Ontario Health

Recommendations for Antiviral Therapy of Highly Pathogenic Avian Influenza A(H5N1)

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Purpose

This document provides recommendations for clinicians on the appropriate prescribing of antiviral therapy for adults and children with highly pathogenic avian influenza (HPAI) A(H5N1).

Recommendations related to HPAI A(H5N1) influenza vaccination and other aspects of HPAI A(H5N1) management (e.g., testing, diagnostics, infection control practices) are beyond the scope of this document. See the **Additional Resources** section for more information about these topics. For information related to antiviral availability and drug coverage, see the drug availability section of Ontario Health's **Influenza Clinical Guidelines and Resources** webpage.

Recommendations Development

The recommendations are informed by best available evidence retrieved from a systematic literature search conducted between January to February 2026 of peer-reviewed studies, review articles, Canadian guidelines, international guidelines and grey literature. The recommendations were developed by the Ontario Health Infectious Diseases (ID) program's guidance development working group with consensus-based feedback and contributions from Ontario Health's Infectious Diseases Advisory Committee (IDAC). This document was reviewed by multidisciplinary clinicians and health care administrators from Ontario Health's Primary Care Program, Renal Program, Systemic Treatment Program (Cancer Care), Regional Clinical Vice-Presidents and the Chief Medical Executive.

This guidance document shall be updated as needed to align with relevant changes in clinical best practice.

See the **Authorship, Contributors and Acknowledgements** section for additional information about the authors and contributors of this guidance document.

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Introduction

Epidemiology

Since 2022, there has been global spread of HPAI A(H5N1) among wild birds and domestic poultry.[1] HPAI A(H5N1) infections in wild and domestic mammalian species have also been reported, although humans infections are less common.[2,3] There were approximately 130 human cases of HPAI A(H5N1) between 2022 and 2025.[4] In 2024, Canada's first domestically acquired human case of HPAI A(H5N1) was reported in British Columbia and remains the country's only confirmed human infection to date.[5] The individual's source of exposure was not identified, but genetic sequencing identified the HPAI A(H5N1) virus matched a strain that was circulating in local poultry and wild birds in British Columbia at the time.[3]

Most human cases of HPAI A(H5N1) occur after close contact with animals or animal products infected with HPAI A(H5N1), or after exposure to environments contaminated by these animals (e.g., live poultry markets, barns).[2,6] Rare instances of limited human-to-human transmission of HPAI A(H5N1) have been reported after close or prolonged contact with an infected person.[7] However, sustained human-to-human transmission of HPAI A(H5N1) has not been established.[8]

HPAI A(H5N1) Disease Overview

HPAI A(H5N1) infection in humans can be asymptomatic or range from mild to severe disease.[6,8,9] Signs and symptoms of HPAI A(H5N1) in humans may include, but are not limited to, new or worsening cough, shortness of breath, conjunctivitis, fever, sore throat, myalgia and lethargy.[10] Other signs and symptoms may include rhinorrhea, diarrhea, fatigue and/or headache.[10] HPAI A(H5N1) infections that progress to severe disease may lead to complications such as pneumonia, respiratory failure, multi-organ failure or death.[1,10]

The cumulative case fatality rate (CFR) for reported human HPAI A(H5N1) infections is approximately 50%.[3,11] However, the CFR may be an overestimate because asymptomatic or mildly symptomatic cases may not be detected.[12]

Risk factors for developing complications associated with HPAI A(H5N1) have not been studied and may vary across different virus subtypes and strains.[3,13] It is hypothesized that individuals at higher risk of developing seasonal influenza-related complications (e.g., individuals aged 65 years and older, children aged younger than 5 years, individuals with certain underlying medical conditions) may also be at greater risk for developing complications associated with HPAI A(H5N1).[14] See Table 2 of Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza** for a list of risk factors that are associated with an increased risk of developing seasonal influenza-related complications.

Goals of Treatment

The goals of treatment in patients with HPAI A(H5N1) infection are to:

- Prevent mortality[15]
- Alleviate HPAI A(H5N1) symptoms and reduce disease severity[15,16]
- Decrease the risk of serious complications (e.g., respiratory failure, organ damage and/or failure)[17]
- Reduce the duration of illness[17]
- Prevent hospitalization[16]
- Limit the risk of person-to-person transmission[2]

Recommendations for HPAI A(H5N1) Treatment

The decision to initiate antiviral therapy should include a clinical assessment of the patient's signs and symptoms, epidemiologic factors (e.g., prevalence and type of influenza virus circulating in the community), along with consideration of their potential exposure to HPAI A(H5N1)-infected animals/persons or contaminated environments. For the latest information on influenza virus activity in Ontario, see Public Health Ontario's (PHO) **Respiratory Virus Tool** and the Canadian Food Inspection Agency's **Avian Influenza Status** webpage to help guide decisions regarding antiviral therapy.

