

## In brief

### Influenza and seasonal prophylaxis with oseltamivir

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### Questions

- 1) What is the place or evidence for seasonal influenza prophylaxis (such as taking oseltamivir for 10 to 12 weeks continuously) in healthcare and aged care settings?
- 2) What is the place or evidence for seasonal influenza prophylaxis in high-risk patients who have or require frequent contact with healthcare facilities (for example, dialysis patients)?

### Summary

- No systematic reviews have been conducted on this topic since 2013. Three older reviews note that there is some evidence for the effectiveness of oseltamivir as seasonal prophylaxis in at-risk adults.<sup>1,2</sup> However, the quality of those studies was evaluated as low.<sup>3</sup> Notably, many older studies and reviews on this topic have been criticised due to their heavy involvement of pharmaceutical sponsors and lack of replication or transparent data.<sup>4</sup>
- In adults, very few studies provide real-life evidence for the use of oseltamivir for seasonal prophylaxis in at-risk adult populations. The few that do exist found a positive benefit in reducing influenza incidence and secondary complications in long-term care residents, dialysis and transplant patients.<sup>5-8</sup>
- In children and adolescents who are immunocompromised, unvaccinated or at risk of influenza complications, there is stronger and more recent evidence to recommended seasonal oseltamivir.<sup>9</sup>
- Statistical modelling suggests that seasonal prophylaxis is effective for reducing influenza incidence and/or complications but may not be cost effective.<sup>10-12</sup>
- Seasonal prophylaxis for hospital workers can reduce staff absences but there is no evidence to date that it reduces influenza incidence for patients.<sup>12-14</sup>
- Most studies highlight that policy and clinical decision making need to take into consideration the side effects and cost effectiveness of seasonal prophylaxis.<sup>11, 14-16</sup>
- Most international jurisdictions do not currently have guidelines on seasonal prophylaxis for influenza. The Canadian antiviral guidelines suggest that seasonal prophylaxis may occur in circumstances where effective vaccines are not available or are contraindicated; or bridging prophylaxis may be considered at the same time as vaccination, when influenza is already circulating.
- In the United States, the Centres for Disease Control and Prevention (CDC) 2021 report did not recommend seasonal or pre-exposure antiviral chemoprophylaxis in most cases.<sup>15</sup> It can be considered for:
  - those who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g. people who are severely immunocompromised)

- those who have the highest risk of influenza-associated complications, such as transplant recipients
- high-risk individuals not yet vaccinated, if influenza is already circulating in the community, given in combination with vaccination.

### Background

- A wide range of evidence and clinical recommendations already exist for the use of oseltamivir for treatment and post-exposure prophylaxis.<sup>17-20</sup>
- To date, oseltamivir has been successfully used in NSW residential care facilities for the purpose of post-exposure prophylaxis.<sup>21, 22</sup>

### Synthesised literature

#### Peer-reviewed literature

##### Adults living in long-term care facilities:

- A 2001 study which recruited 548 frail older adults living in residential care, reported that administering oral oseltamivir, 75mg once daily for 6 weeks, effectively prevented clinical influenza. Oseltamivir administration resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared with placebo. Oseltamivir use was also associated with a significant reduction in the incidence of secondary complications. Although nearly all subjects were taking concomitant medication both before and during the study, oseltamivir was well tolerated.<sup>5, 6</sup>
- A study which statistically modelled transmission in a nursing home setting found that eight weeks of continuous prophylaxis reduced the patient infection attack rate from 0.19 to 0.05 (relative risk 0.23) and the percentage of large outbreaks decreased to 0.03 (relative risk 0.09). Seasonal prophylaxis meant that large outbreaks disappeared and the percentage of departments without any patient infection increased. The study noted that seasonal prophylaxis requires large stocks of antiviral drugs and is therefore costly, so postexposure prophylaxis might still be preferable.<sup>14</sup>

##### Adults in the community at high risk of influenza or associated complications:

- On a dialysis unit, oseltamivir prophylaxis was administered for four weeks. Of the 30 patients, 7 stopped prophylaxis early because of their own decision (n = 3) or reported adverse effects: stomach-ache (n = 1) and muscle aches (n = 3). No cases of influenza were detected until one week after the end of prophylaxis, when one case of influenza occurred.<sup>8</sup>
- In transplant recipients, 12 weeks of oseltamivir prophylaxis is generally well tolerated and can reduce laboratory-confirmed influenza incidence.<sup>7</sup>

##### Healthcare workers:

- A parallel group, double blind, randomised trial of oral oseltamivir versus placebo was conducted over 16 weeks in healthy health professionals at 2 hospitals in Thailand. Oseltamivir was well tolerated and was recommended for primary influenza prophylaxis for up to 16 weeks.<sup>13</sup>
- A modelling study found that eight weeks' prophylaxis with neuraminidase inhibitors (including oseltamivir) for essential staff substantially reduced absenteeism, even in a severe pandemic.<sup>12</sup>

- Another model suggested that extending seasonal prophylaxis in a nursing home to healthcare workers does not prevent many additional infections among nursing home patients when compared with prophylaxis of patients only.<sup>14</sup>

