



**Interim Guidance for Antiviral Prophylaxis and Treatment of Influenza Illness due  
to Avian Influenza A(H7N9) Virus**

Revised: July 12, 2013

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## **Avian Influenza A(H7N9) Virus Infection**

### **Introduction**

This guidance document has been prepared to assist clinicians with the use of antiviral agents for the treatment of patients presenting with clinical influenza-like illness (ILI) symptoms which may be due to avian influenza A(H7N9) virus as well as prevention of disease amongst their close contacts. It is based on current scientific evidence about this emerging virus, and is subject to review and change as new information becomes available. The following guidance should be read in conjunction with other emerging information on avian influenza A(H7N9). These guidelines provide information related to the use of antivirals for the prevention and clinical management of influenza-like illness that are suspected or, are laboratory confirmed to be, due to infection by avian influenza A(H7N9).

### **Background**

On 31 March 2013, the China National Health and Family Planning Commission notified the World Health Organization (WHO) of three cases of human infection with avian influenza A(H7N9). This is the first time that a low pathogenic avian influenza virus is being associated with human fatalities. To date, the avian influenza A(H7N9) virus continues to circulate primarily in China with only one case occurring outside the Chinese mainland, in Taiwan, in a traveler who had a risk exposure in Eastern China. The first known human case became ill on February 19, 2013 and through to May 3, 2013, a case-fatality rate of >20% has been reported by WHO.<sup>1</sup> For the latest updates on the total number of cases and deaths please visit the [Global Alert and Response website](#). Avian

influenza A(H7N9) virus infection has occurred mostly in individuals who have had known or suspected contact with infected birds, chiefly poultry and/or exposure to their environment in poultry markets. Avian influenza A (H7N9) virus has been isolated from the bodily fluids and excreta of poultry.<sup>2</sup> These viruses are genetically concordant with virus obtained from human infections caused by avian influenza A(H7N9) virus.<sup>3</sup> In birds, avian influenza A(H7N9) virus does not appear to cause a readily identifiable illness. Persons with a history of having worked in poultry feeding, transportation, selling, slaughter, or processing or other forms of contact with poultry within 7 days of the onset of illness, carry the highest risk for infection.<sup>2</sup> Sustained human-to-human transmission has not been documented to date. There is no currently available effective human vaccine for the prevention of infection with avian influenza A(H7N9) virus.

#### **Clinical Illness due to avian influenza (H7N9) virus<sup>4,5</sup>**

Published evidence has indicated that influenza in humans due to avian influenza A(H7N9) virus has a median incubation period of 5 days. The most common presenting symptoms of avian influenza A(H7N9) virus infection from a report of 111 cases are: fever (100%) and cough (90.1%) with sputum production and dyspnea seen in 55.9% of patients. Hemoptysis was seen in approximately 25% of patients at presentation.

Radiologic findings consistent with pneumonia were seen in 97.3% of patients at hospital admission with avian influenza A(H7N9) virus infection. Severe disease can develop rapidly. In those who develop severe pneumonia, it typically occurs within 5-7 days of illness onset. Most cases with severe pneumonia have a persistent temperature over 39°C, difficulty breathing, and may have accompanying hemoptysis. Rapid progression to acute respiratory distress syndrome (ARDS), sepsis, and multi-organ dysfunction syndrome has

been described predominantly in those over age 65 years and with coexisting medical conditions. Patients with severe disease have exhibited lymphopenia and thrombocytopenia along with increases of serum lactate dehydrogenase, creatine kinase, aspartate aminotransferase, and C-reactive protein.

### **Clinical Assessment**

Infection with avian influenza H7N9 virus should be suspected on the basis of clinical presentation and a history of travel to jurisdictions where avian influenza A(H7N9) virus is known to be circulating in animals. At present, travel, with or without exposure to birds or close contact with an ill individual in China and Taiwan, are considered the chief risk factors for infection with avian influenza A(H7N9) virus. As of May 27, 2013, other risk factors for infection are not well defined.

