REGEN-COV (Casirivimab and Imdevimab) Treatment for COVID-19: An Expedited Summary of the Clinical and Economic Evidence

Key Messages

This evidence summary was generated to support decision-making on the use of REGEN-COV (casirivimab and imdevimab) during the novel coronavirus disease (COVID-19) pandemic.

We examined the peer-reviewed published and grey literature to determine what is known about REGEN-COV (casirivimab and imdevimab) for the treatment of outpatients or inpatients diagnosed with COVID-19 and found the following:

- High-risk outpatients who received REGEN-COV (2,400 mg or 1,200 mg) experienced a significant reduction in (a) COVID-19-related hospitalizations or death and (b) COVID-19-related hospitalizations through day 29 of follow-up compared with patients who received placebo (GRADE: Moderate)
    - When stratified into subgroups:
        - Seronegative patients who received REGEN-COV (2,400 mg or 1,200 mg) experienced a significant reduction in COVID-19-related hospitalizations or death
        - Seropositive patients who received REGEN-COV 2,400 mg experienced a significant reduction in COVID-19-related hospitalizations or death compared with those who received placebo; no significant difference was observed for patients who received REGEN-COV 1,200 mg
- Inpatients with moderate to severe COVID-19 who received REGEN-COV (8,000 mg) plus usual care experienced no significant reduction in (a) progression to invasive mechanical ventilation or death and (b) 28-day mortality compared with patients treated with usual care alone (GRADE: Moderate)
    - When stratified into subgroups:
        - Seronegative inpatients treated with REGEN-COV (8,000 mg) plus usual care experienced a significant reduction in (a) progression to invasive mechanical ventilation or death, and (b) 28-day mortality compared with patients treated with usual care alone
        - Seropositive inpatients treated with REGEN-COV (8,000 mg) plus usual care experienced no significant reduction in (a) progression to invasive mechanical

ventilation or death, and (b) 28-day mortality compared with patients treated with usual care alone

We also estimated the cost-effectivness and budget impact of using REGEN-COV in Ontario. We found the following:

- REGEN-COV is associated with additional costs ($1,306 and $2,166 per patient, in the oupatient and inpatient settings, respectively) but is more effective than usual care alone
    - In outpatients, for every 1,000 patients treated, REGEN-COV would lead to 35 hospitalizations avoided (number needed to treat [NNT] = 29) and 1.5 deaths prevented (NNT = 667)
    - In inpatients, for every 1,000 patients treated, REGEN-COV would lead to 59 deaths prevented (NNT = 17)
- REGEN-COV is likely more cost-effective in the inpatient setting than in the outpatient setting (incremental cost-effectiveness ratio: $36,500 vs. $871,000 per death prevented)
- In outpatients, REGEN-COV is more costly and less effective than or is dominated by the vaccination strategy
- Given the current pandemic situation, a large demand for REGEN-COV could be expected, resulting in a large total budget impact (including the cost of REGEN-COV and costs related to hospitalization and death):
    - In the outpatient setting, including 360,000 eligible patients, assuming a cost of REGEN-COV of $1,890 per treatment (2,400 mg per patient), the total budget impact is estimated to be an additional $470.16 million
    - In the inpatient setting, including 60,000 eligible patients, assuming a cost of REGEN-COV of $7,560 per treatment (8,000 mg per patient), the total budget impact is estimated to be an additional $129.93 million

Disclaimer
This evidence summary was developed within a week with consultation with experts in the field to address a pressing need for evidence using expedited systematic review methods and is not intended to be an exhaustive analysis. The evidence presented here is considered current as of the literature search date, but other relevant scientific findings may have been reported since completion. The economic analysis results need to be interpreted with caution, particularly when used for making resource allocation policy decisions.

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Background and Context

On August 27, 2021, Ontario Health received a request from the COVID-19 Science Advisory Table for input from the Ontario Health Technology Advisory Committee to inform case usage for REGEN-COV (casirivimab and imdevimab) in Ontario as a treatment for COVID-19 in seronegative people (people who are unvaccinated, partially vaccinated, or fully vaccinated but without a good response and those who have never had COVID-19). In response to that request, this rapid review provides a summary of the clinical and health economic evidence as well as guidance or recommendations from national and international health authorities and organizations and from grey literature.

On June 9, 2021, Health Canada issued an interim order authorization regarding the use of casirivimab and imdevimab in relation to the COVID-19 pandemic. Casirivimab and imdevimab, to be administered together, are indicated for the treatment of mild to moderate COVID-19, confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (aged 12 years and older weighing at least 40 kg) who are at high risk for progression to hospitalization and/or death (Health Canada, 2021a). COVID-19 progression occurs more often in older people and those with underlying medical conditions, with the risk increasing with the number of underlying conditions (Health Canada, 2021b). Health Canada provides a list of underlying medical conditions associated with more severe COVID-19 (Health Canada, 2021b). Examples include chronic lung disease, heart conditions (e.g., heart failure, coronary artery disease, cardiomyopathies, hypertension), diabetes, and overweight or obesity.[1] Each REGEN-COV dose pack contains two vials of monoclonal antibodies for one treatment dose: one vial of 1,332 mg/11.1 mL of casirivimab and one vial of 1,332 mg/11.1 mL imdevimab (Roche Canada, 2021).

To date, casirivimab and imdevimab are not authorized by Health Canada for use in patients who (Roche Canada, 2021):

- Are hospitalized due to COVID-19, or
- Require oxygen therapy due to COVID-19, or
- Require an increase in baseline oxygen flow rate due to COVID-19 (for those on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity)

[1]Overweight = body mass index (BMI) > 25 kg/m^2 but < 30 kg/m^2; obesity = BMI ≥ 30 kg/m^2 but < 40 kg/m^2; severe obesity = BMI ≥ 40 kg/m^2.

Clinical Evidence Summary

Research Questions

- What is the clinical effectiveness of REGEN-COV (casirivimab and imdevimab) for the treatment of outpatients with mild to moderate COVID-19 (confirmed by direct SARS-CoV-2 viral testing) in people (≥ 12 years of age weighing ≥ 40 kg) who are at high risk for hospitalization or death?

- What is the clinical effectiveness of REGEN-COV for the treatment of inpatients with moderate to severe COVID-19 (confirmed by direct SARS-CoV-2 viral testing) in people ≥ 12 years of age weighing ≥ 40 kg?

Methods

Appendix 1 provides the full methods for the clinical evidence summary.

Results

The clinical literature search retrieved 133 publications from the MEDLINE and Embase bibliographic databases published until August 30, 2021 (Appendix 2). The grey literature search yielded an additional 20 items. In total, we included seven eligible studies (six for clinical effectiveness and one for patient preferences and values). Figure A1 (Appendix 3) presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

The following section provides the results from the eligible peer-reviewed publications we identified.

Appendix 7 provides recommendations from guidelines and guidance documents.

REGEN-COV Administered to Outpatients Diagnosed With COVID-19

Table 1 provides the results of studies of REGEN-COV administered to outpatients diagnosed with COVID-19.

Table 1: Study Results—REGEN-COV Administered to Outpatients Diagnosed With COVID-19

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
Weinreich et al, 2021a United States, Mexico, Chile, Romania	Multicentre, randomized, double blind, placebo controlled (phases 1 and 2 of a 3-phase trial) REGEN-COV 2,400 mg (low dose) REGEN-COV 8,000 mg (high dose) Placebo	N = 275 **Included** ≥ 18 years of age Nonhospitalized Confirmed SARS-CoV-2 infection with SARS-CoV-2-positive test result **Excluded** Admitted to hospital prior to randomization or hospitalized (inpatient) at	**Medically attended visit for all patients, no. patients (%)** Combined REGEN-COV: 6/182 (3%) Placebo: 6/93 (6%) Absolute difference: −3 percentage points (95% CI: −16 to 9) **Medically attended visit for seronegative patients, no. patients (%)** Combined REGEN-COV: 5/80 (6%) Placebo: 5/33 (15%)	**Limitations** No stratification based on risk for severe disease According to the authors, medically attended visits "could include telemedicine visits, in-person physician visits, urgent care or ED visits, and hospitalization." However, they provided no breakdown of the individual components reported (either in the

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
	No prespecified primary outcome	randomization for COVID-19 Known allergy or hypersensitivity to components of study drug	Absolute difference: −9 percentage points (95% CI: −29 to 11) **Medically attended visit for seropositive patients, no. patients (%)** Combined REGEN-COV: 1/76 (1%) Placebo: 1/47 (2%) Absolute difference: −1 percentage point (95% CI: −19 to 17) **Any serious adverse event, no. patients (%)** Combined REGEN-COV: 1/176 (1%) Placebo: 2/93 (2%)	journal article or supplementary data) Type 1 error (no hypothesis testing performed due to a lack of a priori information to correctly select end points) **Author conclusions** "A low incidence of serious adverse events that occurred or worsened during the observation period and of infusion-related or hypersensitivity reactions was observed"
Weinreich et al, 2021b United States, Mexico, Chile, Romania	Multicentre, randomized, double blind, placebo controlled (phase 3 of a 3-phase trial) REGEN-COV 2,400 mg REGEN-COV 1,200 mg Placebo Primary outcome: risk of hospitalization or death through to day 29 follow-up	N = 4,057 **Included** ≥ 18 years of age Nonhospitalized Confirmed local SARS-CoV-2-positive diagnostic test result ≤ 72 h Onset of any COVID-19 symptom, as determined by the investigator, ≤ 7 d before randomization One or more risk factors for severe disease **Excluded** Admitted to hospital for COVID-19 prior to randomization or hospitalized (inpatient) at randomization for any reason	**COVID-19-related hospitalization or all-cause death, no. patients (%)** REGEN-COV 2,400 mg: 18/1,355 (1.3%) Placebo: 62/1,341 (4.6%) Relative risk reduction (RRR) 71.3% (95% CI: 51.7 to 82.9), *P* < .0001 REGEN-COV 1,200 mg: 7/736 (1.0%) Placebo: 24/748 (3.2%) RRR 70.4% (95% CI: 31.6 to 87.1), *P* = .0024 **COVID-19-related hospitalization or all-cause death, seronegative patients only, no. patients (%)** REGEN-COV 2,400 mg: 12/940 (1.3%) Placebo: 49/930 (5.3%) RRR 75.8% (95% CI: 54.7 to 87.0), *P* < .0001 REGEN-COV 1,200 mg: 3/500 (0.6%) Placebo: 18/519 (3.5%) RRR 82.7% (95% CI: 41.6 to 94.9), *P* < .0014 **COVID-19-related hospitalization or all-cause death, seropositive patients only, no. patients (%)** REGEN-COV 2,400 mg: 4/323 (1.2%) Placebo: 12/297 (4.0%) RRR 69% (95% CI: 6.0 to 90.0), *P* = .04 REGEN-COV 1,200 mg: 1/177 (0.6%) Placebo: 6/164 (3.7%) RRR 85.0% (95% CI: NA to 98.0), *P* = .0588 **Any serious adverse events, no. patients (%)** REGEN-COV 2,400 mg: 24/1849 (1.3%) REGEN-COV 1,200 mg: 9/827 (1.1%) Placebo: 74/1843 (4%)	**Limitations** Prepublication (not peer reviewed) For the effect estimate of COVID-19-related hospitalization or all-cause death in seropositive patients only, the confidence intervals were very wide **Comments** Patients had ≥ 1 risk factor for severe disease **Author conclusions** The data demonstrate a "reduction in the risk of hospitalization or all-cause death, together with an acceptable safety profile, in high-risk, SARS-CoV-2-positive adults"

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
			Grade ≥2 infusion-related reactions infrequent (< 0.3% in all groups) **COVID-19-related hospitalization, no. patients (%)** REGEN-COV 2,400 mg: 17/1,355 (1.3%) Placebo: 59/1341 (4.4%) RRR 71.5% (95% CI: 51.3 to 83.3) REGEN-COV 1,200 mg: 6/736 (0.8%) Placebo: 23/748 (3.1%) RRR 73.5% (95% CI: 35.3 to 89.1) (Stratification based on serology not reported) **All case death, no. patients (%)** REGEN-COV 2,400 mg: 1/1,355 (< 0.1%) Placebo: 3/1341 (0.2%) RRR 67.0% (95% CI: -216.7 to 96.6) REGEN-COV 1,200 mg: 1/736 (0.1%) Placebo: 1/748 (0.1%) RRR -1.6% (95% CI: -1522 to 93.6) (Stratification based on serology not reported) **Days of hospitalization due to COVID19 (per patient)** *REGEN-COV 2,400 mg (18 patients)* Mean (SD): 8.6 (± 7.07) Median (IQR): 6.0 (3.0 to 11.0) *Placebo (62 patients)* Mean (SD): 10.0 (± 7.16) Median (IQR): 7.0 (5.0 to 13.0) *REGEN-COV 1,200 mg (7 patients)* Mean (SD): 7.0 (± 8.04) Median (IQR): 4.0 (3.0 to 6.0) *Placebo (24 patients)* Mean (SD): 8.4 (± 6.74) Median (IQR): 5.5 (4.0 to 10.5) **Proportion of patients admitted to ICU, no. patients with an event within 29 d (%)** REGEN-COV 2,400 mg: 6/1355 (0.4%) Placebo: 18/1341 (1.3%) RRR 67.0% (95% CI: 17.2 to 86.9) REGEN-COV 1,200 mg: 3/376 (0.4%) Placebo: 7/749 (0.9%) RRR 56.4% (95% CI: −67.8 to 88.7)	

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
Ash et al, 2021 United States	Observational, single centre, case series REGEN-COV (1,200 mg casirivimab, 1,200 mg imdevimab) Primary outcome: 7–14-day ED and hospitalization rates of adult patients given REGEN-COV for outpatient treatment at a community hospital	N = 68 **Included** ≥ 18 years of age Positive result from a direct SARS-CoV-2 viral test **Excluded** NR	Median no. risk factors for patients infused with REGEN-COV = 2 No ED visits or hospitalizations occurred after 7 d of REGEN-COV administration **ED visits within 7 d of REGEN-COV administration, no. patients (%)** Total: 7/68 (10%) ≥ 65 years of age: 5/42 (12%) **Hospitalizations within 7 d of REGEN-COV administration, no. patients (%)** Total: 1/68 (1%) ≥ 65 years of age: 0 (0%) In-hospital mortality: 0 patients **Adverse events** No patients had an allergic reaction during infusion or in the immediate post-infusion period	**Limitations** Retrospective case series Patients offered treatment based upon medication availability, symptom onset, physician preference, and risk factors for disease progression Unclear how many patients were offered REGEN-COV but declined County coroner records not reviewed to confirm mortality in patients who received REGN-COV
Dhand et al, 2021 United States	Observational, single centre, case series REGEN-COV dose NR No prespecified primary outcome	N = 25 **Included** Adults with solid organ transplant diagnosed with COVID-19; unclear if diagnosis confirmed with SARS-CoV-2 viral test **Excluded** NR	Mean time from transplant: 186 mo (range 10–709 mo) Mean patient follow-up: 41 d (range 14–69 d) 0/25 patients experienced symptom progression or required hospitalization due to COVID-19 Secondary bacterial pneumonia in 1 patient successfully treated with 7-d course of antibiotic therapy	**Limitations** Retrospective case series Unclear if COVID-19 diagnosis confirmed with SARS-CoV-2 viral test Use of co-interventions (e.g. other interventions included lowering or stopping mycophenolate [50% of patients] and lowering the dose of a calcineurin inhibitor [20% of patients])
Razonable et al, 2021 United States	Observational, multicentre, propensity-matched control REGEN-COV (casirivimab 1,200 mg, imdevimab 1,200 mg) Primary outcome: rate of hospitalization at days 14, 21, and 28 after infusion	N= 1,392 **Included** ≥ 18 years of age Symptoms of mild to moderate COVID-19 Within 10 d of symptom onset ≥ 1 of the following criteria: age ≥ 65 years, BMI ≥ 35, diabetes, chronic kidney disease, immunosuppressive medication use, or immunocompromising condition	**All-cause hospitalization, day 14, percentage of patients (95% CI)** REGEN-COV: 1.3% (0.7 to 2.5) Control: 3.3% (2.2 to 5.0) Absolute difference: 2.0% (0.5 to 3.7) **All-cause hospitalization, day 21, percentage of patients (95% CI)** REGEN-COV: 1.3% (0.7 to 2.5) Control: 4.2% (3.0 to 6.0) Absolute difference: 2.9% (1.2 to 4.7) **All-cause hospitalization, day 28, percentage of patients (95% CI)** REGEN-COV: 1.6% (0.9 to 2.9) Control: 4.8% (3.5 to 6.7)	**Limitations** Retrospective All patients at high risk of progression to severe COVID-19 Only patients with documented follow-up were included in the analysis of outcomes at days 14, 21, and 28 Data were derived from a single US multisite health care system; therefore, results may not be generalizable to systems with different practices and processes

