

Clinical Management Guideline

Introduction

Avian Influenza (AI), also known as Bird Flu, is an infection caused by type A influenza viruses that primarily infects avian species, but infection with these viruses can occur in humans. Highly pathogenic avian influenza viruses have caused outbreaks in poultry in many countries. In addition to spreading geographically, the virus is gradually expanding the host range (domestic, wild and migratory birds, and animals such as pigs, cats and tigers) and jumping to the humans occasionally.

Although the virus is yet to acquire the ability for efficient human-to-human transmission, this may happen soon due to continuous human exposure in many countries. If this happens, the next influenza pandemic may start with serious consequences on health and resulting in major social, economic and political disruption.

Bhutan is not yet affected by the current avian influenza outbreaks in Asia but is highly vulnerable. It may be affected by H5N1 virus through importation of infected poultry, through migratory birds, or through humans if the virus acquires the ability to spread from person to person in currently affected countries. Bhutan and India have virtually an open border and there is a heavy traffic of people and goods between Bhutan and India. The majority of the poultry import comes from India.

To deliver medical care efficiently to the patients infected with AI during pandemic, MoH has drafted guideline on different aspects of AI so that the health care provider can manage the patients as per the standard procedure both clinically and logistically. The guideline was drafted by a group of technical people from JDWNRH in coordination with DoPH.

Case management (hospital)

Epidemiology

To date most of the cases of Human Avian Influenza are attributed to direct contact with infected poultry or poultry products. So far transmission of bird flu from human-to-human has not been efficient. However, influenza viruses are highly unstable and have the ability to mutate rapidly. This means that changes in the virus could lead to easier spread between people leading to a pandemic influenza. This can result in a serious and prolonged outbreak affecting all aspects of society.

Transmission

- Direct contact with poultry and its product and secretion especially feces
- Contact with contaminated feed, water, equipment and clothing
- Human-to-human transmission: This form of transmission is possible but currently the risk is low. Human-to-human influenza is air borne (droplet infection).

Incubation period/Infectious period

The time from presumed exposure to onset of illness ranges from two to eight days, the median being 4 days. For field investigations and monitoring purposes WHO recommends the use of incubation period of 7 days. An adult is considered infectious 7 days after resolution of fever. In case of children the infectious period is 21 days. All ages and both sexes are said to be equally susceptible.

Clinical presentation of human cases of Avian Influenza and diagnosis

The clinical presentations of human cases of AI are very similar to seasonal influenza. Majority of patients present with fever, cough and difficulty in breathing and diarrhea (an uncommon feature in seasonal influenza). However, features that may differ from normal seasonal influenza include:

1. Longer incubation period
2. Early onset of pneumonia
3. Rapid progression to respiratory distress
4. High Case Fatality Rate(CFR)

The blood picture usually shows consistent lymphopenia and moderate thrombocytopenia and deranged liver function tests. Other findings may include abnormal chest radiographs. Patients may run a fulminant course developing Acute Respiratory distress Syndrome (ARDS) and end with multi organ failure.

Clinical diagnosis

To diagnose a human case of avian influenza in primary health –care setting during the pandemic alert phase, both clinical and epidemiological criteria are to be met. The clinical criteria are for case management where as the epidemiological criteria are primarily for case identification, referral and reporting purposes.

Clinical criteria

The most consistent clinical features include fever >38 degrees centigrade, cough, shortness of breath or breathing difficulty

Common features	Infrequent features	Rare
Onset after 2-8 days of exposure to sick/dying poultry	vomiting	Encephalopathy
Onset similar to seasonal influenza	Abdominal pain	
Fever >38 deg C	Chest pain	
Cough	Bleeding from nose and/or gums	
Difficulty in breathing after 5-7 days of onset	-	
Diarrhoea		
Myalgia		
Primary viral pneumonia		
Rapid deterioration to ARDS and multi organ failure		

Epidemiological criteria

For epidemiologically linking a suspected case to a known AI case, one or more of the following exposure categories are used, in the 7 days prior to symptom onset