Diagnostic testing (e.g., polymerase chain reaction test) may be used to confirm clinical suspicion and to inform decisions on the use of antiviral therapy.[18] Antiviral treatment should not be delayed while waiting for laboratory test results.[16] Confirmation of HPAI A(H5N1) infection by microbiological testing is not a requirement for initiating empiric antiviral therapy.

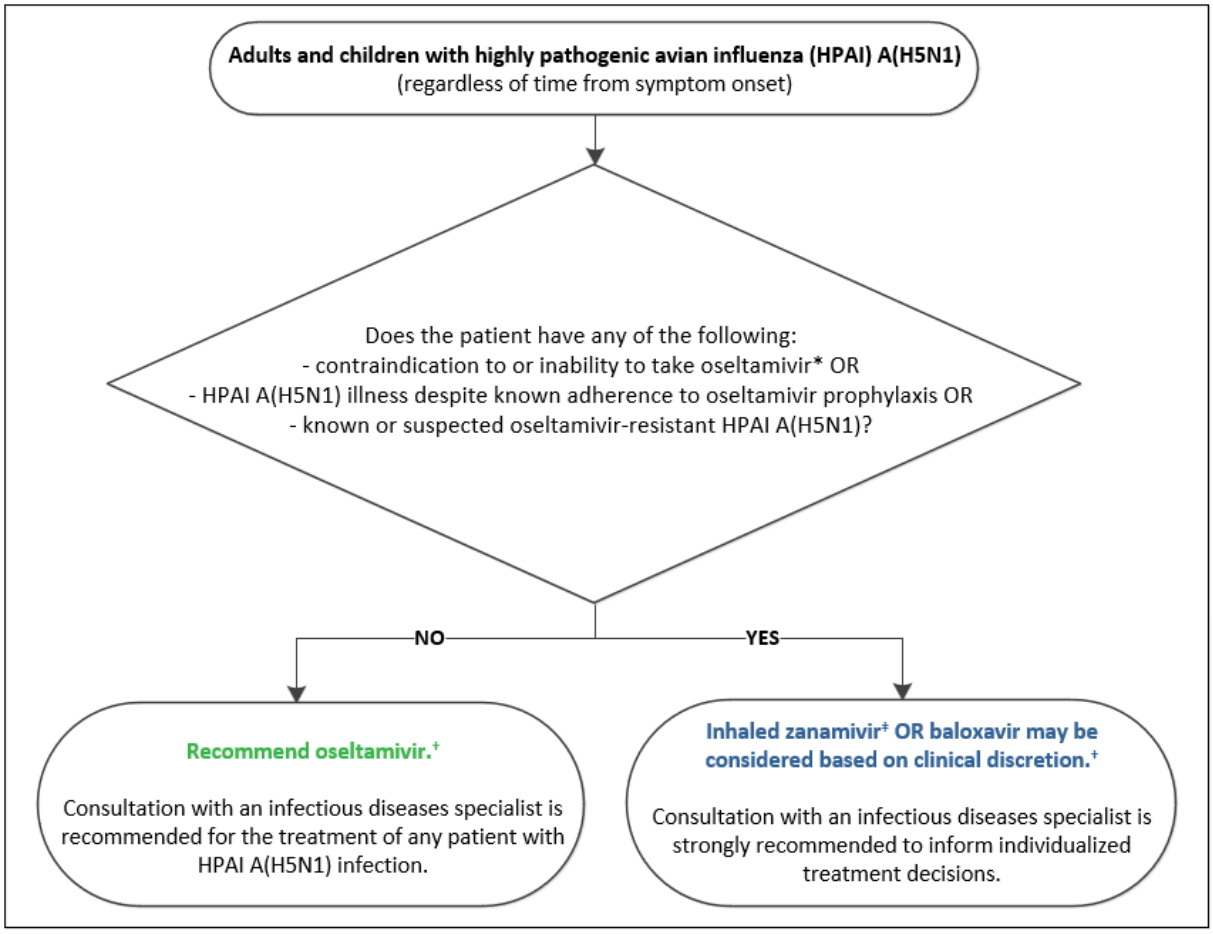
See **Figure 1** for a suggested algorithm to treat adults and children with HPAI A(H5N1).

- Consultation with an ID specialist is recommended for the treatment of HPAI A(H5N1).[2]
  - The treatment of HPAI A(H5N1) with oseltamivir, inhaled (INH) zanamivir, or baloxavir is considered off-label use in Canada.
- Antiviral treatment is recommended for individuals with HPAI A(H5N1), regardless of the time from symptom onset.[19]
  - Antiviral treatment is more likely to be effective if started within 48 hours of HPAI A(H5N1) signs or symptoms.[2] However, treatment should be given to individuals presenting at any point during their illness due to evidence that the virus continues to replicate beyond 48 hours after the onset of signs or symptoms.[2]
- Oseltamivir is recommended as first-line therapy for HPAI A(H5N1).[2]
  - See the supplemental drug information section in Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza** for information about clinically relevant contraindications and administration considerations of oseltamivir.

