

## WHO interim guidelines on clinical management of humans infected by influenza A(H5N1)

These guidelines are based on current knowledge of human influenza A(H5N1) infections deriving from experience during the 1997 outbreak in Hong Kong Special Administrative Region of China (Hong Kong SAR)<sup>1, 2</sup> and from preliminary reports of recent cases in Thailand and Viet Nam (see Annex 1, *Summary of preliminary clinical features of humans infected by influenza A(H5N1)*). As more case data become available, these guidelines will be modified as appropriate.

### Objectives

- Early implementation of infection control precautions to minimize nosocomial spread of disease.
- Proper case management to prevent severe illness and death.
- Early identification and follow-up of persons at risk of infection to facilitate early intervention with antiviral therapy to reduce morbidity and mortality and limit further spread of the disease.

### General considerations

*Existing infection control measures include the application of standard precautions<sup>3</sup> to all patients receiving care in hospitals.*

*If the diagnosis of influenza A(H5N1) infection is being considered on the basis of clinical features, additional precautions should be implemented until that diagnosis can be ruled out.*

These additional precautions are outlined in the section below, *Infection control and prevention of nosocomial spread of influenza A(H5N1)*.

In those countries or territories where influenza A(H5N1) viruses have been identified as a cause of illness in animal populations, the diagnosis of influenza A(H5N1) infection should be included in the differential diagnosis of all persons presenting with severe acute respiratory illness. People who have touched either ill poultry or poultry that died of illness are at the greatest potential risk of infection. For further information, see Annex 2, *Exposures that may have put a person at risk of becoming infected with influenza A(H5N1)*.

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<sup>1</sup> Yuen KY et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. *Lancet*, 1998, 351:467–471.

<sup>2</sup> Chan PK. Outbreak of avian influenza A(H5N1) virus infection in Hong Kong in 1997. *Clinical Infectious Diseases*, 2002, 34:S58–S64.

<sup>3</sup> See USA Hospital Infection Control Practices Advisory Committee (1997), *Recommendations for isolation precautions in hospitals*; available at <http://www.cdc.gov/ncidod/hip/isolat/isopart2.htm>.

***Countries or territories currently experiencing outbreaks of highly pathogenic avian influenza due to influenza A(H5N1) in poultry should vaccinate health care workers (HCWs) at risk with the WHO-recommended seasonal vaccine.***

The rationale is to reduce opportunities for the simultaneous infection of humans with avian and human influenza viruses. In turn, this reduces opportunities for reassortment and for the eventual emergence of a novel influenza virus with pandemic potential.

Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection are available at:

[http://www.who.int/csr/disease/avian\\_influenza/guidelines/seasonal\\_vaccine/en/](http://www.who.int/csr/disease/avian_influenza/guidelines/seasonal_vaccine/en/)

WHO recommendations for the seasonal influenza vaccines are available at:

<http://www.who.int/csr/disease/influenza/vaccinerecommendations/en/>

**Infection control and prevention of nosocomial spread of influenza A(H5N1)**

Transmission of human influenza is by droplets and fine droplet nuclei (airborne). Transmission by direct and indirect contact is also recognized. However, during the 1997 influenza A(H5N1) outbreak in humans in Hong Kong SAR, droplet and contact precautions successfully prevented nosocomial spread of the disease. So far there is no evidence to suggest airborne transmission of the disease in the current outbreaks in Thailand and Viet Nam. Nevertheless, because of the high mortality of the disease and the possibility of the virus mutating to cause efficient human-to-human transmission, WHO is currently recommending the use of high-efficiency masks<sup>4</sup> in addition to droplet and contact precautions. In addition, a negative pressure room – if available – is recommended.

Isolate the patient to a single room. If a single room is not available, cohort patients separately in designated multi-bed rooms or wards; beds should be placed more than 1 metre apart and preferably be separated by a physical barrier (e.g. curtain, partition).

Reinforce standard precautions with droplet and contact precautions. Appropriate personal protective equipment (PPE) for all those entering patients' rooms consists of mask (high-efficiency mask if available or surgical mask), gown, face shield or goggles, and gloves.

Limit the number of HCWs who have direct contact with the patient(s); these HCWs should not look after other patients. The number of other hospital employees (e.g. cleaners, laboratory personnel) with access to the environment of these patients should also be limited. Designated HCWs should all be properly trained in infection control precautions.

Restrict the number of visitors and provide them with appropriate PPE and instruct them in its use.

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<sup>4</sup> High-efficiency masks are US NIOSH certified N-95, European CE approved respirators, or of a comparable national/regional standards applicable to the country of manufacture. Higher level particulate respirators may also be used.