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
		Patients ≥ 55 years of age qualified if they had hypertension, cardiovascular disease, or chronic lung disease Diagnosis confirmed with positive SARS-CoV-2 viral test **Excluded** Clinical manifestations of severe COVID-19 (e.g., new or worsening hypoxemia) Hospitalization for COVID-19 12–17 years of age	Absolute difference: 3.2% (1.4 to 5.1) **ICU admissions, day 14, percentage of patients (95% CI)** REGEN-COV: 0.73% (0.3 to 1.7) Control: 0.87% (0.4 to 1.9) Absolute difference: 0.15% (−0.8 to 1.1) **ICU admissions, day 21, percentage of patients (95% CI)** REGEN-COV: 0.73% (0.3 to 1.7) Control: 0.87% (0.4 to 1.9) Absolute difference: 0.15% (−0.8 to 1.1) **ICU admissions, day 28, percentage of patients (95% CI)** REGEN-COV: 0.73% (0.3 to 1.7) Control: 1.0% (0.5 to 2.1) Absolute difference: 0.30% (−0.7 to 1.3) **Mortality, day 14, percentage of patients (95% CI)** REGEN-COV: 0.15% (0.0 to 1.0) Control: 0.44% (0.1% to 1.4%) Absolute difference: 0.29% (−0.3 to 0.9) **Mortality, day 21, percentage of patients (95% CI)** REGEN-COV: 0.15% (0.0 to 1.0) Control: 0.44% (0.1 to 1.4) Absolute difference: 0.29% (−0.3 to 0.9) **Mortality, day 28, percentage of patients (95% CI)** REGEN-COV: 0.15% (0.0 to 1.0) Control: 0.59% (0.2 to 1.6) Absolute difference: 0.33% (−0.2 to 1.1) **Adverse events (reported in 7 patients)** Fever: n = 4 Shortness of breath: n = 2 Nausea: n = 2 Chest pain: n = 1 Headache: n = 1 Flushing: n = 1 No patient had anaphylaxis All adverse events were mild (National Cancer Institute grade 1) and did not require hospitalization	

Abbreviations: BMI, body mass index; d, day(s); ED, emergency department; ICU, intensive care unit; IQR, interquartile range; mo, month(s); NA, not available; no., number; RRR, relative risk reduction; SD, standard deviation.

REGEN-COV Administered to Inpatients Diagnosed With COVID-19

Table 2 provides the results of studies of REGEN-COV administered to inpatients diagnosed with COVID-19.

Table 2: Study Results—REGEN-COV Administered to Inpatients Diagnosed With COVID-19

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
RECOVERY Collaborative Group, 2021 (preprint) United Kingdom	Multicentre, randomized, controlled, open-label platform trial REGEN-COV 8,000 mg (casirivimab 4,000 mg, imdevimab 4,000 mg) + usual care Usual Care Primary outcome: 28-d mortality assessed among (a) patients without detectable antibodies to SARS-CoV-2 at randomization (seronegative) and (b) overall population	N = 9,785 **Included** Patients admitted to hospital with clinically suspected or laboratory-confirmed SARS-CoV-2 infection No medical history suggesting significant risk to participating in trial **Excluded** Patients who received IV immunoglobulin treatment during current admission Children weighing < 40 kg or aged < 12 y	**28-day mortality, all patients, no. patients (%)** REGEN-COV + usual care: 944/4,839 (20%) Usual care: 1,026/4,946 (21%) Rate ratio 0.94 (95% CI: 0.86 to 1.03), *P* = .17 **28-day mortality, seronegative patients, no. patients (%)** REGEN-COV + usual care: 396/1,633 (24%) Usual care: 451/1,520 (30%) Rate ratio 0.80 (95% CI: 0.70 to 0.91), *P* = .001 **28-day mortality, seropositive patients, no. patients (%)** REGEN-COV + usual care: 411/2636 (16%) Usual care: 383/2636 (15%) Rate ratio 1.09 (95% CI: 0.95 to 1.26) **Progression to invasive mechanical ventilation or death, all patients (composite secondary outcome), no. patients (%)** REGEN-COV + usual care: 1,089/4,556 (24%) Usual care: 1,151/4,642 (25%) Risk ratio 0.96 (95% CI: 0.90 to 1.04) **Progression to invasive mechanical ventilation or death, seronegative patients (composite secondary outcome), no. patients (%)** REGEN-COV + usual care: 487/1,599 (30%) Usual care: 542/1,484 (37%) Risk ratio 0.83 (95% CI: 0.75 to 0.92) **Progression to invasive mechanical ventilation or death, seropositive patients (composite secondary outcome), no. patients (%)** REGEN COV + usual care: 456/2449 (19%) Usual Care: 415/2450 (17%) Risk ratio 1.10 (95% CI: 0.97 to 1.24) **Progression to invasive mechanical ventilation, all patients, no. patients (%)** REGEN-COV + usual care: 479/4,556 (11%) Usual care: 487/4,642 (10%) Risk ratio 1.00 (95% CI: 0.89 to 1.13) **Progression to invasive mechanical ventilation, seronegative patients, no. patients (%)** REGEN-COV + usual care: 189/1,599 (12%) Usual care: 200/1,484 (13%) Risk ratio 0.88 (95% CI: 0.73 to 1.06) (Stratification for seropositive patients not reported) **Infusion reactions occurring within first 72 h[a], all patients, no. patients (%)**	**Limitations** Prepublication (not peer reviewed) Open label Included patients with clinically suspected **or** lab-confirmed COVID-19 infection **Author conclusions** "Based on our findings, any therapeutic use of REGEN-COV in the hospital setting may be best restricted to seronegative patients" In contrast to a previous discontinued trial[b] on inpatients: "In October 2020 the independent data monitoring committee of an industry sponsored trial of REGEN-COV in hospitalised COVID-19 patients recommended that recruitment of patients on high-flow oxygen or mechanical ventilation be suspended because of a potential safety signal. However, we did not observe any evidence that the proportional effect of REGEN-COV on mortality varied by level of respiratory support received at randomisation, either when assessed in all participants or when assessed only in the subgroup of seronegative participants"

Author, year, country	Study design	Population	Results	Limitations/ Comments/ Author conclusions
			Fever REGEN-COV + usual care : 79/1,792 (4%) Usual care : 52/1,714 (3%) *Sudden hypotension* REGEN-COV + usual care : 66/1,792 (4%) Usual care : 39/1,714 (2%) *Thrombotic events* REGEN-COV + usual care: 31/1,792 (2%) Usual care : 24/1,714 (1%) *Sudden worsening in respiratory status* REGEN-COV + usual care: 369/1,792 (21%) Usual care: 372/1,714 (22%) *Clinical hemolysis* REGEN-COV + usual care : 26/1,792 (1%) Usual care : 31/1,714 (2%) **Serious adverse reaction believed to be related to REGEN-COV** Allergic reaction: n = 3 Seizure: n = 2 Acute desaturation: n = 1 Transient loss of consciousness: n = 1	

Abbreviations: CI, confidence interval; d, day(s); no., number; y, year(s).
[a]Information on potential infusion reactions occurring within the first 72 hours after randomization was collected for 1,792 patients in the REGEN-COV group and 1,714 patients in the usual care group (before collection of these data stopped on 19 February 2021).
[b]"REGN-COV2 independent data monitoring committee recommends holding enrollment in hospitalized patients with high oxygen requirements and continuing enrollment in patients with low or no oxygen requirements" (Regeneron, 2020).

Hospitalization and Mortality

Table 3 summarizes the results of the included studies for the hospitalization and mortality of inpatients and outpatients diagnosed with COVID-19 treated with REGEN-COV. Appendix 4 provides the details of the rating of uncertainty according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group criteria.

Table 3: Hospitalization and Mortality—REGEN-COV Administered to Outpatients and Inpatients Diagnosed With COVID-19

Outcome	No. and type of studies, no. of participants	Summary estimate (95% CI)	GRADE rating
Outpatients			
COVID-19-related hospitalization or all-cause death	1 RCT (Weinreich et al, 2021b) N = 4,057	**All patients, no. of patients (%)** REGEN COV 2400 mg: 18/1355 (1.3%) Placebo: 62/1341 (4.6%) RRR 71.3%; 95% CI (51.7% to 82.9%); *P* < .0001 REGEN COV 1200 mg: 7/736 (1.0%) Placebo: 24/748 (3.2%) RRR 70.4%; 95% CI (31.6% to 87.1%); *P* = .0024 **Seronegative patients, no. of patients (%)** REGEN COV 2400 mg: 12/940 (1.3%) Placebo: 49/930 (5.3%) RRR 75.8% (95% CI: 54.7% to 87.0%); *P* < .0001 REGEN COV 1200 mg: 3/500 (0.6%) Placebo: 18/519 (3.5%) RRR 82.7% (95% CI: 41.6% to 94.9%); *P* < .0014 **Seropositive patients, no. patients (%)** REGEN-COV 2,400 mg: 4/323 (1.2%) Placebo: 12/279 (4.0%) RRR 69% (95% CI: 6.0 to 90.0), *P* = .04 REGEN-COV 1,200 mg: 1/177 (0.6%) Placebo: 6/164 (3.7%) RRR 85.0% (95% CI: NR to 98.0), *P* = .0588	Moderate (downgraded for imprecision)
COVID-19-related hospitalization	1 RCT (Weinreich et al, 2021b) N = 4,057	**All patients, no. of patients (%)** REGEN COV 2400 mg: 17/1355 (1.3%) Placebo: 59/1341 (4.4%) RRR = 71.5%; 95% CI (51.3% to 83.3%) REGEN COV 1200 mg: 6/736 (0.8%) Placebo: 23/748 (3.1%) RRR = 73.5%; 95% CI (35.3% to 89.1%) Stratification by serological status not reported.	Moderate (downgraded for imprecision)
Inpatients			
Admission to ICU	0 studies	–	–

Outcome	No. and type of studies, no. of participants	Summary estimate (95% CI)	GRADE rating
Progression to invasive mechanical ventilation or death	1 RCT (RECOVERY Collaborative Group, 2021 [preprint]) N = 9,785	**All patients, no. patients (%)** REGEN-COV + usual care: 1,089/4,556 (24%) Usual care: 1,151/4,642 (25%) Risk ratio 0.96 (95% CI: 0.90 to 1.04) **Seronegative patients, no. patients (%)** REGEN-COV + usual care: 487/1,599 (30%) Usual care: 542/1,484 (37%) Risk ratio 0.83 (95% CI: 0.75 to 0.92) **Seropositive patients, no. patients (%)** REGEN COV + usual care: 456/2449 (19%) Usual Care: 415/2450 (17%) Risk ratio 1.10 (95% CI: 0.97 to 1.24)	Moderate (downgraded due to risk of bias)
28-day mortality	1 RCT (RECOVERY Collaborative Group, 2021 [preprint]) N = 9,785	**All patients, no. patients (%)** REGEN-COV + usual care: 944/4,839 (20%) Usual care: 1,026/4,946 (21%) Rate ratio 0.94 (95% CI: 0.86 to 1.03), *P* = .17 **Seronegative patients, no. patients (%)** REGEN-COV + usual care: 396/1,633 (24%) Usual care: 451 /1,520 (30%) Rate ratio 0.80 (95% CI: 0.70 to 0.91), *P* = .001 **Seropositive patients, no. patients (%)** REGEN-COV + usual care: 411/2636 (16%) Usual care: 383/2636 (15%) Rate Ratio 1.09 (95% CI: 0.95 to 1.26), *P* value not reported	Moderate (downgraded due to risk of bias)

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; no., number; RCT, randomized controlled trial; RRR, relative risk reduction.

Preferences of Outpatients Diagnosed With COVID-19 Regarding the Administration of REGEN-COV

In a brief report from the United States, Ton et al (2021) reported on the experience of a single centre that started administering REGEN-COV to COVID-19-positive outpatients with mild to moderate symptoms on December 7, 2020. The authors noted that by day 20 of the centre providing this treatment, 80% of patients (20/25) consented to receive REGEN-COV and by day 60, 83.2% of patients (153/184) consented to receive REGEN-COV. Ton et al suggested that the high consent rate may be a reflection of public comfort with the new treatment options, possibly owing to positive media coverage and perhaps a reflection of staff knowledge of and comfort describing the infusion process during the screening and consent process.

Economic Evidence Summary

Research Questions

Economic Evidence Review

- What is the cost-effectiveness of using REGEN-COV for the treatment of outpatients with mild to moderate COVID-19 (confirmed by direct SARS-CoV-2 viral testing) who are at high risk for progression to severe COVID-19 compared with usual care?
- What is the cost-effectiveness of using REGEN-COV for the treatment of inpatients with COVID-19 (confirmed by direct SARS-CoV-2 viral testing) compared with usual care?

Primary Economic Evaluation

From the perspective of the Ministry of Health:

- What is the cost-effectiveness of using REGEN-COV for the treatment of eligible outpatients (12 years of age and older, weighing at least 40 kg, and seronegative) with mild to moderate COVID-19 (confirmed by direct SARS-CoV-2 viral testing) who are at high risk for progression to severe COVID-19 compared with usual care?
- What is the cost-effectiveness of using REGEN-COV for the treatment of eligible inpatients (12 years of age and older, weighing at least 40 kg, and seronegative) with moderate to severe COVID-19 (confirmed by direct SARS-CoV-2 viral testing), compared with usual care?

Budget Impact Analysis

From the perspective of the Ministry of Health:

- What is the budget impact of using REGEN-COV for the treatment of eligible outpatients (12 years of age and older, weighing at least 40 kg, and seronegative) with mild to moderate COVID-19 (confirmed by direct SARS-CoV-2 viral testing) who are at high risk for progression to severe COVID-19, including hospitalization or death?
- What is the budget impact of using REGEN-COV for the treatment of eligible inpatients (12 years of age and older, weighing at least 40 kg, and seronegative) with moderate to severe COVID-19 (confirmed by direct SARS-CoV-2 viral testing)?

Methods

The appendix provides the full methods for the economic evidence review, primary economic evaluation, and budget impact analysis.

Results

Economic Evidence Review

The economic literature search retrieved 11 studies (after removing duplicates) from the MEDLINE and Embase bibliographic databases published from inception until August 30, 2021 (Appendix 2). Based on the titles and abstract screening, none of these citations met our inclusion criteria (Appendix 5, Figure A2). Therefore, the cost-effectiveness of using REGEN-COV for the treatment of outpatients and inpatients with COVID-19 is unknown.

Primary Economic Evaluation

COST-EFFECTIVENESS ANALYSIS

Reference Case Results—Outpatients

In the outpatient setting, we estimated that treatment with REGEN-COV costs an additional $1,306 per patient but is more effective than usual care. For every 1,000 patients treated, REGEN-COV would lead to 35 hospitalizations avoided (number needed to treat [NNT] = 29) and 1.5 deaths prevented (NNT = 667) (Table 4). Therefore, for outpatients, the incremental cost-effectiveness ratio (ICER) is an additional $37,400 per hospitalization avoided and $871,000 per death prevented.

Reference Case Results—Inpatients

In the inpatient setting, we estimated that treatment with REGEN-COV costs an additional $2,166 per patient but is more effective than usual care. For every 1,000 patients treated, REGEN-COV would lead to 59 deaths prevented (NNT = 17). Therefore, for inpatients, the ICER is $36,500 per death prevented (Table 5).

