CoLab Network

Drug Utilization Study

Outpatient Nirmatrelvir–Ritonavir and Remdesivir Utilization in Canada

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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

We conducted a retrospective cohort study to determine the outpatient utilization of nirmatrelvir-ritonavir and remdesivir in Canada.

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Nirmatrelvir-Ritonavir

We used administrative health databases from the provinces with readily available data at the time of study, including Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan.

Overall, 212,593 adults filled 218,862 nirmatrelvir-ritonavir prescriptions during the study period (which ranged from January 2022 to June 2023).

Monthly nirmatrelvir-ritonavir use per population was highest in Manitoba and Ontario, growing rapidly during its first year of introduction, with lower and more stable use in British Columbia, Quebec, Alberta, and Saskatchewan. The trend changed when expressed per number of COVID-19 cases. Utilization was greater in Manitoba, was moderate and had similar trends in British Columbia and Ontario, and was lower in Alberta, Quebec, and Saskatchewan.

Approximately 70% of nirmatrelvir-ritonavir recipients were aged 65 years and older, and more than 90% received at least 1 dose of a COVID-19 vaccine, although there were important cross-provincial differences in patient characteristics.

Remdesivir

We obtained aggregate data for outpatient remdesivir prescriptions from the Ontario Ministry of Health, the Saskatchewan Health Authority, and the Winnipeg Regional Health Authority. Outpatient remdesivir infusions are not routinely captured in prescription drug claims.

A total of 2,610 outpatient remdesivir prescriptions were recorded from July 2022 to May 2023 in Ontario, 324 from April 2022 to April 2023 in Saskatchewan, and 407 from April 2022 to May 2023 in Winnipeg, Manitoba. Expressed per unit population, trends in monthly remdesivir utilization were similar. In all provinces, monthly use grew rapidly, peaking in early fall 2022 and declining thereafter.

Patient characteristics are unknown, as only aggregate data were readily available.

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Abbreviations

CNODES	Canadian Network for Observational Drug Effect Studies
INESSS	Institut national d'excellence en santé et en services sociaux
PHAC	Public Health Agency of Canada
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2
SD	standard deviation

Background

Throughout the course of the COVID-19 pandemic, several antiviral therapies have been in use in Canada, including nirmatrelvir-ritonavir (Paxlovid) and remdesivir (Veklury).[1] Nirmatrelvir-ritonavir, a combination of 2 oral antivirals, was approved by Health Canada on January 17, 2022.[2] It is indicated for the treatment of adult patients with mild to moderate COVID-19 with a positive severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) test result, and who are at high risk of progressing to severe disease, including hospitalization or death. The recommended dosage is 300 mg nirmatrelvir (two 150 mg tablets) and 100 mg ritonavir to be taken together twice daily for 5 days.[3] A second nirmatrelvir-ritonavir dosage pack became available July 6, 2022, for use in patients with moderate renal impairment (i.e., an estimated glomerular filtration rate of 30 mL/min to 59 mL/min).[4] This package ("renal pack") contains one 150 mg tablet of nirmatrelvir and one 100 mg tablet of ritonavir to be taken together twice daily for 5 days.

Who may prescribe nirmatrelvir-ritonavir varies by province. In Ontario, in addition to licensed physicians and nurse practitioners, licensed Part A pharmacists were granted authority to prescribe nirmatrelvir-ritonavir under specific conditions, effective December 8, 2022 (refer to Appendix 3).[5] Alberta pharmacists began prescribing nirmatrelvir-ritonavir on May 4, 2022,[6] Saskatchewan pharmacists on May 19, 2022,[7] and Quebec pharmacists on April 1, 2022.[8]

Remdesivir was approved by Health Canada on July 27, 2020.[9] It is administered by IV infusion and is indicated for the treatment of COVID-19 disease in adults and adolescents (aged 12 years and older, weighing at least 40 kg) who are hospitalized with pneumonia and require oxygen supplementation. On April 22, 2022, it was approved for the treatment of adults with a positive SARS-CoV-2 test who are not hospitalized but are at high risk of progressing to severe disease, including hospitalization or death.[10]

Purpose of This Report

The Public Health Agency of Canada (PHAC) is currently responsible for the procurement and allocation of nirmatrelvir-ritonavir and remdesivir to federal, provincial, and territorial health care systems. Information on the outpatient utilization of these therapies is needed to inform PHAC on options for procurement, allocation, and distribution of these drugs across the country. The purpose of this report is to describe the use of nirmatrelvir-ritonavir and remdesivir in the outpatient setting across Canadian provinces for which data were readily available, and to describe the characteristics of patients receiving these therapies.

Rationale
PHAC currently sources and distributes nirmatrelvir-ritonavir and remdesivir to the provinces and territories. Gathering postmarket evidence on their outpatient use is important to help determine fair access in the future.

Policy Issue

PHAC wishes to gather postmarket drug information and evidence to explore options for procurement, allocation, and equitable distribution of nirmatrelvir-ritonavir and remdesivir to facilitate future discussions regarding access to these drugs across Canada.

Policy and Research Questions

1. What is the outpatient utilization of nirmatrelvir-ritonavir (Paxlovid) and remdesivir (Veklury) in Canada?
2. What are the characteristics of patients receiving these therapies?

Methods

Data Sources

Nirmatrelvir-Ritonavir

This study was conducted by the Canadian Network for Observational Drug Effect Studies (CNODES).[11] At the request of PHAC, we conducted a retrospective cohort study using administrative health databases from the provinces of Alberta, British Columbia, Manitoba, Ontario, Quebec, and Saskatchewan, the provinces for which data were readily available at the time of the request. The list of databases used in each province appears in Appendix 1, Table 1. The data include population-based prescription drug claims, physician service claims, hospitalization records, emergency department records, COVID-19 vaccination registries, and the provincial health insurance registry in each province.

Data Sources
For nirmatrelvir-ritonavir, we conducted a retrospective cohort study using administrative health databases from 6 provinces. For remdesivir, we obtained aggregate prescription data from 3 provinces.

Remdesivir

As outpatient remdesivir infusions are not routinely captured in prescription drug claims, we obtained aggregate data for outpatient remdesivir prescriptions from the Ontario Ministry of Health for the province of Ontario, the Saskatchewan Health Authority for the province of Saskatchewan, and the Winnipeg Regional Health Authority for the greater Winnipeg area. For reference, we also obtained data on **inpatient** dispensing of remdesivir to patients in the Winnipeg Regional Health Authority. Data on remdesivir utilization were not readily available for Alberta, British Columbia, or Quebec.

Study Population

Nirmatrelvir-Ritonavir

The study period spanned from January 17, 2017, to the latest date data were available in each province. Study patients were those aged 18 years or older who were dispensed nirmatrelvir-ritonavir with a valid provincial health insurance number between January 17, 2022

(the date of Health Canada approval), and the latest date available in each province. For each patient, the date of the first dispensing of nirmatrelvir-ritonavir served as the cohort entry date, although all claims for each patient were included. We did not confirm each patient's COVID-19 diagnosis, as rapid antigen test results were not routinely recorded, and access to laboratory polymerase chain reaction testing was limited to high-risk groups during the study period. We selected January 17, 2017, as the beginning of the observation period to allow for sufficient lookback for chronic disease detection, particularly as hospital records were incomplete for the 2022–2023 fiscal year. The study accrual period for each province is presented in Appendix 1, Table 2.

Remdesivir

Province-level aggregate data on outpatient remdesivir prescriptions spanned July 1, 2022, through May 31, 2023, in Ontario and April 1, 2022, to April 30, 2023, in Saskatchewan. Aggregate data on outpatient remdesivir prescriptions in Winnipeg, Manitoba, spanned April 1, 2022, to May 31, 2023. As these were aggregate data, no additional information regarding patient characteristics was readily available.

Exposure

Nirmatrelvir-Ritonavir

Exposure to nirmatrelvir-ritonavir was defined as an outpatient prescription drug claim for nirmatrelvir-ritonavir. Appendix 1, Table 3 provides the drug identification numbers we used to identify nirmatrelvir-ritonavir.

Remdesivir

Exposure to remdesivir was based on aggregate data collected and provided by the Ontario Ministry of Health, the Saskatchewan Health Authority, and the Winnipeg Regional Health Authority.

Outcome Measures

Nirmatrelvir-Ritonavir

At the request of PHAC, the outcomes for nirmatrelvir-ritonavir included the number of dispensations (claims), patients, and cost per claim (available in Ontario), and the demographic and clinical characteristics of patients receiving nirmatrelvir-ritonavir. The cost per claim was defined as the total paid by the Ontario Ministry of Health.

Remdesivir

The measure for remdesivir was monthly outpatient prescriptions at the provincial level in Ontario and Saskatchewan, and at the Regional Health Authority level for Winnipeg, Manitoba.

Outcomes of Interest
For nirmatrelvir-ritonavir, we studied monthly outpatient prescriptions and patient demographic and clinical characteristics. For remdesivir, we studied monthly outpatient prescriptions at the provincial level in Ontario and Saskatchewan, and for the greater Winnipeg area in Manitoba.

Patient Characteristics

Nirmatrelvir-Ritonavir

Several patient characteristics were assessed at cohort entry: age, sex, long-term care status (where available), income quintile (based on the Pampalon material index in Alberta,[12] self-reports to BC PharmaCare, the material vulnerability index in Quebec, and the Statistics Canada Census for Manitoba, Ontario, and Saskatchewan), comorbidities, medication use, COVID-19 vaccination status (where available), and health service use. As a general measure of comorbidity, we used the Deyo-Charlson Comorbidity Index[13,14] derived from hospitalization records in the 5 years preceding cohort entry. This is a weighted index originally developed to predict mortality that takes into account the number and seriousness of the comorbid diseases coded on hospital discharge abstracts.
We also identified several chronic disease comorbidities using diagnosis codes on hospitalization records and physician services claims in the 5 years preceding cohort entry: cancer, cardiovascular disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, and diabetes (Appendix 1, Table 4).
In addition, we identified patients who were immunocompromised based on Ontario criteria[15] using hospitalization records, emergency

department records, physician service claims, and prescription drug claims. The definition is a composite that includes history of solid organ transplant, history of allogenic or autologous bone marrow transplant, disorders of the immune system (sickle cell anemia, immune system disorders, HIV, and other immunodeficiency conditions), and autoimmune diseases (rheumatoid arthritis, inflammatory bowel disease, psoriasis or psoriatic arthritis, multiple sclerosis, and systemic autoimmune rheumatoid arthritis) (Appendix 2). We identified claims for several categories of prescription medication in the year preceding entry: antihypertensives, lipid-lowering drugs, antidiabetic drugs, systemic corticosteroids, and nonsteroidal anti-inflammatory drugs (Appendix 1, Table 5). We described patients' COVID-19 vaccination status using each province's COVID-19 vaccination registry (where available), number of outpatient physician visits, and number of hospitalizations in the year preceding cohort entry.

Remdesivir

As only aggregate data were readily available, it was not possible to describe the characteristics of patients receiving remdesivir.

Data Analysis

Nirmatrelvir-Ritonavir

We summarized the characteristics of patients dispensed nirmatrelvir-ritonavir by province, using descriptive statistics. Continuous variables were described as mean (standard deviation [SD]) or median (interquartile range) and number (percentages) for categorical variables.

We reported the monthly number of claims for nirmatrelvir-ritonavir by province, overall, and by dosage form expressed both per 100,000 population (using population estimates from Statistics Canada)[16] and per 100 cases of COVID-19 (using monthly case counts reported by the provinces to the Government of Canada).[17] We documented the distribution of patients by number of exposures during the study period. Finally, we tabulated overall use according to

dosage form, age (18 to 64 years, ≥ 65 years), sex, income quintile, immunocompromised status, and Deyo-Charlson Comorbidity Index score (0, 1, and ≥ 2).

Remdesivir

For Ontario and Saskatchewan, we reported the total number of outpatient remdesivir prescriptions by province and monthly prescriptions by province expressed per 1,000,000 population (using population estimates from Statistics Canada)[16] and per 10,000 cases of COVID-19 (using monthly case counts reported by the provinces to the Government of Canada).[17] We reported the total number of outpatient remdesivir prescriptions in Winnipeg, Manitoba, and monthly prescriptions per 1,000,000 population (using the population estimate for the Winnipeg Regional Health Authority from Statistics Canada).[18]

Findings

Nirmatrelvir-Ritonavir

Overall, 218,862 claims for nirmatrelvir-ritonavir were dispensed to 212,593 adults during the study period. This corresponds to 12,484 claims among 12,074 patients in Alberta from January 2022 to March 2023; 25,907 claims among 24,728 patients in British Columbia from January 2022 to May 2023; 11,431 claims among 11,165 patients from January 2022 to March 2023 in Manitoba; 138,337 claims among 135,238 patients from April 2022 to March 2023 in Ontario; 29,158 claims among 27,892 patients from March 2022 to June 2023 in Quebec; and 1,545 claims among 1,496 patients from January 2022 to December 2022 in Saskatchewan.

