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Health Technology Review

The Cost-Effectiveness and Budget Impact of Remdesivir for Inpatient Treatment 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 remdesivir as an inpatient treatment option for COVID-19 in Canada on the health care system, drug access and uptake, and funding considerations.

We used a state-transition model to conduct a cost-utility analysis (CUA) and budget impact analysis (BIA) of various potential remdesivir uptake scenarios to treat COVID-19 in hospital in 3 cohorts: those younger than ages 65 years, those older than aged 65 years old, and/or those in long-term care.

Results of the CUA suggest that increased use of remdesivir may be cost-effective, depending on treatment uptake, patient cohort, and considerations of uncertainty.

The mean incremental net monetary benefit (iNMB) ranged from $34 million to $848 million, depending on willingness-to-pay (WTP) threshold per quality-adjusted life-year. The largest iNMB resulted from scenarios that had higher uptakes.

Based on average estimates, the budget impact of the scenarios ranged from $35 million (95% credible interval [CrI], –21 million to $89 million) to $148 million (95% CrI, –$94 million to $386 million), suggesting that remdesivir inpatient use will increase costs to the health system. The analysis also found that remdesivir will likely lead to a reduction in deaths. Total inpatient costs contributed the most to the overall total cost. When considering parameter uncertainty, all scenarios showed a possibility that inpatient use of remdesivir could result in cost savings to the health system.

The key limitations of this analysis were that the reference scenario included some inpatient use of remdesivir in 2022, the mortality impact on long-term care was likely underestimated because of data and model limitations, and the therapeutic effects for remdesivir in inpatients were based on literature before the emergence of the Omicron variant.

Table of Contents

List of Tables

List of Figures

Abbreviations

BIA	budget impact analysis
CCRN	Canadian Collaborative Research Network
CI	confidence interval
CIHI	Canadian Institute of Health Information
CrI	credible interval
CUA	cost-utility analysis
HALE	health-adjusted life-expectancy
ICER	incremental cost-effectiveness ratio
iNMB	incremental net monetary benefit
LOS	length of stay
LTC	long-term care
NMB	net monetary benefit
NMV-r	nirmatrelvir-ritonavir
PHAC	Public Health Agency of Canada
POSA	probabilistic one-way sensitivity analysis
PSA	probabilistic sensitivity analysis
QALY	quality-adjusted life-year
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
WTP	willingness to pay

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 range between 2 to 14 days (before to the emergence of the Omicron variant), and 2 to 4 days following the emergence of Omicron. Individuals with COVID-19 may remain asymptomatic and nonetheless be contagious.[2] The 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 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 (outpatient and inpatient use), 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, we issued reimbursement recommendations for NMV-r, remdesivir for inpatients, and remdesivir for outpatients to support the federal, provincial, and territorial drug plans' funding decisions. For remdesivir for inpatients, CDA-AMC recommended it be reimbursed for patients aged at least 12 years and weighing at least 40 kg who have confirmed COVID-19 infection that requires supplemental oxygen due to COVID-19 infection but do not require ventilation.

Before the CDA-AMC reimbursement recommendations 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. The research and policy questions defined in this report were developed in advance of the CDA-AMC reimbursement recommendations for remdesivir, and modelling was based on 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 remdesivir as an inpatient treatment for COVID-19 in Canada on health system costs and health outcomes.

Policy Issue

Health Canada first authorized the use of remdesivir in July 2020 for the inpatient treatment of COVID-19 in adults and youth (aged 12 years and older and weighing at least 40 kg) with pneumonia who require

supplemental oxygen given no drug interactions or side effects.[7,8] In May 2023, the indication was expanded to include pediatric patients at least 4 weeks of age and weighing at least 3 kg who are hospitalized.[9,10] Common side effects of remdesivir treatment include nausea, headache, and cough.[7,11,12] Although there is the potential for drug-drug interactions and/or adverse drug events, most patients complete remdesivir treatment as prescribed.[11] Remdesivir is administered intravenously by a health professional for 5 days in an inpatient setting.

A systematic review[4] found that inpatient use of remdesivir reduces the need for mechanical ventilation and intubation and mortality. The scope of that review did not include questions of cost-effectiveness or budget impact. To address these, we conducted an economic evaluation and BIA of the inpatient use of remdesivir for COVID-19, focusing on inpatient treatment, post–COVID-19 condition, and recovery. We developed a stochastic state-transition model and evaluated 3 cohorts within the hospital setting based on data availability and expected differences in disease severity: those aged younger than 65 years (not in long-term care [LTC]), those aged 65 years and older (not in LTC), and those in LTC. Post–COVID-19 condition was defined as those who experience COVID-19 symptoms for 3 or more months; it 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 the Omicron variants in 2022) and remdesivir's therapeutic effects for inpatient use.

Policy Question

What are the health system impacts, uptake, and funding considerations of offering remdesivir as an inpatient treatment option for COVID-19 in Canada?

Main Take-Aways

This report aims to estimate the health system impacts (i.e., health system costs and health outcomes) of access to and funding for remdesivir treatment in the inpatient setting in Canada. Considerations for this policy question include the effectiveness of remdesivir at reducing length of stay and preventing deaths in hospital, the potential inpatient use of remdesivir if access is expanded, remdesivir's impact on quality of life, the health care system costs associated with COVID-19, and treatment costs associated with inpatient remdesivir.

Objective

The objective was to conduct a CUA and BIA of remdesivir for the inpatient 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 remdesivir as an inpatient treatment for COVID-19 in populations understood to be at increased risk of severe outcomes?

Economic Analysis

Review of Economic Studies

A BIA is required to assess the affordability of implementing the intervention across the entire eligible population, accounting for the resources required to administer the intervention.[13] Considerations of budget constraints and drug supply can have an important role in resource allocation.[14] In the context of inpatient treatments for COVID-19, factors such as the size of the eligible patient population, dose size and timing, 28-day survival, length of stay (LOS), and critical care (also known as intensive care unit) admissions should be considered. Based on data from the Council of the Federation Secretariat, it was estimated that in the first 5 months of 2020, more than $11 billion was spent to address the COVID-19 pandemic in Canada.[15] This included costs for treatment, such as pharmaceuticals and medical supplies, testing, prevention through personal protective equipment, and other health care services and supplies.[15] Treatments and vaccines for COVID-19 in the appropriate patient population, though considered a major investment, have the potential to substantially save costs due to the downstream health care resource use associated with COVID-19.[16,17]

The potential of remdesivir to be cost saving for patients with acute COVID-19 who are hospitalized compared to the standard of care alone is supported by evidence from countries including the US,[18-20] Canada,[21] England and Whales,[22] France,[23] Greece,[24] Turkey,[25] South Africa,[26] China,[26] and the United Arab Emirates.[27] Barnieh et al. (2023)[19] found that remdesivir plus standard of care resulted in net cost saving of US$6,633 per patient. Lau et al. (2022)[28] determined that remdesivir was marginally cost saving (CA$108 per patient) and cost-effective in 74% of simulations using a WTP threshold of CA$50,000. Beraud et al. (2022)[22] found that remdesivir could generate savings of up to €722 per patient. Athanasakis et al. (2023)[23] found that remdesivir was cost saving with an incremental cost-effectiveness ratio (ICER) of –€4,291 per quality-adjusted life-year (QALY) gained. Jo et al. (2021)[25] found that remdesivir for patients hospitalized with COVID-19 who were no ventilated was likely to be cost saving and was associated with US$14.7 million in savings. Subhi et al. (2023)[27] modelled remdesivir plus standard of care and found substantial cost savings of US$3,454 per patient and total savings of US$13,795,962 over a 1-year period. Whittington et al. (2022)[18] concluded that remdesivir had an ICER of US$50,100 per QALY for moderate and severe COVID-19 cases assuming survival benefits. Rafia et al. (2022)[21] found that remdesivir is likely to be cost-effective with an ICER of £11,881 per QALY in patients requiring supplemental oxygen in hospital. Carta and Conversano (2021)[29] found that remdesivir was cost-effective and would lead to substantial health care savings if costs depend on length of hospital stay. Oksuz et al. (2021)[24] found that remdesivir was cost saving due to reduced LOS, rates of intubation, and critical care requirements in patients hospitalized with COVID-19 who require

low-flow oxygen therapy. Jiang et al. (2020)[26] found that remdesivir was cost-effective with an ICER of ¥14,098 per QALY. Dijk et al. (2022)[20] found that remdesivir had an incremental net monetary benefit (iNMB) of $25,249 from a US health care perspective using a lifetime horizon and a WTP threshold of $100,000 per QALY. However, a study by Congly et al. (2021)[30] found that remdesivir was unlikely to be cost-effective for patients hospitalized with moderate COVID-19 infections in the US. Research indicates that remdesivir compared to standard of care for patients hospitalized with COVID-19 has ICERs ranging from –€4,291 (–CA$6,358) to US$50,100 (CA$68,547) per QALY gained[18,21,23,26] and is associated with cost savings ranging from CA$108 to US$6,633 (CA$9,074) per patient hospitalized with COVID-19.[19,22,25,27,28]

Economic Evaluation and Budget Impact

We conducted a CUA and BIA examining inpatient treatment strategies for remdesivir based on COVID-19 data for 2022. We developed a stochastic state-transition model that includes clinical outcomes associated with COVID-19 hospitalization using data from the Canadian Institute of Health Information (CIHI), PHAC,[31] and the scientific literature. To reflect the best available data related to remdesivir effect estimates and severity of COVID-19 infection, the patient population in the model was stratified into 3 cohorts: those younger than aged 65 years (not in LTC), those aged 65 years and older (not in LTC), and those in LTC of any age group. The variation of model inputs allowed for estimates to include 95% CrIs. Costs related to inpatient stay, critical care stay, physician time, and remdesivir (including infusion administration costs) were included in the analysis.

Economic Analyses Overview

We estimated costs, health outcomes, and cost-effectiveness of 5 COVID-19 inpatient treatment scenarios for remdesivir in Canada compared to a baseline. The scope and analytical approach taken in this economic evaluation was based on the best available data identified from clinical reviews, scientific literature, and data repositories. This evaluation was based on data obtained from CIHI and supplemented with data from the literature, including CDA-AMC reviews. CIHI provided COVID-19 data related to COVID-19 disease severity (inpatient, critical care, death, and LOS) for Canada.