- For patients who are contraindicated to or unable to take oseltamivir, OR patients with HPAI A(H5N1) illness despite known adherence to oseltamivir prophylaxis, OR patients with known or suspected HPAI A(H5N1) resistant to oseltamivir:
  - INH zanamivir OR baloxavir may be considered based on clinical discretion. For patients with extrapulmonary HPAI A(H5N1) infection, INH zanamivir is NOT recommended because it may not be as effective due to low systemic absorption.[20,21]
  - Although intravenous (IV) zanamivir or peramivir are also options for treatment, these agents are not marketed in Canada and only available via Health Canada's Special Access Program. See Ontario Health's Influenza Clinical Guidelines and Resources webpage for the latest information on the availability of IV zanamivir or peramivir.

See the Clinical Evidence section for a detailed description of the evidence summary and rationale that support the clinical recommendations.

Figure 1: Treatment Algorithm for Highly Pathogenic Avian Influenza A(H5N1) in Adults and Children



* See the supplemental drug information section in Ontario Health's Recommendations for Antiviral Therapy of Seasonal Influenza for information about clinically relevant contraindications and administration considerations of oseltamivir.

† The treatment of HPAI A(H5N1) with oseltamivir, INH zanamivir, or baloxavir is considered off-label use in Canada.

‡ For patients with extrapulmonary HPAI A(H5N1) infection, INH zanamivir is NOT recommended because it may not be as effective due to low systemic absorption.

Clinical Evidence

Due to the small number of cases and episodic, unpredictable nature of the HPAI A(H5N1) infection in humans, no clinical trial evaluating antiviral treatment has been conducted in individuals with HPAI A(H5N1) to date.[11,22]

Oseltamivir

Oseltamivir is the preferred antiviral treatment for HPAI A(H5N1).[2,19,23] No randomized controlled trial has evaluated the use of oseltamivir compared with placebo for the treatment of HPAI.[11] Oseltamivir for the treatment of HPAI A(H5N1) is based on evidence from observational studies.[2,11]

A multi-country, systematic review of case reports involving adults and children with HPAI A(H5N1) found oseltamivir therapy was associated with a significant decrease in mortality compared with no antiviral therapy, even when treatment was initiated up to 8 days after symptom onset.[24] The survival benefit was observed across all age groups.[24] Another observational study reported consistent findings where a trend towards improved survival was observed with oseltamivir therapy in patients with HPAI A(H5N1) compared with no oseltamivir therapy.[25] One limitation of the systematic review and the observational study is that generalizability of the survival benefit to current clinical practice may be limited, as the effectiveness of oseltamivir against presently circulating HPAI A(H5N1) strains has not been evaluated compared with the strains circulating at the time of the studies.

Early oseltamivir therapy for HPAI A(H5N1) is associated with improved survival.[11,26] Two observational studies of patients with HPAI A(H5N1) found that oseltamivir initiation within 48 hours of symptom onset was associated with improved survival rates compared with initiation more than 48 hours after symptom onset.[27,28] Another observational study in children with HPAI A(H5N1) reported that each day in delay of oseltamivir initiation was associated with an increased odds of death.[29]

Zanamivir

Zanamivir is listed as an option for HPAI A(H5N1) treatment by the Association of Medical Microbiology and Infectious Diseases Canada (AMMI Canada) and the Public Health Agency of Canada (PHAC).[2,20] No clinical trial has evaluated the effectiveness of zanamivir for the treatment of HPAI A(H5N1) in humans.[2,11] The use of zanamivir for the treatment of HPAI A(H5N1) is based on its use to treat other types of avian influenza (e.g., HPAI A[H7N9]), seasonal influenza and from animal studies.[2,11]

Animal studies of INH or IV zanamivir therapy for HPAI A(H5N1) have shown a trend towards reduced viral titres compared with no zanamivir therapy.[30,31] However, this finding should be interpreted with caution because of differences between animal and human physiology.[11] It also remains unclear whether reduced viral titres would result in meaningful clinical benefit.

A retrospective study of people with avian influenza A(H7N9) found no significant difference in mortality or intensive care unit (ICU) admission between individuals who received INH zanamivir and those who did not.[32] The median time from symptom onset to initiation of zanamivir was 8 days, which may limit the generalizability of these findings to patients who initiate zanamivir treatment earlier.[32]

Meta-analyses of randomized controlled trials of adults and children with seasonal influenza have reported mixed findings for the clinical benefit of zanamivir. One meta-analysis showed INH zanamivir therapy reduced the mean time to alleviation of symptoms in patients with non-severe seasonal influenza compared with standard care or placebo by 0.68 days.[33] However, 0.68 days may not be considered a clinically important difference to patients or clinicians. Another meta-analysis found no significant difference between INH or IV zanamivir for mortality within 35 days of therapy compared with those who received standard care or placebo.[34]

Peramivir

Clinical trials have not evaluated the effectiveness of peramivir monotherapy in individuals with HPAI A(H5N1). Peramivir is listed as an option for HPAI A(H5N1) treatment by PHAC based on its use to treat seasonal influenza.[2] However, the World Health Organization (WHO) does not recommend peramivir due to insufficient evidence of its clinical benefit for the treatment of HPAI A(H5N1).[22]

Animal studies of peramivir for HPAI A(H5N1) have reported inconsistent survival benefits for peramivir therapy compared with no antiviral therapy.[35] One animal study found peramivir therapy significantly reduced viral titres in the upper respiratory tract compared with no antiviral therapy.[36] However, it is unknown whether reduced viral titres would result in meaningful clinical benefit and the findings should be interpreted with caution because of differences between animal and human physiology.[11]

A retrospective study of adults and children with avian influenza A(H7N9) did not find any association between the onset of illness and timing of peramivir therapy for mortality or ICU admission.[32] However, the absence of a comparison between peramivir therapy and no antiviral therapy was a limitation of the study.

