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Health Technology Report

The Cost-Effectiveness and Budget Impact of Nirmatrelvir-Ritonavir for COVID-19

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This technology review was conducted by the Alberta Drug and Technology Evaluation Consortium (ADTEC) through the Post-Market Drug Evaluation CoLab Network.

Key Messages

This report aims to estimate the impacts of providing nirmatrelvir-ritonavir as an outpatient treatment for COVID-19 in Canada on the acute care health system, drug access, and funding considerations.

We used a state-transition model to conduct an economic evaluation and budget impact analysis (BIA) of nirmatrelvir-ritonavir based on COVID-19 epidemiology in 2022, when Omicron was the main circulating variant, and in 2 populations at high risk of progressing to severe COVID-19 (those aged ≥ 65 years and those in long-term care [LTC]).

Our cost-utility analysis (CUA) differed from a typical one in that it did not compare a set of treatment alternatives to identify the cost-effective option(s). Instead, we projected costs and health outcomes for a range of possible scenarios to understand under what conditions using nirmatrelvir-ritonavir in a community setting may be cost-effective.

The analysis suggested that increased use of nirmatrelvir-ritonavir may be cost-effective, taking uncertainty into account. However, this result depended on the rate of treatment uptake, the age group or cohort of patients, the severity of the circulating variant, and its therapeutic effects.

The budget impact of the scenarios ranged from $286 million (95% credible interval [CrI], –$18 million to $740 million) to $578 million (95% CrI, –$233 million to $1.8 billion), with total inpatient costs contributing the most to the overall total cost.

The price paid for nirmatrelvir-ritonavir in Canada was not available for inclusion in the model and we made assumptions on prices from other countries. However, the results indicated an estimated break-even price of $370 per treatment based on model assumptions.

In all scenarios, there was an increase in costs and in total quality-adjusted life-years (QALYs). The largest incremental net monetary benefit (iNMB) resulted from treatment scenarios that included individuals aged 65 years and older.

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Abbreviations

BIA	budget impact analysis
CEAC	cost-effectiveness acceptability curve
CIHI	Canadian Institute of Health Information
CrI	credible interval
CUA	cost-utility analysis
ED	emergency department
HALE	health-adjusted life expectancy
iNMB	incremental net monetary benefit
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
LOS	length of stay
LTC	long-term care
NA	not applicable
NMB	net monetary benefit
NMV-r	nirmatrelvir-ritonavir
NR	not reported
PCR	polymerase chain reaction
PHAC	Public Health Agency of Canada
POSA	probabilistic one-way sensitivity analysis
QALY	quality-adjusted life-year
SD	standard deviation
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
WTP	willingness-to-pay

Editorial Note

Canada's Drug Agency (CDA-AMC) completed a Reimbursement Review of nirmatrelvir-ritonavir (Paxlovid), and the Canadian Drug Expert Committee issued a final recommendation on April 11, 2024. It recommended reimbursing nirmatrelvir-ritonavir according to the indication approved by Health Canada, restricted to patients who have severe or moderate immunosuppression.

Prior to the reimbursement recommendation, the Public Health Agency of Canada had commissioned the Post-Market Drug Evaluation program to conduct an economic evaluation and budget impact analysis of nirmatrelvir-ritonavir. The research and policy questions defined in this report were developed in advance of the reimbursement recommendation.

The patient population included in this report is broader than the reimbursement recommendation and does not include patients who are immunocompromised. The data used in this economic evaluation are based on the epidemiology of COVID-19 in 2022 and may not reflect the current state of COVID-19.

Introduction and Rationale

Background

The main symptoms of COVID-19 include fever, sore throat, runny nose, cough, fatigue, and shortness of breath.[1] The incubation period of COVID-19 ranged between 2 and 14 days before the emergence of the Omicron variant, and between 2 and 4 days following the emergence of the Omicron variant. Infected individuals may remain asymptomatic and nonetheless be contagious.[2] Clinical features of COVID-19 related to severity differ by age, vaccination status, variants of concern, and comorbidities with COVID-19 disproportionately impacting older adults and those with weakened immune systems (e.g., those with comorbidities).[2]

In Canada, several drug treatments have received approval for the management of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initially, the federal government — specifically the Public Health Agency of Canada (PHAC) — was responsible for overseeing the procurement and allocation of these drugs for federal, provincial, and territorial (FPT) health care systems. The following drugs were funded by PHAC: nirmatrelvir-ritonavir (NMV-r) (Paxlovid), remdesivir (Veklury), and tocilizumab (Actemra).

To provide reliable and evidence-based guidance, CDA-AMC conducted comprehensive evidence reviews for NMV-r, remdesivir in hospitalized patients and in outpatients, and tocilizumab.[3-6] The primary objective of these reviews was to assess the available evidence on the safety, efficacy, and overall benefits of these drugs in the context of COVID-19 treatment. Subsequently, reimbursement recommendations from CDA-AMC were issued for NMV-r, remdesivir for inpatients, and remdesivir for outpatients, to support FPT drug plans' funding decisions. The recommendation from CDA-AMC for NMV-r was specific to patients who have severe or moderate immunosuppression.

Prior to the reimbursement recommendations from CDA-AMC for NMV-r and remdesivir, PHAC had commissioned the Post-Market Drug Evaluation program to conduct economic evaluations and BIAs of drugs used to treat COVID-19 — including NMV-r, remdesivir, and tocilizumab — to inform policy decisions related to the continued inpatient and/or outpatient purchase and use of these therapies.[7] Hence, the research and policy questions defined in this report were developed in advance of the reimbursement recommendations for NMV-r and remdesivir, and modelling was based upon COVID-19 conditions in Canada in 2022.

Main Take-Aways

Several drug treatments have been authorized for use in Canada to manage COVID-19. This report aims to estimate the impacts of providing NMV-r as an outpatient treatment for COVID-19 in Canada on health system costs and health outcomes.

Policy Issue

Health Canada authorized the use of NMV-r in January 2022. It is indicated for the treatment of mild to moderate COVID-19 infections in adults who have positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death. Treatment must be initiated as soon as possible after a diagnosis of COVID-19, and within 5 days from symptom onset.[8,9] Some side effects include altered sense of taste, diarrhea, muscle pain, high blood pressure, and headache.[8] Although there is potential for drug-drug interactions and/or adverse drug events, most patients complete NMV-r as prescribed.[10]

Access to NMV-r differs by province and by whether a lab-confirmed diagnosis or positive rapid test from a primary care provider is required. Lab-confirmed diagnoses are reported and captured in surveillance systems, while cases identified from rapid testing are not.

At the outset of this research, existing cost-effectiveness studies reported NMV-r to be a cost-effective option compared to standard of care or no NMV-r (i.e., those not treated with NMV-r) in cohorts at the highest risk of developing severe disease.[11-15] These groups included people aged 65 years or older, people living in LTC facilities, and people living with health conditions that would make them more susceptible to or at greater risk of harm from infection. The cost-effectiveness of NMV-r as an outpatient treatment strategy is generally related to its reported ability to reduce the risk of emergency department (ED) visits, hospitalizations, and death, compared to no treatment, placebo, or standard of care.[3]

We conducted an economic evaluation and BIA of the outpatient use of NMV-r for COVID-19, focusing on COVID-19 cases (detected and undetected) and transitions related to outpatient and inpatient treatment, post–COVID-19 condition,[2] and recovery. We developed a stochastic state-transition model and evaluated treatment for the following cohorts based on data availability and expected differences in disease severity: those aged 65 years or older (not in LTC), and those in LTC. Post–COVID-19 condition was defined as experiencing COVID-19 symptoms for 3 or more months; this occurs in approximately 15% of adults who

self-report as having COVID-19.[2] We also address considerations of current testing policies (i.e., using data from the spread of Omicron variants in 2022) and therapeutic effects of NMV-r.

Policy Question

1. What are the health system impacts, access, and funding considerations of offering NMV-r as an outpatient treatment option for COVID-19 in Canada?

Main Take-Aways

The policy question involves several considerations: understanding the transition of COVID-19 into an endemic disease, the provincial and territorial access to NMV-r, the therapeutic effects of NMV-r (including contraindications), identifying cohorts at high risk of developing severe disease, and the potential use of NMV-r if access is expanded.

Objective

The objective was to conduct a CUA and BIA of NMV-r for outpatient treatment of COVID-19 in Canada.

Research Question

We addressed the previously noted policy question by exploring the following research question:

What is the cost-effectiveness, budget impact, and health system impact of NMV-r as an outpatient treatment for COVID-19 in populations understood to be at increased risk of severe outcomes?

Economic Analysis

Review of Economic Literature

A BIA is required to assess the affordability of implementing the intervention across the entire eligible population, accounting for the resources required to put the intervention into effect.[16] Considerations of budget constraints and drug supply can have an important role in resource allocation.[15] In the context of outpatient treatments for COVID-19, factors such as the size of the eligible population over time; prevalence or incidence of the disease; vaccination rates among the eligible population; burden of disease; intervention uptake; and impact on downstream health care resource use, such as inpatient and intensive care unit (ICU) admissions, should be considered. Carrera-Hueso et al. estimated that, in Spain, the COVID-19 burden during the pandemic was 12.3% of the total public health expenditure, greater than the burden associated with cancer, multiple sclerosis, and diabetes.[17] Treatments and vaccines for COVID-19 in the appropriate

patient population, while considered a major investment, have the potential to substantially save costs due to the health care resource use associated with COVID-19.[18,19]

The potential of NMV-r to be cost-saving is supported by evidence from several countries, although generalizability of economic evidence to other settings can be difficult due to differences in factors such as health system structure; local care pathways; and unit costs of health care resources, including drug costs.[20] Wai et al.[12] (data from 2022) found that the use of either NMV-r or molnupiravir was associated with cost-savings in terms of reduced clinic re-attendance and unplanned hospital admissions, and shorter length of hospital stays, compared with standard of care in Hong Kong (NMV-r cost US$331,105.27 per death averted, but saved US$5,502.53 per death averted compared to standard of care). Jo et al.[13] (data from 2022) found that NMV-r was more cost-effective than molnupiravir (compared with standard of care) from a health system perspective in Korea across 3 risk groups: all adult patients (aged 20 years or older), adult patients aged 60 years or older, and adult patients with underlying health conditions. Using a Markov model and a hypothetical cohort of 10 million adult patients in China with mild to moderate COVID-19 infection at a high risk of developing severe disease, Zhang et al.[14] (data from 2022) found that under the current marketing price of NMV-r in China, the use of NMV-r is cost-effective compared to no NMV-r among patients aged 80 years or older, regardless of vaccination status. Savikina et al.[15] used existing literature up to 2022 and found that providing NMV-r to unvaccinated patients at high risk of developing severe disease (also similarly described in other studies)[21,22] was cost-saving, as long as the effectiveness of NMV-r against hospitalization for this population was greater than 33%, while the cost-effectiveness of treating alternative vaccination or risk status populations with NMV-r depended on the willingness-to-pay (WTP) threshold, the likelihood of developing severe disease, and the cost and effectiveness of treatment.

Economic Evaluation

We conducted a CUA examining outpatient treatment strategies for NMV-r. We developed a stochastic state-transition model that included clinical outcomes associated with COVID-19 infection (undetected and lab-confirmed cases through polymerase chain reaction [PCR]) using data from the Canadian Institute of Health Information (CIHI), Alberta Health, and the scientific literature. The model stratified the population into 3 patient cohorts: those younger than 65 years (not in LTC), those aged 65 years or older (not in LTC), and those in LTC. These cohorts aligned well with the best available data related to NMV-r effect estimates and severity. An evaluation of 5 outpatient treatment scenarios focused on cohorts at higher risk of developing severe disease, which included people aged 65 years or older (not in LTC), and those in LTC.

Primary Economic Analysis

To address the research question, an economic evaluation was conducted to assess costs, health outcomes, and cost-effectiveness of 5 COVID-19 outpatient treatment scenarios for NMV-r compared to baseline in Canada. The scope and analytical approach taken in this economic evaluation were based on the best available data identified from clinical reviews, scientific literature, and data repositories. This evaluation was based on Canadian data obtained from CIHI and supplemented with data from Alberta Health and other literature, including reviews by CDA-AMC. CIHI provided COVID-19 data related to severity (for inpatient and critical care [ICU care], deaths, and length of stay [LOS]) for Canada, and Alberta Health provided NMV-r

dispensation data for Alberta. COVID-19 case data by age and geographic location were obtained from the COVID-19 epidemiology update published by PHAC.[23]

The reference scenario was defined as COVID-19 trends in 2022 in Canada. While there were some regional differences in access to NMV-r in 2022, general recommendations included adults with mild to moderate COVID-19 who were at high risk of developing severe disease.[24] Access to NMV-r in 2022 included considerations for risk factors such as vaccination status, age, comorbidities, and specific health settings.[25]

The 5 NMV-r uptake scenarios were selected following consultation with the CoLab team and a clinical expert. The scenarios were selected to represent expected outpatient use of NMV-r, if broadly available, and with consideration for potential drug interactions and adverse events. These scenarios are described as follows:

Reference scenario: COVID-19 cases and hospital dispositions in 2022 in Canada

Scenario 1: NMV-r treatment of infections in 10% of those aged 65 years or older (not in LTC) and 50% of those in LTC (low uptake scenario)

Scenario 2: NMV-r treatment of infections in 20% of those aged 65 years or older (not in LTC) and 75% of those in LTC (moderate uptake scenario)

Scenario 3: NMV-r treatment of infections in 50% of those in LTC (LTC low uptake scenario)

Scenario 4: NMV-r treatment of infections in 75% of those in LTC (LTC high uptake scenario)

Scenario 5: NMV-r treatment of infections in 30% of those aged 65 years or older (not in LTC) and 75% of those in LTC (high uptake scenario)

Type of Economic Evaluation

This economic evaluation used a stochastic state-transition model that included clinical outcomes associated with COVID-19 infection. The advantage of using a state-transition model compared to other analytical methods is that it captures dynamics related to clinical outcomes — such as transfers between inpatient care, critical care, post–COVID-19 condition, and death — while quantifying costs and QALYs for patient pathways within the health system. The stochasticity implemented in the model (analogous to probabilistic sensitivity analysis) allowed for variations in model inputs and reporting of 95% CrIs or standard errors as part of the results. This evaluation was based on data mainly from Canada (excluding Quebec) obtained from CIHI, and supplemented with data from Alberta Health and other literature including reviews by CDA-AMC.[3] The time horizon for this model was 1 year, while lifetime QALY losses due to death were also included in this analysis, with an assumed discount rate of 1.5%.

The state-transition model was stratified into 3 cohorts related to risk of severe outcomes: those younger than 65 years (not in LTC), those aged 65 years or older (not in LTC), and those in LTC. These cohorts aligned well with the best available data related to NMV-r effect estimates and severity.[3,26-29] As outpatient treatment strategies would be available for those with a positive rapid test with a primary care provider consultation, it was important to consider the cohort of infections (undetected and lab-confirmed cases

through PCR) and not solely cases reported to the surveillance system (i.e., lab-confirmed cases through PCR).

As health systems began to reduce community testing for COVID-19 in 2022, an adjustment of cohort size (from lab-confirmed cases to all infections, including infections that were not detected through the formal testing mechanism) was needed to account for a broader outpatient use of NMV-r. The underreporting factor describes total infections for every case detected through the surveillance system. This ratio was obtained by analyzing serological data from the COVID-19 immunity task force[30] and case data for Canada. Since the model population was based on total infections and severity rates (i.e., hospitalization and death rates) were based on lab-confirmed cases, we adjusted the severity rates to per infection quantities using the underreporting factor. The model simulation was stratified into 2 periods: January to August 2022 (Period 1) and September to December 2022 (Period 2) to better adjust for differences in testing policies, severity, and underreporting rates. Overall, these results were combined at the end of the simulations across the 3 cohorts and 2 periods.

The interventions for outpatient treatment focused on those cohorts at higher risk for severe disease, that is, those aged 65 years or older (not in LTC) and those in LTC. A report from CDA-AMC estimating dispensations of NMV-r in British Columbia, Manitoba, Quebec, Ontario, and Saskatchewan between January 2022 and June 2023 estimated that approximately 70% of those dispensed NMV-r (212,593 adults) were aged 65 years or older.[31] The intervention scenarios considered a reasonable uptake (informed by the CoLab team and a clinical expert) and therapy completion rates (related to drug-drug interactions and/or adverse events) for NMV-r. This economic evaluation did not consider the impact of rebound infection after outpatient treatment with NMV-r. A 2022 cohort study within a COVID-19 community assessment clinic in Toronto estimated that 11% of people dispensed NMV-r (60 of 572) had recurrent symptoms within 7 days after treatment; however, none required re-treatment.[10]

Model data were either directly obtained from, combined with, and/or extrapolated from multiple data sources. The underreporting factor — LTC cases — and LOS were extrapolated from other data sources (refer to the Data Inputs section). Where multiple data sources existed, we combined parameters to estimate appropriate ranges, including effect estimates for NMV-r.

We estimated net monetary benefit (NMB), defined as the monetary value of an intervention for a given WTP threshold for an additional unit of health, and it was used to scale both costs and benefits in the same unit. The NMB was estimated for the following 3 WTP thresholds: $30,000; $50,000; and $100,000. We also presented the incremental cost-effectiveness ratio (ICER) for each NMV-r scenario compared to baseline.

