saskatchewan, whereas only those reimbursed by the public drug plan are captured in Nova Scotia and Ontario (Appendix 1, Table 1). Differences in coding practices, to identify health events such as acute exacerbations of COPD, may exist across the provinces. Lastly, our study is limited to 6 provinces in Canada and findings may not be generalizable to other provinces and territories.

Conclusions and Implications for Decision or Policy-Making

Main Take-Aways

- Use of oral fluoroquinolones in the outpatient setting declined in all provinces between 2008 and 2022.
- The 2017 Health Canada regulatory actions were followed by reductions in the rate of fluoroquinolone dispensations and the percentage of antibiotic dispensations that were fluoroquinolones for the 3 selected indications, although a decreasing trend was observed before the regulatory actions.
- Although our findings suggest that the Health Canada regulatory actions could have affected the prescribing of fluoroquinolones, unmeasured factors may have had an impact on prescribing as well.

In our multicentre retrospective cohort study, we observed a decline in the use of the 4 oral fluoroquinolones of interest (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) in the outpatient setting in all 6 provinces between 2008 and 2022, though interprovincial differences were noted. Overall rates of dispensations decreased by approximatively 50% across provinces, sexes, and age groups over the study period. Rates were declining even before risk minimization measures were introduced. The 2017 regulatory actions were followed by reductions in the rate of fluoroquinolone dispensations overall and the percentages of antibiotic dispensations that were fluoroquinolones for the 3 selected indications: UTI (females), acute exacerbation of COPD (patients aged ≥ 66 years), and acute bacterial sinusitis.

In comparison with findings from the previous drug utilization study,[17] we observed a decrease in the use of fluoroquinolones for the treatment of acute bacterial sinusitis, acute exacerbations of COPD, and UTI in all provinces. Fluoroquinolones are no longer being used in the first-line treatment of acute exacerbation of COPD and UTI, which is consistent with guideline recommendations[25-27] and the 2017 Health Canada risk communication. The use of fluoroquinolones for the treatment of acute bacterial sinusitis remained low. Our findings showed that the 2017 regulatory actions were followed by a reduction in the use of fluoroquinolones in general and for the 3 indications of interest (acute bacterial sinusitis, acute exacerbation of COPD, and UTI). However, there was a decrease observed in prescribing of fluoroquinolones before 2017; this decrease may have occurred for several reasons that cannot be measured in administrative data. The impact of regulatory actions on the use of fluoroquinolones has been examined in other countries. In 6 European

countries, changes in fluoroquinolone prescriptions in the primary care setting were observed between 2016 and 2021 across countries.[8] However, these were not temporally related to the 2018 EMA regulatory actions, with the monthly percentage change varying from −4.1% in the UK to −33.3% in Belgium. In the US, fluoroquinolone use declined in association with the 2016 FDA warnings and label changes in 3 drug utilization studies, though the impact varied by patient and provider characteristics or infection type.[11-13] We observed interprovincial variation in the use of fluoroquinolones. These variations are likely explained by a combination of differences or changes in local practices patterns, adherence to treatment guidelines, antibiotic resistance rates, and provincial formulary criteria (Appendix 4). We documented the provincial drug plan coverage for the 4 oral fluoroquinolones in 2016 and 2023 and noted differences across provinces. For example, restrictions on the use of fluoroquinolones occur in all provinces, except British Columbia where ciprofloxacin, moxifloxacin, and norfloxacin use is unrestricted while levofloxacin is not reimbursed. This is in line with our results showing that levofloxacin was rarely used in British Columbia. Norfloxacin use was also unrestricted in Alberta and Ontario. There was also a change in coverage in Ontario, where use of all fluoroquinolones was restricted in 2016 and no longer restricted in 2023. Differences in the study populations available across provinces may also explain some of the interprovincial differences in use; with the Nova Scotia and Ontario populations limited to patients aged 66 years and older. As well, differences in administrative data coding practices for health events of interest may also have contributed to variations in results.

In summary, use of oral fluoroquinolones decreased in all provinces between 2008 and 2022, though interprovincial variations were observed. The 2017 Health Canada risk minimization measures (risk communication, updates to the labels) were followed by reductions in the rate of fluoroquinolone dispensations and percentages of antibiotic dispensations that were fluoroquinolones for the 3 selected indications (acute bacterial sinusitis, acute exacerbation of COPD, and UTI). These findings could suggest that Health Canada regulatory actions affected the prescribing of oral fluoroquinolones. However, unmeasured factors, including health care system and patient characteristics, may have had an impact on fluoroquinolone prescribing as well.

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Authors and Contributors

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Pierre Ernst, as the project lead, drafted the scientific protocol and statistical analysis plan; contributed to the review and interpretation of the study results; and drafted, reviewed, and approved the report.

Lisa M. Lix, as the methods lead and Manitoba site investigator, drafted the scientific protocol and statistical analysis plan; oversaw submission and approval of data access and ethics approval at the Manitoba site; contributed to the review, pooling, and meta-analysis of site-specific results; interpretation of the study results; and drafted, reviewed, and approved the report.

Greg Carney, as the British Columbia site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to British Columbia context; oversaw submission and approval of data access and ethics approval at the British Columbia site; supervised British Columbia analyses and conducted quality checks and review of results before reporting; and reviewed and approved the report.

Nick Daneman, as the content expert and Ontario site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Ontario context; oversaw submission and approval of data access and ethics approval at the Ontario site; supervised Ontario analyses and conducted quality checks and review of results prior to reporting; and reviewed and approved the report.

Matt Dahl, as the lead analyst and Manitoba site analyst, contributed to drafting of the scientific protocol and statistical analysis plan; conducted analyses at the Manitoba site and quality checks of results; contributed to the review and interpretation of the study results; and reviewed and approved the report.

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Devin Manning, as the Nova Scotia site analyst, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to Nova Scotian context; conducted analyses at the Nova Scotia site and quality checks of the results; and reviewed and approved the report.

Tarita Miller, as the British Columbia site analyst, conducted analyses at the British Columbia site and quality checks of the results; and reviewed and approved the report.

Paul Ronksley, as the Alberta site investigator, reviewed and provided feedback on the scientific protocol and statistical analysis plan, particularly with respect to the Alberta context; oversaw submission and approval of data access and ethics approval at the Alberta site; supervised the Alberta analyses, conducted quality checks, and reviewed results prior to reporting; and reviewed and approved the report.

Audray St-Jean, as the research assistant, contributed to drafting of the scientific protocol and statistical analysis plan; contributed to review, pooling of site-specific results, and interpretation of the study results; and drafted, reviewed, and approved the report.

Contributors

Carolina Moriello, as the project manager, reviewed the report; assisted in the development and implementation of the knowledge mobilization plan for the project; and provided project management support.

Xinya Lu, as the Saskatchewan site analyst, was responsible for analysis of data as part of the Saskatchewan analysis team.

Clinical Experts

These individuals kindly provided comments on this report:

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Alberta Health Services

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Conflicts of Interest

Donica Janzen disclosed the following:

Travel funding or payment

CNODES — student travel award

No other conflicts of interest were declared.

Appendix 1: Additional Information on Methods

Please note that this appendix has not been copy-edited.

