

CADTH Health Technology Review

Concurrent or Sequential Administration of Drugs for COVID-19 and Influenza

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Abbreviations

HTA health technology assessment

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Key Messages

- With the continued COVID-19 pandemic and the resurgence of seasonal influenza, there is the potential that some populations may need drugs for the prevention and/or treatment of COVID-19 and/or influenza at the same time (i.e., concurrent use) or close together (i.e., sequential use).
- No evidence was identified regarding the clinical effectiveness, safety, or evidence-based guidelines for the concurrent or sequential use of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir that met the criteria for this review.

Context and Policy Issues

The COVID-19 pandemic has prompted concerns over the circulation of respiratory co-infections, specifically with COVID-19 and influenza. In Canada, approximately 3.9 million cases of COVID-19 have been reported since the beginning of the pandemic in 2020, while influenza accounts for approximately 12,200 hospitalizations and 3,500 deaths each year.^{1,2} During the 2019 to 2020 influenza season in Canada and other northern hemisphere countries, influenza activity dropped in March 2020 due to the implementation of strict public health measures designed to limit the spread of COVID-19.^{3,4} During the 2020 to 2021 influenza season in Canada, the test positivity rate of influenza A and B was 0.0015 (95% CI, 0.001 to 0.002) compared to the pre-pandemic test positivity rate of 0.0028 (95% CI, 0.001 to 0.007).⁴ With the easing of COVID-19 public health restrictions in Canada, there has been a resurgence of seasonal influenza and a continued prevalence of COVID-19.³ The concern of potential respiratory co-infections with COVID-19 and influenza has raised the question of appropriate, effective, and safe treatment in people with or at high risk of coinfection with COVID-19 and influenza. In addition, there is concern over the proper use of preventive therapy for people who may be at risk of poor outcomes if infected with COVID-19, whether that may influence therapeutic and prophylactic treatment considerations if those individuals are infected by COVID-19 and/or influenza, or if they are a close contact of an individual with influenza.

In Canada, there are separate pharmacological options available for the prevention and treatment of COVID-19 and influenza. Cilgavimab and tixagevimab (commonly known as Evusheld) is a long-acting antibody combination therapy approved for use in Canada in April 2022.⁵ Cilgavimab and tixagevimab is used as a pre-exposure prophylaxis for COVID-19 in adults and adolescents who cannot receive the vaccine due to a severe allergy, or are immunocompromized and may not have an adequate response to the vaccine.⁵ Cilgavimab and tixagevimab is administered as 2 separate sequential intramuscular injections (i.e., 1 injection for cilgavimab and 1 injection for tixagevimab) that may provide protection for 6 to 9 months.^{5,6} Nirmatrelvir and ritonavir (commonly known as Paxlovid) is an oral antiviral treatment authorized for adults with mild to moderate COVID-19 who are at high risk for progression to severe COVID-19 (e.g., advanced age, people who are immunocompromized, people who have comorbidities).⁷ Nirmatrelvir and ritonavir treatment includes two 150 mg doses of nirmatrelvir and one 100 mg dose of ritonavir taken twice daily for 5 days.^{7,8} Oseltamivir (commonly known as Tamiflu) is a neuraminidase inhibitor antiviral treatment option for influenza.⁹ Oseltamivir may be offered to patients aged 1 year or older who have been symptomatic for no more than 2 days, and may also be used as a preventive measure for adults and children aged 1 year or older who are in close contact with symptomatic

influenza patients.⁹ For the treatment of symptomatic influenza, oseltamivir should be taken twice daily for 5 days.⁹ For preventive measures, oseltamivir should be taken once daily for 10 days.⁹

These prevention and treatment options for COVID-19 and influenza may be complex, and different variations of either prevention or treatment (or both) regimens may be needed depending on the patient indication. As a result, there is concern for regimen overlap, not only for people with or at high risk of infection with COVID-19 and influenza, but also those who may be at risk of poor outcomes if infected with COVID-19 who have been exposed to or infected with influenza (with or without COVID-19 infection). The objective of this report is to summarize the evidence regarding the clinical effectiveness, safety, and recommendations from evidence-based guidelines for the concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir.

Research Questions

1. What is the clinical effectiveness and safety of concurrent administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir?
2. What is the clinical effectiveness and safety of sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir?
3. What are the evidence-based guidelines regarding concurrent administration or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the international HTA database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were COVID-19, influenza, oseltamivir, cilgavimab/tixagevimab, and nirmatrelvir/ritonavir. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, indirect treatment comparisons, and guidelines. Conference abstracts were excluded. Where possible, retrieval was limited to the human population. The search was also limited to English-language documents published between January 1, 2020 and June 28, 2022.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for

inclusion. The final selection of full-text articles was based on the inclusion criteria presented in [Table 1](#).