The reference scenario was defined as COVID-19 hospitalizations in Canada in 2022. Data used to define the reference scenario include some inpatient remdesivir use as remdesivir was approved for use in July 2020.The proportion of patients in Canada with COVID-19 treated with remdesivir in 2022 within the hospital setting was not available in the literature and represents a limitation in the data.[7]

The 5 remdesivir uptake scenarios were selected to include a focus on high-risk cohorts and assumptions related to inpatient use of remdesivir following discussions with the CoLab team. The drug uptake estimates used in the scenarios were selected to represent expected inpatient use of remdesivir with consideration for potential drug interactions and adverse events. These scenarios assume that patients in hospital have access to remdesivir as an option for inpatient treatment (excluding those receiving mechanical ventilation in critical care) for COVID-19 at various drug uptakes, to evaluate the overall potential impacts to the health care system. The scenarios define the 65 years and older (not in LTC) and individuals in LTC as “high risk” for simplicity in naming scenarios. These scenarios are described as follows:

Reference scenario: COVID-19 hospital dispositions in 2022 in Canada [reference scenario]

Scenario 1: Remdesivir treatment of patients who are hospitalized in 10% of those aged younger than 65 years (not in LTC), 15% of those aged 65 years and older (not in LTC), and 15% of those in LTC (low uptake scenario)

Scenario 2: Remdesivir treatment of patients who are hospitalized in 20% of those aged younger than 65 years (not in LTC), 30% of those aged 65 years and older (not in LTC), and 30% of those in LTC (moderate uptake scenario)

Scenario 3: Remdesivir treatment of patients who are hospitalized in 15% of those aged 65 years and older (not in LTC) and 15% of those in LTC (high-risk low uptake scenario)

Scenario 4: Remdesivir treatment of patients who are hospitalized in 50% of those aged 65 years and older (not in LTC) and 50% of those in LTC (high-risk high uptake scenario)

Scenario 5: Remdesivir treatment of patients who are hospitalized in 30% of those aged younger than 65 years (not in LTC), 50% of those aged 65 years and older (not in LTC), and 50% of those in LTC (high uptake scenario)

Economic Evaluation Methods

We developed a stochastic state-transition model that included clinical outcomes associated with COVID-19 hospitalization. The advantage of using a state-transition model compared to other analytical methods is that it captured 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 [PSA]) 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 the literature, including CDA-AMC reviews. The time horizon included 1 year of simulation, including impacts on inpatient outcomes and post–COVID-19 condition, along with estimates of projected lifetime QALY losses due to death observed in that year. This approach allows for estimating differences in QALY benefit gains or losses compared to the reference scenario.

The state-transition model was stratified into 3 cohorts related to risk of severe outcomes: those aged younger than 65 years (not in LTC), those aged 65 years and older (not in LTC), and those in LTC. 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 severity of COVID-19 observed in the CIHI data. Overall, these results were combined at the end of the simulations across the 3 cohorts and 2 periods.

The intervention scenarios considered various possible remdesivir uptake estimates for inpatients based on reasonable coverage (i.e., the percent of inpatients offered remdesivir as informed by the CoLab team) and therapy completion rates (related to drug-drug interactions and/or adverse events) for remdesivir. Model data were either directly obtained and/or combined from multiple data sources (refer to the Data Inputs section), including the effect estimates for the inpatient use of remdesivir.

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 present the ICER for each scenario compared to baseline.

BIA Methods

The BIA quantifies the health system impacts related to remdesivir inpatient treatment retrospectively using COVID-19 data from Canada in 2022, including the number of patients admitted to the hospital in critical care and not in critical care. This data excludes Quebec due to data limitations related to the release of severity data from CIHI. The time horizon for the 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 analytical approach aimed to answer a counterfactual question about the inpatient use of remdesivir (i.e., if we retrospectively treated a specified fraction of patients with remdesivir in 2022, what would be the difference in health care system costs and quality of life outcomes compared to the reference scenario [COVID-19 hospital dispositions in Canada in 2022]).

For the reference and 5 scenarios described previously, 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 remdesivir treatment were included in the analysis. Administration costs related to the implementation of the inpatient treatment strategy and health care costs related to post–COVID-19 condition were not included.

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 hospitalized with COVID-19 in 2022. The state-transition model stratified COVID-19 hospitalizations according to the cohorts: those aged younger than 65 years (not in LTC), those aged 65 years and older (not in LTC), and those in LTC.

Hospital dispositions from 2022 related to COVID-19 in Canada were obtained from CIHI and are described in Table 1, stratified across cohorts and time periods (period 1 and period 2). Total hospital admissions include those admitted to the critical care unit.

Table 1: Hospital Dispositions From CIHI Related to COVID-19 in Canada (2022)

Hospital disposition (2022)	Age < 65 years old (not in LTC)	Age ≥ 65 years old (not in LTC)	LTC
Period 1: January 2022 to August 2022			
Total hospital admissions	38,062	54,433	6,132
Total critical care admissions	6,457	7,261	370
Total deaths[a]	1,601	8,341	465
Period 2: September 2022 to December 2022			
Total hospital admissions	11,062	27,053	3,696
Total critical care admissions	2,068	3,246	233

Hospital disposition (2022)	Age < 65 years old (not in LTC)	Age ≥ 65 years old (not in LTC)	LTC
Total deaths[a]	532	3,758	226

CIHI = Canadian Institute for Health Information; LTC = long-term care.

Note: Total hospital admissions may include repeat hospitalizations and do not represent total people hospitalized.

[a]Within-facility deaths reported from CIHI based on the Discharge Abstract Database.

Treatment

The inpatient COVID-19 treatment considered was remdesivir. Remdesivir aims to stop the virus from multiplying in cells in the body.[7] This drug is generally administered intravenously by a health professional for 5 days in the hospital. Although treatment can be extended to 10 days, this analysis assumed a 5-day treatment cost.[7]

Perspective

The CUA and BIA were conducted from a Canadian health care payer perspective.

Time Horizon and Discounting

Based on the availability of data and the time-limited impact of remdesivir, 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 year time horizon, no other discounting was applied, as the impact of discounting over the course of a single year is minimal. Simulated individuals are initialized within hospital at the starting time, and after 1 year most are in the Recovered or Dead state, with a very small proportion (< 0.1%) in the Post–COVID-19 Condition state.

Model Structure (CUA BIA)

The model used to conduct both the CUA and BIA was a stochastic state-transition Markov model representing acute care clinical outcomes associated with COVID-19, with states defined as follows:

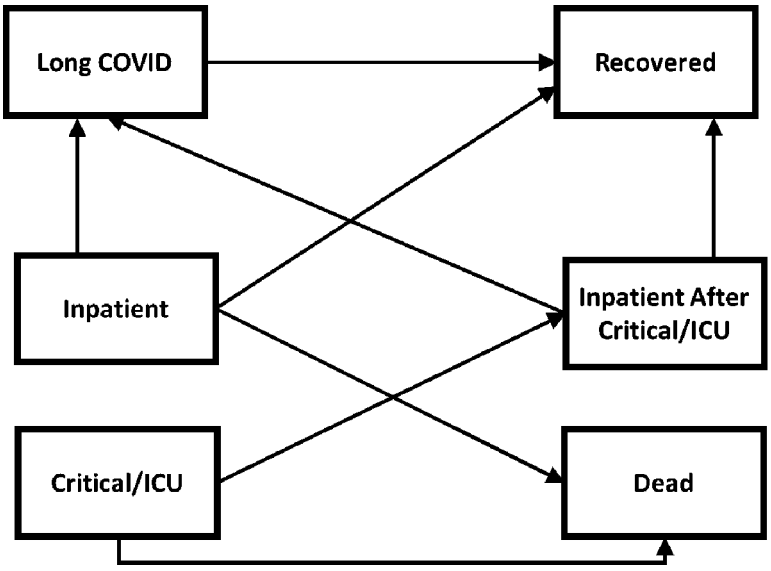
- **Inpatient:** individuals hospitalized but not in critical care
- **Critical:** individuals in critical care who require intensive care unit admission
- **Inpatient After Critical:** individuals having recovered from the Critical state and being monitored before discharge from hospital
- **Post–COVID-19 Condition:** defined consistently with Hanson et al.:[32] “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 (Inpatient and Inpatient After Critical)
- **Dead:** end state; there was no costs associated with this state

Individuals begin in the either the Inpatient or Critical state and may progress either into death or toward recovery. Transitions occur on a daily basis in the model. Individuals in the model do not move directly from inpatient to critical. While inpatient to critical care is a realistic transition, there are insufficient data to determine what proportion of patients entered critical care immediately upon hospitalization rather than after

a delay. Instead, we initialized individuals in both of the hospitalized states in accordance with admission data from CIHI. To capture the time patients spend on the critical care ward, individuals in the model move from the Critical state to the Inpatient After Critical state. Nonetheless, this accurately depicts the average total time patients spend in each hospital state, and thus accurately captures the cost and health-related utilities accrued by their hospital stay. Modelled individuals enter the Dead state from either Inpatient or Critical. The model did not include deaths that occurred in individuals who were not admitted to the hospital. Patients who do not die either recover fully or may first spend time in the Post–COVID-19 Condition state. The proportion of individuals who move to the Post–COVID-19 Condition state differs depending on whether they were in inpatient or critical care, consistent with the proportions reported in Hanson et al.[32] Figure 1 shows model states and transitions.

The stochastic state-transition model described in Figure 1 was stratified into 3 cohorts (not shown): those aged younger than 65 years old (not in LTC), those aged 65 years and older (not in LTC), and those in LTC. The 2022 COVID-19 data were further stratified into 2 periods (not shown) to account for differences in COVID-19 severity outcomes: January to August 2022 (period 1) and September to December 2022 (period 2). The model simulates each cohort and period independently.

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



Data Sources

Table 2 describes key data sources and transformations that were used to estimate model inputs for the CUA and the BIA.

Table 2: Data Source, Transformations, and Additional Comments

Data source	Data transformations	Additional comments
CIHI data (2022)	• Hospital disposition (inpatient,	• Data provided for Canada excluded Quebec due to

Data source	Data transformations	Additional comments
Datasets: • Discharge Abstract Database • Canadian MIS Database (costs)	critical care, LOS, and death) and costs • Total costs were transformed to daily per patient cost using inpatient LOS and critical care LOS	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 die is accounted for). Deaths that occurred outside discharge are not included. • Costs reported by CIHI did not include physician fees; therefore, we added physician fees using a study by Lau et al.[28] • Costs related to post–COVID-19 condition were not included in the analysis (due to limitations in the literature).
Wang et al.(CDA-AMC systematic review)[4]	• Remdesivir effect estimates for hospital LOS and deaths	• Studies considered from Wang et al. for effect estimates were from study periods before the emergence of the Omicron variant (i.e., 2020 to 2021). • Refer to the Clinical Parameters section.

CIHI = Canadian Institute of Health Information; LOS = length of stay; LTC = long-term care.