In adults and children with severe seasonal influenza, an indirect comparison from a meta-analysis of randomized controlled trials showed that peramivir therapy was associated with a significantly shorter mean duration of hospitalization by 1.7 days compared with standard care or placebo.[34] However, a direct comparison found that peramivir therapy was similar to standard care or placebo in time to alleviation of symptoms, risk of mortality and ICU admission within 35 days.[34,37]

Baloxavir

Clinical trials have not evaluated the effectiveness of baloxavir monotherapy in individuals with HPAI A(H5N1).[11,38] However, AMMI Canada, PHAC and the WHO include baloxavir as a treatment option based on its use to treat seasonal influenza in humans and from animal studies that used baloxavir to treat HPAI A(H5N1).[2,20,22]

Animal studies have shown mixed results regarding the effects of baloxavir therapy compared with no baloxavir therapy on mortality and impact on viral titres in animals infected with HPAI A(H5N1).[39,40,41]

In adults and children with non-severe seasonal influenza, meta-analyses of randomized controlled trials showed that baloxavir significantly reduced the mean time to alleviation of symptoms by 1 day and influenza-related complications within 14 days of treatment (defined as pneumonia, bronchitis, otitis media, sinusitis, and other secondary illness, whether treated with antibiotics or not) compared with standard care or placebo.[33,42] However, baloxavir therapy did not show any benefit for mortality or admission to hospital within 29 days.[33] Clinical trials have not been conducted to determine the effectiveness of baloxavir monotherapy for individuals with severe seasonal influenza.

Combination Therapy

Current evidence does not support the use of combination antiviral therapy for HPAI A(H5N1).

In exceptional circumstances where combination therapy may be considered for selected individuals with HPAI A(H5N1) who may be at high risk of developing influenza-related complications (e.g., immunocompromised patients with persistent symptoms and evidence of ongoing viral replication), consultation with an ID specialist is strongly recommended to inform individualized treatment decisions.

A summary of available evidence on selected antiviral combinations is provided below. The list of combination antiviral therapy is not exhaustive.

Neuraminidase Inhibitors

The use of combination therapy with two or more neuraminidase inhibitors (NAIs) for the treatment of HPAI A(H5N1) is not recommended and may increase the risk of patient harm.[43]

Clinical trials have not been conducted to determine the effectiveness of combination therapy with NAIs for individuals with HPAI A(H5N1). One observational study of adults hospitalized with avian influenza A(H7N9) found no significant difference for the duration of viral shedding between oseltamivir and peramivir combination therapy compared with oseltamivir monotherapy.[44]

Clinical studies of seasonal influenza indicate that oseltamivir and zanamivir combination therapy may have antagonistic effects.[45] In one randomized controlled trial of patients with non-severe seasonal influenza, significantly fewer patients who received combination therapy achieved a viral load below 200 cgeq/mL by day 2 or symptom resolution by day 5 compared with those who received oseltamivir monotherapy.[45] Although the same study found that significantly more patients who received combination therapy achieved a viral load below 200 cgeq/mL compared with those who received INH zanamivir monotherapy, there was no significant difference between the two groups for symptom resolution by day 5.[45]

The use of oseltamivir and peramivir combination therapy has been reported in case reports for the treatment of severe seasonal influenza, but there is insufficient evidence that combination therapy with NAIs improved clinical outcomes.[46]

Neuraminidase Inhibitor and Amantadine

The use of combination therapy with a NAI and amantadine in patients with HPAI A(H5N1) is not recommended.

No clinical study has evaluated the effectiveness of this antiviral combination in humans. The limited evidence for NAI and amantadine combination therapy for the treatment of avian influenza A(H5N1) is based on animal and in vitro studies.[47,48]

In mice infected with amantadine-susceptible, low pathogenic avian influenza (LPAI) A(H5N1), oseltamivir and amantadine combination therapy significantly improved survival compared with oseltamivir monotherapy.[47] One limitation of the study was the absence of a comparison between oseltamivir and amantadine combination therapy and oseltamivir monotherapy for survival in mice with amantadine-resistant LPAI A(H5N1).