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in [Table 1](#), they were duplicate publications, or were published before 2020. Guidelines with unclear methodology were also excluded.

Summary of Evidence

Quantity of Research Available

A total of 766 citations were identified in the literature search. Following screening of titles and abstracts, 765 citations were excluded and 1 potentially relevant report from the electronic search was retrieved for full-text review. In addition, 20 potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 21 potentially relevant articles, all were excluded for various reasons; no publications met the inclusion criteria to be included in this report. [Appendix 1](#) presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹⁰ flow chart of the study selection. Additional references of potential interest are provided in [Appendix 2](#).

Table 1: Selection Criteria

Criteria	Description
Population	Q1 to 3: Adults infected with COVID-19 or at risk of poor outcomes if infected with COVID-19 and/or influenza
Intervention	Q1: Concurrent administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir Q2: Sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir Q3: Concurrent administration or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir
Comparator	Q1 to 2: Cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir not administered concurrently or in sequence Q3: Not applicable
Outcomes	Q1 to 2: Clinical effectiveness (e.g., mortality, clinical symptoms, safety [e.g., adverse events]) Q3: Recommendations regarding concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir (e.g., dosing intervals for optimal administration and effect, appropriate and/or inappropriate populations)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Q = question.

Summary of Findings

Clinical Effectiveness of Concurrent Administration

No relevant literature was identified regarding the clinical effectiveness and safety of concurrent administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir; therefore, no summary can be provided.

Clinical Effectiveness of Sequential Administration

No relevant literature was identified regarding the clinical effectiveness and safety of the sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir; therefore, no summary can be provided.

Guidelines

No evidence-based guidelines were identified regarding concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir; therefore, no summary can be provided.

Limitations

No relevant literature was identified regarding the clinical effectiveness and safety of concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir. Additionally, no evidence-based guidelines were identified regarding concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir. This report may be limited by the time frame used for literature searches (extended only to 2020); however, based on the nature of this topic as it relates to COVID-19, it is unlikely that there would be relevant literature that was published before 2020.

Conclusions and Implications for Decision- or Policy-Making

No relevant literature or evidence-based guidelines were identified regarding the concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir; therefore, no conclusions regarding the clinical effectiveness, safety, or evidence-based guidelines can be provided.

The continued COVID-19 pandemic and the resurgence of influenza has highlighted the potential complexity for patient management strategies when considering prevention and treatment regimens for COVID-19 and/or influenza. At the time this review was completed, the drug monographs for cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and oseltamivir do not mention any considerations for drug interactions with one another.¹¹⁻¹³ Further research examining the clinical effectiveness and safety of concurrent or sequential administration of cilgavimab and tixagevimab, nirmatrelvir and ritonavir, and/or oseltamivir is required to investigate the potential impact on patients infected with COVID-19 and influenza, people infected with COVID-19 and exposed to influenza, and people at high-risk of poor outcomes if infected with COVID-19 who have been exposed to or infected with influenza (with or without a COVID-19 infection).