Data Inputs

Table 3 provides the stochastic state-transition model parameters related to inpatient transitions with sample distributions and standard deviations (SDs) among COVID-19 hospitalizations (refer to Table 17 for additional data transformations used in the model). These transitions are stratified by period 1 (January to August 2022) and period 2 (September to December 2022) and cohorts (age < 65 years and not in LTC, age ≥ 65 years and not in LTC, and LTC). Two periods were selected to adjust for differences in COVID-19 severity outcomes. Across both time periods, the Omicron variant was the main variant in circulation. Data sources include CIHI and CDA-AMC systematic reviews (refer to Table 2). Although the target population is Canada, severity parameters obtained from CIHI for Canada did not include data from Quebec and therefore they were not included in the modelling. 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 LOS for the Inpatient and Critical states was estimated (refer to Table 17) from CIHI data. Bayesian inference was used to estimate the distribution of the rate at which patients leave the hospital and critical care. This was determined by first using the method of moments to estimate the Weibull distribution that has the LOS mean, $\bar{\theta}$, and LOS SD, s, given by the hospital and critical care from CIHI data, respectively. Next, a random sample of n LOS values were taken from the estimated Weibull distribution, where n is the number of observations given by the hospital and critical care data from CIHI. Then an exponential distribution,

$EXP(\lambda)$, with an inverse gamma distributed rate, $\lambda \sim INVGAM\left(\frac{n}{\theta}, n\right)$, was fit to the n random samples from the estimated Weibull distribution to determine the distribution of the rate at which patients leave the hospital and critical care.

Death rates were estimated from CIHI data. Due to limitations with the CIHI data, deaths in LTC represent those who died during hospitalization and did not capture residents in LTC who died outside hospital facilities.

The therapeutic effect of remdesivir was obtained from a CDA-AMC systematic review (refer to the Clinical Parameters section).[4] The therapeutic effect for the inpatient use of remdesivir was applied to hospital LOS and death (Inpatient and Critical states).[4] Per patient-day costs were estimated using LOS and total cost estimates from CIHI.

Health utilities were assigned to each state to calculate QALYs from model simulations (refer to Table 5). Baseline health utilities associated with healthy individuals in the Recovered state were obtained from health-adjusted life-expectancy (HALE) tables published by Statistics Canada,[33] and cross-referenced with the average age of cases[34] in modelled cohorts. Health utilities immediately following hospital discharge (assumed to be the same as the utilities for inpatients) and for post–COVID-19 condition were obtained from Poudel et al.[35]

Table 3: Stochastic State-Transition Model Parameters Related to Inpatient Transitions, Including Sample Distribution and SD 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)
$\vec{p}_{c-d}$	Proportion of critical care patients who die	CIHI	Beta	0.169 (± 5%)	0.332 (± 5%)	0.135 (± 5%)
—	Proportion of critical care who are ventilated	CIHI	NA	0.49	0.41	0.31
$\vec{p}_{\mathrm{h}-d}$	Proportion of inpatients who die	CIHI	Beta	0.016 (± 5%)	0.126 (± 5%)	0.072 (± 5%)
Period: September 2022 to December 2022						
$\vec{T}_{ah}$	LOS hospital (days)	CIHI	Weibull	15 (40)	19 (36)	57 (73)

Symbol	Quantity	Source	Sample distribution	Mean (SD): age < 65 years	Mean (SD): age ≥ 65 years	Mean (SD): LTC
$\vec{T}_c$	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)
$\vec{p}_{c-d}$	Proportion of critical care patients who die	CIHI	Beta	0.161 (± 5%)	0.294 (± 5%)	0.073 (± 5%)
—	Proportion of critical care who are ventilated	CIHI	NA	0.45	0.34	0.29
$\vec{p}_{\mathrm{h}-d}$	Proportion of inpatients who die	CIHI	Beta	0.022 (± 5%)	0.118 (± 5%)	0.060 (± 5%)
Period: January 2022 to December 2022						
$\vec{T}_{sr}$	Total time to symptom resolution (days)	Siemieniuk et al.36	Gamma	9.9	9.9	9.9
$\vec{p}_{hrl-l}$	Proportion of hospitalized patients who develop post–COVID-19 condition	Wulf Hanson et al.32	Beta	0.275 (± 5%)	0.275 (± 5%)	0.275 (± 5%)
$\vec{p}_{crl-l}$	Proportion of critical patients who develop post–COVID-19 condition	Wulf Hanson et al.32	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.32	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.

Clinical Parameters

Therapeutic Effect Estimates: Remdesivir for Inpatient Treatment of COVID-19

Table 4 describes therapeutic effects for the inpatient use of remdesivir for hospital LOS (mean difference measure) and mortality (relative risk measure). Estimates of therapeutic effects for hospital LOS and death were not definitive across existing studies,[4,28,37,38] and these uncertainties were included in the model simulation using probability sensitivity analysis. The therapeutic effects are reported as a point estimate with a range of values informed by the minimum and maximum estimates across studies or the 95% confidence interval (CI) within 1 study (refer to Table 18 for additional information). The mortality impact for critical care was only applied to individuals who were not mechanically ventilated in the CIHI data, as there is no evidence of benefit in this population (refer to Table 3 for estimates describing the proportion of people who were mechanically ventilated in critical care).[39-42]

Wang et al. found that remdesivir for the inpatient treatment for COVID-19 would significantly reduce the need for mechanical ventilation and intubation.[4] These effects could not be implemented in the model due to data limitations. Moreover, there is limited evidence of benefit associated with remdesivir in patients who are hospitalized but not receiving supplemental oxygen.[39] We could not identify this population in the CIHI data and therefore included the mortality effect estimates across the entire inpatient population.

Overall, the previously described studies that describe these therapeutic effects were mainly from COVID-19 that occurred before the emergence of the Omicron variant and represent a limitation in the data used in this analysis. In addition, the same therapeutic effects, including its uncertainty, were applied across all 3 cohorts as cohort-specific information was not available from these studies.

Table 4: Effect Estimates for the Inpatient Treatment of COVID-19 With Remdesivir

Symbol	Quantity	Inpatient remdesivir therapy effect			Therapy effect source
		Age < 65 years (range)	Age ≥ 65 years (range)	LTC (range)	
Mean difference (range)					
$\vec{T}_{ah}$	LOS hospital (days)	−0.70 (−4.22 to 1.59)	−0.70 (−4.22 to 1.59)	−0.70 (−4.22 to 1.59)	Beigel et al.[37] and Ali et al.[38]
$\vec{T}_{c}$	LOS critical care (days)	−1.0 (−1.8 to −0.2)	−1.0 (−1.8 to −0.2)	−1.0 (−1.8 to −0.2)	Lau et al.[28]
Relative risk (range)					
$\vec{p}_{c-d}$	Proportion of critical care patients who die[a]	0.81 (0.68 to 0.95)	0.81 (0.68 to 0.95)	0.81 (0.68 to 0.95)	Wang et al.
$\vec{p}_{\mathrm{h}-d}$	Proportion of inpatients who die[a]	0.81 (0.68 to 0.95)	0.81 (0.68 to 0.95)	0.81 (0.68 to 0.95)	

LOS = length of stay; LTC = long-term care.

[a]This proportion is only applied to those that are not mechanically ventilated.

Utilities

The health utility associated with the Recovered state was assumed to be that of healthy individuals; it was estimated from HALE tables published by Statistics Canada[33] and assigned to model cohorts according to the average age of COVID-19 cases 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 equally to the average HALE for individuals in the modelled cohort, thereby capturing the loss of expected lifetime QALYs. For the purpose of taking the difference between treatment and reference scenarios, this approach produces the same result as adding QALYs to all individuals who survive at the end of simulation equal to their HALE, but has the advantage of requiring only data describing individuals who died. However, total simulated QALYs will include the QALYs accrued during 1 year of simulation and the negative quantities equal to the lost lifetime HALE of individuals who died (refer to Table 14). Poudel et al.[35] 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.,[35] is slow following hospitalization, we inferred that the utility during noncritical hospitalization (Inpatient and Inpatient After Critical states) is equal to that immediately after discharge. Additionally, individuals in the Critical state are often either unconscious or have a very low health-related quality of life; therefore, the utility

for the Critical state was assumed to be 0. The utility estimates for the stochastic state-transition model are provided in Table 5.

Table 5: Utility Estimates for the Stochastic State-Transition Model

Symbol	States	Annual utility (SD)	Entry utility (SD)	Source
$\overrightarrow{Ut}_c$	Critical	0	0	Estimate
$\overrightarrow{Ut}_h$	Inpatient	0.60 (0.06)	0	Poudel et al.[35]
$\overrightarrow{Ut}_{d1a}$	Period 1: Dead (age < 65 years)	0	−27.6 (0.04)	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_{d1b}$	Period 1: Dead (age ≥ 65 years or LTC)	0	−6.4 (0.03)	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_{d2a}$	Period 2: Dead (age < 65 years)	0	−27.3 (0.03)	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_{d2b}$	Period 2: Dead (age ≥ 65 years or LTC)	0	−6.0 (0.03)	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_i$	Inpatient After Critical	0.60 (0.06)	0	Poudel et al.[35]
$\overrightarrow{Ut}_l$	Post–COVID-19 Condition	0.76 (0.076)	0	Poudel et al.[35]
$\overrightarrow{Ut}_{r1a}$	Period 1: Recovered (age < 65 years)	0.89 (0.089)	0	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_{r1b}$	Period 1: Recovered (age ≥ 65 years or LTC)	0.73 (0.073)	0	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_{r2a}$	Period 2: Recovered (age < 65 years)	0.89 (0.089)	0	Statistics Canada,[33] PHAC[43]
$\overrightarrow{Ut}_{r2b}$	Period 2: Recovered (age ≥ 65 years or LTC)	0.70 (0.070)	0	Statistics Canada,[33] PHAC[43]

LTC = long-term care; PHAC = Public Health Agency of Canada; SD = standard deviation.

Costs

All costs were reported in 2022 Canadian dollars and, where needed, were inflated to 2022 Canadian dollars using the Consumer Price Index for all items in Canada.[44] Table 6 describes the 2022 hospital resource and drug costs used in the health economic evaluation, including the costs associated with purchasing remdesivir. Costs from CIHI were scaled from total to per-day costs using LOS estimates for inpatient and critical cases. We added per patient-day costs for inpatient and critical care physicians from the literature as these costs were not included in the total costs reported by CIHI.[28] Costs related to the implementation of the inpatient strategy (e.g., administration costs) and health care costs related to post–COVID-19 condition were not included in this analysis.

