Interim Guidelines for Avian Influenza Case Management
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Acronyms

Acronyms

AI  Avian Influenza
ARDS  Acute Respiratory Distress Syndrome
CFR  Case fatality rate
CHC  Community Health Centre
HCW  Health-care worker
HEPA  High-efficiency particulate air filter
HPAI  Highly Pathogenic Avian Influenza
ICU  Intensive Care Unit
IHR  International Health Regulations 2005
ILI  Influenza-like illness
LPAI  Low Pathogenic Avian Influenza
OIE  World Organization for Animal Health
PCR  Polymerase Chain Reaction
PHC  Primary Health Centre
PPE  Personal protective equipment
RRT  Rapid response team
SEARO  South-East Asia Regional Office
WHO  World Health Organization
1.1 Background

Avian influenza (AI), also known as bird flu, is an infection caused by type A influenza viruses that primarily infect avian species, but infections with these viruses can occur in humans. Recently, highly pathogenic avian influenza viruses have caused outbreaks in poultry in some countries of South-East Asia such as Indonesia, Myanmar and Thailand, where the virus has become endemic in many poultry populations.

The potential for avian influenza to cause human diseases was established during outbreaks of avian influenza among poultry-handlers in 1997 in Hong Kong; among 18 human cases, 6 died. Subsequently, clusters of human infections have been reported from Indonesia and Thailand. Currently, the predominant avian influenza virus infecting human beings has been of the H5N1 subtype. Globally, the current outbreak of Highly Pathogenic Avian Influenza (HPAI) with H5N1 has resulted in 306 cases with 185 deaths. To date, most of the human cases of avian influenza are attributed to direct contact with infected poultry or poultry products. Over 36 family clusters have been reported from Indonesia, Thailand and Vietnam and these clusters have been critical as diagnostic aids for the detection of AI infections.

The morbidity and mortality due to avian influenza infections of humans are high in affected countries. Globally, the case fatality rate (CFR) is 60.45% but in Indonesia the CFR is about 80%. Avian influenza also causes lower respiratory tract infection, including pneumonia. Hence, if a H5N1 pandemic occurs, the expected disease burden will be high. There is a need for surge capacity not only for providers such as doctors, nurses and other health-care workers, but also for hospital beds, drugs, diagnostic facilities and personal protective gear. The current scenario of public sectors at the primary health-care level in most countries shows limited beds and facilities for isolation and management. Many patients seek first medical care in the private sector consisting of private nursing homes, many of which also have limited designated isolation wards and case management. As part of pandemic preparedness and response, the public and private health-care facilities have to be upgraded.
Early case detection and treatment within 48 hours using the available antiviral drugs has established that such cases would run a less protracted course and results in early recovery. On the other hand, the case fatality rate is very high (up to 80%) in countries where there is late reporting to health facilities and administration of antivirals.

The purpose of this document is to provide guidance to medical officers in primary health-care for case management of human cases of avian influenza, emphasizing the need for early detection, triage, and prompt start of antivirals and transport of the case to the nearest health facility following standard infection control practices. This guideline is intended for use in the current pandemic alert period, in which there are human AI infections but no evidence for sustained human-to-human transmission.
Avian influenza H5N1 virus is a single-stranded RNA virus belonging to subtype A influenza of the Orthomyxoviridae family. The antigenicity of the virus is determined by the surface glycoproteins; namely heamaglutinin (H) and neuraminidase (N); there are 16 variants of H glycoprotein and 9 variants of N glycoproteins. H5N1 is of particular concern for several reasons: it mutates rapidly and has a documented propensity to acquire genes from viruses infecting other animal species.

The basic epidemiology of human infections by H5N1 avian influenza viruses is not completely understood. Human infection is the result of a complex interaction of viral, host and environmental factors in which the virus type, dose and route of entry, as well immune status and genetic susceptibility of the host, play a role. Environmental factors including aerosols also play a role in transmission. The H5N1 virus can survive in contaminated manure for up to three months. The principal risk factors for human infections of avian influenza are direct or indirect contact with contaminated poultry or poultry products. See Box 1.

