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Drug Utilization Study

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

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This Drug Utilization Study is being conducted by the Canadian Network for Observational Drug Effect Studies (CNODES) through the Post-Market Drug Evaluation CoLab Network.

Table of Contents

List of Tables

Abbreviations

CNODES	Canadian Network for Observational Drug Effect Studies
COPD	chronic obstructive pulmonary disease
UTI	urinary tract infection

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Amendments and Updates

The following amendments were made during the implementation of analyses.

Table 1: Protocol Version Tracking

Section (heading)	Amendment	Rationale
Study Population and Setting	Removed the “prior to January 1, 2008” exclusion for the 3 indication cohorts in objective 1e.	There should be no events before this date based on the inclusion criteria.
Study Variables	Specified that objective 1b onward include all 4 fluoroquinolones of interest. Edited “emergency department records” for “additional relevant data sources where available” in objective 1d.	Edits made during analyses to clarify how to implement this section.
Data Analysis	Removed stratification “separately” by sex in objective 1a. Edited gaps from 7 to 3 days to define treatment episodes in objective 1b. Specified that outcome 1 in objective 2 includes all 4 fluoroquinolones of interest and is overall (not for specific indications). Also edited objective 2 section to clarify outcome models.	Edits made during analyses to clarify how to implement this section.
Appendix 1	Edited definitions for severe diabetes (use of *ICD* code replaced by ATC code for insulin) and indwelling catheter (additional codes added).	Edits made during analyses to clarify how to implement this section.

ATC = Anatomical Therapeutic Chemical; *ICD* = *International Classification of Diseases*.

Abstract

Systemic oral fluoroquinolones, a class of broad-spectrum antibiotics, have been associated with serious adverse effects. On January 23, 2017, Health Canada issued a risk communication to restrict the use of fluoroquinolones due to their disabling and potentially persistent side effects. The labelling of all systemic fluoroquinolones available in Canada was updated accordingly. There is a need to determine if fluoroquinolone utilization patterns have changed since these regulatory actions were implemented. The aims of this study are to update our previous study to describe fluoroquinolone utilization trends from 2008 and 2022 and to assess the impact of the risk minimization measures introduced in 2017. Similar methods to the previous Canadian Network for Observational Drug Effect Studies (CNODES) drug utilization study will be used. We will conduct a retrospective cohort study using administrative health databases from 6 provinces (Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan) between January 1, 2008, and December 31, 2022. We will assess utilization patterns and indications for systemic oral fluoroquinolones available in Canada from 2008 to the present. In addition, we will assess the impact of the 2017 risk minimization measures (risk communication, updates to the labels) on the use of fluoroquinolones through an interrupted time series analysis. These findings will provide important insight on the current trends in fluoroquinolone use in Canada and the impact of regulatory actions on these trends.

The study will only include prescriptions for the oral formulation of fluoroquinolones in the community setting and will not include fluoroquinolone prescriptions dispensed in hospital.

Background and Rationale

Fluoroquinolones, a class of broad-spectrum antibiotics, have been commonly used for a wide range of infections since their introduction in the 1980s. Severe adverse effects have been associated with fluoroquinolone use, including tendon disorders, aortic aneurysms, 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 for which other treatment alternatives are available, such as uncomplicated urinary tract infections (UTIs), acute bacterial sinusitis , and acute exacerbation of chronic obstructive pulmonary disease (COPD).[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 fluroquinolone products marketed in Canada has been updated with a boxed warning and the indications for fluoroquinolones have been restricted. Following a safety review conducted by Health Canada in June 2019, further revisions were made to the labels to include information on potential risks of aneurysm and aortic dissection.[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, these were not temporally related to the regulatory actions. These findings resulted in the EMA issuing a reminder on the restricted use of fluoroquinolones in May 2023.[9] 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.[10-13] In Canada, observational studies[14-16] in response to a previous Health Canada query were conducted to assess the appropriate use of fluoroquinolones and to 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 exacerbation of COPD, and that their use varied widely across provinces.