- Close contact (within one meter) with a person (e.g. caring for, speaking with or touching) who is a suspected, probable or confirmed H5N1 case
- Sustained exposure (e.g. handling, slaughtering, plucking, butchering or preparing for consumption) to poultry or wild birds or their remains or environments contaminated by their faeces in an area where H5N1 infection in animals or humans have been suspected or confirmed in the last month.
- Consumption of raw or undercooked poultry products in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month
- Close contact with a confirmed H5N1 infected animal other than poultry or wild birds (e.g. cat or pig)
- Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.
- Touching birds (well appearing, sick or dead), poultry faeces or surfaces contaminated with faeces
- Consuming uncooked poultry products (including blood) in an affected area
- Close contact with a person from infected area with confirmed or suspected AI case

Any case fulfilling the clinical and epidemiological criteria should be treated as a **suspected case** of H5N1. The health-care provider should also remember that a case may turn up in an area not reporting avian influenza. A recent visit to or having come from an area affected by highly pathogenic avian influenza A and fulfilling the above clinical and epidemiological criteria qualify the patient to be classified as a suspected case.

Case definition of a human case of avian influenza (WHO)

Human influenza cases may be classified as suspected, probable or confirmed. Although the full knowledge of the three categories may be helpful for the attending clinicians at the primary health care level, it will only be possible to diagnose suspected or probable cases,

Suspected H5N1 case (notify DoPH)

A person presenting with unexplained acute lower respiratory illness with fever (>38.0 C) and cough, shortness of breath or difficulty in breathing AND **one or more** modes of exposures, seven days prior to the onset of the symptom:

- (a) Close contact (within 1 meter) with a person (e.g. caring for, speaking with or touching) who is a suspected, probable, or confirmed H5N1 case;
- (b) Exposure (e.g. handling, slaughtering, plucking, butchering, preparing for consumption) to poultry or wild birds or their remains or to environments contaminated by their faeces in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month;
- (c) Consumption of raw or undercooked poultry products in an area where H5N1 infections in animals or humans have been suspected or confirmed in the last month;

- (d) Close contact with a confirmed H5N1 infected animal other than poultry or wild birds (e.g. cat or pig);
- (e) Handling samples (animal or human) suspected of containing H5N1 virus in a laboratory or other setting.

Probable H5N1 case (notify DoPH)

Probable definition 1: A person meeting the criteria for a suspected case AND One of the following additional criteria:

- (a) Infiltrates or evidence of an acute pneumonia on chest radiograph plus evidence of respiratory failure (Hypoxemia, severe tachypnea);
OR
- (b) Positive laboratory confirmation of an influenza A infection but insufficient laboratory evidence for H5N1 infection.

Probable definition 2: A person dying of an unexplained acute respiratory illness who is considered to be epidemiologically linked by time place, and exposure to a probable or confirmed H5N1 case.

Confirmed H5N1 case (notify WHO)

A person meeting the criteria for a suspected or probable case AND a positive standard test conducted in a regional reference laboratory whose H5N1 test results are accepted by WHO as confirmatory.

Diagnostic Procedures

- Rapid antigen detection: Results can be obtained within 15 to 30 mins
- Immunoflorescence assay (A and B and 5 other respiratory viruses)
- Enzyme Immunoassay
- Virus Culture – Provides results in 2 to 10 days: Both shell vial and standard cell culture method may be used.
- RT-PCR – Specific for influenza A virus. Results can be available within a few hours either from clinical swab or infected cell culture

Any case fulfilling the clinical and epidemiological criteria should be treated as a **suspected case** of H5N1 and reported to the DoPH. It is pertinent to remember that a case may turn up in an area not reporting avian influenza. A recent visit to or having come from an area affected by highly pathogenic avian influenza A and fulfilling the above clinical and epidemiological criteria qualify the patient to be classified as a suspected case

If a case meeting the criteria for a suspected case has evidence of an acute pneumonia and signs and symptoms of respiratory failure (hypoxemia, severe tachypnea), it qualifies as a **probable case**. A person dying of an unexplained acute respiratory illness who is considered to be epidemiologically linked by time, place and exposure to a probable or confirmed H5N1 case is also diagnosed as a probable case.

Only a Rapid antigen detection tests is possible in Bhutan. The confirmation of diagnosis requires specific tests for H5N1 virus, which can only be conducted in a specialized laboratory with adequate biosafety practices and infrastructure. Such biosafety level (BSL 2/3 laboratories are not available in Bhutan. However, doctors at all levels must know the criteria for case confirmation, the procedures to send clinical samples and the channel of communication.