**Box 1: High-risk groups**

- Children playing with infected poultry, particularly asymptomatic infected ducks.
- Poultry handlers in live animal markets / wet markets
- Cullers without proper PPE
- Those handling fighting cocks
- Persons plucking and preparing of diseased birds in wet markets / backyard poultry / kitchens
- Consumption of undercooked poultry products
- Consumption of chicken or duck blood
- Hospital functionaries managing human cases of AI without proper PPE

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Interim Guidelines for Avian Influenza Case Management
Chickens, ducks, fowls, geese, turkeys, quail, pigeons, wild birds and migratory birds have been found to be affected by HPAI (H5N1). Lack of biosecurity in poultry farms and during transportation, handling and processing as well as in live animal markets and wet poultry markets all may increase the risk of transmission. Social customs such as cock fighting in some countries of the Region pose additional risks for the population involved in such activities. Consumption of partly cooked meat and speciality dishes made from raw flesh, as well as the handling of poultry raw meat and blood, may also transmit the virus to humans. No human case has been documented in an at-risk population consuming well-cooked poultry.

The virus is known to survive in favorable conditions outside the host for over a month. Therefore, indirect contact with bird droppings from infected farms or backyard poultry, and the use of untreated poultry droppings as fertilizer may also be a source of infection. The risk of transmission to cullers using appropriate personal protection equipment (PPE) however is extremely low, as it is for healthcare workers handling suspected cases using appropriate infection control measures.

The time from presumed exposure to onset of illness ranges from two to eight days, the median being four days. In Thailand, the time between onset of illness to the development of acute respiratory distress was around 6 days, with a range of 4 to 13 days. In severe cases in Turkey, clinicians have observed respiratory failure three to five days after symptom onset. WHO recommends H5N1 incubation period of seven days be used for field investigations and the monitoring be done one day prior to onset of symptoms until 7 days after resolution of fever, or up to 21 days (in children).

The studies on the cases reported in Indonesia and Vietnam suggest that both sexes are more or less equally susceptible, the median age being about 20, the range being 2-58 years.
3 Clinical presentation of human cases of Avian Influenza and diagnosis

3.1 Clinical presentation

Clinical familiarity with seasonal influenza signs and symptoms would be advantageous in diagnosing human cases of avian influenza. However, the clinical features may differ in terms of longer incubation period, early onset of pneumonia, rapid progress to respiratory distress and high CFR. Among patients studied in Thailand and Vietnam, a majority of them presented with fever, cough and dyspnoea, and more than 50 percent had developed diarrhoea, an uncommon feature in seasonal influenza. The blood picture showed consistent lymphopenia and moderate thrombocytopenia and deranged liver function tests. Over 80 percent of the patients had abnormal chest radiographs. Over 50 percent of the cases ran a fulminant course developing Acute Respiratory Distress Syndrome (ARDS) and ending with multi-organ failure. The commonly observed clinical features of cases with H5N1 infection have been summarized in Box 2.

3.2 Clinical diagnosis

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

3.2.1 Clinical criteria

The most consistent clinical features include fever of >38°C, cough, and shortness of breath or difficulty breathing.
### Box 2: Clinical features

- Onset after 2-8 days of exposure to sick/dying poultry
- Onset similar to seasonal influenza
- Fever >38°C
- Cough
- Difficulty in breathing after 5-7 days of onset
- Diarrhoea
- Primary viral pneumonia
- Rapid deterioration to ARDS and multi-organ failure

**Infrequent features:**
- Vomiting
- Abdominal pain
- Chest pain
- Bleeding from nose and/or gums
- Encephalopathy (rare)

### 3.2.2 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 seven days prior to symptom onset:

- Close contact (within one metre) 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 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;
- 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.

Box 3: Direct contact with poultry is defined as:

| • Touching birds (well-appearing, sick or dead);          |
| • Touching poultry faeces or surfaces contaminated with faeces; |
| • Consuming uncooked poultry products (including blood) in an affected area; |
| • Close contact with a person from an infected area with confirmed or suspected novel influenza is defined as being within three feet (one metre) of that person during their illness. |

According to WHO case-definition criteria (see Annex 1), human avian influenza cases may be classed as suspected, probable or confirmed. However, at the primary health-care level, it may only be possible to diagnose suspected or probable cases, although full knowledge of the three categories may be helpful for the attending doctors.