An in vitro study with amantadine-susceptible LPAI A(H5N1) found that oseltamivir and amantadine combination therapy reduced virus titres to a greater extent than either drug alone.[48] However, for amantadine-resistant LPAI A(H5N1), an in vitro study found that virus titres were comparable between oseltamivir and amantadine combination therapy and oseltamivir monotherapy.[48]

No clinical studies have been published on the combination of other NAIs (e.g., zanamivir or peramivir) with amantadine for the treatment of HPAI A(H5N1).

Neuraminidase Inhibitor and Baloxavir

There is insufficient evidence to support the use of combination therapy with a NAI and baloxavir in patients with HPAI A(H5N1). However, NAI and baloxavir combination therapy is listed by AMMI Canada as an option for the treatment of oseltamivir-resistant HPAI A(H5N1).[20]

Although favourable clinical and virologic outcomes for combination therapy with a NAI and baloxavir have been suggested by animal studies, no clinical study has evaluated this regimen in humans with HPAI A(H5N1).[40] In mice with oseltamivir- and baloxavir-susceptible HPAI A(H5N1), combination therapy significantly decreased 21-day mortality and viral titres in the lung by day 1 post treatment compared with oseltamivir monotherapy.[40] One limitation of the study was the lack of comparison between combination therapy and baloxavir monotherapy.

Cases of critically ill patients with HPAI A(H5N6) treated with a NAI and baloxavir have been reported.[49] However, comparative clinical or virologic outcomes between NAI and baloxavir combination therapy and monotherapy of either drug have not been evaluated.[49]

In hospitalized adults and children with severe seasonal influenza, a randomized controlled trial (FLAGSTONE) found that NAI and baloxavir combination therapy did not improve clinical outcomes compared with NAI monotherapy.[50] Even though combination therapy significantly reduced the duration of viral shedding compared with NAI monotherapy, no significant difference was observed between the two treatment groups for time to clinical improvement, mortality, time to hospital discharge, ICU admission, ICU length of stay or duration of mechanical ventilation.[50] A post hoc analysis of the FLAGSTONE trial in a subgroup of patients with one or more risk factors for influenza-related complications (defined as immunosuppression, diabetes and/or chronic lung diseases) found that NAI and baloxavir combination therapy was associated with a significantly shorter duration of viral shedding and a significantly lower risk of 28-day mortality compared with NAI monotherapy.[51] However, no significant difference was seen between the two treatment groups for other clinical outcomes such as time to clinical improvement, ICU admission rate or hospital discharge.[51]

Neuraminidase Inhibitor, Baloxavir and Amantadine

There is insufficient evidence to support the use of combination therapy with a NAI, baloxavir and amantadine in patients with HPAI A(H5N1).

In 2024, a Canadian case report described the use of a triple antiviral therapy regimen with oseltamivir, baloxavir and amantadine to treat a critically ill, hospitalized adolescent patient with HPAI A(H5N1).[52] Although no clear source of infection was identified, the patient was infected with the same strain of HPAI A(H5N1) that was circulating in wild birds and poultry in British Columbia at the time.[53,54] HPAI A(H5N1) virus cultured from the patient's respiratory specimens was susceptible to NAIs, baloxavir and amantadine.[52] Serial respiratory specimens collected throughout the patient's course of antiviral therapy did not show any evidence of treatment-emergent resistance.[52] The patient recovered from the infection and was discharged from the hospital.[55] Due to the observational nature of the case report, the comparative clinical or virologic effectiveness of triple antiviral therapy versus single or dual antiviral therapy remains uncertain.[20]

Supplemental Information: Antiviral Activity and Susceptibility

HPAI A(H5N1) viruses are generally susceptible to neuraminidase inhibitors (e.g., oseltamivir, zanamivir) and polymerase acidic endonuclease inhibitors (e.g., baloxavir).[20,56]

Neuraminidase Inhibitors

A study of genetic sequences from publicly available databases (e.g., Global Initiative on Sharing All Influenza Data, GenBank) found that less than 1% of HPAI A(H5N1) viruses circulating globally in humans and other animals during 2022 to 2023 showed reduced susceptibility to NAIs.[57] The human case of domestically acquired HPAI A(H5N1) in Canada was susceptible to oseltamivir and zanamivir.[52] Influenza A viruses that possess the H275Y or H274Y mutation in the neuraminidase enzyme are cross-resistant to oseltamivir and peramivir, but remain susceptible to zanamivir.[20,58,59]

Treatment-emergent resistance

Oseltamivir treatment-emergent resistance to HPAI A(H5N1) has been observed in a human case report.[60,61]

The development of zanamivir treatment-emergent resistance in individuals with HPAI A(H5N1) has not been studied. The development of zanamivir treatment-emergent resistance is less commonly reported in patients with seasonal influenza.[33,62] The case reports generally occurred in immunocompromised individuals, where viral replication may be prolonged.[62,63]

Due to the limited available data on peramivir use for HPAI A(H5N1) treatment, the rate of treatment-emergent resistance in humans following peramivir therapy is unclear. Case reports of peramivir treatment-emergent resistance have been observed in individuals infected by other strains of influenza A (e.g., H1N1).[64]