Table 4: Cost-Effectiveness Analysis Results—Reference Case (Per-Person Estimates), Outpatients

REGEN-COV (new scenario)		Probability	Treatment cost[a]	Serological testing cost[a]	Hospitalization cost[a]	Total cost, $[a]
	Not hospitalized	0.98870	$2,126	$0	$0	$2,126
	Hospitalized, survived	0.01056	$23	$0	$243	$266
	Hospitalized, died	0.00074	$2	$0	$37	$39
	Total	**1.00000**	**$2,150**	**$0**	**$280**	**$2,430**
Usual care (current scenario)						
	Not hospitalized	0.95377	$0	$0	$0	$0
	Hospitalized, survived	0.04400	$0	$0	$1,012	$1,012
	Hospitalized, died	0.00224	$0	$0	$112	$112
	Total	**1.00000**	**$0**	**$0**	**$1,124**	**$1,124**
Incremental outcomes (REGEN-COV vs. usual care)						
Incremental cost, $[a]						$1,306
Incremental effectiveness						
Hospitalizations						-0.035[c]
Deaths						-0.0015[d]
Incremental cost-effectiveness ratio[b]						
Additional cost/hospitalization avoided						$37,382
Additional cost/death prevented						$871,308

[a]All costs are in 2021 Canadian dollars.

[b]ICER = incremental costs/incremental effectiveness.

[c]The number needed to prevent one hospitalization = 1/0.035 = 29.

[d]The number needed to prevent one death = 1/0.0015 = 667.

Note: Results may appear incorrect due to rounding. Negative numbers in incremental effectiveness indicate reductions.

Table 5: Cost-Effectiveness Analysis Results—Reference Case (Per-Person Estimates), Inpatients

REGEN-COV (new scenario)		Probability	Treatment cost[a]	Serological testing cost[a]	Hospitalization cost[a]	Total cost[a]
	Hospitalized, survived	0.7626	$5,964	$57	$13,413	$19,434
	Hospitalized, died	0.2374	$1,856	$18	$11,868	$13,742
	Total	**1.0000**	**$7,820**	**$75**	**$25,282**	**$33,177**
Usual care (current scenario)						
	Hospitalized, survived	0.7033	$0	$0	$16,176	$16,176
	Hospitalized, died	0.2967	$0	$0	$14,836	$14,836
	Total	**1.0000**	**$0**	**$0**	**$31,011**	**$31,011**
Incremental outcomes (REGEN-COV vs. usual care)						
Incremental cost, $[a]						$2,166
Incremental effectiveness						
Deaths						−0.0593[c]
Incremental cost-effectiveness ratio[b]						
Additional cost/death prevented						$36,493

[a]All costs are in 2021 Canadian dollars.

[b]ICER = incremental cost/incremental effectiveness.

[c]The number needed to prevent one death = 1/0.0593 = 17.

Note: Results may appear incorrect due to rounding. Negative numbers in incremental effectiveness indicate reductions.

SCENARIO ANALYSIS

In scenario analyses, we explored whether the cost-effectiveness results were sensitive to changes in the values of important input parameters or assumptions (Table 6). We also conducted a scenario analysis with Ontario-based probabilities for the outcomes of hospitalization, intensive care unit (ICU) admission, and death (Appendix 7).

Table 6: Scenario Analyses—Parameter Values and Assumptions

Scenario	Reference case	Sensitivity analysis
Scenario 1: Comparator	**Outpatient and inpatients** Current scenario: treatment with usual care New scenario: treatment with REGEN-COV	**Outpatients** Current scenario: vaccines to prevent COVID-19 (assume that vaccination reduces the probabilities of hospitalization and death by 95% [relative risk reduction]) New scenario: REGEN-COV to treat COVID-19 **Inpatients** Not applicable since vaccination is not a treatment option in the inpatient setting
Scenario 2: Cost of REGEN-COV	**Outpatients and inpatients** Included cost of REGEN-COV ($1,890/dose pack) to consider cost burden to public health care payer	**Outpatients and inpatients** • Excluded cost of REGEN-COV since it is provided for free by the Public Health Agency of Canada • Considered cost of half a dose pack (i.e., 1,200 mg, same clinical effectiveness) in outpatients only
Scenario 3: Cost of drug administration	**Outpatients and inpatients** Assume REGEN-COV administered via 1-hour intravenous infusion with 1-hour monitoring after infusion ($260 per patient)	**Outpatients and inpatients** Assume REGEN-COV administered via subcutaneous injection ($15 per patient)
Scenario 4: Cost of COVID-19 hospitalization for patients who die	**Outpatients and inpatients** Assume $50,000 per patient (cost of COVID-19 hospitalization with ICU admission)	**Outpatients and inpatients** Assume $23,000 per patient (cost of an average COVID-19 hospitalization)
Scenario 5: Baseline probability of hospitalization	**Outpatients** 4.4% (based on REGEN-COV clinical trial by Weinreich et al, 2021b) **Inpatients** Not applicable	**Outpatients** 10% in high-risk outpatient population (based on Public Health Ontario data and expert opinion [assume the same relative risk reduction as seen in clinical trial]) **Inpatients** Not applicable
Scenario 6: Baseline probability of death	**Outpatients** 0.2% (based on REGEN-COV clinical trial by Weinreich et al, 2021b) **Inpatients** Not applicable	**Outpatients** 4.1% (based on Public Health Ontario data and expert opinion [assume the same relative risk reduction as seen in clinical trial]) **Inpatients** Not applicable

Abbreviation: ICU, intensive care unit.

The cost-effectiveness results were substantially affected by changes in vaccination status at baseline, the cost of REGEN-COV, and baseline probabilities of hospitalization or death in the outpatient setting:

- Scenario 1: When we compared the REGEN-COV treatment strategy with the vaccine strategy (for the prevention of SARS-CoV-2 infection), vaccination dominated REGEN-COV, as the vaccine is less costly and more effective
- Scenario 2: When we assumed that the cost of the drug was covered by the Public Health Agency of Canada and thus excluded this cost from our analysis, REGEN-COV dominated usual care, as REGEN-COV is less costly and more effective than usual care (cost savings of $584 per person in outpatients and $5,394 in inpatients (scenario 2a). When we assumed a lower cost associated with the use of a 1,200 mg dose in outpatients, the ICERs decreased compared with the reference case (scenario 2b). According to Weinreich et al (2021b), the 1,200 mg dose also leads to a significant reduction in COVID-19-related hospitalizations or death
- Scenario 3: When we assumed a lower drug administration cost (subcutaneous injection instead of intravenous infusion), the ICERs became slightly smaller compared with those of the reference case
- Scenario 4: When we assumed the cost of hospitalization leading to death to be lower ($23,000 per patient instead of $50,000 per patient), the ICERs became slightly larger compared with those of the reference case
- Scenarios 5 and 6: When we assumed higher baseline probabilities of hospitalization or death in the outpatient setting (using estimates from Ontario; expert consultation, September 7, 2021) and applied the same relative risk reduction as in the clinical trial by Weinreich et al (2021b), REGEN-COV became more cost-effective compared with usual care because the magnitude of benefit is larger (a greater reduction in hospitalizations and deaths)

Table 7 provides the results of our scenario analyses.

Table 7: Scenario Analysis Results

	ICER, $/health outcome	
Scenario	**Outpatients**	**Inpatients**
Reference case		
ICER, $/hospitalization avoided	37,382 (ΔC = $1,306; ΔE = −0.035)	NA
ICER, $/death prevented	871,308 (ΔC = $1,306; ΔE = −0.0015)	36,500 (ΔC = $2,166; ΔE = −0.059)
Scenario 1: Treatment with REGEN-COV vs. a hypothetical scenario in which all patients are vaccinated		
ICER, $/hospitalization avoided	Dominated by vaccine (ΔC = $2,298; ΔE = 0.009)	NA
ICER, $/death prevented	Dominated by vaccine (ΔC = $2,298; ΔE = 0.0006)	NA

Scenario	ICER, $/health outcome	
	Outpatients	Inpatients
Scenario 2a: Cost of REGEN-COV excluded		
ICER, $/hospitalization avoided	Cost saving (ΔC = −$584; ΔE = −0.035)	NA
ICER, $/death prevented	Cost saving (ΔC = −$584; ΔE = −0.0015)	Cost saving (ΔC = −$5,394; ΔE = −0.059)
Scenario 2b: Cost of REGEN-COV reduced by half to correspond to a 1,200 mg dose		
ICER, $/hospitalization avoided	10,333 (ΔC = $361; ΔE = −0.035)	NA
ICER, $/death prevented	240,838 (ΔC = $361; ΔE = −0.0015)	NA
Scenario 3: REGEN-COV administered subcutaneously		
ICER, $/hospitalization avoided	30,369 (ΔC = $1,061; ΔE = −0.035)	NA
ICER, $/death prevented	707,853 (ΔC = $1,061; ΔE = −0.0015)	32,365 (ΔC = $1,921; ΔE = −0.059)
Scenario 4: Cost of COVID-19 hospitalization		
ICER, $/hospitalization avoided	38,540 (ΔC = $1,346; ΔE = −0.035)	NA
ICER, $/death prevented	898,308 (ΔC = $1,346; ΔE = −0.0015)	63,493 (ΔC = $3,768; ΔE = −0.059)
Scenario 5: Baseline probability of hospitalization, outpatients only		
ICER, $/hospitalization avoided	4,220 (ΔC = $327; ΔE = −0.078)	NA
ICER, $/death prevented	218,200 (ΔC = $327; ΔE = −0.0015)	NA
Scenario 6: Baseline probability of death		
ICER, $/hospitalization avoided	122 (ΔC = $7; ΔE = −0.061)	NA
ICER, $/death prevented	271 (ΔC = $7; ΔE = −0.027)	NA

Abbreviations: ΔC, incremental costs; ΔE, incremental effectiveness; ICER, incremental cost-effectiveness ratio; NA, not applicable.
Note: Negative costs indicate savings. Negative numbers in incremental effectiveness indicate reductions (e.g., negative incremental hospitalization means hospitalization avoided). Results might appear inexact due to rounding. All costs expressed in 2021 Canadian dollars.

Budget Impact Analysis

REFERENCE CASE RESULTS—OUTPATIENTS

In the outpatient setting, we estimated that 360,000 patients would be eligible for REGEN-COV treatment (Appendix 6, Figure A4).

In the current scenario, all patients would receive usual care (managed at home). About 15,839 of these patients may become hospitalized (due to progression to severe COVID-19) and survive, and 805 may become hospitalized and die. The total cost was estimated to be $404.56 million ($364.30 million in hospitalization costs for patients who survived and $40.27 million in hospitalization costs for those who died).

In the new scenario, all patients would each receive one dose pack of REGEN-COV (2,400 mg) via a 1-hour intravenous infusion (plus a 1-hour observation after infusion) and then be discharged home. About 3,801 of these patients may become hospitalized and survive, and 266 may become hospitalized and die. The total cost was estimated to be $874.72 million ($774.00 million for the cost of REGEN-COV and its administration, $87.43 million in hospitalization costs for patients who survived, and $13.29 million in hospitalization costs for those who died).

Therefore, the total budget impact was estimated to be an additional cost of $470.16 million (an additional cost of $774.00 million for the cost of REGEN-COV and its administration, a savings of $276.86 million from hospitalizations avoided, and a savings of $26.98 million from deaths prevented). This represents an additional cost of $1,306 per patient (an additional $2,150 for the cost of REGEN-COV and its administration and a savings of $844 in hospitalization costs).

Table 8 provides the results of the outpatient reference case.

Table 8: Budget Impact Analysis Results—Reference Case, Outpatients

Total costs and budget impact over 1 year, $ million	
Current scenario (usual care)	
Total	**404.56**
Drug and administration	0
Hospitalization for patients who survived	364.3
Hospitalization for patients who died	40.27
New scenario (REGEN-COV)	
Total	**874.72**
Drug and administration	774.00
Hospitalization for patients who survived	87.43
Hospitalization for patients who died	13.29
Budget impact[a]	
Total	470.16
Drug and administration	774.00
Hospitalization for patients who survived	−276.86[b]
Hospitalization for patients who died	−26.98[c]

Notes for Table 8

Note: Results may appear inexact due to rounding. Negative costs indicate savings. All costs expressed in 2021 Canadian dollars.

[a]Budget impact per patient: $1,306 (an additional $2,150 for the cost of REGEN-COV and its administration with a savings of $844 in hospitalization costs). Hospitalization cost per patient, usual care = 4.4% × $23,000 + 0.2% × $50,000 = $1,124. Hospitalization cost per patient, REGEN-COV = 4.4% × (1 – 0.76) × $23,000 + 0.2% × (1 – 0.67) × $50,000 = $280. Hospitalization cost savings per patient = $1,124 – $280 = $844.

[b]The lower hospitalization cost is due to the number of hospitalizations avoided in patients who survived.

[c]The lower hospitalization cost is due to the number of deaths prevented.

REFERENCE CASE RESULTS—INPATIENTS

In the inpatient setting, we estimated that 60,000 patients would be eligible for REGEN-COV treatment (Appendix 6, Figure A4).

In the current scenario, all patients would be hospitalized and receive usual care. About 42,197 of these patients may survive, and 17,803 may die. The total cost was estimated to be $1,860.67 million ($970.54 million in hospitalization costs for those who survived and $890.13 million in hospitalization costs for those who died).

In the new scenario, all patients would each receive four dose packs of REGEN-COV (8,000 mg) via a 1-hour intravenous infusion (plus a 1-hour observation after infusion). About 45,758 of these patients may survive, and 14,242 may die. The total cost was estimated to be $1,990.61 million ($473.70 million for the cost of REGEN-COV, its administration, and serological testing; $804.80 million in hospitalization costs for those who survived; and $712.11 million in hospitalization costs for those who died).

Therefore, the total budget impact was estimated to be an additional cost of $129.93 million (an additional cost of $473.70 million for the cost of REGEN-COV, its administration, and serological testing; a savings of $165.74 million from a shorter hospital length of stay; and a savings of $178.03 million from deaths prevented). This represents an additional cost of $2,166 per patient (an additional $7,895 for the cost of REGEN-COV, its administration, and serological testing and a savings of $5,729 in hospitalization costs).

Table 9 provides the results of the inpatient reference case.

Table 9: Budget Impact Analysis Results—Reference Case, Inpatients

Total costs and budget impact over 1 year, $ million	
Current scenario (usual care)	
Total	1,860.67
Drug, administration, serological testing	0.00
Hospitalization for patients who survived	970.54
Hospitalization for patients who died	890.13
New scenario (REGEN-COV)	
Total	1,990.61
Drug, administration, serological testing	473.70
Hospitalization for patients who survived	804.8
Hospitalization for patients who died	712.11
Budget impact	
Total	129.93
Drug, administration, serological testing	473.70
Hospitalization for patients who survived	−165.74[b]
Hospitalization for patients who died	−178.03[c]

Note: Results may appear inexact due to rounding. Negative costs indicate savings. All costs expressed in 2021 Canadian dollars.

[a]Budget impact per patient: $2,166 (an additional $7,895 for the cost of REGEN-COV, its administration, and serological testing with a savings of $5,729 in hospitalization costs). Hospitalization cost per patient, usual care = 70.3% × $23,000 + 29.7% × $50,000 = $31,011. Hospitalization cost per patient, REGEN-COV = 76.3% × $23,000 × (13/17) + 29.7% × (1 – 0.20) × $50,000 = $25,282. Hospitalization cost savings per patient = $31,011 − $25,282 = $5,729.

[b]The lower hospitalization cost is due to a shorter hospital length of stay in patients who survived.

[c]The lower hospitalization cost is due to the number of deaths prevented.

SCENARIO ANALYSIS

In scenario analyses, we explored whether the budget impact results were sensitive to changes in the values of important input parameters or assumptions (Table 10; see Appendix 6 for more details).