Any case fulfilling the clinical and epidemiological criteria should be treated as a suspected case of H5N1. The primary health-care physician 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. (Information on countries and areas affected with H5N1 are available on the WHO website at www.who.int/en; World Organization for Animal Health web site at www.oie.int; and Centres for Disease Control website at www.cdc.gov/travel).

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 of avian influenza. 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. 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 primary health-care infrastructure; however, the
physicians working at this level must know the criteria for case confirmation, the laboratories to which clinical samples are to be sent and the channel of communication. A person meeting the criteria for a suspected or probable case is classified as confirmed when a standard tests is positive and conducted in a national, regional or international influenza laboratory whose H5N1 test results are accepted by WHO as confirmatory. See WHO criteria for accepting positive results of H5N1 infection in humans from national reference laboratory (http://www.who.int/csr/disease/avian_influenza/whoacceptancecriteria.pdf).
4 Case management

4.1 General considerations for primary health-care personnel

The public health and veterinary health authorities may follow an aggressive stamping-out strategy in Member countries or areas where avian influenza in poultry is reported for the first time or re-emerges after AI-free status. An event-based active surveillance system would be followed in a radius of 3 km including the infected zone. The suspected cases would be picked up from the community by the health and surveillance workers. Cases also may report on their own to the primary health-care facilities. The efforts would be augmented by rapid response teams from the local, provincial or central level. Primary health-care physicians in the affected area would be tasked to be a part of the surveillance and response required to confirm the clinical and epidemiological criteria of suspected cases picked up by the surveillance system. They would also do triage on the suspected cases reporting directly at the primary or community health centre, and if suspected follow a step-by-step approach for case management. See section 4.2 for further details.

In areas where the disease is endemic, the primary health-care physicians would expect sporadic cases. An effective community-based surveillance system, if existing, would facilitate early reporting of the cases to the primary health-care physicians.

If a seasonal influenza outbreak or any influenza-like illness (ILI) caused by other respiratory viruses co-exists in the affected area, it would be difficult to differentiate between seasonal and avian influenza on clinical and epidemiological criteria alone, resulting in a substantial burden on the primary health-care personnel and difficult clinical, decision-making.
4.2 Step-by-step approach to case management at the primary health-care level

The above situations call for a step-by-step approach to be followed when a patient meets both the clinical and epidemiologic criteria for a suspected case:

- Follow standard infection control precautions, including respiratory hygiene/cough etiquette while handling the patient as detailed in the foregoing chapter.
- If the patient meets the clinical and epidemiological criteria for a suspected case of H5N1 infection, notify the health authorities immediately to facilitate initiation of public health measures. International Health Regulations (IHR 2005) will require the international notification to WHO by Member States of laboratory-confirmed human cases of avian influenza.
- Obtain clinical specimens such as nasopharyngeal swab, throat swab, nasal swab, wash or aspirate, and tracheal aspirate (for intubated patients). Store specimens at 4°C in viral transport media until transported for testing. If staff is not trained in collecting clinical samples, request help from the local rapid response team (RRT) or laboratory personnel. If the patient is not hospitalized, collect acute (within seven days of illness onset) and convalescent serum specimens (three weeks after onset of illness), refrigerate at 4°C and transport to the identified laboratory. Primary health-care physicians should refer for further information to “WHO guidelines for the collection of human specimens for laboratory diagnosis of avian influenza infection” available at: http://www.who.int/csr/disease/avian_influenza/guidelines/humanspecimens/en/index.html
- Decide on triage for inpatient or outpatient management. Clinical decision-making is vital to decide whether to treat at community level or to refer to identified health facilities for indoor management.

4.3 Antiviral treatment

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 even waiting for the laboratory confirmation. However, before starting treatment, the primary health-care medical staff should contact the consulting physician at the nearest avian influenza reference hospital 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 laboratory reports are negative, a strong epidemiological link is an indication to continue treatment. The primary or community health centre or pharmacy should have adequate stocks of antivirals. If not available, it should be requisitioned from the local, state, provincial or central authorities immediately. Delay in commencement of therapy may increase the mortality rates. Self-medication in the absence of appropriate clinical diagnosis is discouraged.

Two broad groups of antiviral drugs are available against influenza viruses, the neuraminidase inhibitors and amantadine derivatives. The former has two commercially available preparations, oseltamivir and zanamivir, while amantadine and rimantadine belong to the latter group.