Table 1: List of Databases Used in Each Province

Province	Study population	Database				
		Prescription drug claims (dispensing captured)[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
British Columbia	All	BC PharmaNet	BC Medical Services Plan	CIHI Discharge Abstract Database	BC Ministry of Health Client Roster	NA
Manitoba	All	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	All	Prescription Drug Plan Historical Claims (all)	Medical Services Branch	CIHI Discharge Abstract Database	Person Health Registration System	NACRS[b]

BC = British Columbia; CIHI = Canadian Institute for Health Information; ICES = Institute for Clinical Evaluative Sciences; 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]Emergency department data available from 2012 and onward in Saskatchewan. The proportion of emergency department visits captured in NACRS has increased over time.

Table 2: List of Codes for Acute Bacterial Sinusitis, Acute Exacerbation of COPD, and UTI Cohorts

Indication cohort	Codes for inclusion	Codes for exclusion
Acute bacterial sinusitis	Acute sinusitis: • ICD-9-CM: 461.x • ICD-10-CA: J01.x	NA
Acute Exacerbation of COPD	COPD: • 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
Uncomplicated UTI	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 (defined as a dispensation for insulin): • ATC: A10 Infection of the kidney/pyelonephritis:

Indication cohort	Codes for inclusion	Codes for exclusion
		• 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

ATC = anatomic therapeutic chemical; CCI = Canadian Classification of Health Interventions; CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; COPD = chronic obstructive pulmonary disease; ICD = International Classification of Diseases, Ninth revision or Tenth revision, with Canadian enhancements; NA = not applicable; UTI = urinary tract infection.

Source for codes for UTI cohort exclusions: Suskind et al. 2016 Urology.[21]

Table 3: List of Codes to Define Exposure

Exposure	Generic name or substance class	ATC codes
All oral fluoroquinolones	Fluoroquinolones	J01M
4 oral fluoroquinolones of interest	Ciprofloxacin	J01MA02
	Levofloxacin	J01MA12
	Moxifloxacin	J01MA14
	Norfloxacin	J01MA06
Other nonfluoroquinolones oral antibiotics	Vancomycin	A07AA09
	Fidaxomycin	A07AA12
	Tetracycline	J01A
	Amphenicols	J01B
	Beta-lactam antibiotics	J01C
	Cephalosporins	J01DB, J01DC, J01DD
	Sulfonamides and trimethoprim	J01E
	Macrolides and lincosamides	J01F
	Aminoglycosides	J01G
	Combinations of antibacterials	J01R
	Other antibacterials	J01X
	Metronidazole	P01AB01

ATC = anatomic therapeutic chemical.

Note: Excluding codes for IV (also used for inhalation) and topical formulations.

Appendix 2: Additional Results for Fluoroquinolone Utilization (Objective 1)

Please note that this appendix has not been copy-edited.

Table 4: Overall Dispensation Numbers and Crude Rates (per 1,000 Population) for All Fluoroquinolones and the 4 Fluoroquinolones of Interest

Calendar year	All fluoroquinolones				4 fluoroquinolones of interest			
	N dispensations	N individuals	N denominator	Crude rate[a]	N dispensations	N individuals	N denominator	Crude rate[a]
2008	1,204,697	817,107	11,166,613	107.9	1,200,033	814,802	11,166,613	107.5
2009	1,219,473	831,220	11,377,659	107.2	1,216,058	829,577	11,377,659	106.9
2010	1,267,541	862,641	11,614,916	109.1	1,265,028	861,453	11,614,916	108.9
2011	1,267,125	866,036	11,839,822	107.0	1,265,318	865,152	11,839,822	106.9
2012	1,245,042	855,093	12,136,802	102.6	1,243,375	854,248	12,136,802	102.4
2013	1,223,222	843,323	12,473,034	98.1	1,221,771	842,576	12,473,034	98.0
2014	1,209,802	839,322	12,764,519	94.8	1,208,485	838,646	12,764,519	94.7
2015	1,174,397	819,166	12,996,938	90.4	1,173,760	818,857	12,996,938	90.3
2016	1,097,689	774,997	13,273,312	82.7	1,097,677	774,996	13,273,312	82.7
2017	1,004,397	715,591	13,523,741	74.3	1,004,385	715,590	13,523,741	74.3
2018	972,440	691,725	13,770,760	70.6	972,428	691,724	13,770,760	70.6
2019	895,023	638,851	14,062,227	63.6	895,006	638,848	14,062,227	63.6
2020	713,615	499,620	14,256,724	50.1	713,592	499,619	14,256,724	50.1
2021	646,309	451,333	14,495,068	44.6	646,280	451,332	14,495,068	44.6
2022	670,819	473,849	14,916,605	45.0	670,819	473,849	14,916,605	45.0

Notes: (1) Data aggregated for all 6 provinces and ages. Data available in Alberta for patients aged ≥ 18 years, and in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) All fluoroquinolones (all molecules) and 4 fluoroquinolones of interest (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin).

[a]Crude dispensation rate per 1,000 population, by calendar year.

Table 5: Overall Dispensation Numbers and Crude Rates (per 1,000 Population) for the 4 Fluoroquinolones by Age

Calendar year	4 fluoroquinolones of interest			
	N dispensations	N individuals	N denominator	Crude rate[a]
Patients aged < 18 years				
2008	7,154	6,197	1,391,763	5.1
2009	6,800	5,935	1,394,052	4.9
2010	6,415	5,585	1,400,792	4.6
2011	5,768	5,046	1,405,036	4.1
2012	5,217	4,594	1,408,277	3.7
2013	4,670	4,176	1,414,288	3.3
2014	4,830	4,228	1,425,072	3.4
2015	4,129	3,586	1,433,931	2.9
2016	3,944	3,460	1,456,270	2.7
2017	3,108	2,753	1,472,971	2.1
2018	2,986	2,588	1,483,462	2.0
2019	2,696	2,359	1,494,694	1.8
2020	1,936	1,655	1,501,363	1.3
2021	1,688	1,428	1,498,111	1.1
2022	1,828	1,562	1,526,341	1.2
Patients aged 18 to 65 years				
2008	526,989	397,588	6,745,368	78.1
2009	535,673	406,742	6,868,711	78.0
2010	552,339	419,936	7,010,626	78.8
2011	548,285	417,408	7,140,689	76.8
2012	534,618	409,416	7,317,155	73.1
2013	515,184	396,902	7,494,073	68.7
2014	510,209	394,605	7,661,650	66.6
2015	482,897	374,694	7,745,692	62.3
2016	451,399	352,127	7,852,385	57.5
2017	398,628	313,362	7,936,631	50.2
2018	371,108	291,196	8,016,763	46.3
2019	337,668	265,030	8,125,456	41.6
2020	263,013	202,027	8,169,210	32.2
2021	224,246	170,793	8,230,476	27.2

Calendar year	4 fluoroquinolones of interest			
	N dispensations	N individuals	N denominator	Crude rate[a]
2022	228,481	177,159	8,438,938	27.1
Patients aged ≥ 66 years				
2008	665,890	411,017	3,029,483	219.8
2009	673,585	416,900	3,114,897	216.2
2010	706,274	435,932	3,203,497	220.5
2011	711,265	442,698	3,294,097	215.9
2012	703,540	440,238	3,411,369	206.2
2013	701,917	441,498	3,564,673	196.9
2014	693,446	439,813	3,677,797	188.5
2015	686,734	440,577	3,817,315	179.9
2016	642,334	419,409	3,964,658	162.0
2017	602,649	399,475	4,114,138	146.5
2018	598,334	397,940	4,270,536	140.1
2019	554,642	371,459	4,442,077	124.9
2020	448,643	295,937	4,586,150	97.8
2021	420,346	279,111	4,766,481	88.2
2022	440,510	295,128	4,951,326	89.0

Notes: (1) Data aggregated for all 6 provinces. Data available in Alberta for patients aged ≥ 18 years, and in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

[a]Crude dispensation rate per 1,000 population, by calendar year.