Given the uncertainty about the current trends in fluoroquinolone use in Canada, there is a need to determine if utilization patterns have changed following the regulatory actions by Health Canada, specifically with respect to risk communication, labelling revisions on the risk of disabling and persistent serious adverse effects, and the updating of restrictions to authorized indications. At the request of Health Canada, the previous Canadian Network for Observational Drug Effect Studies (CNODES) drug utilization study[16] will be updated to determine the impact of the regulatory actions applied in 2017 on fluoroquinolone use in Canada.

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?

Policy Impact

The findings of this study will be used by Health Canada to determine if further regulatory actions are required.

Research Questions

1. What are the utilization patterns and indications for systemic 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?

Objectives

The main objectives of this study are 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 are:

1. To assess utilization patterns and indications for systemic 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 of interest by year from 2008 to 2022.
    c) To describe the use of oral fluoroquinolones of interest by prescriber group or specialty.

d) To describe the most common indications for each oral fluoroquinolone of interest by year from 2008 to 2022.

e) To determine the rate and percentage of prescriptions for oral fluoroquinolones of interest 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 of interest over time by estimating change in prescribing rates and percentage of overall antibiotic use.

Research Methods

Study Design

We will conduct a retrospective cohort study using administrative health databases from the provinces of Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan.

Study Population and Setting

The study population will consist of individuals registered in the provincial health administrative databases in each province between January 1, 2008, and December 31, 2022 (last year of data available). We selected 2008 as the beginning of the study period because all provinces have complete data available as of this year. Due to the prescription drug data availability and limited use of fluoroquinolones in children, inclusion will be limited to those aged 18 years and older for 4 provinces, and those aged 66 years and older for Nova Scotia and Ontario. Because utilization among children is expected to be very low based on findings of the previous study,[16] patients younger than 18 years will only be included in objective 1a (to describe the annual frequency and rate of use of oral fluoroquinolones overall and for each fluoroquinolone of interest from 2008 to present) in the 3 provinces for which data are available (British Columbia, Manitoba, and Saskatchewan). If utilization among children in recent years is unexpectedly high, inclusion of this population in all objectives will be considered.

Overall Fluoroquinolone Utilization

To address objectives 1a to 1d, the study population will consist of all individuals with a dispensation for an oral systemic fluoroquinolone in the outpatient setting between January 1, 2008, and December 31, 2022.

To address objective 1e, we will create a study cohort for each indication of interest. In each province, we will assess the outpatient medical service claims to identify acute bacterial sinusitis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*]: 461.x; *ICD, Tenth Revision*, with Canadian enhancements [*ICD-10-CA*]: J01.x), chronic obstructive pulmonary disease (COPD) (ICD-9-CM: 490.x, 491.x, 492.x, 496.x; *ICD-10-CA*: J40.x to J44.x), and UTI (*ICD-9-CM*: 595.x, 599.x; *ICD-10-CA*: N30.x, N39.x) events in patients aged 18 years and older between January 1, 2008, and December 31, 2022. Cohort entry date will be defined by the date of the medical service claim. Specific exclusions will be applied

to restrict each indication cohort to patients with uncomplicated disease (defined similarly as in the previous study; described subsequently). Patients will be eligible to enter the study cohorts multiple times, provided they meet all the criteria.

Acute Bacterial Sinusitis Cohort Exclusion Criteria

For the acute bacterial sinusitis cohort, patients with a hospitalization for any reason or a diagnosis of acute sinusitis in outpatient medical service claims in the preceding 30 days will be excluded. We will exclude acute bacterial sinusitis events occurring less than 5 days before the latest date of data available at each site. We will also exclude 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 COPD cohort, we will exclude patients younger than 66 years on the COPD index date, which is defined as the service date for a medical service claim with a COPD diagnosis. To limit the study cohort to uncomplicated acute exacerbations of COPD, we will exclude patients with an event, any hospitalization, or use of oral antibiotics or oral corticosteroids in the prior 90 days. We will exclude events occurring less than 5 days before the latest date of data available at each site. We will also exclude patients with less than 365 days of health care coverage before the COPD index date. Patients with a history of heart failure or ischemic heart disease (*ICD-9-CM*: 410.x to 414.x, 428.x; *ICD-10-CA*: I24.x to I25.x, I50.x) in medical service claims or hospitalization discharge abstracts in the 365 days before or on the acute exacerbation of COPD index date will be excluded because patients with concomitant significant cardiac disease are at higher risk of negative outcomes and are therefore considered to have a complicated disease. We will also exclude those patients with less than 5 days of coverage after the event date. Of note, there is no specific diagnostic code for acute exacerbation of COPD so we will assume that a visit to a health practitioner for COPD represents an exacerbation, especially if accompanied by an antibiotic dispensation. Also, we will document COPD visits at which antibiotics were not dispensed.