### 4.3.1 Oseltamivir

The evidence for effectiveness of oseltamivir in human H5N1 disease is based on virological data from in vitro, animal models and limited human studies, as well as extrapolation from the results of trials in patients with ordinary human influenza. There is no direct clinical trial evidence that shows that oseltamivir is effective in human H5N1 disease because such studies have not yet been conducted. Without such trials, the optimal dose and duration of oseltamivir treatment is uncertain in H5N1 disease, and therefore doses of oseltamivir used for seasonal human influenza continue to be recommended.

#### 4.3.1.1 Dose and duration of treatment with oseltamivir

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):** 75 mg twice daily

The clinical course, and presumably, some aspects of the immunopathogenesis, of human H5N1 disease (in particular the severe form) may be different from normal seasonal influenza, requiring a different dosing approach. Normal recommended duration of treatment is five days. Some experts advise a higher dose (150 mg twice daily) if the patient has pneumonic disease or shows rapid deterioration in clinical status. Similarly, the duration of treatment may be increased to 10 days if clinical improvement is not as expected after 5-day therapy. Such decisions are to be taken on a case-by-case basis, in consultation with a clinical expert in the nearest avian influenza hospital.
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 on the use of oseltamivir in pregnant women. The animal toxicology studies do not indicate direct or indirect harmful effects with respect to pregnancy or fetal development. 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.

4.3.1.2 Packing and storage
Available in bleb packing of 10 capsules each containing 75 mg of oseltamivir and oral suspension - 12 mg per ml.

4.3.1.3 Adverse reactions
In terms of safety and adverse effects, evidence from the trials in seasonal influenza shows that although oseltamivir is generally well tolerated, gastrointestinal 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, dermititis and conjunctivitis have also been observed. There is no recommendation for dose reduction in patients with hepatic disease.

4.3.2 Choice of drug
Among the drugs currently available, oseltamivir is the drug of choice. Member States have ensured its availability. Another drug that could be used if oseltamivir is not available is zanamivir (neuraminidase inhibitor). In case H5N1 develops resistance to neuraminidase inhibitors, amantadine and rimantadine (M2 inhibitors) could be of use in a combination therapy for which there has been no clinical trial. The latter group of drugs on its own are known to develop rapid resistance. A brief description of these drugs is given in Annex II.

4.4 Antibacterial drugs
Antibacterial agents should be administered, if required, as per locally accepted clinical practice guidelines. Followings are brief principles of administration of antibacterial agents:
• 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.

4.5 Other pharmaceutical interventions

Immunomodulating drugs have not been found to be beneficial in treatment of Acute Respiratory Distress Syndrome (ARDS) or sepsis-associated multi-organ failure. In H5N1 disease, no data is available in human studies or animal models. 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.

4.6 Symptomatic treatment

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

4.7 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. Types of oxygen devices depend on the severity of hypoxic conditions which can be started from oxygen cannula, simple mask, partial re-breathing mask (mask with reservoir bag) and non-re-breathing mask. In children, one can also use an oxygen hood or head boxes.

Patients with severe pneumonia and acute respiratory failure (SpO2 < 90% and PaO2 < 60 mmHg with oxygen therapy) must be supported with mechanical
ventilation. Invasive mechanical ventilation is preferred. Non-invasive ventilation is an option when mechanical ventilation is not available. To reduce the spread of infectious aerosols, consider using HEPA filters on expiratory ports of the ventilator circuit/high-flow oxygen masks.

Aerosol-generating procedures can create aerosols of different sizes. Examples of aerosol-generating procedures include: endotracheal intubation, nebulized medication administration, diagnostic sputum induction, airway suction, chest physical therapy and positive pressure ventilation. Aerosol-generation procedures should be performed with full PPE. If splashing with blood or other body fluids is anticipated, a waterproof apron should be worn. (See section 7 for details.)

### 4.8 Transportation to identified hospital

If clinical findings or epidemiological link establish a human case of avian influenza, the patient should be transported to the next higher level of care. The ambulance should have basic facilities for oxygen therapy and non-invasive ventilation. If the patient is mechanically ventilated, then 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. Health-care workers (HCWs) should use standard droplet precautions if accompanying or handling a suspected or confirmed AI case during transport. The identified hospital 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. (See section 7 for details.)
5 Preventive therapy of close contacts

As has been discussed in role of antivirals in treatment of avian influenza, the efficacy of currently available antiviral agents against influenza is not fully understood. Irrational use and overuse of antiviral agents can lead to the emergence of resistant viruses, raising another critical barrier in the fight against pandemic.