Appendix 3, Figure 1 plots the monthly claims for nirmatrelvir-ritonavir by province per 100,000 population, Figure 2 by province and dosage form, and Figure 3 per 100 COVID-19 cases. Expressed per unit population, monthly utilization was greatest in Manitoba

Nirmatrelvir-Ritonavir Use
During the study period, 212,593 adults filled 218,862 nirmatrelvir-ritonavir prescriptions. More than 90% received only 1 course of treatment, and less than 10% were dispensed the recommended lower dosage for renal impairment.

Use Patterns
Monthly nirmatrelvir-ritonavir use per population was highest in Manitoba and Ontario, with rapid growth in the first year, and lower and more stable use in other provinces. The trend changed when expressed by the number of COVID-19 cases.

and Ontario and grew rapidly over the study period. In Manitoba, utilization peaked at more than 150 claims per 100,000 in October 2022 and declined to about 80 claims per 100,000 in March 2023. In Ontario, utilization reached approximately 40 claims per 100,000 in June 2022, grew to more than 120 claims per 100,000 in January 2023 and declined to about 80 claims per 100,000 in March 2023. Pharmacists were granted authority to prescribe nirmatrelvir-ritonavir in April 2022 in Quebec, May 2022 in Alberta and Saskatchewan, and December 2022 in Ontario (Appendix 3, Figure 1).
In British Columbia, utilization peaked in May 2022 at approximately 40 claims per 100,000 and remained relatively stable over the study period, declining to about 30 claims per 100,000 by the end of the study. Utilization in Quebec peaked in April 2022 at just more than 50 claims per 100,000, then remained relatively stable, and declined from about 20 to 5 claims per 100,000 from January 2023 to June 2023. Nirmatrelvir-ritonavir utilization was lower in Alberta and Saskatchewan and remained relatively stable at around 15 to 30 claims and 10 to 20 claims per month per 100,000 through March 2023 and December 2022, respectively.

Appendix 3, Figure 2 stratifies nirmatrelvir-ritonavir utilization by dosage form as of July 2022, when the renal pack became available in Canada. As anticipated, in all 6 provinces, the original dosage pack remained dominant, with the renal pack dispensed less frequently in Alberta, Manitoba, Quebec, and Saskatchewan, where it represented 6.8%, 5.8%, 5.3%, and 3.4% of dispensations, respectively, versus 9.3% and 9.9% in British Columbia and Ontario.

When expressed per number of COVID-19 cases (Appendix 3, Figure 3), the pattern of nirmatrelvir-ritonavir utilization differed from that expressed per capita (Appendix 3, Figure 1), with utilization in British Columbia exceeding that in Ontario and growing more rapidly over the study period. However, utilization per cases remained greater and rose more rapidly in Manitoba (Appendix 3, Figure 3).
In Alberta, Saskatchewan, and Quebec, utilization per cases was lower throughout the study period.

Appendix 3, Table 8 describes the characteristics of nirmatrelvir-ritonavir recipients at the time of first dispensing by province. The mean age of patients ranged from 59.4 years (SD = 16.9) in Saskatchewan to 70.0 years (SD = 15.6) in Ontario. Nirmatrelvir-ritonavir was more frequently dispensed to those aged 65 years and older in all provinces (from 51.6% in Manitoba to 71.0% in Ontario) except in Saskatchewan (43.7%). In all provinces, recipients were more likely to be female, who comprised more than 57% of recipients overall and 60% in Alberta and Saskatchewan. The comorbidity profile of patients varied considerably by province. Whereas 10.5% of Ontarians, 12% of Manitobans, and 14.2% of Albertans had a Deyo-Charlson Comorbidity Index score greater than or equal to 2, this was the case for 23.2%, 27.4%, and 36.1% of patients in British Columbia, Quebec, and Saskatchewan, respectively. The prevalence of specific comorbidities also varied, ranging from 20.3% (Saskatchewan) to 33.1% (British Columbia) for cardiovascular disease, and from 18.5% (Ontario) to 57.2% (British Columbia) for those who were immunocompromised. Prior use of systemic corticosteroids ranged from 11.2% in Ontario and 15.0% in Manitoba to about 30% in British Columbia and Saskatchewan, although other medications more commonly used in older patients, such as antihypertensives, lipid-lowering drugs, and antidiabetic drugs, were more similarly used across provinces. This is consistent with the fact that, whereas comprehensive drug claim data are available for patients younger than 65 years in Alberta, British Columbia, Manitoba, and Saskatchewan, all provinces have such data for patients aged 65 years and older. Nineteen percent and 12.6% of those receiving nirmatrelvir-ritonavir were unvaccinated (i.e., received no COVID-19 vaccine doses) in Alberta and British Columbia versus 3.7% in Ontario, 4.1% in Manitoba, and 7.2% in Quebec. COVID-19 vaccination status data were not available for Saskatchewan.

Appendix 3, Table 9 reports the distribution of patients by number of nirmatrelvir-ritonavir claims. More than 8% of patients in British Columbia and 4.0% of patients in Quebec received more than 1 course of nirmatrelvir-ritonavir versus approximately 2% to 3% in the other study provinces.

Patient Characteristics
Approximately 70% of nirmatrelvir-ritonavir recipients were 65 years or older, and well over 90% were vaccinated for COVID-19, although there were important cross-provincial differences in patient characteristics.

Appendix 3, Table 10 describes the distribution of Ontario Ministry of Health payments for nirmatrelvir-ritonavir. Eleven percent of claims contained a total paid value of zero. Among the remainder, the mean and median payments were $13.10 and $13.25, respectively. The approved dispensing fee for nirmatrelvir-ritonavir in Ontario is $13.25.[5] This compares with up to $12.15 in Alberta,[19] $10 in British Columbia,[20] $15 or the pharmacy's Usual and Customary Fee, whichever is lower, in Manitoba,21 $10.61 ($10.38 between April 1, 2022, and March 31, 2023) in Quebec,22 and $20 in Saskatchewan.[7]

Appendix 3, Table 11 reports the total number of nirmatrelvir-ritonavir recipients by province and dosage form according to age category, sex, income quintile, immunocompromised status, and Deyo-Charlson Comorbidity Index. As anticipated, in all 6 provinces, the renal dosage pack was more frequently dispensed to patients aged 65 years and older and those with a Deyo-Charlson Comorbidity Index score greater than or equal to 2. There was no meaningful difference in the distribution according to sex, income quintile, or immunocompromised status.

Remdesivir

A total of 2,610 outpatient remdesivir prescriptions were recorded from July 2022 to May 2023 in Ontario, 324 from April 2022 to April 2023 in Saskatchewan, and 407 from April 2022 to May 2023 in greater Winnipeg, Manitoba. Importantly, over the same time period, 1,763 remdesivir prescriptions were dispensed to Winnipeg **inpatients**. Thus, utilization by outpatients represented just 20% of overall remdesivir use in Winnipeg.

Monthly prescriptions expressed per 1,000,000 population are plotted in Figure 4. In general, trends in remdesivir utilization were roughly similar in Ontario, Saskatchewan, and in Winnipeg, Manitoba. In Ontario, utilization grew rapidly from July 2022 to October 2022, peaking at around 37 prescriptions per 1,000,000, dropping precipitously in November 2022 to 19.5 prescriptions per 1,000,000, and then declined gradually thereafter, closing the study period with just 0.5 prescriptions per 1,000,000 in May 2023.

Remdesivir Use
A total of 2,610 outpatient remdesivir prescriptions were recorded from July 2022 to May 2023 in Ontario, 324 from April 2022 to April 2023 in Saskatchewan, and 407 from April 2022 to May 2023 in Winnipeg, Manitoba.

Use Patterns
Expressed per unit population, trends in monthly remdesivir utilization were similar. In all provinces, monthly use grew rapidly, peaking in early fall 2022, and then declining thereafter.

In Saskatchewan, utilization increased from 10 to approximately 40 prescriptions per 1,000,000 between April 2022 and October 2022 and, with the exception of an uptick in March 2023, declined to about 5 prescriptions per 1,000,000 by April 2023. In Winnipeg, utilization was highest in April and May 2022 at about 115 to 120 prescriptions per 1,000,000, falling to 20 to 40 prescriptions per 1,000,000 between June 2022 and November 2022 and, with the exception of an increase in February and March 2023, declined to about 4 prescriptions per 1,000,000 by May 2023. When expressed per number of COVID-19 cases (Figure 5), monthly remdesivir utilization was relatively greater over the study period in Saskatchewan, peaking in March 2023 at more than 350 prescriptions per 10,000 cases. Utilization was generally lower and more stable in Ontario, sitting at 100 to 150 prescriptions per month per 10,000 cases from September 2022 to March 2023.

Strengths and Limitations

To our knowledge, this is the first population-based analysis of nirmatrelvir-ritonavir and remdesivir utilization in Canada, and it is among few Canadian studies that describe patients receiving nirmatrelvir-ritonavir.[23,24] However, the study had important limitations. First, as rapid antigen test results are not routinely captured in provincial registries, and access to polymerase chain reaction testing was limited during the study period, it was not possible to confirm that patients receiving nirmatrelvir-ritonavir were SARS-CoV-2 positive. Although we cannot know whether patients met nirmatrelvir-ritonavir prescribing criteria, we believe it is unlikely that many patients were dispensed nirmatrelvir-ritonavir without evidence of a positive COVID-19 test. For example, to prescribe nirmatrelvir-ritonavir in Ontario, pharmacists must confirm and document both the date of the patient's positive COVID-19 test and the date of symptom onset.[5] Second, the provincial COVID-19 case counts we used to standardize monthly nirmatrelvir-ritonavir and remdesivir utilization estimates are likely to heavily underestimate the actual number of COVID-19 cases in the community, given the widespread use of rapid antigen tests that go unreported.

Limitations
Our study included data from 6 Canadian provinces. The findings may not be generalizable to other jurisdictions.

Related, the potential for differential case detection and reporting by province may have introduced bias in utilization per case comparisons. Third, there is potential for misclassification of nirmatrelvir-ritonavir use by patients with renal impairment. Some patients with renal impairment will have been dispensed the standard dosage pack before introduction of the renal dosage pack, and possibly afterward, due to limitations of drug supply.[5,6] The extent to which supply issues contributed to interprovincial variation in renal pack utilization (and misclassification) is unknown. Fourth, as in any study of prescription drug claims, some percentage of dispensations will go unused. This is a particularly important consideration in drug outcome studies, but less so here, where we are mainly concerned with drug supply. Fifth, due to lags in availability of hospital discharge records, patient characteristics based upon hospital discharge diagnoses were incomplete, particularly for patients entering the cohort later, and this varied by province. As such, more recently accrued patients would be at greater risk for incomplete comorbidity profiles, and this may have contributed to interprovincial variation in patient characteristics. Sixth, because prescription drug claim data for medications other than nirmatrelvir-ritonavir were available only for those aged 65 years old and older or receiving social assistance in Ontario, and those without private drug insurance in Quebec, this may have contributed to underestimation of concurrent drug use and immunocompromised status in patients living in Ontario and Quebec relative to patients in the other study provinces. Seventh, data for outpatient use of remdesivir were only available for Ontario, Saskatchewan, and Winnipeg, Manitoba, and these data were only available in aggregate form. Because person-level data were not available, it was not possible to describe remdesivir recipients. This would require access to patient-level data and additional time to negotiate data-sharing agreements and import and link the records — time that was not available to us for this study. Finally, our study was limited to the Canadian provinces for which data were readily available at the time of the study request and may not generalize to others.

Discussion

We observed rapidly rising utilization of nirmatrelvir-ritonavir during its first year of introduction in Manitoba (from approximatively 20 claims per 100,000 population to more than 150 claims per 100,000 in October 2022) and Ontario (from approximately 40 claims per 100,000 population in June 2022 to more than 120 claims per 100,000 in January 2023). A lower and more stable use per unit population was observed in British Columbia, Quebec, Alberta, and Saskatchewan (ranging from 30 to 40 claims, 20 to 40 claims, 15 to 30 claims, and 10 to 20 claims per 100,000, respectively, over the study period). Expressed per monthly cases of COVID-19, nirmatrelvir-ritonavir utilization was greater and grew more rapidly in Manitoba, was moderate and had similar trends in British Columbia and Ontario, and was lower across the study period in the remaining provinces. In all provinces, more than 90% of patients received only 1 course of outpatient therapy, and fewer than 10% were dispensed the lower dosage form for patients with renal impairment.