Target Populations and Setting

Based on the best available data, the target population and setting for the state-transition model was the population in Canada who were infected with COVID-19 in 2022. The state-transition model stratified COVID-19 infections according to the cohorts: those younger than 65 years (not in LTC), those aged 65 years or older (not in LTC), and those in LTC.

Treatment

The outpatient COVID-19 treatment considered was NMV-r, which is a combination of 2 antiviral drugs — nirmatrelvir and ritonavir — that aim to stop SARS-CoV-2 from replicating (nirmatrelvir) and improve the medication potency (ritonavir).[32] NVM-r is orally administered within 5 days of onset of symptoms and is taken twice daily for 5 days.[32]

Perspective

The analysis was conducted from a Canadian health care payer perspective.

Time Horizon and Discounting

Based on the availability of data and the time-limited impact of NMV-r, we used a 1-year time horizon. However, to capture the full impact of preventing deaths, lifetime QALY losses due to death were also included in this analysis, with an assumed discount rate of 1.5%. As all other events were only simulated over a 1-year time horizon, no other discounting was applied, as the impact of discounting over the course of a single year is minimal. All simulated individuals were initialized with infection at the starting time, and after 1 year most were in the Recovered or Dead state, with a very small proportion (0.05%) in the Post–COVID-19 Condition state. In addition, the use of case and hospitalization data before 2022 (or pre-Omicron) may not be representative to current severity rates (including mixed population immunity) and endemic management of COVID-19 (i.e., reduced community testing aligned with other respiratory viruses).

Model Structure (Cost-Effectiveness Analysis and BIA)

The model used to conduct this analysis was a stochastic state-transition Markov model representing clinical outcomes associated with COVID-19 infection, with states defined as follows:

- **Outpatient (COVID-19 Infection)**: Individuals infected with COVID-19, but not in hospital
- **Inpatient**: Individuals hospitalized but not in critical care
- **Critical**: Individuals in critical care requiring ICU admission
- **Inpatient After Critical**: Individuals having recovered from the Critical state and being monitored before discharge from hospital
- **Post–COVID-19 Condition**: Consistent with definition by Hanson et al.[33]: “Having at least 1 of the 3 symptom clusters (persistent fatigue with bodily pain or mood swings; cognitive problems; or ongoing respiratory problems) 3 months after symptomatic SARS-CoV-2 infection.”
- **Recovered**: Individuals having recovered from disease states (Outpatient, Inpatient, Inpatient after Critical)
- **Dead**: End state; there were no costs associated with this state.

Individuals beginning in the Outpatient state could move to 1 of the hospitalized states (Inpatient or Critical), after which they progressed either to the Dead or Recovered states. The time-step of the model was 1 day. Individuals in the model did not move directly from Inpatient to Critical. Although this would be a realistic transition, data were not sufficient to determine what proportion of patients entered critical care immediately upon hospitalization rather than after a delay. Therefore, in the model, patients who were at some point in

critical care spent all of their inpatient time in the Inpatient After Critical state. This nonetheless consistently depicted the average total time spent in hospital states for patients, and thus accurately captured costs and health-related utilities accrued by their hospital stay. Modelled individuals entered the Dead state from either the Inpatient or Critical states. In reality, deaths occurred in individuals that were not admitted to hospital as well, especially coming from LTC facilities; however, the data on deaths directly from LTC were not available and therefore not included in this model. Patients that did not die, either recovered fully or first spent time in the Post–COVID-19 Condition state before moving to the Recovered state. The proportion of individuals that moved to the Post–COVID-19 Condition state differed depending on whether they were in the Outpatient, Inpatient, or Critical state, consistent with proportions reported in Hanson et al.[33] The model accounted for underreporting, and therefore the Outpatient state represented all those infected with COVID-19. For COVID-19, lab-confirmed cases reported to the surveillance system did not capture all infections in the community. For an outpatient treatment strategy in which NMV-r could be given to people with a positive rapid test (not reported to the surveillance system), we considered total infections, and the model adjusted transition rates to severe outcomes (i.e., hospitalization) based on the case-infection rate (how many cases detected per community infection). Figure 1 shows model states and transitions.

The stochastic state-transition model was stratified into 3 cohorts: those younger than 65 years (not in LTC), those aged 65 years or older (not in LTC), and those in LTC. Interventions for outpatient treatment only targeted those at higher risk for severity (i.e., those aged 65 years or older [not in LTC], and those in LTC). As outpatient treatment strategies would be available to those with a positive rapid test following consultation with a primary care provider, it is important to consider the time period of the infections. The transition to endemic management of COVID-19 in 2022, and accompanying changes in case-detection rates, highlighted a need to stratify the data into 2 periods: January to August 2022 (period 1) and September to December 2022 (period 2).

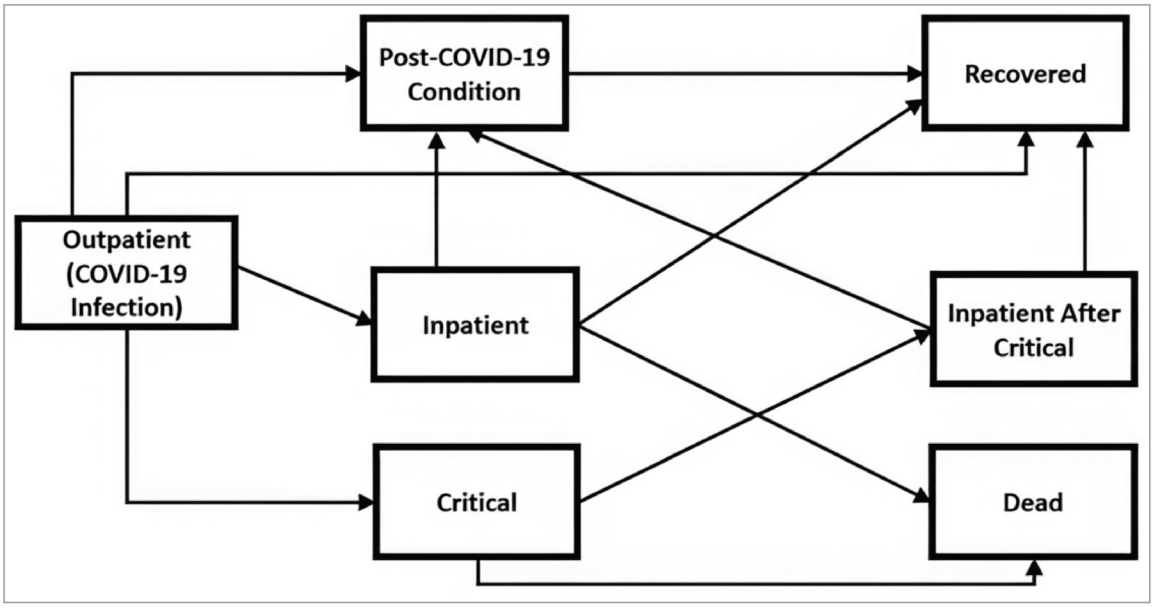
Data Inputs

Table 1 describes the stochastic state-transition model parameters related to outpatient and inpatient transitions with sample distributions and standard deviations (SDs) among COVID-19 cases (refer to Table 21 for additional data transformations). These transitions are stratified by period 1 (January to August 2022) and period 2 (September to December 2022), and by cohort (those aged < 65 years, those aged ≥ 65 years, and those in LTC). Two periods were selected to adjust for differences in community testing across different time periods in 2022 (as COVID-19 testing became more aligned with testing efforts for other respiratory viruses). Across both time periods, the Omicron variant was the main variant in circulation. Data sources used in the analysis include data from CIHI, Alberta Health, PHAC,[23] and the COVID-19 Immunity Task Force.[30] Because COVID-19 severity parameters obtained from CIHI for Canada do not include Quebec, COVID-19 cases used to initialize the model and model input parameters were adjusted to also not include Quebec (refer to Table 2, Table 3, and Table 4). All model parameters except for time to symptom resolution were varied based on the SD. This simulation method is analogous to a probabilistic sensitivity analysis. Proportion and time-related transition parameters were assumed to follow the beta and gamma distributions, respectively. For parameters that did not have SDs, assumed SDs of plus or minus 5% of model inputs were used.

The underreporting factor defined as the number of cases detected per infection in the community was estimated using seroprevalence and time series lab-confirmed cases of COVID-19 data in Canada (including Quebec) by age group (those aged < 65 years, those aged ≥ 65 years) (refer to the Clinical Parameters and Model Validation sections). This ratio was used to scale from case to infection rates for transitions from the Outpatient state to the Inpatient, Critical, and Post–COVID-19 Condition states. Initial community infections were obtained using the underreporting factor, population totals from Canada (excluding Quebec), and the case distribution by LTC status in Alberta (refer to Table 4).

The LOS for the Inpatient and Critical states was estimated (refer to Table 21) from CIHI data. Bayesian inference was used to estimate the distribution of the rate patients leave Inpatient and Critical states. This was determined by first using the method of moments to estimate the Weibull distribution that had the LOS mean, $\bar{\theta}$, and LOS standard deviation, s, given by the hospitalization data from CIHI, respectively. Next, a random sample of n LOS values was taken from the estimated Weibull distribution, where n was the number of observations given by the hospitalization data from CIHI. Then, an exponential distribution, $EXP(\lambda)$, with an inverse gamma distributed rate, $\lambda \sim INVGAM\left(\frac{n}{\theta}, n\right)$, is fit to the n random samples from the estimated Weibull distribution to determine the distribution of the rate at which patients leave the Inpatient and Critical states.

Figure 1: Model Diagram of the State-Transition Model for COVID-19



ICU = intensive care unit.

Note: "Critical" refers to individuals in critical care requiring ICU admission.

The model is stratified into 3 cohorts of COVID-19 infections: those younger than 65 years, those aged 65 years or older, and those in LTC (not shown). This model simulates each cohort and period independently (i.e., period 1: January 2022 to August 2022 and period 2: September 2022 to December 2022).

The death rate was estimated from CIHI data. However, due to data availability, in this analysis deaths in LTC represent people who died during hospitalizations, and this does not capture LTC residents who died outside these facilities.

The therapeutic effect of NMV-r was obtained using Alberta Health data and a systematic review previously conducted by CDA-AMC (refer to the Clinical Parameters section). The therapeutic effect for NMV-r described a range of estimates from multiple sources, which was applied to inpatient admissions, inpatient LOS, and deaths from Inpatient and Critical states. Per patient-day costs were estimated using LOS and total cost estimates from CIHI.

Health utilities were assigned to each state for the purpose of calculating QALYs from running the model (Table 7). Baseline health utilities associated with healthy individuals were obtained from health-adjusted life expectancy (HALE) tables published by Statistics Canada,[34] and cross-referenced with the average age of cases[35] in modelled cohorts. Health utilities immediately following hospital discharge and for post–COVID-19 condition were obtained from Poudel et al.,[36] and were further used to infer health utilities for inpatients and outpatients, respectively.

Table 1: Stochastic State-Transition Model Parameters Related to Outpatient and Inpatient Transitions Including Sample Distributions and SDs Among COVID-19 Cases

Symbol	Quantity	Source	Sample distribution	Mean (SD): age < 65 years	Mean (SD): age ≥ 65 years	Mean (SD): LTC
Period: January 2022 to August 2022						
$\vec{T}_{ah}$	LOS hospital (days)	CIHI	Weibull	10 (26)	16 (25)	43 (55)
$\vec{T}_{c}$	LOS critical care (days)	CIHI	Weibull	9 (16)	9 (14)	9 (17)
$\vec{T}_{ah\_c}$	LOS hospital among those admitted to critical care (days)	CIHI	Weibull	22 (44)	23 (30)	58 (72)
$\vec{p}_{o-h}$	Proportion of all lab-confirmed cases that are admitted to inpatient hospital	CIHI	Beta	0.028 (± 5%)	0.359 (± 5%)	0.05 (± 5%)
$\vec{p}_{o-\mathrm{c}}$	Proportion of all lab-confirmed cases that are admitted to critical	CIHI	Beta	0.006 (± 5%)	0.055 (± 5%)	0.003 (± 5%)
$\vec{p}_{c-d}$	Proportion of critical patients that die	CIHI	Beta	0.169 (± 5%)	0.332 (± 5%)	0.135 (± 5%)
$\vec{p}_{\mathrm{h}-d}$	Proportion of inpatients that die	CIHI	Beta	0.016 (± 5%)	0.126 (± 5%)	0.072 (± 5%)
$\vec{r}_{\mathrm{eff}}$	Underreporting factor	CIHI[30]	Beta	0.082 (± 5%)	0.117 (± 5%)	0.117 (± 5%)

Symbol	Quantity	Source	Sample distribution	Mean (SD): age < 65 years	Mean (SD): age ≥ 65 years	Mean (SD): LTC
Initial total cases		CIHI	NA	1,113,626	131,443	114,427
Period: September 2022 to December 2022						
$\vec{T}_{ah}$	LOS hospital (days)	CIHI	Weibull	15 (40)	19 (36)	57 (73)
$\vec{T}_{c}$	LOS critical care (days)	CIHI	Weibull	9 (18)	8 (16)	8 (9)
$\vec{T}_{ah\_c}$	LOS hospital among those admitted to critical care (days)	CIHI	Weibull	29 (64)	27 (58)	71 (103)
$\vec{p}_{o-h}$	Proportion of all lab-confirmed cases that are admitted to inpatient hospital	CIHI	Beta	0.143 (± 5%)	0.280 (± 5%)	0.217 (± 5%)
$\vec{p}_{o-\mathrm{c}}$	Proportion of all lab-confirmed cases that are admitted to critical	CIHI	Beta	0.033 (± 5%)	0.038 (± 5%)	0.015 (± 5%)
$\vec{p}_{c-d}$	Proportion of critical patients that die	CIHI	Beta	0.161 (± 5%)	0.294 (± 5%)	0.073 (± 5%)
$\vec{p}_{\mathrm{h}-d}$	Proportion of inpatients that die	CIHI	Beta	0.022 (± 5%)	0.118 (± 5%)	0.060 (± 5%)
$\vec{r}_{\mathrm{eff}}$	Underreporting factor	CIHI[30]	Beta	0.038 (± 5%)	0.066 (± 5%)	0.066 (± 5%)
Initial total lab-confirmed cases		CIHI	NA	62,932	85,129	15,929
Period: January 2022 to December 2022						
$\vec{T}_{sr}$	Total time to symptom resolution (days)	Siemieniuk et al[37]	Gamma	9.9	9.9	9.9
Period: January 2022 to December 2022						
$\vec{p}_{orl-l}$	Proportion of cases that develop post–COVID-19 condition	Wulf Hanson et al[33]	Beta	0.057 (± 5%)	0.057 (± 5%)	0.057 (± 5%)
$\vec{p}_{hrl-l}$	Proportion of hospitalized patients that develop post–COVID-19 condition	Wulf Hanson et al[33]	Beta	0.275 (± 5%)	0.275 (± 5%)	0.275 (± 5%)
$\vec{p}_{crl-l}$	Proportion of critical patients that develop post–COVID-19 condition	Wulf Hanson et al[33]	Beta	0.431 (± 5%)	0.431 (± 5%)	0.431 (± 5%)
$\vec{T}_{l}$	Mean duration of post–COVID-19 condition (days)	Wulf Hanson et al[33]	Gamma	139.903 (± 7)	139.903 (± 7)	139.903 (± 7)

CIHI = Canadian Institute of Health Information; LOS = length of stay; LTC = long-term care; NA = not applicable; SD = standard deviation.

Note: Case-infection ratio is interpreted as lab-confirmed cases per infection in the community. This is estimated as the reciprocal of the underreporting factor (refer to the Clinical Parameters section).

Estimation of the Population in Canada by Cohort

Because CIHI data for severity did not include data from Quebec, we adjusted COVID-19 cases used in the model to also not include Quebec. Data sources from Alberta Health, PHAC, and the National Institute of Public Health Quebec were used to estimate COVID-19 cases for all of Canada for model periods in 2022 by the following model cohorts: those younger than 65 years, those aged 65 years or older, and those in LTC. Table 2 provides the proportion of contributions by age distribution of COVID-19 cases in Quebec since 2020. These age-specific proportions were used to distribute total COVID-19 cases for Quebec across the model periods (January 2022 to August 2022 and September 2022 to December 2022) and age (refer to Table 2). (Note: For the 60 to 69 age group, the midpoint was used to distribute between the age cohorts). Table 3 describes the estimation of COVID-19 cases in Canada with and without the Quebec cases. These totals were stratified by LTC status using the estimates obtained from Alberta Health described in Table 4 (refer to the initial total cases in Table 1).

Table 2: Estimation of COVID-19 Cases in Quebec

Age group, in years	Proportion of total COVID-19 cases in Quebec (since 2020)	Number of COVID-19 cases in Quebec (January 2022 to August 2022)	Number of COVID-19 cases in Quebec (September 2022 to December 2022)
0 to 9	0.066	34,111	7,204
10 to 19	0.083	43,150	9,113
20 to 29	0.155	80,209	16,939
30 to 39	0.161	83,456	17,625
40 to 49	0.157	81,363	17,183
50 to 59	0.127	65,848	13,906
60 to 69	0.080	41,741	8,815
70 to 79	0.069	35,722	7,544
80 to 89	0.068	35,037	7,399
90+	0.035	18,363	3,878
Total	**1.000**	**518,998**[23]	**109,608**[23]

PHAC = Public Health Agency of Canada.