Baloxavir

HPAI A(H5N1) viruses with reduced susceptibility to baloxavir are rare.[56] A surveillance study reported that 0.54% of HPAI A(H5N1) viruses that were circulating globally in 2022 to 2023 had reduced susceptibility to baloxavir.[57] Similarly, surveillance studies of HPAI A(H5N1) viruses associated with human infection in the United States between 2023 and 2025 found that baloxavir resistance rates ranged from 0% to 1.4%.[56,65]

Cross-resistance between baloxavir and NAIs has not been identified.[66] Baloxavir is active against selected NAI-resistant strains of HPAI A(H5N1) viruses (e.g., H274Y, H275Y or N294S).[40,66,67] However, some influenza viruses may carry amino acid substitutions associated with reduced susceptibility to both baloxavir and NAIs.[66]

Treatment-emergent resistance

Baloxavir treatment-emergent resistance has not been reported in humans with HPAI A(H5N1) based on limited data from its use for this indication.[11,52] However, baloxavir treatment-emergent resistance was observed in a study of mice with HPAI A(H5N1).[68] The study also found that delayed baloxavir therapy (starting 14 days post infection) was associated with an increased likelihood of developing treatment-emergent resistance compared with earlier initiation of baloxavir therapy (starting fewer than 6 days post infection).[68]

In clinical studies of seasonal influenza, the observed rate of treatment-emergent resistance to baloxavir ranged from 2% to 23%.[33,69] The studies also found that treatment-emergent resistance following a single dose of baloxavir was more common in children younger than 5 years old compared with adults and adolescents (40% versus 7%).[70]

Amantadine

Amantadine is not recommended by AMMI Canada for the treatment of HPAI A(H5N1) because of historically high rates of resistance.[20] Although HPAI A(H5N1) viruses susceptible to amantadine have been reported in some surveillance studies, susceptibility to amantadine among HPAI A(H5N1) viruses remains variable, depending on the specific clade and/or strain of the circulating virus.[56,57,65]

The rate of amantadine treatment-emergent resistance in humans is unclear due to the very limited available data on amantadine use to treat HPAI A(H5N1).

Supplemental Information: Antiviral Agents

Oseltamivir

Oseltamivir is the preferred antiviral agent for the treatment of HPAI A(H5N1) by PHAC even though it has not been approved by Health Canada for this indication.[71]

Dose and duration recommendations for HPAI A(H5N1) treatment

Table 1 outlines age-specific dosing recommendations for the treatment of HPAI A(H5N1).

Higher dosing of oseltamivir for patients with influenza has not demonstrated any improvement in clinical or virologic outcomes.[43] One randomized controlled trial of adults and children with severe influenza that compared double dose oseltamivir (150 mg orally twice daily) with standard dose oseltamivir (75 mg orally twice daily) found no significant difference between the two treatment groups for mortality, need for supplemental oxygen or mechanical ventilation, admission to the ICU or viral shedding by day 5.[72] The generalizability of the study's findings to patients with HPAI A(H5N1) may be limited because only 7% of the patients in the trial had HPAI A(H5N1).[72] No dose adjustment of oseltamivir is required for obese individuals.[73,74]

Oseltamivir is not approved for use in infants younger than 1 year of age.[71,75] Oseltamivir dosing recommendations for this age group are adapted from national and international guidelines for the treatment of seasonal influenza.[75–78] Due to limited data for oseltamivir use in infants younger than 1 year of age, treatment should only be considered after a thorough risk assessment and in consultation with specialist(s) as required (e.g., ID, pediatrician).[2]

The recommended duration of oseltamivir for HPAI A(H5N1) treatment is 5 days.[2,20] In exceptional circumstances where a prolonged course of oseltamivir therapy beyond 5 days may be considered for selected patients (e.g., severely ill hospitalized patients, patients with persistent symptoms and evidence of ongoing viral replication), consultation with an ID specialist is strongly recommended.[2,79]

Table 1. Oseltamivir Dose Recommendations for HPAI A(H5N1) Treatment[#]

Age and Weight Group	Dose
13 years and older, AND weight greater than 40 kg	75 mg orally (PO) or by oro/nasogastric tube (OG/NG) twice daily[2]
13 years and older, AND weight less than or equal to 40 kg	60 mg PO/OG/NG twice daily[46]
1 to 12 years, AND weight greater than 40 kg	75 mg PO/OG/NG twice daily[2]
1 to 12 years, AND weight greater than 23 to 40 kg	60 mg PO/OG/NG twice daily[2]
1 to 12 years, AND weight greater than 15 kg to 23 kg	45 mg PO/OG/NG twice daily[2]
1 to 12 years, AND weight less than or equal to 15 kg	30 mg PO/OG/NG twice daily[76]
Full-term infants 9 months to younger than 12 months	3.5 mg/kg/dose PO/OG/NG twice daily[**,75,76]
Full-term infants younger than 9 months	3 mg/kg/dose PO/OG/NG twice daily[75,76]
Premature infants, AND older than 40 weeks postmenstrual age (PMA)	3 mg/kg/dose PO/OG/NG twice daily[75,76]
Premature infants, AND 38 through 40 weeks PMA	1.5 mg/kg/dose PO/OG/NG twice daily[76]
Premature infants, AND younger than 38 weeks PMA	1 mg/kg/dose PO/OG/NG twice daily[76]