Uncomplicated UTI Cohort Exclusion Criteria

For the UTI cohort, we will exclude patients with recurrent UTI based on a diagnosis for UTI in outpatient medical service claims or a diagnosis for UTI in hospital discharge abstracts in the prior 90 days. We will exclude events occurring less than 5 days before the latest date of data available at each site. Patients with less 365 days of health care coverage before the UTI event and less than 5 days of coverage after the event date will be excluded. We will exclude patients with any hospitalization in the 30 days before the UTI event. We will also exclude patients with male or missing sex (because UTIs in males are considered complicated[17]) and with a diagnosis suggesting a complicated UTI in medical service claims or hospitalization discharge abstracts in the 365 days before cohort entry. These diagnoses include structural abnormality of the urinary tract (including stones), ureteral abnormalities, vesicoureteral reflux, neurogenic bladder, neurologic conditions, pregnancy (in the 270 days prior), or severe diabetes (refer to Appendix 1, Table 2).[18] We will also exclude patients with an infection of the kidney or with pyelonephritis in the 90 days prior, a diagnosis of a sexually transmitted infection within 14 days, or an indwelling catheter in the 3 months prior as well as patients in palliative or long-term care (if data are available).

Impact Assessment Analysis

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

Study Variables

Exposures

All dispensations for oral systemic fluoroquinolones will be examined (Anatomical Therapeutic Chemical [ATC] code J01M). Analyses by specific fluoroquinolone molecules will be limited to ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin. All IV (also used for inhalation) and topical fluoroquinolone formulations will be excluded. For objectives 1e and 2 (change in percentage of overall antibiotic use), antibiotic exposure will be determined by the first antibiotic dispensation (oral systemic fluoroquinolone [ATC code J01M] or other oral antibiotic [ATC code J01 excluding J01M]) for the period within 5 days before and 5 days after the index date for the indication.

Outcomes of Interest

Overall Fluoroquinolone Utilization

We will document the yearly number and rate of dispensations per 1,000 population of fluoroquinolones overall (i.e., for all molecules), for the 4 fluoroquinolones of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin combined) and by molecule (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) (objective 1a) as well as 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 will be documented by assigning each dispensation for a fluoroquinolone of interest to a prescriber and identifying the prescriber group or specialty. These categories will be limited by the data available in each provincial database but should include family physician, specialist physician (as many subcategories as possible), and non-physician prescribers (as many subcategories as possible, including nurse practitioners and pharmacists). We will also document the percentage of fluoroquinolone dispensations to long-term care residents in provinces where data are available.

For objective 1d, we will document 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 for a fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin), we will assess the medical service claims and hospital discharge abstracts (plus additional relevant data sources where available) 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 is before or after the dispensation date) *ICD-9* or *ICD-10* code will be assigned to the dispensation. For hospital discharge abstracts, the date of admission or discharge will be the date of the diagnosis, and this determination will be made using additional criteria. Only the primary (i.e., most responsible) diagnosis

will be used for hospital discharge abstracts. In addition, we will document the number and percentage of all dispensations for the 4 fluoroquinolones of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) in which no diagnosis was assigned, overall and by molecule.

For each indication cohort (objective 1e), we will document the annual frequency and percentage of events initially treated with an oral fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin). We will document the percentage of events not treated with an antibiotic and the top 10 most common antibiotic dispensations (based on frequencies) associated with the event. We will also estimate the yearly number and rate of fluoroquinolone dispensations per 1,000 population for each indication.

