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Avian Influenza

Prevention and Control of Influenza due to Avian Influenza Virus A (H5N1)

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:: Clinical Picture

The reported symptoms of avian influenza in humans have ranged from typical influenza-like symptoms (e.g., fever, cough, sore throat and muscle aches) to eye infections, pneumonia, acute respiratory distress, viral pneumonia, and other severe and life-threatening complications.

Published information about the clinical course of human infection with H5N1 avian influenza is limited to studies of cases in the 1997 Hong Kong outbreak. In that outbreak, patients developed symptoms of fever, sore throat, cough and, in several of the fatal cases, severe respiratory distress secondary to viral pneumonia. Previously healthy adults and children, and some with chronic medical conditions, were affected.

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:: Laboratory Diagnosis

Laboratory diagnosis depends upon the demonstration of the virus and or a rising antibody titre. Following tests are available (kits for these are being developed and may be available soon):

1. Virus culture
2. RT-PCR
3. Immunofluorescence using monoclonal antibody to H5N1
4. Serological tests (ELISA and IFAT) for detection of specific antibody

Of these, virus culture can be done in laboratories with infrastructure, skills and reagents for isolation of influenza virus and confirmation of H5N1 subtype. These facilities are available only in a limited number of laboratories. A list of some of the reference laboratories that can provide diagnostic services can be seen at Annex 1.

Primers for performing RT-PCR tests are being developed and expected to be available shortly. The information on these primers shall be made available on websites of WHO, CDC, Atlanta, Ga and other institutes which may develop these.

Direct immunofluorescence test can be used to ascertain presence of virus using H5N1 specific monoclonal antibody conjugated with a fluoresceing dye.

The laboratory tests for the diagnosis of influenza A/H5 infection included in the case definition are considered the standard for the identification of these viruses. WHO recommends that laboratory results for influenza A/H5 are corroborated by a national influenza centre or other national reference laboratory. Any sample or isolate that is a non-typable influenza A (i.e. non-H3 or non-H1 subtype) should be sent immediately to a WHO collaborating centre on influenza or other WHO-recommended reference laboratory (see Annex 1). WHO also recommends that the first positive laboratory identification of influenza A/H5 virus in humans in any country or territory be confirmed by one of the WHO reference laboratories for diagnosis of influenza A/H5 infection. In addition, and until further notice, WHO requests that all human influenza A/H5 virus isolates or samples be sent to one of the WHO reference laboratories for diagnosis of influenza A/H5 infection.

Tests for diagnosing all influenza strains of animals and humans are rapid and reliable. Many laboratories in the WHO global influenza network have the necessary high-security facilities and reagents for performing these tests as well as considerable experience. Rapid bedside tests for the diagnosis of human influenza are also available, but do not have the precision of the more extensive laboratory testing that is currently needed to fully understand the most recent cases and determine whether human infection is spreading, either directly from birds or from person to person

Rapid tests for diagnosis of influenza type A

Commercial rapid diagnostic tests are available that can be used by to detect influenza viruses within 30 minutes. These rapid tests provide information upto type level. Which means that by using rapid kits one can obtain a fairly reliable indication about the presence of Influenza A virus. Confirmation of H5N1 subtype can be done only in a well equipped laboratory with all

facilities and adequate biocontainment measures (details given in annex 1). Since most of the rapid tests have good specificity, a negative test can give broad indication about absence of influenza virus in specimen. As of now no commercial kit is available that can diagnose infection due to H5N1 subtype. The types of specimens acceptable for use (i.e., throat swab, nasal wash, or nasal swab) also vary by test.

Despite the availability of rapid diagnostic tests, collecting clinical specimens for viral culture is critical, because only culture isolates can provide specific information regarding circulating influenza subtypes and strains. This information is needed to establish diagnosis of avian influenza.

Keeping their limitations in mind, rapid diagnostics for influenza have proven to be valuable in early diagnosis which enables treatment in a timely fashion. Anti-influenza treatments must be administered within 48 hours of onset of symptoms in order to be effective. Some of the rapid kits appear to be quite sensitive (mean of 87.4%; range of 74-100%) for detection of virus in nasopharyngeal specimens and is preferred for screening for influenza.

7.1 Collection of human specimens

General information

Respiratory virus diagnosis depends on the collection of high-quality specimens, their rapid transport to the laboratory and appropriate storage before laboratory testing. Virus is best detected in specimens containing infected cells and secretions. Specimens for the direct detection of viral antigens or nucleic acids and virus isolation in cell cultures should be taken during the first 3 days after onset of clinical symptoms.