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 Table 1.

**Table 1: Chemoprophylaxis against avian influenza**

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<th>Group</th>
<th>Description</th>
<th>Chemoprophylaxis</th>
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<td>High risk</td>
<td>Sharing household with or caring for a patient.</td>
<td>Oseltamivir in dose of 75 mg/day or zanamivir to continue for 7-10 days after last exposure. If oseltamivir/zanamivir not available, use amantadine or rimantadine for all except pregnant women and persons with impaired renal functions.</td>
</tr>
<tr>
<td></td>
<td>Unprotected close contact (&lt;1 metre) with patient.</td>
<td></td>
</tr>
<tr>
<td>Moderate risk</td>
<td>Persons handling sick animals or decontaminating environment without PPE. 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.</td>
<td>May be provided the same chemoprophylaxis as with high-risk group.</td>
</tr>
<tr>
<td>Low Risk</td>
<td>Health-care worker with PPE or contact &gt;1 metre with a patient. Cullers of non-infected animals. Persons with PPE handling sick/dead birds or contaminated environment.</td>
<td>Probably no chemoprophylaxis needed.</td>
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It must be remembered that the protection offered by chemoprophylaxis lasts only during its duration. In addition, health-care workers must be immunized with vaccines against seasonal influenza to prevent reassortment during co-infection with human and avian viruses.

### 5.1 Oseltamivir

No clinical trial has evaluated oseltamivir for chemoprophylaxis of H5N1 infection. Three randomized controlled trials investigated the effect of oral oseltamivir on post-exposure influenza (relative risk reductions of 50% to 89%). There is no evidence about the effects of post-exposure chemoprophylaxis in health-care workers potentially exposed to the H5N1 virus or workers handling dead or diseased birds or engaged in the decontamination of animal environments.

When considering chemoprophylaxis of H5N1 infection, high priority should be given to standard infection control practices. The recommended chemoprophylaxis dose is 75 mg once daily in adults and the following weight-adjusted doses in children, for a period of 7 to 10 days:

- **Children (over 1 year):**
  - under 16 kg body weight: 30 mg once daily
  - 16-23 kg body weight: 45 mg once daily
  - 24-40 kg body weight: 60 mg once daily
  - over 40 kg body weight: 75 mg once daily

There is no evidence available for the chemoprophylactic use of oseltamivir in children less than one year old.

### 5.2 Zanamivir

No clinical trial has evaluated zanamivir for chemoprophylaxis of H5N1 infection. There is no evidence about the effects of post-exposure chemoprophylaxis in health-care workers potentially exposed to the H5N1 virus or workers involved in decontamination of avian influenza A (H5N1) virus.

Zanamivir is available for oral inhalation only, using a disk inhaler device. The recommended dose of inhaled zanamivir in adults and children aged five years and older is 10 mg once daily as chemoprophylaxis for 7 to 10 days after last known exposure. Zanamivir may be active against some strains of oseltamivir-resistant H5N1 virus.
Core priority behaviours that could be widely adopted for empowering individuals with specific actions to protect themselves and their families include hand hygiene; staying away from poultry, cough etiquettes etc. To reduce transmission the following "flu-W I S E" behaviours are recommended. These are:

**Wash:** Hand hygiene is an important measure to prevent the spread of influenza. Washing hands with soap removes sundry germs including H5N1 virus. Wash hands as often as possible with soap and water after any contact with poultry/poultry products or respiratory secretions.

Surfaces can become contaminated, and touching them can transmit the virus. Cleaning and disinfecting surfaces can kill the virus. Clean surfaces that have the potential to get contaminated as regularly as is expedient.

**Inform:** Promoting the sharing of correct information, especially on risk behaviour in the primary health-care set up. This includes information on healthy food markets, consumption of well-cooked poultry products and the responsibility to notify the health agencies about suspected bird deaths and ILI.

**Stay Apart:** The virus is transmitted when in close contact with poultry and poultry products. Children should be kept away from domestic poultry. As far as possible the birds should be secured in a cage kept away from human dwellings. If the community is reporting ILI, then those with fever and respiratory symptoms should maintain a distance of at least one meter.