Overall, approximately 70% of nirmatrelvir-ritonavir recipients were aged 65 years or older, and more than 90% were vaccinated against COVID-19, although we did observe important cross-provincial differences in patient characteristics. For example, whereas 10.5% of patients in Ontario, 12.0% of patients in Manitoba, and 14.2% of patients in Alberta had a Deyo-Charlson Comorbidity Index score of 2 or greater, this was the case for 23.2%, 27.4%, and 36.1% of patients in British Columbia, Quebec, and Saskatchewan, respectively. The prevalence of specific comorbidities, such as immunocompromised status, was also considerably lower in Manitoba and Ontario than in the 4 other study provinces. These differences may be partially due to interprovincial variation in vaccine coverage and the clinical criteria for nirmatrelvir-ritonavir therapy (Appendix 4). For example, in Manitoba and Ontario, those aged 60 years or older who present with a COVID-19 diagnosis within 5 days of symptom onset are eligible to receive nirmatrelvir-ritonavir, regardless of vaccination status or other factors. In Alberta, Quebec, and Saskatchewan such patients must be at least undervaccinated

(i.e., fewer than 2 doses, or 3 in Alberta, of a 2-dose vaccine or 1 dose of a single-dose vaccine). In addition, these criteria have changed over time. For example, in Quebec, eligibility was extended in December 2022 to all adults with a complete primary vaccination course who are perceived to be at high risk of complications from COVID-19. That pharmacists are authorized to prescribe nirmatrelvir-ritonavir in Alberta, Ontario, Quebec, and Saskatchewan also may have contributed something to the interprovincial variation in utilization, although this authority came early in Quebec, Alberta, and Saskatchewan, and utilization there remained relatively low throughout the study period. Another potential factor could be product supply, particularly where the renal dosage pack is concerned (Appendix 4). The patient characteristics we observed were similar to those reported in 2 recent studies of nirmatrelvir-ritonavir effectiveness from Ontario and Quebec, although their study entry criteria and accrual periods meant far fewer patients were ultimately included in these studies than in ours, which was population-based and inclusive of all patients dispensed nirmatrelvir-ritonavir.[23,24] Another study from British Columbia examined effectiveness among individuals with different risks of complications from COVID-19.[25] As expected, because the ingredient costs were covered by the federal government, the median payment per claim in Ontario was $13.25, equivalent to the approved dispensing fee for nirmatrelvir-ritonavir. By comparison, the dispensing fees are $12.15 in Alberta, $10 in British Columbia, $15 in Manitoba, $10.61 in Quebec, and $20 in Saskatchewan. Pharmacist nirmatrelvir-ritonavir consulting fees were not included in our cost assessment.

In general, trends in monthly remdesivir utilization were roughly similar in Ontario, Saskatchewan, and Winnipeg, Manitoba, and remdesivir was used less frequently than nirmatrelvir-ritonavir, which was anticipated based on the clinical criteria for use of the 2 drugs (Appendix 4, Table 12). Importantly, utilization by outpatients in Winnipeg represented just 20% of overall remdesivir use in Winnipeg. We are not aware of other data on the utilization of remdesivir in inpatients with COVID-19 versus outpatients in Canada.

Data on remdesivir utilization were not readily available for Alberta, British Columbia, or Quebec. Also, because person-level data were not readily available, it was not possible to characterize patients who received remdesivir. More detailed studies of patients taking remdesivir and related outcomes will require access to patient-level exposure data that will permit linkage to other readily available health administrative data sources.

We are aware of observational studies of the safety and effectiveness of outpatient remdesivir and nirmatrelvir-ritonavir, but no population-based studies of drug utilization per se.

Conclusion

Nirmatrelvir-ritonavir utilization in British Columbia, Quebec, and Saskatchewan increased through the first 4 to 5 months of the study period, while that for Alberta continued to increase gradually to October 2022. Utilization for these 4 provinces declined thereafter. For Ontario and Quebec, utilization grew rapidly, peaking toward the end of the first year at multiple times the utilization of the other provinces. As a fraction of COVID-19 cases, utilization increased consistently over the study period in all provinces. While it is difficult to elucidate trend drivers from these data, declining utilization per population and increasing utilization per case may suggest a declining population with identified clinically relevant disease, and therefore, by the start of 2023, subsiding demand. Differences in patient characteristics were observed across the provinces, most likely because of local variation in vaccine coverage and nirmatrelvir-ritonavir access criteria and prescribing policies.

Outpatient remdesivir in the provinces for which utilization data were available was low overall, though markedly higher in Manitoba at the beginning of the study period. Similar to nirmatrelvir-ritonavir, utilization gradually decreased from October 2022, also suggesting declining demand in this patient setting.

References

1. COVID-19 treatments. Ottawa (ON): Health Canada; 2022: https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugs-vaccines-treatments/treatments.html. Accessed 2023 May 4.
2. Paxlovid. Ottawa (ON): Health Canada; 2023: https://covid-vaccine.canada.ca/paxlovid/product-details. Accessed 2023 May 4.
3. Paxlovid (nirmatrelvir/ritonavir): 300 mg nirmatrelvir (two 150 mg tablets) and 100 mg ritonavir tablets [product monograph]. Kirkland (QC): Pfizer Canada; 2024 Jan 02. https://covid-vaccine.canada.ca/info/pdf/paxlovid-pm-en.pdf. Accessed 2024 Mar 12.
4. Health professional risk communication: Paxlovid (nirmatrelvir and ritonavir) - dosing and dispensing in renal impairment, risk of serious adverse reactions due to drug interactions, and English-only labels. *(Recalls and safety alerts)*. Ottawa (ON): Health Canada; 2022: https://recalls-rappels.canada.ca/en/alert-recall/paxlovid-nirmatrelvir-and-ritonavir-dosing-and-dispensing-renal-impairment-risk. Accessed 2023 Jun 5.
5. Executive Officer notice: prescribing & dispensing publicly funded Paxlovid™ in Ontario pharmacies. Toronto (ON): Ontario Ministry of Health; 2022: https://files.ontario.ca/moh-executive-officer-notice-en-2023-04-21.pdf. Accessed 2023 Jun 14.
6. Government of Alberta. Expanding Paxlovid accessibility; 2022: https://www.alberta.ca/release.cfm?xID=82493A9DBDEEC-B852-AA3F-6EFADF340E2ADA0A. Accessed 2023 Oct 31.
7. Paxlovid (nirmatrelvir and ritonavir) distribution, prescribing and assessment: pharmacy process and billing instructions. Regina (SK): Saskatchewan Ministry of Health; 2022: https://formulary.drugplan.ehealthsask.ca/PDFs/Updated%20Paxlovid%20Distribution%20Prescribing%20and%20Assessment%20Phase%202%20-%20Pharmacy%20Process%20and%20Billing%20Instructions.pdf. Accessed 2023 Jun 14.
8. Pandémie de la COVID-19 - les pharmaciens peuvent dorénavant prescrire l'antiviral PaxlovidMC [news release]. Québec (QC): Ministère de la Santé et des Services sociaux; 2022: https://www.msss.gouv.qc.ca/ministere/salle-de-presse/communique-3513/. Accessed 2023 Jun 23.
9. Details for: Veklury. Ottawa (ON): Health Canada; 2022: https://covid-vaccine.canada.ca/info/veklury-en.html. Accessed 2023 May 9.
10. Regulatory decision summary for Veklury. Ottawa (ON): Health Canada; 2022: https://covid-vaccine.canada.ca/info/regulatory-decision-summary-detail.html?linkID=RDS00942. Accessed 2023 Jun 29.
11. Suissa S, Henry D, Caetano P, et al. CNODES: the Canadian Network for Observational Drug Effect Studies. *Open Med*. 2012;6(4):e134-140.
12. Pampalon R, Hamel D, Gamache P, Raymond G. A deprivation index for health planning in Canada. *Chronic Dis Can*. 2009;29(4):178-191.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.
14. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.
15. Ontario regulation 560/22: controlled acts filed December 9, 2022 under Regulated Health Professions Act, 1991, S.O. 1991, c. 18. Toronto (ON): Government of Ontario; 2022: https://www.ontario.ca/laws/regulation/r22560. Accessed 2023 Jun 29.

16. Table 17-10-0009-01: population estimates, quarterly. Ottawa (ON): Statistics Canada; 2023: https://doi.org/10.25318/1710000901-eng. Accessed 2023 Jun 22.

17. COVID-19 epidemiology update: summary. Ottawa (ON): Government of Canada; 2023: https://health-infobase.canada.ca/covid-19/#a5. Accessed 2023 Jun 26.

18. 2021 Census of Population geographic summary: Winnipeg Regional Health Authority [health region], Manitoba. Ottawa (ON): Statistics Canada; 2023: https://www12.statcan.gc.ca/census-recensement/2021/search-recherche/productresults-resultatsproduits-eng.cfm?Lang=E&GEOCODE=2022A00074601. Accessed 2024 Feb 2.

19. A reference guide: PaxlovidTM dispensing. Edmonton (AB): Alberta Blue Cross; 2022: https://www.ab.bluecross.ca/pdfs/paxlovid-reference-guide.pdf. Accessed 2023 Oct 31.

20. Paxlovid: a guide for B.C. pharmacists. Victoria (BC): Government of British Columbia; 2023: https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/pharmacies/monitoring-paxlovid-ade. Accessed 2023 Jun 29.

21. Claims submission procedure – COVID-19 oral antiviral drugs Winnipeg (MB): Manitoba Health, Seniors and Long-Term Care; 2022: https://www.gov.mb.ca/health/pharmacare/profdocs/csp_cod.pdf. Accessed 2023 Aug 30.

22. Tarifs établis dans l'Annexe III de l'Entente 2022-2025. Québec (QC): Régie de l'assurance maladie; 2022: https://www.ramq.gouv.qc.ca/SiteCollectionDocuments/professionnels/manuels/260-pharmaciens/historique/tableau_tarifs.pdf. Accessed 2023 Aug 30.

23. Schwartz KL, Wang J, Tadrous M, et al. Population-based evaluation of the effectiveness of nirmatrelvir-ritonavir for reducing hospital admissions and mortality from COVID-19. *CMAJ*. 2023;195(6):E220-E226.

24. Kabore JL, Laffont B, Diop M, et al. Real-world effectiveness of nirmatrelvir/ritonavir on coronavirus disease 2019-associated hospitalization prevention: a population-based cohort study in the province of Quebec, Canada. *Clin Infect Dis*. 2023;77(6):805-815.

25. Dormuth CR, Kim JD, Fisher A, Piszczek J, Kuo IF. Nirmatrelvir-ritonavir and COVID-19 mortality and hospitalization among patients with vulnerability to COVID-19 complications. *JAMA Netw Open*. 2023;6(10):e2336678.

Authors

CNODES disclaimer: The opinions, results, and conclusions contained in this report are those of the authors. No endorsement by the Public Health Agency of Canada, CADTH, the participating provincial governments and data stewards, the participating research centres, Statistics Canada, or the Canadian Institute for Health Information (CIHI) is intended or should be inferred.

Clinical Review

Michael Paterson, the project lead and Ontario site investigator, drafted the scientific protocol and statistical analysis plan; oversaw submission and approval of data access in Ontario; reviewed the Ontario results prior to reporting; drafted, reviewed, and approved the final draft of the report; and responded to and incorporated input from reviewers.

Colin Dormuth, the British Columbia site investigator and analyst, reviewed the scientific protocol, particularly with respect to the British Columbia context; oversaw submission and approval of data access and ethics approval at the British Columbia site, conducted analyses and review of results prior to submitting; and reviewed and approved the final draft of the report.

Donica Janzen, the Saskatchewan site investigator, reviewed and provided feedback on the scientific protocol, particularly with respect to the Saskatchewan context; oversaw submission and approval of data access and ethics approval at the Saskatchewan site; supervised the Saskatchewan site analyst and conducted the code check; reviewed results prior to submitting; and reviewed and approved the final draft of the report.

Alan Katz, the Manitoba site investigator, provided substantial contributions to conception and design, acquisition of data, and analysis and interpretation of the study results; and contributed to drafting and revising the report.

Paul Ronksley, the Alberta site investigator, reviewed and provided feedback on the scientific protocol, particularly with respect to the Alberta context; oversaw submission and approval of data access and ethics approval at the Alberta site; supervised the Alberta site analyses and review of results before submitting; and reviewed and approved the final draft of the report.

Sylvia Aponte-Hao, an analyst from Aberta Drug and Technology Evaluation Consortium (ADTEC), extracted data and performed data linkage for all of the Alberta data. Sylvia performed all statistical analysis for the Alberta results, including the completion of the required tables, and reviewed the final report and provided appropriate comments where needed.

Matt Dahl, as the Manitoba site analyst, provided running of the analysis for the Manitoba site, reviewed and provided any feedback on analysis plan, reviewed final report for accuracy.

Tayler Dawn-Scory, the Alberta site analyst, supervised the Alberta site analyses and conducted quality checks and review of the results before submitting; as well as reviewed the final draft of the report.

Houssem Missaoui, an analyst from the Institut national d'excellence en santé et en services sociaux (INESSS), extracted and analyzed data related to the prescription of nirmatrelvir-ritonavir by applying the protocol detailed by CADTH to complete the report for the Quebec province portion. Houssem reviewed the report and requested clarification as needed.