Table 6: Crude Dispensation Rates (per 1,000 Population) for the 4 Fluoroquinolones Among Patients Aged < 18 Years, Overall and by Province

Calendar year	Crude dispensation rate (per 1,000 population)			
	Overall	BC	MB	SK
2008	5.1	5.3	5.0	4.8
2009	4.9	4.9	5.2	4.5
2010	4.6	4.5	5.0	4.4
2011	4.1	4.1	4.2	4.1
2012	3.7	3.6	4.1	3.6
2013	3.3	3.2	3.6	3.3
2014	3.4	3.1	3.8	3.8
2015	2.9	2.6	3.4	3.2
2016	2.7	2.5	3.1	3.1

Calendar year	Crude dispensation rate (per 1,000 population)			
	Overall	BC	MB	SK
2017	2.1	1.9	2.4	2.5
2018	2.0	1.7	2.5	2.4
2019	1.8	1.6	2.1	2.3
2020	1.3	1.1	1.7	1.6
2021	1.1	0.9	1.5	1.5
2022	1.2	0.9	1.6	1.7

BC = British Columbia; MB = Manitoba; SK = Saskatchewan.

Notes: (1) Overall represents data aggregated for all 3 provinces. Data not available in Alberta, Nova Scotia, and Ontario. (2) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Table 7: Crude Dispensation Rates (per 1,000 Population) for the 4 Fluoroquinolones by Age and Sex

Calendar year	Patients aged 18 to 65 years							Patients aged ≥ 66 years						
	Overall	AB	BC	MB	NS	ON	SK	Overall	AB	BC	MB	NS	ON	SK
Females														
2008	103.8	93.6	112.7	118.2	—	—	85.2	233.4	216.1	230.7	260.2	195.3	241.0	197.9
2009	104.0	98.5	109.0	118.7	—	—	84.4	230.2	217.8	226.4	258.9	199.9	236.4	193.8
2010	104.4	104.6	104.4	121.3	—	—	83.8	235.5	231.9	221.4	272.4	196.0	243.0	199.3
2011	100.8	107.7	95.4	114.4	—	—	82.1	229.6	236.8	208.2	264.1	194.4	237.2	194.9
2012	95.6	105.6	85.9	111.7	—	—	79.9	220.4	233.3	195.0	262.8	179.6	227.2	193.0
2013	89.8	98.8	79.7	108.5	—	—	75.8	211.1	223.2	184.6	258.3	170.4	217.5	189.2
2014	86.9	96.4	74.6	107.8	—	—	77.5	201.7	213.1	178.5	251.7	144.1	206.9	192.9
2015	80.5	87.4	69.9	102.4	—	—	72.3	191.4	196.8	170.8	248.0	135.6	196.1	185.4
2016	72.9	78.2	62.4	97.2	—	—	69.5	169.0	178.7	154.5	230.1	113.6	169.1	176.9
2017	62.2	66.3	53.2	84.2	—	—	59.0	150.6	153.4	135.3	207.7	95.4	153.0	158.1
2018	56.8	59.6	48.5	79.3	—	—	55.6	143.6	142.6	124.6	199.9	86.3	148.2	152.8
2019	50.3	52.8	42.3	71.5	—	—	50.9	126.7	125.1	108.3	175.9	66.4	132.2	135.2
2020	38.4	40.7	30.3	59.3	—	—	41.4	97.8	102.2	80.7	141.5	52.0	100.6	112.2
2021	31.8	33.4	24.4	49.0	—	—	38.2	87.0	89.6	69.3	127.0	42.9	90.3	105.2
2022	31.5	32.0	24.8	49.8	—	—	38.4	86.3	86.2	67.5	127.6	38.1	90.7	108.2
Males														
2008	52.6	43.5	60.6	59.8	—	—	43.7	202.5	180.3	192.0	216.5	169.5	213.1	185.7
2009	52.2	45.5	58.0	60.3	—	—	42.8	198.7	179.3	190.3	208.1	169.0	208.6	175.9
2010	53.4	48.7	58.7	59.6	—	—	41.4	201.8	187.4	194.5	219.2	159.4	210.0	180.5
2011	53.0	51.4	56.0	57.5	—	—	41.1	199.0	194.4	188.6	211.0	163.2	206.7	174.0

Calendar year	Patients aged 18 to 65 years							Patients aged ≥ 66 years						
	Overall	AB	BC	MB	NS	ON	SK	Overall	AB	BC	MB	NS	ON	SK
2012	50.8	50.3	52.1	56.4	—	—	41.1	188.9	189.1	176.6	206.4	154.4	194.6	176.1
2013	48.1	48.0	48.8	54.0	—	—	38.8	179.7	179.4	167.1	202.6	143.1	185.4	164.5
2014	46.7	47.5	46.2	52.4	—	—	39.1	172.7	176.7	157.6	200.7	128.8	178.0	162.5
2015	44.5	44.7	43.4	52.4	—	—	39.8	166.2	166.0	152.3	199.2	126.2	170.6	165.6
2016	42.3	42.6	40.2	50.5	—	—	39.9	153.7	156.6	143.4	185.8	114.0	155.3	166.0
2017	38.5	39.1	36.6	46.5	—	—	34.6	141.6	142.2	132.3	173.9	98.1	143.8	148.9
2018	36.0	36.0	33.6	45.7	—	—	35.0	136.0	131.2	122.3	170.0	87.5	141.0	147.3
2019	33.0	32.7	30.8	41.9	—	—	33.0	122.7	119.6	108.5	152.1	69.0	128.3	131.6
2020	26.1	25.8	23.5	35.1	—	—	28.0	97.9	95.7	86.1	129.0	58.0	101.1	114.4
2021	22.8	22.2	20.7	29.5	—	—	26.4	89.6	87.5	75.7	115.5	48.1	94.0	106.4
2022	22.7	22.0	20.5	30.7	—	—	26.8	92.0	87.1	77.2	122.6	43.6	97.3	111.1

AB = Alberta; BC = British Columbia; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.

Notes: (1) Overall represents data aggregated for 4 provinces (patients aged 18 to 65 years) and all 6 provinces (patients aged ≥ 66 years). Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Table 8: Top 3 Most Common Indications Associated With a Fluoroquinolone Dispensation Among Patients Aged 18 to 65 Years by Province and Calendar Year

Province	Missing Indication or indication ranking	Calendar year		
		2008	2016	2022
AB	Missing indication	13.1%	13.7%	11.9%
	1	595 cystitis	595 cystitis	595 cystitis
	2	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	3	466 acute bronchitis and bronchiolitis	466 acute bronchitis and bronchiolitis	789 other symptoms involving abdomen and pelvis
BC	Missing indication	16.0%	16.8%	17.4%
	1	595 cystitis	595 cystitis	595 cystitis
	2	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	3	788 symptoms involving urinary system	788 symptoms involving urinary system	788 symptoms involving urinary system
MB	Missing indication	14.8%	12.9%	12.6%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	466 acute bronchitis and bronchiolitis	466 acute bronchitis and bronchiolitis	789 other symptoms involving abdomen and pelvis

Province	Missing Indication or indication ranking	Calendar year		
		2008	2016	2022
	3	595 cystitis	789 other symptoms involving abdomen and pelvis	V72 special investigations and examination
SK	Missing indication	9.8%	9.0%	9.0%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	595 cystitis	595 cystitis	595 cystitis
	3	486 pneumonia, organism unspecified	009 ill-defined intestinal infections	562 diverticula of intestine

AB = Alberta; BC = British Columbia; ICD-9 = International Classification of Diseases, Ninth Revision; MB = Manitoba; SK = Saskatchewan.

