

CADTH Health Technology Review

Oseltamivir for the Prevention of Influenza in Residents of Long-Term Care Facilities

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Key Messages

- The clinical effectiveness of oseltamivir for the prevention of influenza in residents of long-term care facilities compared to no prophylaxis is unclear. The evidence we identified is inconclusive due to limitations in the quality of studies.
- We did not find any evidence on the safety of oseltamivir for preventing influenza in long-term care facilities.
- We did not find any studies on the clinical effectiveness or safety of oseltamivir prophylaxis in long-term care facilities compared to placebo.

Context and Policy Issues

Influenza is a common acute viral respiratory infection caused by influenza viruses of the *Orthomyxoviridae* family.¹ Worldwide, influenza affects around a billion people every year, resulting in millions of hospitalizations.² In Canada, it is estimated that influenza results in approximately 3,500 deaths and more than 12,000 hospitalizations annually, making influenza a major public health concern² and 1 of the top 10 leading causes of death.³ The clinical spectrum of the symptoms and signs of influenza is wide, ranging from asymptomatic infections to severe cases resulting in respiratory, cardiac, gastrointestinal, and other complications, and death.¹ Residents of long-term care facilities, nursing homes, or other chronic care facilities are considered a high-risk group for influenza complications and death² because of their increased age, comorbidities, and shared living conditions.

While influenza is self-resolved and would not require medical care in most affected individuals, people in high-risk groups (e.g., residents of long-term care facilities, individuals with chronic health conditions, adults 65 years of age or older) may require medical care, and treatment.² Antiviral drugs such as neuraminidase inhibitors reduce the spread of the virus in the respiratory tract by blocking the release of progeny virions.¹ Oseltamivir, zanamivir, and peramivir are the neuraminidase inhibitors available for treatment and prophylaxis in Canada.² In addition to the seasonal influenza vaccines, pre- and post-exposure prophylaxis using antiviral drugs play an important role in controlling the spread of influenza outbreaks in the community, as well as high-risk settings like long-term care facilities.^{2,4} While prophylaxis with oseltamivir has been found to be protective against symptomatic influenza in community and household settings, the evidence in institutional settings such as long-term care facilities is sparse and unclear.^{4,5}

The purpose of this report is to summarize the evidence regarding clinical effectiveness of oseltamivir for the prevention of influenza in residents of long-term care facilities.

Research Question

What is the clinical effectiveness of oseltamivir for the prevention of influenza in residents of long-term care facilities?

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, and 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 oseltamivir, long-term care, and flu prevention. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was completed on October 13, 2022, and limited to English-language documents published since January 1, 2016.

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 2016. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded.⁶

Critical Appraisal of Individual Studies

The included publications were critically appraised by 1 reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)⁷ for systematic reviews, and the Downs and Black checklist⁸ for randomized and non-randomized studies. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Table 1: Selection Criteria

Criteria	Description
Population	Adults residing in long-term care facilities
Intervention	Oseltamivir administered as prophylaxis
Comparator	Placebo, no prophylaxis
Outcomes	Clinical benefits (e.g., influenza incidence, quality of life) and harms (e.g., neuropsychiatric events, adverse events)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

Summary of Evidence

Quantity of Research Available

A total of 371 citations were identified in the literature search. Following screening of titles and abstracts, 341 citations were excluded and 30 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of the potentially relevant articles, 26 publications were excluded for various reasons, while 4 publications met the inclusion criteria and were included in this report. These comprised 1 overview of reviews,⁹ 1 systematic review,¹⁰ and 2 non-randomized studies.^{11,12} Overview of reviews or “umbrella review” refers to evidence synthesis of existing systematic reviews.¹³ [Appendix 1](#) presents the PRISMA¹⁴ flow chart of the study selection.

Additional references of potential interest are provided in [Appendix 5](#).

Summary of Study Characteristics

One overview of reviews,⁹ 1 systematic review,¹⁰ and 2 non-randomized studies^{11,12} were included in this report. Characteristics of included studies are summarized in the following sections.

Both the overview of reviews⁹ and the systematic review¹⁰ had broader inclusion criteria than the present report. Specifically, they evaluated the clinical effectiveness of oseltamivir as treatment or prophylaxis for influenza in a general population (all individuals and settings). Residents of semi-closed or institutional settings (e.g., long-term care homes) were considered as a subgroup of interest in both publications.^{9,10} None of the included studies in the systematic review were conducted in the population and setting relevant to the current report.¹⁰ The overview of reviews identified 1 systematic review which evaluated the effectiveness of oseltamivir prophylaxis in long-term care home residents.⁹ Only the characteristics and results of the subset of relevant studies will be described in this report.

Additional details regarding the characteristics of included publications are provided in [Appendix 2](#).

Study Design

The overview of reviews by Doll et al.(2017)⁹ searched for systematic reviews and meta-analyses published from 1995 to 2015 across multiple electronic databases. They included 27 systematic reviews; among which 1 (Rainwater-Lovett et al. [2014]) was relevant to the current report.

The systematic review by Boikos et al. (2017)¹⁰ searched for randomized controlled trials and observational studies published from 2009 to 2015. Although 165 studies were included in the systematic review, none were conducted among residents of long-term care facilities.

The included primary studies were a prospective cohort study by Dronavalli et al. (2020)¹¹ and a retrospective cohort study by Shah et al. (2019).¹² Both studies were analyses of routinely collected administrative data from influenza outbreaks in long-term care facilities. The study period in the Dronavalli et al. study¹¹ was from 2015 to 2018, whereas the study period in the Shah et al.¹² study was the 2017 to 2018 influenza season.