Type of specimens

A variety of specimens are suitable for the diagnosis of virus infections of the **upper respiratory tract**:

- ▶ nasal swab
- ▶ nasopharyngeal swab
- ▶ nasopharyngeal aspirate
- ▶ nasal wash
- ▶ throat swab.

In addition to swabs from the upper respiratory tract, invasive procedures can be performed for the diagnosis of virus infections of the lower respiratory tract where clinically indicated:

- ▶ transtracheal aspirate
- ▶ bronchoalveolar lavage
- ▶ lung biopsy
- ▶ post-mortem lung or tracheal tissue.

Specimens for the laboratory diagnosis of highly pathogenic avian influenza A/H5 should be collected in the following order of priority :

- ▶ nasopharyngeal aspirates
- ▶ acute serum
- ▶ convalescent serum.

Specimens for direct detection of viral antigens by immunofluorescence staining of infected cells should be refrigerated and processed within 1–2 hours. Specimens for use with commercial near-patient tests should be stored in accordance with the manufacturer's instructions. Specimens for virus isolation should be refrigerated immediately after collection and inoculated into susceptible cell cultures as soon as possible. If specimens cannot be processed within 48–72 hours, they should be kept frozen at or below –70 °C.

Respiratory specimens should be collected and transported in virus transport media. A number of media that are satisfactory for the recovery of a wide variety of viruses are commercially available. Procedure for specimen collection is described in Annex 2.

7.2 Storage and transport of specimens

To preserve the viral integrity in specimens for inoculation, place specimens should be placed in appropriate viral transport medium and stored at recommended temperatures: for respiratory samples and frozen tissues -70 oC, for serum 4-8 oC for 24-48 hrs, or at -20oC for longer periods. Expert advice should be sought when in doubt about storage conditions related to the type of test to be done. Details of storage and transportation can be seen at Annex 3

Labelling and documentation

Specimen labeling : Each specimen should be labeled with the patient ID number and date collected.

Accompanying documentation : The package should include a linelist for all specimens including patient name and ID number, date collected, samples collected, clinical contact name and phone number, and submitter contact name and phone number (Annex 2).

7.3 Biosafety guidelines

1. The laboratories must apply good laboratory practices and standard precautions.
2. The virology work, PCR as well as preparations for transportation of infectious material should be performed in Biosafety Level (BSL) 2 facilities using BSL-3 practices
3. The following activities require BSL-3 facilities and BSL-3 work practices :
 - ▶ Culture-based attempts to isolate the agent, including inoculation onto cell culture, and eggs.
 - ▶ Initial characterization of agents recovered in cultures of specimens.
 - ▶ Any procedure that may generate aerosols or droplets and these should be performed in a biosafety cabinet.
4. Laboratory workers should wear following personal protective equipment
 - ▶ Protective clothing, preferably coveralls plus impermeable apron or long cuffed sleeves surgical gowns plus impermeable apron;
 - ▶ Disposable examination gloves;
 - ▶ Masks: the minimum requirement are well-fitted surgical masks. Where available the use of N95 masks is recommended.
 - ▶ Goggles.
 - ▶ Boots or some protective foot cover that can be disinfected
 - ▶ Frequent hand washing

When a procedure or process cannot be conducted within a biological safety cabinet, then appropriate combinations of personal protective equipment (e.g. respirators, face shields) and physical containment devices (e.g. centrifuge safety cups or sealed rotors) must be used.

In cases where laboratory facilities do not meet at least basic laboratory BSL2 containment conditions, consideration should be given to referral of specimens to suitably equipped reference laboratories (link to the list of reference labs) for primary diagnostic tests.

For laboratories that meet BSL3 containment standards and are operated by staff trained in the use of appropriate BSL3 work practices the following procedures can be undertaken:

- ▶ Performance of diagnostic tests that involve propagation of viral agents in vitro or in vivo
- ▶ Work involving the replication of influenza H5 virus in cell culture and/or storage of cell culture isolates
- ▶ Recovery of viral agents from cultures of influenza H5 specimens
- ▶ Manipulations involving growth or concentration of influenza H5 virus



:: Management of Case

The management of a case with avian influenza does not differ from that of influenza due to a primarily human pathogenic virus. Antiviral drugs, some of which can be used for both treatment and prevention, should be theoretically effective against influenza A virus strains in otherwise healthy adults and children. However, preliminary studies with Hong Kong isolates of 1997 have shown resistance to amantadine and rimantadine. It is believed that oseltamivir may be an effective drug for which reliable evidence is awaited.