Table 10: Scenario Analyses—Parameter Values and Assumptions

Scenario	Reference case	Scenario analysis
Scenario 1: Comparator	**Outpatients and inpatients** Current scenario: usual care New scenario: REGEN-COV	**Outpatients** Current scenario: vaccines to prevent COVID-19 (assume that vaccination reduces the probabilities of hospitalization and death by 95% [relative risk reduction]) New scenario: REGEN-COV to treat COVID-19 **Inpatients** Not applicable since vaccination is not a treatment option in the inpatient setting
Scenario 2: Number of eligible patients	**Outpatients** 360,000 patients (unlimited supply) **Inpatients** 60,000 patients (unlimited supply)	**Outpatients** • 400 patients (only 400 dose packs currently available, assume 1 dose pack [2,400 mg] per outpatient) • 800 patients (only 400 dose packs currently available, assume 1/2 dose pack [1,200 mg] per outpatient) **Inpatients** 100 patients (only 400 dose packs currently available, assume 4 dose packs per inpatient)
Scenario 3: Cost of REGEN-COV	**Outpatients and inpatients** Included cost of REGEN-COV ($1,890/dose pack) to consider cost burden to public health care payer	**Outpatients and inpatients** Excluded cost of REGEN-COV since it is provided for free by the Public Health Agency of Canada
Scenario 4: Cost of drug administration	**Outpatients and inpatients** Assume REGEN-COV administered via 1-hour intravenous infusion with 1-hour monitoring after infusion ($260 per patient)	**Outpatients and inpatients** Assume REGEN-COV administered via subcutaneous injection ($15 per patient)
Scenario 5: Cost of COVID-19 hospitalization for patients who die	**Outpatients and inpatients** Assume $50,000 per patient (cost of COVID-19 hospitalization with ICU admission)	**Outpatients and inpatients** Assume $23,000 per patient (cost of an average COVID-19 hospitalization)
Scenario 6: Baseline probability of hospitalization	**Outpatients** 4.4% (based on REGEN-COV clinical trial by Weinreich et al, 2021b) **Inpatients** Not applicable	**Outpatients** 10% in high-risk outpatient population (based on Public Health Ontario data and expert opinion [assume the same relative risk reduction as seen in clinical trial]) **Inpatients** Not applicable
Scenario 7: Baseline probability of death	**Outpatients** 0.2% based on REGEN-COV clinical trial (Weinreich et al, 2021b) **Inpatients** Not applicable	**Outpatients** 4.1% based on Public Health Ontario data and expert opinion (assume the same relative risk reduction as seen in clinical trial) **Inpatients** Not applicable

The results of our analysis for scenario 1 suggest there is an advantage to having all people vaccinated in the outpatient settings versus providing treatment with REGEN-COV, as vaccines are very effective at preventing SARS-CoV-2 infection and would thus lead to fewer COVID-19-related hospitalizations and deaths. Also, the cost of the vaccine ($76 per person) is much lower than the cost of REGEN-COV ($1,890 per outpatient).

In scenario 2, we assumed that there are only 400 dose packs of REGEN-COV currently available and estimated the budget impact if these dose packs were used to treat a limited number of patients. Assuming one dose pack (2,400 mg at $1,890) is used to treat one outpatient, the current supply could be used to treat 400 eligible outpatients. The resulting total budget impact would be an additional cost of $0.52 million in the outpatient setting (scenario 2a). If half of one dose pack (1,200 mg at $945) is used to treat one outpatient, the target population would double to 800 eligible people, and the total budget impact would be about $0.29 million, owing to larger savings in hospitalization costs (scenario 2b). Assuming four dose packs are needed to treat one inpatient, the current supply could be used to treat 100 eligible inpatients. The resulting total budget impact would be an additional cost of $0.22 million (scenario 2a). The budget impact is smaller in the inpatient setting since we expected a greater reduction in hospitalization costs (resulting from more deaths prevented in the inpatient setting and presumably fewer ICU admissions). As discussed by Verma et al (2021), this is a limited supply problem that begs for the use of an ethical framework to establish an equitable and fair allocation of REGEN-COV treatment during the COVID-19 pandemic.

The budget impact in both outpatient and inpatient settings became smaller when we excluded the cost of REGEN-COV (scenario 3) or assumed a lower drug administration cost (scenario 4).

In scenario 5, when we assumed the cost of hospitalization for patients who died was lower, cost savings were reduced, so the overall budget impact was larger than in the reference case.

In scenarios 6 and 7, the total budget impact became much smaller than that of the reference case due to a larger reduction in hospitalizations and deaths among those treated with REGEN-COV. (Higher baseline probabilities of hospitalization and death from Ontario were used while applying the same relative risk reduction as used in the clinical trial by Weinreich et al (2021b), so the magnitude of the benefit was larger).

Table 11 provides the results of our scenario analyses.

Table 11: Scenario Analysis Results

	Budget impact, $ million	
	Outpatients	**Inpatients**
Reference case		
Total	**470.16**	**129.93**
REGEN-COV, administration, serological testing	774.00	473.7
Hospitalization for patients who survived	−276.86	−165.74
Hospitalization for patients who died	−26.98	−178.03
Scenario 1: Treatment with REGEN-COV vs. a hypothetical scenario in which all patients are vaccinated		
Total	**827.13**	**Not applicable**
REGEN-COV, administration, serological testing	746.64	–
Hospitalization for patients who survived	69.22	–
Hospitalization for patients who died	11.28	–
Scenario 2a: Limited supply of REGEN-COV (400 dose packs (2,400mg): 400 outpatients and 100 inpatients)		
Total	**0.52**	**0.22**
REGEN-COV, administration, serological testing	0.86	0.79
Hospitalization for patients who survived	−0.31	−0.28
Hospitalization for patients who died	−0.03	−0.30
Scenario 2b: Limited supply of REGEN-COV (400 dose packs (1,200 mg): 800 outpatients)		
Total	**0.29**	**Not applicable**
REGEN-COV, administration, serological testing	0.96	–
Hospitalization for patients who survived	−0.62	–
Hospitalization for patients who died	−0.06	–
Scenario 3: Cost of REGEN-COV excluded		
Total	−210.24	−323.67
REGEN-COV, administration, serological testing	93.60	20.10
Hospitalization for patients who survived	−276.86	−165.74
Hospitalization for patients who died	−26.98	−178.03
Scenario 4: REGEN-COV administered subcutaneously		
Total	381.96	115.23
REGEN-COV, administration, serological testing	685.80	459.00
Hospitalization for patients who survived	−276.86	−165.74
Hospitalization for patients who died	−26.98	−178.03
Scenario 5: Cost of COVID-19 hospitalization		
Total	484.72	226.07
REGEN-COV, administration, serological testing	774.00	473.70

	Budget impact, $ million	
	Outpatients	**Inpatients**
Hospitalization for patients who survived	−276.86	−165.74
Hospitalization for patients who died	−12.41	−81.89
Scenario 6: Baseline probability of hospitalization		
Total	117.74	Not applicable
REGEN-COV, administration, serological testing	774.00	–
Hospitalization for patients who survived	−629.28	–
Hospitalization for patients who died	−26.98	–
Scenario 7: Baseline probability of death		
Total	2.68	Not applicable
REGEN-COV, administration, serological testing	774.00	–
Hospitalization for patients who survived	−276.86	–
Hospitalization for patients who died	−494.46	–

Note: Negative costs indicate savings. Results may appear inexact due to rounding. All costs expressed in 2021 Canadian dollars.

Guidance on the Use of REGEN-COV From Other Canadian and International Jurisdictions

Other Canadian Jurisdictions

In British Columbia and Quebec, the use of REGEN-COV could be considered on a case-by-case basis in patients with confirmed COVID-19 infection and mild (British Columbia) or mild to moderate (Quebec) symptoms who are:

- Not hospitalized for COVID-19, and
- Not considered adequately immunized, and
- At high risk of life-threatening complications due to other comorbidities or their treatment

In Quebec, if a suboptimal vaccine response is suspected or anticipated by the treating physician, REGEN-COV could be considered under the conditions listed above in patients considered adequately immunized and in children and pregnant women considered adequately immunized or not. REGEN-COV treatment should start as soon as possible, ideally within 7 days or less from the start of symptoms. Use of REGEN-COV is not recommended in patients hospitalized for COVID-19, unless under exceptional circumstances.

Table A6 (Appendix 7) provides additional conditions for the use of REGEN-COV in Canadian jurisdictions.

International Jurisdictions

We identified guidance on the use of REGEN-COV from Australia, Belgium, France, Germany, Italy, Switzerland, and the United States based on documents issued between April and August 2021. In the United Kingdom, REGEN-COV has been approved for the prevention and treatment of acute COVID-19 infection, but conditions for treatment are still in development, and it is unclear when the treatment will be available to patients.

In Belgium, France, Germany, Italy, Switzerland, and the United States, conditions for the use of REGEN-COV in patients diagnosed with COVID-19 generally include:

- Not being hospitalized
- Being 12 years of age or older
- Having mild to moderate symptoms
- Starting treatment within 5–10 days of symptom onset
- Presenting with risk factors for a severe disease course

Table A7 (Appendix 7) provides additional conditions for the use of REGEN-COV in international jurisdictions.

The use of REGEN-COV in hospitalized patients is permitted in Australia (conditional recommendation in seronegative patients with moderate to critical COVID-19), Germany, and Switzerland. In the United States, although the use of REGEN-COV is not authorized in patients hospitalized with severe COVID-19, it may be available through expanded access programs for patients who have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection.

Ethical Considerations Related to the Use of REGEN-COV

For an ethical framework for drug shortages during the COVID-19 pandemic, see https://jcb.utoronto.ca/wp-content/uploads/2021/04/Ethical-Framework-for-Drug-Shortages-during-COVID-Pandemic.pdf

For an example of applying an ethical framework to a drug shortage situation with respect to the COVID-19 pandemic, see https://covid19-sciencetable.ca/sciencebrief/strategies-to-manage-tocilizumab-supply-during-the-covid-19-pandemic/

Discussion

Strengths

- This report was a rapid analysis based on Ontario data where available
- A relevant Cochrane review (Kreuzberger et al, 2021) was published after our literature search was completed did not identify any additional studies

Limitations

- Key clinical and cost parameters were based on pre-print or unpublished sources
- The size of the eligible patient population is uncertain and if it is smaller, the budget impact will be smaller
- This evidence summary was developed within a week to address a pressing need for evidence using expedited systematic review and economic methods and is not intended to be an exhaustive analysis. The evidence presented here is considered current as of the literature search date, but other relevant scientific findings may have been reported since completion. The economic analysis results should be interpreted with caution, particularly when used for making resource allocation policy decisions

Conclusions

We examined the peer-reviewed published and grey literature to determine what is known about REGEN-COV (casirivimab and imdevimab) for the treatment of outpatients or inpatients diagnosed with COVID-19 and found the following:

- High-risk outpatients who received REGEN-COV (2,400 mg or 1,200 mg) experienced a significant reduction in (a) COVID-19-related hospitalizations or death and (b) COVID-19-related hospitalizations through day 29 of follow-up compared with patients who received placebo (GRADE: Moderate)
    - When stratified into subgroups:
        - Seronegative patients who received REGEN-COV (2,400 mg or 1,200 mg) experienced a significant reduction in COVID-19-related hospitalizations or death
        - Seropositive patients who received REGEN-COV 2,400 mg experienced a significant reduction in COVID-19-related hospitalizations or death compared with those who received placebo; no significant difference was observed for patients who received REGEN-COV 1,200 mg
- Inpatients with moderate to severe COVID-19 who received REGEN-COV (8,000 mg) plus usual care experienced no significant reduction in (a) progression to invasive mechanical ventilation or death and (b) 28-day mortality compared with patients treated with usual care alone (GRADE: Moderate)
    - When stratified into subgroups:

  - Seronegative inpatients treated with REGEN-COV (8,000 mg) plus usual care experienced a significant reduction in (a) progression to invasive mechanical ventilation or death, and (b) 28-day mortality compared with patients treated with usual care alone
  - Seropositive inpatients treated with REGEN-COV (8,000 mg) plus usual care experienced no significant reduction in (a) progression to invasive mechanical ventilation or death, and (b) 28-day mortality compared with patients treated with usual care alone

We also estimated the cost-effectiveness and budget impact of using REGEN-COV in Ontario and found the following:

- REGEN-COV is associated with additional costs ($1,306 and $2,166 per patient, for outpatients and inpatients, respectively) but is more effective than usual care alone
  - In outpatients, for every 1,000 patients treated, REGEN-COV would lead to 35 hospitalizations avoided (number needed to treat [NNT] = 29) and 1.5 deaths prevented (NNT = 667)
  - In inpatients, for every 1,000 patients treated, REGEN-COV would lead to 59 deaths prevented (NNT = 17)
- REGEN-COV is likely more cost-effective for inpatients than outpatients (incremental cost-effectiveness ratio: $36,500 vs. $871,000 per death prevented)
- In outpatients, REGEN-COV is more costly and less effective than or is dominated by the vaccination strategy
- Given the current pandemic situation, a large demand for REGEN-COV could be expected, resulting in a large total budget impact (including the cost of REGEN-COV and costs related to hospitalization and death):
  - In the outpatient setting, including 360,000 eligible patients, assuming a cost of REGEN-COV of $1,890 per treatment (2,400 mg per patient), the total budget impact is estimated to be an additional $470.16 million
  - In the inpatient setting, including 60,000 eligible patients, assuming a cost of REGEN-COV of $7,560 per treatment (8,000 mg per patient), the total budget impact is estimated to be an additional $129.93 million

Appendices

Appendix 1: Methods—Clinical and Economic Evidence Reviews

Literature Search

We performed a literature search on August 30, 2021, to retrieve studies published from database inception until the search date. A second literature search was performed on August 31, 2021, using the clinical strategy and applying an economic and costing filter. We used the Ovid interface in MEDLINE and Embase for both searches. A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords.

We performed a targeted grey literature search of the websites of relevant health organizations, repositories of medical procedural guidance, and pre-publication registries. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

- Full-text publications in English
- Studies published between database inception and August 30, 2021
- Guidance, guidelines, health technology assessments, systematic reviews, randomized controlled trials, observational studies
- Cost–utility, cost-effectiveness, cost–benefit, or cost–consequence analyses or systematic reviews of economic analyses (economic evidence review only)

POPULATION

- outpatients with mild to moderate COVID-19 (confirmed by direct SARS-CoV-2 viral testing) in people (≥ 12 years and weighing ≥ 40 kg) who are high risk for hospitalization or death
- Inpatients (adults and adolescents aged 12 years and older) diagnosed with COVID-19, confirmed by SARS-CoV-2 virus testing

INTERVENTION

- Treatment with REGEN-COV for COVID-19 infection

COMPARATORS

- No treatment with REGEN-COV for COVID-19 infection
- Usual care or placebo

OUTCOME MEASURES

- Health outcomes: hospitalization or hospitalization with admission to ICU (for severe COVID-19), death, adverse events

- Costs, incremental costs, incremental effectiveness, incremental cost-effectiveness ratio (economic analysis only)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using the Covidence systematic review management software (Covidence, 2020) and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and included eligible studies.

Data Extraction

We extracted relevant data on study characteristics, methods, and outcomes.