Country of Origin

The authors of the overview of reviews⁹ and the systematic review¹⁰ were from Canada. The non-randomized studies were conducted in Australia¹¹ and England.¹²

Patient Population

All individuals (general population) were of interest in the overview of reviews.⁹ Residents of closed or semi-closed institutional settings, including residents of long-term care homes, were considered as a specific subgroup of priority. The number and characteristics of participants within the relevant systematic review (Rainwater-Lovett et al. [2014]) were not reported.⁹

The participant population in the non-randomized studies comprised residents of care homes¹² or aged care facilities¹¹ that had confirmed influenza outbreaks. In the Dronavalli et al.¹¹ study, 10,064 residents from 86 aged care facilities were included in the study. Among them, 4,395 (43.6%) received oseltamivir prophylaxis. In the study by Shah et al.,¹² 3,498 residents from 109 care homes were included in the study. Among them, 2,200 residents received oseltamivir prophylaxis. The demographic and clinical characteristics of the residents (e.g., age, sex, comorbid conditions such as malignancy or diabetes) were not reported in either study.^{11,12}

Interventions and Comparators

The intervention of interest in all included publications was oseltamivir prophylaxis.^{9,11,12}

The dose and frequency of the intervention was not reported in the overview of reviews.⁹ In the non-randomized study by Shah et al.,¹² oseltamivir prophylaxis was given within 36 to 48 hours of exposure for a duration of 10 days (based on the recommendation by Public Health England). The rate of adherence to these recommendations was unclear.¹² The timing, dose, frequency, and duration of oseltamivir prophylaxis given to the participants was not reported in the study by Dronavalli et al.¹¹

In all included publications, oseltamivir prophylaxis was compared to no prophylaxis.^{9,11,12}

Outcomes

The clinical effectiveness outcomes considered in the included publications were secondary transmission (1 overview of reviews),⁹ attack rate (2 non-randomized studies),^{11,12} oseltamivir prophylaxis failure (2 non-randomized studies),^{11,12} rate of hospitalization (1 non-randomized study),¹² and mortality (1 non-randomized study).¹² A definition for attack rate was not provided in the non-randomized studies;^{11,12} however, in epidemiological studies, attack rate has been defined as the proportion of individuals in a defined population who get infected during an outbreak.¹⁵ Dronavalli et al.¹¹ defined prophylaxis failure as the ratio of attack rate in residents who received oseltamivir prophylaxis to those who did not receive oseltamivir prophylaxis.

Although several safety outcomes were examined in the overview of reviews,⁹ results specific to the population of interest in the current report (residents of long-term care facilities) were not reported. Safety outcomes were not reported in the non-randomized studies.^{11,12}

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in [Appendix 3](#).

Overview of Reviews and Systematic Review

The objectives and inclusion criteria for the overview of reviews⁹ and the systematic review¹⁰ were clearly described. Population, intervention, comparators, and outcomes of interest were clear, and appropriate to the objective of the reviews. The methods of both publications were established a priori in the form of published protocol.^{9,10} There were some post hoc deviations from the protocol, which were justified. A comprehensive literature search was conducted to identify eligible studies. Multiple electronic databases and reference lists were searched. The search was performed within 24 months of completion of the publications.^{9,10} Study selection, data extraction, and quality assessment of the included primary studies¹⁰ (or individual systematic reviews, in the case of the Doll et al. overview⁹) was conducted by 2 independent reviewers. Discrepancies were resolved by discussion and a third reviewer. In the overview of reviews,⁹ the quality of the included systematic reviews was assessed using appropriate and validated tools, such as the AMSTAR questionnaire and the enhanced Overview Quality Assessment Questionnaire (eOQAQ). The Grading of Recommendations Assessment Development and Evaluation (GRADE) framework was used to assess the quality of evidence. In the systematic review,¹⁰ risk of bias in the primary studies was assessed using GRADE criteria. Domains such as randomization, allocation concealment, blinding, selection bias, and residual confounding were considered while evaluating the quality of the studies. Neither publication conducted a quantitative synthesis of evidence considering the possible heterogeneity across the individual studies.^{9,10} Results of the qualitative synthesis were reported clearly in both publications. Limitations of the review were discussed, and conclusions were reported with appropriate caveats.^{9,10} The overview of reviews by Doll et al.⁹ had some additional strengths specific to the methodology of overview. The authors used a clear definition of systematic reviews. A reproducible literature search, selection flow chart, and quality assessment of primary studies was considered in defining systematic reviews. Overlap of primary studies across the included systematic reviews was examined and presented using an overlap matrix table. Individual systematic reviews with complete overlap of primary studies with others were excluded. There were no informal indirect comparisons of results across different systematic reviews.⁹

The overview⁹ had some limitations as well. Although the authors examined the overlap of primary studies across the systematic reviews, and those with complete overlap were excluded from the overview, there was still up to 35% overlap across primary studies. Because of this, it is possible that aggregate results of narrative synthesis were drawn from data counted two or more times. The detailed characteristics of each included systematic reviews were not reported. Results or conclusions from all included systematic reviews were also not provided. Lastly, the quality of the primary studies across the included systematic reviews was unclear. Methodological limitations of the randomized controlled trials and observational studies would affect the overall validity of the results of the overview.⁹ The main limitation of the systematic review by Boikos and colleagues¹⁰ was that the detailed characteristics and results of included primary studies were not reported. However, considering that they included 165 primary studies, the omission could be due to publication constraints. It was also unclear whether publication biases and their sources (if any) were explored. Sources of funding for individual studies were also not reported.¹⁰ Overall, the included overview of reviews and systematic review were of moderate to high quality, and well designed with detailed reporting.^{9,10}

Non-Randomized Studies

The 2 non-randomized studies^{11,12} were epidemiological outbreak control cohort studies using secondary administrative data from long-term care facilities in Australia¹¹ and England¹².