Ask HCWs with direct patient contact to monitor their own temperature twice daily and report to hospital authorities any febrile event. An HCW who has a fever (>38 °C) and who has had direct patient contact should be treated immediately (see *Case Management* below).

Offer post-exposure prophylaxis (for example, oseltamivir 75 mg daily orally for 7days) to any HCW who has had potential contact with droplets from a patient without having had adequate PPE.

HCWs who are unwell should not be involved in direct patient care since they are more vulnerable and may be more likely to develop severe illness when exposed to influenza A(H5N1) viruses.

Dispose of waste properly by placing it in sealed, impermeable bags which should be clearly labelled "Biohazard" and incinerated. Linen and reusable materials that have been in contact with patients should be handled separately and disinfected.

### **Case management**

Take respiratory and blood specimens for laboratory testing for influenza and other infections as clinically indicated (see *Recommended laboratory tests to identify influenza A/H5 virus in specimens from patients with an influenza-like illness*, available at [http://www.who.int/csr/disease/avian\\_influenza/guidelines/labtests/en/](http://www.who.int/csr/disease/avian_influenza/guidelines/labtests/en/)).

Treat with a neuraminidase inhibitor such as oseltamivir (75 mg orally, twice daily for 5 days) as early in the clinical course as possible.<sup>5</sup> Refer to product information sheets for dosage and current limitations on paediatric use.

If clinically indicated, hospitalize patients under appropriate infection control precautions as described in previous sections.

If a case is assessed as not requiring hospitalization, educate the patient and his or her family on personal hygiene and infection control measures (e.g. hand-washing, use of a paper or surgical mask by the ill person, and restriction of social contacts), and instruct the patient to seek prompt medical care if the condition worsens. As resources permit, follow up non-hospitalized patients by home visits or telephone contact.

Provide supportive care. Monitor oxygen saturation and treat desaturation with supplemental oxygen as required. As nebulizers and high-air-flow oxygen masks have been potentially implicated in the nosocomial spread of severe acute respiratory syndrome, use these measures only if clinically justified and apply them under strict infection control, including airborne transmission precautions.

Take respiratory and blood specimens serially to check for possible bacterial infection. Consider intravenous antibiotic therapy to control secondary bacterial infections as required.

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<sup>5</sup> The benefits of oseltamivir, the optimal dosage and schedule for later-stage intervention in severe influenza illness are unknown. Please contact [WHOinflueza@who.int](mailto:WHOinflueza@who.int) for information on clinical trial protocols.

Do not use amantadine or rimantadine because of the risk of increasing the selective pressure for development of a resistant influenza virus with pandemic potential. Preliminary results from WHO collaborating centres suggest that influenza A(H5N1) viruses recently isolated from humans are resistant to amantadine and rimantadine (see *Avian influenza A(H5N1) – update 22: Susceptibility of H5N1 viruses to antiviral drugs*, available at [http://www.who.int/csr/don/2004\\_02\\_12a/en/](http://www.who.int/csr/don/2004_02_12a/en/)).

Avoid administration of salicylates (such as aspirin) in children under 18 years of age because of the risk of Reye syndrome. Use paracetamol or ibuprofen, either orally or by suppository, for management of fever as clinically indicated.

Immunomodulators such as corticosteroids should be used only in the context of clinical trials. The immune response of humans with influenza A(H5N1) infection requires further study.

Do not use ribavirin. There is no evidence to support its effectiveness against influenza viruses; moreover, adverse reactions such as anaemia are frequent and may further compromise the patient.

### **Discharge policy**

Studies are required to provide better understanding of viral excretion patterns in humans infected with the influenza A(H5N1) viruses associated with the current outbreaks in Thailand and Viet Nam. Until further evidence is available, WHO recommends that infection control precautions for adult patients remain in place for 7 days after resolution of fever.

Previous human influenza studies have indicated that children younger than 12 years can shed virus for 21 days after onset of illness. Therefore, infection control measures for children should ideally remain in place for this period. Where this is not feasible (because of a lack of local resources), the family should be educated on personal hygiene and infection control measures (e.g. hand-washing and use of a paper or surgical mask by a child who is still coughing). Children should not attend school during this period.