A person meeting the criteria of suspected or probable case is classified as confirmed when a standard test is positive and conducted in a regional reference laboratory whose H5N1 test results are accepted by WHO as confirmatory.

Case Management

A triage protocol will be helpful to:

- a) Identify persons who might have pandemic influenza,
- b) Separate them from others to reduce the risk of disease transmission, and
- c) Identify the type of care they require (i.e., home care or hospitalization).

A step by step approach will be followed to manage all suspect and probable cases meeting clinical and epidemiological criteria.

Step-by-step approach to case management

Triage room

- Follow standard infection control precautions, including respiratory hygiene/cough etiquette while handling the patients
- If the patient meets the clinical and epidemiological criteria for a suspected case of H5N1 infection, notify relevant authority (doctor)
- Admit to pre designated isolation facility taking appropriate precautions (PPE, universal infection control procedures) during transfer of patients. (depending on severity and bed capacity)

In the isolation ward

- History and isolation of patient
- Make arrangement to carry out relevant tests
 - i. Collection of clinical specimens and biochemical tests
 - ii. Other investigations : X-ray chest
 - iii. Supportive and secondary treatment depending on condition of patient and lab/Xray results

Admission criteria

Based on pandemic situation and existing bed, staff capacity admission criteria should be reviewed regularly and decision taken for inpatient (isolation room) or out patient management.

- Admission priority should be given to serious patients having signs of pneumonia and ARDS
- Patients having ARDS may need ventilator support and should be treated in an ICU
- In case of a major pandemic when hospitals are overwhelmed with patients home care and advice for less serious cases may be considered as an option.

Treatment

Antiviral

Antiviral drugs are the mainstay of the treatment. To be effective, administration of antiviral drugs should be administered within 24-48 hours after exposure. If the case meets the clinical and epidemiological criteria, then treatment with antivirals should be started immediately without waiting for the laboratory confirmation. However before starting treatment the triage nurse should contact the clinician/medical specialist to review the clinical presentation of the patient and obtain advice on treatment modality.

Even if a case is detected late by the physician, antiviral therapy is still warranted. And even if the laboratory reports are negative, a strong epidemiological link is an indication to continue treatment.

The antiviral drug oseltamivir is currently available in the country and it is under the commercial name of Tamiflu

Dose and duration of treatment with oseltamivir (Tamiflu)

Available in bleb packing of 10 capsules each containing 75 mg of oseltamivir and oral suspension – 12 mg/ml. The recommended dose against influenza is:

Children (over 1 year):

Under 16 kg body weight	: 30 mg twice daily
16-23 kg body weight	: 45 mg twice daily
24-40 kg body weight	: 60 mg twice daily
Over 40 kg body weight	: 75 mg twice daily

Adults and adolescents (13 years or older): 75mg twice daily. Normal recommended duration of treatment is five days.

Adverse reactions

In terms of safety and adverse effects, evidence from the trials in seasonal influenza shows that although oseltamivir is generally well tolerated, gastro intestinal side effects (transient nausea, vomiting) may increase with increasing doses, particularly above 300 mg per day. Occasionally it may cause

bronchitis, insomnia and vertigo. Less commonly, angina, pseudo- membranous colitis and peritonsillar abscess have also been reported. There have been occasional reports of anaphylaxis and skin rashes.

In children, the most frequently reported side effect is vomiting. Infrequently abdominal pain, epistaxis, bronchitis, otitis media, dermatitis and conjunctivitis have also been observed.

Precautions

Self medication in the absence of appropriate clinical diagnosis is discouraged.

Oseltamivir dosage should be reduced in patients with renal impairment, if creatinine clearance is 10-30 ml/mol; the dose is reduced to 75 mg once daily.

Adequate data is not available in pregnant women. Decisions to use oseltamivir in pregnant women should be made on a case by case basis where the potential benefit to the mother justifies the potential risk to the fetus

There is no recommendation for dose reduction for patients with hepatic disease

Treatment decisions are to be taken on a case by case basis, in consultation with the medical specialist (JDWNRH)

Antibacterial drugs

Antibacterial agents should be administered, if required, following points are to be considered.