**Etiquettes related to cough:** An infected person can spray droplets containing viruses during coughing and sneezing. Cover the mouth and nose during coughing or sneezing with a tissue paper, mask or handkerchief. The tissue/mask has to be disposed of appropriately and the hands washed immediately.

HCWs in primary health-care settings have a major responsibility in communicating the risks to the community and instilling behaviours for risk mitigation.
7 Infection control measures

7.1 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.
7.2 Standard infection control precautions for primary health-care facilities

7.2.1 Hand hygiene

Hand hygiene practices are to be followed by the at-risk population, preferably before and after any contact with poultry, their excreta or contaminated surfaces and equipment and in case of contact with patients. Hand-washing should also follow the removal of PPE. Hands can be washed using soap and water or alcohol rub. Every opportunity is to be taken to disseminate information about the importance of hand-washing and the technique.

7.2.2 Respiratory hygiene/cough etiquettes

Persons suspected of having AI should be provided with three-layered surgical masks. They should be explained about the public health importance of using a mask. If a mask is not available they should be asked to cover their mouth and nose with a tissue/clean cloth when coughing and dispose of the same in waste containers; the patient should also be educated to stand or sit at least one meter (3 feet away) from others, if possible.

7.2.3 Personal protective equipment (PPE)

The PPE includes shoe covers, head cover, mask, gown, goggles and gloves. Health-care workers should receive training on the use of recommended infection control precautions as well as on the underlying concept that forms the basis for these recommendations.

Medical masks (surgical or procedure mask) should be used for routine patient care. A particulate respirator (N95, EU FFP2, or equivalent) should be used for performing aerosol-generating procedures and a user seal check should be performed each time a disposable particulate respirator is worn. Use clean, non-sterile ambidextrous gloves and long sleeved gown if direct contact with the patient is anticipated. If cloth gowns are used, a waterproof apron should be worn over the gown and protective eyewear (face shields/goggles/visors) applied if splashing or spraying of potentially infectious material is anticipated as per standard precautions.

7.3 Isolation facilities

Primary health-care facilities (primary/community health centres) should initiate infection control precautions promptly when AI infection is suspected. It may take
some time for the primary health-care physician to arrange for transport for those requiring admission to higher centres; in the meantime such patients should be put under isolation precautions.

7.3.1 Preparation of isolation facility

Ideally the patient should be placed in an adequately ventilated room. If isolation room/single room is not available, suspected and confirmed AI-infected patients may be cohorted separately in designated multi-bed rooms or wards with beds placed at least one meter apart from each other. These uncarpeted rooms/areas should be clearly segregated from other patient-care areas. Doors to such rooms or areas must be kept closed when not being used for entry or egress. If possible, isolation rooms should have their own hand-washing sink, toilet, and bath facilities. The number of persons entering the isolation room should be limited to the minimum number necessary for patient care and support. Whenever possible, HCWs assigned to isolation/cohorted patient-care units should not be assigned to other patient care areas.

Infection control precautions should be indicated through appropriate signage on the door. Stock linen and PPE as needed outside the isolation room. Stock the sink area with soap as well as with alcohol-based hand rubs. Biomedical waste disposal bags and touch-free bin should be placed at point of care/ante room. A puncture-proof container for sharps should be available inside the isolation room. Daily cleaning and disinfection of the isolation room/area is recommended.

The isolation room should have an adequate stock of oseltamivir and other essential drugs. Non-critical patient-care equipment (e.g. stethoscope, thermometer, and sphygmomanometer) should be dedicated to the patient, if possible. Any patient-care equipment that is required for use by other patients should be thoroughly cleaned and disinfected prior to use. Consider having basic life support equipment, ventilator, pulse oximeters, suction unit and portable X-ray equipment available in the isolation room/cohort areas. A checklist may be useful to ensure that all equipment is available. The equipments could be mobilized to primary health-care facility with sufficient medical and supportive staff. Best practices followed in some Member countries involve setting up of isolation and critical care at the community level in the existing facilities for managing uncomplicated suspect/probable cases of AI. This practice has avoided the need to shift patients over long distances and was also acceptable to the community.

7.3.2 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 (if used, e.g. during an aerosol-generating procedure).
• 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 protective eyewear and discard in biomedical waste bin.
• Remove hair cover 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.