Critical Appraisal of Evidence

We evaluated the quality of the body of evidence for two outcomes—hospitalization in outpatients and admission to ICU in inpatients—according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook* (Schünemann et al, 2013). The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Appendix 2: Literature Search Strategies

Clinical Evidence Search

Search date: August 30, 2021

Databases searched: Ovid MEDLINE and Embase

Database segments: Embase <1980 to 2021 Week 34>, Ovid MEDLINE(R) ALL <1946 to August 27, 2021>

Search strategy:

---

1 (regencov* or regen cov* or regncov* or regn cov* or regn cov2).ti,ab,kf. (49)
2 (casirivimab* and imdevimab*).ti,ab,kf. (68)
3 (REGN10933* and REGN10987*).ti,ab,kf. (14)
4 ronapreve*.ti,ab,kf. (0)
5 (regeneron* adj4 (monoclonal* or antibod* or covid* or nCoV* or SARS-CoV-2* or SARSCOV2* or SARSCOV-2*)).ti,ab,kf. (26)
6 or/1-5 (129)
7 6 use medall (70)
8 (regencov* or regen cov* or regncov* or regn cov* or regn cov2).tw,kw,du,dy,tn,av. (62)
9 (casirivimab* and imdevimab*).tw,kw,du,dy,tn,av. (121)
10 (REGN10933* and REGN10987*).tw,kw,du,dy,tn,av. (19)
11 ronapreve*.tw,kw,du,dy,tn,av. (0)
12 (regeneron* adj4 (monoclonal* or antibod* or covid* or nCoV* or SARS-CoV-2* or SARSCOV2* or SARSCOV-2*)).tw,kw,du,dy,tn,av. (26)
13 or/8-12 (185)
14 13 use emez (116)
15 7 or 14 (186)
16 remove duplicates from 15 (133)

Economic Evidence Search

Search date: August 30, 2021

Databases searched: Ovid MEDLINE and Embase

Database segments: Embase <1980 to 2021 Week 34>, Ovid MEDLINE(R) ALL <1946 to August 30, 2021>

Search strategy:

---

1 (regencov* or regen cov* or regncov* or regn cov* or regn cov2).ti,ab,kf. (49)
2 (casirivimab* and imdevimab*).ti,ab,kf. (69)
3 (REGN10933* and REGN10987*).ti,ab,kf. (14)
4 ronapreve*.ti,ab,kf. (0)
5 (regeneron* adj4 (monoclonal* or antibod* or covid* or nCoV* or SARS-CoV-2* or SARSCOV2* or SARSCOV-2*)).ti,ab,kf. (26)
6 or/1-5 (130)
7 economics/ (262158)

8 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (921118)
9 economics.fs. (437094)
10 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1036501)
11 exp "costs and cost analysis"/ (607078)
12 (cost or costs or costing or costly).ti. (274667)
13 cost effective*.ti,ab,kf. (352782)
14 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (235219)
15 models, economic/ (13196)
16 markov chains/ or monte carlo method/ (92732)
17 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (51037)
18 (markov or markow or monte carlo).ti,ab,kf. (151090)
19 quality-adjusted life years/ (43299)
20 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (83004)
21 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (143707)
22 or/7-21 (2848909)
23 6 and 22 (13)
24 23 use medall (4)
25 (regencov* or regen cov* or regncov* or regn cov* or regn cov2).tw,kw,du,dy,tn,av. (62)
26 (casirivimab* and imdevimab*).tw,kw,du,dy,tn,av. (122)
27 (REGN10933* and REGN10987*).tw,kw,du,dy,tn,av. (19)
28 ronapreve*.tw,kw,du,dy,tn,av. (0)
29 (regeneron* adj4 (monoclonal* or antibod* or covid* or nCoV* or SARS-CoV-2* or SARSCOV2* or SARSCOV-2*)).tw,kw,du,dy,tn,av. (26)
30 or/25-29 (186)
31 Economics/ (262158)
32 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (136950)
33 Economic Aspect/ or exp Economic Evaluation/ (498813)
34 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (1043139)
35 exp "Cost"/ (607078)
36 (cost or costs or costing or costly).ti. (274667)
37 cost effective*.tw,kw. (356042)
38 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (240305)
39 Monte Carlo Method/ (74050)
40 (decision adj1 (tree* or analy* or model*)).tw,kw. (51558)
41 (markov or markow or monte carlo).tw,kw. (152724)
42 Quality-Adjusted Life Years/ (43299)
43 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (83505)
44 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (144653)
45 or/31-44 (2429273)
46 30 and 45 (14)
47 46 use emez (10)
48 24 or 47 (14)

49 remove duplicates from 48 (11)

Grey Literature Search

Performed: August 30,2021

Websites searched:
WHO Coronavirus disease (COVID-19) Pandemic
https://covid-vaccine.canada.ca/info/regulatory-decision-summary-detailTwo.html?linkID=RDS00823
https://covid.cadth.ca/
https://www.medrxiv.org/
https://covid19.nih.gov/
twitter.com
https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19.html
https://www.cdc.gov/coronavirus/2019-ncov/index.html
https://www.fda.gov/emergency-preparedness-and-response/counterterrorism-and-emerging-threats/coronavirus-disease-2019-covid-19

Keywords used: REGEN-COV, casirivimab, imdevimab, ronapreve, COVID-19, monoclonal antibody, regeneron

Appendix 3: PRISMA Flow Diagram—Clinical Search Strategy

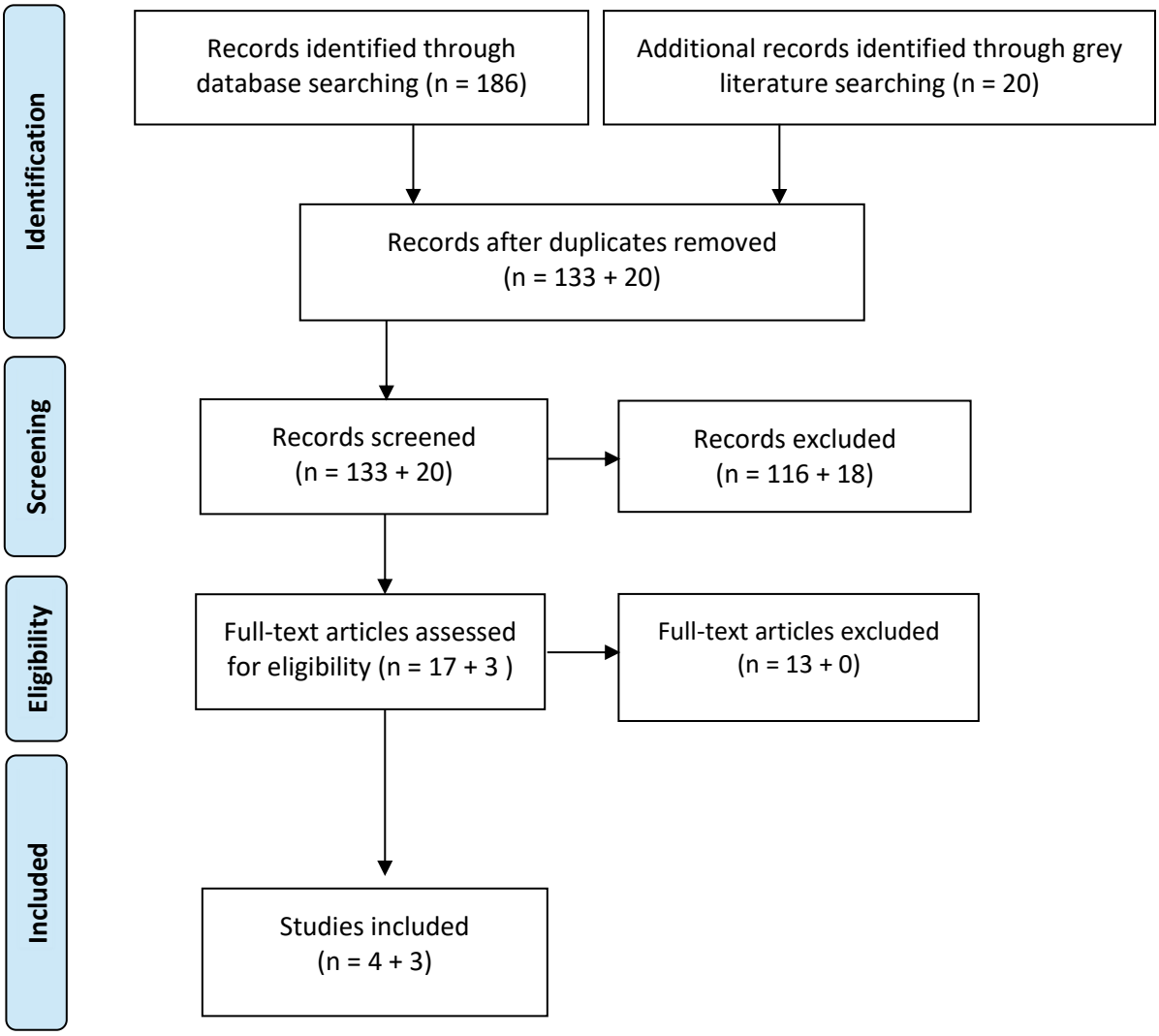

Figure A1: PRISMA Flow Diagram—Clinical Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al (2009).

Appendix 4: Critical Appraisal of Clinical Evidence

Table A1: GRADE Evidence Profile for REGEN-COV Administered to Outpatients or Inpatients

Number and type of studies (author, year)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Outpatients							
Hospitalization							
1 RCT (Weinreich et al, 2021b) 3 observational studies (Ash et al, 2021; Dhand et al, 2021; Razonable et al, 2021)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[a]	Undetected	None	⨁⨁⨁ Moderate
Hospitalization or death							
1 RCT (Weinreich et al, 2021b)	No serious limitations	No serious limitations	No serious limitations	Serious limitations (−1)[b]	Undetected	None	⨁⨁⨁ Moderate
Inpatients							
Admission to intensive care unit							
0 studies	–	–	–	–	–	–	–
Progression to invasive mechanical ventilation							
1 RCT (RECOVERY Collaborative Group, 2021 [preprint])	Serious limitations (−1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
28-day mortality							
1 RCT (RECOVERY Collaborative Group, 2021 [preprint])	Serious limitations (−1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.

[a]Wide confidence interval for REGEN-COV 1,200 mg: relative risk reduction 73.5% (95% CI: 35.3% to 89.1%).

[b]Wide confidence interval for REGEN-COV 1,200 mg: relative risk reduction 70.4% (95% CI: 31.6% to 87.1%).

[c]Open-label trial.

Appendix 5: PRISMA Flow Diagram—Economic Search Strategy

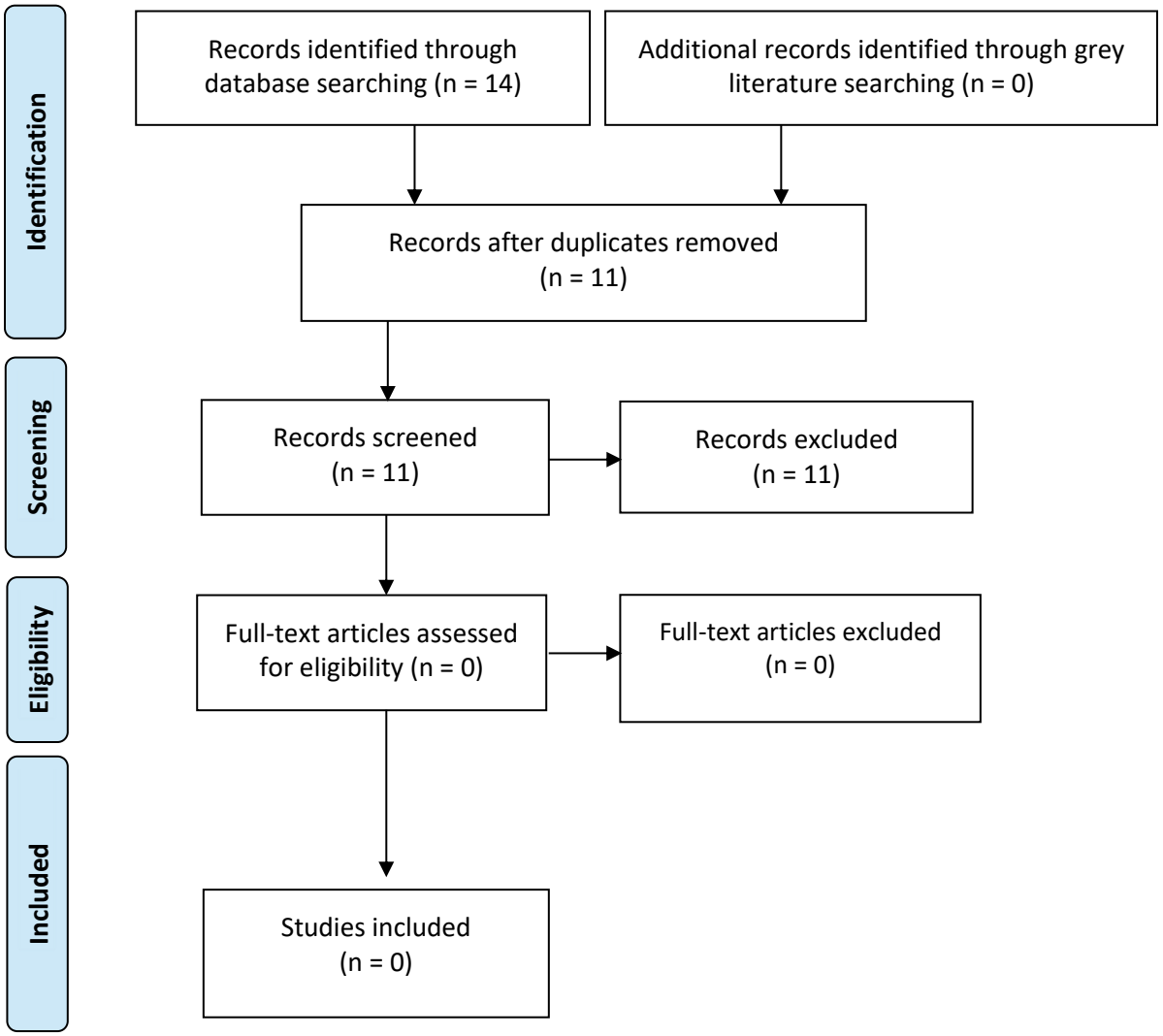

Figure A2: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al (2009).

Appendix 6: Budget Impact Analysis Methods

Analytic Framework

We estimated the cost-effectiveness and budget impact of using REGEN-COV in the outpatient setting and in the inpatient setting in Ontario, by calculating the differences in health outcomes and costs between two scenarios: (1) usual care without REGEN-COV (the current scenario) and (2) treatment with REGEN-COV (the new scenario). Figure A3 presents the schematic model of the budget impact.

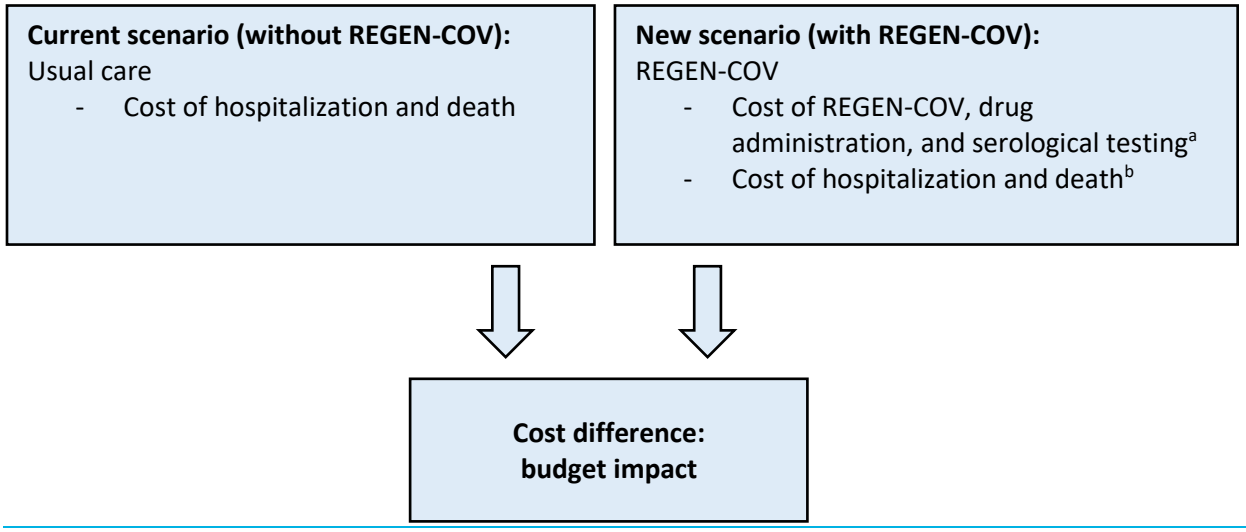

Figure A3: Schematic Model of Budget Impact

[a]Serological testing cost is included in only the inpatient setting.
[b]In the outpatient setting, the benefit of REGEN-COV is the reduced numbers of hospitalizations and deaths. In the inpatient setting, the benefit of REGEN-COV is the reduced number of deaths and the shorter length of stay in hospital (all patients are already hospitalized in this setting).