The administration of remdesivir as an inpatient treatment for COVID-19 includes a 5-day infusion using six 100 mg vials (2 vials for the first infusion followed by 1 vial each for the rest of the infusions).[7] Although

patients could receive remdesivir for up to 10 days, the proportion who do so is unknown. Therefore, costs were estimated based on the 5-day infusion of remdesivir. Total costs for remdesivir treatment within the hospital adjusted to 2022 Canadian dollars ranged from $3,196 to $4,243.[28,45,46]

Table 6: Hospital Resource and Drug Costs

Hospital resource or drug cost	Cost	Treated state	Source
Period 1: Hospital stay, inpatient (per day)			
Age < 65 years old	$1,368 (SD = 68.39)	Inpatient or Inpatient After Critical	CIHI
Age ≥ 65 years old	$1,118 (SD = 55.92)		
LTC	$913 (SD = 45.66)		
Period 1: Hospital stay, critical care (per day)			
Age < 65 years old	$3,713 (SD = 185.66)	Critical	CIHI
Age ≥ 65 years old	$3,640 (SD = 182.01)		
LTC	$4,573 (SD = 228.65)		
Period 2: Hospital stay, inpatient (per day)			
Age 65 years old	$1,182 (SD = 59.09)	Inpatient or Inpatient After Critical	CIHI
Age ≥ 65 years old	$1,042 (SD = 52.10)		
LTC	$874 (SD = 43.69)		
Period 2: Hospital stay, critical (per day)			
Age < 65 years old	$3,668 (SD = 183.40)	Critical	CIHI
Age ≥ 65 years old	$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.[28]
Critical care physician (per patient-day)	$254.70 (SD = $128.22)	Critical	Lau et al.[28]
Remdesivir Treatment	$3,720 (range, $3,196 to $4,243)	Inpatient or Critical	Government of Canada[7] Lau et al.[28] Gilead Sciences[45] NICE[46]

CIHI = Canadian Institute of Health Information; LTC = long-term care; NICE = National Institute for Health and Care Excellence; SD = standard deviation.
Notes: Period 1 was January to August 2022 and period 2 was September to December 2022. Cost conversion to US dollars was US$1 = CA$1.36.

Scenario Analysis and Sensitivity Analysis

Five treatment scenarios and 1 reference scenario were considered in this health economic evaluation, all of which are described in Table 7. We include both scenarios targeting inpatient treatment of remdesivir to all cohorts, as well as those focused on cohorts considered at higher risk of severe COVID-19, specifically those aged 65 years and older and in LTC. The reference scenario represented the standard of care during 2022 and included some inpatient use of remdesivir in adults and youth (aged 12 years and older and

weighing at least 40 kg) with pneumonia who required supplemental oxygen.[7] The baseline use of remdesivir within the hospital was not available in the literature. Therefore, scenarios described in Table 7 would include additional remdesivir use above what was provided to patients in the reference scenario. The 5 scenarios were selected following discussions with the CoLab team. Uptake was defined as a reasonable estimate of remdesivir use if broadly available for inpatient treatment of COVID-19 with consideration for potential drug interactions and adverse events. Therefore, these scenarios assumed that a fraction of people who were hospitalized (including those who did not meet the criteria outlined in July 2020[7]) could have had access to remdesivir as an inpatient option for COVID-19 treatment, and evaluates the impact of that access to the health care system.

Furthermore, probabilistic sensitivity analyses were undertaken to address parameter uncertainty associated with 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 affects the cost-effectiveness estimates in the model. The SDs for the model parameters used in the stochastic state-transition model are provided in Table 3, Table 4, Table 5, and Table 6. Standard distributional forms were taken to describe probability distribution functions relating to input parameters (proportions and utilities were characterized by the beta distribution 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 is optimal compared to baseline ($NMB_{scenario} > NMB_{baseline}$). Scenario analysis results include NMB, iNMB, and ICERs, including quadrant location.

Table 7: Scenario Descriptions for Remdesivir for the Inpatient Treatment of COVID-19

Scenario	Justification
Reference scenario: COVID-19 hospital dispositions in 2022 (Canada). Note: The standard of care during 2022 would include inpatient treatment of remdesivir. The overall proportion of inpatient use of remdesivir was unavailable in the literature.	The reference scenario focused on representing COVID-19 epidemiology in 2022. Data from 2022 were selected to conduct an economic evaluation as these were the data at the time the analysis was undertaken. During this period, there was a transition of management policies toward COVID-19 as an endemic disease.
Scenario 1 (low uptake): Remdesivir treatment of patients who were hospitalized in 10% of those aged < 65 years (not in LTC), 15% of those aged ≥ 65 years (not in LTC) and 15% of those from LTC.	Scenario 1 included inpatient treatment of those aged < 65 years (not in LTC) along with those who have a higher severity risk.
Scenario 2 (moderate uptake): Remdesivir treatment of hospitalized patients in 20% of those aged < 65 years (not in LTC), 30% of those aged ≥ 65 years (not in LTC) and 30% of those from LTC.	In scenario 2, the magnitude of inpatient uptake of remdesivir was increased to capture the potential for higher uptake of the drug; specifically, uptake was doubled in all cohorts.
Scenario 3 (high-risk low uptake): Remdesivir treatment of those who were hospitalized in 15% of those aged ≥ 65 years (not in LTC) and 15% of those from LTC.	Scenario 3 had a focus on inpatient uptake of remdesivir in individuals at highest risk of severe COVID-19, specifically those aged ≥ 65 years (not in LTC) and the LTC cohort, with uptake consistent with scenario 1.

Scenario	Justification
Scenario 4 (high-risk high uptake): Remdesivir treatment of those who were hospitalized in 50% of those aged ≥ 65 years (not in LTC) and 50% of those from LTC.	Scenario 4 had a focus on high inpatient uptake of remdesivir in individuals at highest risk of severe COVID-19, specifically those aged ≥ 65 years (not in LTC) and the LTC cohort.
Scenario 5 (high uptake): Remdesivir treatment of those who were hospitalized in 30% of those aged < 65 years (not in LTC), 50% of those aged ≥ 65 years (not in LTC) and 50% of those from LTC.	Scenario 5 was a combined scenario of the highest projected inpatient uptake of remdesivir in those aged < 65 years (not in LTC), those aged ≥ 65 years (not in LTC), and the LTC cohort.

LTC = long-term care.

Uncertainty

As model simulations incorporate uncertainty within model inputs, a probabilistic one-way sensitivity analysis (POSA)[47] [n = 1,000 simulations] was used to estimate impacts of changing a key model input on total costs of selected treatment scenarios (scenario 2 — moderate uptake, scenario 4 — high-risk high uptake, and scenario 5 — high uptake) and the reference scenario through systematic sampling between a given range of the model input. Scenario 2, scenario 4, and scenario 5 were selected to provide a range of remdesivir uptake from moderate to high. Table 8 provides the key model inputs examined for the POSA using total costs as an outcome.

The POSA can assess whether the budget impact (scenario cost minus reference scenario cost) will cost (a strategy that costs more compared to the reference scenario) or save (a strategy that costs less compared to the reference scenario) the health care system money.

Table 8: POSA of Key Model Inputs

Model parameter	Cohort (age < 65 years, age ≥ 65 years, LTC, and all)	Range (total discrete points within the range)
Therapy effect of remdesivir (inpatient use) on critical care LOS	All	−1.8 to 0 days (10)
Mean hospital LOS for LTC and those aged ≥ 65 years	Age ≥ 65 years, LTC	25 to 40 days (10)
Total per patient cost: inpatient unit	All	$10,000 to $25,000 (10)

LOS = length of stay; LTC = long-term care; POSA = probabilistic one-way sensitivity analysis.

Notes: Case admission proportion has not been adjusted for infections. The model makes this adjustment within the simulation.

Model Validation

Overall, the validation of the model structure and model inputs occurred through discussions with the Canadian Collaborative Research Network (CCRN) and CoLab team, to ensure that the model was consistent with current clinical knowledge and practice in Canada. 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 inputs included clarifications from CIHI (related to a data request), data from the literature, and discussions with the CoLab team, where necessary.

Internal validity for the reference scenario as described in Table 9 included a comparison of data and model simulations (across the 3 cohorts and 2 periods) for initial model conditions (defined as the starting values for the population cohorts) and total deaths, including 95% CIs. The total deaths in hospital from model simulations compared well to the data.

Internal validity for scenarios (or treatment effects) was assessed by evaluating simulations at extreme values such as nullifying the cost of remdesivir on cost-effectiveness outcomes. This included creating scenarios that focused on 1 cohort and the therapeutic effect of remdesivir to determine if the results were reasonable compared to crude estimates. Overall results were compared to other similar economic evaluations (if available) for external validity.

Table 9: Internal Model Validation of Initial Conditions and Reference Scenario

Internal model validation	Reference scenario (data)	Reference scenario (model, with 95% CrI): N = 5,000 simulations
Total deaths	14,923	14,920 (13,650 to 16,240)

CrI = credible interval.

Model Assumptions

There were several model assumptions required to either supplement missing information or to simplify the model. These assumptions are listed in Table 10.

Table 10: Key Model Assumptions

Related model parameter or structure	Assumption	Additional comments
Time horizon	• The 1-year time horizon was structured around the availability of data. The use of case and hospitalization data before 2022 (or before the Omicron variants) may not be 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).	• If COVID-19 severity rates after 2022 are lower (or higher) than those used in this report, overall results would overestimate (or underestimate) the overall cost-effectiveness of the inpatient strategy.
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 differences in severity estimates. • COVID-19 severity data reported by CIHI do not include data from Quebec.	NA
Costs	• Costs related to the implementation of the inpatient strategy (e.g., administration costs) and health care costs related to post–COVID-19 condition were not included in this analysis. • The reference scenario assumed minimal use of remdesivir and those costs and effect considerations were not included.	NA