Aspirin and Influenza

Children or teenagers who have flu-like symptoms – and particularly fever – should not be given aspirin as it may cause a rare but serious illness called Reye syndrome. Children or teenagers with the flu should get plenty of rest, drink lots of liquids, and take medicines that contain no aspirin to relieve symptoms. Paracetamol or ibuprofen given orally or by suppository will generally be sufficient.

8.1 Infection control and prevention of nosocomial spread

Isolate the patient to a single room. If a single room is not available, cohort confirmed and suspect cases separately in designated multi-bed rooms or wards. In such a case, the distance between beds should be at least 1m and preferably separated by a physical barrier (e.g. curtain, partition).

Reinforce implementation of standard precautions with droplet and contact precautions*. Appropriate personal protective equipment (PPE) on patient visit/care consists of: mask (high efficiency masks, surgical masks as a second alternative), gown, face shield or goggles and gloves.

Transmission of human influenza is mostly by droplets. Direct or indirect contact and airborne transmissions are also recognized, the latter can involve fine-droplet nuclei suspended in the air for considerable duration of time. However, during the last Hong Kong H5N1 outbreak in humans in 1997, droplet and contact precautions successfully managed patients without nosocomial spread of the disease. So far there is no evidence suggesting airborne transmission of the disease from the current outbreak in Viet Nam, but because of the high mortality of the disease and possibility of mutation of the virus to cause efficient human-to-human transmission, WHO is currently recommending the use of high efficiency masks in addition to droplet and contact precautions for care of human cases of H5N1. For same reason, a negative pressure room may be preferred if available.

Limit the number of the HCWs who have direct contact with the patient(s) and they should not look after other patients. Designated HCWs should be properly trained on infection control precautions. Other hospital employees (e.g. cleaners, lab personnel) and visitors should also be restricted and provided with appropriate PPE.

HCWs with direct patient contact should monitor their temperature twice daily and report the hospital authority on every ill event. HCWs who had potential contact with droplets under circumstances without adequate personal protective equipment should be considered for post-exposure prophylaxis with oseltamivir 75 mg / day, 7days for single exposure.

All HCWs who are unwell in particular with fever and/or respiratory symptoms should not come to work. They should remain at home and report their symptoms to the hospital authority to seek further advice.

Waste should be discarded properly in a sealed impermeable bag clearly labelled as 'Biohazard' and incinerated. Linen and reusable materials that have been in contact with suspect or confirmed AI patients should be handled separately and disinfected properly.

8.2 Medical treatment

Treat with a neuraminidase inhibitor such as oseltamivir (75mg twice orally for 5 days) as early in the clinical course as possible. For paediatric patients, see standard dosage information. Provide supportive care as required. Monitor oxygen saturation and treat desaturation with supplemental oxygen as required

Amantadine and rimantadine should not be used because this may increase the selective pressure for an amantadine/rimantadine resistant pandemic reassortant virus if the patient is co-infected by H5N1 and currently circulating human influenza A viruses. Ribavirin should not be used for treatment of suspected H5N1 virus infections, since there is substantial first pass hepatic metabolism and therefore no clinical benefit is expected; furthermore, anemia associated with ribavirin is an adverse reaction that is not infrequent.

Respiratory specimen and blood specimen should be taken on admission and checked serially to look for possible bacterial infection. Consider antibiotic IV therapy to cover secondary bacterial infections as required.

8.3 Discharge policy

Further studies on viral excretion in the current outbreak is required. For the time being, infection control precautions should remain in place for 7 days after resolution of fever. For children younger than 12 years, infection control measures should remain in place for 21 days after the onset of illness. Where this discharge policy is not applicable due to local resources and should full recovered patients within 21 days after the onset of illness discharged, the family will need to be educated on personal hygiene and infection control measures and not attend school during this period.

8.4 Public health measures

Report all suspect and confirmed cases to the local health authority and seek advice. Identify the contacts and person who were exposed to the common source of infection and put them under observation. They should be followed up for 1 week. Persons under observation should be asked to check the temperature twice daily and report all ill health events.

If such a person developed (i) sudden onset of fever over 38 degrees, and/or (ii) other respiratory symptoms, immediately prescribe oseltamivir 75mg bid for 5 days. Hospitalize the person and manage under appropriate infection control precautions. Take respiratory and blood samples and the samples should be sent to the designated laboratory for further testing on H5N1. If a case should be managed at home, the family will need to be educated on personal hygiene and infection control measures.