Key Assumptions

- It is expected that the demand for REGEN-COV will be high in the current and future waves of the pandemic. Individuals who do not have existing immunity (i.e., those who are seronegative, either because they are unvaccinated or because they are immunocompromised/ immunosuppressed and cannot mount an adequate immune response to vaccination) are at highest risk of serious outcomes from infection with COVID-19. Demand for REGEN-COV will therefore correlate with the number of non-immune individuals. To approximate the size of the non-immune population, we assumed that the majority of people are seronegative because they are not fully vaccinated (only a minority are seronegative because their body cannot produce enough antibodies). According to data from Public Health Ontario, currently about 4.8 million people (of all ages) in Ontario are not fully vaccinated. Among these, about 3 million people are over the age of 12 years
- In the reference case analysis, we included the cost of REGEN-COV ($1,890 per 2,400 mg dose) to consider the cost burden on the public health care payer. In a scenario analysis, we excluded the cost of REGEN-COV since the treatment is currently provided for free by the Public Health Agency of Canada

- For this analysis, we considered only costs incurred to patients within 28 days after receiving treatment (the follow-up time of the clinical trial), such as the cost of REGEN-COV treatment, drug administration and patient monitoring (during and for 1 hour after the infusion), serological testing (in the inpatient setting only), and hospitalization
- For treatment with REGEN-COV, we assumed 1 dose pack would be administered per patient in an outpatient setting (2,400 mg) and 4 dose packs would be administered per patient in an inpatient setting (8,000 mg) (according to the product monograph, each dose pack [i.e., carton] contains 2 vials per package: 1 vial of 1,332 mg/11.1 mL of casirivimab and 1 vial of 1,332 mg/11.1 mL imdevimab)
- In the reference case analysis, we assumed REGEN-COV would be administered by intravenous infusion (involving a 1-hour infusion and 1 hour of in-hospital monitoring after the infusion); in the scenario analysis, we examined subcutaneous injection as an alternative
- In the outpatient setting, we assumed that no follow-up (or remote monitoring) would be required after patients are discharged home
- We did not consider the cost of treatment-related adverse events, assuming that these are rare and usually mild (e.g., infusion-related reactions)
- Patients who died would incur higher hospitalization costs ($50,000/patient, the cost of a COVID-19 hospitalization with an ICU admission) compared with those who were hospitalized and survived ($23,000/patient, the average cost of a COVID-19 hospitalization)
- The uptake of REGEN-COV in both outpatient and inpatient settings was assumed to be 100%

Target Population

We examined two target populations potentially eligible for REGEN-COV treatment:

- Outpatients: Individuals aged 12 years or older diagnosed with mild to moderate COVID-19 and treated in an outpatient setting. Eligibility for REGEN-COV is based on clinical criteria, such as mild to moderate COVID-19 with at least one underlying risk factor at baseline (expert consultation, August 30, 2021)
- Inpatients: Individuals aged 12 years or older diagnosed with COVID-19 and treated in the hospital. Eligibility for REGEN-COV is based on clinical criteria (expert consultation, August 30, 2021)

We estimated the number of eligible patients in both settings using publicly available Ontario data and expert opinion (Statistics Canada, 2021; Canadian Institute for Health Information [CIHI], 2021; Public Health Ontario Data Tool, 2021). Our approach and estimates were confirmed with clinical experts. We estimated that there would be about 360,000 patients eligible for REGEN-COV treatment in the outpatient setting and about 60,000 patients in the inpatient setting. Table A2 and Figure A4 present our approach and calculations.

Table A2: Size of the Target Population: Outpatient and Inpatient Settings

	Value	Source/Assumptions
Outpatient setting		
Individuals at risk of being infected with SARS-CoV-2 in Ontario (12 y+)	3,000,000	Public Health Ontario, 2021; expert opinion
Probability of being infected in the next 6–12 mo	100%	Expert opinion
Probability of being diagnosed with COVID-19	40%	Expert opinion; Yanes-Lane et al, 2020
Number of individuals diagnosed with COVID-19 in the next 6–12 mo (12 y+)	1,200,000	Calculation (3 million × 100% × 40%)
Proportion of people with mild to moderate COVID-19 (managed as outpatients) and eligible for REGEN-COV (50 y+ or with risk factors)	30%	Expert opinion; Wu et al, 2020
Number of individuals eligible for REGEN-COV in outpatient setting	**360,000**	**Calculation (1.2 million × 30%)**
Inpatient setting		
Number of individuals diagnosed with COVID-19 in the next 6–12 mo (12 y+)	1,200,000	Calculation (3 million × 100% × 40%)
Proportion of patients hospitalized	5%	Public Health Ontario, 2021; expert opinion
Number of individuals with moderate to severe COVID-19 eligible for REGEN-COV	**60,000**	**Calculation (1,200,000 × 5%)**

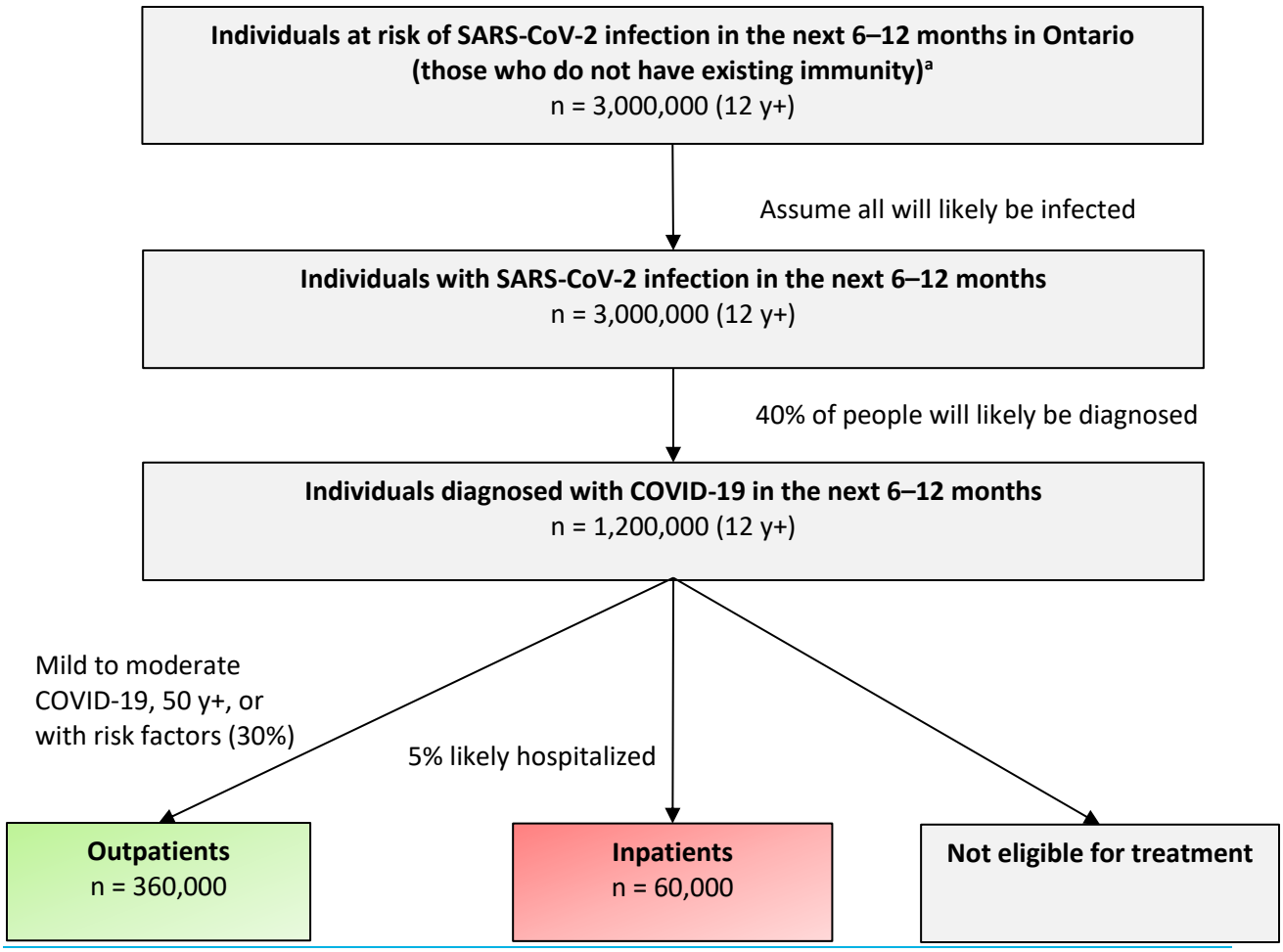

Figure A4: Estimation of the Target Population in Ontario

[a]Either because they are unvaccinated or because they are immunocompromised/immunosuppressed and cannot mount an adequate immune response to vaccination.

Clinical Parameters

The clinical parameters were obtained from the literature and are summarized in Table A3 (baseline probabilities of hospitalization and death) and Table A4 (treatment effect of REGEN-COV).

Based on the results of a clinical trial comparing REGEN-COV versus placebo in an outpatient setting (Weinreich et al, 2021b), the probability of hospitalization and the probability of death in the placebo (usual care) group were about 4.4% and 0.2%, respectively (Table A3). The relative risk reduction of the REGEN-COV versus placebo was 0.76 (95%CI: 0.55–0.87) for the hospitalization outcome and 0.67 (95%CI: −0.22 to 0.97) for the death outcome (Table A4).

Based on the results of a clinical trial by the RECOVERY group (2021) in an inpatient setting (i.e., hospitalized patients with COVID-19), the probability of death was 30% in the placebo group and 24% in the REGEN-COV group (relative risk: 0.80 [95% CI, 0.70–0.91]; which suggests a relative risk reduction of

20%). This study also reported a shorter median hospital length of stay with REGEN-COV treatment (placebo vs. REGEN-COV: 17 vs. 13 hospitalization days).

In a scenario analysis (scenario 1) where we compared the REGEN-COV treatment strategy with the vaccine strategy (for the prevention of SARS-CoV-2 infection), we assumed that the vaccine is 95% effective (a 95% relative risk reduction on both the probability of hospitalization and the probability of death in the outpatient setting).

Table A3: Clinical Parameters—Usual Care

Model parameter	Value	Reference
Outpatient cohort		
Probability of hospitalization	0.044	Weinreich et al, 2021b
Probability of death	0.002	Weinreich et al, 2021b
Inpatient cohort[a]		
Probability of death	0.30	RECOVERY Collaborative Group, 2021
Median duration of hospitalization (days)	17	RECOVERY Collaborative Group, 2021

[a]Among seronegative patients.

Table A4: Clinical Parameters—REGEN-COV

Intervention	Value	Reference
Outpatient cohort		
Relative risk reduction, hospitalization (seronegative patients)	0.76	Weinreich et al, 2021b
Relative risk reduction, death (overall)	0.67	Weinreich et al, 2021b
Inpatient cohort[a]		
Relative risk reduction, death	0.20	RECOVERY Collaborative Group, 2021
Median duration of hospitalization (days)	13	RECOVERY Collaborative Group, 2021

[a]Among seronegative patients.

Cost Parameters

The cost parameters are presented in Table A5. All costing estimates are expressed in 2021 Canadian dollars. Based on the clinical trial information and expert consultation, a higher dose of REGEN-COV (8,000 mg) is required to treat inpatients with severe COVID-19. Therefore, we accounted for the difference in the number of REGEN-COV dose packs used (1 dose pack per patient in an outpatient setting vs. 4 dose packs per patient in an inpatient setting). We estimated the cost of REGEN-COV based on publicly available information ($1,500 USD per treatment for outpatients, or $1,890 CAD using an exchange rate of 1.26) and assumed that the drug would be administered via a 1-hour infusion in the

reference case ($200 per hour, which includes the cost of infusion supplies, labour, and overhead) (Stewart et al, 2018). As suggested in clinical reports, we also accounted for 1 hour of additional nursing time needed to monitor patients in hospital after the REGEN-COV infusion ($60 per hour) (Health Quality Ontario, 2017). We obtained the costs of COVID-19 hospitalizations from CIHI (2021).

In the inpatient setting, the use of REGEN-COV led to shorter hospital lengths of stay. To estimate the cost of hospitalization in the REGEN-COV group (with a median duration of hospitalization of 13 days), we first calculated the cost per diem using the cost of hospitalization in the usual care group ($1,353/day [$23,000 per hospital stay / 17 days]), and then multiplied this cost by 13 days. As a result, the cost of hospitalization in the REGEN-COV group was estimated to be $17,588 per hospital stay.

Table A5: Cost Parameters

Variable	Unit cost, $[a]	Duration/ quantity	Total cost per person, $	Reference
Cost of REGEN-COV, outpatient	1,890	1	1,890	Estimate based on unpublished data (link)[b]
Cost of REGEN-COV, inpatient	1,890	4[c]	7,560	Estimate based on unpublished data (link)[b,c]
Cost of drug administration (infusion supplies, labour, and overhead)	200/hour	1 hour	200	Stewart et al, 2018
Cost of in-hospital monitoring, after receiving REGEN-COV	60/hour	~1 hour	60	Health Quality Ontario, 2017
Cost of COVID hospitalization, average	23,000	1	23,000	CIHI, 2021 (link to the source table)
Cost of COVID hospitalization with death	50,000	1	50,000	CIHI, 2021 (link to the source table)
Cost of serological testing, in inpatient setting only	75	1	75	Estimate from LifeLabs, 2021
Cost of drug administration (subcutaneous), *scenario only*	60/hour	~¼ hour	15	Health Quality Ontario, 2017
Cost of vaccine (2 doses), *scenario only*	38	2	76	Estimate based on unpublished data: link

[a]All costs are expressed in 2021 Canadian dollars.
[b]Exchange rate for US to Canadian dollars was 1.26, for the cost of REGEN-COV of $1,500 USD per dose pack (link to source).
[c]Number of dose packs for inpatients confirmed in expert consultation (2,400 mg for outpatient and 8,000 mg for inpatient).

Internal Validation

Formal internal validation was conducted by a secondary health economist. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. For each research question (i.e., outpatient and inpatient settings), we estimated the following outcomes for the current scenario (usual care) and new scenario (treatment with REGEN-COV):

- Total costs and disaggregated costs by category: REGEN-COV drug cost, REGEN-COV administration cost, serological testing cost, hospitalization cost (all expressed in 2021 Canadian dollars)
- Health outcomes: number of hospitalizations or deaths

From these estimates, we calculated an *incremental cost-effectiveness ratio* (ICER), expressed as cost per additional hospitalization, and a *net budget impact* (i.e., the difference in the total costs between the two scenarios). All analyses were performed deterministically using point estimates in Microsoft Excel.

Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and assumptions. In consultations with clinical experts, we conducted the following additional analyses:

- **Scenario 1—In the outpatient setting, comparing the use of REGEN-COV for treatment of COVID-19 to the use of vaccine for prevention of SARS-CoV-2 infection:** For this analysis, we compared the total cost of a scenario where REGEN-COV is used to treat COVID-19 and the total cost of a hypothetical scenario where everyone is vaccinated. We assumed that the probability of hospitalization in vaccinated individuals is 0.22% and the probability of death in vaccinated individuals is 0.011% (from breakthrough infection), based on expert opinion (assuming the vaccine has a 95% relative risk reduction on baseline probabilities of hospitalization and death)
- **Scenario 2—Limited REGEN-COV supply:** Currently, there are only 400 dose packs of REGEN-COV available in Ontario. We assumed that these can be used to treat either 400 outpatients or 100 inpatients, given a Health Canada approved 2,400 mg per dose pack. We also examined changes in the results if 1,200 mg is used for outpatients (i.e., $945 per treatment and 800 outpatients)
- **Scenario 3—Excluding the cost of REGEN-COV:** In the reference case, we included the cost of REGEN-COV ($1,890 per treatment with 2,400 mg) to consider the cost burden on the public health care payer. In this analysis, we excluded the cost of REGEN-COV since the treatment is currently provided for free by the Public Health Agency of Canada
- **Scenario 4—Varying the cost of drug administration:** In the reference case, the cost of REGEN-COV administration is $260 per patient (intravenous infusion). In this analysis, the cost of REGEN-COV administration is $15 per patient (subcutaneous injection)
- **Scenario 5—Varying the cost of COVID-19 hospitalization for patients who died:** In the reference case, we assumed the cost of hospitalization for patients who died would be more costly ($50,000/patient, which is the cost of a COVID-19 hospitalization with ICU admission). In

this analysis, we assumed the cost of a hospitalization for patients who died is equal to the average COVID-19 hospitalization cost ($23,000/patient, which is the cost of an average COVID-19 hospitalization)

- **Scenario 6—Varying the baseline probability of hospitalization based on Ontario data:** For this analysis, we assumed the probability of hospitalization is 10% in a high-risk outpatient population in Ontario vs. the 4.4% seen in a clinical trial (Weinreich et al, 2021b)
- **Scenario 7—Varying the baseline probability of death based on Ontario data:** For this analysis, we assumed the probability of death is 4.1% in high-risk outpatient population in Ontario vs. the 0.2% seen in clinical trial (Weinreich et al, 2021b)

Appendix 7: Ontario-Based Scenario Analysis

We conducted an additional Ontario-based scenario analysis using baseline probabilities of hospitalization, intensive care unit (ICU) admission and death from Ontario data (email communication with clinical expert, September 2021) and effectiveness data for REGEN-COV from the published evidence (RECOVERY Collaborative Group, 2021; Weinreich et al, 2021b). Table A6 provides the clinical parameters used for this analysis.