Sources: National Institute of Public Health Quebec[38] and PHAC.[23]

Table 3: Estimation of COVID-19 Cases in Canada

Period	Age < 65 years	Age ≥ 65 years	Total
Cases (Canada)			
January 2022 to August 2022	1,529,746	348,749	1,878,495
September 2022 to December 2022	150,356	123,243	273,598
Cases (Quebec)			
January 2022 to August 2022	409,006	109,992	518,998
September 2022 to December 2022	86,379	23,229	109,608
Cases (Canada excluding Quebec)			
January 2022 to August 2022	1,120,740	238,757	1,359,497
September 2022 to December 2022	63,977	100,013	163,990

PHAC = Public Health Agency of Canada.

Sources: National Institute of Public Health Quebec[38] and PHAC.[23]

Table 4: Case Distribution by LTC Status in Alberta

Period	Age < 65 years (LTC cases out of total cases)	Age ≥ 65 years (LTC cases out of total cases)
January 2022 to August 2022	0.006 (1,210 out of 190,638)	0.449 (16,371 out of 36,423)
September 2022 to December 2022	0.016 (176 out of 10,776)	0.149 (1,544 out of 10,375)

LTC = long-term care.

Source: Alberta Health.

Clinical Parameters

Therapeutic Effect Estimates: NMV-r for Outpatient Treatment of COVID-19

Based on the best available evidence, Alberta Health data (refer to Table 22) and selected studies (based on cohort and availability of data) from the previously conducted systematic review conducted by CDA-AMC[3] (refer to Table 23) were used to obtain a range (minimum and maximum of point estimates) of effect estimates for NMV-r as an outpatient treatment for COVID-19. This constructed range allowed for an internal sensitivity analysis of NMV-r effects and analysis of model outcomes as distributions. Relative risks were obtained or estimated directly from the data and/or published studies.

Alberta Health provided data related to NMV-r dispensations; this included total people with NMV-r dispensations who were cases (PCR confirmed), total people admitted to inpatient units within 30 days after their dispensation date, LOS for people admitted to inpatient units who had a dispensation for NMV-r, and total deaths of people who were dispensed NMV-r. These data were used to estimate the relative risks compared to all case rates provided by Alberta Health. In 2022, approximately 1% and 6% of cases in Alberta were dispensed NMV-r in period 1 (January 2022 to August 2022) and Period 2 (September 2022 to

December 2022), respectively. NMV-r had an impact on all hospitalizations (admission rate and LOS) and death rates (from inpatient and critical states). Table 22 provides the relative risk calculations obtained from the Alberta Health data and Table 23 describes how the range in effect estimates were obtained. As we do not know what the uptake of NMV-r will be in the outpatient population, we assumed various coverage rates as part of a scenario analysis (refer to the Scenario Analysis and Sensitivity Analysis sections).

Table 5 provides the relative risk estimates obtained from Eze et al.[3] and Alberta Health data. The effect estimates for inpatient rates (admission rates and LOS) and death rates include a point estimate and the range of values. The point estimate was the midpoint of the range coming from the high and low estimates obtained from Alberta Health, and selected studies from the Eze et al.[3,27-29,39] and Alberta Health data. In Table 5, NMV-r therapy effects were assumed to be the same for people aged 65 years or older and in LTC.

Table 5: Therapeutic Table of NMV-r Effect Estimates for the Outpatient Treatment of COVID-19

Symbol	Quantity	NMV-r therapy effect (relative risk)		Therapy effect source
		Age ≥ 65 years (range)	LTC (range)	
Period 1: January 2022 to August 2022				
$\vec{T}_{h\_therapy}$	Length of inpatient stay	0.63 (0.61 to 0.65)	0.63 (0.61 to 0.65)	Eze et al.,[3] Alberta Health data
$\vec{p}_{o-h\_therapy}$	Proportion of all cases that are admitted to inpatient unit	0.41 (0.29 to 0.53)	0.41 (0.29 to 0.53)	
$\vec{p}_{o-c\_therapy}$	Proportion of all cases that are admitted to critical care unit	0.46 (0.39 to 0.53)	0.46 (0.39 to 0.53)	
$\vec{p}_{h-d\_therapy}$	Proportion of inpatient individuals that die	0.43 (0.17 to 0.69)	0.43 (0.17 to 0.69)	
$\vec{p}_{c-d\_therapy}$	Proportion of critical individuals that die	0.43 (0.17 to 0.69)	0.43 (0.17 to 0.69)	
Period 2: September 2022 to December 2022				
$\vec{T}_{h\_therapy}$	Length of inpatient stay	0.68 (0.65 to 0.71)	0.68 (0.65 to 0.71)	Eze et al.[3] Alberta Health data
$\vec{p}_{o-h\_therapy}$	Proportion of all cases that are admitted to inpatient unit	0.37 (0.21 to 0.53)	0.37 (0.21 to 0.53)	
$\vec{p}_{o-c\_therapy}$	Proportion of all cases that are admitted to critical care unit	0.46 (0.39 to 0.53)	0.46 (0.39 to 0.53)	
$\vec{p}_{h-d\_therapy}$	Proportion of inpatient individuals that die	0.40 (0.17 to 0.62)	0.40 (0.17 to 0.62)	
$\vec{p}_{c-d\_therapy}$	Proportion of critical individuals that die	0.40 (0.17 to 0.62)	0.40 (0.17 to 0.62)	

LTC = long-term care; NMV-r = nirmatrelvir-ritonavir.

Source: Eze et al.[3] and Alberta Health data.

Underreporting Factor

The underreporting factor (interpreted as the number of COVID-19 infections in the community per lab-confirmed case) was estimated using serology (anti-N or infection acquired) data,[30] COVID-19 lab-confirmed cases from PHAC,[23] and the 2022 population of Canada.[40] Serology estimates were obtained for dates that closely aligned with the 2-period stratification in the model: January 1, 2022, to August 31, 2022, and September 1, 2022, to December 31, 2022. The serology dates used were January 4, 2022; August 28, 2022; and December 27, 2022 (Table 24). Serology estimates were only available by age categorized as younger than 60 years and 60 years or older, and were assumed to be the same as those for age categorized as younger than 65 years and 65 years or older (the age groups used in the model). Table 25 describes the detailed estimation of total infections using the underreporting factor. Because the serology data included Quebec, to appropriately estimate the underreporting factor, we had to use an estimate of lab-confirmed cases that included Quebec. However, in the model, we used total infections excluding Quebec, as the severity data obtained from CIHI did not include Quebec. Therefore, case and infection totals in Table 24 and Table 25 are different compared to estimates in Table 1 and Table 6.

The underreporting factor was estimated by aligning the successive difference in serology estimates between the 3 dates (January 4, 2022; August 28, 2022; and December 27, 2022) with COVID-19 lab-confirmed cases obtained from PHAC for the 2 periods (January 1, 2022, to August 31, 2022, and September 1, 2022, to December 31, 2022). Although serology dates were not aligned directly with the PHAC data, this would have minimal impacts on the underreporting estimates obtained using this approach.

The difference in serology (January 11, 2022, to August 27, 2022, and August 27, 2022, to December 27, 2022) (Table 24) was multiplied by the 2022 population of Canada (those aged < 65 years: 29.0 million, and those aged ≥ 65 years: 10.0 million) and proportion case contribution of those aged 65 years or older and those in LTC (Table 25) to obtain new infections that occurred between each date range and among cohorts.

Total infections were divided by total cases obtained from PHAC (January 1, 2022, to August 31, 2022; September 1, 2022, to December 31, 2022) to obtain the underreporting factor (Table 24 and Table 25). Table 6 provides the underreporting factor for COVID-19 cases in Alberta by the 3 cohort groups and 2 periods. The underreporting factor was then used in the model to adjust the transitions into higher severity states (i.e., inpatient or critical care) based on total infections rather than lab-confirmed cases (which is how they were estimated in the data).

As shown in Table 6, the underreporting factor for LTC was assumed to be the same as it was for the cohort of those aged 65 years or older. The underreporting factor was likely lower for LTC; however, this magnitude of difference was not available in the literature.

Table 6: Underreporting Factor and Initial Total Infections for COVID-19 Cases in Canada

Period 1 (January 2022 to August 2022)			Period 2 (September 2022 to December 2022)		
Age < 65 years	Age ≥ 65 years	LTC	Age < 65 years	Age ≥ 65 years	LTC
Initial conditions: total initial infections					
13,563,890	1,119,486	974,563	1,672,553	1,284,167	240,284
Underreporting factor (interpretation: number of COVID-19 infections in the community per case detected)					
12.2	8.5	8.5	26.6	15.1	15.1

LTC = long-term care.

Utilities

The health utility associated with the recovered state was assumed to be that of healthy individuals and is estimated from HALE tables published by Statistics Canada[34] and assigned to model cohorts according to the average age of individuals with COVID-19 in that cohort. We estimated recovered utilities separately for the 2 time periods captured in the model. Within the model-simulated time of 1 year, the accrued QALYs lost due to death did not fully account for the overall QALYs lost from patient deaths, which extended beyond 1 year. As a result, upon entry into the Dead state in the model, a fixed QALY decrement (accounting for discounting) was applied equal to the average HALE for individuals in the modelled cohort, thereby capturing the loss of expected lifetime QALYs. Poudel et al.[36] reported health utilities for patients with COVID-19 immediately upon discharge from hospital, as well as for post–COVID-19 condition. Due to a lack of published studies providing health utilities during hospitalization, and with the observation that the recovery of health utility back to baseline, as reported by Poudel et al.,[36] is slow following hospitalization, we inferred that the utility during noncritical hospitalization (inpatient and inpatient after critical) is equal to that immediately after discharge. Additionally, health utilities during the period of infection of outpatients were not available from published studies, so we assumed the health utility of the Outpatient state was the same as that of post–COVID-19 condition, as reported by Poudel et al.[36] Finally, individuals in the Critical state were often either unconscious or had a very low health-related quality of life, and the utility for the Critical state was assumed to be 0 for simplicity. The utility estimates for the stochastic state-transition model are described in Table 7.

Table 7: Utility Estimates for the Stochastic State-Transition Model

Symbol	State	Annual utility (SD)	Entry utility (SD)	Source
$\overrightarrow{Ut}_o$	Outpatient	0.76 (0.076)	0	Poudel et al.[36]
$\overrightarrow{Ut}_c$	Critical	0	0	Estimate
$\overrightarrow{Ut}_h$	Inpatient	0.60 (0.06)	0	Poudel et al.[36]
$\overrightarrow{Ut}_{d1a}$	Period 1: Dead (age < 65 years)	0	–27.6 (0.04)	Statistics Canada and PHAC[34,41]

Symbol	State	Annual utility (SD)	Entry utility (SD)	Source
$\overrightarrow{Ut}_{d1b}$	Period 1: Dead (age ≥ 65 years or LTC)	0	–6.4 (0.03)	Statistics Canada and PHAC[34,41]
$\overrightarrow{Ut}_{d2a}$	Period 2: Dead (age < 65 years)	0	–27.3 (0.03)	Statistics Canada and PHAC[34,41]
$\overrightarrow{Ut}_{d2b}$	Period 2: Dead (age ≥ 65 years or LTC)	0	–6.0 (0.03)	Statistics Canada and PHAC[34,41]
$\overrightarrow{Ut}_{i}$	Inpatient After Critical	0.60 (0.06)	0	Poudel et al.[36]
$\overrightarrow{Ut}_{l}$	Post–COVID-19 Condition	0.76 (0.076)	0	Poudel et al.[36]
$\overrightarrow{Ut}_{r1a}$	Period 1: Recovered (age < 65 years)	0.89 (0.089)	0	Statistics Canada and PHAC[34,41]
$\overrightarrow{Ut}_{r1b}$	Period 1: Recovered (age ≥ 65 years or LTC)	0.73 (0.073)	0	Statistics Canada and PHAC[34,41]
$\overrightarrow{Ut}_{r2a}$	Period 2: Recovered (age < 65 years)	0.89 (0.089)	0	Statistics Canada and PHAC[34,41]
$\overrightarrow{Ut}_{r2b}$	Period 2: Recovered (age ≥ 65 years or LTC)	0.70 (0.070)	0	Statistics Canada and PHAC[34,41]

LTC = long-term care; SD = standard deviation.

Costs

All costs were reported in 2022 Canadian dollars and, where necessary, were inflated to 2022 Canadian dollars using the Consumer Price Index for all items in Canada. Table 8 provides the hospital resource and drug costs used in the health economic evaluation, including the costs associated with NMV-r purchasing and dispensation.[42-45] Costs from CIHI were scaled from total to per-day costs using LOS estimates for the Inpatient and Critical states. We added per patient-day costs for inpatient and ICU physicians from the literature[46] because these costs were not included in the total costs reported by CIHI. Costs related to the implementation of the outpatient strategy (e.g., administration costs) and health care costs related to post–COVID-19 condition were not included in this analysis.

Table 8: Hospital Resource and Drug Costs

Hospital resource or drug cost	Cost (SD or range) in 2022 Canadian dollars	Treated state	Source
Period 1: Hospital stay, inpatient (per patient-day)			
Age < 65 years	$1,368 (SD = 68.39)	Inpatient or Inpatient After Critical	CIHI
Age ≥ 65 years	$1,118 (SD = 55.92)		
LTC	$913 (SD = 45.66)		

Hospital resource or drug cost	Cost (SD or range) in 2022 Canadian dollars	Treated state	Source
Period 1: Hospital stay, ICU (per day)			
Age < 65 years	$3,713 (SD = 185.66)	Critical	CIHI
Age ≥ 65 years	$3,640 (SD = 182.01)		
LTC	$4,573 (SD = 228.65)		
Period 2: Hospital stay, inpatient (per day)			
Age < 65 years	$1,182 (SD = 59.09)	Inpatient or Inpatient After Critical	CIHI
Age ≥ 65 years	$1,042 (SD = 52.10)		
LTC	$874 (SD = 43.69)		
Period 2: Hospital stay, critical care (per day)			
Age < 65 years	$3,668 (SD = 183.40)	Critical	CIHI
Age ≥ 65 years	$3,366 (SD = 168.31)		
LTC	$4,107 (SD = 205.34)		
Inpatient physician (per patient-day)	$48.73 (SD = 16.30)	Inpatient or Inpatient After Critical	Lau et al.[46]
ICU physician (per patient-day)	$254.70 (SD = 128.22)	Critical	Lau et al.[46]
NMV-r (per patient)[a]	$725 (range, $685 to $1918)	COVID-19 infections: Outpatient	Institute for Clinical and Economic Review, AARP, Zilber,[43-45] and CDA-AMC
Dispensation cost (per patient)	$22.15		Alberta Blue Cross[47]

CIHI = Canadian Institute of Health Information; ICU = intensive care unit; LTC = long-term care; NMV-r = nirmatrelvir-ritonavir; SD = standard deviation.

[a]The price range was determined from publicly available information on drug costs in the US and Europe.

Note: Period 1 was from January 2022 to August 2022 and period 2 was from September 2022 to December 2022.

Note: The cost conversion to US dollars was US$1 = CA$1.37.

Sources: CIHI Institute for Clinical and Economic Review (2022),[43] Nania (2023),[44] Zilber (2023),[45] CDA-AMC, Lau et al.,[46] Alberta Blue Cross.[47]

Scenario Analysis and Sensitivity Analysis

Five scenarios and 1 reference scenario were considered in this health economic evaluation, all of which are described in Table 9. All scenarios described in Table 9 highlight targeting outpatient treatment of NMV-r to the cohorts of those aged 65 years or older and those in LTC, as it was understood that these groups were at a higher risk for severe COVID-19. Although immunocompromised stratifications were highlighted in Dormuth et al.[7] as a meaningful population to study, this could not be further explored due to data limitations. The 5 scenarios were selected following consultation with the CoLab team and a clinical expert. Uptake was defined as a reasonable estimate of NMV-r use if funded publicly for outpatient treatment of COVID-19. The scenarios were selected to represent expected outpatient use of NMV-r if broadly available and with consideration for potential drug interactions and adverse events. For the reference scenario, we assumed

minimal use of NMV-r. The NMV-r utilization among cases based on Alberta Health data during 2022 was 4.6% (for patients aged 65 years or older) and 0.8% (for patients aged younger than 65 years). These utilization estimates reported among cases when adjusted for infections would represent minimal utilization. As a result, the reference scenario did not include costs related to NMV-r treatment.

Furthermore, probabilistic sensitivity analyses were undertaken to address parameter uncertainty associated with the cost-effectiveness of scenarios compared to the reference scenario, across the 3 cohorts and 2 time periods (5,000 simulations). The probabilistic results describe the extent to which parameter uncertainty affected the cost-effectiveness estimates in the model. The SDs for the model parameters used in the stochastic state-transition model are described in Table 1, Table 5, Table 6, Table 7, and Table 8. Standard distributional forms were taken to describe probability distribution functions relating to input parameters (proportions and utilities were characterized by the beta distribution, while LOS and costs were characterized by gamma distributions.

