AMMI Canada Statement on Antiviral Therapy for HPAI and Reported Oseltamivir Resistance in Canada

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Highly pathogenic avian influenza (HPAI) A(H5Nx) clade 2.3.4.4b viruses have been circulating in North America since late 2021. Since their initial incursion, they have been associated with unprecedented mortalities in wild birds, domestic poultry and marine mammals throughout the Americas, and are now seen across all global regions except Oceania. Furthermore, transmission among dairy cattle and poultry in the United States has led to growing numbers of human cases, and there was a severe human case in Canada with no known infected animal exposure.[1,2]

In Canada, over 13 million domestic birds have been destroyed as of December 2024 in an attempt to control the spread of HPAI.[3] There have been multiple spillover events to free-ranging mammals, resulting in severe and fatal disease.[4] The majority of highly pathogenic H5Nx viruses circulated in Canada are H5N1, though H5N2 and H5N5 have been reported.[5] Although the majority of contemporary H5N1 viruses are susceptible to neuraminidase inhibitors, resistance has been described in wild and domestic birds.[6,7] Ongoing surveillance for H5Nx viruses in wild and domestic avian and mammalian species provides critical information regarding the prevalence of potential antiviral resistance mutations. In November 2024, an oseltamivir-resistant HPAI H5N1 virus (bearing the H275Y mutation) was detected from domestic poultry in a geographically restricted area in Western Canada. Phenotypic testing demonstrated retention of zanamivir susceptibility.[8] Provided the majority of H5N1 viruses in Canada remain susceptible to oseltamivir, we continue to recommend previously outlined guidance in the 2023 AMMI Canada update on influenza, section 5, *Emerging issues related to HPAI* virus:[9]

Antiviral recommendations for HPAI

A. Treatment recommendations for HPAI infection in adults:

Oseltamivir 75 mg orally twice daily for 5 days.

B. Chemoprophylaxis recommendations after exposure to HPAI:

Exposure* to a person infected with HPAI or a discrete time-limited exposure to poultry or other zoonotic source of HPAI: Oseltamivir 75 mg orally twice daily x 10 days.

Chemoprophylaxis should be limited to discrete exposure events to confirmed cases and prolonged long-term use is not advised at this time.

*Exposure as defined by local public health and infection prevention and control.

Key considerations when prescribing anti-viral medication for HPAI prevention (chemoprophylaxis) or treatment

1. For chemoprophylaxis after exposure to highly pathogenic avian influenza virus (as opposed to seasonal influenza viruses), neuraminidase inhibitor **treatment** doses are recommended (75mg po bid); once daily dosing is reserved for seasonal influenza virus chemoprophylaxis.
2. The recommended duration for chemoprophylaxis therapy is 10 days. This accounts for regimens used in pre-clinical studies and potentially longer incubation period of avian influenza viruses in humans compared to seasonal influenza strains.[10,11] Furthermore, this ensures an adequate course of therapy and mitigation of the emergence of resistance in the event infection occurs, given evidence of prolonged shedding in humans relative to seasonal influenza viruses.[12-15] In addition, human cases of HPAI without clear sources of exposure have emerged, and potential for cryptic inter-species (mammalian) transmission further underscore uncertainties around clearly ascertaining timing of exposure.[1,2,16]
3. Zanamivir may be considered an alternative to oseltamivir for chemoprophylaxis or treatment and should be used according to the treatment dosing outlined in the AMMI Canada Foundations document for seasonal influenza.[17]
4. **In situations where oseltamivir-resistant H5N1 (NA:H275Y) is known or highly suspected,** inhaled zanamivir is recommended for chemoprophylaxis or treatment, recognizing that inhaled NAIs may not be effective for severe and/or extra-pulmonary, HPAI infection. For chemoprophylaxis, full doses (10mg or two 5mg inhalations, twice daily) for 10 days should be considered. Zanamivir is approved for use in Canada; however ready access of some formulations may be challenging. While there is evidence that the D1.1 genotype bearing the NA:H275Y mutation that circulated in British Columbia in 2024 remained susceptible to zanamivir (but not peramivir),[8] other neuraminidase mutations may confer resistance to zanamivir. Reaching out to an Infectious Disease specialist or pharmacist is recommended.
5. In the event of human HPAI infection, consideration should be given to initiating anti-viral **treatment** for that individual even if more than 48 hours from the symptom onset have elapsed, due to the potential for severe illness with individual HPAI infection ongoing viral replication, and population risks in the event of transmission to others.
6. There are no clinical data to inform the effectiveness of baloxavir for treatment of HPAI specifically; recommendations on its use are largely extrapolated from studies on seasonal influenza virus infection. For severe seasonal influenza, there are very

limited clinical data supporting using either baloxavir alone or in combination therapy with standard-of-care neuraminidase inhibitor,[8] and no substantive clinical data for management of severe illness due to HPAI clade 2.3.4.4b. The addition of baloxavir (40mg orally if <80kg, 80mg orally if >80mg, X1), to neuraminidase inhibitors may be considered for cases of **severe, complicated, or progressive illness** or those at higher risk for complications due to influenza infection due to **underlying medical conditions.** Although combination therapy for severe seasonal influenza did not improve clinical outcomes, viral loads were reduced.[18,19] Also, in a small case series (n=5), it was suggested that the addition of baloxavir to oseltamivir resulted in more rapid clearance of H5N6 virus, compared with oseltamivir monotherapy.[20] Baloxavir, in combination with inhaled zanamivir also presents a reasonable treatment option for oseltamivir-resistant HPAI. Mutations associated with baloxavir resistance have emerged during treatment for seasonal influenza.[21] Baloxavir is approved but not marketed in Canada, and thus requested through the Special Access Program.

7. Due to high levels of resistance to amantadine, it is not recommended as a treatment option.

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