Notes: (1) Data not available in Nova Scotia and Ontario. (2) Indications are presented as ICD-9 code and associated term. (3) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Table 9: Top 3 Most Common Indications Associated With a Fluoroquinolone Dispensation Among Patients Aged ≥ 66 Years by Province and Calendar Year

Province	Missing diagnosis or indication ranking	Calendar year		
		2008	2016	2022
AB	Missing indication	9.9%	9.3%	9.7%
	1	595 cystitis	595 cystitis	595 cystitis
	2	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	3	466 acute bronchitis and bronchiolitis	466 acute bronchitis and bronchiolitis	788 symptoms involving urinary system
BC	Missing indication	10.9%	10.9%	11.3%
	1	595 cystitis	595 cystitis	595 cystitis
	2	788 symptoms involving urinary system	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	3	599 other disorders of urethra and urinary tract	788 symptoms involving urinary system	788 symptoms involving urinary system
MB	Missing indication	11.9%	11.0%	10.5%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	486 pneumonia, organism unspecified	486 pneumonia, organism unspecified	V72 special investigations and examination
	3	496 chronic airway obstruction, not elsewhere classified	496 chronic airway obstruction, not elsewhere classified	401 essential hypertension
NS	Missing indication	12.0%	10.6%	14.8%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract

Province	Missing diagnosis or indication ranking	Calendar year		
		2008	2016	2022
	2	486 pneumonia, organism unspecified	496 chronic airway obstruction, not elsewhere classified	496 chronic airway obstruction, not elsewhere classified
	3	496 chronic airway obstruction, not elsewhere classified	486 pneumonia, organism unspecified	799 other ill-defined and unknown causes of morbidity and mortality
ON	Missing indication	14.8%	15.8%	16.7%
	1	595 cystitis	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	599 other disorders of urethra and urinary tract	595 cystitis	595 cystitis
	3	466 acute bronchitis and bronchiolitis	486 pneumonia, organism unspecified	787 symptoms involving digestive system
SK	Missing indication	7.3%	7.9%	9.1%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	486 pneumonia, organism unspecified	595 cystitis	595 cystitis
	3	496 chronic airway obstruction, not elsewhere classified	486 pneumonia, organism unspecified	496 chronic airway obstruction, not elsewhere classified

AB = Alberta; BC = British Columbia; ICD-9 = International Classification of Diseases, Ninth Revision; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.

Notes: (1) Indications are presented as ICD-9 code and associated term. (2) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Table 10: Top 3 Most Common Indications Associated With a Fluoroquinolone Dispensation Among Females by Province and Calendar Year

Province	Missing diagnosis or indication ranking	Calendar year		
		2008	2016	2022
AB	Missing indication	11.4%	11.9%	10.6%
	1	595 cystitis	595 cystitis	595 cystitis
	2	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	3	466 acute bronchitis and bronchiolitis	466 acute bronchitis and bronchiolitis	789 other symptoms involving abdomen and pelvis
BC	Missing indication	13.5%	14.1%	14.1%
	1	595 cystitis	595 cystitis	595 cystitis
	2	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract

Province	Missing diagnosis or indication ranking	Calendar year		
		2008	2016	2022
	3	788 symptoms involving urinary system	788 symptoms involving urinary system	788 symptoms involving urinary system
MB	Missing indication	13.4%	12.4%	10.9%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	595 cystitis	595 cystitis	789 other symptoms involving abdomen and pelvis
	3	466 acute bronchitis and bronchiolitis	466 acute bronchitis and bronchiolitis	595 cystitis
NS	Missing indication	12.9%	11.6%	15.9%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	486 pneumonia, organism unspecified	496 chronic airway obstruction, not elsewhere classified	496 chronic airway obstruction, not elsewhere classified
	3	496 chronic airway obstruction, not elsewhere classified	486 pneumonia, organism unspecified	562 diverticula of intestine
ON	Missing indication	17.2%	18.6%	19.2%
	1	595 cystitis	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	599 other disorders of urethra and urinary tract	595 cystitis	595 cystitis
	3	466 acute bronchitis and bronchiolitis	486 pneumonia, organism unspecified	787 symptoms involving digestive system
SK	Missing indication	8.8%	8.6%	8.6%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	595 cystitis	595 cystitis	595 cystitis
	3	486 pneumonia, organism unspecified	486 pneumonia, organism unspecified	562 diverticula of intestine

AB = Alberta; BC = British Columbia; ICD-9 = International Classification of Diseases, Ninth Revision; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.

Notes: (1) Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) Indications are presented as ICD-9 code and associated term. (3) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

Table 11: Top 3 Most Common Indications Associated With a Fluoroquinolone Dispensation Among Males by Province and Calendar Year

Province	Missing diagnosis or indication ranking	Calendar year		
		2008	2016	2022
AB	Missing indication	13.5%	13.0%	11.5%
	1	466 acute bronchitis and bronchiolitis	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	599 other disorders of urethra and urinary tract	595 cystitis	595 cystitis
	3	595 cystitis	466 acute bronchitis and bronchiolitis	788 symptoms involving urinary system
BC	Missing indication	15.7%	14.7%	14.9%
	1	788 symptoms involving urinary system	595 cystitis	788 symptoms involving urinary system
	2	595 cystitis	788 symptoms involving urinary system	595 cystitis
	3	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
MB	Missing indication	14.5%	11.9%	12.8%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	466 acute bronchitis and bronchiolitis	466 acute bronchitis and bronchiolitis	601 inflammatory diseases of prostate
	3	486 pneumonia, organism unspecified	486 pneumonia, organism unspecified	V72 special investigations and examination
NS	Missing indication	10.3%	9.4%	13.6%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	496 chronic airway obstruction, not elsewhere classified	496 chronic airway obstruction, not elsewhere classified	799 other ill-defined and unknown causes of morbidity and mortality
	3	486 pneumonia, organism unspecified	486 pneumonia, organism unspecified	496 chronic airway obstruction, not elsewhere classified
ON	Missing indication	11.4%	12.3%	13.9%
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	466 acute bronchitis and bronchiolitis	486 pneumonia, organism unspecified	595 cystitis
	3	486 pneumonia, organism unspecified	595 cystitis	600 hyperplasia of prostate
SK	Missing indication	8.7%	8.5%	9.6%