- Suspected human cases of H5N1, if not having pneumonia, do not require antibiotic therapy.
- Patients with community-acquired pneumonia should receive antibacterial therapy.
- Stop antibiotic treatment if initial bacteriological studies are negative and H5N1 is confirmed.
- Patients on mechanical ventilation should be administered antibacterial drugs prophylactically to prevent hospital-associated infections.
- Secondary bacterial infection requires appropriate anti biotic therapy

Symptomatic treatment

- Paracetamol or ibuprofen is prescribed for fever, myalgias and headache.
- The patient is advised to drink plenty of fluids.
- Smokers - advised to avoid smoking.
- For sore throat, a short course of topical decongestants, saline nasal drops, throat lozenges and steam inhalation may be beneficial.

Other pharmaceutical interventions

- High-dose corticosteroids in particular have no evidence of benefit and there is potential for harm.
- Low-dose corticosteroids (hydrocortisone 200-400 mg/day) may be useful in persisting septic shock(SBP < 90).
- Salicylate is strictly contra-indicated in any suspected/ confirmed patients of avian influenza due to its potential to cause Reye's syndrome.

Other important considerations

Respiratory support

Patients may report to a primary health care facility with ARDS or pneumonia that rapidly progresses to ARDS. Patients with signs of tachypnea, dyspnea, respiratory distress and oxygen saturation less than 90 percent should be supplemented with oxygen therapy. Patients with severe pneumonia and acute respiratory failure ($SpO_2 < 90\%$ and $PaO_2 < 60$ mmHg with oxygen therapy) must be supported with mechanical ventilation.

Transportation to hospital

If clinical findings or epidemiological link establish a human case of avian influenza, the patient may be referred from other health facilities in the district. The ambulance should have basic facilities for oxygen therapy and non-invasive ventilation. The patient should be accompanied by a trained technician. Aerosol-generating procedures should be avoided during transport unless life-saving.

If patient is not in respiratory distress, then the mouth and nose should be covered by ordinary surgical mask to contain droplets expelled during coughing. Drivers and health personnel should use standard droplet precautions if accompanying or handling a suspected or confirmed AI case during transport. The doctor on duty should be informed of the patient's arrival in advance. After the patient is admitted to the hospital, the patient cabin of the ambulance and reusable patient-care equipment should be sanitized using phenolic disinfectants or quaternary ammonia compounds or sodium hypochlorite.

During transportation of the patient the ambulance shall not stop enroute unless unavoidable. This is to ensure that the infection does not spread to the community.

Chemoprophylaxis: Preventive therapy of close contacts (Post exposure)

Irrational and overuse of antiviral agents can lead to the emergence of resistant viruses, raising another critical barrier in the fight against pandemic. Only post exposure cases merits chemoprophylaxis

Three groups have been defined, based on the risk profile, which are usually considered as candidates for chemoprophylaxis. The dose of chemoprophylactic agents is half that used for therapeutic purposes. A brief description of the risk groups and indications for chemoprophylaxis are given in the table below.

Table 1: Chemoprophylaxis against avian influenza

Level of risk	Risk groups	Chemoprophylaxis
High risk	Sharing household with or caring for a Patient. Unprotected close contact (<1 meter) with patient.	Oseltamivir in dose of 75 mg/day to continue for 7-10 days after last exposure.
Moderate risk	Persons handling sick animals or decontaminating environment without PPE.	May be provided the same chemoprophylaxis as with high-risk group.

	Direct exposure to sick/dead animals Infected with H5N1. Health-care worker in direct contact with patient without complete PPE. Laboratory personnel who might have an unprotected exposure.	
Low Risk	Health-care worker with PPE or contact >1 metre with a patient. Cullers of non-infected animals. Persons with PPE handling sick/dead birds or contaminated environment.	Probably no Chemoprophylaxis needed.

It must be remembered that the protection offered by chemoprophylaxis is short duration.

Infection control measures

General considerations

- Non-compliance with the basic level of infection control precautions, such as hand hygiene, appropriate use of facial protection (nose, mouth and eye protection) masking, cough etiquettes, cleaning and disinfection of contaminated equipments and surfaces, have resulted in nosocomial infections putting health care workers and others at risk. The following generic principles should be applied:
- Initiate infection control precautions promptly when AI infection is suspected
- Standard contact and droplet precautions should be the minimum to be used in all healthcare facilities when providing care for a suspected or confirmed AI-infected patient.
- Respiratory hygiene and cough etiquette should be used by all patients with respiratory symptoms to prevent the transmission of pathogens.
- Perform hand hygiene practices before and after any patient contact and after contact with contaminated items, regardless of whether gloves are worn or not.
- HCWs who collect or transport clinical specimens should adhere to recommended infection control precautions in order to minimize the possibility of exposure to infection.
- Standard precautions are to be followed while transporting the patient to a health-care facility. Aerosol-generating procedures should be avoided as far as possible during transit.
- AI virus can survive in the environment over different periods of time ranging from a few hours to several days. Therefore, cleaning followed by disinfection should be carried out for contaminated surfaces and equipment.