It has also been suggested that close contact, in the two weeks prior to illness onset with an individual who has recently traveled to a country where human cases of avian influenza A(H7N9) virus have recently been detected should also be considered a risk factor for infection.<sup>6</sup>

### **History**

Patients presenting with new onset respiratory symptoms should be assessed for the clinical features of ILI. ILI is defined as an acute onset of respiratory illness with fever, cough and with one or more of the following: sore throat, arthralgia, myalgia or prostration which is likely due to influenza. The symptoms of influenza are summarized in Table 1.

**Table 1.**

**Influenza Symptoms**

Typical	Common	Sometimes
Sudden onset of cough and fever	Sore throat Coryza Fatigue/malaise/prostration Myalgias/artralgias Headache	Vomiting Diarrhea Nausea

Atypical presentations of influenza that can be seen at the extremes of age and in immunocompromised persons have not yet been described with avian influenza A(H7N9) virus human infection. People with chronic lung conditions may present with a change in or worsening cough. Based on seasonal influenza data, elderly individuals may present on occasion without fever and with atypical presentations. Obtaining a travel history remains a best practice and could be significant for avian influenza A(H7N9) virus (e.g., a patient coming from China with or without a contact history with infected birds). Enquire about contact within the prior two weeks with ill persons particularly those who may have a history of travel to a country where human cases of avian influenza A(H7N9) virus have recently been detected.<sup>5</sup> or known to be circulating in animals (currently China and Taiwan). An occupational or exposure history to animals may be relevant in determining potential contact with infected avian species.

Patients who initially present with uncomplicated influenza may progress rapidly to more severe disease. Severe or progressive disease requires immediate medical attention and hospitalization . Severity indicators and signs of disease progression are listed in Table 2.

**Table 2.**

<b>* Signs of severe or progressive influenza</b>
<ol style="list-style-type: none"><li>1. Shortness of breath, wheezing, rapid or difficulty breathing</li><li>2. Chest pain</li><li>3. Signs of pneumonia</li><li>4. Hemoptysis</li><li>5. Sudden dizziness</li><li>6. Confusion/disorientation/seizures</li><li>7. Severe or persistent vomiting</li><li>8. High fever lasting more than 3 days</li><li>9. Hypotension</li><li>10. Bluish or grey skin color</li><li>11. Flu-like symptoms that improve but then return with fever and worsening cough</li></ol> <p><b>Additional symptoms in infants and young children:</b></p> <ol style="list-style-type: none"><li>12. Not waking up or interacting</li><li>13. Not eating or drinking enough fluids</li><li>14. Irritability; not wanting to play or be held</li></ol>

### **Diagnostic criteria**

The following criteria for the diagnosis of avian influenza A(H7N9) virus infection have been adapted from published data.<sup>2,7</sup>

#### **1. Exposure criteria.**

- a. Confirmed exposure history or close contact with a laboratory-confirmed or suspected case of avian influenza A(H7N9) virus infection within 14 days prior to illness onset.

AND/OR

- b. Travel to, or close contact within 14 days prior to illness onset, with a person having recent travel to a country where human cases of avian influenza A(H7N9) virus have been detected or avian influenza A(H7N9) virus is known to be circulating in animals. The following link provides up to date

information on countries of interest.

<[http://www.who.int/influenza/human\\_animal\\_interface/influenza\\_h7n9/en](http://www.who.int/influenza/human_animal_interface/influenza_h7n9/en)>

## 2. Clinical case definitions with laboratory criteria

- a. **Suspected case or Person under investigation:** Clinical symptoms consistent with acute influenza (see Table 1) plus any positive exposure criterion (see above).
- b. **Probable case:** Clinical symptoms consistent with acute influenza (see Table 1) plus any positive exposure criterion AND preliminary laboratory testing indicates a positive test for influenza A, not H3 or H1.
- c. **Confirmed case:** Clinical symptoms consistent with acute influenza AND a laboratory confirmation of avian influenza A(H7N9) virus by PCR, viral isolation or a four-fold or greater increase in serum antibodies specific for avian influenza A(H7N9) in paired sera.
- d. **Severe case:** A confirmed, presumptive or suspected case complicated by respiratory failure or other organ failure with or without pneumonia.