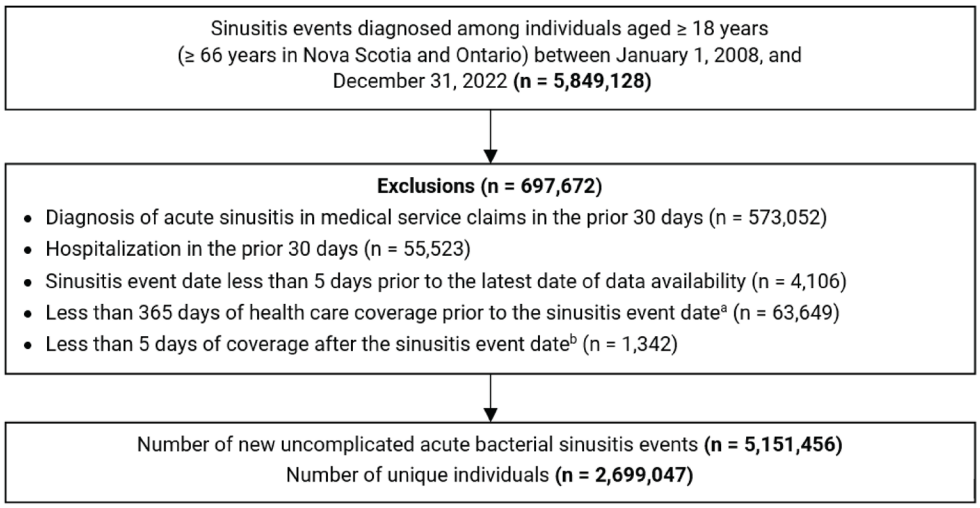
Province	Missing diagnosis or indication ranking	Calendar year		
		2008	2016	2022
	1	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract	599 other disorders of urethra and urinary tract
	2	486 pneumonia, organism unspecified	486 pneumonia, organism unspecified	562 diverticula of intestine
	3	Z21 radiological examination - no diagnosis specified[a]	601 inflammatory diseases of prostate	601 inflammatory diseases of prostate

AB = Alberta; BC = British Columbia; ICD-9 = International Classification of Diseases, Ninth Revision; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.

Notes: (1) Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) Indications are presented as ICD-9 code and associated term. (3) The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

[a]SK-specific diagnosis code in outpatient medical service claims.

Figure 28: Flow Chart of Study Cohort Construction for Acute Bacterial Sinusitis



Notes: (1) Data aggregated for all 6 provinces. Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) Patients were allowed to enter the cohort multiple times with a new event.

[a]Patients with less than 365 days of health care coverage before the event date could not be identified in Alberta due to the unavailability of start of coverage date.

[b]Death or out-migration date was used a proxy for the end of coverage date in Alberta.

Table 12: Top 5 Most Common Antibiotic Dispensations Associated With Incident Acute Bacterial Sinusitis Events by Province and Year

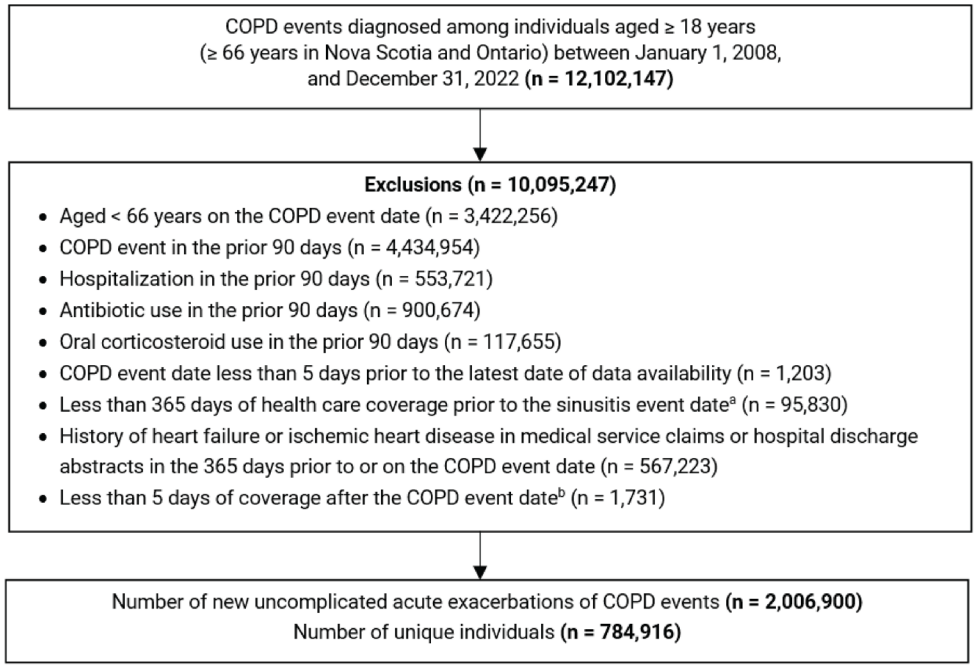
Province	No antibiotic or molecule ranking	Calendar year		
		2008	2016	2022
AB	No antibiotic	45.6%	26.8%	29.7%
	1	amoxicillin	amoxicillin	amoxicillin
	2	clarithromycin	clarithromycin	azithromycin
	3	azithromycin	azithromycin	doxycycline
	4	**moxifloxacin**	doxycycline	clarithromycin
	5	**levofloxacin**	**levofloxacin**	**levofloxacin**
BC	No antibiotic	32.3%	32.0%	30.5%
	1	amoxicillin	amoxicillin	amoxicillin
	2	clarithromycin	clarithromycin	doxycycline
	3	azithromycin	azithromycin	azithromycin
	4	**moxifloxacin**	doxycycline	clarithromycin
	5	cefuroxime	**moxifloxacin**	cefuroxime
MB	No antibiotic	20.2%	19.1%	20.8%
	1	amoxicillin	amoxicillin	amoxicillin
	2	azithromycin	azithromycin	azithromycin
	3	clarithromycin	amoxicillin/clavulanate	amoxicillin/clavulanate
	4	**moxifloxacin**	clarithromycin	doxycycline
	5	amoxicillin/clavulanate	cefuroxime	clarithromycin
NS	No antibiotic	33.5%	33.9%	33.3%
	1	amoxicillin	amoxicillin	amoxicillin
	2	cefuroxime	amoxicillin/clavulanate	amoxicillin/clavulanate
	3	clarithromycin	doxycycline	doxycycline
	4	amoxicillin/clavulanate	cefuroxime	cefuroxime
	5	azithromycin	clarithromycin	clarithromycin
ON	No antibiotic	36.7%	33.7%	34.1%
	1	amoxicillin	amoxicillin	amoxicillin
	2	clarithromycin	azithromycin	azithromycin
	3	azithromycin	clarithromycin	clarithromycin
	4	cefprozil	cefprozil	doxycycline
	5	**moxifloxacin**	cefuroxime	cefprozil
SK	No antibiotic	23.1%	21.5%	20.5%
	1	amoxicillin	amoxicillin	amoxicillin

Province	No antibiotic or molecule ranking	Calendar year		
		2008	2016	2022
	2	azithromycin	azithromycin	amoxicillin/clavulanate
	3	cephalexin	amoxicillin/clavulanate	azithromycin
	4	clarithromycin	clarithromycin	doxycycline
	5	doxycycline	doxycycline	clarithromycin

AB = Alberta; BC = British Columbia; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.

Note: (1) Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) Fluoroquinolone molecules are in bold.

Figure 29: Flow Chart of Study Cohort Construction for Acute Exacerbations of COPD



COPD = chronic obstructive pulmonary disease.

Notes: (1) Data aggregated for all 6 provinces. (2) Patients were allowed to enter the cohort multiple times with a new event.

[a]Patients with less than 365 days of health care coverage before the event date could not be identified in Alberta due to the unavailability of start of coverage date.

[b]Death or out-migration date was used a proxy for the end of coverage date in Alberta.