The study objectives were clear, and the outcomes of interest were appropriate and clearly defined. It is likely that the staff, places, and facilities where the residents lived were representative of the care that the majority of patients receive.^{11,12}

The studies had several limitations. Since the studies were conducted using administrative data, all residents of care homes that had an influenza outbreak were included in the analysis. There was no randomized allocation, allocation concealment, or blinding of participants. The baseline demographic or clinical characteristics of study participants were not reported. It was unknown whether potential confounding factors such as age, comorbidities (e.g., malignancy, diabetes), or vaccination status were balanced between participants in the intervention and comparator groups.^{11,12} This could introduce confounding bias. The frequency, dosage, and timing of oseltamivir prophylaxis given to the participants was not reported in 1 study.¹¹ The timing and duration of prophylaxis was reported in the other study.¹² However, the individual compliance to the medication was unknown.^{11,12} Adverse events related to oseltamivir prophylaxis were not reported in either study.^{11,12} It was unclear whether data on adverse events were captured in the respective administrative databases. There were several reporting issues in the study by Dronavalli et al.,¹¹ such as inconsistent reporting of numerical data and possible percentage calculation errors. For example, the authors reported that the rate of prescribing oseltamivir prophylaxis was 54%; however, it was also reported elsewhere that 4,392 residents out of 10,064 total residents received oseltamivir prophylaxis, which is 43.6%.¹¹ These inconsistencies in reporting lowered the internal validity of the findings. Since the intervention group (oseltamivir prophylaxis group) was defined based on exposure to prophylaxis (oseltamivir), there was a risk of immortal time bias, which was not corrected in the study with a time-dependent variable. Immortal time bias occurs when, by design, participants in the exposed group are considered immortal before the exposure to intervention, since they must survive to receive the intervention and be included in the intervention group.¹⁶ As a result of the incorrect management of immortal time, the benefit of oseltamivir prophylaxis may be overestimated in all of the comparisons. Overall, the non-randomized studies were of low quality due to several major limitations.^{11,12}

Summary of Findings

[Appendix 4](#) presents the main study findings.

Clinical Effectiveness of Oseltamivir Prophylaxis Versus No Prophylaxis

Secondary Transmission

The overview of reviews by Doll et al.⁹ reported results from a systematic review (Rainwater-Lovett et al. [2014]) regarding the effectiveness of oseltamivir prophylaxis in long-term care facilities for the outcome secondary transmission. There were no significant differences in secondary transmission of influenza between residents who received oseltamivir prophylaxis and the residents who did not receive prophylaxis. The results were similar (no significant difference) for different influenza types (influenza A alone, as well as influenza A or B). The analysis was not stratified based on pre-exposure or post-exposure prophylaxis.

There were 10 primary studies in the systematic review by Rainwater-Lovett et al.(2014); however, the number of participants across those studies was unclear.⁹ Doll et al. reported that the quality of evidence from this systematic review was lowered due to some concerns regarding risk of bias and imprecision.⁹

Attack Rate

Two non-randomized studies^{11,12} reported results regarding attack rate, which is the proportion of individuals in a defined population who get infected during an outbreak.

Dronavalli et al.¹¹ found that the attack rate in aged care facilities that used oseltamivir prophylaxis was 17% lower than in facilities where no antiviral prophylaxis was used (1.9% versus 18.9%). The number needed to treat to prevent 1 influenza case was 6. However, results of a between-groups statistical comparison were not reported; therefore, it is unclear whether this difference in rates is statistically significant. Results from the non-randomized study by Shah et al.¹² (N = 3,498) showed that the attack rate in the oseltamivir prophylaxis group was significantly higher than in the no prophylaxis group (27% versus 20.1%; $P < 0.001$). In both studies, instances of influenza-like illnesses were counted when calculating the attack rate. It is unclear how many cases were laboratory-confirmed in the Shah et al. study.¹² The inconsistency in these findings could be due to multiple reasons, including: methodological limitations such as confounding bias, patient compliance to prophylactic medication being unclear, limited quality of the data source, or poor definition of influenza cases resulting in possible overestimation.

Oseltamivir Prophylaxis Failure

Oseltamivir prophylaxis failure, defined as the ratio of attack rates in residents who received oseltamivir prophylaxis to those who did not, was calculated and reported by Dronavalli et al.¹¹ The risk ratio of oseltamivir prophylaxis failure was 0.10 (95% CI, 0.08 to 0.12), suggesting that the use of the antiviral drug was associated with a 90% prevention of influenza cases.

When calculated at the facility level (instead of the patient level), it was found that the risk of oseltamivir prophylaxis failure was statistically significantly higher in aged care facilities with a higher prophylactic use.¹¹ The authors proposed that this could be because of confounding by indication. Confounding by indication occurs when there is a bias in the intervention–outcome relationship due to the indication for intervention.^{17,18} For example, oseltamivir prophylaxis use in the facilities was dictated by outbreak; a more severe outbreak could mean a higher uptake of prophylaxis. A severe outbreak could also result in spread of infection to more individuals, which would affect the outcome attack rate. Validity of facility-level results are further reduced by the likely differences in resident population such as age and comorbidities, and factors such as size, infrastructure, staff, and quality ranking of the long-term care facilities. Results of an analysis adjusting for these factors were not reported.¹¹

Rate of Hospitalization

Rate of hospitalization was reported in 1 non-randomized study of 3,498 participants.¹² There was no difference in hospitalization rates due to influenza-related illness between patients who received oseltamivir prophylaxis and patients who did not.

Mortality

Death due to influenza-like illness was reported in 1 non-randomized study of 3,498 participants.¹² There was no difference in death rates due to influenza-related illness between patients who received oseltamivir prophylaxis and patients who did not.

Harms

No relevant evidence was identified regarding the harms of oseltamivir prophylaxis compared to no prophylaxis among residents of long-term care facilities; therefore, no summary can be provided.

In their overview of reviews, Doll et al.⁹ found that treatment or prophylaxis with neuraminidase inhibitors (e.g., oseltamivir, zanamivir) was not associated with a higher risk of adverse events or serious adverse events in the general population. There was a higher risk of side effects such as nausea and vomiting, and a lower risk of diarrhea, associated with oseltamivir use. The authors were inconclusive about the association between neuraminidase inhibitors and neuropsychiatric side effects. However, it should be noted that these conclusions were for a general population in all settings. Harms outcomes specifically in long-term care home settings were not reported.

Clinical Effectiveness of Oseltamivir Prophylaxis Versus Placebo

No relevant evidence was identified regarding the clinical effectiveness of oseltamivir prophylaxis compared to placebo among residents of long-term care facilities; therefore, no summary can be provided.

