

NPS Position Statement September 2006

Role of the neuraminidase inhibitors oseltamivir (Tamiflu) and zanamivir (Relenza) in seasonal influenza

Summary

- Influenza vaccination is the primary strategy for preventing influenza and its complications, particularly in at-risk people.
- Reserve neuraminidase inhibitors for use in laboratory-confirmed influenza and when they can be administered within 48 hours of exposure or symptom onset. Influenza virus infection cannot be accurately diagnosed on clinical grounds alone.
- Judicious use of neuraminidase inhibitors will reduce the likelihood of resistance emerging and preserve the potential usefulness of these agents in serious epidemics.
- Avoid use of neuraminidase inhibitors for treating seasonal influenza in otherwise healthy people, as they have a small absolute benefit (1–1.5 fewer days of illness).
- Neuraminidase inhibitors can be considered for treating influenza in people at risk of serious illness and complications. However, fewer studies have been done in at-risk people and there is little evidence of benefit.
- Consider neuraminidase inhibitors for control of influenza outbreaks in residential aged-care facilities. Consult the local public health unit and employ infection-control procedures.
- Neuraminidase inhibitors are not currently recommended as travel prophylaxis for avian influenza.

Which drugs are available?

Two neuraminidase inhibitors are available in Australia:

- oseltamivir (Tamiflu) — capsule or powder for oral solution
- zanamivir (Relenza) — inhaled via a diskhaler.

Neuraminidase is a viral surface enzyme that enables the spread of budding virions from infected cells to the surface of adjacent cells; inhibition prevents this activity, reducing viral replication within the infected host.

Treatment must be started early (within 48 hours of symptoms emerging) to interrupt viral replication effectively.

Adverse effects

Nausea and vomiting are the most common adverse effects of oseltamivir; limit these by taking with food. Bronchospasm has been reported rarely with zanamivir, and skin hypersensitivity reactions have been reported rarely with both drugs.¹ Unusual adverse reactions have been reported in Japanese children (see [Use of neuraminidase inhibitors in children](#), below).

Practical limitations when prescribing neuraminidase inhibitors

The effectiveness of neuraminidase inhibitors is likely to be lower in clinical practice than in clinical trials because:

- to be effective, these drugs must be started as soon as possible within 48 hours of contact with an influenza case or symptom onset; many patients will present after 48 hours
- in trials, the benefits of neuraminidase inhibitors were clearer in laboratory-confirmed cases than influenza-like illness; however:
 - clinical diagnosis does not accurately differentiate influenza from influenza-like illness (20% to 40% of clinical diagnoses are not confirmed by laboratory tests at times when influenza is circulating).²
 - influenza laboratory testing is rarely done in primary care settings, and rapid point-of-care tests are relatively expensive and have a high false-negative rate (around 20%). Nonetheless they may help guide treatment in some circumstances.^{3,4}
 - Standard physical infection control and hygiene are important whether or not neuraminidase inhibitors are used.

Risk of resistance

Oseltamivir modifies the neuraminidase receptor to enable it to bind, while zanamivir binds to it directly. Mutations in the neuraminidase receptor can prevent oseltamivir from binding; this is one mechanism for resistance.⁵ Resistance to the neuraminidase inhibitors remains rare in Australia⁶ and was detected in 0.4% of circulating influenza strains worldwide in 2001–02* data.⁷ During oseltamivir treatment children develop resistance at higher rates (4–18%^{8,9}) than those reported for adults (0.33%⁹), including in one case of H5N1 avian influenza.¹⁰

Resistance to another group of antivirals, the adamantanes[†], increased dramatically in the US from 2% in 2003–04 to 92% of H3N2 isolates[‡] in 2004–05, and these drugs cannot currently be used in influenza.¹² In vitro, resistance to neuraminidase inhibitors is apparently more difficult to induce than resistance to the adamantanes¹³, nonetheless the rapid evolution of adamantane resistance is a salutary reminder that overuse can diminish the usefulness of antiviral drugs.^{5,14}

Place in therapy and recommendations for seasonal influenza

Neuraminidase inhibitors are not an alternative to vaccination for preventing influenza and its complications. They have a limited role in treating influenza or as post-exposure prophylaxis after contact with influenza cases. (See Tables 1 and 2).

Consider the potential benefits and harms at both an individual and population level when prescribing neuraminidase inhibitors for seasonal influenza.

Prevention of influenza and its complications

Vaccination remains the first-line strategy for reducing morbidity and mortality from influenza and complications in at-risk groups (see Box 1).^{11,15} Currently only around 42% of at-risk people aged below 65 years are vaccinated against influenza.¹⁵

Box 1: At-risk groups recommended for influenza vaccination¹¹

- People aged 65 years and over*
- Aboriginal and Torres Strait Islanders aged 50 years and over*
- Children and adults with chronic cardiac conditions or chronic suppurative lung diseases, or chronic illnesses requiring regular medical follow-up (e.g. diabetes, renal disease, metabolic disease or immunosuppression)
- People with immune deficiency, including HIV–AIDS
- Residents of long-term care facilities
- Contacts of at-risk patients, including health care providers

*Pneumococcal vaccination is recommended in people aged 65 years and over, and Aboriginal and Torres Strait Islanders aged 50 years and over.¹¹

* Surveillance is ongoing and reports on more recent data are expected.⁷

† Amantadine (Symmetrel), also used for parkinsonism and rimantadine (not available in Australia).