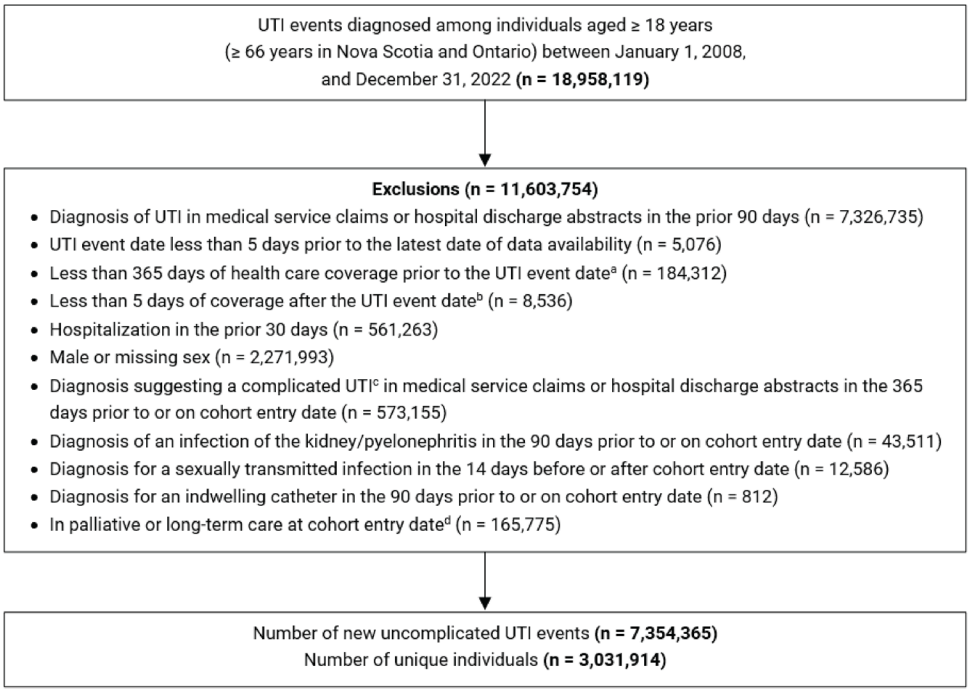
Table 13: Top 5 Most Common Antibiotic Dispensations Associated With Incident Acute Exacerbations of COPD Events by Province and Year

Province	No antibiotic or molecule ranking	Calendar year		
		2008	2016	2022
AB	No antibiotic	79.5%	83.5%	87.8%
	1	clarithromycin	amoxicillin	amoxicillin
	2	**levofloxacin**	azithromycin	azithromycin
	3	azithromycin	**levofloxacin**	doxycycline
	4	amoxicillin	doxycycline	**levofloxacin**
	5	**moxifloxacin**	clarithromycin	clarithromycin
BC	No antibiotic	67.1%	81.0%	90.3%
	1	clarithromycin	amoxicillin	doxycycline
	2	amoxicillin	doxycycline	amoxicillin
	3	azithromycin	clarithromycin	azithromycin
	4	**moxifloxacin**	azithromycin	**moxifloxacin**
	5	cefuroxime	**moxifloxacin**	cefuroxime
MB	No antibiotic	60.4%	59.2%	73.1%
	1	azithromycin	azithromycin	azithromycin
	2	amoxicillin	amoxicillin	amoxicillin
	3	clarithromycin	**levofloxacin**	amoxicillin/clavulanate
	4	**levofloxacin**	clarithromycin	doxycycline
	5	**moxifloxacin**	amoxicillin/clavulanate	**levofloxacin**
NS	No antibiotic	64.6%	72.8%	83.2%
	1	azithromycin	doxycycline	doxycycline
	2	amoxicillin	amoxicillin	amoxicillin
	3	doxycycline	clarithromycin	amoxicillin/clavulanate
	4	clarithromycin	cefuroxime	cefuroxime
	5	cefuroxime	amoxicillin/clavulanate	azithromycin
ON	No antibiotic	86.0%	84.3%	87.5%
	1	clarithromycin	amoxicillin	amoxicillin
	2	**moxifloxacin**	azithromycin	azithromycin
	3	azithromycin	**moxifloxacin**	**moxifloxacin**
	4	amoxicillin	**levofloxacin**	doxycycline
	5	**levofloxacin**	clarithromycin	**levofloxacin**
SK	No antibiotic	61.3%	72.5%	80.0%
	1	doxycycline	azithromycin	azithromycin

Province	No antibiotic or molecule ranking	Calendar year		
		2008	2016	2022
	2	azithromycin	doxycycline	doxycycline
	3	amoxicillin	amoxicillin	amoxicillin/clavulanate
	4	clarithromycin	clarithromycin	amoxicillin
	5	cephalexin	**moxifloxacin**	**moxifloxacin**

AB = Alberta; BC = British Columbia; COPD = chronic obstructive pulmonary disease; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.
Note: Fluoroquinolone molecules are in bold.

Figure 30: Flow Chart of Study Cohort Construction for Uncomplicated UTI



UTI = urinary tract infection.
Notes: (1) Data aggregated for all 6 provinces. Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) Patients were allowed to enter the cohort multiple times with a new event.
[a]Patients with less than 365 days of health care coverage before the event date could not be identified in Alberta due to the unavailability of start of coverage date.
[b]Death or out-migration date was used a proxy for the end of coverage date in Alberta.
[c]Diagnosis for complicated UTI includes structural abnormality of urinary tract (including stones), ureteral abnormality or vesicoureteral reflux, neurogenic bladder, neurologic conditions, pregnancy (in the 270 days prior), or severe diabetes.
[d]In provinces where data are available. Palliative care data not available in Alberta.

Table 14: Top 5 Most Common Antibiotic Dispensations Associated With Incident Uncomplicated UTI Events by Province and Year

Province	No antibiotic or molecule ranking	Calendar year		
		2008	2016	2022
AB	No antibiotic	45.2%	28.3%	29.7%
	1	**ciprofloxacin**	nitrofurantoin	nitrofurantoin
	2	nitrofurantoin	**ciprofloxacin**	**ciprofloxacin**
	3	sulfamethoxazole	sulfamethoxazole	cefixime
	4	**norfloxacin**	cefixime	sulfamethoxazole
	5	amoxicillin	fosfomycin	fosfomycin
BC	No antibiotic	30.0%	29.2%	29.5%
	1	**ciprofloxacin**	nitrofurantoin	nitrofurantoin
	2	nitrofurantoin	**ciprofloxacin**	cefixime
	3	sulfamethoxazole/ trimethoprim	sulfamethoxazole/ trimethoprim	fosfomycin
	4	amoxicillin	fosfomycin	**ciprofloxacin**
	5	**norfloxacin**	cefixime	sulfamethoxazole/ trimethoprim
MB	No antibiotic	24.1%	24.2%	23.9%
	1	**ciprofloxacin**	**ciprofloxacin**	nitrofurantoin
	2	sulfamethoxazole/ trimethoprim	nitrofurantoin	**ciprofloxacin**
	3	nitrofurantoin	sulfamethoxazole/ trimethoprim	sulfamethoxazole/ trimethoprim
	4	amoxicillin	amoxicillin	amoxicillin
	5	cephalexin	cephalexin	fosfomycin
NS	No antibiotic	26.9%	26.9%	33.6%
	1	nitrofurantoin	nitrofurantoin	nitrofurantoin
	2	sulfamethoxazole/ trimethoprim	sulfamethoxazole/ trimethoprim	cephalexin
	3	**ciprofloxacin**	**ciprofloxacin**	sulfamethoxazole/ trimethoprim
	4	amoxicillin	amoxicillin	amoxicillin/clavulanate
	5	**norfloxacin**	**norfloxacin**	amoxicillin
ON	No antibiotic	39.0%	39.3%	37.2%
	1	nitrofurantoin	nitrofurantoin	nitrofurantoin
	2	**norfloxacin**	**ciprofloxacin**	fosfomycin