Impact Assessment Analysis

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

Covariates

Utilization will be stratified by molecule (ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin), age group (18 to 65 years and ≥ 66 years), and sex (females, males) (specific details described subsequently). Results for children (< 18 years) will be included only for objective 1a. Objectives 1b onward will not be completed for those younger than 18 years of age unless utilization among this population is higher than expected.

Data Analysis

Statistical Analysis Plan

Overall Fluoroquinolone Utilization

For objective 1a, we will estimate the yearly (using calendar year) number and rate per 1,000 population (using population estimates from provincial registries) of fluoroquinolone dispensations overall, for the 4 fluoroquinolones of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin combined), and by molecule. Dispensations rates will be estimated by age groups (< 18 years, 18 to 65 years) as well as by sex. Age at the time of prescription will be used.

Duration and daily dosage for each fluoroquinolone dispensation will be calculated using the quantity dispensed, medication strength, and days supply (objective 1b). Duration and daily dose will be 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 will be reported by province for each fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin). Analyses will be stratified by age group (18 to 65 years and ≥ 66 years).

For objective 1c, the yearly (using calendar year) number and percentage of fluoroquinolone dispensations will be reported by prescriber group and province. The percentages of fluoroquinolone dispensations to long-term care residents will be documented in provinces where data are available.

The yearly (calendar year) most frequent (i.e., the top 10 frequencies) indications for fluoroquinolone prescriptions will be documented overall and by molecule (objective 1d). These analyses will be stratified by age group (18 to 65 years and ≥ 66 years) and separately by sex. Results will be reported by province.

For objective 1e, we will document the annual frequency and percentage of events initially treated with a fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin combined) by province, overall and by molecule. This will be estimated by calculating the percentage of fluoroquinolone dispensations among all antibiotic dispensations within a year. We will estimate 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.

Impact Assessment Analysis

To address objective 2, an interrupted time series analysis will be 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 will be used. The first segment will be from January 1, 2008, to December 31, 2016. The second segment will be from January 1, 2017, to February 29, 2020. The third segment will be from March 1, 2020, to December 31, 2022; the post-risk minimization period will be divided into 2 segments to address the potential impact of COVID-19 on fluoroquinolone dispensations. The outcomes that will be modelled are rate of fluoroquinolone dispensations per 1,000 population and percentage of antibiotic dispensations that are an oral fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin).

We will estimate the age- and sex-adjusted rate of fluoroquinolone dispensations per 1,000 population by month for the period between January 1, 2008, and December 31, 2022. To do this, we will count the number of dispensations for an oral fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin) by age group (18 to 29 years and then 10-year age groups [i.e., 30 to 39 years and so on] to ≥ 80), sex, month, and segment. The data will be modelled using a negative binomial distribution, with the natural logarithm of the population as the model offset. The model covariates will be age group, sex, month, and segment; only main effects will be included in the model. We will not stratify by age group and sex, but rather control for these covariates to maximize statistical power to detect an effect of risk minimization measures. To account for the dependence in monthly number of dispensations, generalized estimating equations will be used, assuming a first-order autoregressive structure. The model-based age- and sex-adjusted fluoroquinolone rates (per 1,000 population) by month and segment will be estimated. A second model will also include the main effects for all covariates as well as the 2-way interaction of month and segment. We will also estimate the relative rate for the second and third segments using the first segment as the reference. We will estimate 95% confidence intervals for each relative rate. For each segment, we will estimate the slope (rate of change) and its 95% confidence interval. In addition, we will conduct a sensitivity analysis using a lag period of 6 months after the risk minimization measures (i.e., segment 2 will begin on July 1, 2017) to account for time for implementation of changes.