### Laboratory diagnosis

Laboratory testing for avian influenza A(H7N9) virus should follow the PHAC Interim Guidance for laboratory testing. <[http://ammi.ca/media/54083/cphln\\_sari\\_-\\_protocol\\_final.pdf](http://ammi.ca/media/54083/cphln_sari_-_protocol_final.pdf)>

Influenza A and B by RT-PCR with subtyping (H3N2 or H1N1) will be the primary method for detection of influenza. Influenza A positive viruses that cannot be subtyped

will be further characterized. Provincial laboratories that have the capacity will perform H7N9 subtyping by RT-PCR or by sequencing methods (e.g. sequence the M gene). Those that lack this capacity will rely on the NML for further characterization. . All H7N9 positive specimens are referred to the NML for confirmation.

### **Clinical Management**

1. **Isolation.** Suspected, probable and confirmed cases should be placed in a single room and be managed according to PHAC Interim Guidance for Avian Influenza A(H7N9) virus for Infection Prevention and Control in Acute Care Settings <<http://www.phac-aspc.gc.ca/eri-ire/h7n9/guidance-directives/h7n9-ig-dp-eng.php>> including use of Routine Practices, Contact and Droplet Precautions and Airborne Precautions in the context of Aerosol Generating Medical Procedures (AGMP).
2. **Symptomatic treatment.** Oxygen and other supportive measures as indicated. There are no data to support the use of anti-inflammatory therapies, such as corticosteroids in the management of avian influenza A(H7N9) virus infection.
3. **Antivirals.** An appropriate antiviral drug regimen for influenza virus infection should be administered as soon as the diagnosis of avian influenza A(H7N9) virus infection is considered. The results of definitive laboratory testing for infection with avian influenza A(H7N9) virus should not delay the initiation of antiviral therapy. Antiviral therapy is advisable up to 5 days after onset of illness and can still be considered beyond 5 days in some circumstances.

## **Principles of antiviral treatment for avian influenza A(H7N9) virus**

Avian influenza A(H7N9) virus is reported to be susceptible to neuraminidase inhibitors (NIs) such as: oseltamivir and zanamavir but resistant to M2 ion channel blockers (adamantanes) such as amantadine and rimantadine. Experience with antiviral treatment of avian influenza A(H7N9) virus illness is limited and the rate of emergence of drug resistance is unknown. In a recent report, antiviral treatment with NIs was associated with a reduction of viral load in throat swab specimens in 11 surviving patients with avian influenza A(H7N9) infection.<sup>8</sup> In this same report, 3 patients had persistent high viral loads in the specimens from the respiratory tract in spite of antiviral therapy and ultimately required ECMO (extracorporeal membrane oxygenation). Resistance to neuraminidase inhibitors developed in viral isolates from two of these three ECMO-dependent patients. In both patients the reported NA mutation (Arg292Lys) was found in viral isolates only after antiviral therapy was started and ultimately became the predominant population within 7-9 days into treatment. This mutation is known to confer resistance to both oseltamivir and zanamivir. Both of the latter patients were receiving concomitant corticosteroids, which may be a risk factor for the emergence of NI resistance in patients with persistent viral shedding while on antiviral therapy. Before or simultaneously with the initiation of antiviral therapy, respiratory specimens should be collected and submitted for diagnostic laboratory testing. NIs for influenza should ideally be initiated within 48 hours of symptom onset. However, due to the high case-fatality rate with avian influenza A(H7N9) virus infection, it is recommended that influenza antiviral therapy be administered independent of the time of onset of ILI.