Related model parameter or structure	Assumption	Additional comments
Death transition: from Recovered, and LTC	• Deaths were only modelled from Inpatient and Critical states. Death transitions from other model states are 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 outside discharge are not included.	• LTC cases can also die outside of the hospital; therefore, not capturing these deaths could limit the cost-effectiveness of remdesivir in this population.
Inpatient and critical care model inputs for LTC	• The LTC data obtained from CIHI have limitations related to how LTC is defined by administrative data and model inputs for this cohort have more uncertainty.	• If inpatient model inputs for LTC are underestimated (a model input that has a therapeutic effect); this would likely also underestimate the cost-effectiveness of scenarios that focus on the treatment of the LTC cohort.
Remdesivir treatment	• Treatment longer than a 5-day infusion were not accounted for in the analysis. The proportions of people treated longer than 5 days was not available in literature.	• Adding the additional treatment costs associated with a longer-term infusion may reduce the cost-effectiveness of remdesivir as an inpatient strategy,
Remdesivir therapeutic effects	• Because of data limitations, remdesivir therapy effects were assumed to be the same for all cohorts (aged < 65 years [not in LTC], aged ≥ 65 years [not in LTC], and LTC). • We were not able to capture the effects of remdesivir on reducing the likelihood of the need for mechanical ventilation and intubation. • We applied mortality reductions to all those in the inpatient state. Based on the literature, there may be a differential effect on those not receiving supplemental oxygen.[39] However, we were unable to apply reductions to mortality for those within the inpatient state who received supplemental oxygen because of data limitations. • We applied mortality reductions to all those in the critical state who were not mechanically ventilated.[40-42] • We indirectly accounted for remdesivir therapy effects on post–COVID-19 condition as proportions transitions differed by in-hospital states.	• The assumption around the therapeutic effect on mechanical ventilation would reduce cost-effectiveness for the inpatient population. • The assumption around mortality reductions across the inpatient state would increase cost-effectiveness for the inpatient population.
Remdesivir inpatient scenarios	• Costs related to infusion administration were not included in this analysis. • We assumed all those treated with remdesivir completed the 5-day treatment course.	NA
Remdesivir reference scenario	• The reference scenario represents the standard of care during 2022 and included some inpatient use of remdesivir in adults and youth (aged 12 years and older and weighing at least 40 kg) with pneumonia	• For the LTC cohort, which is a very high risk and accessible population, it is possible they were more likely to have received remdesivir when they

Related model parameter or structure	Assumption	Additional comments
	who require supplemental oxygen.[7] The baseline use of remdesivir within the hospital was not available in the literature; therefore, scenarios described in Table 7 would include additional remdesivir use above what was provided to patients in the reference scenario.	were inpatients in 2022; therefore, the treatment effects may already have been seen in the reference population (reducing the hospitalization and mortality rate in this population).
Utilities	• Utilities for model state were the same across cohorts and periods except for the Recovered state. Utilities also do not differ by treatment arm.	NA
Utilities: Inpatient, Inpatient After Critical states	• Due to a lack of studies reporting health utilities for COVID-19 while in hospital, we assume 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.	• If utilities are lower during hospitalization, this could improve the cost-effectiveness of remdesivir for inpatients.
Utilities: Critical state	• Individuals are either unconscious or have a very low health-related quality of life, and the utility for critical was assumed to be 0 for simplicity.	• If utilities for those in critical care are higher than 0, this could reduce the cost-effectiveness of remdesivir in inpatients.
Utilities: deaths	• Estimated lifetime QALYs lost due to death are subtracted from QALY totals estimated from the 1-year model simulation. These projected lifetime QALYs are assumed to be equal to the average for a given cohort, and do not account for possible correlations with age and recovery from COVID-19.	• We discounted lifetime QALY losses associated with mortality at a rate of 1.5% to account for the lifetime impact of mortality.

CIHI = Canadian Institute of Health Information; LTC = long-term care; NA = not applicable; QALY = quality-adjusted life-year.

Assumptions Related to the BIA

A complete list of model assumptions is described in Table 10. In Table 11, we describe the BIA model assumptions that were addressed using POSA.

Table 11: Model Assumptions Addressed by POSA for Remdesivir as an Inpatient Treatment for COVID-19

Assumption	How it was tested in the scenario analysis	Additional comments
Remdesivir therapeutic effect on critical care LOS	A POSA was conducted to determine the therapeutic effect of critical care LOS, which included the possibility of no effect compared to the reference scenario.	This assumption was assessed due to data limitations in the literature about remdesivir effects on critical care LOS.

LOS = length of stay; LTC = long-term care; POSA = probabilistic one-way sensitivity analysis.

Results

Cost-Effectiveness Analysis Results

Main Take-Aways

The results of the CUA suggest that inpatient use of remdesivir may be cost-effective at different WTP thresholds. This is supported by a positive mean iNMB and ICERs below $30,000 per QALY. We observed consistency across scenarios focusing on individuals considered high risk (those aged 65 years and older and LTC) and/or all cohorts, with the highest iNMB observed in the scenario with high uptake across all cohorts. However, there is considerable uncertainty in results, as the 95% CrIs of most scenarios show the iNMB crossing 0 (except scenarios 4 and 5 with a WTP threshold greater than $100,000 per QALY).

Detailed results of the CUA are provided in Table 12 (NMB) and Table 14 (ICERs) with disaggregated results described in Table 13 and Table 15. In Canada (excluding Quebec), COVID-19 hospitalizations during 2022 totalled about 140,000, with 14,900 deaths in hospital. People in hospital with COVID-19 experience a temporary loss of quality of life captured in the model; we also captured, for those who died, a loss of lifetime QALYs (refer to Table 5). Approximately 11% of patients who were admitted to the hospital with COVID-19 (14,923 deaths out of 140,438 hospitalizations) died during 2022 (refer to Table 1), and this QALY loss is captured in the reference scenario and reflected in the NMB results (refer to Table 12 and Table 14). The 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 estimate −41,683 total QALYs over 1 year, which includes the QALY decrement with discounting for the estimated lifetime QALYs lost due to deaths among those who are hospitalized. The net negative QALYs in the simulated scenarios arises from the fact that the estimated lifetime QALYs lost due to deaths exceed the positive QALYs accrued during 1 year of simulation (refer to the Utility Estimation section).

If we assume a WTP per QALY of $50,000 then the total dollar value of QALYs lost in the reference scenario population is −2,084,000,000, or −$14,839 per hospital admission. We then estimate 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 $109 million (−$113 million, $330 million) at a WTP threshold of $50,000 per QALY when compared to the reference scenario. The full set of results for all scenarios is presented in Table 12 (with 95% CrIs). Disaggregated results described in Table 13 and Table 15 highlight the breakdown by state and scenario of QALY and health care costs. The largest positive contribution of QALY and health care costs are from the Recovered and Inpatient states, respectively. However, the QALY loss due to death was greater than the QALY gain within Recovered states (refer to Table 13).

In Table 14 we present ICERs for remdesivir inpatient uptake scenarios compared to a common baseline (the reference scenario). As we analyzed potential future states and not treatment strategies to be implemented, we did not calculate ICERs when all scenarios were compared to one another as would be typical in cost-

effectiveness analysis. Rather, our aim was to illustrate the cost-effectiveness of remdesivir under different possible use patterns and not to identify a single cost-effective strategy.

Key Results

- The NMB of the reference scenario is –$4.6 billion, –$5.4 billion, and –$7.5 billion for a WTP per QALY value of $30,000, $50,000, and $100,000, respectively (refer to Table 12). These numbers are estimated from approximately 140,000 hospital admissions related to COVID-19 during 2022 in Canada (excluding Quebec). The negative NMB is a result of lifetime QALYs lost associated with COVID-19 deaths.
- The NMB per reported hospital admission for the reference scenario is –$32,809, –$38,745, and –$53,585 for a WTP per QALY value of $30,000, $50,000, and $100,000, respectively.
- The iNMB showed the difference for each modelled scenario relative to the reference scenario (refer to Table 12). Although there is a QALY loss in the reference scenario, there was an increase in total QALYs in all scenarios (refer to Table 14), with the iNMB showing the relative change in valuation of QALYs versus health care costs.
- The therapeutic effect of remdesivir for inpatient use is mainly to reduce deaths in hospital, and there are 2 death-related factors driving the results — the QALY loss associated with death and total number of deaths by cohort. Although total deaths among those aged younger than 65 years is lower than the high-risk cohort (age ≥ 65 years and in LTC), the QALY loss is greater for those aged younger than 65 years compared to the high-risk cohort (refer to Table 1). As a result, the largest iNMB results are from scenarios that include a moderate to high uptake of remdesivir in inpatients across all cohorts (scenarios 2 and 5) or alternatively, a high uptake among those at high risk (scenario 4). At a WTP threshold of at least $30,000, the mean iNMB showed that all scenarios would be cost-effective compared to the reference scenario.
- Although mean estimates for iNMB for all scenarios were cost-effective at a WTP threshold of at least $30,000, there remains uncertainty as most scenarios had 95% CrIs cross 0 (except scenarios 4 and 5 at a WTP threshold of $100,000 per QALY), suggesting some model runs found negative iNMBs (refer to Table 12 and Table 13).
- The mean ICER results were comparable across most scenarios; however, scenario 1 had the lowest mean ICER followed by scenarios 2 and 5. All these scenarios focus on inpatient treatment of remdesivir in all cohorts. Scenario 3 and 4 had a higher ICER, which may be due to competing dynamics between total deaths and the QALY loss for deaths within the those aged 65 years and older and from LTC compared to those aged younger than 65 years (refer to Table 12 and Table 14). Moreover, as noted previously, the limitations associated with the LTC data (e.g., not capturing deaths outside of hospital) may have limited the cost-effectiveness of inpatient remdesivir treatment in this cohort.

Reference Scenario

The reference scenario represents the standard of care during 2022 and included some inpatient use of remdesivir in adults and youth (age ≥ 12 years and weighing at least 40 kg) with pneumonia who require supplemental oxygen.[7] The baseline use of remdesivir within the hospital was not available in the literature.

Sensitivity Analysis

The model simulations incorporated a probabilistic sensitivity analysis and the results in Table 12 include 95% CrIs to account for parameter uncertainty. Model inputs, including parameter ranges, SDs, and sampling distributions, are provided in Table 3, Table 4, Table 5, and Table 6. In Table 14 we present the ICERs for each of the scenarios relative to a common baseline of the reference scenario. Based on Table 12, although scenarios 2, 4, and 5 had the largest mean iNMB for WTP thresholds of at least $30,000, with considerations of uncertainty, most scenarios showed the possibility of a negative iNMB (i.e., incremental value is less than the cost of the intervention compared to the reference scenario) except for scenarios 4 and 5 at a WTP threshold of $100,000 per QALY. Disaggregated results stratified by model states are provided in Table 13 and Table 15, and highlight that most of the QALY increases and decreases are accrued in the Recovered (positive) and Death (negative) states.