Results of the probabilistic analysis are presented using a cost-effectiveness acceptability curve that highlights the probability that each scenario was optimal compared to baseline ($NMB_{scenario} > NMB_{baseline}$). Scenario analyses describe the NMB and the iNMB and provide ICERs including quadrant location.

Table 9: Scenario Descriptions for NMV-r as Outpatient Treatment

Scenario	Justification
Reference scenario: COVID-19 cases and hospital dispositions in 2022, assuming minimal use (≤ 5%) of NMV-r	The reference scenario focused on representing COVID-19 epidemiology in 2022.
Scenario 1 (low uptake): NMV-r treatment of infections (undetected and lab-confirmed cases) in 10% of those aged ≥ 65 years (not in LTC) and 50% of those in LTC	Scenario 1 was decided upon through consultation with a clinical expert on voluntary observational outpatient uptake of NMV-r among those aged ≥ 65 years and assumed high uptake among those in LTC.
Scenario 2 (moderate uptake): NMV-r treatment of infections in 20% of those aged ≥ 65 years (not in LTC) and 75% of those in LTC	In scenario 2, the magnitude of outpatient uptake of NMV-r among patients aged ≥ 65 years was increased by a 10% increment based on the observational information provided by the clinical expert. The uptake for LTC was increased arbitrarily to 75% to signify higher uptake in consideration of drug interactions and adverse events.
Scenario 3 (LTC low uptake): NMV-r treatment of infections in 50% of those in LTC	Scenario 3 had a focus on outpatient uptake of NMV-r in the LTC cohort similar to scenario 1.
Scenario 4 (LTC high uptake): NMV-r treatment of infections in 75% of those in LTC	Scenario 4 had a focus on outpatient uptake of NMV-r in the LTC cohort similar to scenario 2.
Scenario 5 (high uptake): NMV-r treatment of infections in 30% of those aged ≥ 65 years (not in LTC) and 75% of those in LTC	Scenario 5 was a combined scenario of the highest projected outpatient uptake of NMV-r among patients aged ≥ 65 years and patients in LTC.

LTC = long-term care; NMV-r = nirmatrelvir-ritonavir.

Model Validation

Overall, the validation of the model structure and model inputs occurred through consultations with the Canadian Collaborative Research Network (CCRN), CoLab team, Alberta Health, CIHI, and a clinical expert

to ensure that the model was consistent with current clinical knowledge and Canadian practice. The structure of the stochastic state-transition model was extended from previous work that included multiple iterations and discussions with CCRN. Methods for obtaining model parameters included input from Alberta Health and CIHI (related to a data request) and consultations with the CoLab team and a clinical expert, where necessary.

Internal validity for the reference scenario described in Table 10 included a comparison of severity and serology data and model simulations (across the 3 cohorts and 2 periods) for initial model conditions (defined as the starting values for the population cohorts), as well as total inpatient admissions, critical care admissions, and deaths (including 95% CrIs) that occurred in 2022. Deaths were captured over 1 year, which provided the total that was validated; however, lifetime impacts of those deaths were captured using QALYs.

Initial model conditions represented total infections, which were estimated using serology data[30] (infection acquired anti-N) for Alberta. Serology estimates for patients younger than 60 years and patients aged 60 years or older were assumed to be the same as those for patients younger than 65 years and patients aged 65 years or older, due to data limitations. Table 25 describes the detailed estimation of initial total infections using the 2022 population of Canada,[40] total cases (from CIHI), and serology[30] data. A key limitation with serology data is that it does not account for or quantify reinfection. Reinfection during Omicron (2022) was estimated by the Centers for Disease Control to be from 10.3% (December 19, 2021, to March 19, 2022) to 28.8% (November 6, 2022, to December 31, 2022), compared to 2.7% with the Delta variant (September 5, 2021, to December 18, 2021).[48] Therefore, in this model, initial infections may have been underestimated due to the inability to capture reinfection with serology data.

The initial conditions stratified by cohorts (those younger than 65 years, those aged 65 years or older, and those in LTC) and time periods (January 1, 2022, to August 31, 2022; September 1, 2022, to December 31, 2022) were validated using the serology estimates from January 4, 2022, to December 27, 2022. The serology estimates for the latter period were as follows: for those younger than 65 years, 0.732; for those aged 65 years or older, 0.579; and for all ages, 0.693 (Table 10). Because serology data were not stratified for LTC, the proportion contributions of those aged 65 years or older and those in LTC (Table 24) were used to distribute total infections (for those aged ≥ 65 years). This assumption has minimal impact because approximately 94% of cases of individuals in LTC were among individuals aged 65 years or older in 2022. Initial infections across periods and/or cohorts were summed and divided respectively to the population in Canada. These estimates described in Table 10 showed comparable results overall and by age group. The total inpatient and critical care admissions and deaths from model simulations compared well to the data (Table 10).

Internal validity for scenarios (or treatment effects) was assessed by evaluating simulations at extreme values such as nullifying the cost of NMV-r on cost-effectiveness outcomes for scenarios 1 to 5. This included creating scenarios focusing on 1 cohort and the therapeutic effect of NMV-r to determine if results were reasonable compared to crude estimates.

Table 10: Internal Model Validation of Initial Conditions and Reference Scenario

Internal model validation	Validated estimate (data)	Model estimates
Age	**Serology estimate[30]**	**Proportion infected of total population using case data and underreporting factor[23]**
Total	0.693	0.704
Age < 65 years	0.732	0.775
Age ≥ 65 years	0.579	0.496
Admissions	**Total inpatient and critical admissions in the reference scenario (CIHI data)**	**Reference scenario (model, with 95% CrI): n = 5,000 simulations**
Total inpatient admissions	120,803	120,802 (120,124 to 121,462)[b]
Total critical admissions	19,635	19,634 (19,360 to 19,905)[b]
Total deaths	14,923	14,923 (13,637 to 16,259)

CIHI = Canadian Institute for Health Information; CrI = credible interval.

Note: Serology data for those younger than 60 years and those aged 60 years or older were extrapolated to those younger than 65 years and those aged 65 years or older (difference between January 4, 2022, and December 27, 2022).

Model Assumptions

There were several model assumptions required to either supplement missing information or to simplify the model. These assumptions are listed in Table 11.

Table 11: Key Model Assumptions

Related model parameter or structure	Assumption	Additional comments
Cases	• Cases were defined as those detected through laboratory testing by the surveillance system.	NA
Infections	• Infections were defined as both cases detected and undetected by the surveillance system (i.e., lab-confirmed and not–lab-confirmed infections).	• This was estimated using the underreporting factor informed by serology data.
Time horizon	• The 1-year time horizon was structured around the availability of data. The use of case and hospitalization data before 2022 (or pre-Omicron) may not have been representative of current severity rates (including mixed population immunity) and endemic management of COVID-19 (i.e., reduced community testing aligned with other respiratory viruses).	NA
Overall model structure	• Stratified model into 2 periods (period 1: January 2022 to August 2022; period 2: September 2022 to December 2022) to account for transitions toward current management policies of COVID-19 as an endemic disease.	NA

Related model parameter or structure	Assumption	Additional comments
CIHI data	• Severity data reported by CIHI included reinfections. • Severity data reported by CIHI did not include data from Quebec	• The reinfections in the data were not adjusted.
PHAC data	• For initial cases and infections, cases in Quebec were not included. For estimating the underreporting factor, total COVID-19 cases for Canada (including Quebec) were used to align to the serology data.	NA
Serology data	• A key limitation was that the data did not quantify or include reinfections.	• Initial conditions and underreporting factor were estimated using the best available data.
Costs	• Costs related to the implementation of the outpatient strategy (other than dispensation and purchasing costs) and health care costs related to post–COVID-19 condition were not included in this analysis. • The reference scenario assumed minimal use of NMV-r; therefore, NMV-r costs were not accounted for this scenario. Note: Based on the Alberta Health data in 2022, the utilization among cases was 4.6% for those aged 65 years or older and 0.8% for those younger than 65 years; utilization adjusted for total infections will be much lower and negligible. • The costs considered beyond outpatient treatment included acute care facilities only.	• Health care costs related to COVID-19 management within LTC facilities for patients who could benefit from NMV-r were not captured in the analysis. This may have underestimated the cost-effectiveness of NMV-r in the LTC cohort.
Death transition: from Outpatient, Recovered, and LTC states	• Deaths were only modelled from the Inpatient and Critical states. Death transitions from other model states were challenging to estimate from death data (i.e., interpretations of cause of death as primary, secondary, and contributing cause and location of death [for LTC data]). The LTC cohort was based on the discharge disposition. Estimates such as deaths in facility would be based only on institution transfer from type code. Deaths that occurred following discharge were not included.	• Those in LTC were more likely to die outside of hospital and, therefore, not capturing these deaths could limit the cost-effectiveness of NMV-r in this population.
Post–COVID-19 Condition transition: from Outpatient state	• Incidence of post–COVID-19 condition following recovery from nonhospitalized acute infection was calculated with probability of post–COVID-19 condition per case and adjusted to a rate per infection based on estimated reporting efficiency.	NA
Inpatient and critical care model inputs for LTC	• The LTC data obtained from CIHI had limitations related to how LTC was defined by administrative data, and model inputs for this cohort had more uncertainty.	• If inpatient model inputs for LTC were underestimated (a model input that had a therapeutic effect); this would likely also underestimate the cost-effectiveness of scenarios that focus on outpatient treatment of the LTC cohort.

Related model parameter or structure	Assumption	Additional comments
		• For the LTC cohort, it is possible they received NMV-r in 2022; therefore, the treatment effects may have already been observed in the reference population (reducing overall hospitalization and mortality rate in this population).
NMV-r dispensation	• Because dispensation data were aligned to total infections and therefore serology data (that did not account for reinfections), repeat dispensations were not captured in the CUA and the BIA.	NA
NMV-r therapeutic effects	• Due to data limitations, NMV-r therapy effects were assumed to be the same for people aged 65 years or older and in LTC and for deaths from inpatient and critical care units. • The model indirectly accounted for NMV-r therapy effects on post–COVID-19 condition because proportion transitions to the Post–COVID-19 Condition state differed by the Outpatient and In-Hospital states.	NA
NMV-r outpatient scenarios	• Costs related to the implementation of the NMV-r outpatient strategy (e.g., administration of the program) were not included in this analysis; however, NMV-r procurement costs and dispensation were captured. • Lab-confirmed cases and infections would have equal uptake of NMV-r in all scenarios.	• If NMV-r uptake was greater among cases (confirmed by laboratory testing) compared to infections, this would increase the cost-effectiveness of scenarios.
Underreporting factor	• This was estimated for each period and applied in the simulation. • Serology estimates were only provided by age group stratifications (< 60 years and ≥ 60 years), which were extrapolated to the model cohort groups (< 65 years and ≥ 65 years). • The use of serology estimates did not account for reinfections and censoring of data related to immunity detection. • The underreporting factor for LTC was assumed to be equivalent to that for patients aged 65 years or older; this underreporting factor was likely smaller for LTC due to increased COVID-19 testing within facilities compared to the community setting.	• Transitions toward management of COVID-19 as endemic resulted in a gradual reduction in community testing in 2022 • This was likely less significant in period 1 (January 2022 to August 2022) than period 2 (September 2022 to December 2022).
Utilities	• Utilities for model state were the same across cohorts and periods, except for the Recovered state. Utilities also did not differ by treatment arm.	NA
Utilities: Outpatient and Post–COVID-19 Condition states	• Due to a lack of studies reporting health utilities for outpatients with COVID-19 during their period of infection, utilities were assumed to be the same	NA

Related model parameter or structure	Assumption	Additional comments
	in the Outpatient state and the Post–COVID-19 Condition state.	
Utilities: Inpatient state and Inpatient After Critical state	• Due to a lack of studies reporting health utilities for COVID-19 while in hospital, we assumed the health utility of inpatients (noncritical) to be that reported immediately after discharge. This was justified by the fact that recovery of utility back to baseline is very slow after discharge.	• Using utilities immediately following discharge could underestimate the impact of NMV-r and therefore reduce its cost-effectiveness.
Utilities: Critical state	• Individuals are either unconscious or have a very low health-related quality of life while in critical care; therefore, the utility for the Critical state was assumed to be 0 for simplicity.	NA

BIA = budget impact analysis, CIHI = Canadian Institute of Health Information; CUA = cost-utility analysis; LTC = long-term care; NA = not applicable; NMV-r = nirmatrelvir-ritonavir; PHAC = Public Health Agency of Canada.

Cost-Effectiveness Analysis Results

Main Take-Aways

The results of the CUA suggested that increased use of NMV-r may be cost-effective at commonly used thresholds depending on the rate of treatment uptake, the care setting (LTC or not), and the age group of patients. In scenarios that included NMV-r treatment for both individuals aged 65 years and older and those in LTC, there was potential for cost-effectiveness, taking into account uncertainty. However, scenarios that only included LTC were not as cost-effective as other scenarios. These results may have been influenced by not factoring in the benefits of preventing deaths within LTC facilities, and not considering health care costs associated with reducing the severity of COVID-19 infection within those facilities. Other factors not considered in the model that may have affected cost-effectiveness include the severity of the circulating variants and the therapeutic effect of NMV-r on the circulating variants.

Detailed results of the cost-effectiveness analysis are provided in Table 12 (NMB) and Table 14 (ICERs) with disaggregated results described in Table 13 and Table 15. Using PHAC data on lab-confirmed cases, combined with serology data to estimate total infections that occurred in the population in Canada, we estimated that in a 1-year period during 2022, approximately 18,854,943 people, or 62.7% of people living in Canada (excluding Quebec), were infected with COVID-19. Most infected people only experienced a brief illness and temporary loss of quality of life.

While this may be a small effect at an individual level, given the high prevalence of COVID-19, it represents a significant health burden at a population level. This is reflected in our results when presented as NMB. NMB represents the value of a treatment scenario in dollars for a given WTP per unit of outcome, minus the cost of providing care. For our reference scenario, we estimated 15,954,930 total QALYs over 1 year for the infected population. If we assume a WTP per QALY of $50,000, then the total value of the health of the reference scenario population is $801,530,000,000, or $42,510 per person infected. We then estimated

the expected QALYs and NMB for each of the 5 alternate scenarios. From this, we can calculate the iNMB of each scenario relative to the reference scenario. For example, in scenario 1, the iNMB is $114 (95% CrI, –$540 to $562), in millions of dollars, when compared to the reference scenario at a WTP threshold of $50,000 per QALY. The full set of values for all scenarios is presented in Table 12. Results in Table 12 are the deterministic estimates with 95% CrIs to account for parameter uncertainty. Disaggregated results described in Table 13 highlight the breakdown by state and scenario of QALY and health care costs. The largest contribution of QALY and health care costs were from the Recovered and Inpatient states, respectively.

In Table 14, we present ICERs when scenarios are compared to a common baseline (the reference scenario). Because we were analyzing potential future states, not treatment strategies to be implemented, we did not calculate ICERs when all scenarios were compared to 1 another, as would be typical in cost-effectiveness analyses. Rather, our aim was to illustrate the cost-effectiveness of NMV-r under different possible usage patterns, not to identify a single cost-effective strategy.

Key Results

- Considering data from 2022, NMB across all modelled scenarios, including the reference scenario, was in excess of $477 billion, $798 billion, and $1.599 trillion, for WTP thresholds per QALY of $30,000, $50,000, and $100,000, respectively (Table 12). These numbers result from the fact that simulations depicted a year of outcomes for all infected individuals in Canada (62.7% of the total population), as well as the HALE loss due to all COVID-19 related deaths, where these QALY totals were valued at the given WTP threshold.
- The NMB per person infected for the reference scenario was $25,328, $42,332, and $84,842 for WTP thresholds per QALY of $30,000, $50,000, and $100,000, respectively.
- iNMB shows the difference from the reference scenario, and ranged from –$338 million to $139 million, –$278 million to $617 million, and –$126 million to $1.81 billion, for WTP thresholds per QALY of $30,000, $50,000, and $100,000, respectively (Table 12). There was an increase in costs and an increase in total QALYs in all scenarios (Table 14), with iNMB showing the relative change in valuation of QALYs versus costs. The largest iNMB results from scenarios that included treatment for individuals aged 65 years or older, namely scenarios 2 and 5, with scenario 5 having the largest iNMB.
- At a WTP threshold of $50,000, the deterministic iNMB showed that scenario 1 (low uptake), scenario 2 (moderate uptake), and scenario 5 (high uptake) would be cost-effective compared to the reference scenario.
- Scenario 5 (high uptake) was the most cost-effective option based on the deterministic estimate of iNMB and ICER; however, there was some uncertainty (i.e., the 95% CrI) for the $30,000 and $50,000 WTP thresholds (refer to Table 12 and Table 14).
- Scenario 3 (LTC low uptake) and scenario 4 (LTC high uptake) may have been biased toward less cost-effective results, based on the following model assumptions (Table 8):

- The underreporting factor for individuals in LTC was assumed to be the same as that for individuals aged 65 years or older. In reality, case detection in the LTC cohort was likely higher than it was in the cohort of individuals aged 65 years or older. As a result, the model may have assumed that there were more infections in the LTC cohort than in reality and therefore assumed a lower likelihood of severe disease (i.e., hospitalization).
- The reporting of deaths was based on those transferred from an LTC facility to an acute hospital setting, who also died. Deaths that occurred outside discharge were not included, which is more likely to happen in the LTC population.
- It is possible that more LTC residents received NMV-r in 2022 and therefore the treatment effects may have already been realized in the reference population (thereby reducing overall LTC hospitalization and mortality rates).