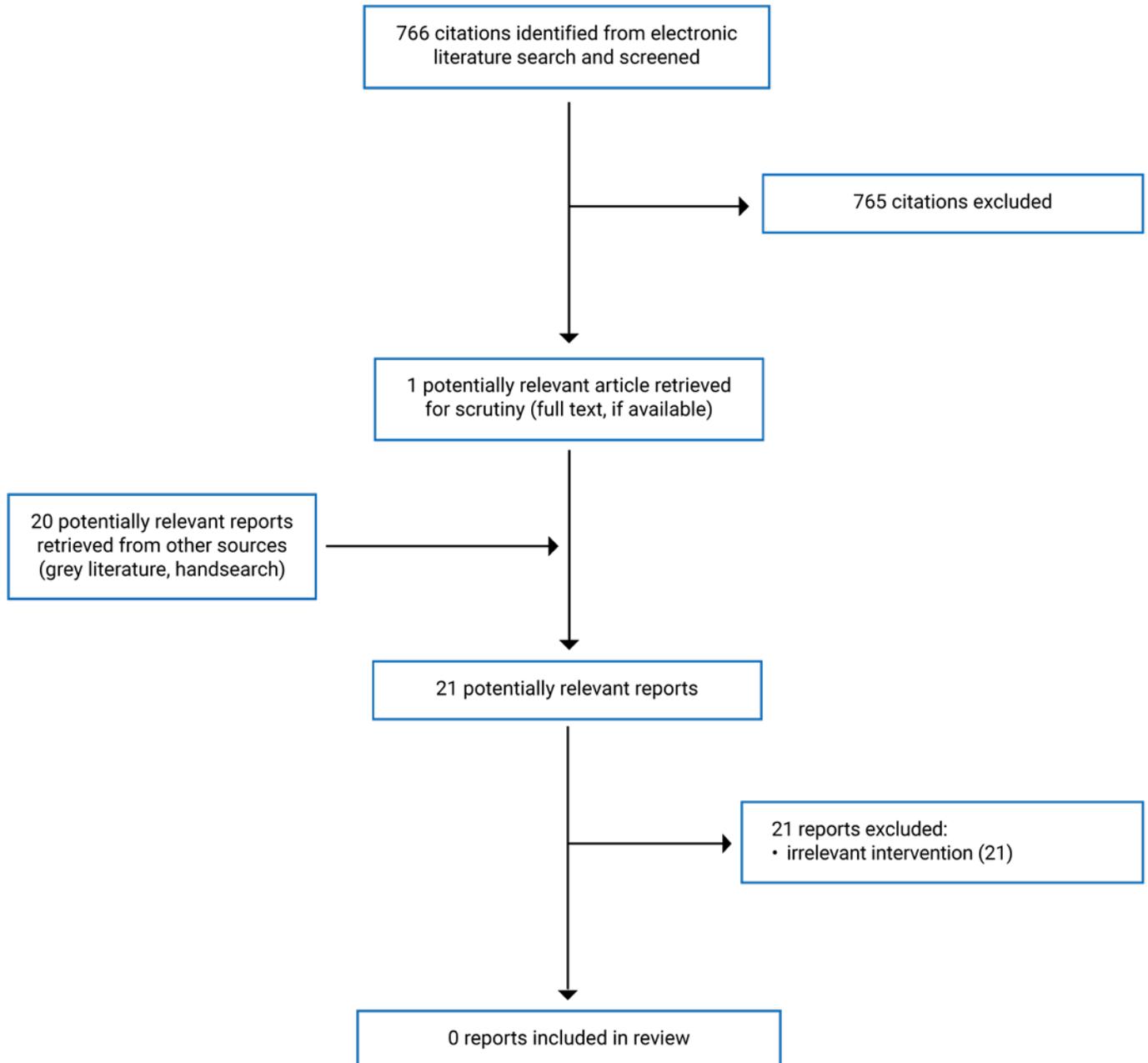
The lack of published evidence precludes the creation of appropriate guidance for health care providers to refer to for the care of this patient population. COVID-19 is an evolving landscape, and future preventive and treatment options may become available that could impact, alter, or expand concurrent or sequential administration of drugs.

References

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11. Evusheld: tixagevimab and cilgavimab injection solution, 100 mg/mL (tixagevimab) and 100 mg/mL (cilgavimab), intramuscular use, anti-SARS-CoV-2 spike protein monoclonal antibodies [product monograph]. Mississauga (ON): AstraZeneca Canada Inc; 2022: https://pdf.hres.ca/dpd_pm/00065403.PDF. Accessed 2022 Aug 2.
12. Paxlovid: nirmatrelvir tablets; ritonavir tablets, 150 mg nirmatrelvir; 100 mg ritonavir co-packaged for oral use [product monograph]. Kirkland (QC): Pfizer Canada ULC; 2022: https://pdf.hres.ca/dpd_pm/00066256.PDF. Accessed 2022 Aug 2.
13. Tamiflu: oseltamivir capsule, 30 mg, 45 mg and 75 mg oseltamivir (as oseltamivir phosphate), oseltamivir powder for oral suspension, 6 mg/mL oseltamivir (as oseltamivir phosphate) when reconstituted, antiviral agent [product monograph]. Mississauga (ON): Hoffmann-La Roche Limited; 2017: https://pdf.hres.ca/dpd_pm/00038482.PDF. Accessed 2022 Aug 2.

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: References of Potential Interest

Note that this appendix has not been copy-edited.

Guidelines and Recommendations

Concurrent or Sequential Treatment Not Specified

Agarwal A, Rochweg B, Lamontagne F, et al. A living WHO guideline on drugs for Covid-19. *BMJ* 2020;370:m3379. <https://www.bmj.com/content/bmj/370/bmj.m3379.full.pdf>. Accessed 2022 Jul 6. See: *Nirmatrelvir/ritonavir (Update 9, published 22 April 2022), pages 7 and 8.*

Review Articles

Rios P, Radhakrishnan A, Antony J, et al. Effectiveness and safety of antiviral or antibody treatments for coronavirus [non peer-reviewed preprint]. medRxiv; 2020: doi: [10.1101/2020.03.19.20039008](https://www.medrxiv.org/content/10.1101/2020.03.19.20039008). <https://www.medrxiv.org/content/10.1101/2020.03.19.20039008v2>. Accessed 2022 Jul 6.