Use of PPE

All HCWs providing care for suspected or confirmed AI patients should use PPE. The following steps are reemphasized:

- Perform hand hygiene, preferably with an alcohol-based hand rub or soap and water.
- Put on a fluid-resistant gown.
- Put on disposable particulate respirator.
- Perform user seal check of particulate respirator.
- Put on hair cover
- Use face shield or goggles.
- Put on gloves (make sure gloves cover cuffs of gown sleeves).
- Shut the door after entering / leaving.

After performing the procedure, leave the isolation room/area or the ante room and observe the following steps:

- Remove gloves and discard in biomedical waste bin (gloves may be peeled from hands when gown is removed).
- Perform hand hygiene, preferably with an alcohol-based hand rub or soap and water.
- Remove hair cover and discard in biomedical waste bin Remove protective eyewear and discard in biomedical waste bin.
- Remove medical mask or particulate respirator by grasping elastic band; do not touch front of particulate respirator (fronts of masks may be contaminated) and discard in biomedical waste bin.
- Perform hand hygiene preferably with an alcohol-based hand rub or soap and water.

Role of parents/relatives in infection control

Parents/legal guardians of paediatric patients should be strongly supported to accompany the patient throughout the hospitalization period. They should also be educated to use surgical masks, hand hygiene and respiratory etiquette and may even assist in providing care to AI-infected patients in special situations (e.g. lack of resources). Family members who accompany suspected AI-infected patients to the health-care facility can be assumed to potentially have been exposed to AI and should be assessed accordingly. Visitors should be restricted to those necessary for the patient's well-being and care. During home care, the members of the family should be educated in respiratory etiquette and made aware of the need to keep at least one meter distance from the patient.

Duration of infection control precautions

If the primary health-care facilities have the capacity to manage uncomplicated human cases of H5N1, the infection control precautions recommended above should be implemented during the time the patient is infectious. Until further evidence is available, infection control precautions should continue in an adult patient for 7 days after resolution of fever and 21 days after onset of illness for children younger than 12 years because of the longer period of viral shedding in children. If the patient insists on returning home following resolution of fever, it may be considered, provided the patient and household members follow infection control measures at home. The cases could be monitored by the health-care workers in the community.

Specimen collection and transport to designated laboratories

The clinical specimens should be collected following standard procedures. Primary health-care physicians and laboratory personnel in the affected areas should be trained in collecting clinical samples in the appropriate medium. Health-care workers who collect specimens from AI-infected patients should wear PPE. Specimens for transport must be placed in leak-proof specimen bags, which have a separate sealable pocket for the specimen (i.e. a plastic biohazard specimen bag). Personnel who transport specimens should be trained in safe handling practices and decontamination procedures in case of a spill. Specimens should be delivered by hand wherever possible. The laboratory must be notified by telephone when the specimen is on its way. Primary health-care physicians should refer for further information to specimen collection guidelines

Discharge Policy

In adults the virus shedding takes place up to 7 days and in children 21 days after resolution of fever. So the patient and the family must be made aware of it and educated on it. Ideally patient needs isolation till they become non-infectious. Health care worker attending the patient needs to practice infection control measures till the prescribed period as above.

Visitor's Register

A register should be kept outside the isolation/quarantine units which will record the name and contact numbers of the people visiting the patients. This helps the health facilities for contact tracing in case the visitors fall sick.

Vaccine

The highly unstable nature of influenza virus makes it difficult to predict which antigenic combination would cause next pandemic. The currently available seasonal influenza vaccine does not give protection against the H5N1 infection. Very limited quantity of vaccine against H5N1 is produced in the developed countries and is in an early trial phase with good antibody response. In a resource limited country of ours, vaccine for protection against AI is not viable at current scenario. However, WHO recommends use of seasonal influenza vaccine in health care workers caring for H5N1 patients to prevent re-assortment.