Xinya Lu, the Saskatchwan site analyst, conducted the analysis work and reviewed the report.

Jean-Luc Kaboré, an analyst from INESSS, participated in the data analysis for Quebec and in the revising of the report.

Mike Benegiri, the Quebec site investigator, provided project coordination for Quebec at INESSS.

Audray St-Jean, the research assistant, contributed to conception and design, interpretation of study results, and drafting and revising the report.

Ruby Sheng, the Ontario site analyst, conducted preparation and in-depth analysis of the Ontario cohort, generated essential study results following predefined data templates, and undertook revision and provided feedback for the Ontario section of the report.

Fangyun Wu, the Ontario site analyst, supervised data analysis and reviewed the report.

Contributors

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Database (Hospital Separations); BC MOH (2021): Consolidation File (MSP Registration & Premium Billing); BC MOH (2021): Provincial Immunization Registry; and BC MOH (2021): Provincial Laboratory Information Solution. You can find further information regarding these data sets by visiting the PopData project webpage.

Parts of this material are based on data and/or information compiled and provided by the provincial ministries of health, Statistics Canada, and CIHI. This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta/Alberta Health nor Alberta Health Services express any opinion in relation to this study. The CNODES team is comprised of many researchers who have provided significant support to the project led by the CNODES steering committee.

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Conflicts of Interest

Donica Janzen disclosed the following:

Travel funding or payment

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Michael Paterson disclosed the following:

Employee of the Institute for Clinical Evaluative Sciences (ICES), funded by the Ontario Ministry of Health.

No other conflicts of interest were declared.

For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH 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 CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.

Appendix 1: Additional Information on Methods

Note that this appendix has not been copy-edited.

Table 1

List of Databases Used in Each Province

Site	Databases					
	Prescription drug claims (and dispensing captured)	Physician service claims	Hospital records	Emergency department records	COVID-19 vaccination	Health insurance registry
Alberta	Pharmaceutical Information Network (all)	Practitioner Claims	CIHI Discharge Abstract Database	NACRS	Immunization and Adverse Reaction Information System	Provincial Registry
British Columbia	BC PharmaNet (all)	BC Medical Services Plan	CIHI Discharge Abstract Database	NACRS	BC Ministry of Health COVID Vaccination Database	BC Ministry of Health Client Roster
Manitoba	Drug Program Information Network (all)	Medical Claims/ Medical Services	CIHI Discharge Abstract/ Manitoba Abstract Data Elements	Not available	COVID-19 Vaccinations Data	Manitoba Health Insurance Registry
Ontario	ODB Program (covers all residents for nirmatrelvir-ritonavir, and those ≥ 65 years and social assistance recipients for other medications)	OHIP Claims History Database	CIHI Discharge Abstract Database	NACRS	COVaxON	OHIP Registered Person's Database
Quebec	RAMQ Pharmaceutical Services (covers all residents for nirmatrelvir-ritonavir, and those aged ≥ 65 years, social assistance recipients, and those without a private drug insurance)	Services médicaux rémunérés à l'acte RAMQ Medical Services	Maintenance et exploitation des données pour l'étude de la clientèle hospitalière	Banque de données communes des urgences	Quebec Vaccination Registry	Fichier d'inscription des personnes assurées RAMQ Membership Registry
Saskatchewan	Prescription Drug Plan Historical Claims (all)	Medical Services Branch	CIHI Discharge Abstract Database	NACRS	Not available	Person Health Registration System

BC = British Columbia; CIHI = Canadian Institute for Health Information; COVaxON = Ontario's COVID-19 vaccination database; NACRS = National Ambulatory Care Reporting System; ODB = Ontario Drug Benefit; OHIP = Ontario Health Insurance Plan; RAMQ = Régie de l'assurance maladie du Québec.

Table 2

Dates of the Accrual Period in Each Province

Site	Date of first dispensing for nirmatrelvir-ritonavir	End date of data availability[a]
Alberta	January 27, 2022	March 31, 2022
British Columbia	January 26, 2022	May 31, 2023
Manitoba	January 26, 2022	March 31, 2023
Ontario	April 9, 2022	March 31, 2023
Quebec	March 17, 2022	June 30, 2023
Saskatchewan	January 26, 2022	December 31, 2022

[a] Hospital records available until March 31, 2022, in British Columbia and Manitoba.

Table 3

List of Codes to Define Exposure

Medication	ATC	DIN	PIN[a]
Nirmatrelvir-ritonavir (Paxlovid)	J05AE30	02524031 02527804 (dosage for moderate renal impairment)	Alberta: NA British Columbia: NA Manitoba: NA Ontario: 09858154 (nirmatrelvir-ritonavir dispensing fee) 09858162 (nirmatrelvir-ritonavir renal dosage dispensing fee) Quebec: NA Saskatchewan: NA
Remdesivir (Veklury)	J05AB16	02502143	–

ATC = anatomical therapeutic chemical; DIN = drug identification number; NA = not applicable; PIN = product identification number.

[a] Source for PIN codes in Ontario: https://files.ontario.ca/moh-executive-officer-notice-en-2023-04-21.pdf.

Table 4

List of Codes to Define Chronic Disease Comorbidities

Condition	ICD-9 codes	ICD-10-CA codes	Comment
Cancer	140.x-172.x 174.x-209.x	C00.x-C43.x C45.x-C97.x	Excludes nonmelanoma skin cancer
Cardiovascular disease	410.x 412.x 413.x 415.x 426.x 427.x 428.x	I05.x-I08.x I20.x-I25.x I34.x-I37.x I42.x-I43.x I50.x Z45.0 Z95.0 Z95.2 Z95.3	Includes ischemic heart diseases, congestive heart failure, cardiomyopathy, valvular heart disease, pacemaker or defibrillator
Chronic kidney disease	403.x 585.x	E10.2 E11.2 E13.2 E14.2 I12 I13 N08.x N18.x N19	—
Chronic liver disease	571.x 573.3*	K70.x K71.x K74.x K75.4	Includes cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease or autoimmune hepatitis *ICD-9-CM code 573.3 to be used with data that include at least 4 digits
COPD	491.x 492.x 496.x	J40.x-J44.x	—
Diabetes mellitus	250.x	E10.x-E14.x	—

ICD-9 = International Classification of Diseases, 9th Revision; ICD-10-CA = International Classification of Diseases, 10th Revision, Canadian Modification.

Note: Comorbidities were assessed using hospitalization records (any diagnostic position) and physician claims in the 5 years preceding cohort entry.

Table 5

List of ATC Codes Used to Identify Prescription Medications

Medication group	ATC codes	Comment
Antihypertensive	C02 C03 C07 C09 C10BX G04CA04	Includes angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, calcium-channel blockers, diuretics, and combination products
Lipid-lowering	C10A C10B	Includes statins, other lipid-lowering drugs (fibrates, bile acid sequestrants, nicotinic acid and derivates, and others), and combination products
Antidiabetic	A10	Includes metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase 4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors, alpha-glucosidase inhibitors, meglitinides, insulin, and combination drugs
Systemic corticosteroid	H02A H02B R03BA (plus additional DINs found from R03AK06-R03AK14, R03AL08, R03AL09, R03AL11, R03AL12)	Includes oral and injectables corticosteroids
NSAID	M01A	Includes statins, other lipid-lowering drugs (fibrates, bile acid sequestrants, nicotinic acid and derivates, and others), and combination products

ATC = anatomical therapeutic chemical; DIN = drug identification numbers; NSAID = nonsteroidal anti-inflammatory drug.

Note: Medication use was assessed using prescription drug claims data in the year prior to cohort entry.

Appendix 2: Case Definition for Immunocompromised Status

Note that this appendix has not been copy-edited.

Notes:

- The following definitions, used in Ontario, were used to define immunocompromised status. For each of the conditions, a flag (0/1) was created with a value of 1 indicating that an individual has the relevant condition. Individuals with a value of 1 for any of these conditions are defined as immunocompromised.
- The immunocompromised status definition was assessed in the 5 years prior to cohort entry using the following data sources: hospitalization records, same day surgery records, emergency department records (where available), physician claims and prescription drug claims.

History of solid organ transplant (discharge abstract database [DAD] Canadian Classification of Health Interventions [CCI] codes): Refer to Table 6.

Table 6

List of CCI Codes for Solid Organ Transplant

Organ transplant	CCI code	Notes
Renal transplant	1PC85: TRANSPLANT, KIDNEY	Living or deceased donor
Liver transplant	1OA85: TRANSPLANT, LIVER	
Heart transplant	1HY85: TRANSPLANT HEART WITH LUNG(S) 1HZ85: TRANSPLANT, HEART NEC	
Lung transplant	1GR85: TRANSPLANT, LOBE OF LUNG 1GT85: TRANSPLANT, LUNG NEC	Living or deceased donor
Pancreas transplant	1OJ85: TRANSPLANT, PANCREAS 1OK85:TRANSPLANT, PANCREAS WITH DUODENUM	

Organ transplant	CCI code	Notes
Small intestine transplant	1NK85:TRANSPLANT, SMALL INTESTINE 1NP85:TRANSPALNT SMALL AND LARGE INTESTINE	

CCI = Canadian Classification of Health Interventions.

History of allogenic/autologous bone marrow transplant (DAD, OHIP, or comparable): Identify those who had a history of allogenic bone marrow transplant before index date using the following combination of diagnostic codes:

- DAD CCI codes: 1WY19, 1LZ19HHU7, 1LZ19HHU8
- OHIP Fee code: Z426 (BONE MARROW TRANSPLANT TEAM FEE.INFUSION INTO RECIPIENT).

Disorders of the immune system:

Sickle cell anemia: Use DAD records to look for any hospitalization with any diagnosis code with:

- ICD-10: D57.0-D57.2, D57.8.

Immune system disorders:

- Any hospitalization, ED (emergency department) visit or physician billing (DAD, NACRS [National Ambulatory Care Reporting System], OHIP [or comparable]; each from database inception) with the following codes:
  - DAD/NACRS: ICD-10: D80, D81, D82, D83, D84, D89
  - OHIP: ICD-9: 279 (Hypogammaglobulinemia, agammaglobulinemia, other immunity disorders).
- Receipt of other immunocompromising drug (including antineoplastics) in the 6 months before index, refer to Table 7.

Table 7

List of ATC Codes Used to Identify Immunocompromising Drugs

Group	ATC code	Comments
Immunosuppressants	L04AA L04AB L04AC L04AD L04AX	Includes selective immunosuppressants, tumor necrosis factor alpha inhibitors, interleukin inhibitors, calcineurin inhibitors, and other immunosuppressants
Immunostimulants	L03AA L03AB L03AC L03AX	Includes colony stimulating factors, interferons, interleukins, and other immunostimulants
Hormone antagonists and related agents	L02BA L02BB L02BG L02BX	Includes anti-estrogens, anti-androgens, aromatase inhibitors, and other hormone antagonists and related agents
Antineoplastic agents	L01A L01B L01C L01D L01E L01F L01X	Includes alkylating agents, antimetabolites, plant alkaloids and other natural products, cytotoxic antibiotics and related substances, protein kinase inhibitors, monoclonal antibodies and antibody drug conjugates, and other antineoplastic agents
Corticosteroids for systemic use	H02AA H02AB	Includes corticosteroids for systemic use and combination products

ATC = anatomical therapeutic chemical.

HIV:

ICES HIV database or

- 3 physician claims on separate dates in 5 years with an ICD-9 diagnosis code of "042", "043", or "044"
- DAD record with an HIV ICD-10 diagnosis code (any) of "B20", "B21", "B22", "B23", "B24".

Other immunodeficiency conditions (DAD): Any hospitalization (any diagnosis field) with the following codes:

- Neutropenia (ICD-10 D70; ICD9 288.0);
- Functional disorders of polymorphonuclear neutrophils & genetic anomalies of leukocytes (ICD-10 D71-D72; ICD-9 288.1, 288.2);
- Hyposplenism, hypersplenism and chronic congestive splenomegaly (ICD-10 D73.0, D73.1, D73.2; ICD-9 289.4 or 289.5);
- Asplenia (ICD-9 759.0; ICD-10 Q89.0).

Autoimmune disease

Rheumatoid arthritis:

ICES ORAD Database or

- At least 1 DAD diagnosis (any) for RA: ICD-10 M05, M06
- At least 3 OHIP (physician) claims on separate dates with a diagnosis code for RA: ICD-9 714.

Inflammatory bowel disease:

ICES OCCC Database or

At least 5 health contacts on separate dates including hospital admissions/physician claims/ED visits with an IBD diagnosis:

- Crohn Disease (CD)
  ICD-9: 555 (any of dxcode)
  ICD-10: K50 (any of dx10code)

- Ulcerative Colitis (UC)
  ICD-9: 556 (any of dxcode)
  ICD-10: K51 (any of dx10code).