7.4 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.
7.5 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.

7.6 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.


7.7 Infection control during transport to health-care facilities

Suspected/probable AI patients transported from the primary health-care facility should follow standard infection control practices. A medical mask should be placed on all patients to contain droplets expelled during coughing. Health-care workers
should use standard droplet precautions during transport of the patient in a vehicle. As much as possible, aerosol-generating procedures (e.g. mechanical ventilation) should be avoided during transport. The receiving facility should be informed of the arrival of the patient in advance and the type of care required based on the current triage. After use the emergency vehicle should be sanitized and reusable patient-care equipment disinfected.

7.8 Waste management

All waste from AI patients generated in the isolation room/area should be considered as clinical infectious waste and should be treated and disposed of in accordance with national regulations pertaining to such waste. When transporting waste outside the isolation room/area, use gloves followed by hand hygiene.

7.9 Environmental cleaning and disinfection

AI virus is inactivated by a number of disinfectants including phenolic disinfectants, quaternary ammonia compounds, alcohol and sodium hypochlorite. Patient rooms/areas should be cleaned at least daily and terminally at discharge. In addition to daily cleaning of floors and other horizontal surfaces, special attention should be given to cleaning and disinfecting frequently touched surfaces. To avoid possible aerosolization of AI virus, sweeping with wet cloth should be performed. Horizontal surfaces should be dusted by moistening a cloth with a small amount of disinfectant.

If possible, place contaminated patient-care equipment in suitable bags before removing it from the isolation room/area. Clean heavily soiled equipment and then apply a disinfectant effective against influenza virus before removing it from the isolation room/area. When transporting contaminated patient-care equipment outside the isolation room/area, use gloves followed by hand hygiene. Use standard precautions and follow current recommendations for cleaning and disinfection or sterilization of reusable patient-care equipment.
Programme management and coordination in primary health-care facility

8.1 Role of primary health care

As avian influenza spreads geographically, re-emerges in countries/areas where it has been stamped out earlier and becomes endemic in some countries, the primary health-care infrastructure would play an increasing role in preventing human cases of avian influenza by detecting cases early and initiating anti-viral treatment. By limiting human exposure to avian influenza virus, the probability of reassortment of these viruses in humans is reduced and hence the development of a pandemic virus. The primary health-care interventions would also be instrumental in reducing morbidity and mortality.

8.2 Role of national authorities in case management

Provision of appropriate treatment to the patients with H5N1 infection at the primary health-care level requires considerable commitment and allocation of resources by the national authorities to ensure that appropriate infrastructure, guidelines, supplies and trained human resources are available. Some of the essential actions by the national authorities are summarized in Box 4.

<table>
<thead>
<tr>
<th>Box 4: Guidelines for national authorities</th>
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<tbody>
<tr>
<td>• Integrate role of primary health-care in National Influenza Pandemic Preparedness Plan</td>
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<tr>
<td>• Train primary health-care staff in patient assessment and management of avian influenza and data collection</td>
</tr>
<tr>
<td>• Provide resources and develop infrastructure for care</td>
</tr>
<tr>
<td>• Clinical management</td>
</tr>
<tr>
<td>• Infection control practices</td>
</tr>
<tr>
<td>• Logistics and transportation of patients</td>
</tr>
<tr>
<td>• Designate health-care facilities for managing patients</td>
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</table>
In addition to the primary health facilities, in many instances, patients may receive alternative treatment in the private sector, and through community services including temples, schools and the traditional system of medicine. The guiding principles of treatment remain the same: initiation of antiviral therapy within 24-48 hours, transport to the next higher level of health care and exercising precautions for infection control as described in the earlier sections.
Conclusion

Highly pathogenic avian influenza A(H5N1) virus have caused many human fatalities and poses an increasing pandemic threat. The guidelines for case management provide quick guidance to medical officers in primary health care for case management of human cases of avian influenza. The primary health care infrastructure has an increasing role in preventing and controlling human cases of avian influenza through early case detection and early initiating of antiviral treatment. Case management of a patient with avian influenza has strong implications for reducing mortality and morbidity as well as in pre-empting the pandemic. Its success depends on strong national commitment, logistics arrangements, strengthening of infrastructure and upgrading the skills of health-care workers. The time is ripe for initiating suitable steps to empower primary health care for effective case management for AI.
Suspected H5N1 case

A person presenting with unexplained acute lower respiratory illness with fever (>38°C) and cough, shortness of breath or difficulty in breathing.