After this, we will estimate the monthly age- and sex-adjusted percentages of all antibiotic dispensations that are an oral fluoroquinolone of interest (i.e., ciprofloxacin, levofloxacin, moxifloxacin, and norfloxacin)

between January 1, 2008, and December 31, 2022. This analysis will be by principal indication (UTI, acute bacterial sinusitis, acute exacerbation of COPD — using the 3 cohorts created in objective 1e). To do this, we will calculate the percentages by age group (18 to 29 years and then 10-year age groups [i.e., 30 to 39 years and so on] to ≥ 80), sex, month, and segment. For the UTI analysis, the cohort will be limited to females only, so no sex-adjusted analyses will be conducted. For acute exacerbation of COPD, the age groups will be limited to 66 years and older to produce age-adjusted results. The monthly percentages will be modelled using a linear regression model with age group, sex, month, and segment as covariates; only main effects will be included in the model. Generalized estimating equations with a first-order autoregressive structure will be used to account for dependence in the time series data. We will estimate the model-based age- and sex-adjusted percentages by month and segment for each principal indication. A second model will include the main effects for all covariates as well as the 2-way interaction of month and segment. The same estimates will be produced as for the previous analysis.

Meta-Analysis

Results for objective 1 will be presented by province or overall (i.e., aggregated for all provinces) as appropriate. For objective 2, province-specific estimates will be pooled using the Der Simonian and Laird random-effects models.[19] The amount of between-province heterogeneity will be estimated using the I^2 statistic. Province-specific estimates will also be reported.

Data Sources

We will use administrative health databases from the provinces of Alberta, British Columbia, Manitoba, Nova Scotia, Ontario, and Saskatchewan. Briefly, the databases that will be used include prescription drug claims, provider registry files (if applicable), medical service claims, hospitalization records, and provincial health insurance registration files in each province.

Limitations

To our knowledge, this represents the first study to assess the impact of the 2017 Health Canada risk minimization measures on the utilization of fluoroquinolones in Canada. Our results will provide an important update on the utilization patterns and indications for fluoroquinolones since 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 actually prescribed for the indication listed as the diagnosis for the medical visit. In addition, exposure is defined as drug dispensations which may not represent actual consumption. Third, we are unable to document all influences on prescribing rates, such as antibiotic resistance rates, antibiotic stewardship programs, or provincial formulary prescribing criteria, that may have varied over the study period. 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.[20] Fourth, another limitation is the data

availability in each province, with Nova Scotia and Ontario limited to those aged 66 years and older. Finally, our study is limited to 6 Canadian provinces, and findings may not be generalizable to other provinces and territories.

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Appendix 1: Additional Information

Table 2: List of Diagnoses Suggesting a Complicated UTI

Condition	*ICD-9-CM*	*ICD-10-CA*	ATC code
Stones	592.x, 594.x	N20.x, N21.x	NA
Ureteral abnormalities or vesicoureteral reflux	593.x	N13.x, N28.x, R80.x	NA
Neurogenic bladder	344.x, 596.x	N32.x	NA
Neurologic condition	323.x, 336.x, 337.x, 340.x, 341.x, 342.x, 343.x, 344.x, 952.x	G04.x, G05.x, G35.x, G36.x, G37.x, G80.x, G82.x, G83.x, G90.x, G92.x, G95.x, S14.x	NA
Pregnancy	V22.x, V23.x	Z33.x, Z34.x, Z35.x	NA
Severe diabetes	NA	NA	A10A
Infection of the kidney or pyelonephritis	590, 590.1, 590.2, 590.8, 590.9	N10, N12, N15.1, N16	NA
Sexually transmitted disease	090 to 099	A50-A64	NA
Indwelling catheter	*ICD-9-CM* codes: 57.94, V53.6, 996.64, 996.76, 996.31 CCP code: 69.94	*ICD-10-CA* codes: T830.x, Y84.6, Z46.6, Z96.0 CCI code: 1.PM.52.CA-TS	NA

ATC = Anatomical Therapeutic Chemical; CCI = Canadian Classification of Health Interventions; CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; *ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification*; *ICD-10-CA = International Classification of Diseases, Tenth Revision, with Canadian enhancements*; NA = not applicable; UTI = urinary tract infection.

Source: Codes are from Suskind et al. (2016).[18]

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

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CDA-AMC is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

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