Psoriasis/psoriatic arthritis:

- Psoriasis: 1 hospitalization or 3 physician billings on separate dates
  - DAD:
    - ICD-9: 696.1, 696.8;
    - ICD-10: L40.0, L40.1, L40.2, L40.3, L40.4, L40.8, L40.9
  - OHIP: ICD-9: 696
- Psoriatic arthritis: 1 hospitalization or 3 physician billings on separate dates
  - DAD:
    - ICD-9: 696.0
    - ICD-10: L40.5, M07.0, M07.1, M07.2, M07.3, M09.0
  - OHIP: ICD-9: 721.

Multiple sclerosis:

- At least one hospitalization (DAD) or 5 physician billings on separate dates (OHIP [or comparable])
  - DAD:
    - ICD-9: 340
    - ICD-10: G35
  - OHIP: ICD-9: 340.

Systemic autoimmune rheumatoid disease (OHIP [or comparable], DAD):

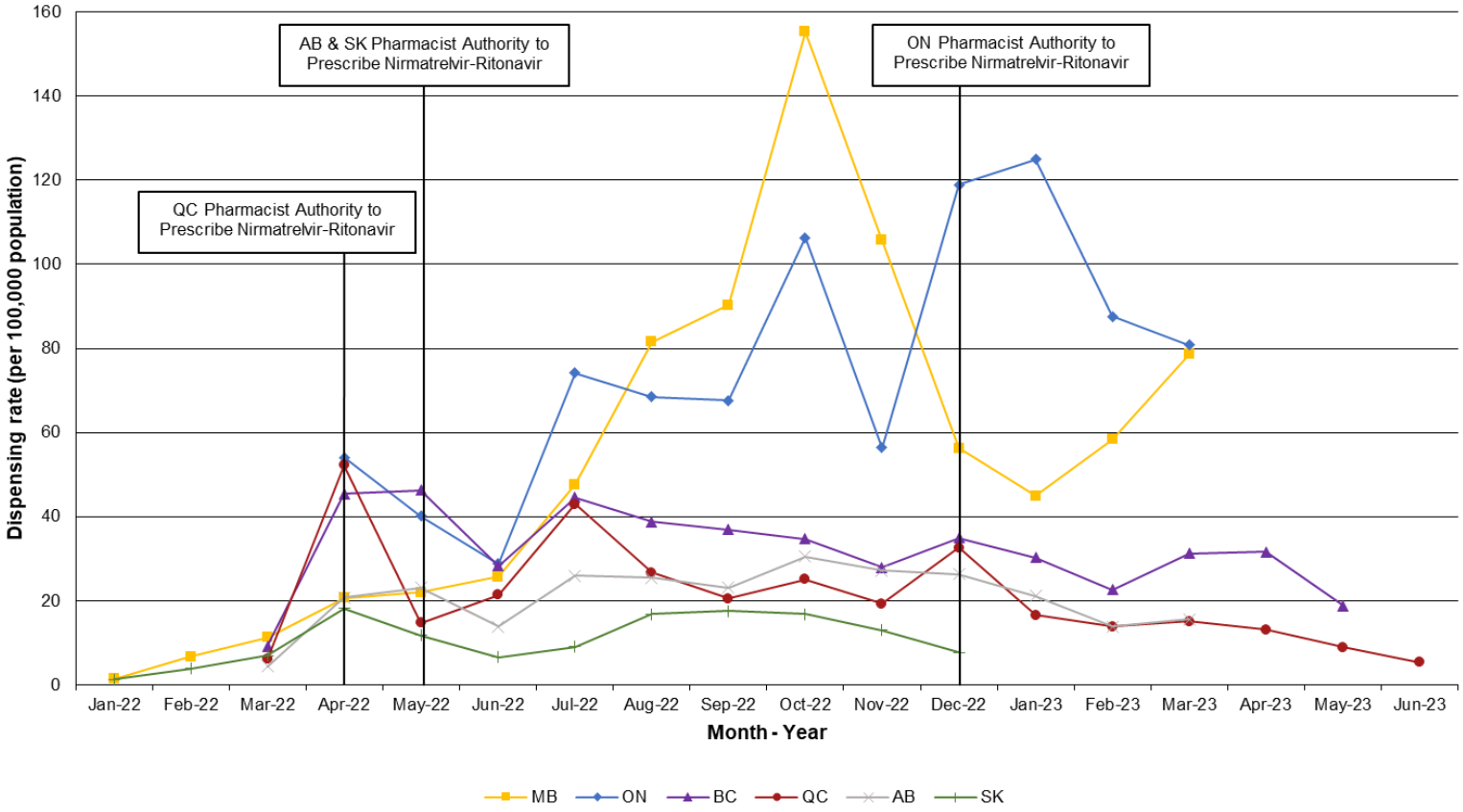
- At least 3 outpatient visits on separate dates with OHIP (or comparable) connective tissue disease diagnosis codes (dx = 710).
- At least one hospitalization with one of the connective tissue disease diagnosis codes (any)
  - ICD-9: 710.0-710.9
  - ICD-10: M32, M33, M34, M35.0.

Appendix 3: Main Findings

Note that this appendix has not been copy-edited.

Figure 1

Monthly Claims for Nirmatrelvir-Ritonavir by Province per 100,000 Population

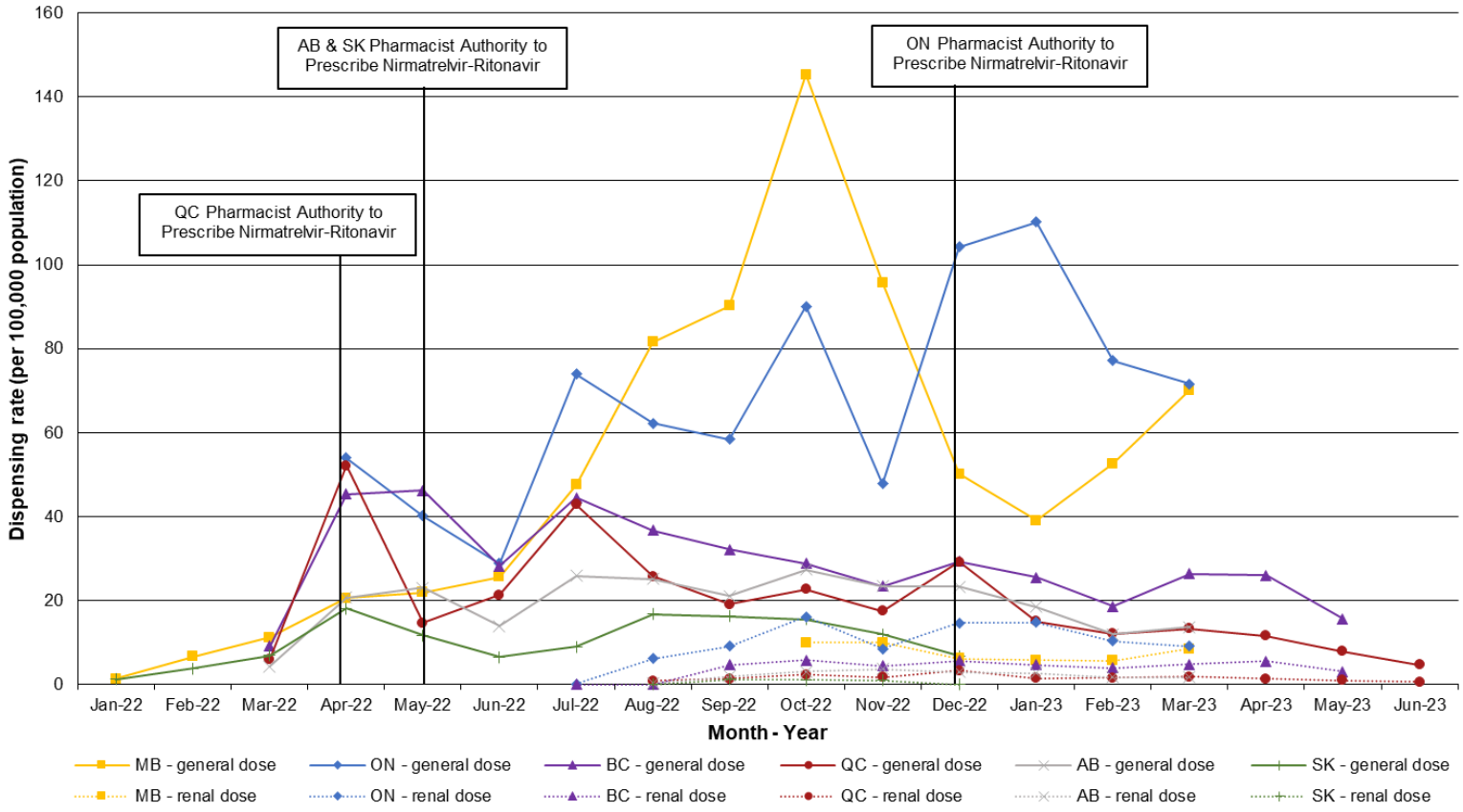


AB = Alberta; Apr = April; Aug = August; BC = British Columbia; Dec = December; DIN = drug identification number; Feb = February; Jan = January; Jul = July; Jun = June; Mar = March; MB = Manitoba; Nov = November; Oct = October; ON = Ontario; QC = Quebec; Sep = September; SK = Saskatchewan.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions for AB and BC in January and February 2022.

Figure 2

Monthly Claims for Nirmatrelvir-Ritonavir by Province and Dosage Form per 100,000 Population



AB = Alberta; Apr = April; Aug = August; BC = British Columbia; Dec = December; DIN = drug identification number; Feb = February; Jan = January; Jul = July; Jun = June; Mar = March; MB = Manitoba; Nov = November; Oct = October; ON = Ontario; QC = Quebec; Sep = September; SK = Saskatchewan.

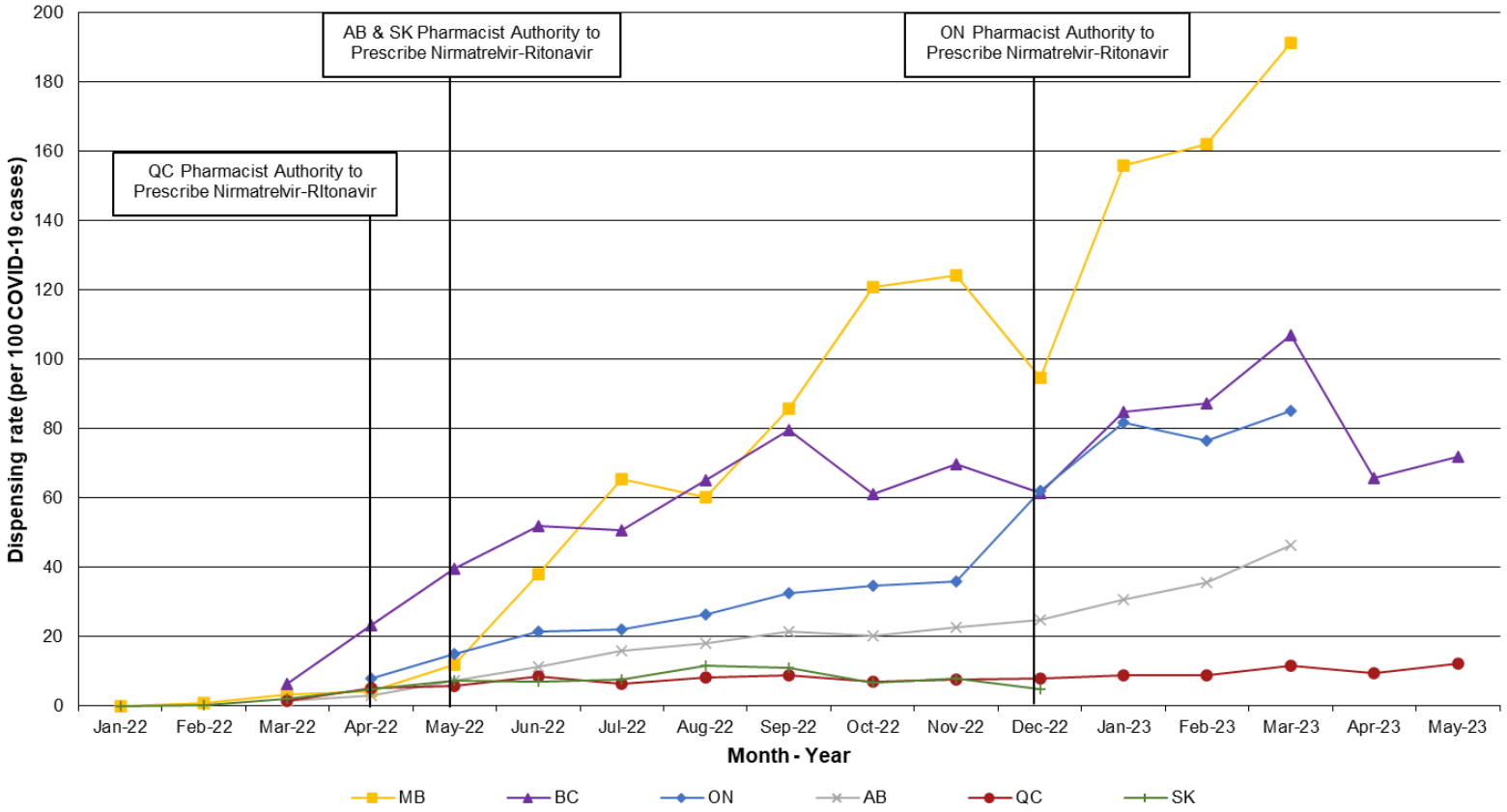
Notes: The nirmatrelvir-ritonavir renal dose was approved for use in Canada on July 6, 2022.