Table A6: Clinical Inputs, Reference Case and Ontario Scenario Analysis, Outpatients and Inpatients

Usual care	Mean value, reference case	Reference	Mean value, Ontario scenario	Reference
Outpatients				
Probability of hospitalization	0.044	Weinreich et al, 2021b	0.152	ON data,[a] age ≥ 50 y, expert consultation
Probability of ICU admission	NA	NA	0.048	ON data, age ≥ 50 y, expert consultation
Probability of death	0.002	Weinreich et al, 2021b	0.061	ON data, age ≥ 50 y, expert consultation
Inpatients				
Probability of death	0.30	RECOVERY Collaborative Group, 2021	0.31	ON data, expert consultation
Probability of ICU admission	NA	NA	0.21 (calculated)	21% of all hospitalizations are in ICU, age ≥ 12 y, ON data
Median duration of hospitalization (no. days)	17	RECOVERY Collaborative Group, 2021	17	RECOVERY Collaborative Group, 2021
Effectiveness: REGEN-COV vs. usual care	**Mean value, reference case (95% CI)[a]**	**Reference**	**Mean value, Ontario scenario (95% CI)[b]**	**Reference**
Outpatients				
Relative risk reduction, hospitalization (seronegative patients)	**2,400 mg** 0.76 (0.55; 0.87)	Weinreich et al, 2021b (dose 2,400 mg)	**1,200 mg** 0.83 (0.42 to 0.95) **2,400 mg** 0.76 (0.55 to 0.87)	Weinreich et al, 2021b
Relative risk reduction, ICU admission (all patients)	NA	NA	**1,200 mg** 0.56 (−0.67 to 0.89) **2,400 mg** 0.67 (0.17 to 0.87)	Weinreich et al, 2021b
Relative risk reduction, death (all patients)	**2,400 mg** 0.67 (-0.22; 0.97)	Weinreich et al, 2021b	NA (0)	Assumed no risk reduction due to imprecision

Effectiveness: REGEN-COV vs. usual care	Mean value, reference case (95% CI)[a]	Reference	Mean value, Ontario scenario (95% CI)[b]	Reference
Inpatients				
Relative risk reduction, death (seronegative patients), calculated using risk ratio for death	**8,000 mg** 0.20 Risk ratio: 0.80 (0.70 to 0.91)	RECOVERY Collaborative Group, 2021	**8,000 mg** 0.20 Risk ratio: 0.80 (0.70 to 0.91)	RECOVERY Collaborative Group, 2021
Relative risk reduction, ICU admission (seronegative patients), calculated using risk ratio for ventilation	NA	NA	**8,000 mg** 0.13 Risk ratio: 0.87 (0.77 to 0.98)	RECOVERY Collaborative Group, 2021 (ventilation outcome)
Median duration of hospitalization (no. days)	13	RECOVERY Collaborative Group, 2021	13	RECOVERY Collaborative Group, 2021

Abbreviations: CI, confidence interval; ICU, intensive care unit; NA, not applicable; y, years.
[a]Ontario data provided by clinical expert via email communication, September 2021.
[b]All analyses were done deterministically. For reference, we have provided 95% CIs for the effectiveness estimates.

Scenario Analysis Assumptions

- The results of the REGEN-COV trials (Recovery Collaboration Group, 2021; Weinreich et al, 2021b) are generalizable to the Ontario setting:
    - Outpatients: We applied the relative risk reductions (RRRs) observed in the study by Weinreich el al (2021b) to the Ontario baseline probabilities of hospitalization and ICU admission
        - We assumed no reduction in the probability of death in the outpatient setting owing to the wide CI reported by Weinreich et al (2021b)
    - Inpatients: We applied the RRRs observed in the RECOVERY trial (2021) to the Ontario baseline probabilities of ventilation (used as a surrogate for ICU admission to facilitate comparison between the inpatient and outpatient settings) and death
- We conducted the analysis deterministically using point estimates, so it did not consider any uncertainty

Scenario Analysis Limitations

- The Ontario baseline probabilities of hospitalization, ICU admission, and death are much larger than those observed in the study on high-risk outpatients by Weinreich et al (2021b)
    - Hospitalization: 15.2% (Ontario, aged ≥ 50 years, unvaccinated) versus 3.1% (Weinreich et al, 2021b, placebo)
    - ICU admission: 4.8% (Ontario, aged ≥ 50 years, unvaccinated) versus 0.9% (Weinreich et al, 2021b, placebo)

  - Death: 6.1% (Ontario, aged ≥ 50 years, unvaccinated) versus 0.1% (Weinreich et al, 2021b, placebo)

- In Ontario, the probability of death is much larger than the probability of ICU admission, suggesting that more deaths have occurred outside the ICU in Ontario than in the study by Weinreich et al (2021b)
- Outpatients: The treatment effect of REGEN-COV 1,200 mg on ICU admission is not statistically significant
  - The RRR on the probability of ICU admission (for all patients, as an estimate for only seronegative patients is unavailable) is 56.4% (95% CI: −67.8% to 88.7%)
- Based on the point estimates from Weinreich et al (2021b), a dose of REGEN-COV of 1,200 mg has a larger treatment effect on reducing hospitalizations than a dose of 2,400 mg in seronegative patients (Weinreich et al, 2021b, Table 2)
  - The RRR on the probability of hospitalization is 82.7% (1,200 mg) versus 75.8% (2,400 mg)

Results

Based on the incremental cost per ICU admissions avoided, the results of this scenario analysis (Table A7) suggest that REGEN-COV 1,200 mg may be a dominant strategy (i.e., less costly and more effective) compared with usual care in the outpatient setting, assuming the results from Weinreich et al (2021b) are generalizable to Ontario. REGEN-COV 1,200 mg may lead to a savings of $727 per patient ($4,066 for REGEN-COV vs. $4,794 for usual care), while reducing the numbers of hospitalizations and ICU admissions (based on the point estimate of the RRRs for hospitalization [82.7%] and ICU admissions [56.4%]; it should be noted that the effect of treatment with REGEN-COV 1,200 mg on ICU admissions is not statistically significant). Owing to uncertainty in the reduction of death, we did not estimate an incremental cost-effectiveness ratio (ICER) using death as an outcome in the outpatient setting.

In the inpatient setting, REGEN-COV 8,000 mg is more costly (an incremental cost of $2,400 per person) but also more effective than usual care. The ICERs are estimated to be $86,971 per ICU admission avoided and $38,069 per death prevented. It should be noted that the treatment effects of REGEN-COV 8,000 mg on ICU admissions and death are statistically significant.

Table A7: Comparison of Results—Reference Case Versus Ontario Scenario Analyses

Analysis	Results[a,b]	
Reference case[c]	**Outpatients (REGEN-COV, 2,400 mg)**	**Inpatients (REGEN-COV, 8,000 mg)**
Incremental effectiveness: hospitalizations	–0.035	NA
Incremental effectiveness: ICU admissions	Not estimated (RRR in seronegative patients not reported)	Not estimated (ICU admissions not reported as an outcome)
Incremental effectiveness: deaths	**–0.001**	**–0.059**
NNT: 1 hospitalization avoided	29	NA
NNT: 1 ICU admission avoided	Not estimated	Not estimated
NNT: 1 death prevented	**667**	**17**
Incremental cost per person, $	**1,306**	**2,166**
ICER: $/hospitalization avoided	37,382	NA
ICER: $/ICU admission avoided	Not estimated	Not estimated
ICER: $/death prevented	**871,308**	**36,493**
Budget impact, $ million, all eligible patients	**470.16**	**129.93**
Budget impact, $ million, limited supply (400 dose packs)	**0.52 (400 outpatients)**	**0.22 (100 inpatients)**
Ontario scenario analysis (based on Ontario data)[d,e]	**Outpatients (REGEN-COV 1,200 mg)**	**Inpatients (REGEN-COV 8,000 mg)**
Incremental effectiveness: hospitalizations	–0.068	Not applicable
Incremental effectiveness: ICU admissions	**–0.013**	**–0.028[f]**
Incremental effectiveness: deaths	0.000 (assume no difference)[g]	–0.063
NNT: 1 hospitalization avoided	15	NA
NNT: 1 ICU admission avoided	**75**	**36**
NNT: 1 death prevented	Likely very large	16
Incremental cost per person, $	**–727**	**2,400**
ICER: $/hospitalization avoided	Dominant	NA
ICER: $/ICU admission avoided	**Dominant**	**86,971**
ICER: $/death prevented	Cost saving, no difference in death	38,069
Budget impact, $ million, all eligible patients	**–261.89**	**144.0**
Budget impact, $ million, limited supply (400 dose packs)	**–0.58 (800 outpatients)**	**0.24 (100 inpatients)**

Analysis	Results[a,b]	
Additional Ontario scenario analysis (based on Ontario data)[e]	**Outpatients (REGEN-COV 2,400 mg)**	**Inpatients (REGEN-COV 8,000 mg)**
Incremental effectiveness: hospitalizations	−0.066	NA
Incremental effectiveness: ICU admissions	**−0.016**	**−0.028[f]**
Incremental effectiveness: deaths	0.000 (assume no difference)	−0.063
NNT: 1 hospitalization avoided	15	NA
NNT: 1 ICU admission avoided	62	**36**
NNT: 1 death prevented	Likely very large	16
Incremental cost per person, $	**191**	**2,400**
ICER: $/hospitalization avoided	2,885	NA
ICER: $/ICU admission avoided	**11,950**	**86,971**
ICER: $/death prevented	Likely very large	38,069
Budget impact, $ million, all eligible patients	**68.9**	**144.0**
Budget impact, $ million, limited supply (400 dose packs)	**0.08 (400 outpatients)**	**0.24 (100 inpatients)**

Abbreviations: ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; NA, not applicable; NNT, number needed to treat; RRR, relative risk reduction.

[a]All costs are in 2021 Canadian dollars.

[b]ICER = incremental costs/incremental effectiveness.

[c]The reference case results were presented to the Ontario Health Technology Advisory Committee on September 13, 2021.

[d]Tables A8, A9, and A10 provide the full results of the analyses for outpatients treated with REGEN-COV 1200 mg, outpatients treated with REGEN-COV 2,400 mg, and inpatients treated with REGEN-COV 8,000 mg, respectively.

[e]Ontario data provided by clinical expert via email communication, September 2021.

[f]The RECOVERY trial (2021) did not report ICU admissions as an outcome, so ventilation was used as a surrogate outcome.

[g]In the outpatient setting, the incremental outcome was assumed to be 0 because of the large uncertainty in the prevention of death with REGEN-COV (RRR: 0.67, 95% CI: −0.22 to 0.97; Weinreich et al, 2021).

Note: Results may appear incorrect due to rounding. Negative numbers in incremental effectiveness indicate reductions. Negative costs indicate cost savings.

Table A8: Ontario Scenario Analysis—REGEN-COV 1,200 mg: Cost-Effectiveness Analysis Results (Per-Person Estimates), Outpatients

		Probability	Treatment cost, $[a]	Serological testing cost, $[a]	Hospitalization cost, $[a]	Total cost, $[a]
REGEN-COV (new scenario)						
	Not hospitalized	0.917	1,105	0	0	1,105
	Hospitalized, non-ICU, survived	0.037	44	0	846	890
	Hospitalized, non-ICU, died	0.011	14	0	264	278
	Hospitalized, ICU, survived	0.025	30	0	1,226	1,255
	Hospitalized, ICU, died	0.011	13	0	526	539
	Total	**1.000**	**1,205**	**0**	**2,861**	**4,066**
Usual care (current scenario)						
	Not hospitalized	0.848	0	0	0	0
	Hospitalized, non-ICU, survived	0.037	0	0	846	846
	Hospitalized, non-ICU, died	0.066	0	0	1,527	1,527
	Hospitalized, ICU, survived	0.025	0	0	1,226	1,226
	Hospitalized, ICU, died	0.024	0	0	1,195	1,195
	Total	1.000	**0**	**0**	4,794	4,794
Incremental outcomes (REGEN-COV vs. usual care)						
Incremental cost, $[a]						**–727**
Incremental effectiveness						
Hospitalizations						–0.068[b]
ICU admissions						–0.013[c]
Deaths						0.000[d]

	Probability	Treatment cost[a]	Serological testing cost[a]	Hospitalization cost[a]	Total cost, $[a]
Incremental cost-effectiveness ratio[e]					
Additional cost per hospitalization avoided, $[a]					**Dominant**
Additional cost per ICU admission avoided, $[a]					**Dominant**
Additional cost per death prevented, $[a]					NA (cost saving, no difference in death)

Abbreviation: ICU, intensive care unit.

[a]All costs are in 2021 Canadian dollars.

[b]The number needed to treat to prevent one hospitalization = 1/0.068 = 14.6.

[c]The number needed to treat to prevent one ICU admission = 1/0.013 = 74.7.

[d]The reduction in the number of deaths was assumed to be 0, because of the large uncertainty in the effectiveness estimate (RRR: 0.67, 95% CI: −0.216 to 0.97).

[e]Incremental cost-effectiveness ratio = incremental costs/incremental effectiveness.

Note: Results may appear incorrect due to rounding. Negative numbers in incremental effectiveness indicate reductions. Negative numbers in costs indicate savings. “Dominant” indicates that treatment with REGEN-COV is less costly and more effective than usual care.

Table A9: Ontario Scenario Analysis—REGEN-COV 2,400 mg: Cost-Effectiveness Analysis Results (Per-Person Estimates), Outpatients

REGEN-COV (new scenario)		Probability	Treatment cost, $[a]	Serological testing cost, $[a]	Hospitalization cost,$[a]	Total cost, $[a]
	Not hospitalized	0.915	1,967	0	0	1,967
	Hospitalized, non-ICU, survived	0.037	79	0	846	925
	Hospitalized, non-ICU, died	0.016	35	0	370	404
	Hospitalized, ICU, survived	0.025	53	0	1,226	1,278
	Hospitalized, ICU, died	0.008	17	0	394	411
	Total	**1.000**	**2,150**	**0**	**2,835**	**4,985**
Usual care (current scenario)						
	Not hospitalized	0.848	0	0	0	0
	Hospitalized, non-ICU, survived	0.037	0	0	846	846
	Hospitalized, non-ICU, died	0.066	0	0	1,527	1,527
	Hospitalized, ICU, survived	0.025	0	0	1,226	1,226
	Hospitalized, ICU, died	0.024	0	0	1,195	1,195
	Total	1.000	**0**	**0**	4,794	4,794
Incremental outcomes (REGEN-COV vs. usual care)						
Incremental cost, $[a]						**191**
Incremental effectiveness						
Hospitalizations						−0.066[b]
ICU admissions						−0.016[c]
Deaths						0.000[d]
Incremental cost-effectiveness ratio[e]						
Additional cost per hospitalization avoided, $[a]						**2,885**
Additional cost per ICU admission avoided, $[a]						**11,950**
Additional cost per death prevented, $[a]						NA (very high)

Notes for Table A9

[a]All costs are in 2021 Canadian dollars.

[b]The number needed to treat to prevent one hospitalization = 1/0.066 = 15.1.

[c]The number needed to treat to prevent one ICU admission = 1/0.016 = 62.4.

[d]The reduction in the number of deaths was assumed to be 0, because of the large uncertainty in the effectiveness estimate (RRR: 0.67, 95% CI: −0.216 to 0.97).

[e]Incremental cost-effectiveness ratio = incremental costs/incremental effectiveness.

Note: Results may appear incorrect due to rounding. Negative numbers in incremental effectiveness indicate reductions. Negative numbers in costs indicate savings. "Dominant" indicates that treatment with REGEN-COV is less costly and more effective than usual care.