Table 12: NMB ($) and iNMB ($) Estimates for Remdesivir Inpatient 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)	–$4,608 (–$5,083 to –$4,183)	–$5,441 (–$6,167 to –$4,803)	–$7,525 (–$8,906 to –$6,288)
iNMB (95% CrI)	NA	NA	NA
Scenario 1 (low uptake)			
NMB (95% CrI)	–$4,560 (–$5,041 to –$4,136)	–$5,332 (–$6,062 to –$4,697)	–$7,261 (–$8,636 to –$6,058)
iNMB (95% CrI)	$48 (–$98 to $194)	$109 (–$113, $330)	$264 (–$159, $694)
Scenario 2 (moderate uptake)			
NMB (95% CrI)	–$4,514 (–$5,019 to –$4,067)	–$5,224 (–$5,979 to –$4,566)	–$7,000 (–$8,397 to –$5,733)
iNMB (95% CrI)	$94 (–$119 to $304)	$217 (–$81 to $507)	$526 (–$7 to $1,050)
Scenario 3 (high-risk low uptake)			
NMB (95% CrI)	–$4,574 (–$5,046 to –$4,147)	–$5,362 (–$6,075 to –$4,715)	–$7,332 (–$8,696 to –$6,109)
iNMB (95% CrI)	$34 (–$54.3 to $123)	$79.4 (–$48.1 to $209)	$194 (–$42 to $436)

Cost-effectiveness estimate ($ in millions)	WTP threshold: $30,000	WTP threshold: $50,000	WTP threshold: $100,000
Scenario 4 (high-risk high uptake)			
NMB (95% CrI)	–$4,496 (–$4,999 to –$4,035)	–$5,178 (–$5,935 to –$4,487)	–$6,883 (–$8,329 to –$5,617)
iNMB (95% CrI)	$111 (–$110 to $334)	$263 (–$28 to $555)	$642 ($128 to $1,150)
Scenario 5 (high uptake)			
NMB (95% CrI)	–$4,457 (–$5,001 to –$3,968)	–$5,091 (–$5,881 to –$4,396)	–$6,677 (–$8,109 to –$5,404)
iNMB (95% CrI)	$151 (–$154 to $463)	$350 (–$47 to $751)	$848 ($163 to $1,550)

CrI = credible interval; iNMB = incremental net monetary benefit; NA = not applicable; NMB = net monetary benefit; QALY = quality-adjusted life-year; WTP = willingness to pay.

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

Parameter	Baseline	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)	–$1,251	–$1,158	–$1,066	–$1,182	–$1,023	–$952
By health state						
Inpatient	$100	$99	$99	$100	$98	$98
Critical	$0	$0	$0	$0	$0	$0
Inpatient After Critical	$12	$12	$12	$12	$12	$12
Dead	–$4,166	–$4,081	–$3,997	–$4,105	–$3,962	–$3,893
Post–COVID-19 condition	$293	$294	$295	$294	$296	$296
Recovered	$2,511	$2,518	$2,525	$2,517	$2,532	$2,535
Total value of QALYs (WTP: $50,000) (B)	–$2,084	–$1,929	–$1,776	–$1,970	–$1,705	–$1,586
By health state						
Inpatient	$167	$166	$164	$166	$164	$163
Critical	$0	$0	$0	$0	$0	$0
Inpatient After Critical	$20	$20	$21	$20	$21	$21
Dead	–$6,944	–$6,802	–$6,661	–$6,841	–$6,603	–$6,488
Post–COVID-19 condition	$489	$490	$492	$490	$493	$494
Recovered	$4,184	$4,197	$4,209	$4,195	$4,220	$4,225
Total value of QALYs (WTP: $100,000) (C)	–$4,168	–$3,858	–$3,552	–$3,940	–$3,409	–$3,172

Parameter	Baseline	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (LTC low uptake)	Scenario 4 (LTC high uptake)	Scenario 5 (high uptake)
By health state						
Inpatient	$333	$331	$329	$332	$328	$326
Critical	$0	$0	$0	$0	$0	$0
Inpatient After Critical	$41	$41	$41	$41	$41	$42
Dead	–$13,888	–$13,604	–$13,323	–$13,682	–$13,205	–$12,976
Post–COVID-19 condition	$977	$980	$983	$980	$986	$987
Recovered	$8,368	$8,393	$8,417	$8,390	$8,440	$8,449
Total costs (D)	$3,357	$3,403	$3,448	$3,392	$3,474	$3,505
By health state						
Inpatient	$2,387	$2,431	$2,474	$2,420	$2,498	$2,528
Critical	$660	$660	$660	$660	$660	$660
Inpatient After Critical	$310	$312	$314	$312	$315	$317
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 threshold						
$30,000 $[(A_{Sc} – D_{Sc}) – (A_{Base} – D_{Base})]$	—	$47	$94	$34	$111	$151
$50,000 $[(B_{Sc} – D_{Sc}) – (B_{Base} – D_{Base})]$	—	$109	$217	$79	$263	$350
$100,000 $[(C_{Sc} – D_{Sc}) – (C_{Base} – D_{Base})]$	—	$264	$526	$194	$642	$848

Base = baseline; iNMB = incremental net monetary benefit; NMB = net monetary benefit; QALY = quality-adjusted life-year; Sc = scenario; WTP = willingness to pay.

Table 14: ICERs for Remdesivir Inpatient Treatment Scenarios, Relative to a Common Baseline

Scenarios	Cost (millions)	Incremental cost (millions)	QALYs	Incremental QALYs	ICER
Reference scenario	$3,357	—	−41,683	—	NA
Scenario 1 (low uptake)	$3,403	$46	−38,583	3,100	$14,689
Scenario 2 (moderate uptake)	$3,448	$91	−35,515	6,167	$14,779
Scenario 3 (high-risk low uptake)	$3,392	$35	−39,396	2,287	$15,293
Scenario 4 (high-risk high uptake)	$3,474	$116	−34,095	7,588	$15,340
Scenario 5 (high uptake)	$3,505	$148	−31,723	9,960	$14,863

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; NA = not applicable.

Note: Total QALYs are negative because of the estimated loss of lifetime QALYs due to deaths (refer to the Utilities section for details).

Table 15: Disaggregated Results of the ICERs for Remdesivir Inpatient Treatment Scenarios, Relative to a Common Baseline

Scenarios	Cost (millions)	Incremental cost (millions)	QALYs	Incremental QALYs	ICER
Reference scenario	$3,357	$0	−41,683	—	NA
Inpatient	$2,387	$0	3,333	—	—
Critical	$660	$0	0	—	—
Inpatient After Critical	$310	$0	406	—	—
Dead	$0	$0	−138,880	—	—
Post–COVID-19 condition	$0	$0	9774	—	—
Recovered	$0	$0	83,683	—	—
Scenario 1 (low uptake)	3,403	46	−38,583	3,100	$14,689
Inpatient	$2,431	$44	3,311	−21.485	—
Critical	$660	$0	0	0	—
Inpatient After Critical	$312	$2	409	3	—
Dead	$0	$0	−136,040	2842	—
Post–COVID-19 condition	$0	$0	9,803	29	—
Recovered	$0	$0	83,931	248	—
Scenario 2 (moderate uptake)	$3,448	$91	−35,515	6,167.40	$14,779
Inpatient	$2,474	$87	3,289	−43.137	—
Critical	$660	$0	0	0	—
Inpatient After Critical	$314	$4	412	6	—
Dead	$0	$0	−133,230	5653	—
Post–COVID-19 condition	$0	$0	9,834	60	—
Recovered	$0	$0	84,174	491	—
Scenario 3 (high-risk low uptake)	$3,392	$35	−39,396	2,286.70	$15,293
Inpatient	$2,420	$33	3,317	−15.795	—
Critical	$660	$0	0	0	—
Inpatient After Critical	$312	$2	408	2	—
Dead	$0	$0	−136,820	2057	—
Post–COVID-19 condition	$0	$0	9,801	27	—
Recovered	$0	$0	83,900	216	—
Scenario 4 (high-risk high uptake)	$3,474	$116	−34,094	7,588.20	$15,340
Inpatient	$2,498	$111	3,280	−53.086	—
Critical	$660	$0	0	0	—
Inpatient After Critical	$315	$5	413	7	—

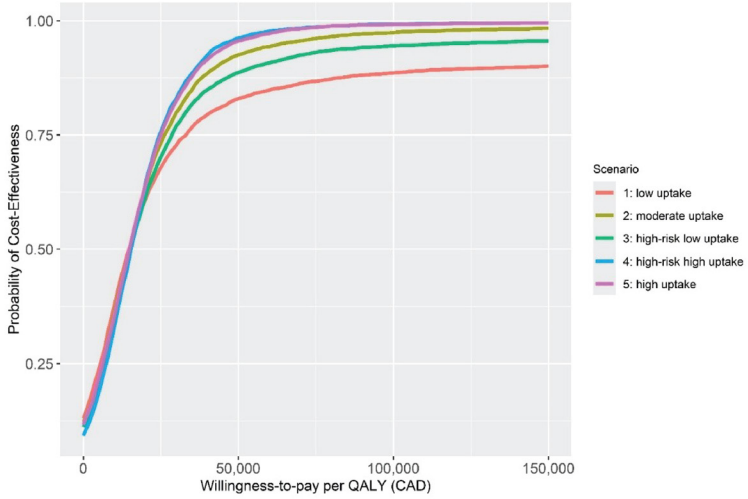
Scenarios	Cost (millions)	Incremental cost (millions)	QALYs	Incremental QALYs	ICER
Dead	$0	$0	−132,050	6825	—
Post–COVID-19 condition	$0	$0	9,865	91	—
Recovered	$0	$0	84,401	718	—
Scenario 5 (high uptake)	$3,505	$148	−31,723	9,959.90	$14,863
Inpatient	$2,528	$141	3,262	−70.217	—
Critical	$660	$0	0	0	—
Inpatient After Critical	$317	$7	415	10	—
Dead	$0	$0	−129,760	9114	—
Post–COVID-19 condition	$0	$0	9,874	100	—
Recovered	$0	$0	84,491	807	—

ICER = incremental cost-effectiveness ratio; LCT = long-term care; NA = not applicable; QALY = quality-adjusted life-year.

Cost-Effectiveness Acceptability Curves

For each $1,000 increment of WTP 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 15 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 of $0, this analysis simply shows the proportion of simulations for which the scenario in question has the lowest cost. As WTP threshold increases, there is an increase in the numbers of scenario simulations that have higher expected NMBs 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 has a higher probability of cost-effectiveness (i.e., highest NMB) compared to the reference scenario. For scenarios 2 (moderate uptake), 4 (high-risk high uptake), and 5 (high uptake), 75% of all simulations had a greater NMB compared to the reference scenarios for a WTP threshold of at least $25,000 per QALY. These trends deviate slightly for scenarios 2, 4, and 5 for a WTP threshold exceeding $25,000 per QALY, with these scenarios demonstrating a higher probability of being cost-effective. At a $50,000 WTP threshold per QALY, scenarios 4 and 5 had the highest probability of being cost-effective compared to the reference scenario.