Limitations

The findings of this report should be interpreted in light of the limitations. Relevant evidence from the overview of reviews⁹ was limited to 1 systematic review. No relevant studies were included in the systematic review by Boikos et al.¹⁰ Although these publications were of moderate to high quality, very little relevant evidence was included in them.^{9,10} The 2 non-randomized studies^{11,12} had several major methodological limitations, as described in the Summary of Critical Appraisal section. Therefore, a lack of good-quality evidence regarding the clinical effectiveness of oseltamivir for preventing influenza among residents of long-term care facilities was the main limitation of this report.

No evidence regarding oseltamivir prophylaxis compared to placebo in the setting of long-term care facilities was found. No relevant evidence regarding the harms or safety of oseltamivir prophylaxis compared to no prophylaxis or placebo among residents of long-term care facilities was identified. It was unclear whether the evidence from the overview of reviews⁹ was based on studies conducted in Canada. The 2 non-randomized studies were conducted in Australia¹¹ and England¹²; therefore, the generalizability of the findings to Canadian settings is not clear.

Conclusions and Implications for Decision- or Policy-Making

One overview of reviews,⁹ 1 systematic review,¹⁰ and 2 non-randomized studies^{11,12} regarding the clinical effectiveness of oseltamivir prophylaxis in residents of long-term care facilities were included in this report. The overview of reviews⁹ and the systematic review¹⁰ were of moderate to high quality, while the 2 non-randomized studies^{11,12} had several major methodological limitations. Since the systematic review¹⁰ did not include any relevant primary studies, evidence from the overview of reviews⁹ and the non-randomized studies^{11,12} were summarized in this report. A systematic review (included in the overview of reviews⁹) found no differences in the secondary transmission of influenza between long-term care home

residents who received oseltamivir prophylaxis and residents who did not receive oseltamivir prophylaxis. Evidence from 1 non-randomized study¹¹ suggested that oseltamivir prophylaxis was associated with a prevention of 90% of influenza cases compared to no prophylaxis. However, due to probable confounding bias, immortal time bias, and methodological limitations, the validity of the results is very low. The evidence regarding the effectiveness of oseltamivir prophylaxis on attack rate (proportion of individuals in a defined population who get infected during an outbreak) of influenza was inconsistent and very uncertain.^{11,12} A non-randomized study found no differences in hospitalization rates and mortality due to influenza-like illness between residents who received oseltamivir prophylaxis and those who did not receive oseltamivir prophylaxis.¹² No evidence regarding harms of oseltamivir prophylaxis compared to no prophylaxis among residents of long-term care facilities was identified. No evidence regarding the clinical effectiveness and harms of oseltamivir prophylaxis compared to placebo among residents of long-term care facilities was identified.

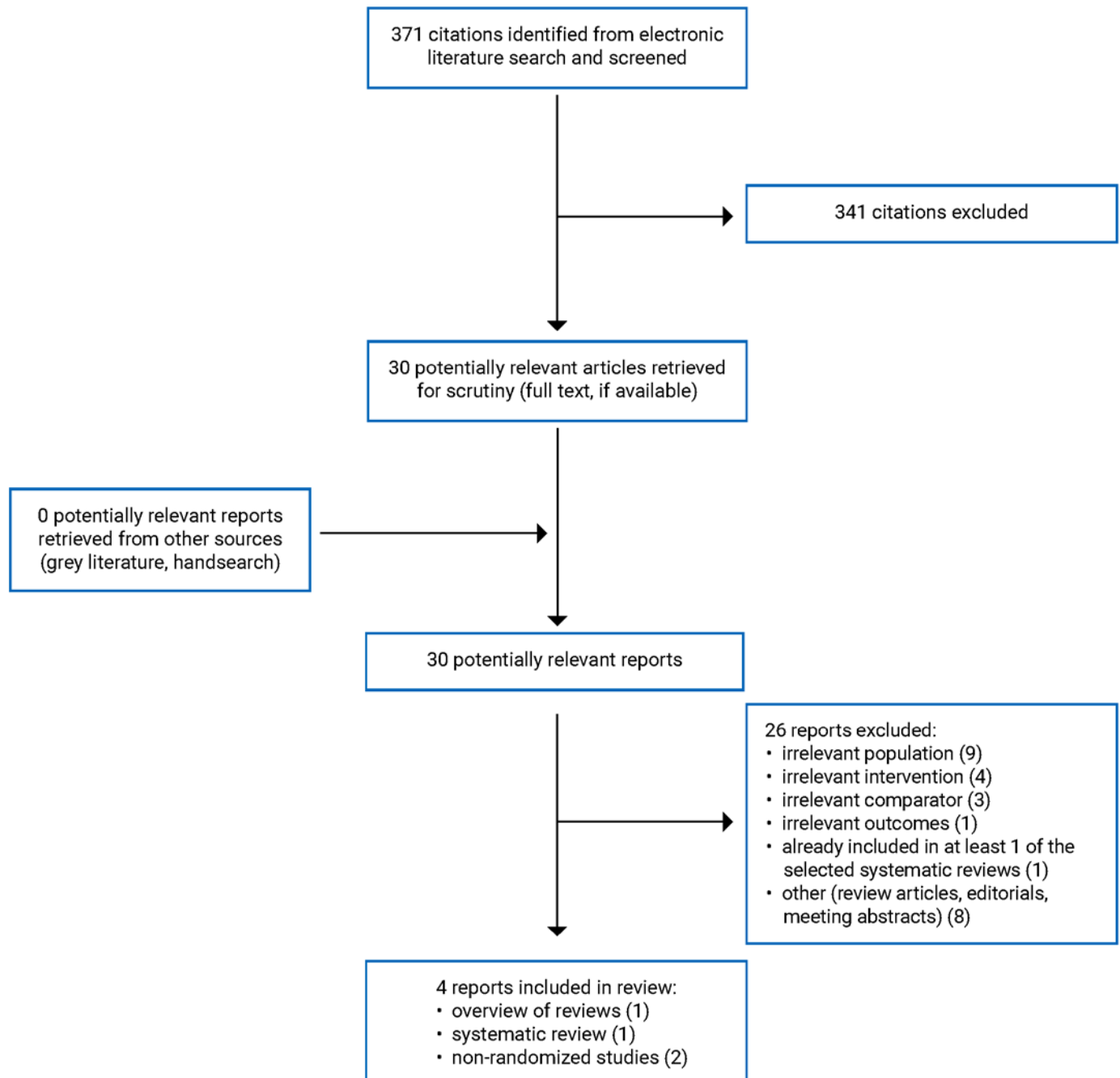
Influenza is a major public health concern associated with significant clinical¹ and economic implications.¹⁹ This report highlights the lack of high-quality studies appropriately designed to examine the effectiveness of oseltamivir prophylaxis in long-term care home settings. A CADTH report published in 2017 concluded that oseltamivir was effective in preventing influenza in a general population.²⁰ Considering the risk of neuropsychiatric²¹ and other serious adverse events associated with oseltamivir, the decision to use oseltamivir in high-risk populations should be based on a risk–benefit analysis. Well-designed future studies are warranted in this population to assess the clinical effectiveness and safety of oseltamivir prophylaxis.