### **Public health measures**

Report to the local public health authority all patients for whom the diagnosis of influenza A(H5N1) virus infection is being considered. Refer to national procedures for reporting and see *WHO guidelines for global surveillance of influenza A/H5* (available at [http://www.who.int/csr/disease/avian\\_influenza/guidelines/globalsurveillance/en/](http://www.who.int/csr/disease/avian_influenza/guidelines/globalsurveillance/en/))

Identify contacts<sup>6</sup> as well as those persons who may have been exposed to the common source of infection. These persons should be monitored for 7 days after their last exposure to the implicated patient or to the common source and asked to check their temperature

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<sup>6</sup> Contacts are persons who shared a defined setting (household, extended family, hospital or other residential institution, military barracks or recreational camps) with a person for whom the diagnosis of influenza A(H5N1) is being considered while this person was in his or her infectious period (i.e. from 1 day before onset of symptoms to 7 days after onset of symptoms, or to the date prescribed by national public health authorities or to the date indicated in the section *Discharge policy*).

twice daily. If a person who is being monitored develops fever ( $>38\text{ }^{\circ}\text{C}$ ) and cough or shortness of breath, he or she should be treated immediately (see *Case Management* above).

## Annex 1

### Summary of preliminary clinical features of humans infected by influenza A(H5N1)

The incubation period for classic human influenza viruses is 2–3 days (range 1–7 days). However, the incubation period of influenza A(H5N1) is currently uncertain. Based on limited experience from 6 cases in Viet Nam, the median time between exposure and onset of illness is 3 days (range 2–4 days).

Cases have been characterized by high fever (above 38 °C), cough and shortness of breath.

Lower respiratory symptoms or signs developed early and include dyspnoea and auscultatory signs. Clinically apparent pneumonia with chest X-ray changes was seen in all patients, although the X-ray changes were nonspecific and included diffuse, multifocal or patchy infiltrates, interstitial infiltrates, and segmental or lobular consolidation with air bronchograms. The illness rapidly progressed to respiratory distress and subsequent respiratory failure within 1 week of the onset of symptoms. Most cases have died in spite of ventilatory support.

Common laboratory findings were lymphopenia ( $<1 \times 10^9$ /litre) and slightly or moderately raised alanine aminotransferase and aspartate transaminase.

For further information please see:

- *Preliminary clinical and epidemiological description of influenza A(H5N1) in Viet Nam*, available at [http://www.who.int/csr/disease/avian\\_influenza/guidelines/vietnamclinical/en/](http://www.who.int/csr/disease/avian_influenza/guidelines/vietnamclinical/en/)

and

- Avian influenza A(H5N1). *Weekly Epidemiological Record*, 2004, 79(7):65–70, available at <http://www.who.int/wer/2004/en/wer7907.pdf>

Annex 2

**Exposures that may have put a person at risk of becoming infected with influenza A(H5N1)**

Countries and territories where influenza A/H5 viruses have been identified as a cause of illness in human or animal populations since 1 October 2003	Countries and territories where influenza A/H5 viruses have NOT been identified as a cause of illness in human or animal populations since 1 October 2003
<p>During the 7 days before the onset of symptoms, one or more of the following:</p> <ul style="list-style-type: none"> <li>• contact (within 1 metre) with live or dead domestic fowl<sup>1</sup> or wild birds;</li> <li>• exposure to settings where domestic fowl were or had been confined in the previous 6 weeks;</li> <li>• contact (within touching or speaking distance) with a person for whom the diagnosis of influenza A(H5N1) is being considered;</li> <li>• contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in death.</li> </ul>	<p>History of travel, during the 7 days before the onset of symptoms, to a country or territory with reported highly pathogenic avian influenza (HPAI) activity due to influenza A (H5N1) in the animal populations, <b>AND</b> one or more of the following:</p> <ul style="list-style-type: none"> <li>• contact (within 1 metre) with live or dead domestic fowl<sup>1</sup> or wild birds in any setting;</li> <li>• exposure to settings in which domestic fowl were or had been confined in the previous 6 weeks;</li> <li>• contact (within touching or speaking distance) with a confirmed human case of influenza A/H5 infection;</li> <li>• contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in death.</li> </ul>
	<p>During the 7 days before the onset of symptoms, one or more of the following:</p> <ul style="list-style-type: none"> <li>• living in an area in which there are rumours of deaths of domestic fowl;</li> <li>• occupational exposure.<sup>2</sup></li> </ul>
<p>During the 7 days before the onset of symptoms, having worked in a laboratory where there is processing of samples from persons or animals suspected of having HPAI.</p>	

<sup>1</sup> Domestic fowl are birds that are commonly reared for their flesh, eggs, or feathers and are kept in a yard or similar enclosure, including chickens, ducks, geese, turkeys, guinea fowl.

<sup>2</sup> At-risk occupations such as a domestic fowl worker, domestic fowl processing plant worker, domestic fowl culler (catching, bagging, or transporting birds, disposing of dead birds), worker in live animal market, chef working with live or recently killed domestic fowl, dealer or trader in pet birds, health care worker.