**Antiviral treatment is recommended in the following situations** (see Algorithm at [http://www.ammi.ca/media/54231/h7n9\\_algorithm\\_final.pdf](http://www.ammi.ca/media/54231/h7n9_algorithm_final.pdf))

1. At the time a diagnosis of avian influenza A(H7N9) virus infection is suspected, probable or confirmed (see Diagnostic criteria above) even for apparently uncomplicated ILI in a healthy person.
2. Patients with ILI who do not fulfil the exposure criteria for avian influenza A(H7N9) virus infection but have one or more of the following:
  - a. Rapid progression of influenzal illness. (see Table 2)
  - b. Pneumonia of unknown etiology consistent with influenza.
3. Due to the potential for seasonal influenza and other respiratory viruses to be circulating at the same time as a patient presents with ILI that might be due to avian influenza A(H7N9), clinicians should be cognizant of whether there is increased seasonal influenza virus activity in their communities through sites such as FluWatch or information from local Public Health officials. If this is the case, then initiation of antiviral therapy should follow previously published guidelines for seasonal influenza as appropriate.<sup>9</sup> In the absence of increased influenza activity in the community, a severely ill patient should be subject to a more thorough diagnostic evaluation or consultation with an infectious disease specialist.

**Antiviral dosing for treatment** (see Appendix A ,Tables 3 and 4)

Dosing of neuramindase inhibitors for treatment of avian influenza A(H7N9) virus infection should follow the recommendations for seasonal influenza as indicated in Table

3.<sup>9</sup> Recommendations for dosing of NIs in renal failure are outlined in Table 4. There is no currently available evidence that higher doses of NIs are needed in the treatment of avian influenza A(H7N9) infection. A recently published double-blind randomized controlled trial carried out in Singapore, Thailand and Vietnam, which compared oral oseltamivir at double versus standard dose in patients with either severe seasonal influenza, A/H1N1-pdm09 or avian influenza A(H5N1) infection, there were no virological or clinical advantages with using higher doses of oseltamivir in patients with severe influenza that were admitted to hospital.<sup>10</sup>

**Antiviral chemoprophylaxis and dosing recommendations** (see Appendix A)

It should be noted that there is no evidence of sustained human-to-human transmission of avian influenza A(H7N9) virus at this time, so the potential benefit of antiviral chemoprophylaxis needs to be seen in that context.

There are no data on the use of antiviral chemoprophylaxis for the prevention of illness due to avian influenza A(H7N9) virus infection. Extrapolation of the effectiveness of chemoprophylaxis for seasonal influenza virus infection suggest that this may be a useful strategy pending the availability of an effective vaccination. However, in the absence of clear outbreaks of avian influenza A(H7N9) virus infection or evidence of sustained human-to-human transmission, there is a limited role for antiviral chemoprophylaxis.

Should data become available on the use of antiviral chemoprophylaxis for avian influenza A(H7N9) virus infection, an update to will be issued in a timely fashion.

Details on the use of NIs for chemoprophylaxis of seasonal influenza can be found in the most recently published Canadian guidelines for antiviral therapy of seasonal influenza.<sup>3</sup>