References

1. Uyeki TM, Hui DS, Zambon M, Wentworth DE, Monto AS. Influenza. *Lancet (London, England)*. 2022;400(10353):693-706. [PubMed](#)
2. Government of Canada. Flu (influenza): For health professionals 2022; <https://www.canada.ca/en/public-health/services/diseases/flu-influenza/health-professionals.html>. Accessed 2022 Nov 7.
3. Canada S. Deaths, 2019. 2020; <https://www150.statcan.gc.ca/n1/daily-quotidien/201126/dq201126b-eng.htm>. Accessed 2022 Nov 8.
4. Lansbury LE, Brown CS, Nguyen-Van-Tam JS. Influenza in long-term care facilities. *Influenza and other Respiratory Viruses*. 2017;11(5):356-366. [PubMed](#)
5. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America*. 2019;68(6):e1-e47. [PubMed](#)
6. Yuan Y, Wang RT, Xia J, Cao HJ. Interventions for preventing influenza: An overview of Cochrane systematic reviews and a Bayesian network meta-analysis. *J*. 2021;19(6):503-514.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. [PubMed](#)
8. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384. [PubMed](#)
9. Doll MK, Winters N, Boikos C, Kraicer-Melamed H, Gore G, Quach C. Safety and effectiveness of neuraminidase inhibitors for influenza treatment, prophylaxis, and outbreak control: a systematic review of systematic reviews and/or meta-analyses. *Journal of Antimicrobial Chemotherapy*. 2017;72(11):2990-3007. [PubMed](#)
10. Boikos C, Caya C, Doll MK, et al. Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009-15. *Journal of Antimicrobial Chemotherapy*. 2017;72(6):1556-1573. [PubMed](#)
11. Dronavalli M, Lord H, Alexander K, Boonwaat L, Pal N, Fletcher-Lartey SM. Effectiveness of Oseltamivir Prophylaxis in Influenza Outbreaks in Residential Aged Care. *J Epidemiol Glob Health*. 2020;10(2):184-189. [PubMed](#)
12. Shah A, Harries AD, Cleary P, McGivern M, Ghebrehewet S. Use of prophylactic antivirals and care home characteristics associated with influenza in care homes with confirmed outbreaks. *Public Health*. 2019;177:48-56. [PubMed](#)
13. Pollock M FR, Becker LA, Pieper D, Hartling L. Chapter V: Overviews of Reviews. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, ed. *Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022)*: Cochrane; 2022.
14. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol*. 2009;62(10):e1-e34. [PubMed](#)
15. Centers for Disease Control and Prevention. Principles of epidemiology in public health practice: centers for disease control and prevention. 2012; <https://www.cdc.gov/csels/dsepd/ss1978/glossary.html>. Accessed 2022 Nov 7.
16. Catalogue of Bias Collaboration. Immortal time bias. 2020; <https://catalogofbias.org/biases/immortal-time-bias/>. Accessed 2022 Nov 7.
17. Joseph KS, Mehrabadi A, Lisonkova S. Confounding by Indication and Related Concepts. *Current Epidemiology Reports*. 2014;1(1):1-8.
18. Catalogue of Bias Collaboration. Confounding by indication. 2018; <https://catalogofbias.org/biases/confounding-by-indication>. Accessed 2022 Nov 7.
19. de Courville C, Cadarette SM, Wissinger E, Alvarez FP. The economic burden of influenza among adults aged 18 to 64: A systematic literature review. *Influenza and Other Respiratory Viruses*. 2022;16(3):376-385. [PubMed](#)
20. The use of antivirals for influenza prophylaxis: a review of the clinical effectiveness. Ottawa (ON): CADTH; 2017: <https://www.cadth.ca/use-antivirals-influenza-prophylaxis-review-clinical-effectiveness>. Accessed 2022 Nov 7.
21. Zareifopoulos N, Lagadinou M, Karela A, Kyriakopoulou O, Velissaris D. Neuropsychiatric Effects of Antiviral Drugs. *Cureus*. 2020;12(8):e9536-e9536. [PubMed](#)

Appendix 1: Selection of Included Studies

Figure 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Note that this appendix has not been copy-edited.

Table 2: Characteristics of Included Overview of Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Doll et al. (2017) ⁹ Canada Funding source: Public Health Agency of Canada (PHAC), Canadian Pandemic Influenza Preparedness Task Group (CPIP-TG)	Overview of SRs Number of SRs included: 27 Number of relevant SRs: 1 SR	All individuals (general population). Relevant to the current report, subgroups of priority included closed or semi-closed institutional settings (e.g., long-term care facilities)	Eligible intervention: All types of NIs for prevention and treatment of influenza Relevant intervention: Oseltamivir prophylaxis Eligible comparator: Another NI, standard care alone, no treatment, or placebo Relevant comparator: No treatment, placebo	Outcomes: Secondary transmission of symptomatic and asymptomatic influenza, safety (e.g., adverse events, psychiatric events, diarrhea)

NI = neuraminidase inhibitor; SR = systematic review.