Reference Scenario

The reference scenario was defined as COVID-19 cases and hospital disposition in Canada in 2022, assuming minimal use of NMV-r. Based on the Alberta Health data, case utilization of NMV-r in 2022 was 4.6% and 0.8% among individuals aged 65 years or older and those younger than 65 years, respectively. The utilization estimates when adjusted for infections (undetected and confirmed cases) would be lower. Costs related to NMV-r dispensations were not included in the reference scenario.

Sensitivity Analysis

The model simulations incorporated a probabilistic sensitivity analysis, and results in Table 12 include 95% CrIs to account for parameter uncertainty. Model inputs including parameter ranges, SDs, or sampling distributions are provided in Table 1, Table 5, Table 6, Table 7, and Table 8. In Table 14, we present the ICER for each of the scenarios relative to a common baseline of the reference scenario. Based on Table 12, scenarios 2 and 5 would be cost-effective (with consideration of the 95% CrI) when compared to the reference scenario at a WTP threshold of $100,000 per QALY. Similarly, Table 14 shows that scenario 5 (ICER = $24,171) followed by scenario 2 ($31,148) had the lowest ICER values. Disaggregated results stratified by model states are described in Table 13 and Table 15 and highlight that most of the QALY costs independent of WTP were in the recovered state.

Table 12: NMB ($) and iNMB ($) Estimates for NMV-r Outpatient Treatment Scenarios (in Millions) by 3 WTP per QALY Thresholds: $30,000, $50,000, and $100,000 (N = 5,000 Simulations per Scenario)

Cost-effectiveness estimate ($ in millions)	WTP threshold: $30,000	WTP threshold: $50,000	WTP threshold: $100,000
Reference scenario			
NMB (95% CrI)	$477,559 ($383,860 to $542,142)	$798,171 ($642,051 to $905,776)	$1,599,700 ($1,287,530 to $1,814,810)
iNMB (95% CrI)	NA	NA	NA

Cost-effectiveness estimate ($ in millions)	WTP threshold: $30,000	WTP threshold: $50,000	WTP threshold: $100,000
Scenario 1 (low uptake)			
NMB (95% CrI)	$477,493 ($383,931 to $541,850)	$798,285 ($642,267 to $905,496)	$1,600,270 ($1,288,110 to $1,814,930)
iNMB (95% CrI)	–$65.9 (–$710 to $370)	$114 (–$540 to $562)	$563 (–$130 to $1,070)
Scenario 2 (moderate uptake)			
NMB (95% CrI)	$477,539 ($384,171 to $541,937)	$798,491 ($642,620 to $905,692)	$1,600,870 ($1,288,910 to $1,815,390)
iNMB (95% CrI)	–$19.5 (–$1,070 to $685)	$320 (–$743 to $1,040)	$1,170 ($60.7 to $1,940)
Scenario 3 (LTC low uptake)			
NMB (95% CrI)	$477,333 ($383,757 to $541,659)	$797,986 ($641,988 to $905,207)	$1,599,620 ($1,287,570 to $1,814,350)
iNMB (95% CrI)	–$225 (-$682 to $77.6)	–$185 (–$640 to $119)	–$84.2 (–$548 to $226)
Scenario 4 (LTC high uptake)			
NMB (95% CrI)	$477,220 ($383,707 to $541,541)	$797,894 ($641,949 to $905,154)	$1,599,580 ($1,287,580 to $1,814,090)
iNMB (95% CrI)	–$338 (–$1,020 to $113)	–$278 (–$964 to $174)	–$126 (–$811 to $334)
Scenario 5 (high uptake)			
NMB (95% CrI)	$477,698 ($384,326 to $542,078)	$798,788 ($642,992 to $905,930)	$1,601,510 ($1,289,650 to $1,815,920)
iNMB (95% CrI)	$139 (–$1,100 to $960)	$617 (–$635 to $1,450)	$1,810 ($528 to $2,720)

CrI = credible interval; iNMB = incremental net monetary benefit; LTC = long-term care; NA = not applicable; NMB = net monetary benefit; NMV-r: = nirmatrelvir-ritonavir; QALY = quality-adjusted life-year; WTP = willingness-to-pay.

Notes: Infections included both undetected and lab-confirmed cases (i.e., 18,854,943 total infections [excluding Quebec] [62.7%] of the total population in Canada excluding Quebec) in 2022.

Table 13: Disaggregated Results (Mean Values Only) of NMB and iNMB Estimates for NMV-r Outpatient Treatment Scenarios (in Millions) by 3 WTP per QALY Thresholds: $30,000, $50,000, and $100,000 (N = 5,000 Simulations per Scenario)

Parameter	Reference	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (LTC low uptake)	Scenario 4 (LTC high uptake)	Scenario 5 (high uptake)
Total value of QALYs (WTP = $30,000) (A)	**$480,920**	**$481,190**	**$481,430**	**$480,980**	**$481,010**	**$481,640**
By health state						
Outpatient	$11,634	$11,634	$11,634	$11,634	$11,634	$11,634
Inpatient	$100	$87	$79	$92	$88	$74
Critical	$0	$0	$0	$0	$0	$0
Inpatient After Critical	$12	$12	$11	$12	$12	$11

Parameter	Reference	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (LTC low uptake)	Scenario 4 (LTC high uptake)	Scenario 5 (high uptake)
Dead	–$4,169	–$3,927	–$3,713	–$4,115	–$4,089	–$3,525
Post–COVID-19 Condition	$982	$967	$956	$976	$973	$948
Recovered	$472,360	$472,410	$472,460	$472,380	$472,390	$472,490
Total value of QALYs (WTP = $50,000) (B)	**$801,530**	**$801,980**	**$802,380**	**$801,630**	**$801,680**	**$802,730**
By health state						
Outpatient	$19,391	$19,391	$19,391	$19,391	$19,391	$19,391
Inpatient	$167	$146	$131	$153	$146	$124
Critical	$0	$0	$0	$0	$0	$0
Inpatient After Critical	$20	$19	$19	$20	$19	$18
Dead	–$6,949	–$6,546	–$6,188	–$6,859	–$6,814	–$5,875
Post–COVID-19 Condition	$1,636	$1,612	$1,594	$1,627	$1,622	$1,580
Recovered	$787,270	$787,360	$787,430	$787,300	$787,320	$787,490
Total value of QALYs (WTP = $100,000) (C)	**$1,603,100**	**$1,604,000**	**$1,604,800**	**$1,603,300**	**$1,603,400**	**$1,605,500**
By health state						
Outpatient	$38,781	$38,781	$38,781	$38,781	$38,781	$38,781
Inpatient	$333	$291	$263	$306	$293	$248
Critical	$0	$0	$0	$0	$0	$0
Inpatient After Critical	$41	$39	$37	$39	$39	$36
Dead	–$13,898	–$13,091	–$12,375	-$13,718	–$13,628	–$11,750
Post–COVID-19 Condition	$3,272	$3,225	$3,187	$3,253	$3,244	$3,159
Recovered	$1,574,500	$1,574,700	$1,574,900	$1,574,600	$1,574,600	$1,575,000
Total costs (D)	**$3,360**	**$3,696**	**$3,888**	**$3,646**	**$3,789**	**$3,938**
By health state						
Outpatient	$0	$636	$1,044	$456	$683	$1,224
Inpatient	$2,387	$2,123	$1,938	$2,231	$2,153	$1,831
Critical	$663	$638	$617	$656	$653	$600
Inpatient After Critical	$311	$298	$289	$304	$300	$283
Dead	$0	$0	$0	$0	$0	$0
Post–COVID-19 Condition	$0	$0	$0	$0	$0	$0
Recovered	$0	$0	$0	$0	$0	$0
iNMB by WTP						
$30,000 $[(A_{Sc} – D_{Sc}) – (A_{Base} – D_{Base})]$	—	–$66	–$19	–$225	–$338	$139

Parameter	Reference	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (LTC low uptake)	Scenario 4 (LTC high uptake)	Scenario 5 (high uptake)
$50,000 [($B_{Sc}$ – D_{Sc}) – (B_{Base} – D_{Base})]	—	$114	$320	–$185	–$278	$617
$100,000 [($C_{Sc}$ – D_{Sc}) – (C_{Base} – D_{Base})]	—	$563	$1,167	–$84	–$126	$1,812

Base = baseline; iNMB = incremental net monetary benefit; LTC = long-term care; NMB = net monetary benefit; NMV-r = nirmatrelvir-ritonavir; QALY = quality-adjusted life-year; Sc = scenario; WTP = willingness-to-pay.

Table 14: ICERs for NMV-r Outpatient Treatment Scenarios, Relative to a Common Baseline

Scenarios	Cost (in millions)	Incremental cost (in millions)	QALYs	Incremental QALYs	ICERs
Reference scenario	$3,360	—	16,030,630	—	NA
Scenario 1 (low uptake)	$3,696	$335	16,039,610	8,983.90	$37,334
Scenario 2 (moderate uptake)	$3,888	$528	16,047,580	16,952	$31,148
Scenario 3 (LTC low uptake)	$3,646	$286	16,032,650	2,018.60	$141,700
Scenario 4 (LTC high uptake)	$3,789	$429	16,033,650	3,026.40	$141,750
Scenario 5 (high uptake)	$3,938	$578	16,054,530	23,898	$24,171

ICER = incremental cost-effectiveness ratio; LTC = long-term care; NMV-r = nirmatrelvir-ritonavir; QALY = quality-adjusted life-year.

Table 15: Disaggregated Results of the ICERs for NMV-r Outpatient Treatment Scenarios, Relative to a Common Baseline

Scenarios	Cost (in millions)	Incremental cost (in millions)	QALYs	Incremental QALYs	ICER
Reference scenario	**$3,360**	**—**	**16,031,000**	**—**	**NA**
Outpatient	$0	$0	387,810	0	—
Inpatient	$2,387	$0	3,331.60	0	—
Critical	$663	$0	0	0	—
Inpatient After Critical	$311	$0	406.97	0	—
Dead	$0	$0	–138,980	0	—
Post–COVID-19 Condition	$0	$0	32,718	0	—
Recovered	$0	$0	15,745,000	0	—
Scenario 1 (low uptake)	**$3,696**	**$335**	**16,040,000**	**8,984**	**$37,334**
Outpatient	$636	$636	387,810		—
Inpatient	$2,123	–$264	2,911.40	–420	—
Critical	$638	–$24	0	0	—
Inpatient After Critical	$298	–$13	386.93	–20	—

Scenarios	Cost (in millions)	Incremental cost (in millions)	QALYs	Incremental QALYs	ICER
Dead	$0	$0	–130,910	8,065	—
Post–COVID-19 Condition	$0	$0	32,247	–471	—
Recovered	$0	$0	15,747,000	1,830	—
Scenario 2 (moderate uptake)	**$3,888**	**$528**	**16,048,000**	**16,952**	**$31,148**
Outpatient	$1,044	$1,044	387,810	0	—
Inpatient	$1,938	–$449	2,627.10	–705	—
Critical	$617	–$45	0	0	—
Inpatient After Critical	$289	–$22	372.94	–34	—
Dead	$0	$0	–123,750	15,226	—
Post–COVID-19 Condition	$0	$0	31,873	–845	—
Recovered	$0	$0	15,749,000	3,309	—
Scenario 3 (LTC low uptake)	**$3,646**	**$286**	**16,033,000**	**2,019**	**$141,700**
Outpatient	$456	$456	387,810	0	—
Inpatient	$2,231	–$156	3,060.80	–271	—
Critical	$656	–$7	0	0	—
Inpatient After Critical	$304	–$7	394.81	–12	—
Dead	$0	$0	–137,180	1,796	—
Post–COVID-19 Condition	$0	$0	32,532	–186	—
Recovered	$0	$0	15,746,000	691	—
Scenario 4 (LTC high uptake)	**$3,789**	**$429**	**16,034,000**	**3,026**	**$141,750**
Outpatient	$683	$683	387,810	0	—
Inpatient	$2,153	–$234	2,925.50	–406	—
Critical	$653	–$10	0	0	—
Inpatient After Critical	$300	–$11	388.64	–18	—
Dead	$0	$0	–136,280	2,693	—
Post–COVID-19 Condition	$0	$0	32,440	–278	—
Recovered	$0	$0	15,746,000	1,036	—
Scenario 5 (high uptake)	**$3,938**	**$578**	**16,055,000**	**23,898**	**$24,171**
Outpatient	$1,224	$1,224	387,810	0	—
Inpatient	$1,831	–$556	2,478	–854	—
Critical	$600	–$63	0	0	—

Scenarios	Cost (in millions)	Incremental cost (in millions)	QALYs	Incremental QALYs	ICER
Inpatient After Critical	$283	–$28	364.99	–42	—
Dead	$0	$0	–117,500	21,477	—
Post–COVID-19 Condition	$0	$0	31,589	–1,129	—
Recovered	$0	$0	15,750,000	4,446	—

ICER = incremental cost-effectiveness ratio; LTC = long-term care; NA = not applicable; NMV-r = nirmatrelvir-ritonavir; QALY = quality-adjusted life-year.

Cost-Effectiveness Acceptability Curves

For each $1,000 increment of WTPs per QALY from $0 to $150,000, we computed the probability (calculated as the proportion of 5,000 simulations) of each of the scenarios shown in Table 9 having the highest NMB when compared pairwise to the reference scenario. Figure 2 shows the probability that a scenario was cost-effective across this range of WTP per QALY values when compared to the reference scenario. At a WTP threshold of $0, this analysis simply shows the proportion of simulations for which the scenario in question has the lowest cost. As WTP increases, there is an increase in the numbers of scenario simulations that have higher expected NMB than the reference scenario due to better QALY outcomes. Although the reference scenario is not shown for each pairwise comparison, graph lines crossing 0.5 and greater for "Probability of Cost-Effectiveness" indicate when each scenario had a higher probability of cost-effectiveness (highest NMB) compared to the reference scenario. The high uptake scenario (scenario 5) had the highest probability of being cost-effective at conventional estimates of WTP between $25,000 and $150,000 per QALY. In this scenario, high drug uptake is expected to lead to reductions in the number of individuals requiring admission to hospital, leading to improvements in quality of life and lower acute care resource use costs.

Budget Impact Analysis

A BIA was conducted to quantify health system impacts related to NMV-r outpatient treatment scenarios retrospectively compared to COVID-19 data in 2022. A stochastic state-transition model (described previously in Figure 1) was used to quantity health system costs related to 5 scenarios compared to the reference scenario (Table 9). The variation of model inputs allowed for budget impact estimates to include 95% CrIs. Costs related to inpatient units, critical care units, physician time, and NMV-r (including dispensation fee) were included in the analysis. Costs related to the administrative implementation costs of the outpatient treatment strategy were not included. The main data sources for cases and severity data were obtained from CIHI and PHAC.[23] In describing the methods in this section of the report, we focused on areas where the BIA methods differ from those used in the CUA. Where the methods or data used are the same as the CUA, we refer readers to the relevant sections and page numbers in the CUA section of the report.

The initial state for the stochastic state-transition model were COVID-19 infections and described transitions related to outpatient and inpatient treatment, post–COVID-19 condition, and recovery. Clinical features of COVID-19 related to severity differ by age, vaccination status, variants of concern, and comorbidities. COVID-19 disproportionately impacts older adults compared to younger adults and is generally associated with weakened immune systems (in general or related to comorbidities).[2] Model stratification by this cohort

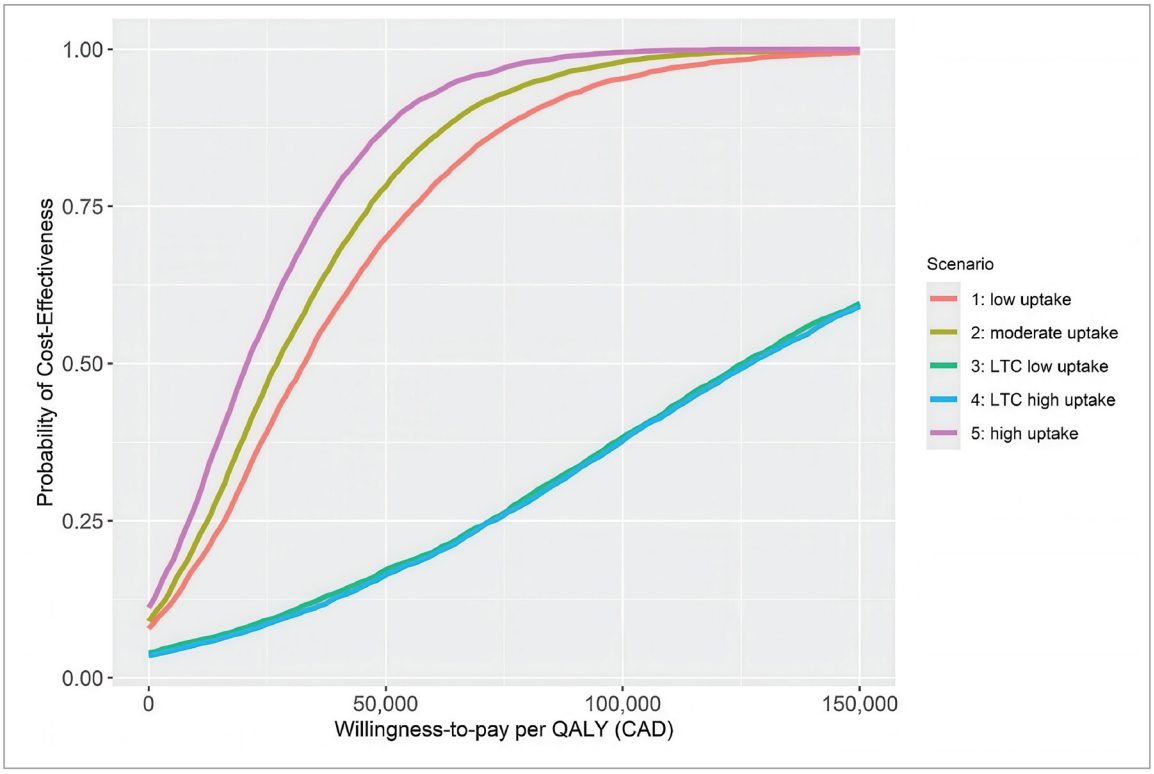
represented an important consideration. Post–COVID-19 condition was defined as those the experience of COVID-19 symptoms for 3 or more months, and it generally occurs in approximately 15% of adults after COVID-19 infection.[2] This was included as a state in the model.