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



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

BIA Results

Main Take-Aways

The results of the BIA suggest that remdesivir for inpatients is likely to cost the health system money. This finding was consistent across all cohorts and a range of uptake scenarios. Overall, the scenarios with the lowest uptake generally had the lowest budgetary impact; however, these scenarios also had substantial higher mortality. While the results of the sensitivity analysis suggest that under certain circumstances remdesivir for inpatients may save costs for the health system, this occurred in fewer simulations than those in which we saw an increase in cost.

The results of the BIA are presented in Table 16. Total costs for the scenarios considered ranged from $3.39 billion to $3.51 billion. Additional outcomes in the BIA included overall number of deaths and patients developing post–COVID-19 condition. Scenario 3 had the lowest expected cost, and scenario 5 the highest. Overall, the increase in health care costs for all scenarios compared to the reference scenario were driven mainly by the cost of the inpatient treatment of remdesivir. Although there were marginal reductions in cost for inpatient and critical care, total costs of the treatment were greater than the reductions in health care costs. When accounting for parameter uncertainty, no scenarios have an unambiguously positive or negative budget impact compared to the reference scenario.

Key Results

- The results of the BIA are presented in Table 16 for the reference scenario and 5 remdesivir inpatient treatment scenarios for all cohorts (aged < 65 years, aged ≥ 65 years, and those from LTC) and 2 periods (January 2022 to August 2022 and September 2022 to December 2022).
- Based on the mean estimates, the budget impact of the scenarios ranged from $35 million (95% CrI, –$21 million to $89 million) for scenario 3 (high-risk low uptake) to $148 million (95% CI, –$94 million to $386 million) for scenario 5 (high uptake).
- There are observed increases in the number of post–COVID-19 condition cases in the treatment scenarios compared to the reference scenario, this is because more deaths are averted in the treatment scenarios. There were reductions in deaths across the 5 scenarios with scenario 5 (high uptake) having the greatest mortality reduction, with 1,180 deaths averted.
- Total inpatient costs contributed the most to the total cost.
- Mean results for all scenarios showed an increased cost to the health system when compared to the reference scenario.
- The BIA shows that all scenarios have a potential for cost savings based on parameter uncertainty (95% CrI) results (without the consideration of utility). The lower limit of the 95% CrI of budget impact ranged from –$21 million (scenario 3) to –$94 million (scenario 5).
- While none of the scenarios show cost savings on average, in every instance the total cost of treatment exceeded the net budget impact, suggesting that a break-even price for the drug occurs when the total cost of the drug is reduced by the net budget impact. In scenario 1, for instance, a budget impact of 0 would be achieved if the total cost of treatment, $70.6 million, were reduced by the net budget impact of $45.5 million, down by 65% to $25.1 million, or $1,349 per course (note that the total number of hospitalizations treated by scenario can be derived from Table 1 and Table 7).

Table 16: Budget Impact Analysis ($) in Millions Across 5 Remdesivir Inpatient Treatment Scenarios

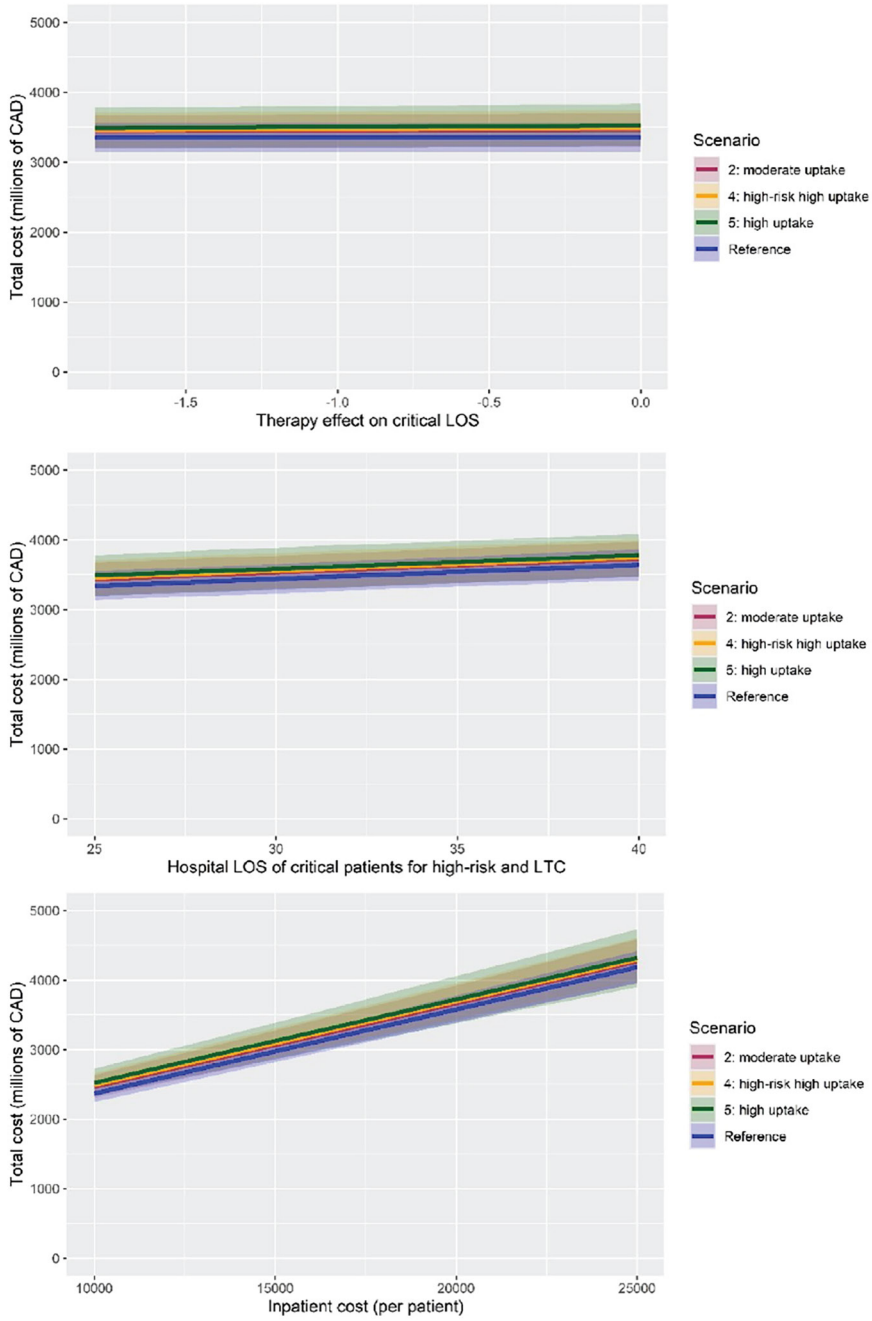
Description	Reference scenario	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (high-risk low uptake)	Scenario 4 (high-risk high uptake)	Scenario 5 (high uptake)
COVID-19 disposition (95% CrI)						
Total post–COVID-19 condition	36,820 (33,410 to 40,467)	36,926 (33,531 to 40,623)	37,039 (33,661 to 40,719)	36,917 (33,505 to 40,603)	37,153 (33,762 to 40,840)	37,182 (33,756 to 40,891)
Total deaths	14,920 (13,650 to 16,290)	14,560 (13,290 to 15,930)	14,210 (12,960 to 15,600)	14,590 (13,330 to 15,970)	13,830 (12,540 to 15,290)	13,740 (12,440 to 15,200)

Description	Reference scenario	Scenario 1 (low uptake)	Scenario 2 (moderate uptake)	Scenario 3 (high-risk low uptake)	Scenario 4 (high-risk high uptake)	Scenario 5 (high uptake)
Costs (in millions) (95% CrI)						
Total inpatient	$2,390 ($2,200 to $2,580)	$2,430 ($2,240 to $2,640)	$2,470 ($2,250 to $2,720)	$2,420 ($2,240 to $2,620)	$2,500 ($2,260 to $2,750)	$2,530 ($2,250 to $2,820)
Total critical	$970 ($891 to $1,060)	$972 ($892 to $1,060)	$974 ($893 to $1,070)	$972 ($891 to $1,060)	$975 ($895 to $1,070)	$977 ($894 to $1,070)
Total inpatient and critical	$3,360 ($3,160 to $3,570)	$3,400 ($3,200 to $3,620)	$3,450 ($3,210 to $3,700)	$3,390 ($3,190 to $3,610)	$3,470 ($3,220 to $3,750)	$3,510 ($3,210 to $3,830)
Total Remdesivir cost	$0 ($0 to $0)	$70.6 ($68.3 to $73.2)	$141 ($137 to $146)	$52.1 ($52.1 to $52.1)	$174 ($174 to $174)	$229 ($222 to $237)
Total costs	$3,360 ($3,160 to $3,570)	$3,400 ($3,200 to $3,620)	$3,450 ($3,210 to $3,700)	$3,390 ($3,190 to $3,610)	$3,470 ($3,220 to $3,750)	$3,510 ($3,210 to $3,830)
Budget Impact: Scenario Cost – Reference Scenario (in millions)	NA	$45.5 (–$32.3 to $123)	$91.1 (–$58.7 to $241)	$35 (–$20.9 to $89.4)	$116 (–$55.1 to $285)	$148 (–$93.8 to $386)

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

Note: Total costs shown for inpatient and critical care include the cost of remdesivir treatment within these states.

Figure 3: POSA Results



CAD = Canadian dollars; CrI = credible interval; LOS = length of stay; LTC = long-term care; POSA = probabilistic one-way sensitivity analysis.
Note: Solid lines show mean cost and shaded ribbons show the 95% CrI.

In Figure 3, a POSA was conducted for the reference scenario, scenario 2 (moderate uptake), scenario 4 (high-risk high uptake), and scenario 5 (high uptake) for remdesivir's effect on LOS in the Critical state, total hospital LOS for patients in critical care, and inpatient cost (per patient) (refer to Table 8 for POSA ranges).

In the POSA for remdesivir's effect on LOS in the Critical state, the change in LOS is relatively small when compared to the total LOS in the Critical state. This small effect, combined with the fact that only a fraction of individuals become critical, means that while the reduction of time spent in the critical state would reduce costs, this reduction is relatively small. The POSA for the LOS for patients in the critical state shows the degree to which different total hospital stay times of patients who reach the critical state affect the overall costs. Critical care stays represent the highest daily cost, but are associated with fewer admissions compared to inpatient units, resulting in this quantity showing little impact on overall costs. Although not all scenarios are shown in the POSA, scenario 2 (moderate uptake), scenario 4 (high-risk high uptake), and scenario 5 (high uptake) include a range of treatment options impacting each cohort.