**Appendix A.** (Adapted from Reference 8)

**Table 3.** Oseltamivir and zanamivir treatment of influenza in adults, children and youth

Medication		Treatment (5 days)	Prevention (10 days)
<b>Oseltamivir<sup>1</sup></b>			
<b>Adults</b>			
		75 mg twice daily†	75 mg once daily
<b>Children ≥ 12 months</b>			
Body Weight (kg)	Body Weight (lbs)		
≤15 kg	≤33lbs	30 mg twice daily	30 mg once daily
> 15 kg to 23 kg	>33 lbs to 51 lbs	45 mg twice daily	45 mg once daily
>23 kg to 40 kg	>51 lbs to 88 lbs	60 mg twice daily	60 mg once daily
>40 kg	>88 lbs	75 mg twice daily	75 mg once daily
<b>Children 3 months to &lt; 12 months<sup>2*</sup></b>			
		3 mg/kg/dose twice daily	3 mg/kg/dose once per day
<b>Children &lt; 3 months<sup>3*</sup></b>			
		3 mg/kg/dose twice daily	Not recommended unless situation judged critical due to limited data on use in this age group
*Please note that antivirals are not authorized for the routine treatment of seasonal influenza illness in infants less than 1 year of age. Such use may be considered on a case-by-case basis.			
† In severely ill adults consider a dose of 150 mg twice daily, if renal function is normal.			
<b>Zanamivir<sup>4</sup></b>			
<b>Adults</b>			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
<b>Children (≥7 years or older for treatment and chemoprophylaxis)</b>			
		10 mg (two 5-mg inhalations) twice daily	10 mg (two 5-mg inhalations) once daily
<p>1. Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available in 30 mg, 45 mg, and 75 mg capsules, and as a powder for oral suspension that is reconstituted to provide a final concentration of either 6 mg/ml or 12 mg/mL. If the commercially manufactured oral suspension is not available, the capsules may be opened and the contents mixed with a sweetened liquid to mask the bitter taste or a suspension can be compounded by retail pharmacies (final concentration 6 mg/mL). When dispensing commercially manufactured Oseltamivir (TAMIFLU) Powder for Oral Suspension (6 mg/ml or 12 mg/mL), pharmacists should ensure the units of measure on the</p>			

prescription instructions match the dosing device.

2. Weight-based dosing is preferred. However, if weight is not known, dosing by age for treatment of influenza (give two doses per day) or prophylaxis (give one dose per day) in full-term infants younger than 1 year of age may be necessary: 0-3 months = 12 mg per dose for treatment (not for prophylaxis); 3-5 months = 20 mg per dose; 6-11 months = 25 mg per dose.
3. Current weight-based dosing recommendations are not intended for premature infants. Premature infants may have slower clearance of oseltamivir due to immature renal function, and doses recommended for full term infants may lead to very high drug concentrations in this age group. Very limited data from a cohort of premature infants demonstrated that oseltamivir concentrations among premature infants given 1 mg/kg body weight twice daily were similar to those observed with the recommended treatment doses in term infants (3 mg/kg body weight twice daily). Observed drug concentrations were highly variable among premature infants. The Infectious Diseases Society of America 2011 recommendations for pediatric pneumonia suggest 2 mg/kg/day divided twice daily. Currently available data are insufficient to recommend a specific dose of oseltamivir for premature infants; it is strongly suggested that an infectious disease physician or clinical pharmacist should be consulted.
4. Zanamivir is administered by inhalation using a proprietary “Diskhaler” device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for persons with chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease that increase the risk of bronchospasm. Intravenous formulations of zanamivir are under clinical investigation but are not authorized for use in Canada. In specific circumstances, intravenous zanamivir may be obtained through the Special Access Programme of Health Canada (<http://www.hc-sc.gc.ca/dhp-mps/acces/drugs-drogues/index-eng.php>).

**Table 4.**

Recommended oseltamivir regimens for treatment of patients with renal impairment

Creatinine clearance	Treatment	Prevention
>30mL/min	75mg twice daily	75 mg once daily
>10–30mL/min	75mg once daily OR 30mg suspension twice daily OR 30mg capsule twice daily	75 mg on alternate days or 30 mg once daily
≤10mL/min (renal failure)*	Single 75mg dose for the duration of illness	No data
Dialysis patients*	Low-flux HD: 30mg after alternate dialysis sessions High-flux HD: 75mg after each dialysis session CAPD dialysis: 30mg once weekly CRRT high-flux dialysis: 30mg daily or 75mg q48hrs	75 mg every 5 days
The following dosing regimen has been suggested for children based on limited data. In children greater than 1 year of age, after alternate HD sessions (7.5 mg for children weighing > 15 kg; 10 mg for children weighing 16–23 kg; 15 mg for children weighing 24–40 kg, and 30 mg for children weighing > 40 kg). While this may provide a framework for guidance, it is strongly suggested that an infectious disease physician or clinical pharmacist should be consulted.		

\*Experience with the use of oseltamivir in patients with renal failure is limited. These regimens have been suggested based on the limited available data. Consultation with an infectious physician or clinical pharmacist is recommended.

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