Province	No antibiotic or molecule ranking	Calendar year		
		2008	2016	2022
	3	**ciprofloxacin**	sulfamethoxazole	**ciprofloxacin**
	4	sulfamethoxazole	amoxicillin	sulfamethoxazole
	5	amoxicillin	**norfloxacin**	amoxicillin
SK	No antibiotic	25.8%	23.4%	24.9%
	1	nitrofurantoin	nitrofurantoin	nitrofurantoin
	2	sulfamethoxazole/ trimethoprim	**ciprofloxacin**	**ciprofloxacin**
	3	**ciprofloxacin**	sulfamethoxazole/ trimethoprim	sulfamethoxazole/ trimethoprim
	4	amoxicillin	fosfomycin	fosfomycin
	5	cephalexin	cephalexin	amoxicillin/clavulanate

AB = Alberta; BC = British Columbia; MB = Manitoba; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan; UTI = urinary tract infection.

Note: (1) Data available in Nova Scotia and Ontario for patients aged ≥ 66 years. (2) Fluoroquinolone molecules are in bold.

Appendix 3: Additional Results for Impact Assessment Analysis (Objective 2)

Please note that this appendix has not been copy-edited.

Table 15: Relative Rate and Slope Estimate of Dispensation Rates for the 4 Fluoroquinolones by Study Segment and Province

Segment	Relative rate[a] (95% CI)	Slope estimate (95% CI)
Alberta		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9981 (0.9977, 0.9985)
Segment 2: January 1, 2017, to February 29, 2020	0.48 (0.44, 0.51)	0.9838 (0.9825, 0.9851)
Segment 3: March 1, 2020, to December 31, 2022	0.35 (0.31, 0.40)	0.9916 (0.9897, 0.9936)
British Columbia		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9952 (0.9943, 0.9961)
Segment 2: January 1, 2017, to February 29, 2020	0.48 (0.44, 0.52)	0.9912 (0.9904, 0.9920)
Segment 3: March 1, 2020, to December 31, 2022	0.32 (0.28, 0.37)	0.9968 (0.9958, 0.9977)
Manitoba		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9977 (0.9970, 0.998)
Segment 2: January 1, 2017, to February 29, 2020	0.56 (0.52, 0.60)	0.9885 (0.9870, 0.990)
Segment 3: March 1, 2020, to December 31, 2022	0.46 (0.41, 0.51)	0.9941 (0.9928, 0.995)
Nova Scotia		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9955 (0.9948, 0.9961)
Segment 2: January 1, 2017, to February 29, 2020	0.36 (0.33, 0.38)	0.9843 (0.9829, 0.9856)
Segment 3: March 1, 2020, to December 31, 2022	0.22 (0.19, 0.24)	0.9892 (0.9875, 0.9908)
Ontario		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9970 (0.9966, 0.9974)
Segment 2: January 1, 2017, to February 29, 2020	0.56 (0.53, 0.59)	0.9920 (0.9906, 0.9935)
Segment 3: March 1, 2020, to December 31, 2022	0.44 (0.40, 0.49)	0.9992 (0.9976, 1.0008)
Saskatchewan		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9984 (0.9977, 0.9991)
Segment 2: January 1, 2017, to February 29, 2020	0.63 (0.58, 0.70)	0.9900 (0.9882, 0.9917)
Segment 3: March 1, 2020, to December 31, 2022	0.58 (0.51, 0.66)	0.9973 (0.9961, 0.9986)

CI = confidence interval.

Note: The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

[a]Adjusted dispensation rate (per 1,000 population) in segment 2 and 3, using segment 1 as the reference.

Table 16: Relative Rate and Slope Estimate of Dispensation Rates for the 4 Fluoroquinolones by Study Segment and Province, Without 6-Month Washout Period for Implementation of Risk Minimization Measures

Segment	Relative rate[a] (95% CI)	Slope estimate (95% CI)
Alberta		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9989 (0.9983, 0.9994)
Segment 2: July 1, 2017, to February 29, 2020	0.49 (0.45, 0.54)	0.9918 (0.9895, 0.9941)
Segment 3: March 1, 2020 to December 31, 2022	0.34 (0.30, 0.39)	0.9894 (0.9876, 0.9913)
British Columbia		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9952 (0.9943, 0.9961)
Segment 2: July 1, 2017, to February 29, 2020	0.46 (0.42, 0.50)	0.9916 (0.9905, 0.9927)
Segment 3: March 1, 2020, to December 31, 2022	0.32 (0.28, 0.37)	0.9968 (0.9958, 0.9977)
Manitoba		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9983 (0.9976, 0.9989)
Segment 2: July 1, 2017, to February 29, 2020	0.56 (0.51, 0.60)	0.9929 (0.9912, 0.9947)
Segment 3: March 1, 2020, to December 31, 2022	0.45 (0.40, 0.50)	0.9931 (0.9919, 0.9943)
Nova Scotia		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9954 (0.9948, 0.9959)
Segment 2: July 1, 2017, to February 29, 2020	0.32 (0.30, 0.34)	0.9843 (0.9830, 0.9855)
Segment 3: March 1, 2020, to December 31, 2022	0.16 (0.13, 0.20)	0.9790 (0.9734, 0.9847)
Ontario		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9971 (0.9967, 0.9975)
Segment 2: July 1, 2017, to February 29, 2020	0.53 (0.49, 0.56)	0.9920 (0.9902, 0.9937)
Segment 3: March 1, 2020, to December 31, 2022	0.44 (0.40, 0.49)	0.9991 (0.9976, 1.0007)
Saskatchewan		
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9991 (0.9984, 0.9998)
Segment 2: July 1, 2017, to February 29, 2020	0.65 (0.59, 0.72)	0.9958 (0.9938, 0.9979)
Segment 3: March 1, 2020, to December 31, 2022	0.57 (0.50, 0.64)	0.9961 (0.9948, 0.9974)

CI = confidence interval.

Note: The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

[a]Adjusted dispensation rate (per 1,000 population) in segment 2 and 3, using segment 1 as the reference.

Table 17: Relative Rate and Slope Estimate of Percentage of Dispensations for the 4 Fluoroquinolones by Indication and by Study Segment and Province