Eze et al.[3] highlighted that NMV-r mainly had an impact on inpatient (admission rate and LOS) and death rates (from the Inpatient and Critical states). These therapeutic effects were implemented in the model for the BIA. Post–COVID-19 condition impacts related to NMV-r outpatient treatment were indirectly accounted for because proportion transitions to this state were higher in individuals who had been hospitalized.

Decision Problem

This BIA quantified the health system impacts related to NMV-r outpatient treatment retrospectively using COVID-19 data in 2022. Canadian data obtained from CIHI related to cases and severity in 2022 were used for the BIA. Canadian data related to cases and severity excluded Quebec due to data limitations related to the release of severity data. The time horizon for the model was 1 year. The analytical approach aimed to answer a counterfactual question about NMV-r outpatient treatment strategies (i.e., if we had a NMV-r outpatient treatment strategy in 2022, what would the difference in health care system costs be compared

Figure 2: Cost-Effectiveness Acceptability Curves Estimating the Probability of the Scenario Having a Greater NMB at a Given WTP Than the Reference Scenario (N = 5,000 Simulations, Each With Different Parameter Samples)



CAD = Canadian dollars; LTC = long-term care; NMB = net monetary benefit; QALY = quality-adjusted life-year; WTP = willingness to pay.

to the reference scenario [COVID-19 cases and hospital dispositions in Canada in 2022]). The stochastic state-transition model (described previously in Figure 1) was stratified into 3 cohorts (those aged < 65 years, those aged ≥ 65 years, and those in LTC) across 2 time periods: January 2022 to August 2022 (period 1) and September 2022 to December 2022 (period 2). The cut-offs at the age of 65 years were used to better align with case and severity data and NMV-r effect estimates reported in the literature.

Table 9 provides a description of the reference and 5 scenarios. The variation of model inputs allowed for budget impact estimates to include 95% CrIs. Costs related to inpatient units, critical care units, physician time, and NMV-r (including dispensation fees) were included in the analysis. Costs related to the administrative implementation costs of the outpatient treatment strategy and health care costs related to post–COVID-19 condition were not included.

Study Design and Methods

The stochastic state-transition model and methods were previously described in the Model Structure, Data Inputs, Clinical Parameters, and Costs sections.

Patient Population

The patient population included those younger than 65 years (not in LTC), those aged 65 years or older, and those in LTC. The subgroups for the proposed NMV-r outpatient treatment scenarios included patients aged 65 years or older and those in LTC. Table 11 provides the case rate per 100 using data obtained from CIHI. The severity case rates per 100 lab-confirmed cases were generally higher for patients aged 65 years or older and those in LTC (Table 16). The transition to reduced community testing aligned with other respiratory viruses was reflected in magnitude differences of hospital disposition outcomes between period 1 and period 2, especially among those younger than 65 years and in LTC.

Table 16: Hospital Case Rates per 100 for Hospital (Including Critical) and Critical Admissions in Canada (2022)

Hospital disposition	Age < 65 years	Age ≥ 65 years	LTC
Period 1: January 2022 to August 2022			
Inpatient admission rate per 100 lab-confirmed cases	2.8	35.9	5.0
Critical admission rate per 100 lab-confirmed cases	0.6	5.5	0.3
Death rate per 100 lab-confirmed cases	0.1	6.3	0.4
Period 2: September 2022 to December 2022			
Inpatient admission rate per 100 lab-confirmed cases	14.3	28.0	21.7
Critical admission rate per 100 lab-confirmed cases	3.3	3.8	1.5
Death rate per 100 lab-confirmed cases	0.8	4.4	1.4

ICU = intensive care unit; LTC = long-term care.

Note: Inpatient admission rate per 100 lab-confirmed cases does not include those that were also admitted to critical care (the ICU).

Source: CIHI (2022).

Intervention Scenarios and/or Strategies

Table 9 provides a description of the reference and 5 scenarios. NMV-r outpatient scenarios considered population groups understood at higher risk for severity (those aged ≥ 65 years and those in LTC) (Table 16). Because these scenarios describe voluntary NMV-r outpatient treatment, a reasonable uptake was an important consideration informed through the CoLab team and a clinical expert. The uptake of NMV-r among those aged 65 years or older infected with COVID-19 ranged between 10% and 30%. The uptake of NMV-r among those in LTC ranged higher, between 50% and 75%. Although the choice of percentage uptake considered potential drug interactions and adverse events, most patients were reported to complete NMV-r as prescribed.[10]

These scenarios assume that cases and infected people would have equal uptake of NMV-r as an outpatient treatment strategy. The impact of this assumption on BIA results is challenging to interpret.

The reference scenario was defined as COVID-19 cases and hospital disposition in Canada in 2022, assuming minimal use of NMV-r. Case utilization of NMV-r from Alberta Health in 2022 was 4.6% among those aged 65 years or older and 0.8% among those younger than 65 years. These utilization estimates would be lower when adjusted for infections (undetected and confirmed cases); therefore, costs and impacts related to NMV-r dispensations were not included in the reference scenario.

Time Horizon

The time horizon was 1 year. There was no discounting included in this analysis. The 1-year time horizon was structured around the availability of data. In addition, the use of case and hospitalization data before 2022 (or pre-Omicron) may not have been representative of current severity rates (including mixed population immunity) and endemic management of COVID-19 (i.e., reduced community testing aligned with other respiratory viruses).

Perspective

The analysis was conducted from a Canadian health care payer perspective.

Analytic Framework Description

The BIA was undertaken using the decision analytic model framework described in the report of the cost-effectiveness analysis in previous sections. We estimate the expected health system costs for 5 different scenarios compared to a reference scenario of NMV-r use according to patient age (age ≥ 65 years, age < 65 years), rate of uptake of interventions, and whether patients resided in an LTC facility. The scenarios are described in Table 9. We used the stochastic nature of the cost-effectiveness model to conduct probabilistic analysis of expected budget impacts, accounting for parameter uncertainty in the existing evidence base.[49] We reported estimated budget impact and resource use as means and CrIs.

Analytic Framework

The stochastic state-transition model and methods were previously described in the Model Structure, Data Inputs, Clinical Parameters, and Costs sections.

Clinical Inputs

Refer to Clinical Parameters in the Economic Evaluation section.

Data Sources

Table 17 describes key data sources and transformations that were used to estimate model inputs for the BIA. Additional details can be referred to in previous sections within the Economic Evaluation section. The case data obtained from PHAC likely included reinfections. LTC distribution among cases obtained from Alberta Health was extrapolated to Canadian case totals due to data limitations. Severity data obtained from CIHI did not include information from Quebec and case totals were adjusted accordingly (Table 2, Table 3, and Table 4). For the estimation of initial conditions and underreporting factor (Table 6, Table 10, Table 24, and Table 25), additional assumptions were made to align to serology data, which captured the number of people previously infected and did not include reinfections. Also, assumptions were made to equate hospital disposition parameters of those in LTC with those aged 65 years or older, and the underreporting factor of this cohort may have had an impact on cost estimates.

Table 17: Data Source, Transformations, and Additional Comments

Data source	Data transformations	Additional comments
CIHI data (2022) Datasets: • Discharge Abstract Database • Canadian MIS Database (costs)	• Hospital disposition (inpatient, critical care, LOS, and death) and costs • Total costs were transformed to daily per patient cost using inpatient LOS and critical care LOS.	• Data provided at the Canadian level excluded Quebec due to limitations in reporting. • The LTC cohort was based on the discharge disposition. Estimates such as deaths in facility would be based on institution transfer from type code (i.e., those transferred to an acute hospital facility who subsequently dies is accounted for). Deaths that occurred outside discharge were not included. Costs did not include physician fees, and this was included using a study by Lau et al.[46] • Costs related to post–COVID-19 condition were not included in the analysis (limitations in the literature).
PHAC data	• COVID-19 cases for Canada in 2022 by age group and period (January 2022 to August 2022 and September 2022 to December 2022); this included adjustments that excluded Quebec cases to align with CIHI data to estimate hospital disposition rates (Data Inputs section, Table 2, Table 3, and Table 4).	• For estimating the underreporting factor, cases for Canada (including Quebec) were used to align with the serology data.
Alberta Health data Datasets: • Provincial Surveillance Information • Communicable Disease	• Alberta Health LTC case distributions in 2022 were used to extrapolate to the Canadian case data obtained from PHAC. • Drug utilization data were used to estimate baseline use and effect estimates (Data	• Due to data limitations, Alberta LTC case distributions were extrapolated to case distributions in Canada. This may have had an impact on the results if the contribution of LTC cases (high-risk cohort) was overestimated or underestimated. Sensitivity

Data source	Data transformations	Additional comments
Reporting System • Communicable Disease and Outbreak Management • Pharmaceutical Information Network • Continuing Care Reporting System	Inputs and Clinical Inputs in the Economic Evaluation section).	analysis will be conducted to evaluate the impact of this assumption.
Seroprevalence data	• Infection acquired (anti-N) serology data were used to estimate the underreporting factor (Clinical Inputs in the Economic Evaluation section).	• The underreporting factor for those aged ≥ 65 years was assumed to be the same for LTC. If the LTC cohort had a higher ratio than estimated, this would lead to costs being overestimated, because a large number of infections would have been inferred and treated. • This did not quantify or include reinfections. Underreporting factors and initial infections were aligned to serology data and did not account for reinfections.
Eze et al.[3]	• NMV-r effect estimates against inpatient (admissions and LOS) and death (inpatient and critical) were used.	• Effect estimates were aligned with Alberta Health data. • Potential effects of NMV-r on post–COVID-19 condition were not directly included; these were indirectly included because transition proportions to post–COVID-19 condition differed based on outpatient and/or inpatient state (Clinical Parameters in the Economic Evaluation section).

CIHI = Canadian Institute of Health Information; LOS = length of stay; LTC = long-term care; MIS = management information system; NMV-r = nirmatrelvir-ritonavir; PHAC = Public Health Agency of Canada.

Cost Inputs

Refer to Costs in Economic Evaluation section.

Data Sources

Refer to Table 17 for additional details about cost inputs with CIHI[26] and Lau et al.[46] as the data sources. Costs related to the implementation of the outpatient strategy and health care costs related to post–COVID-19 condition were not included in this analysis.

Tables of Inputs

Refer to the Data Inputs, Clinical Parameters, Utilities, and Costs subsections in the Economic Evaluation section, as well as Table 21, Table 22, Table 23, Table 24, and Table 25 in the appendices.

Scenario Analyses

Table 9 provides a description of the 6 scenarios (including the reference scenario). NMV-r outpatient scenarios considered population groups understood to be at higher risk for severity (those aged ≥ 65 years

and those in LTC) (Table 16). Because these scenarios describe voluntary NMV-r outpatient treatment, a reasonable uptake was an important consideration informed through the CoLab team and a clinical expert. The uptake of NMV-r in the cohort of individuals aged 65 years or older ranged between 10% and 30%. The LTC cohort uptake of NMV-r ranged higher, between 50% and 75%. Although the choice of percentage uptake considered potential drug interactions and adverse events, most patients were reported to complete NMV-r as prescribed.[10] Based on this, we assumed that those treated would all complete NMV-r as prescribed. These scenarios also assumed that cases and infected people would have equal uptake of NMV-r as an outpatient treatment strategy. The impact of this assumption on BIA results is challenging to interpret.

Uncertainty

As model simulations incorporate uncertainty within model inputs, a POSA[50] (N = 1,000 simulations) was used to estimate impacts to total costs of selected treatment scenarios (scenario 2 [moderate uptake] and scenario 5 [high uptake]) and the reference scenario through systematic sampling between a given range. Scenario 2 and scenario 5 were selected to provide a range of NMV-r uptake from moderate to high. Table 13 provides the key model inputs examined for the POSA using total costs as an outcome.

A POSA can assess whether the budget impact (scenario cost – reference scenario cost) will cost money (a strategy that costs more compared to no strategy or reference) or save money (a strategy that costs less compared to no strategy or reference) from the perspective of the health care system. In the POSA analysis for NMV-r drug cost, the range from $100 to $2,500 per treatment course was wide to allow for the estimation of a break-even price (i.e., where total health care costs were the same for the treatment and reference scenario).

Limitations related to LTC data were examined through the POSA for key model inputs such as the underreporting factor, LTC case distribution, NMV-r therapeutic effects on LOS, and inpatient admission. This provided insights to budget impact estimates related to parameters that had more uncertainty related to the data source.

Table 18: POSA of Key Model Inputs

Model parameter	Cohort (age < 65 years, age ≥ 65 years, LTC, and all)	Range (total discrete points within the range)
NMV-r drug cost (per treatment course)	All	$100 to $2,500 (10)
Total per patient cost: inpatient unit	All	$10,000 to $25,000 (10)
Relative overreporting adjustment of LTC cases (i.e., 0.4 of initial LTC COVID-19 cases are redistributed to those aged ≥ 65 years to account for the overestimation)	LTC	0.4 to 1.0
Underreporting factor	LTC	0.06 to 0.12
Case inpatient admission proportion (NMV-r treated)	Age ≥ 65 years	0.4 to 1.0 (10)

Model parameter	Cohort (age < 65 years, age ≥ 65 years, LTC, and all)	Range (total discrete points within the range)
Case inpatient admission proportion (NMV-r treated)	LTC	0.4 to 1.0 (20)

LTC = long-term care; NMV-r = nirmatrelvir-ritonavir; POSA = probabilistic one-way sensitivity analysis.

Note: The case admission proportion was not adjusted for infections. The model made this adjustment within the simulation.

Table of Assumptions

A complete list of model assumptions is described in Table 11. However, in Table 19, we describe model assumptions that are most relevant to the BIA.

Table 19: Key Model Assumptions Related to the BIA for NMV-r as an Outpatient Treatment for COVID-19

Assumption	How it was tested in the scenario analysis	Additional comments
The underreporting factor for LTC was assumed to be the same as it was for those aged ≥ 65 years. This was likely an underestimate because there was likely more testing in LTC facilities compared to the community.	A POSA was conducted for the LTC case-infection ratio that described an approximate range, which included estimates for period 1 and period 2.	This assumption will overestimate the cost of the outpatient treatment scenario and economic impact.
LTC case distribution was extrapolated from Alberta to the population in Canada.	A POSA was conducted for the LTC case distribution that included a lower bound informed by grey literature.[51] The lower bound was considered using a relative overreporting adjustment reduction (i.e., 0.4 or 40% of initial COVID-19 cases among those in LTC were redistributed to those aged ≥ 65 years to account for the overestimation of initial LTC cases).	NA
NMV-r drug cost was assumed to range between $685 and $1,918.	A POSA was conducted to examine a wider range of NMV-r cost to determine a price point where costs would break even (with model uncertainty included in the simulations) when compared between the scenario and the reference scenario.	The price range was determined from publicly available information on drug costs in the US and Europe.

LTC = long-term care; NA = not applicable; NMV-r = nirmatrelvir-ritonavir; PHAC = Public Health Agency of Canada; POSA = probabilistic one-way sensitivity analysis.

BIA Results

Main Take-Aways

The results of the BIA suggested that scenarios involving increased use of NMV-r among people aged 65 years and older and those in LTC have the potential to be cost-saving, taking into account uncertainty. On average, assuming an NMV-r cost of $785, all scenarios showed higher costs to the health system compared to the reference scenario. Our model showed that the break-even point for NMV-r to not increase costs to the health system was $370. Scenarios focusing on LTC cohorts may have been affected due to the emphasis on direct health care costs and mortality within a hospital setting, and the potential treatment effects of NMV-r already realized in this cohort in the reference scenario.

The results of the BIA are presented in Table 20. Total costs for the scenarios considered ranged from $3.36 billion to $3.94 billion. Key outcomes in the BIA included inpatient admissions, critical care admissions, patients developing post–COVID-19 condition, and mortality. The reference scenario had the lowest expected cost, and scenario 5 had the highest. When accounting for parameter uncertainty, scenarios 1, 2, and 5 had a positive or negative budget impact compared to the reference scenario.