Table 3: Characteristics of Included Systematic Review

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Boikos et al. (2017) ¹⁰ Canada Funding source: Public Health Agency of Canada	Systematic review of RCTs and observational studies Number of studies included: 165 Number of relevant primary studies: None	All individuals (general population). Relevant to the current report, subgroups of priority included closed or semi-closed institutional settings (e.g., long-term care facilities)	Eligible intervention: All types of NIs for prevention and treatment of influenza Relevant intervention: Oseltamivir prophylaxis Eligible comparator: Another NI, standard care alone, no treatment, or placebo Relevant comparator: No treatment, placebo	Outcomes: Secondary transmission of symptomatic and asymptomatic influenza, safety (e.g., adverse events), viral shedding, resistance development

NI = neuraminidase inhibitor; RCT = randomized controlled trial.

Table 4: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design and setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Dronavalli et al. (2020) ¹¹ Australia Funding source: Not funded	Prospective cohort study of administrative data Setting: Aged care facilities in a local health district in NSW, Australia Period: 2015 to 2018	Residents in aged care facility Number of residents: 10,064 Number of facilities = 86 Mean number of residents per facility = 117 (range 14 to 476) Oseltamivir prophylaxis, n = 4,392 (reported as 54%, possible calculation error in the publication) No prophylaxis, n = 5,672 Mean vaccination rates across the aged care facilities, % = 88% (SD 18%)	Intervention: Oseltamivir prophylaxis Comparator: No prophylaxis	Outcomes: Prophylaxis failure, attack rate, outbreak duration, death, hospitalization rates
Shah et al. (2019) ¹² UK Funding source: Not funded	Retrospective cohort study using routinely collected data Setting: Long-term care facilities (care homes) that had a confirmed influenza outbreak in the Cheshire and Merseyside, and Cumbria and Lancashire areas of England Period: 2017 to 2018 influenza season	Residents in care homes Number of residents: 3,498 Number of facilities = 109 Oseltamivir prophylaxis, n = 2,200 No Prophylaxis, n = 1,298	Intervention: Antiviral prophylaxis (oseltamivir for 10 days) Comparator: No prophylaxis	Outcomes: Attack rate, mortality, hospitalization rate

NSW = New South Wales; SD = standard deviation.

Appendix 3: Critical Appraisal of Included Publications

Note that this appendix has not been copy-edited.

Table 5: Strengths and Limitations of Overview of Reviews Using AMSTAR 2⁷

Strengths	Limitations
Doll et al. (2017)⁹	
<p>The research questions and inclusion criteria for the review were clearly reported. Population, intervention, comparators, and outcomes of interest were appropriate to the objective of the overview.</p> <p>The protocol for the overview methods were published a priori. They were available for review. Some deviations related to subgroups for interest were made, but they were reasonable and justified in the publication.</p> <p>A comprehensive literature search was conducted to identify eligible studies. Multiple electronic databases were searched. Reference lists were hand-searched for other potentially relevant articles. Search was conducted within 24 months of publications of the overview.</p> <p>SRs with or without meta-analyses were eligible for inclusion. SRs were defined as those with a systematic database search, selection flow chart and a quality assessment. Reasonable exclusion criteria were provided.</p> <p>Overlap in primary studies across the included SRs were examined. The authors included an overlap matrix. SRs in which all primary studies were covered in 1 or more of other included SRs were excluded from the overview.</p> <p>Quality of the included SRs were assessed using the AMSTAR tool and the eOQAQ tool. GRADE framework was used to assess the quality of evidence. Quality assessment of the included SRs were reported clearly.</p> <p>Study selection, data extraction, and quality assessment of the included SRs were conducted by 2 independent reviewers. Discrepancies were resolved by discussion and a third reviewer.</p> <p>A quantitative synthesis (meta-analysis) was not conducted considering the possible heterogeneity and overlap of primary studies. The rationale was appropriate.</p> <p>Informal indirect comparisons across the SRs were not conducted.</p> <p>Results of the qualitative synthesis were reported clearly. Limitations of the review were discussed. Conclusions were reported with appropriate caveats.</p>	<p>Even though the authors examined the overlap of primary studies across the SRs and those with complete overlap was excluded from the overview, there were still up to 35% overlap of primary studies. Because of this, it is possible that summary estimates maybe from the same data.</p> <p>The detailed characteristics of each included SR were not reported. Results or conclusions from all included SRs were also not provided.</p> <p>A list of excluded studies, and reason for exclusion, was provided.</p> <p>The quality of the primary studies across the included SRs were unclear. Methodological limitations of the RCTs and observational studies would affect the overall validity of the results of the overview.</p>

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; eOQAQ = enhanced Overview Quality Assessment Questionnaire; GRADE = Grading of Recommendations Assessment Development and Evaluation; RCT = randomized controlled trial; SR = systematic review.

Table 6: Strengths and Limitations of Systematic Review Using AMSTAR 2⁷

Strengths	Limitations
Boikos et al. (2017)¹⁰	
<p>The research questions and inclusion criteria for the review were clearly reported. Population, intervention, comparators, and outcomes of interest were appropriate to the objective of the SR.</p> <p>The protocol for the overview methods was published a priori. Some deviations related to subgroups for interest were made, but they were reasonable and justified in the publication.</p> <p>A comprehensive literature search was conducted to identify eligible studies. Multiple electronic databases were searched. Reference lists were hand-searched for other potentially relevant articles. Search was conducted within 24 months of publications of the overview. Search strategy was reported. Publication restrictions were reasonable.</p> <p>Study selection, data extraction, and quality assessment of the included studies was conducted in duplicate by 2 reviewers. Discrepancies were resolved through consensus or with the help of a third reviewer.</p> <p>A list of excluded studies, and reason for exclusion, was provided.</p> <p>Risk of bias in the included studies was assessed using the GRADE criteria. Domains such as randomization, allocation concealment, blinding, selection bias, and residual confounding were considered while evaluating the quality of the studies.</p> <p>A quantitative synthesis (meta-analysis) was not conducted considering the possible heterogeneity in the included studies. The rationale was appropriate.</p> <p>Results of the qualitative synthesis were reported clearly. Limitations of the review were discussed. Conclusions were reported with appropriate caveats.</p> <p>The authors reported that there were no potential conflicts of interests.</p>	<p>RCTs and observational studies were eligible for inclusion. However, an explanation for including both these study designs were not provided.</p> <p>Detailed characteristics of included studies were not provided. Results or conclusions from all included primary studies were also not provided.</p> <p>Funding sources of individual studies were not reported.</p> <p>Publication bias was not evaluated.</p>

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; GRADE = Grading of Recommendations Assessment Development and Evaluation; RCT = randomized controlled trial; SR = systematic review.