Summary of Findings

Main Take-Aways

Overall, both the CUA and BIA suggest that the use of inpatient remdesivir could be cost-effective. The sensitivity analysis shows that at a WTP threshold of $50,000, 75% of model simulations found remdesivir to be cost-effective across all scenarios. This result was consistent for both high uptake scenarios, which included only high-risk cohorts, and scenarios that included all cohorts. While these scenarios may have increased health system costs (with the mean BIA for all scenarios being greater than 0), there are overall benefits to the population in terms of preventing both deaths and QALY losses.

It is important to interpret these results bearing in mind that the CUA presented in this analysis differs from a typical CUA in that we do not compare a set of treatment alternatives to identify the cost-effective option. Rather, we project cost and health outcomes for a range of possible future scenarios to understand under what conditions using remdesivir in an inpatient setting would be cost-effective relative to the reference scenario. The CUA and BIA include a probabilistic sensitivity analysis of 5,000 model simulations to provide a distribution of results reported as 95% CrIs.

The CUA and BIA results suggest that the use of inpatient remdesivir has the potential to be cost-effective, although this is dependent on model uncertainty and the maximum WTP per QALY. When we accounted fully for parameter uncertainty through probabilistic sensitivity analysis, at a WTP threshold of $50,000 or less per QALY, all scenarios would have the potential to be cost-effective compared to the reference scenario (i.e., though most scenario iNMB estimates cross 0 in the 95% CrIs) (refer to Table 12). At this WTP, more than 75% of simulations of all scenarios were cost-effective. As the therapeutic effect of remdesivir had the greatest impact on reducing deaths, the overall results included a consideration for the differential impact of death on lifetime QALY loss in those aged younger than 65 years and those aged 65 years and older and/or those from LTC. While total deaths among those aged younger than 65 years is lower than those aged 65 years and older and/or those from LTC, the QALY loss is greater for those aged younger than 65 years. This

was likely why we observed similarities in iNMB for scenarios assessing all 3 cohorts and those focused on high-risk cohorts with comparable uptakes (e.g., scenarios 4 and 5).

For scenarios 1 (low uptake), 2 (moderate uptake), and 5 (high uptake), which include all cohorts having access to the inpatient use of remdesivir, the ICERs were the lowest with $14,689, $14,779, and $14,863, respectively (refer to Table 14). Scenarios 3 (high-risk low uptake) and 4 (high-risk high uptake), which excluded patients under the age of 65 and had the same ratio of patients from LTC to patients older than 65 years, resulted in both having similar ICERs of $15,293 and $15,340, respectively. While scenario 4 (high-risk high uptake) had a higher ICER compared to scenario 2 (moderate uptake), the difference was impacted by the QALY value of death across all cohorts.

The average BIA results also indicated that the treatment scenarios were more costly to the health system (refer to Table 16). However, when considering uncertainty, all scenarios also showed the potential for cost savings to the health care system. Overall, scenarios focused on low uptake (e.g., scenarios 1 and 3) had the lowest mean BIA results. While the results of the BIA indicated that increased use of remdesivir within the hospital may increase health system costs, across all treatment scenarios, we also found substantial reductions in deaths compared to the reference scenario. Overall, the CUA and the BIA suggest that if the future state were to resemble any of the scenarios, but in particular higher uptake scenarios (e.g., scenario 2 [moderate uptake], scenario 4 [high-risk high uptake], or scenario 5 [high uptake]), it may cost the health system money but it may also have an overall benefit to the population in terms of deaths and QALY losses prevented.

Limitations

The model assumptions and limitations are described in Table 10. Some of the key limitations included:

- The reference scenario represents the standard of care during 2022 and included some inpatient use of remdesivir in adults and youth (aged 12 years and older and weighing at least 40 kg) with pneumonia who required supplemental oxygen.[7] The baseline use of remdesivir within the hospital was not available in the literature. Therefore, scenarios described in Table 7 would include additional remdesivir use above what was provided to patients in the reference scenario.
- The mortality impact in LTC is likely underestimated due to data and model limitations that only capture deaths in hospital but not deaths in LTC facilities. This would reduce the cost-effectiveness of inpatient remdesivir in this population.
- The analysis assumed 5-day infusion of remdesivir within a hospital setting cost. While it is possible to have an infusion for up to 10 days, the proportion of those who needed more than 5 days was not available in the literature. While a range of costs are used, if a substantial proportion of individuals receive the 10-day infusion, this could increase the costs associated with remdesivir and reduce its cost-effectiveness in hospital.

- The therapeutic effects for remdesivir use within the hospital setting were based on literature before the emergence of the Omicron variant. Additional studies are needed to verify if the therapeutic effects used in this analysis remain the same considering the new variants in circulation. If remdesivir is less effective against new variants, this would reduce its overall cost-effectiveness.
- Although there was limited evidence of therapeutic benefit for remdesivir associated with patients who were hospitalized but not receiving supplemental oxygen,[39] this population could not be identified in the CIHI data. Therefore, we applied the mortality effect estimates across the entire inpatient population. This may overestimate the overall impact of remdesivir on mortality for inpatients.
- Utilities for patients admitted to hospital are likely overestimated in the CUA due to limited data related to in-hospital estimates. This would lead to underestimation of 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.

Conclusions and Implications for Decision- or Policy-Making

This report evaluated the costs and benefits associated with inpatient use of remdesivir at various potential uptake levels across 3 cohorts (those aged < 65 years, those aged ≥ 65 years, and those from LTC). Overall, we found that inpatient remdesivir may be cost-effective, with probabilistic sensitivity analysis results demonstrating that at a WTP threshold of $50,000, 75% of model simulations found remdesivir to be cost-effective across all scenarios. However, we also found that inpatient remdesivir is likely to cost the health system money, with the mean BIA for all scenarios being greater than 0. Key parameters that may impact these results include the therapeutic effects estimates of remdesivir on mortality and LOS, remdesivir costs, inpatient costs, and lifetime QALY loss associated with mortality from COVID-19. Our results were consistent with the findings from the literature from a number of countries, which found that at a WTP of $50,000 per QALY gained remdesivir for inpatients was likely to be cost-effective.[18,21,23,26]

Our analysis also had to make some overall modelling assumptions that could impact these results. Specifically, we modelled COVID-19 hospitalization from the year 2022; therefore, if there are changes to the severity outcomes associated with COVID-19 hospitalization over this time, this may impact the cost-effectiveness of remdesivir. Moreover, the effect estimates of remdesivir were based on studies conducted before the Omicron variant; therefore, we assumed the therapeutic effects on hospitalization would be similar following the emergence of the Omicron variant.

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Health Economics

Marie Betsy Varughese contributed to the methodology, analysis of model inputs, interpretation of results, writing, editing, and reviewing of the report.

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

Ellen Rafferty contributed to the methodology, analysis of model inputs, interpretation of results, writing, editing, and reviewing of the report

Weston Roda contributed to the methodology, interpreting results, and writing of the report.

Danica Wolitski conducted the literature review and contributed to the writing of the report.

Jeff Round contributed to the conceptualization and design of the model and analysis, reviewing and interpreting analysis results, and writing and editing 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 Work Safety

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 Current) – Related to modelling infectious diseases, including COVID-19

Jeff Round disclosed the following:

Research Funding or Grants Aid 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 and 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): Auto-Injector Device for Trauma Patients

Rostrum Medical Innovations Inc. (2022): Lung Protection Ventilation in Intensive Care Units Patients

Involvement with Projects or Scientific Advice

CADTH and Health Canada Real-World Evidence Reporting Guidance expert committee member (2022 to 2023)

Weston Roda declared the following:

Research Funding or Grants Aid to My Institution

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

Involvement With Projects or Scientific Advice

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

Health Care Sector Stocks

Cotrustee 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: Supplementary Material

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

Table 17: Stochastic State-Transition Model Related Parameters as Examples (Among COVID-19 Cases) From CIHI Data 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	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 critical of total hospitalizations	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
$\vec{T}_{h}$	$\frac{(\vec{T}_{ah} - p_{ah\_c} \times \left(\vec{T}_{c} + \left(1 - p_{c\_d}\right) \times \vec{T}_{i}\right)}{1 - p_{ah\_c}}$	LOS inpatient (days)	CIHI	8	16	42
$Cost_{h}$	$Total\ inpatient\ cost \div \vec{T}_{h}$	Inpatient cost per day	CIHI	$1,368	$1,118	$913
$Cost_{i}$	$\left(Total\ ICU\ cost - (Cost_{h} \times \vec{T}_{i})\right) \div \vec{T}_{c}$	Critical 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	CIHI	29	27	71
$\vec{T}_{c}$	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

Symbol	Transformation	Quantity	Source	Estimate: age < 65 years	Estimate: age ≥ 65 years	Estimate: LTC
p_{ah_c}	NA	Proportion of critical of total hospitalizations	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
$\vec{T}_h$	$\frac{(\vec{T}_{ah} - p_{ah\_c} \times (\vec{T}_c + (1 - p_{c\_d}) \times \vec{T}_i)}{1 - p_{ah\_c}}$	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
$Cost_i$	$(Total\ ICU\ cost - (Cost_h \times \vec{T}_i)) \div \vec{T}_c$	Critical cost per day	CIHI	$3,668	$3,366	$4,107

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

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

Table 18: An Overview of Studies Used for Remdesivir Inpatient Effect Estimates

Characteristics / Therapeutic effect (point estimates of relative risk)	Beigel et al. 2020[37]	Ali et al. 2020[38]	Lau et al. 2022[28]	CDA Systematic Review 2023[4]	Overall estimate
Study period	February to April 2020	August 2020 to April 2021	August 2020 to April 2021	NA	NA
Cohort	Adults 18 years and older with COVID-19	Adults with COVID-19	Adults with COVID-19	NA	NA
Location	Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore	Canada	Canada	NA	NA
Sample size	1,062	1,281	1,281	NA	NA
LOS Hospital	Mean difference (days): −2.34 (95% confidence intervals: −4.22 to −0.46)[4]	Mean difference (days): 0.66 (95% confidence interval: −2.75 to 1.59)[4]	NA	NA	Mean difference (days): −0.70 (range: −4.22 to 1.59)[a]
LOS critical care	NA	NA	Mean difference (days): −1.0 (95% confidence interval: −1.8 to −0.2)	NA	Mean difference (days): −1.0 (95% confidence interval: −1.8 to −0.2)

Characteristics / Therapeutic effect (point estimates of relative risk)	Beigel et al. 2020[37]	Ali et al. 2020[38]	Lau et al. 2022[28]	CDA Systematic Review 2023[4]	Overall estimate
Mortality	NA	NA	NA	Relative risk: 0.81 (95% confidence interval: 0.68 to 0.95)	Relative risk: 0.81 (95% confidence interval: 0.68 to 0.95)

NA = not applicable.

[a]Point estimate is the weighted average and minimum/maximum values across the 2 studies.

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.