[#] The dosing recommendation is adapted from seasonal influenza treatment guidance.[2,46,75,76]

[**] The American Academy of Pediatrics recommends 3.5 mg/kg orally twice daily instead of 3 mg/kg orally twice daily for infants in this age group to achieve target oseltamivir exposure.[76,80] It is unknown whether the higher dose will improve efficacy or prevent the development of antiviral resistance.[81] However, there is no evidence that the 3.5 mg/kg dose increases adverse events in infants from this age group.[81]

Dose adjustment for renal impairment

See Tables 4 and 5 of Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza** for oseltamivir dose adjustments for renal impairment. Renal dose adjustment of oseltamivir to treat HPAI A(H5N1) is based on its use for seasonal influenza treatment.

Dose adjustment for hepatic impairment

No dose adjustment is necessary for patients with mild to moderate hepatic impairment.[71] The safety and efficacy of oseltamivir in patients with severe hepatic impairment has not been studied.[71]

Other drug-related information

For information related to administration considerations, pregnancy, breastfeeding/chest-feeding, clinically relevant contraindications, drug-drug interactions and adverse drug effects, see the supplemental drug information section for oseltamivir in Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza**.

Drug availability and coverage

For information related to oseltamivir availability and drug coverage, see the drug availability section of Ontario Health's **Influenza Clinical Guideline and Resources** webpage.

Zanamivir

The treatment of HPAI A(H5N1) with INH zanamivir is considered off-label use in Canada.[21] Consultation with an ID specialist is recommended prior to initiating zanamivir for HPAI A(H5N1) therapy.

AMMI Canada recommends INH zanamivir as an alternative to oseltamivir for the treatment of HPAI A(H5N1) when oseltamivir-resistant HPAI A(H5N1) is known or suspected.[20] However, INH zanamivir may be not be as effective for patients with severe and/or extrapulmonary HPAI A(H5N1) infection due to low bioavailability.[20]

Dose and duration recommendations for HPAI A(H5N1) treatment

Table 2 outlines age-based dosing recommendations for INH zanamivir adapted from its use to treat non-severe seasonal influenza due to limited data available on zanamivir therapy for HPAI A(H5N1)[79]. No dose adjustment of INH zanamivir is required for obese individuals.[82]

The recommended duration of zanamivir for HPAI A(H5N1) treatment is 5 days.[20,82] In exceptional circumstances where a prolonged course of zanamivir therapy beyond 5 days may be considered for selected patients (e.g., severely ill hospitalized patients, patients with persistent symptoms and evidence of ongoing viral replication), consultation with an ID specialist is strongly recommended.[2,79]

Table 2: Inhaled Zanamivir Dose Recommendations for HPAI A(H5N1) Treatment[††]

Age	Dose
7 years and older	10 mg INH twice daily[21,82] (A second dose should be administered on the first day of treatment whenever possible, provided there is at least 2 hours between doses. On subsequent days, doses should be 12 hours apart at approximately the same time each day.)
Younger than 7 years	Health Canada has not approved INH zanamivir for use in this age group.[‡‡,21]

[††] The dosing recommendations are adapted from the dosing used to treat non-severe seasonal influenza.[20]

[‡‡] AMMI Canada and PHAC do not have dosing recommendations for INH zanamivir in children younger than 7 years of age.[2,82] However, some countries have approved the use of INH zanamivir for seasonal influenza based on limited efficacy data for children aged 5 to 7 years.[46,83,84] The safety and effectiveness of INH zanamivir have not been assessed in pediatric patients under 5 years of age.[21]

Dose adjustment for renal impairment

No dosage adjustment is provided for INH zanamivir in the manufacturer's labelling for individuals with renal impairment.[21]

Dose adjustment for hepatic impairment

No dose adjustment is provided for INH zanamivir in the manufacturer's labelling for individuals with hepatic impairment.[21]

Other drug-related information

For information related to administration considerations, pregnancy, breastfeeding/chest-feeding, clinically relevant contraindications, drug-drug interactions and adverse drug effects, see the supplemental drug information section for zanamivir in Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza**.

The use of IV zanamivir for the treatment of HPAI A(H5N1) is considered off-label use in Canada and this formulation is only available through Health Canada's **Special Access Program**. For additional information about **IV zanamivir**, see the supplemental drug information section for zanamivir in Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza**.

Drug availability and coverage

For information related to zanamivir availability and drug coverage, see the drug availability section of Ontario Health's **Influenza Clinical Guidelines and Resources** webpage.

Baloxavir

Baloxavir is not approved for HPAI A(H5N1) treatment in Canada.[66] Consultation with an ID specialist is recommended prior to initiating baloxavir for off-label treatment of HPAI A(H5N1).