Table 7: Strengths and Limitations of Clinical Studies Using the Downs and Black Checklist⁸

Strengths	Limitations
Dronavalli et al. (2020)¹¹	
<p>The objective of the study was clearly described.</p> <p>The study outcomes were described in the methods section. They were valid and appropriate for the study objective.</p> <p>Results of univariate regression analysis were reported. Analysis was conducted using Poisson regression, which was appropriate. Effect estimates along with confidence intervals and P values were reported.</p> <p>All participants in the cohort were recruited over the same period of time.</p> <p>It is likely that the staff, places, and facilities where the residents lived were representative of the care that the majority of patients receive.</p>	<p>This was a non-randomized study using prospective administrative data. Therefore, all residents in aged care facilities were included. No specific exclusion criteria were applied. There was no randomization or blinding.</p> <p>The baseline characteristics of participants were not reported. Distribution of possible confounding factors like age, comorbidities, or vaccination status across the groups were not reported. This could introduce confounding bias. Results of the adjusted analysis, if conducted, were not available in the publication.</p> <p>The frequency and dose of oseltamivir prophylaxis given to the residents was unclear. Individual compliance to the medication was not reported. This could affect the internal validity of the results.</p> <p>Adverse events that may have been a consequence of oseltamivir prophylaxis were not reported. It was unclear whether data on adverse events was captured in the administrative database.</p> <p>All residents in the database were included in the analysis. It was unclear whether anyone was excluded from the database from being lost to follow-up.</p> <p>Since the intervention group (oseltamivir prophylaxis group) was defined based on exposure to prophylaxis (oseltamivir), there was a risk of immortal time bias which was not corrected in the study with a time dependent variable. Immortal time bias occurs when by design, participants in the exposed group are considered immortal before the exposure to intervention, since they must survive to receive the intervention and be included in the intervention group. As a result of the incorrect management of immortal time, the benefit of oseltamivir prophylaxis may be overestimated in all of the comparisons.</p>
Shah et al. (2019)¹²	
<p>The objective of the study was clearly described.</p> <p>The study outcomes were valid and appropriate for the study objective.</p> <p>Frequency of oseltamivir given as prophylaxis was reported.</p> <p>Results of univariate regression analysis was reported. Analysis was conducted using Poisson regression, which was appropriate. Effect estimates along with confidence intervals and P values were reported.</p> <p>All participants in the cohort were recruited over the same period of time.</p> <p>It is likely that the staff, places, and facilities where the</p>	<p>This was a retrospective observational study using administrative data. Therefore, all residents in aged care facilities were included. No specific exclusion criteria were applied. There was no randomization or blinding.</p> <p>The baseline characteristics of participants were not reported, rather they were reported at the facilities level. Distribution of possible confounding factors like age, comorbidities, or vaccination status across the groups was not reported. This could introduce confounding bias. Results of the adjusted analysis, if conducted, were not available in the publication.</p> <p>Frequency of oseltamivir given as prophylaxis was reported. However, individual compliance to the medication was not reported. This could affect the internal validity of the results.</p>

Strengths	Limitations
<p>residents lived were representative of the care majority of patients receive.</p>	<p>Adverse events that may have been a consequence of oseltamivir prophylaxis were not reported. It was unclear whether data on adverse events were captured in the administrative database.</p> <p>All residents in the database were included in the analysis. It was unclear whether anyone was excluded from the database from being lost to follow-up.</p> <p>Since the intervention group (oseltamivir prophylaxis group) was defined based on exposure to prophylaxis (oseltamivir), there was a risk of immortal time bias which was not corrected in the study with a time dependent variable. Immortal time bias occurs when by design, participants in the exposed group are considered immortal before the exposure to intervention, since they must survive to receive the intervention and be included in the intervention group. As a result of the incorrect management of immortal time, the benefit of oseltamivir prophylaxis may be overestimated in all of the comparisons.</p>

Appendix 4: Main Study Findings

Note that this appendix has not been copy-edited.

Table 8: Summary of Findings by Outcome – Secondary Transmission

Study citation and study design	Result
Doll et al. (2017) ⁹ Overview of reviews	<p>One SR (Rainwater-Lovett et al. [2014]) reported results regarding oseltamivir prophylaxis in outbreak settings in long-term care facilities.</p> <p>Secondary transmission of influenza, compared to no prophylaxis</p> <p>Influenza A alone: OR = 1.55 (95% CI, 0.62 to 3.98)</p> <p>Influenza A or B: OR = 1.27 (95% CI 0.56 to 2.76)</p> <p>However, the analysis was not stratified based on pre-exposure or post-exposure prophylaxis.</p> <p>Two SRs included in the review included at least 1 primary study conducted in a non-community setting, such as long-term care facilities, elderly residential homes, or a health care setting. Results from these SRs showed that pre-exposure or post-exposure prophylaxis with oseltamivir “consistently and significantly lowered the odds or risk of symptomatic influenza.” Prophylaxis with oseltamivir or zanamivir “did not reduce the odds or risk of secondary transmission of asymptomatic influenza.” Since data were not reported from either of these SRs, independent corroboration of this findings could not be conducted.</p>

CI = confidence interval; OR = odds ratio; SR = systematic review.