AND

One or more of the following exposures in the seven days prior to the onset of the symptom:

(a) Close contact (within 1 metre) 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 WHO)

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
One of the following positive results conducted in a national, regional or international
influenza laboratory whose H5N1 test results are accepted by WHO as confirmatory:

(a) Isolation of an H5N1 virus;

(b) Positive H5 PCR results from tests using two different PCR targets, e.g.
primers specific for influenza A and H5 HA;

(c) A fourfold or greater rise in neutralization antibody titer for H5N1 based
on testing of an acute serum specimen (collected 7 days or less after
symptom onset) and a convalescent serum specimen. The convalescent
neutralizing antibody titer must also be 1:80 or higher;

(d) A micro-neutralization antibody titer for H5N1 of 1:80 or greater in a
single serum specimen collected on Day 14 or later after symptom onset
and a positive result using a different serological assay, for example, a
horse red blood cell hemagglutination inhibition titer of 1:160 or greater
or an H5-specific western blot positive result.
Zanamivir

There are very few studies describing animal and in vitro data about the effects of zanamivir on the H5N1 virus. Zanamivir has been approved by the US Food and Drug Administration for treatment of influenza in individuals age = 7 years. It is available as a nasal spray/inhaler and the recommended dose is 10 mg twice daily for 5 days, in adults and children =7 years.

Adverse reactions

Headache and nausea are commonly reported and rarely may result in increased incidence of bronchospasm. These events do not require discontinuation of treatment.

Amantadine

If oseltamivir or zanamivir is not available, and especially if the virus is known or likely to be susceptible to amantadine or rimantadine, the clinician might administer amantadine or rimantadine alone as first-line treatment to patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus. Current evidence shows that most strains of H5N1 are resistant to M2 inhibitor.

No controlled clinical trial has evaluated amantadine for the treatment of H5N1 infection. There is insufficient evidence in the reported studies to evaluate the benefit of amantadine on mortality or duration of hospitalization in either seasonal influenza or H5N1 infection. The development of resistance is a frequent problem of amantadine.

Availability

Amantadine is available as 100 mg tablet and in capsule and syrup form

Dose

Adults between 10-65 years 100 mg twice daily
Children 1-9 years (max 150 mg/day)
5 mg/kg/day/in two divided doses
For patients with impaired creatinine clearance, proportionately reduced dose should be administered. This drug must be used cautiously with patients on neuropsychiatric drugs or with seizure disorders.

**Adverse reactions**

Nausea, dizziness and insomnia, but these do not warrant discontinuation of treatment.

**Rimantadine**

No controlled clinical trial has evaluated rimantadine for the treatment of H5N1 infection. There is insufficient evidence in the reported studies to evaluate the benefit of rimantadine on mortality or duration of hospitalization in either seasonal influenza or H5N1 infection. There are some considerations of likely development of drug resistance and the incidence of toxic effects from rimantadine.

**Availability**

Rimantadine is available in tablet form

**Dose**

For patients >12 years 100 mg twice daily
100 mg/day for patients with impaired renal or hepatic functions

**Adverse reactions**

Nausea, dizziness and insomnia have been reported subsequent to administration of this drug, but these do not warrant discontinuation of treatment.

A summary of antiviral drugs that can be used in management of avian influenza is given in Table 2.

**Table 2: Antiviral drugs against H5N1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Group</th>
<th>Drug</th>
<th>Adult dose</th>
<th>When to use</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Neuraminidase inhibitor</td>
<td>Oseltamivir</td>
<td>75 mg twice daily x 5 days 10 mg x twice daily x 5 days</td>
<td>First line</td>
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<tr>
<td></td>
<td></td>
<td>Zanamivir</td>
<td></td>
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<tr>
<td>2.</td>
<td>Adamantine derivatives</td>
<td>Amantadine</td>
<td>100 mg x twice daily x 5 days</td>
<td>First line if neuraminidase inhibitors are not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rimantadine</td>
<td></td>
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</tr>
</tbody>
</table>
Interim Guidelines for Avian Influenza Case Management
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