Table A10: Ontario Scenario Analysis—REGEN-COV 8,000 mg: Cost-Effectiveness Analysis Results (Per-Person Estimates), Inpatients

REGEN-COV (new scenario)		Probability	Treatment cost, $[a]	Serological testing cost, $[a]	Hospitalization cost, $[a]	Total cost, $[a]
	Hospitalized, non-ICU (no ventilation)	0.563	4,404	42	9,904	14,350
	Hospitalized, ICU (ventilation)	0.185	1,444	14	9,234	10,692
	Hospitalized, died	0.252	1,972	19	12,609	14,600
	Total	**1.000**	**7,820**	**75**	**31,748**	**39,643**
Usual care (current scenario)						
	Hospitalized, non-ICU (no ventilation)	0.472	0	0	10,867	10,867
	Hospitalized, ICU (ventilation)	0.212	0	0	10,614	10,614
	Hospitalized, died	0.315	0	0	15,762	15,762
	Total	**1.000**	**0**	**0**	**37,243**	**37,243**
Incremental outcomes (REGEN-COV vs. usual care)						
Incremental cost, $[a]						**2,400**
Incremental effectiveness						
Ventilation						−0.0276[b]
Deaths						−0.063[c]
Incremental cost-effectiveness ratio[d]						
Additional cost per ventilation prevented, $[a]						**86,971**
Additional cost per death prevented, $[a]						**38,069**

[a]All costs are in 2021 Canadian dollars.

[b]The number needed to treat to prevent one ventilation = 1/0.028 = 36.

[c]The number needed to treat to prevent one death = 1/0.063 = 16.

Notes for Table A10 continued

[d]Incremental cost-effectiveness ratio = incremental cost/incremental effectiveness.

Note: Results may appear incorrect due to rounding. Negative numbers in incremental effectiveness indicate reductions.

Conclusions

On a per-patient level, treating outpatients with REGEN-COV 1,200 mg would prevent fewer ICU admissions than treating inpatients with REGEN-COV 8,000 mg (probabilities for reductions in ICU admissions for outpatients and inpatients, respectively: 1.3% vs. 2.8%).

The estimated number needed to treat (NNT) to prevent one ICU admission is about 75 (calculated as 1/0.013) in the outpatient setting and about 36 in the inpatient setting (calculated as 1/0.028).

However, when treatment dosages are considered, the current supply in Ontario of 400 dose packs could be used to treat 4 to 8 times (2,400 mg and 1,200 mg, respectively) more outpatients than inpatients.

Based on the incremental cost per ICU admission avoided, using REGEN-COV 1,200 mg in the outpatient setting seems reasonable (ICER: dominant [less costly and more effective] in outpatients vs. $86,971 per ICU admission avoided in inpatients). This finding is based on the statistically nonsignificant RRR point estimate of the probability of ICU admissions for REGEN-COV 1,200 mg.

Appendix 8: Jurisdictional Scan—Guidance and Recommendations on the Use of REGEN-COV

Table A6: Canadian Guidance

Province, Organization(s)	Date	Guidance or recommendations
British Columbia, Ministry of Health, British Columbia Centre for Disease Control	Jul 6, 2021	**Use of REGEN-COV may be considered on a case-by-case basis in patients:** • With mild disease, and • Who are inadequately immunized (unimmunized, partially immunized, or have an inadequate immune response), and • Are at high risk of developing severe COVID-19-related complications
Quebec, Institut National d'Excellence en Santé et Services Sociaux	Jul 2, 2021	**Use of REGEN-COV, if available in Canada, could be considered on a case-by-case basis in patients:** • With confirmed COVID-19 infection with mild to moderate symptoms, and • Who are considered not adequately immunized,[a] and • Who are not hospitalized for COVID-19, and • Who are at a high risk of life-threatening complications due to a concomitant condition[b] or its treatment, and • In whom there is a concern that a humoral immune response cannot be developed For these patients, REGEN-COV should be administered as soon as possible, ideally ≤ 7 days from the start of symptoms **Use of REGEN-COV, if available in Canada, could be considered on a case-by-case basis if the potential benefits outweigh the risks in patients:** • With confirmed COVID-19 infection with mild to moderate symptoms, and • Who are considered adequately immunized,[a] and • Are not hospitalized for COVID-19, and • Who are at a high risk of life-threatening complications due to a concomitant condition[b] or its treatment, and • In whom a suboptimal vaccine response is suspected[c] or anticipated by the treating physician For these patients, REGEN-COV should be administered as soon as possible, ideally ≤ 7 days from the start of symptoms **Use of REGEN-COV, if available in Canada, could be considered on a case-by-case basis if the potential benefits outweigh the risks in children and pregnant women:** • With a confirmed COVID-19 infection with mild to moderate symptoms, and • Who are considered adequately immunized[a] or not, and • Who are not hospitalized for COVID-19, and • Who are at a high risk of life-threatening complications due to a concomitant condition[d] or its treatment, and • In whom a suboptimal vaccine response is suspected or anticipated by the treating physician

	For these patients, REGEN-COV should be administered as soon as possible, ideally ≤ 7 days from the start of symptoms **Use of REGEN-COV is not recommended outside of research settings in:** • Asymptomatic patients with a confirmed COVID-19 infection, who are not hospitalized due to COVID-19 or • Patients hospitalized for COVID-19, unless under exceptional circumstances

[a]Adequate immunization: two doses of a vaccine authorized in Canada or a prior infection confirmed by real-time polymerase chain reaction plus one vaccine dose.

[b]Inclusion criteria for randomized controlled trials (not to be interpreted as an indication to treat all patients with these criteria, as the immune response is not necessarily compromised): one or more of the following risk factors: obesity, chronic renal disease (creatinine clearance < 60 mL/min), diabetes type 1 or 2, immunosuppressive disease, treatment with immunosuppressants, age ≥ 65 years, age 55 years and a cardiovascular disease, hypertension, or a chronic respiratory disease (e.g., asthma of moderate severity, chronic obstructive pulmonary disease).

[c]Some of the following conditions appear to pose a higher risk of developing a suboptimal vaccine response according to the literature consulted at the time of publication of this rapid response: solid organ transplant (heart, lungs, liver, kidneys, or pancreas) that requires immunosuppressant treatment (e.g., tacrolimus, corticosteroids, mycophenolate, azathioprine, cyclosporine, belatacept, sirolimus, everolimus, mTOR inhibitor), solid cancer, Hodgkin's lymphoma, non-Hodgkin's lymphoma, multiple myeloma or chronic lymphocytic leukemia with chemotherapy or immunotherapy (e.g., mercaptopurine, methotrexate, proteasome inhibitor, Bruton's tyrosine kinase inhibitor, immunomodulators), chronic inflammatory diseases being treated with methotrexate and antibodies against CD20 (ocrelizumab or rituximab).

[d]One or more of the following risk factors (based on the inclusion criteria of clinical trials; not to be interpreted as an indication to treat all patients meeting these criteria, as the development of an immune response is not necessarily compromised): obesity, chronic kidney disease (creatinine clearance < 60 mL/min), diabetes type 1 or 2, immunosuppressive disease, or use of immunosuppressive therapy.

Table A7: International Guidance

Country, organization	Date	Guidance or recommendations
Australia, National COVID-19 Clinical Evidence Task Force	Report published Aug 25, 2021; exact date of recommendation not provided	**Conditional recommendation for use of REGEN-COV**: • Consider using in seronegative patients hospitalized with moderate to critical COVID-19 **Use of REGEN-COV not recommended outside of research settings:** • Do not use in mild or asymptomatic outpatients with COVID-19 outside of RCTs with appropriate ethical approval **Use of REGEN-COV not recommended:** • Do not use in seropositive patients hospitalized with moderate to critical COVID-19

Belgium, Belgian Society of Infectiology and Clinical Microbiology	Jul 2021	**Use of REGEN-COV:**
		• Patients with a confirmed COVID-19 diagnosis with mild to moderate disease severity, and
		• Age ≥ 12 years old, and
		• Symptom onset < 10 days, SARS-CoV-2, and positive test < 5 days, and
		• Who are immunocompromised[a] or have at least one comorbidity[b]
		  ○ Immunocompromised patients are eligible regardless of SARS-CoV-2 serology
		  ○ Patients with at least one comorbidity but who are not immunocompromised are eligible only if they are negative for a SARS-CoV-2 spike protein IgG serology
		Approval from a multidisciplinary expert panel is required before starting treatment

France, Ministry of Health	Not provided	**Use of REGEN-COV:** *In patients ≥ 80 years old* • Diagnosed with COVID-19, and • Not hospitalized for COVID-19, and • Who are at an early stage of the disease (upon obtaining a positive RT-PCR result or at a maximum of 5 days from start of symptoms) *In patients 12–79 years old* • Who meet the conditions above *plus* immunodeficiency due to a medical condition or its treatment[c] or who are at risk of complications[d] **Additional conditions (all age groups listed above)[e]** Use REGEN-COV in the following situations: • In areas where the circulation of variants carrying a mutation in position 484 is important • If a mutation in position 484 is identified before treatment administration • In areas where the circulation of the Delta variant is important • If the Delta variant is identified before treatment is administered

Country, organization	Date	Guidance or recommendations
Germany, Robert Koch Institute Permanent Working Group of Competence and Treatment Centers for High-Consequence Infectious Diseases	Jul 16, 2021	Monoclonal antibodies including REGEN-COV were under investigation at the time of writing of the report but were available in selected pharmacies in Germany as part of a Ministry of Health initiative **Indications where treatment with REGEN-COV is potentially useful in adult and pediatric patients ≥ 12 years (≥ 40 kg body weight):** • Outpatients with COVID-19 in the early phase of the disease (≤ 7 days from symptom onset, maximum 72 hours from positive PCR test),[f] who are asymptomatic or have mild to moderate symptoms, and who have risk factors for a severe disease course • Patients with a hospital-acquired infection (maximum 72 hours from positive PCR test[f]), who are asymptomatic or have mild to moderate symptoms, and who have risk factors for a severe disease course • Hospitalized COVID-19 patients (maximal low-dose oxygen substitution), ≤ 7 days from symptom onset[f] The use can also be considered in the later phase of the disease among patients with high-risk factors, especially patients undergoing B-cell depletion therapy and who lack the ability to produce specific SARS-CoV-2 antibodies
Italy, Ministry of Health	Apr 26, 2021	**Use of REGEN-COV has been made available for:** • Patients diagnosed with COVID-19 with mild to moderate symptoms of recent onset (≤ 10 days), and • Age > 12 years, and • Who are not hospitalized for COVID-19, and • Not on oxygen therapy for COVID-19, and • In whom there is the presence of ≥ 1 risk factor[g] **Use not recommended in patients:** • Hospitalized for COVID-19 • Who are receiving oxygen therapy for COVID-19 • And who are already on chronic oxygen therapy due to an underlying comorbidity unrelated to COVID-19 and that requires an increase in the oxygen flow rate due to COVID-19
Switzerland, National COVID-19 Science Task Force	Aug 17, 2021	**REGEN-COV can be provided to patients:** • At high risk for complications (those who are immunocompromised, very elderly, or have comorbidities) • Early after the first symptoms occur (in either the outpatient or inpatient setting)
United Kingdom, United Kingdom Government	Aug 20, 2021	REGEN-COV has been approved for the prevention and treatment of acute COVID-19 infection, but it is unclear when the treatment will be available to patients Details about conditions for treatment administration were not provided
United States, National Institutes of Health COVID-19 Treatment Guidelines Panel	Aug 4, 2021, update	**Use REGEN-COV (casirivimab 600 mg/imdevimab 600 mg) in** nonhospitalized patients aged ≥ 12 years with mild to moderate COVID-19 who are at high risk of clinical progression[h] • Treatment should be started as soon as possible after the patient receives a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test (NAAT) and within 10 days of symptom onset **Use should be considered in** patients with mild to moderate COVID-19 who are hospitalized for a reason other than COVID-19, if they otherwise meet the emergency use authorization criteria for outpatient treatment

Country, organization	Date	Guidance or recommendations
		Not currently authorized for use in patients hospitalized with severe COVID-19; however, it may be available through expanded access programs for patients who have not developed an antibody response or who are not expected to mount an effective immune response to SARS-CoV-2 infection **Contraindications for use of REGEN-COV—**not authorized for: • Patients hospitalized for COVID-19, • Who require oxygen therapy due to COVID-19, or • Who are on chronic oxygen therapy due to an underlying non-COVID-19-related comorbidity and who require an increase in oxygen flow rate from baseline because of COVID-19

Abbreviations: IgG, immunoglobulin G; PCR, polymerase chain reaction; RCT, randomized controlled trial; RT-PCR, real-time polymerase chain reaction.

[a]Hematological malignancy, solid cancer undergoing treatment, solid organ or hematopoietic stem cell transplantation, primary immune deficiency, human immunodeficiency virus (HIV) with CD4 < 200/mm^3 and/or detectable viral load, prednisolone ≥ 20 mg ≥ 14 days, or other immunosuppressive drugs (according to the Superior Health Council list of [potentially] immunosuppressive drugs), sickle cell anemia, and major thalassemia.

[b]Age ≥ 65 years old, obesity (body mass index ≥ 30 kg/m^2), cardiovascular disease including uncontrolled hypertension, chronic lung disease including asthma, diabetes type 1 or 2, chronic kidney disease (estimated glomerular filtration rate < 30 mL/min) including hemodialysis, chronic liver disease (Child Pugh B or C), and chronic neurological disease.

[c]Ongoing chemotherapy, solid organ transplantation, allogeneic hematopoietic stem cell transplantation, kidney disease with glomerular filtration rate < 30 mL/min or dialysis, systemic lupus or vasculitis with immunosuppressive therapy, corticosteroid treatment > 10 mg/day of prednisone equivalent for > 2 weeks, immunosuppressive treatment including rituximab, and uncontrolled HIV infection or acquired immunodeficiency syndrome (AIDS).

[d]Idiopathic pulmonary fibrosis, amyotrophic lateral sclerosis, rare liver pathologies including autoimmune hepatitis, myopathies with forced vital capacity < 70%, other rare pathologies, trisomy 21, obesity (body mass index > 30), chronic obstructive pulmonary disease and chronic respiratory failure, complicated arterial hypertension, heart failure, diabetes type 1 or 2, and chronic renal failure.

[e]The identification of COVID-19 variants is mandatory.

[f]Within this time frame a negative antibody status is probable. Test results for antibody status (anti-spike) should not delay the start of therapy.

[g]Body mass index ≥ 35, chronically undergoing peritoneal dialysis or hemodialysis, uncontrolled diabetes mellitus (HbA1c ≥ 9.0% or 75 mmol/mol) or with chronic complications, a primary immunodeficiency, a secondary immunodeficiency (particularly onco-hematological patients being treated with immunosuppressive or myelosuppressive drugs or < 6 months from suspension of treatment), age ≥ 65 years (in this case ≥ 1 additional risk factor must be present), age ≥ 55 years and cardio-cerebrovascular disease (including hypertension with concomitant organ damage), or chronic obstructive pulmonary disease and/or another chronic respiratory disease (pulmonary fibrosis or needing oxygen therapy for reasons other than COVID-19), age 12–17 years and a body mass index ≥ 85th percentile for age and sex, sickle cell anemia, congenital or acquired heart disease, neurodevelopmental disease, dependence on technological devices (e.g., patients with tracheotomy, gastrostomy, etc.), or asthma or other respiratory diseases requiring daily medication.

[h]Medical conditions or other factors that were represented in clinical trials that evaluated monoclonal antibodies: age ≥ 65 years, obesity (body mass index > 30), diabetes, cardiovascular disease (including congenital heart disease) or hypertension, and chronic lung diseases (e.g., chronic obstructive pulmonary disease, moderate to severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension). Other conditions or factors that had limited representation in clinical trials but are considered risk factors for progression to severe COVID-19 by the Centers for Disease Control and Prevention: an immunocompromising condition or immunosuppressive treatment, being overweight (body mass index 25–30) as the sole risk factor, chronic kidney disease, pregnancy, sickle cell disease, neurodevelopmental disorders (e.g., cerebral palsy) or other conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies), and medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation that is not related to COVID-19). Other factors (e.g., race or ethnicity) or medical conditions may also place individual patients at high risk for progression to severe COVID-19.

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