‡ Most influenza viruses circulating since 1977 are the H1N1 and H3N2 subtypes of influenza A. The avian influenza virus of current concern is an H5N1 virus.¹¹

In older people living in the community, vaccines provide 30–70% protection from hospitalisation for pneumonia and influenza. For people living in institutions, vaccines are 50–70% effective in preventing hospitalisation or pneumonia and are 80% effective in preventing death.¹³

Some at-risk people may not develop full immunity with vaccination; consider antivirals in these circumstances (see Table 1).

Do neuraminidase inhibitors reduce the risk of complications?

There is limited evidence that neuraminidase inhibitors reduce complications of influenza requiring antibiotics in at-risk populations (Table 2).^{4,16} The results should be treated with caution because the available data come from industry-sponsored reviews of published and unpublished data^{19,20,28} that report sub-analyses of trials not designed to assess complication rates. The rationale

Table 1: Prevention of influenza — recommendations for using neuraminidase inhibitors	
RECOMMENDATION	QUALITY OF EVIDENCE
Healthy adults	
<p>Reserve for use in post-exposure prophylaxis when the exposed person is in close contact with at-risk people and may infect them with influenza</p> <ul style="list-style-type: none"> The likelihood of influenza cases was 80–90% lower than placebo in post-exposure prophylaxis (oseltamivir, odds ratio [OR] 0.10, 95% confidence interval [CI] 0.03 to 0.34; zanamivir OR 0.19, 95% CI 0.09 to 0.38)¹⁶ Neuraminidase inhibitors do not prevent influenza-like illness in otherwise healthy adults¹⁷ 	Randomised controlled trials (RCTs) in seasonal prophylaxis (see <i>Note</i> below) and a small number of trials in post-exposure prophylaxis
At-risk adults	
<p>Consider for outbreak control in residential aged care facilities with local public health unit advice</p> <ul style="list-style-type: none"> Guidelines recommend treating cases, all asymptomatic residents (regardless of vaccination status) and unvaccinated staff in residential aged-care facilities^{4,18} Few people (20%) in post-exposure prophylaxis trials were vaccinated^{16,19,20}, so efficacy in vaccinated at-risk people is largely unknown. In one oseltamivir trial, infection rates were substantially reduced despite 80% vaccination rates (OR 0.08, 95% CI 0.01 to 0.61, p = 0.002)²¹ <p>Consider for prophylaxis in at-risk people unprotected by influenza vaccine¹¹, at times when influenza is circulating²²</p> <ul style="list-style-type: none"> Vaccination may be less effective in at-risk people with poor immunocompetence, or when the circulating strain does not match the annual vaccine^{22,23} 	One RCT each for oseltamivir and zanamivir prophylaxis in elderly residential facilities. ^{16,21} Observational, uncontrolled data of use for outbreak control in residential aged care ^{13,24,25}
Children	
Not indicated for prophylaxis in children (<12 years)	No trials ²⁶

Note: Two prevention strategies have been studied in trials of neuraminidase inhibitors — seasonal prophylaxis (4–6 weeks’ treatment when influenza was circulating in the community), and post-exposure prophylaxis (5–10 days’ treatment after exposure to someone with influenza). Because annual influenza vaccination provides effective prophylaxis at relatively low cost, the use of neuraminidase inhibitors for seasonal prophylaxis is not discussed in this document.

for prescribing antibiotics may have differed between trials so this is only an indirect measure of complication rates.²

In the data available, compared with placebo both oseltamivir and zanamivir reduced complications requiring antibiotics in patients with confirmed influenza.^{19,20,28} With oseltamivir, lower respiratory tract

infections requiring antibiotics (including bronchitis and pneumonia) were reduced (19% vs 12%, OR 0.6, 95% CI 0.4 to 0.9¹⁶, n = 769) but there was no effect on upper respiratory tract infections (sinusitis and otitis media).²⁰ There were similar results for zanamivir; both upper and lower respiratory tract infections were included in the analysis (13% vs 24%, OR 0.5, 95% CI 0.2 to 1.04).¹⁶