Dose and duration recommendations for HPAI A(H5N1) treatment

National and international guidelines have not established standardized dosing regimens for baloxavir to treat HPAI A(H5N1) because no clinical trial has evaluated baloxavir's efficacy for this indication. Table 3 outlines the baloxavir dosing regimen and treatment duration used by the FLAGSTONE clinical trial to treat severe seasonal influenza in patients aged 12 years and older.[50] The weight-based baloxavir dosing regimen utilized in the FLAGSTONE trial was also used by a small case series to treat HPAI A(H5N6).[49] In the case series, patients were treated with baloxavir every 3 days until viral RNA was undetectable by repeat reverse-transcriptase polymerase chain reaction (RT-PCR) testing.[49] In the Canadian case report where baloxavir was used as part of combination therapy with oseltamivir and amantadine to treat a patient with HPAI A(H5N1), baloxavir 80 mg was administered every 48 hours until viral RNA was no longer detectable from respiratory specimens.[52,55] No dose adjustment of baloxavir is required for obese individuals.[66]

The optimal duration of baloxavir for the treatment of HPAI A(H5N1) is unknown.[23] In circumstances where a course of baloxavir therapy beyond 2 doses may be considered for selected patients (e.g., severely ill hospitalized patients, patients with persistent symptoms and evidence of ongoing viral replication), reassessment by an ID specialist is strongly recommended.[2,79]

Table 3. Baloxavir Dose Recommendations for HPAI A(H5N1) Treatment for Individuals Aged 12 Years and Older[##]

Weight	Dose
40 kg to less than 80 kg	40 mg PO on day 1 and day 4, with an additional dose on day 7 if no clinical improvement by day 5[***,50]
80 kg or greater	80 mg PO on day 1 and day 4, with an additional dose on day 7 if no clinical improvement by day 5[***,50]

[##] The dosing recommendations are adapted from the dosing used to treat severe seasonal influenza.

[***] No clinical improvement was defined in the clinical trial as fulfilling at least one of the following criteria: ongoing mechanical ventilation, persistent fever, being severely immunocompromised, having pneumonia, confirmed or suspected influenza-related complication.[50]

Dose adjustment for renal impairment

No dose adjustment for baloxavir is provided in the manufacturer's labelling for individuals with renal impairment.[66] The safety and efficacy of baloxavir have not been established in patients with renal impairment.[50,66] As baloxavir is primarily excreted through the fecal pathway, renal impairment is unlikely to have a significant impact on its clearance.[66]

Dose adjustment for hepatic impairment

No dose adjustment is required in patients with mild (Child-Pugh class A) to moderate (Child-Pugh class B) hepatic impairment.[66] Baloxavir has not been studied in patients with severe hepatic impairment.[66]

Other drug-related information

For information related to administration considerations, pregnancy, breastfeeding/chest-feeding, clinically relevant contraindications, drug-drug interactions and adverse drug effects, see the supplemental drug information for baloxavir in Ontario Health's **Recommendations for Antiviral Therapy of Seasonal Influenza**.

Drug availability and coverage

For information related to baloxavir availability and drug coverage, see the drug availability section of Ontario Health's **Influenza Clinical Guidelines and Resources** webpage.

Additional Resources

- Ontario Health:
  - Influenza clinical guidelines and resources
- Ontario Ministry of Health:
  - Ontario public health standards - influenza disease protocol
  - Avian influenza
- Public Health Ontario:
  - Laboratory testing for respiratory viruses
  - Ontario respiratory virus tool
- Public Health Agency of Canada:
  - Avian influenza A(H5N1) for health professionals
  - Pandemic risk scenario analysis for influenza A(H5N1)
- Association of Medical Microbiology and Infectious Disease Canada:
  - Statement on antiviral therapy for HPAI and reported oseltamivir resistance in Canada
  - Update on influenza: management and emerging issues
- International guidelines:
  - Infectious Diseases Society of America: antivirals for novel influenza A virus infections
  - U.K. Health Security Agency: guidance for the management of people exposed to birds or other animals infected with influenza A(H5)
  - U.S. Centers for Disease Control and Prevention: interim guidance on the use of antiviral medications for treatment of human infections with novel influenza A viruses associated with severe human disease
  - World Health Organization: clinical practice guidelines for influenza
- Drug product monographs:
  - Baloxavir product monograph (Canada)
  - Oseltamivir product monograph (Canada)
  - Peramivir product monograph (Canada)
  - Zanamivir (inhaled) product monograph (Canada)
  - Zanamivir (intravenous) product monograph (European Medicines Agency)
  - Amantadine product monograph (Canada)

Questions

For any questions on the contents of this document, please contact the Provincial Drug Reimbursement Programs (PDRP) at OH-CCO_InfoPDRP@ontariohealth.ca.

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About IDAC

IDAC provides Ontario Health with timely evidence-based clinical and health system guidance on infectious diseases matters. It is a multidisciplinary committee comprised of health care professionals practising throughout Ontario who specialize or have a focus in treating infectious diseases in the hospital or community setting.

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