### Additional considerations:

- For high-risk groups, treatment (post-infection) with antivirals is less effective but is more feasible and cost effective than seasonal prophylaxis and is preferable in the case of limited drug availability.<sup>11</sup>
- In a paediatric study, children aged 1 to 12 years received oseltamivir for 6 weeks. In 3 out of 49 participants, adverse events occurred which were likely treatment related (nausea or vomiting). The tolerability profile was similar to pooled safety data from treatment studies in children.<sup>23</sup>
- A systematic review of harm and mortality found that the use of oseltamivir increases the risk of nausea, vomiting, psychiatric events in adults and vomiting in children. The review concluded that the balance between benefits and harms should be considered when making decisions about use of such treatments for either prophylaxis or treatment of influenza.<sup>16</sup>

### Systematic reviews:

- For adults with chronic health conditions, three reviews from 2009 to 2013 identified that there were very few (one or two) eligible studies with which to make a judgement about the effectiveness of seasonal prophylaxis with oseltamivir.
  - Two reviews noted that, based on the limited evidence, oseltamivir was effective in preventing symptomatic (although not necessarily laboratory-confirmed) influenza in at-risk elderly subjects.<sup>1, 2</sup>
  - One estimated that the incremental cost utility of seasonal influenza prophylaxis was expected to be £38,000–£428,000 per Quality-Adjusted Life Year gained.<sup>1</sup>
  - A third review concluded that there was no clear or high-quality evidence available on the benefits of oseltamivir and similar drugs for elderly and at-risk groups, or their effects on hospitalisation and mortality, based on the available studies being of low quality. It additionally noted that nausea, vomiting and diarrhea were significant side effects.<sup>3</sup>
- A more recent (2019) review of evidence for children and adolescents concluded that those at risk of complicated influenza can be recommended seasonal oseltamivir; especially in unvaccinated or immunocompromised children for whom vaccination may be less effective.<sup>9</sup>

## Grey literature

### Australia

- The 2017 Australian guidelines on influenza management in residential care facilities,<sup>24</sup> as well as guidelines from NSW<sup>20</sup> and Victoria,<sup>25</sup> do not mention seasonal prophylaxis.

### United Kingdom

- The 2021 guidance on antivirals to treat influenza does not discuss seasonal prophylaxis; however, does state that 'Prolonged treatment can be associated with the development of antiviral resistance, particularly in immunosuppressed patients, and antiviral resistance monitoring is recommended'.

### United States

The CDC's summary for clinicians on influenza antiviral medications for the 2021–22 influenza season reported:<sup>15</sup>

- Annual influenza vaccination is the best way to prevent influenza because vaccination can be given well before influenza virus exposures occur and can provide safe and effective immunity throughout the influenza season.
- The CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis, to limit the possibilities that antiviral-resistant viruses could emerge. Indiscriminate use of chemoprophylaxis might promote resistance to antiviral medications, or reduce antiviral medication availability for treatment of people at higher risk for influenza complications or who are severely ill.
- In general, CDC does not recommend seasonal or pre-exposure antiviral prophylaxis, but antiviral medications can be considered for post-exposure prophylaxis to prevent influenza in certain situations.
- Common adverse events are nausea, vomiting and headache. There have been reports of serious skin reactions and sporadic, transient neuropsychiatric events.

Recent clinical practice guidelines by the Infectious Diseases Society of America reported:<sup>26</sup>

- Antiviral drugs should not be used for routine or widespread chemoprophylaxis outside of institutional outbreaks; antiviral chemoprophylaxis can be considered in certain situations:
  - for adults and children aged  $\geq 3$  months who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated, unavailable, or expected to have low effectiveness (e.g. people who are severely immunocompromised)
  - for adults and children aged  $\geq 3$  months who have the highest risk of influenza-associated complications, such as recipients of hematopoietic stem cell transplant in the first 6 to 12 months posttransplant, and lung transplant recipients.
  - in conjunction with prompt administration of inactivated influenza vaccine for unvaccinated adults and children aged  $\geq 3$  months who are at high risk of developing complications from influenza in whom influenza vaccination is expected to be effective (but not yet administered) when influenza activity has been detected in the community.
  - for unvaccinated adults, including healthcare personnel, and for children aged  $\geq 3$  months who are in close contact with people at high risk of developing influenza complications during periods of influenza activity when influenza vaccination is contraindicated or unavailable and these high-risk people are unable to take antiviral chemoprophylaxis.
- Clinicians can consider educating patients and parents of patients to arrange for early empiric initiation of antiviral treatment as an alternative to antiviral chemoprophylaxis.
- Clinicians should use oseltamivir (or inhaled zanamivir) if preexposure chemoprophylaxis for influenza is required, rather than an adamantane antiviral.

### Canada

The 2019 guidelines<sup>27</sup> recommend that:

- Seasonal prophylaxis may occur in circumstances where effective vaccines are not available or are contraindicated. Although efficacious in clinical trials, the practicality and effectiveness of seasonal prophylaxis in practice have not been established.
- Bridging prophylaxis may be considered to prevent influenza until vaccine-induced immunity develops; and refers to two weeks of prophylaxis which commences from the time of vaccination (with an inactivated influenza vaccine) during the influenza season.
- A 2020 update to the guidelines was produced; however, the comments on seasonal prophylaxis were not among those updated.<sup>28</sup>

### Europe

The 2017 expert opinion review<sup>29</sup> reported:

- There is no agreed definition and time period for prophylaxis during the influenza season. Regimens as long as 16 weeks for oseltamivir have been studied and well tolerated; however, failure to complete prophylaxis may be more likely in children due to nausea and stomach discomfort.

## Method

To inform this brief, PubMed, MedRxiv and Google searches were conducted using terms related to influenza, oseltamivir and tamiflu on 20 May 2022.

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