Segment	Acute Bacterial Sinusitis		UTI		Acute Exacerbation of COPD	
	Relative rate[a] (95% CI)	Slope estimate (95% CI)	Relative rate[a] (95% CI)	Slope estimate (95% CI)	Relative rate[a] (95% CI)	Slope estimate (95% CI)
Alberta						
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9922 (0.9919, 0.9926)	Reference	0.9901 (0.9897, 0.9906)	Reference	0.9973 (0.9964, 0.9983)
Segment 2: January 1, 2017, to February 29, 2020	0.36 (0.35, 0.37)	0.9906 (0.9897, 0.9916)	0.23 (0.22, 0.25)	0.9857 (0.9847, 0.9866)	0.42 (0.37, 0.47)	0.9883 (0.9850, 0.9916)
Segment 3: March 1, 2020, to December 31, 2022	0.23 (0.21, 0.26)	0.9808 (0.9777, 0.9840)	0.17 (0.16, 0.19)	0.9895 (0.9878, 0.9912)	0.28 (0.25, 0.33)	0.9850 (0.9801, 0.9898)
British Columbia						
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9920 (0.9914, 0.9926)	Reference	0.9869 (0.9863, 0.9876)	Reference	0.9974 (0.9968, 0.9980)
Segment 2: January 1, 2017, to February 29, 2020	0.40 (0.37, 0.42)	0.9940 (0.9918, 0.9962)	0.25 (0.23, 0.27)	0.9878 (0.9864, 0.9892)	0.59 (0.55, 0.62)	0.9921 (0.9895, 0.9947)
Segment 3: March 1, 2020, to December 31, 2022	0.26 (0.24, 0.28)	0.9842 (0.9818, 0.9866)	0.15 (0.13, 0.18)	0.9885 (0.9865, 0.9905)	0.47 (0.45, 0.50)	0.9881 (0.9851, 0.9911)
Manitoba						
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9910 (0.9899, 0.9920)	Reference	0.9965 (0.9960, 0.9969)	Reference	0.9987 (0.9971, 1.0003)
Segment 2: January 1, 2017, to February 29, 2020	0.41 (0.37, 0.45)	0.9932 (0.9905, 0.9959)	0.36 (0.34, 0.38)	0.9877 (0.9860, 0.9894)	0.63 (0.54, 0.74)	0.9923 (0.9867, 0.9980)
Segment 3: March 1, 2020, to December 31, 2022	0.21 (0.17, 0.26)	0.9782 (0.9730, 0.9835)	0.28 (0.25, 0.31)	0.9924 (0.9909, 0.9939)	0.44 (0.39, 0.50)	0.9848 (0.9798, 0.9899)
Nova Scotia						
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9899 (0.9875, 0.9923)	Reference	0.9943 (0.9933, 0.9953)	Reference	0.9947 (0.9932, 0.9963)

Segment	Acute Bacterial Sinusitis		UTI		Acute Exacerbation of COPD	
	Relative rate[a] (95% CI)	Slope estimate (95% CI)	Relative rate[a] (95% CI)	Slope estimate (95% CI)	Relative rate[a] (95% CI)	Slope estimate (95% CI)
Segment 2: January 1, 2017, to February 29, 2020	0.25 (0.17, 0.38)	0.9785 (0.9666, 0.9906)	0.26 (0.25, 0.27)	0.9812 (0.9793, 0.9831)	0.30 (0.25, 0.36)	0.9835 (0.9767, 0.9904)
Segment 3: March 1, 2020, to December 31, 2022	0.11 (0.06, 0.21)	0.9890 (0.9573, 1.0219)	0.17 (0.14, 0.20)	0.9900 (0.9830, 0.9970)	0.25 (0.16, 0.37)	0.9936 (0.9764, 1.0110)
Ontario						
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9942 (0.9938, 0.9945)	Reference	0.9922 (0.9914, 0.9930)	Reference	0.9960 (0.9956, 0.9965)
Segment 2: January 1, 2017, to February 29, 2020	0.46 (0.44, 0.48)	0.9951 (0.9928, 0.9975)	0.37 (0.35, 0.39)	0.9929 (0.9914, 0.9944)	0.41 (0.40, 0.43)	0.9880 (0.9869, 0.9890)
Segment 3: March 1, 2020, to December 31, 2022	0.37 (0.35, 0.39)	0.9886 (0.9867, 0.9905)	0.31 (0.29, 0.32)	0.9946 (0.9942, 0.9951)	0.32 (0.30, 0.35)	0.9878 (0.9854, 0.9903)
Saskatchewan						
Segment 1: January 1, 2008, to December 31, 2016	Reference	0.9958 (0.9951, 0.9965)	Reference	0.9973 (0.9958, 0.9988)	Reference	0.9976 (0.9966, 0.9985)
Segment 2: January 1, 2017, to February 29, 2020	0.62 (0.56, 0.68)	0.9954 (0.9923, 0.9985)	0.53 (0.47, 0.60)	0.9940 (0.9928, 0.9951)	0.89 (0.77, 1.03)	0.9990 (0.9939, 1.0041)
Segment 3: March 1, 2020, to December 31, 2022	0.50 (0.43, 0.59)	0.9901 (0.9821, 0.9982)	0.50 (0.45, 0.55)	0.9982 (0.9959, 1.0006)	0.57 (0.42, 0.79)	0.9837 (0.9700, 0.9976)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; UTI = urinary tract infection.

Note: The fluoroquinolones are ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin.

[a]Adjusted percentage of dispensations in segment 2 and 3, using segment 1 as the reference.

Appendix 4: Summary of Provincial Drug Plan Coverage

Please note that this appendix has not been copy-edited.

Table 18: Provincial Drug Plan Coverage for the 4 Oral Fluoroquinolones of Interest in 2016 and 2023

Molecule	Year[a]	AB	BC	MB	NS	ON	SK
Ciprofloxacin	2016	L	B	L	L	L	L
	2023	L[b]	B	L[b]	L[b]	B[b]	L
Levofloxacin	2016	L	NB	L[c]	L[c]	L[c]	L
	2023	L	NB	L[c]	L[c]	B[c]	L
Moxifloxacin	2016	L	B	L	L	L	L
	2023	L	B	L	L	B	L
Norfloxacin	2016	B	B	L	L	B	L
	2023	B	B	L	L	B	L

AB = Alberta; B (benefit) = no specific requirements for reimbursement; BC = British Columbia; L (limited) = restricted to specific criteria or special authorization; MB = Manitoba; NB (nonbenefit) = not available through the public drug plan; NS = Nova Scotia; ON = Ontario; SK = Saskatchewan.

Note: Information assessed in October 2016 through the National Prescription Drug Utilization Information System (NPDUIS) Database developed by the Canadian Institute of Health Information (CIHI) and in November 2023 through the provincial ministries' websites.

(1)AB (Interactive Drug Benefit List): https://idbl.ab.bluecross.ca/idbl/load.do and https://idbl.ab.bluecross.ca/idbl/DBL/60042.pdf.

(2)BC (BC PharmaCare Formulary): https://pharmacareformularysearch.gov.bc.ca/.

(3)MB (Manitoba Pharmacare Program Drug Formulary Lookup): https://web22.gov.mb.ca/eFormulary/ and https://residents.gov.mb.ca/forms.html?d=details&pub_id=10541&filter_keyword=drug+benefits#page=46 (effective date: October 26, 2023).

(4)NS (Nova Scotia Pharmacare): https://novascotia.ca/dhw/pharmacare/formulary.asp and https://novascotia.ca/dhw/pharmacare/documents/formulary.pdf.

(5)ON (Ontario Drug Benefit Formulary Search): https://www.formulary.health.gov.on.ca/formulary/.

(6)SK (Saskatchewan Drug Plan): https://formulary.drugplan.ehealthsask.ca/SearchFormulary and https://formulary.drugplan.ehealthsask.ca/PDFs/APPENDIXA.pdf.

[a]Sources for coverage criteria in November 2023.

[b]Ciprofloxacin 500 mg XL not a benefit in Alberta, Manitoba, and Nova Scotia. All general benefit except for ciprofloxacin 10 g/100 mL oral suspension and XL 500 mg extended-release tablets which are limited use in Ontario.

[c]Levofloxacin 750 mg not a benefit.

For more information on CoLab and its work, visit colab.cda-amc.ca.

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About CDA-AMC: CDA-AMC is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CDA-AMC and its Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.