Prevention and Control

9.1 Strategy

- **Remove animal reservoir**
 - ▶ Control outbreaks by safe slaughter of poultry
 - ▶ Restrict movement of poultry from infected areas

- **Understand the extent of problem in humans**
 - ▶ Enhanced surveillance
 - ▶ Epidemiological investigations (human to human transmission)
 - ▶ Laboratory support

- **Reduce the risk of human infections from occupational exposures**
 - ▶ Protection of occupationally exposed persons
 - ▶ Infection control in health care settings

The above mentioned strategy can be implemented by following mechanisms:

9.2 Control in poultry

- Early identification
- Destruction of the entire infected cohort as per the guidelines of FAO/OIE
- Vaccination of uninfected flocks
- Proper disposal
- Early notification
- Close coordination with health department

FAO/OIE/WHO has recommended that stamping out is the preferred control option for an outbreak of HPAI and should be used on all flocks exhibiting clinical disease. It has been highly effective in controlling confined outbreaks of HPAI where there is limited spread and low risk of re-introduction. At the same time there is no justification to recommend the systematic elimination of wildlife or swine for the management of HPAI outbreaks.

Role of vaccination of birds

FAO/OIE/WHO recommend that countries may consider vaccination as an option in those situations where massive culling is either not feasible or not desirable. Vaccination reduces susceptibility to infection and shedding and hence reduces incidence of new cases and viral load. It, thus, complements other control measures. The vaccination must be carried out with quality vaccines which comply with international standards as referred in OIE Manual of Standards.

Stamping-out and vaccination are not mutually exclusive, and the mix or sequence of measures may differ between vaccine production systems and stages of a control programme.

9.3 Control in human beings

The essential components to control an outbreak in human beings include:-

- Early identification
- Isolation of both suspect and probable cases
- Tracing and monitoring close contacts of all suspect / probable cases identified,
- Barrier nursing
- Public information

Several measures can help minimize the global public health risks that could arise from large outbreaks of highly pathogenic H5N1 avian influenza in birds. An immediate priority is to halt further spread of epidemics in poultry populations. This strategy works to reduce opportunities for human exposure to the virus. Vaccination of persons at high risk of exposure to infected poultry, using existing vaccines effective against currently circulating human influenza strains, can reduce the likelihood of co-infection of humans with avian and influenza strains, and thus

reduce the risk that genes will be exchanged. Workers involved in the culling of poultry flocks must be protected, by proper clothing and equipment, against infection. These workers should also receive antiviral drugs as a prophylactic measure.

When cases of avian influenza in humans occur, information on the extent of influenza infection in animals as well as humans and on circulating influenza viruses is urgently needed to aid the assessment of risks to public health and to guide the best protective measures. Thorough investigation of each case is also essential. While WHO and the members of its global influenza network, together with other international agencies, can assist with many of these activities, the successful containment of public health risks also depends on the epidemiological and laboratory capacity of affected countries and the adequacy of surveillance systems already in place.

Protection of human beings involved in mass slaughter of potentially infected animals

WHO recommends that

A. Cullers and transporters should be provided with appropriate PPE

- ▶ Protective clothing, preferably coveralls plus an impermeable apron or surgical gowns with long cuffed sleeves plus an impermeable apron
- ▶ Heavy duty rubber gloves that may be disinfected
- ▶ N95 respirator masks are preferred. Standard well-fitted masks should be used if N95 respirators are not available
- ▶ Goggles
- ▶ Rubber or polyurethane boots that can be disinfected or protective foot covers that can be discarded

B. All persons who have been in close contact with infected animals should wash their hands frequently with soap and water. Cullers and transporters should disinfect their hands after the operation.

C. Environmental clean-up should be carried out in areas of culling, using the same protective measures as above

D. All persons exposed to infected chickens or to farms under suspicion should be under close monitoring by local health authorities and provided medical care as described earlier, if needed

E. They should be vaccinated with the current WHO recommended vaccine to avoid simultaneous infection with human influenza and avian influenza and to minimize the possibility of a re-assortment of the virus's genes

While all these activities can reduce the likelihood that a pandemic strain will emerge, the question of whether another influenza pandemic can be averted cannot be answered with certainty.

9.4 Vaccination

Vaccination of human beings is possible with currently available vaccines against influenza with the objective of limiting the risk of reassortment and emergence of an influenza virus with pandemic potential that readily spreads from human to human. However, it must be made clear to the vaccinee as well as the health authorities that human vaccination with current inter-pandemic vaccine will not protect humans from infection with avian H5N1 influenza. The vaccine may be administered to cullers who are involved in destruction of poultry, people living and working on poultry farms where H5N1 infection is reported or suspected and health care workers involved in daily care of known or confirmed human cases of influenza due to H5N1 subtype. A specific vaccine is under development and may become available within 6-12 months.



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