Table 2: Treating influenza — recommendations for using neuraminidase inhibitors

RECOMMENDATION	QUALITY OF EVIDENCE
Healthy adults	
<p>Not recommended because of relatively small treatment benefit with a low risk of influenza complications</p> <ul style="list-style-type: none"> • Illness duration is reduced by a median of only 1–1.5 days²⁷ (usual duration of illness 6–7 days)¹⁶ • Symptoms improve 22% more often than with placebo (hazard ratio 1.22, 95% CI 1.1 to 1.3; 9 trials, n = 4985¹⁷)* 	Randomised controlled trials (RCTs) and systematic reviews.
At-risk adults	
<p>Consider treatment in at-risk patients if within 48 hours of symptom onset</p> <ul style="list-style-type: none"> • Recommendations to treat at-risk groups are based on greater potential harm with untreated illness not greater treatment efficacy^{13,23} • Limited data are available for at-risk groups. These do not show a consistent treatment benefit^{13,16} • Illness duration is reduced by less than one day (not statistically significant)^{16,27}; (usual duration of illness 10 days)¹⁶ • Some data show a reduction in complications with treatment; but few studies are in at-risk people^{13,16} 	A few RCTs in the elderly and people with mild–moderate asthma or COPD ¹⁹ No data on people with chronic disease, chronic cardiac conditions, the immunocompromised or Aboriginal and Torres Strait Islander people ^{28,29}
Children	
<p>Avoid use unless there is serious potential for harm with untreated illness</p> <ul style="list-style-type: none"> • Illness duration is reduced by around 1 day^{16,26} • Serious adverse events have been reported in Japanese children, although causality was not established³⁰ • Children develop resistance to neuraminidase inhibitors more quickly than adults (see below) • There is weak evidence that oseltamivir reduces the incidence of otitis media and bronchitis, but no data on reducing hospitalisation²⁶ • There are insufficient data on benefit in at-risk children²⁶ 	RCTs, Cochrane systematic review A few trials included 6–12-year-old children with asthma but there are no data in other at-risk children ^{16,26}

Note: Unless otherwise specified, estimates and effect sizes in Tables 1 and 2 are based on full trial populations (i.e. influenza-like illness and confirmed influenza cases), as this scenario is more likely in clinical practice; unless otherwise specified, results are for combined zanamivir and oseltamivir.

* From a meta-analysis of trials using different time points. The hazard ratio refers to the likelihood that symptoms will be alleviated by the time points designated within each individual trial.¹⁷

Oseltamivir did not reduce complications in people with influenza-like illness.¹⁶

There are few data to indicate whether neuraminidase inhibitors reduce the risk of pneumonia, hospitalisations or mortality in at-risk people; the available evidence

suggests an absolute reduction in the risk of pneumonia of about 1%.^{2,31}

Neuraminidase inhibitors appear to reduce complication rates in healthy people; however, the overall risk of complications in this group is low (OR 0.4, 95% CI 0.2 to 0.90).¹⁷

Use of neuraminidase inhibitors in children

Zanamivir is licensed for use in children > 5 years old. Oseltamivir is licensed for use in children > 1 year old; the manufacturer warns against use in children < 1 year old, in whom the blood–brain barrier is incompletely developed.²⁹

Neuraminidase inhibitors are not approved in Australia for prevention of influenza in children and a Cochrane review (2003) found no relevant trials.

There have been reports of neuropsychiatric events (including delirium, convulsions and encephalitis),

hypersensitivity reactions and sudden death with oseltamivir in children, almost entirely from Japan which has the highest usage of oseltamivir worldwide.³⁰ An FDA review of clinical trial and post-marketing data concluded that the neuropsychiatric events were not clearly drug-related but might be related to higher rates of influenza-related encephalitis in Japan. Skin hypersensitivity reactions were considered more likely to be related to drug use, and a surveillance and monitoring program is in place in the US and Japan.³⁰

Travel prophylaxis and avian influenza

There are no systematic data on use of neuraminidase inhibitors in H5N1 avian flu, although there is *in vitro* and *in vivo* evidence that recent strains of the H5N1 virus are susceptible to oseltamivir.³² Case reports in people with H5N1 have not demonstrated any substantial effect in treatment, although most cases presented after 48 hours of illness.³³ Because there is currently no human-to-human transmission of H5N1, effectiveness in post-exposure prophylaxis cannot be assessed.

WHO rapid guidelines recommend neuraminidase inhibitors for people with H5N1 influenza; those with close, unprotected contact with known or suspected H5N1 cases; or if supply allows, people in near contact with infected people or birds. The WHO notes that neuraminidase inhibitors are recommended not because of evidence of efficacy in avian influenza but because there are no treatment alternatives; hence recommendations are based on seasonal influenza guidelines.³⁴

Unless the timing of exposure to an infected person is known, neuraminidase inhibitors would need to be taken by travellers for the duration of possible exposure; 6 weeks was the maximal duration of use in trials, and long-term safety is unknown. Standard infection control and hygiene remains important while travelling.

Consult travel advice in areas of reported avian flu activity. Advice may change if a pandemic occurs. For more information about avian influenza and pandemic preparedness see the following websites:

- Australian Government Department of Health and Ageing: www.health.gov.au/internet/wcms/publishing.nsf/Content/health-avian_influenza-index.htm
- World Health Organization: www.who.int/csr/disease/avian_influenza/en/

Expert reviewers

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