Key Results

- Results of the BIA are presented in Table 20 for the reference scenario and 5 NMV-r outpatient treatment scenarios for all cohorts (age < 65 years, age ≥ 65 years, and LTC) and 2 periods (January 2022 to August 2022 and September 2022 to December 2022).
- Based on the deterministic analysis, for all of Canada, the annual budget impact of the scenarios ranged from $286 million (95% CrI, $–18 million to $740 million) for scenario 3 (LTC low uptake) to $578 million (95% CrI: –$233 million to $1.8 billion) for scenario 5 (high uptake).
- These results were based on assumed drug cost inputs, namely the assumed average drug cost of $785, which is above the estimated break-even price point of $370 (based on the outcome of POSA) based on the model assumptions.
- There were observed reductions in total inpatient admissions, post–COVID-19 condition, and deaths across the 5 scenarios. For scenario 5, the reduction in mean inpatient admissions, post–COVID-19 condition, and deaths were the greatest, at 17,010; 4,330; and 3,430, respectively.
- Total inpatient costs contributed the most to the overall total cost. Although NMV-r treatment reduced hospital admission rates, the reductions achieved for mean total inpatient and critical care costs did not offset other costs across all treatment strategies based on NMV-r costs of $685 to $1,918 per treatment.
- Deterministic results for all scenarios showed an increased cost to the health care system compared to the reference scenario, as the range of NMV-r treatment costs included in the analysis ($685 to $1,918) did not include the $370 break-even cost estimate.

- The BIA showed that all scenarios had a potential for cost-savings based on parameter uncertainty (95% CrI) results.
- Consistent with the CUA analysis, scenario 3 (LTC low uptake) and scenario 4 (LTC high uptake) may have been impacted by the following model assumptions:
  - The underreporting factor for LTC was assumed to be the same as it was for those aged 65 years or older. In reality, case detection in the LTC cohort was likely higher than in the cohort of those aged 65 years or older, and therefore would assume a lower likelihood of severe disease (i.e., hospitalization) than in reality.
  - The reporting of deaths was based on those transferred from an LTC facility who died in an acute hospital setting. Deaths that occurred outside discharge, which can also occur in the LTC population, were not included.
  - As a population that is more regularly tested for COVID-19, available to receive outpatient treatments, and at very high risk for severe disease, it is possible more LTC residents received NMV-r in 2022; therefore, the treatment effects may have already been realized in the reference population (thereby reducing overall LTC hospitalization and mortality rates).

Table 20: BIA Across 5 NMV-r Outpatient Treatment Scenarios

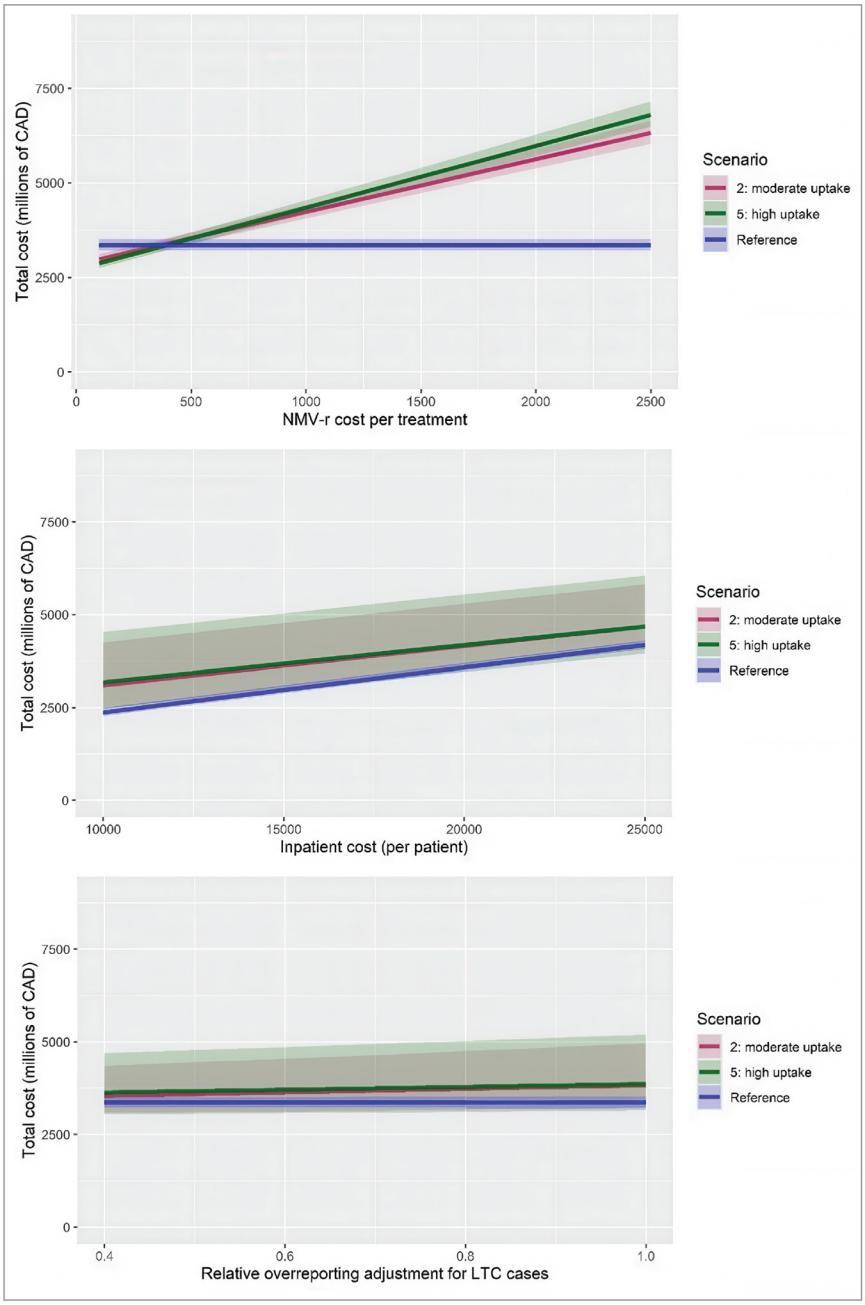
Description	Reference scenario	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (LTC low uptake)	Scenario 4 (LTC high uptake)	Scenario 5 (high uptake)
COVID-19 disposition (95% CrI)						
Total inpatient	120,750 (119,100 to 122,320)	113,680 (111,690 to 115,630)	108,010 (105,520 to 110,570)	117,960 (116,250 to 119,580)	116,570 (114,780 to 118,280)	103,740 (100,740 to 106,970)
Total critical	19,690 (18,240 to 21,260)	18,960 (17,540 to 20,470)	18,310 (16,940 to 19,800)	19,530 (18,080 to 21,090)	19,450 (18,000 to 21,000)	17,740 (16,400 to 19,200)
Total post–COVID-19 condition	122,950 (113,800 to 132,230)	121,140 (112,040 to 130,300)	119,690 (110,570 to 128,830)	122,220 (113,110 to 131,410)	121,850 (112,750 to 131,030)	118,620 (109,540 to 127,670)
Total deaths	14,930 (13,980 to 15,920)	13,640 (12,770 to 14,550)	12,500 (11,700 to 13,360)	14,640 (13,710 to 15,630)	14,500 (13,560 to 15,500)	11,500 (10,730 to 12,340)
Costs (in millions) (95% CrI)						
Total inpatient	$2,390 ($2,250 to $2,520)	$2,120 ($2,000 to $2,250)	$1,940 ($1,820 to $2,060)	$2,230 ($2,100 to $2,360)	$2,150 ($2,030 to $2,280)	$1,830 ($1,720 to $1,950)
Total critical	$974 ($879 to $1,080)	$937 ($844 to $1,040)	$906 ($817 to $1,010)	$960 ($866 to $1,070)	$953 ($858 to $1,060)	$883 ($794 to $983)
Total inpatient and critical	$3,360 ($3,220 to $3,510)	$3,060 ($2,930 to $3,200)	$2,840 ($2,710 to $2,980)	$3,190 ($3,050 to $3,340)	$3,110 ($2,970 to $3,260)	$2,710 ($2,590 to $2,850)
Total NMV-r cost	NA	$524 ($524 to $524)	$861 ($861 to $861)	$376 ($376 to $376)	$563 ($563 to $563)	$1,010 ($1,010 to $1,010)
Total costs	$3,360 ($3,220 to $3,510)	$3,700 ($3,260 to $4,340)	$3,890 ($3,200 to $4,930)	$3,650 ($3,320 to $4,110)	$3,790 ($3,320 to $4,470)	$3,940 ($3,130 to $5,160)
Budget impact: scenario cost – reference scenario (in millions)	NA	$335 (–$84.7 to $973)	$528 (–$164 to $1,570)	$286 (–$18 to $740)	$429 (–$22.4 to $1,110)	$578 (–$233 to $1,800)

BIA = budget impact analysis; CrI = credible interval; LTC = long-term care; NA = not applicable; NMV-r = nirmatrelvir-ritonavir.

Note: Pharmacy dispensation fees are included in the outpatient treatment cost of $22.15. The BIA was estimated based on 3,035,861 total infections (66.8% of the total population) in 2022.

Based on the NMV-r outpatient treatment scenarios, the break-even cost estimated using the POSA (Figure 3) was estimated at $370 per treatment. An NMV-r cost per treatment less than $370 would indicate cost-savings for the health care system. Although not all scenarios are shown in the POSA, scenario 2 (moderate uptake) and scenario 5 (high uptake) reduced the most deaths and inpatient admissions while

Figure 3: POSA Results



CAD = Canadian dollars; LTC = long-term care; NMV-r = nirmatrelvir-ritonavir; POSA = probabilistic one-way sensitivity analysis.

showing potential for cost-savings to the health care system, based on the 95% CrI. Scenarios displayed in Figure 3 are the reference (negligible treatment), moderate uptake, and high uptake (refer to Table 9 for details). Figures shown were computed with 1,000 simulations each. Solid lines show mean cost, and shaded ribbons show the 95% CrI.

Summary of Findings

Main Take-Aways

Overall, the CUA and BIA suggested that if the future resembles scenario 5 (high uptake), NMV-r may be cost-effective and could lead to the largest expected reductions in inpatient admissions, post–COVID-19 condition, and deaths. When considering health care system costs within the hospital setting, scenario 3 (LTC low uptake) showed the lowest expected budget impact, while scenario 5 had the highest budget impact and the highest incremental QALY gain. For scenarios focused only on LTC cohorts, limitations in reported death data and a focused analysis in an acute hospital setting likely influenced these results.

We conducted a CUA and BIA to determine the cost-effectiveness, budget impact, and health system impact of NMV-r as an outpatient treatment for COVID-19 in populations who may be at increased risk of developing severe COVID-19. We focused on the population aged 65 years or older and those in LTC, as the initial implementation advice from January 2022 prioritized treating based on age.[52] We did not stratify cohorts by vaccination status or the presence of comorbidities. We used 2022 data from Canada to inform our model.

The CUA differed from a typical CUA, in that we did not compare a set of treatment alternatives (such as standard of care or other antivirals) to identify the cost-effective option(s). Rather, we projected cost and health outcomes for a range of possible scenarios to understand under what conditions using NMV-r in a community setting could be cost-effective.

These results were based on assumed drug cost inputs, namely the assumed average drug cost of $785, which is more than the estimated break-even price point of $370 per treatment (based on the outcome of POSA) based on the model assumptions.

The CUA results suggest that increased use of NMV-r may be cost-effective, although this is dependent on the maximum WTP per QALY. If the WTP threshold is $50,000 or more per QALY, then scenarios 1, 2, and 5 have the potential to be cost-effective compared to the reference scenario. Scenarios 3 and 4 have the potential to be cost-effective at any WTP threshold greater than approximately $141,700 per QALY.

We also reported the expected NMB and iNMB. Over a 1-year time horizon in 2022, an estimated 18 million people in Canada were reported to have had COVID-19, although the vast majority of cases were relatively mild. The NMB was expected to be favourable in all scenarios and for all levels of WTP per QALY. While this would suggest that NMV-r had a net positive impact, this only applied unambiguously to the reference

scenario. Examination of the results of the iNMB analysis showed that for scenarios 3 and 4, iNMB was expected to be negative when the WTP threshold was less than $50,000 per QALY. When we accounted fully for parameter uncertainty through probabilistic sensitivity analysis, only scenarios 2 and 5 at a WTP threshold of $100,000 per QALY did not have 95% CrIs that cross 0.

Results of the BIA indicated that increased use of NMV-r may lead to an increase in health system costs, but will lead to reductions in inpatient admissions, post–COVID-19 condition, and deaths. While the deterministic results showed that, in scenarios 1 to 5, health system costs would increase relative to the reference scenario, there was significant parameter uncertainty in the model. This was captured using probabilistic sensitivity analysis over 5,000 model simulations to give a distribution of results reported as 95% CrIs. Based on the uncertainty, all scenarios included values where increased NMV-r use may be cost-saving to the health system.

2022 represented a unique time in which a large proportion of people were infected with COVID-19, with increased projected costs of an NMV-r outpatient treatment strategy. In future years, the volume of cases scaled to infections should be considered for determining the volume of NMV-r needed for an outpatient treatment strategy. Overall, the CUA and the BIA suggested that if the future state were to resemble scenario 5 (high uptake), it may be cost-effective and would have the largest expected reductions in inpatient admissions, post–COVID-19 condition, and deaths. Scenario 3 (LTC low uptake) had the lowest expected budget impact, while scenario 5 had the highest budget impact but also had the highest incremental QALY gain (refer to Table 20).

Limitations

It is important to consider the results of the health economic evaluation in light of the limitations and uncertainties of the model.

Our results were impacted by data limitations related to death in LTC populations. This impact was not captured in this analysis because only deaths in health care facilities were considered. To fully capture the impacts of NMV-r as an outpatient strategy among the LTC cohort, we would need to include the deaths prevented within these facilities and include considerations for health care costs considerations in nonacute settings. Moreover, we were unable to capture health care cost increases associated with managing COVID-19 within LTC facilities. Finally, we are unable to know how many individuals within the LTC population received NMV-r in 2022 and would be part of the reference population, limiting the potential treatment effects in this population. All of these factors likely reduced the cost-effectiveness of NMV-r in this population.

The scenarios presented in this analysis assume that cases and infected people would have equal uptake of NMV-r as an outpatient treatment strategy. The impact of this assumption is challenging to interpret because the utilization of this drug between cases identified by surveillance systems and infections is not known in literature. If utilization is greater among cases than infections, results would be more cost-effective.

Evidence from clinical trials and other research often stratified patients using a cut-off age of 65 years, while many FPT policies for access to NMV-r treatment were based on a cut-off age of 60 years. As a result, it was not always possible to apply treatment effectiveness parameters to an exactly matched age group as observed in the administrative data. To align better with the clinical data, an age cut-off of 65 years and older was selected for the model. If the case and severity rates are similar to those observed in the population aged 60 years and older, then total costs would be proportionally higher, but the differences and/or trends in the BIA should be generally consistent with the results in the report.

Utilities for patients admitted to hospital were likely overestimated in the CUA due to limited data related to in-hospital estimates. This would lead to underestimation of the cost-effectiveness for scenarios presented in the CUA. Research is ongoing to estimate quality of life in patients with COVID in different settings, and this may provide more robust utility estimates for future evaluations.

At the time of treatment, the negotiated price in Canada for NMV-r was confidential, so treatment costs were estimated based on publicly available sources. A POSA was conducted to estimate the break-even treatment price point, identified as $370 per treatment, suggesting that a cost per treatment less than this value would be cost-saving for the health care system. The cost of $370 per treatment falls below the range of publicly available estimates ($685 to $1,918), and below the $1,288 retail price of a 5-day treatment course of NMV-r.

Although the COVID-19 data included people with more than 1 infection in a year (i.e., reinfections), the serology data used to scale case data to infections in the community did not account for reinfections. In addition, the model structure did not track reinfections to ensure key model estimates such as QALYs and deaths were not overestimated. Repeat dispensations were also not captured in the total costs of the strategy. This could underestimate the costs of the outpatient treatment strategy.

The therapeutic effect estimates for NMV-r were obtained from studies conducted during 2022, when Omicron was the main circulating variant. Furthermore, these results were based on the epidemiology of COVID-19 in 2022 (i.e., case counts and severity data) and therefore, changes to the virulence of the virus may impact the cost-effectiveness of NMV-r in the future. For instance, if the severity of COVID-19 decreases in those aged 65 years or older and LTC population then NMV-r may become less cost-effective for these populations over time. Similarly, if the severity of COVID-19 increases then NMV-r may become more cost-effective for these populations over time.