The nirmatrelvir-ritonavir general dose corresponds to 300 mg nirmatrelvir and 150 mg ritonavir (DIN 02524031), and the renal dose to 150 mg nirmatrelvir and 100 mg ritonavir (DIN 02527804).

Values between 1 and 5 inclusively were suppressed due to privacy restrictions for AB and BC in January and February 2022.

Figure 3

Monthly Claims for Nirmatrelvir-Ritonavir by Province per 100 COVID-19 Cases

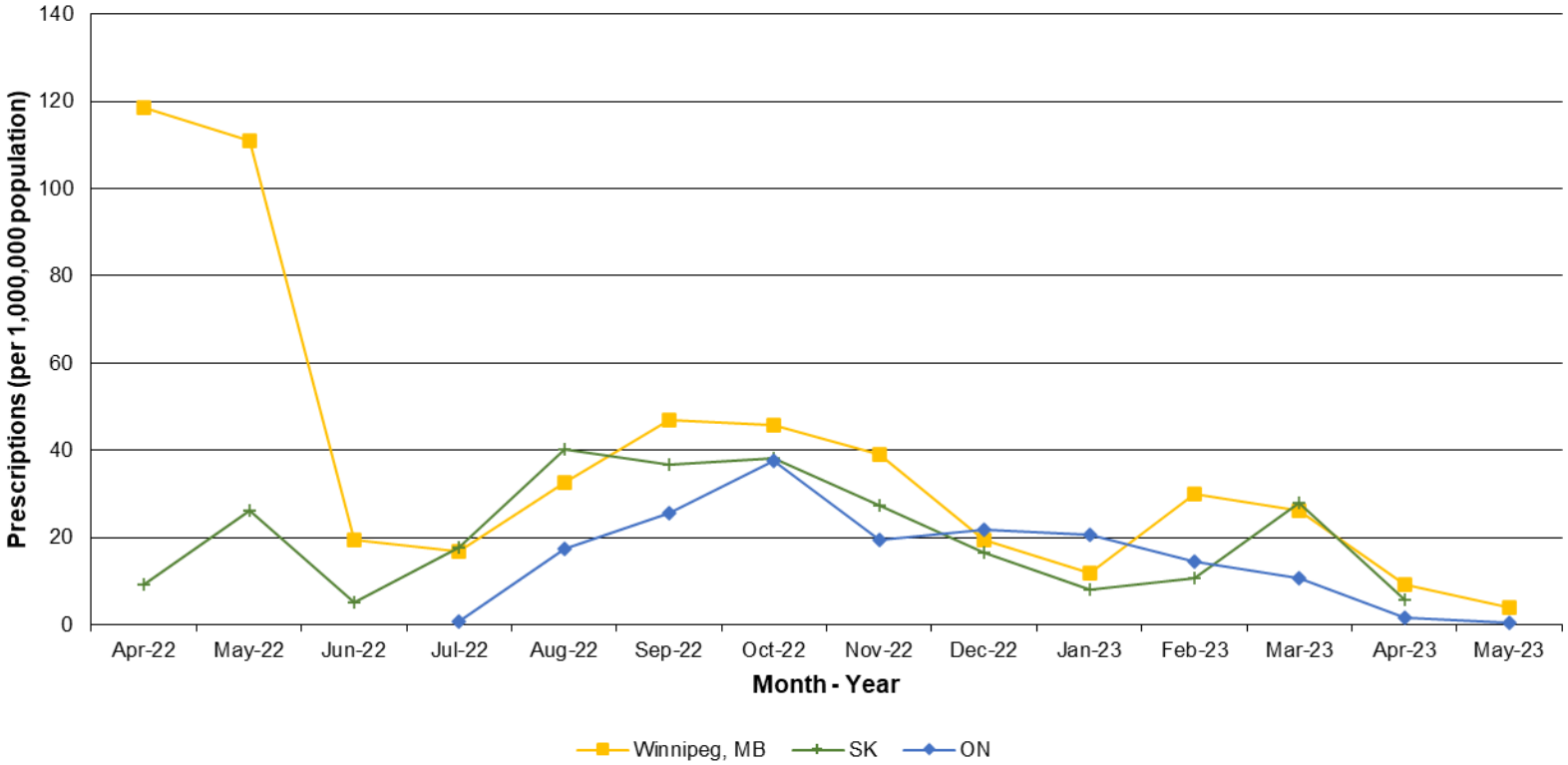


AB = Alberta; Apr = April; Aug = August; BC = British Columbia; Dec = December; Feb = February; Jan = January; Jul = July; Jun = June; Mar = March; MB = Manitoba; Nov = November; Oct = October; ON = Ontario; QC = Quebec; Sep = September; SK = Saskatchewan.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions for AB and BC in January and February 2022.

Figure 4

Monthly Outpatient Prescriptions for Remdesivir in Ontario, Saskatchewan, and Winnipeg, Manitoba, per 1,000,000 Population

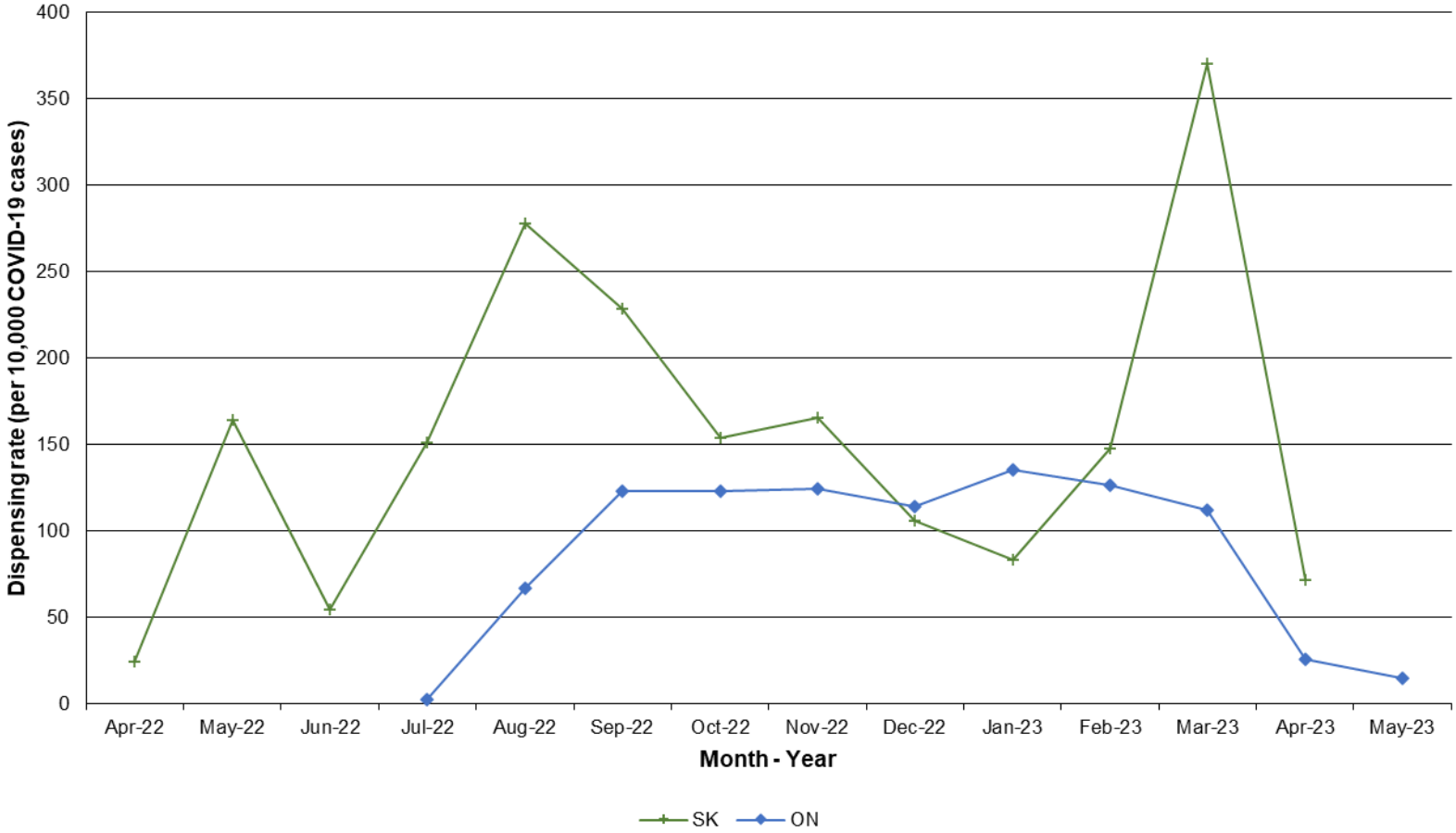


Apr = April; Aug = August; Dec = December; Feb = February; Jan = January; Jul = July; Jun = June; Mar = March; MB = Manitoba; Nov = November; Oct = October; ON = Ontario; Sep = September; SK = Saskatchewan.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions for SK in May 2023.

Figure 5

Monthly Outpatient Prescriptions for Remdesivir in Ontario and Saskatchewan per 10,000 COVID-19 Cases



Apr = April; Aug = August; Dec = December; Feb = February; Jan = January; Jul = July; Jun = June; Mar = March; Nov = November; Oct = October; ON = Ontario; Sep = September; SK = Saskatchewan.

Note: Values between 1 and 5 inclusively were suppressed due to privacy restrictions for SK in May 2023.

Table 8

Characteristics of Patients Dispensed Nirmatrelvir-Ritonavir by Province

Characteristics	Alberta (n = 12,074)	British Columbia (n = 24,728)	Manitoba (n = 11,165)	Ontario (n = 135,238)	Quebec (n = 27,892)	Saskatchewan (n = 1,496)
Age, years						
Mean (SD)	64.4 (18.0)	69.2 (16.4)	63.3 (17.3)	70.0 (15.6)	66.2 (16.0)	59.4 (16.9)
18-64, n (%)	5,531 (45.8)	8,158 (33.0)	5,402 (48.4)	39,290 (29.1)	11,204 (40.2)	843 (56.4)
≥65, n (%)	6,543 (54.2)	16,570 (67.0)	5,763 (51.6)	95,948 (71.0)	16,688 (59.8)	653 (43.7)
Sex, n (%)						
Males	4,770 (39.5)	10,678 (43.2)	4,573 (41.0)	57,609 (42.6)	11,810 (42.3)	603 (40.3)
Females	7,304 (60.5)	14,050 (56.8)	6,592 (59.0)	77,629 (57.4)	16,082 (57.7)	893 (59.7)
Income quintile, n (%)						
1st (lowest)	2,889 (23.9)	4,836 (19.6)	1,866 (16.7)	22,510 (16.6)	5,299 (19.0)	209 (14.0)
2nd	2,476 (20.5)	5,997 (24.3)	1,884 (16.9)	24,750 (18.3)	5,004 (17.9)	267 (17.9)
3rd	2,059 (17.1)	1,698 (6.9)	2,170 (19.4)	25,716 (19.0)	5,063 (18.2)	355 (23.7)
4th	2,067 (17.1)	2,681 (10.8)	2,250 (20.2)	27,732 (20.5)	5,435 (19.5)	293 (19.6)
5th (highest)	1,670 (13.8)	3,043 (12.3)	2,673 (23.9)	33,867 (25.0)	6,019 (21.6)	360 (24.1)
Missing	913 (7.6)	6,473 (26.2)	322 (2.9)	663 (0.5)	1,072 (3.8)	12 (0.8)