Table 9: Summary of Findings by Outcome – Attack Rate

Study citation and study design	Result
Dronavalli et al. (2020) ¹¹ Prospective cohort study	<p>Total number of residents, N = 10,064</p> <p>Attack rate, n (%)</p> <p>Oseltamivir prophylaxis group = 810 out of 4,392 (1.9%)</p> <p>No prophylaxis group: 1070 out of 5,672 (18.9%)</p> <p>ARR = 17%, statistical significance NR</p> <p>NNT = 6</p>
Shah et al. (2019) ¹² Retrospective cohort study	<p>Total number of residents, N = 3,498</p> <p>Attack rate, n (%)</p> <p>Oseltamivir prophylaxis group = 594 (27%)</p> <p>No prophylaxis group: 261 (20.1%)</p> <p>P < 0.001</p>

ARR = absolute risk reduction; NNT = number needed to treat; NA = not applicable; NR = not reported.

Table 10: Summary of Findings by Outcome – Oseltamivir Prophylaxis Failure

Study citation and study design	Result
Dronavalli et al. (2020) ¹¹ Prospective cohort study	<p>Total number of residents, N = 10,064</p> <p>OP failure at resident level:</p> <p>Risk Ratio of OP failure: 0.10 (95% CI, 0.08 to 0.12); P < 0.0001</p> <p>OP failure at aged care facility level:</p> <p>Risk Ratio of OP failure: 6.5 (95% CI, 2.86 to 14.77); P < 0.0001</p> <p>Increased risk of OP failure in facilities with high prophylaxis utilization rate.</p> <p>OP in aged care facilities with dementia wards:</p> <p>Compared to aged care facilities without dementia wards, those with dementia wards had 44% “lower OP failure rates.” Data NR.</p> <p>OP in high-care only aged care facilities:</p> <p>Compared to other aged care facilities, facilities exclusively providing high care had “87% lower” OP failure “indicating oseltamivir was more effective in preventing clinical cases in the high care setting” (p. 187).¹¹ Data NR.</p>

CI = confidence interval; NR = not reported; OP = oseltamivir prophylaxis.

Table 11: Summary of Findings by Outcome – Rate of Hospitalization

Study citation and study design	Result
Shah et al. (2019) ¹² Retrospective cohort study	<p>Total number of residents, N = 3,498</p> <p>Hospitalization rate due to influenza related illness, n (%):</p> <p>Oseltamivir prophylaxis group = 120 (5.5%)</p> <p>No prophylaxis group: 70 (5.4)</p> <p>P = 0.94</p>

Table 12: Summary of Findings by Outcome – Mortality

Study citation and study design	Result
Shah et al. (2019) ¹² Retrospective cohort study	<p>Total number of residents, N = 3,498</p> <p>Death due to influenza related illness, n (%):</p> <p>Oseltamivir prophylaxis group = 10 (0.45)</p> <p>No prophylaxis group: 10 (0.77)</p> <p>P = 0.23</p>

Appendix 5: References of Potential Interest

Note that this appendix has not been copy-edited.

Previous CADTH Reports

The Use of Antivirals for Influenza Prophylaxis: A Review of the Clinical Effectiveness. Ottawa (ON): CADTH. 2017. <https://www.cadth.ca/use-antivirals-influenza-prophylaxis-review-clinical-effectiveness> Accessed 2022 Nov 8

Systematic Reviews

Heneghan CJ, Onakpoya I, Jones MA, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Assess.* 2016;20(42):1-242. [PubMed](#)

Non-Randomized Studies

Cheng HY, Chen WC, Chou YJ, Huang ASE, Huang WT. Containing influenza outbreaks with antiviral use in long-term care facilities in Taiwan, 2008-2014. *Influenza Other Respi Viruses.* 2018;12(2):287-292. [PubMed](#)

Singh D, Jiang D, Van Caesele P, Loepky C. The effect of timing of oseltamivir chemoprophylaxis in controlling influenza A H3N2 outbreaks in long-term care facilities in Manitoba, Canada, 2014-2015: a retrospective cohort study. *Infect Control Hosp Epidemiol.* 2018;39(8):955-960. [PubMed](#)

Ye M, Jacobs A, Khan MN, et al. Evaluation of the use of oseltamivir prophylaxis in the control of influenza outbreaks in long-term care facilities in Alberta, Canada: a retrospective provincial database analysis. *BMJ Open.* 2016;6(7):e011686. [PubMed](#)

Jones M, Tett SE, Del Mar C. Psychiatric adverse events in oseltamivir prophylaxis trials: Novel comparative analysis using data obtained from clinical study reports. *Pharmacoepidemiol Drug Saf.* 2018;27(11):1217-1222. [PubMed](#)

Yip JLY, Kapadia S, Ahmed A, Millership S. Outbreaks of influenza-like illness in care homes in the East of England: impact of variations in neuraminidase inhibitor provision. *Public Health.* 2018;162:98-103. [PubMed](#)

Guidelines and Practice Recommendations

Guidelines for the use of Oseltamivir in Long Term Care Facilities. Winnipeg (MB): Winnipeg Regional Health Authority. 2021. <https://professionals.wrha.mb.ca/old/extranet/ipc/files/guideline-use-of-oseltamivir-in-ltc.pdf> Accessed 2022 Nov 8

Use of Oseltamivir (Tamiflu®) for the Management of Influenza Outbreaks in Special Care Homes. Regina (SK): eHealth Saskatchewan. 2017. <https://www.ehealthsask.ca/services/manuals/Documents/cdc-section-9-AntiviralUseforInfluenzaOutbreaksinSpecialCareHomes.pdf> Accessed 2022 Nov 8

Tzouveleakis A, Bouros D. CDC and PHE recommendations for the antiviral treatment and prophylaxis of influenza. *Pneumon.* 2016;29(4):282-287.

Review Articles

Lehnert R, Pletz M, Reuss A, Schaberg T. Antiviral Medications in Seasonal and Pandemic Influenza. *Dtsch.* 2016;113(47):799-807. [PubMed](#)

Smith LE, D'Antoni D, Jain V, Pearce JM, Weinman J, Rubin GJ. A systematic review of factors affecting intended and actual adherence with antiviral medication as treatment or prophylaxis in seasonal and pandemic flu. *Influenza Other Respi Viruses.* 2016;10(6):462-478. [PubMed](#)