Conclusions and Implications for Decision- or Policy-Making

The research and policy questions defined in this report were developed based on the advice and guidance from CDA-AMC on NMV-r developed for PHAC that included age, vaccination status, comorbidities, and place of residence considerations.[52] The studies that evaluated efficacy and effectiveness were conducted in a population that were exposed to different strains of SARS-CoV-2 in 2022. Furthermore, during the pandemic, risk factors for severe disease were reported to be older age, cardiovascular disease, diabetes mellitus, hypertension, cerebrovascular disease, dementia, and other chronic diseases. Although

vaccinations and previous infection helped to provide protections against severity, many groups remained at higher risk of severe COVID-19 than the general population, including older age groups, those with immunosuppression, and those with cardiovascular disease and other chronic diseases.[53,54]

The analyses presented in this report were conducted using 2022 data, which represented a year of the pandemic when a large proportion of the population were infected with COVID-19. For subsequent years, the reduced volume of infections compared to 2022 should be considered in a similar analysis to determine utilization of NMV-r for an outpatient treatment strategy. In addition, future work should also include new evidence related to therapeutic effects for NMV-r on populations after 2022 to determine patient populations that would benefit from this treatment.

Overall, the CUA and BIA suggest that if the future state were to resemble scenario 5 (high uptake) it may be cost-effective and would have the largest expected reductions in inpatient admissions, post–COVID-19 condition, and deaths. Scenario 3 (LTC low uptake) has the lowest expected budget impact, while scenario 5 has the highest budget impact and the highest incremental QALY gain. For scenarios that focused on LTC cohorts only, data limitations related to reported deaths and a focused analysis in an acute hospital setting likely impacted these results.

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Karsten Hempel constructed the model (including methods); ran simulations; and contributed to model inputs, interpretation, and writing of the report.

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Conflicts of Interest

Marie Betsy Varughese disclosed the following.

Research Funding or Grants Paid to My Institution:

CIHR: Long Covid Impact on Nurse Workforce Supply

PHAC/NSERC: One Society Network – Pandemic Preparedness Research Network

Simon Fraser University (2023 to 2024): Methods – Model Uncertainty

Involvement With Projects or Scientific Advice:

PHAC-EMNID Working Group (2020 to Present): Related to modelling infectious diseases, including COVID-19

Jeff Round disclosed the following.

Research Funding or Grants Paid to My Institution:

Canadian Clinical Research Network: Modelling the Value of Research Using COVID-19 Treatments as an Example

Canadian Immunization Research Network: Health-Related Quality of Life in Individuals With COVID-19

PHAC/NSERC: One Society Network – Pandemic Preparedness Research Network

CIHR: Long COVID Impact on Nurse Workforce Supply

AstraZeneca Canada Inc. (September 2021 to March 2023): Health Technology Innovation Platform (HTIP)

Boehringer Ingelheim (Canada) Ltd. (July 2020 to July 2022): HTIP

Novartis Pharma Canada Inc. (April 2020 to April 2022): HTIP

Takeda Canada Inc. (April 2020 to April 2022): HTIP

GlaxoSmithKline Canada (June 2020 to June 2022): HTIP

MACH32 Medical Devices (2022): Autoinjector device for trauma patients

Rostrum Medical Innovations Inc. (2022): Lung protection ventilation in ICU patients

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CADTH – Health Canada Real-World Evidence Reporting Guidance Expert Committee member (2022 to 2023)

Weston Roda declared the following.

Research Funding or Grants Paid to My Institution:

Children's Hospital Eastern Ontario: Newborn Screening Spinal Muscular Atrophy

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PHAC-EMNID Working Group: Related to modelling infectious diseases, including COVID-19

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Co-trustee of a family trust with health care sector stock shares in MRK, ABBV, JNJ, LLY, and CI

Ellen Rafferty declared the following.

Research Funding or Grant Paid to My Institution:

CIHR: Long COVID Impact on Nurse Workforce Supply

PHAC/NSERC: One Society Network – Pandemic Preparedness Research Network

Canadian Immunization Research Network: Estimation of long-term COVID-19 health state utility values

Involvement With Projects or Scientific Advice:

PHAC-EMNID Working Group (2020 to Present): Related to modelling infectious diseases, including COVID-19

Karsten Hempel disclosed the following.

Research Funding or Grants Paid to My Institution:

CIHR: Long COVID Impact on Nurse Workforce Supply

Canadian Clinical Research Network: Modelling the value of research using COVID-19 treatments as an example

Characterization of COVID-19 vaccine safety epidemiology and safety signal detection for adverse events following immunization in Alberta

No other conflicts of interest were declared.

Appendix 1: Supplemental Material

Note that this appendix has not been copy-edited.

Table 21: Stochastic State-Transition Model–Relaed Parameters (Among COVID-19 Cases) From CIHI With Key Data Transformations

Symbol	Transformation	Quantity	Source	Estimate: age < 65 years	Estimate: age ≥ 65 years	Estimate: LTC
Period 1: January 2022 to August 2022						
$\vec{T}_{ah}$	NA	LOS hospital (days)	CIHI	10	16	43
$\vec{T}_{ah\_c}$	NA	LOS hospital among those admitted to critical care (days)	CIHI	22	23	58
$\vec{T}_{c}$	NA	LOS critical (days)	CIHI	9	9	9
$\vec{T}_{i}$	$\vec{T}_{ah\_c} - \vec{T}_{c}$	LOS for inpatient after critical (days)	CIHI	13	14	49
p_{ah_c}	NA	Proportion of total hospitalizations that are critical	CIHI	0.170	0.133	0.060
$\vec{p}_{c-d}$	NA	Proportion of critical patients that die	CIHI	0.169	0.332	0.135
$\vec{T}_{h}$	$\frac{(\vec{T}_{ah} - p_{ah\_c} \times (\vec{T}_{c} + (1 - p_{c\_d}) \times \vec{T}_{i})}{1 - p_{ah\_c}}$	LOS inpatient (days)	CIHI	8	16	42
$Cost_{h}$	$Total\ inpatient\ cost \div \overline{\vec{T}}_{h}$	Inpatient cost per day	CIHI	$1,368	$1,118	$913
$Cost_{i}$	$(Total\ ICU\ cost - (Cost_{h} \times \vec{T}_{i})) \div \vec{T}_{c}$	Critical care cost per day	CIHI	$3,713	$3,640	$4,573
Period 2: September 2022 to December 2022						
$\vec{T}_{ah}$	NA	LOS hospital (days)	CIHI	15	19	57
$\vec{T}_{ah\_c}$	NA	LOS hospital among those admitted to critical care (days)	CIHI	29	27	71

Symbol	Transformation	Quantity	Source	Estimate: age < 65 years	Estimate: age ≥ 65 years	Estimate: LTC
$\vec{T}_c$	NA	LOS critical (days)	CIHI	9	8	8
$\vec{T}_i$	$\vec{T}_{ah\_c} - \vec{T}_c$	LOS for inpatient after critical (days)	CIHI	19	19	63
p_{ah_c}	NA	Proportion of total hospitalizations that are critical	CIHI	0.190	0.120	0.063
$\vec{p}_{c-d}$	NA	Proportion of critical patients that die	CIHI	0.161	0.294	0.073
$\vec{T}_h$	$\frac{(\vec{T}_{ah} - p_{ah\_c} \times \left(\vec{T}_c + \left(1 - p_{c\_d}\right) \times \vec{T}_i\right)}{1 - p_{ah\_c}}$	LOS inpatient (days)	CIHI	13	19	57
$Cost_h$	$Total\ inpatient\ cost \div \vec{T}_h$	Inpatient cost per day	CIHI	$1,182	$1,042	$874
$Cost_i$	$\left(Total\ ICU\ cost - (Cost_h \times \vec{T}_i)\right) \div \vec{T}_c$	Critical care cost per day	CIHI	$3,668	$3,366	$4,107

CIHI = Canadian Institute of Health Information; LOS = length of stay; LTC = long-term care; NA = not applicable.

Note: Case-infection ratio is interpreted as cases per infection in community. (Refer to Clinical Parameters section).

Table 22: NMV-r Effect Estimates (for Outpatient Treatment of COVID-19) on Inpatient (Admission Rate and LOS) and Death Rates Using Alberta Health Data

Case rates	Age group	Alberta Health: All cases (A)	Alberta Health data: Cases with NMV-r dispensation (B)	Relative risk (B ÷ A)
Period 1: January 2022 to August 2022				
Inpatient admission rate	< 65 years	0.04	0.02	0.58
	≥ 65 years	0.24	0.07	0.29
Inpatient: average LOS	< 65 years	12.0 days	8.1 days	0.68
	≥ 65 years	20.6 days	12.5 days	0.61
Death rate	< 65 years	9.8×10^{-4}	7.6×10^{-4}	0.77
	≥ 65 years	3.6×10^{-2}	2.5×10^{-2}	0.69
Period 2: September 2022 to December 2022				
Inpatient admission rate	< 65 years	0.19	0.06	0.34
	≥ 65 years	0.39	0.08	0.21
Inpatient: average LOS	< 65 years	15.4 days	14.2 days	0.92
	≥ 65 years	23.0 days	16.4 days	0.71
Death rate	< 65 years	5.4×10^{-3}	4.0×10^{-3}	0.74
	≥ 65 years	5.2×10^{-2}	3.2×10^{-2}	0.62

LOS = length of stay; NMV-r = nirmatrelvir-ritonavir.

Note: NMV-r effect estimates for death were based on all deaths (not limited to hospitals only). The effect estimates were assumed to be the same for both those aged 65 years or older and those in long-term care.

Table 23: Overview of Studies Used for NMV-r Effect Estimates

Characteristics or therapeutic effect (point estimates of relative risk)	Aggarwal et al.[27]	Shah et al.[28]	Al-Obiadi et al.[29]	Kabore et al.[39]	Alberta Health	Alberta Health
Study period (age cohort)	March to August 2022 (18 years and older)	April to September 2022 (18 years and older)	June to September 2022 (18 years and older)	March to August 2022 (all ages)	January to August 2022(≥ 65 years)	September – December 2022(≥ 65 years)
Location	US	US	US	Canada	Alberta	Alberta
All cause hospitalization (all ages)	NA	NA	**0.42**	**0.31**	NA	NA
All cause hospitalization (≥ 65 years)	**0.39**	**0.53**	NA	NA	NA	NA
Inpatient hospitalization (≥ 65 years)	NA	NA	NA	NA	**0.29**	**0.21**
Death (all ages)	**0.17**	NA	**0.33**	NA	NA	NA
Death (≥ 65 years)	NA	NA	NA	NA	**0.69**	**0.62**
LOS Hospital	0.65	NA	NA	NA	NA	NA
Inpatient LOS (≥ 65 years)	NA	NA	NA	NA	**0.61**	**0.71**

LOS = length of stay; NA = not applicable; NMV-r = nirmatrelvir-ritonavir.

Table 24: Underreporting Factor for COVID-19 Cases in Alberta

Date	Serology estimate[30]		Difference in serology estimate		Cases between dates (PHAC Data[23])		Case-infection-ratio (total infections per cases detected)	
	< 65 years	≥ 65 years	< 65 years	≥ 65 years	< 65 years	≥ 65 years	< 65 years	≥ 65 years
January 4, 2022	0.083	0.05	NA	NA	NA	NA	NA	NA
August 28, 2022	0.693	0.417	0.610	0.367	1,449,320	429,175	12.2	8.5
December 27, 2022	0.815	0.629	0.122	0.212	133,407	140,191	26.6	15.1

NA = not applicable; PHAC = Public Health Agency of Canada.

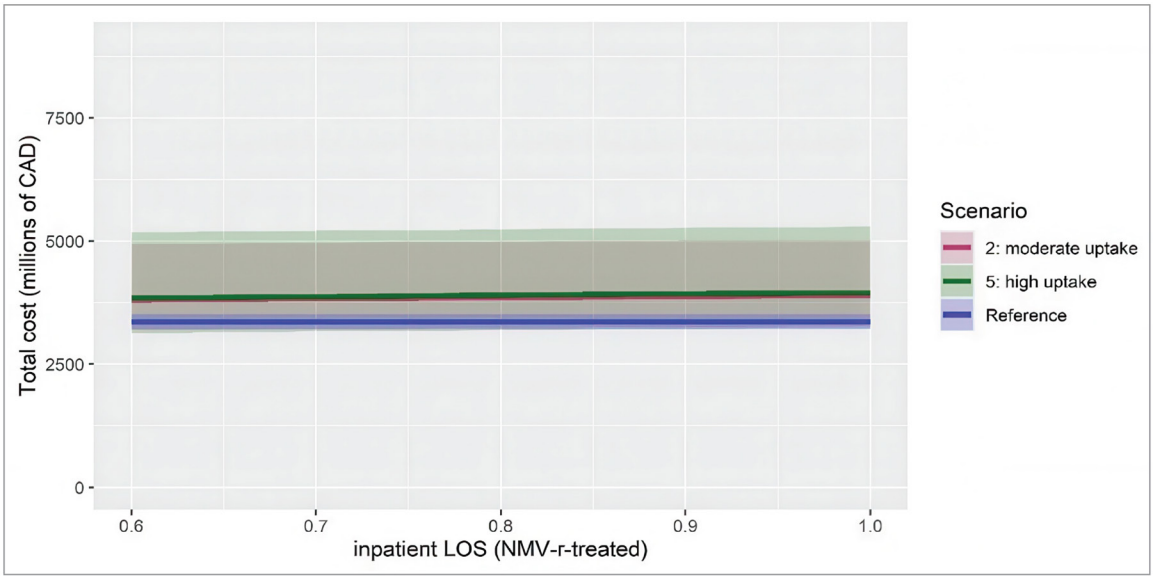
Note: Serology estimates were available by age younger than 60 years and age 60 years or older, which were extrapolated to the age groups used in the model (i.e., those aged < 65 years and those aged ≥ 65 years). "Cases between dates" were obtained from PHAC for data stratified by the 2 periods (January 1, 2022, to August 31, 2022, and September 1, 2022, to December 31, 2022).

Table 25: Validation of Total Infected in the Population in Canada

Data type	Period 1 (January to August 2022)			Period 2 (September to December 2022)		
	Age < 65 years	Age ≥ 65 years	LTC	Age < 65 years	Age ≥ 65 years	LTC
2022 Canada population (A)	28,959,289	9,970,613		28,959,289	9,970,613	
Total cases	1,520,036	191,997	166,461	147,900	104,902	20,797
Proportion of total cases (< 65 years; ≥ 65 years, and LTC) (B)	1	0.536 (191,997 out of 358,458)	0.464 (166,461 out of 358,458)	1	0.835 (104,902 out of 125,699)	0.165 (20,797 out of 125,699)
Difference in serology[30] (C)	0.610	0.367	0.367	0.122	0.212	0.212
Total infections (A × B ÷ C)	18,513,940	1,635,215	1,417,728	3,930,760	1,582,431	313,714

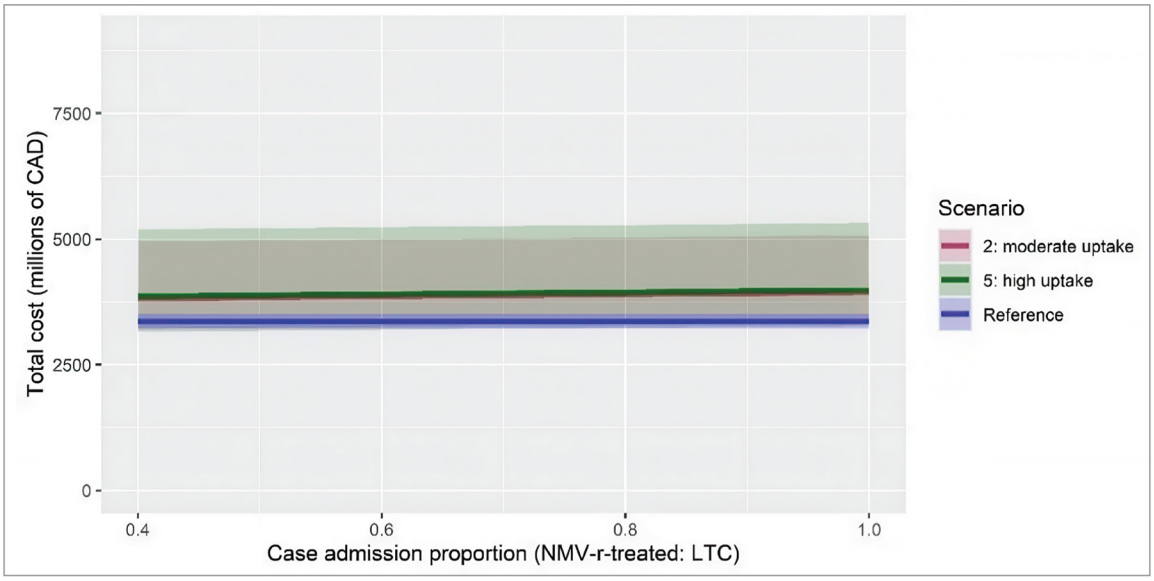
LTC = long-term care.

Figure 4: POSA Showing Total Cost (in Millions of CAD) Versus Inpatient LOS for All Individuals Treated With NMV-r



CAD = Canadian dollars; LOS = length of stay; NMV-r = nirmatrelvir-ritonavir; POSA = probabilistic one-way sensitivity analysis.

Figure 5: POSA Showing Total Cost (in Millions of CAD) Versus Case Admission Proportion for Individuals Aged 65 Years and Older Treated With NMV-r



CAD = Canadian dollars; LTC = long-term care, NMV-r = nirmatrelvir-ritonavir; POSA = probabilistic one-way sensitivity analysis.

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.