Characteristics	Alberta (n = 12,074)	British Columbia (n = 24,728)	Manitoba (n = 11,165)	Ontario (n = 135,238)	Quebec (n = 27,892)	Saskatchewan (n = 1,496)
Month of claim, n (%)						
January, 2022	S	S	19 (0.2)	–	–	15 (1.0)
February, 2022	S	S	93 (0.8)	–	–	46 (3.0)
March, 2022	197 (1.6)	480 (1.9)	157 (1.4)	–	523 (1.9)	82 (5.3)
April, 2022	927 (7.7)	2,286 (9.2)	286 (2.6)	8,075 (6.0)	4,506 (16.2)	216 (14.0)
May, 2022	1,029 (8.5)	2,416 (9.8)	305 (2.7)	5,989 (4.4)	1,266 (4.5)	139 (9.0)
June, 2022	616 (5.1)	1,476 (6.0)	359 (3.2)	4,281 (3.2)	1,832 (6.6)	78 (5.1)
July, 2022	1,152 (9.5)	2,324 (9.4)	664 (5.9)	11,100 (8.2)	3,663 (13.1)	108 (7.0)
August, 2022	1,125 (9.3)	2,004 (8.1)	1,139 (10.2)	10,164 (7.5)	2,262 (8.1)	201 (13.0)
September, 2022	1,016 (8.4)	1,928 (7.8)	1,260 (11.3)	10,049 (7.4)	1,718 (6.2)	210 (13.6)
October, 2022	1,336 (11.1)	1,808 (7.3)	2,170 (19.4)	15,918 (11.8)	2,115 (7.6)	202 (13.1)
November, 2022	1,199 (9.9)	1,432 (5.8)	1,472 (13.2)	8,377 (6.2)	1,591 (5.7)	156 (10.1)
December, 2022	1,130 (9.4)	1,773 (7.2)	778 (7.0)	17,714 (13.1)	2,658 (9.5)	92 (6.0)
January, 2023	909 (7.5)	1,528 (6.2)	613 (5.5)	18,672 (13.8)	1,335 (4.8)	–
February, 2023	597 (4.9)	1,131 (4.6)	788 (7.1)	12,986 (9.6)	1,097 (3.9)	–
March, 2023	659 (5.5)	1,507 (6.1)	1,062 (9.5)	11,913 (8.8)	1,184 (4.2)	–
April, 2023	–	1,555 (6.3)	–	–	1,034 (3.7)	–
May, 2023	–	900 (3.6)	–	–	694 (2.5)	–
June, 2023	–	–	–	–	414 (1.5)	–

Characteristics	Alberta (n = 12,074)	British Columbia (n = 24,728)	Manitoba (n = 11,165)	Ontario (n = 135,238)	Quebec (n = 27,892)	Saskatchewan (n = 1,496)
Comorbidities, n (%)						
Deyo-Charlson Comorbidity Index Score						
0	9,231 (76.5)	15,204 (61.5)	8,767 (78.5)	112,428 (83.1)	17,752 (63.6)	733 (49.0)
1	1,132 (9.4)	3,799 (15.4)	1,059 (9.5)	8,666 (6.4)	2,500 (9.0)	223 (14.9)
≥2	1,711 (14.2)	5,725 (23.2)	1,339 (12.0)	14,144 (10.5)	7,640 (27.4)	540 (36.1)
Cancer	3,409 (28.2)	6,169 (24.9)	2,056 (18.4)	25,917 (19.2)	10,320 (37.0)	390 (26.1)
Cardiovascular disease	3,209 (26.6)	8,175 (33.1)	2,338 (20.9)	37,638 (27.8)	7,978 (28.6)	303 (20.3)
Chronic kidney disease	1,204 (10.0)	3,760 (15.2)	634 (5.7)	8,830 (6.5)	2,304 (8.3)	62 (4.1)
Chronic liver disease	45 (0.4)	1,036 (4.2)	551 (4.9)	3,849 (2.9)	831 (3.0)	36 (2.4)
COPD	1,511 (12.5)	4,248 (17.2)	1,284 (11.5)	11,074 (8.2)	3,479 (12.5)	194 (13.0)
Diabetes	3,289 (27.2)	8,054 (32.6)	3,043 (27.3)	29,326 (21.7)	6,569 (23.6)	377 (25.2)
Immunocompromised status, n (%)						
Yes	4,901 (40.6)	14,144 (57.2)	2,609 (23.4)	25,034 (18.5)	10,995 (39.4)	844 (56.4)
No	7,173 (59.4)	10,584 (42.8)	8,556 (76.6)	110,204 (81.5)	16,897 (60.6)	652 (43.6)
Medication use, n (%)[a]						
Antihypertensive	6,126 (50.7)	13,611 (55.0)	5,724 (51.3)	67,506 (49.9)	12,434 (44.6)	758 (50.7)
Lipid-lowering	4,180 (34.6)	9,802 (39.6)	3,924 (35.1)	56,856 (42.0)	10,166 (36.4)	483 (32.3)
Antidiabetic	2,630 (21.8)	5,537 (22.4)	2,214 (19.8)	23,219 (17.2)	4,627 (16.6)	304 (20.3)

Characteristics	Alberta (n = 12,074)	British Columbia (n = 24,728)	Manitoba (n = 11,165)	Ontario (n = 135,238)	Quebec (n = 27,892)	Saskatchewan (n = 1,496)
Systemic corticosteroid	2,496 (20.7)	7,396 (29.9)	1,672 (15.0)	15,177 (11.2)	5,215 (18.7)	433 (28.9)
NSAID	2,227 (18.4)	3,047 (12.3)	1,902 (17.0)	13,441 (9.9)	3,416 (12.2)	320 (21.4)
COVID-19 vaccination doses, n (%)[b]						
0	2,242 (18.6)	3,108 (12.6)	460 (4.1)	5,022 (3.7)	2,011 (7.2)	–
1	3,546 (29.4)	6,050 (24.5)	90 (0.8)	921 (0.7)	358 (1.3)	–
2	4,000 (33.1)	13,480 (54.5)	1,216 (10.9)	11,393 (8.4)	1,826 (6.5)	–
>2	2,286 (18.9)	2,090 (8.5)	9,399 (84.2)	117,902 (87.2)	23,697 (85.0)	–
Health service use						
Number of outpatient physician visits						
Mean (SD)	27.0 (25.1)	20.2 (15.8)	11.7 (10.2)	11.2 (10.3)	13.8 (16.8)	15.9 (11.7)
Median (IQR)	20.0 (10-36)	16.0 (10-27)	9.0 (5-15)	9.0 (4-15)	9.0 (4-17)	13.0 (8-21)
0, n (%)	192 (1.6)	349 (1.4)	345 (3.1)	5,246 (3.9)	1,282 (4.6)	0 (0.0)
1-2, n (%)	393 (3.3)	673 (2.7)	845 (7.6)	12,743 (9.4)	3,153 (11.3)	0 (0.0)
3-4, n (%)	595 (4.9)	1,013 (4.1)	1,262 (11.3)	16,115 (11.9)	3,568 (12.8)	0 (0.0)
≥5, n (%)	10,894 (90.2)	22,693 (91.8)	8,713 (78.0)	101,134 (74.8)	19,889 (71.3)	1,496 (100.0)
Number of hospitalizations						
Mean (SD)	0.2 (0.5)	1.7 (1.6)	0.1 (0.3)	0.1 (0.5)	0.2 (0.7)	0.2 (0.7)

Characteristics	Alberta (n = 12,074)	British Columbia (n = 24,728)	Manitoba (n = 11,165)	Ontario (n = 135,238)	Quebec (n = 27,892)	Saskatchewan (n = 1,496)
Median (IQR)	0.0 (0-0)	1.0 (0-1)	0 (0-0)	0 (0-0)	0.0 (0-0)	0.0 (0-0)
0, n (%)	10,638 (88.1)	16,908 (68.4)	10,685 (95.7)	122,053 (90.3)	23,571 (84.5)	1,278 (85.4)
1-2, n (%)	1,340 (11.1)	6,646 (26.9)	467 (4.2)	12,208 (9.0)	3,854 (13.8)	185 (12.4)
≥3, n (%)	96 (0.8)	1,174 (4.7)	13 (0.1)	977 (0.7)	467 (1.7)	33 (2.2)
Long-term care resident, n (%)[c]						
Yes	918 (7.6)	—	—	12,571 (9.3)	78 (0.3)	—
No	11,156 (92.4)	—	—	122,667 (90.7)	27,814 (99.7)	—

COPD = chronic obstructive pulmonary disease; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug; S = value suppressed; SD = standard deviation.

Notes: Data are presented at the patient level.

Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

[a] Medication use only available for those covered by the public drug plan in Ontario.

[b] COVID-19 vaccination status not available for Saskatchewan.

[c] Long-term care residence status incomplete for British Columbia, Manitoba, and Saskatchewan.

Table 9

Distribution of Number of Nirmatrelvir-Ritonavir Claims per Patient by Province

Number of claims per patient	Alberta	British Columbia	Manitoba	Ontario	Quebec	Saskatchewan
	n (%)					
1	11,721 (97.1)	23,727 (91.6)	10,911 (97.7)	132,244 (97.8)	26,707 (95.8)	1,459 (97.5)
2	336 (2.8)	1,860 (7.2)	242 (2.2)	2,901 (2.2)	1,113 (4.0)	37 (2.5)
≥3	17 (0.1)	320 (1.2)	12 (0.1)	93 (0.1)	72 (0.3)	0 (0.0)

Table 10

Mean and Median Paid per Nirmatrelvir-Ritonavir Claim in Ontario[a]

Province	Mean (SD)	Median	25th percentile	75th percentile	Min	Max
Ontario	13.10 (0.81)	13.25	13.25	13.25	0.01	13.25

Max = maximum; Min = minimum; SD = standard deviation.

Note: Values given are in Canadian dollars.

[a] Data are reported for 123,120 claims with nonzero values; 15,217 claims (11%) reported total payments of zero.

Table 11

Number (%) of Nirmatrelvir-Ritonavir Recipients by Province and Dosage Form According to Patient Subgroup

Subgroup	Alberta		British Columbia		Manitoba		Ontario		Quebec		Saskatchewan	
	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose
Total	11,271	834	22,416	2,381	10,538	652	122,150	13,541	26,414	1,551	1,449	52
Age (years), n (%)												
18-64	5,459 (48.4)	76 (9.1)	8,012 (35.7)	153 (6.4)	5,342 (50.7)	68 (10.4)	37,995 (31.0)	1,357 (10.0)	11,098 (42.0)	119 (7.7)	837 (57.8)	7 (13.5)
≥65, n (%)	5,812 (51.6)	758 (90.9)	14,404 (64.3)	2,228 (93.6)	5,198 (49.3)	585 (89.7)	84,155 (68.7)	12,184 (90.0)	15,316 (58.0)	1,432 (92.3)	612 (42.2)	45 (86.5)
Sex, n (%)												
Males	4,470 (39.7)	319 (38.2)	9,595 (42.8)	1,116 (46.9)	4,302 (40.8)	278 (42.6)	52,148 (42.6)	5,638 (41.6)	11,212 (42.4)	624 (40.2)	590 (40.7)	14 (26.9)
Females	6,801 (60.3)	515 (61.8)	12,821 (57.2)	1,265 (53.1)	6,236 (59.2)	374 (57.4)	70,002 (57.1)	7,903 (58.4)	15,202 (57.6)	927 (59.8)	859 (59.3)	38 (73.1)
Income quintile, n (%)												
1st (lowest)	2,706 (24.0)	190 (22.8)	4,178 (18.6)	675 (28.3)	1,745 (16.6)	126 (19.3)	20,045 (16.4)	2,564 (18.9)	5,006 (18.9)	304 (19.6)	204 (14.1)	S
2nd	2,333 (20.7)	146 (17.5)	5,322 (23.7)	693 (29.1)	1,773 (16.8)	115 (17.6)	22,156 (18.1)	2,674 (19.7)	4,714 (17.8)	302 (19.5)	258 (17.8)	10 (19.2)
3rd	1,933 (17.2)	135 (16.2)	1,571 (7.0)	133 (5.6)	2,051 (19.5)	125 (19.2)	23,215 (18.9)	2,600 (19.2)	4,823 (18.3)	249 (16.1)	343 (23.7)	12 (23.1)

Subgroup	Alberta		British Columbia		Manitoba		Ontario		Quebec		Saskatchewan	
	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose	NMV-r general dose	NMV-r renal dose
4th	1,914 (17.0)	161 (19.3)	2,478 (11.1)	208 (8.7)	2,128 (20.2)	127 (19.5)	25,151 (20.5)	2,665 (19.7)	5,125 (19.4)	329 (21.2)	281 (19.4)	14 (26.9)
5th (highest)	1,558 (13.8)	114 (13.7)	2,881 (12.9)	165 (6.9)	2,562 (24.3)	116 (17.8)	30,990 (25.3)	2,964 (21.9)	5,749 (21.8)	284 (18.3)	352 (24.3)	9 (17.3)
Missing	827 (7.3)	88 (10.6)	5,986 (26.7)	507 (21.3)	280 (2.7)	44 (6.7)	593 (0.5)	74 (0.5)	997 (3.8)	83 (5.3)	11 (0.8)	S
Deyo-Charlson Comorbidity Index Score, n (%)												
0	8,770 (77.8)	479 (57.4)	14,032 (62.6)	1,198 (50.3)	8,351 (79.2)	437 (67.0)	103,135 (84.2)	9,602 (70.9)	17,025 (64.5)	758 (48.9)	722 (49.8)	13 (25.0)
1	1,017 (9.0)	118 (14.1)	3,394 (15.1)	421 (17.7)	980 (9.3)	81 (12.4)	7,393 (6.0)	1,323 (9.8)	2,379 (9.0)	125 (8.1)	216 (14.9)	7 (13.5)
≥2	1,484 (13.2)	237 (28.4)	4,990 (22.3)	762 (32.0)	1,211 (11.5)	134 (20.6)	11,622 (9.5)	2,616 (19.3)	7,010 (26.5)	668 (43.1)	511 (35.3)	32 (61.5)
Immunocompromised status, n (%)												
Yes	4,699 (41.7)	212 (25.4)	13,012 (58.0)	1,184 (49.7)	2,500 (23.7)	124 (19.0)	22,159 (18.1)	2,998 (22.1)	10,521 (39.8)	507 (32.7)	822 (56.7)	24 (46.2)
No	6,572 (58.3)	622 (74.6)	9,404 (42.0)	1,197 (50.3)	8,044 (76.3)	528 (81.0)	99,991 (81.6)	10,543 (77.9)	15,893 (60.2)	1,044 (67.3)	627 (43.3)	28 (53.8)

DIN = drug identification number; NMV-r = nirmatrelvir-ritonavir; S = value suppressed.

Notes: Values between 1 and 5 inclusively were suppressed due to privacy restrictions.

The number of patients in each province is greater than in Table 8, given that patients could receive multiple claims for nirmatrelvir-ritonavir during the study period and could contribute to both dosage groups, patients were characterized at the time of their first dispensing in each dosage category.

The nirmatrelvir-ritonavir general dose corresponds to 300 mg nirmatrelvir and 150 mg ritonavir (DIN 02524031), and the renal dose to 150 mg nirmatrelvir and 100 mg ritonavir (DIN 02527804). The nirmatrelvir-ritonavir renal dose was approved for use in Canada on July 6, 2022.

Appendix 4: Nirmatrelvir-Ritonavir and Remdesivir Prescribing Criteria in Each Study Province

Note that this appendix has not been copy-edited.

Table 12

Nirmatrelvir-Ritonavir and Remdesivir Prescribing Criteria in Each Study Province

Province	Eligibility Criteria
Nirmatrelvir-ritonavir (Paxlovid)	
Alberta[a]	For outpatient use for individuals with mild to moderate COVID-19 symptoms who have a positive test for COVID-19, are at risk for severe outcomes and can receive treatment **within 5 days** from the start of symptoms. Patients considered high risk for severe outcomes 1. Immunocompromised • Have received a transplant – solid organ or stem cell (Transplant patients should NOT be offered Paxlovid due to the potential for life-threatening drug interactions but are eligible for other therapies, such as Remdesivir) • Is an oncology patient who as received a dose of any IV or oral chemotherapy or other immunosuppressive treatment since December 2020 • Has an inflammatory condition (e.g., rheumatoid arthritis, lupus, inflammatory bowel disease) and has received a dose of any systemic immunosuppressive treatment since December 2020 • Has sickle cell anemia • Has had their spleen removed • Has pulmonary hypertension • Is receiving treatment for tuberculosis 2. Living in long-term care or designated support living 3. Age 18 or older with 3 or more high risk comorbidities 4. Age 50 or older (40 or older for First Nations, Métis or Inuit) with 2 or more high risk comorbidities 5. Age 60 or older (50 or older for First Nations, Métis or Inuit) with 1 or more high risk comorbidities. High risk comorbidities include: • Received fewer than 3 doses of COVID vaccine • Diabetes (taking medication for treatment) • Obesity (BMI > 30) • Chronic kidney disease (estimated glomerular filtration rate, < 60 ml per minute per 1.73 m2 of body-surface area) • Congestive heart failure (New York Heart Association class II, III, or IV) • Chronic obstructive pulmonary disease, and moderate-to-sever asthma • Pregnancy

Province	Eligibility Criteria
British Columbia[b]	- Confirmed COVID-19 AND symptomatic for 5 days or less; OR - Pre-emptive prescription for future use; AND - Are at increased risk for disease progression, including either: • Any adult identified as clinically extremely vulnerable (CEV) Group 1, Group 2 and Group 3, regardless of number of vaccine doses • 18-69 OR 18-59 if Indigenous AND 0 or 1; or 2 vaccine doses with ≥1 serious chronic medical condition (defined below) • 70+ OR 60+ if Indigenous AND 0 or 1; or 2 vaccine doses; OR 3 vaccine doses with ≥1 serious chronic medical condition (defined below) CEV Group 1 includes severe immunocompromise, Group 2 includes moderate immunocompromise; and Group 3 includes high-risk conditions. Serious chronic medical conditions include: stroke, heart failure or heart disease; chronic kidney or liver disease, diabetes, chronic lung disease such as COPD, bronchiectasis or interstitial lung disease, neurological disease such as Parkinson disease.
Manitoba[c]	- Adults who have developed symptoms that began in the last 5 to 7 days; AND - Have tested positive for COVID-19; AND - Are at higher risk of severe outcomes, including: • Not fully vaccinated, • Not received a booster dose, • Not previously infected with COVID-19, • Older adult, • One or more chronic medical conditions, • Moderately to severely immunocompromised, due to a medical condition or treatment, • Obese, or • Pregnant.
Ontario[d]	Individuals who have a confirmed COVID-19 diagnosis (based upon a positive PCR, rapid molecular, or rapid antigen test), presented within 5 days of symptom onset, are not on supplemental oxygen, and who meet one or more of the following criteria: - 60 years of age or older; - 18 years of age or older and immunocompromised; - 18-59 years of age and higher risk of severe COVID-19, including: • those who have one or more comorbidities that put them at higher risk of severe COVID-19 disease; OR • those with inadequate immunity, i.e., unvaccinated or incomplete primary series; OR completed primary series and last COVID-19 vaccine dose and last SARS-CoV-2 infection was more than 6 months ago.

Province	Eligibility Criteria
Quebec[e]	- Adults who are moderately to severely immunocompromised owing to an underlying condition or the treatment they are receiving for this condition (regardless of their vaccination status); - People aged 60 or older, not adequately vaccinated (fewer than two doses) or not protected against COVID-19; - People aged 18 or older, not adequately vaccinated (fewer than two doses) or not protected against COVID-19, and presenting one of the following health conditions: • hemoglobinopathy, • obesity with a body mass index greater than or equal to 35, • diabetes, • chronic kidney disease, • liver failure, • high blood pressure, • cardiovascular and atherosclerotic disease, • chronic respiratory disease (for example, chronic obstructive pulmonary disease or moderate to severe asthma); - Adolescents weighing at least 40 kg (88 lbs) and pregnant women, who present with at least one of the conditions listed above and who are not adequately vaccinated (fewer than 2 doses) or not protected against COVID-19, after discussion with a medical specialist or an experienced health professional; - Exceptionally, adults who are adequately protected or vaccinated presenting with a very high risk of COVID-19 complications (for example, very old age, several co-existing medical conditions among those listed above, especially if uncontrolled, and with poor protection against the circulating variant despite a complete vaccination series), after discussion with a medical specialist or an experienced health professional. Since December 12, 2022, eligibility for Paxlovid treatment was extended to: - Adults with complete primary vaccination and who are at high risk of COVID-19 complications according to clinical judgment (e.g., very advanced age [70+] and at least one comorbidity increasing the risk of complications (conditions listed above) AND last vaccine dose received more than 6 months ago). And the criteria for adolescent and pregnant women were modified as follows: -Adolescent weighing at least 40 kg (88 lbs) and pregnant women who are at high risk of COVID-19 complications (conditions listed above) and incomplete vaccination OR with anticipation of suboptimal protection against hospitalization due to circulating variants despite complete primary vaccination OR with the last dose of vaccine received more than six months ago, AND after discussion with a medical specialist or an experienced health professional.

Province	Eligibility Criteria
Saskatchewan[f]	- Positive PCR test or rapid antigen test - ≤ day 5 since symptom onset - Mild COVID-19 signs and symptoms - At least 90 days have elapsed since symptoms from previous infection (if applicable) have resolved - No more than one previous treatment course with an early COVID-19 antiviral (i.e., Paxlovid and/or remdesivir) - Immunocompromised by complex disease state or medication regardless of COVID-19 vaccination status (defined below) - Unvaccinated or under-vaccinated: age ≥18 to <55 with ≥1 high risk factor (defined below) OR age ≥55 - Fully vaccinated: age ≥70 with ≥3 high risk factors (defined below), age ≥70 and Indigenous with ≥2 high risk factors, OR age ≥70 living in the North with ≥2 high risk factors - Specific high-risk factors for severe disease progression that determine eligibility include: • Body mass index ≥30 kg/m2 • Chronic kidney disease with a decreased creatine clearance (≥30 to <60 mL/min) • Cardiovascular or cerebrovascular disease • Diabetes mellitus (Type 1 and 2) • Chronic lung disease • Neurodevelopmental disorders • Sickle cell disease Definition of immunocompromised: - Active treatment for cancer - Hematopoietic stem cell transplant recipient - Moderate or severe primary immunodeficiency - Solid organ transplant recipient - Immunocompromised due to medication Fully vaccinated: Defined as the patient having received two doses of a two-dose vaccine or one dose of a single-dose vaccine.
Remdesivir (Veklury)	
Manitoba[g]	Patient must meet ALL 6 minimum requirements, including specific reason for Remdesivir: - 18 years of age or older - Symptom onset must be within 7 days of initiating therapy - Positive COVID-19 test - Not eligible for Paxlovid, specify reason - Patient is not currently receiving hydroxychloroquine - Specify reason for patient to receive Remdesivir

Province	Eligibility Criteria
Ontario[h]	Remdesivir is an antiviral medication that must be taken intravenously (IV) via designated clinics. Remdesivir treatment must begin within 7 days of the start of symptoms and requires a referral from a physician (doctor) or nurse practitioner. Eligibility criteria: Remdesivir is only prescribed to people who cannot take Paxlovid because they are on certain medications or have certain medical conditions.
Saskatchewan[i]	- Adults older than 18 years who test positive (PCR or rapid test) with mild or moderate COVID-19 symptoms - Within 7 days of developing symptoms - Do not have any medical conditions that would make treatment inappropriate - Are not taking any medications that may cause potential drug interactions - Are immunocompromised, regardless of vaccination status - 70 years and older with designated risk factors, regardless of vaccination status - Meet one of the following criteria: • Have a medical condition that puts them at high risk and not up-to-date on their vaccination • Are 55 to 69 years old and not up-to-date on their vaccination

PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Note: These are the current summary prescribing recommendations and criteria. For further details, refer to the following sources.

[a] Nirmatrelvir/ritonavir (Paxlovid™) outpatient treatment in Alberta: https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-paxlovid-faq-hcw.pdf.

[b] Paxlovid prescription form in British Columbia: https://www2.gov.bc.ca/assets/gov/health/forms/2368fil.pdf.

[c] Treatment for COVID-19 in Manitoba: https://www.manitoba.ca/covid19/treatment.html

[d] Access to COVID-19 antiviral treatment (Paxlovid) in Ontario: https://www.ontariohealth.ca/sites/ontariohealth/files/2022-04/Guidance%20for%20health%20care%20providers%20-%20Access%20to%20Paxlovid%20-%20EN.pdf. Ontario Regulation 107/96, Regulated Health Professions Act, 1991: https://www.ontario.ca/laws/regulation/r22560

[e] Oral COVID-19 treatment (PaxlovidTM) in Quebec: https://www.quebec.ca/en/health/health-issues/a-z/2019-coronavirus/symptoms-transmission-treatment/oral-treatment-against-covid-19-paxlovidmc. New criteria of eligibility since December 12, 2022 (available in French only): https://www.inesss.qc.ca/fileadmin/doc/INESSS/COVID-19/INESSS_OIPI_Paxlovid_VF.pdf

[f] Mild COVID-19 Infection: Guidelines for Prescribing Paxlovid in Saskatchewan: https://medsask.usask.ca/professional-practice/paxlovid-hcp/prescribing-paxlovid-for-covid-19.php.

[g] COVID-19 IV antiviral outpatient and personal care home treatment in Manitoba: https://sharedhealthmb.ca/files/covid-19-treatment-referral-form.pdf

[h] COVID-19 testing and treatment in Ontario: https://www.ontario.ca/page/covid-19-testing-and-treatment#section-5.

[i] COVID-19 treatments in Saskatchewan: https://www.saskatchewan.ca/government/health-care-administration-and-provider-resources/treatment-procedures-and-guidelines/emerging-public-health-issues/2019-novel-coronavirus/testing-information/