EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

# TECHNICAL REPORT

## ECDC SCIENTIFIC ADVICE

**Oseltamivir Prophylaxis Following Suspected Exposure of Humans to Highly Pathogenic Avian Influenza (HPAI) with Particular Reference to HPAI type A/H5N1**
**Version 30th April 2006**

# Oseltamivir prophylaxis following suspected exposure of humans to Highly Pathogenic Avian Influenza (HPAI) with particular reference to HPAI type A/H5N1

## Background

This document was stimulated by requests from Member States seeking expert guidance over what to do in relation to exposure of humans to dead birds with proven or suspected highly pathogenic avian influenza type A/H5N1 infection. It was agreed within ECDC and by the Advisory Forum that it would be useful to list a wider number of the situations where we were aware that the issue has arisen, including exposure to other Avian Influenza (AIs) types . The document should be read with existing ECDC guidance on Highly Pathogenic Avian Influenza, notably the Occupational Guidance http://www.ecdc.eu.int/avian_influenza/occupational_exposure.php.

### Using this Document

This guidance is not intented to replace national guidance already prepared by Member States (MS) and should always be used in the light of a local or national risk assessment of the particular circumstance. Rather the guidance has been developed recognizing that not all MS have specific guidance, that a document like this could save them time and that there are advantages to some standardisation across Europe. It is intended to be treated as guidance and not as a set of rules or regulations.

The evidence base underpinning this guidance has a number of gaps and the base itself is, at present, under review by the World Health Organization. Relevant publications are listed towards the end of the document. Hence this is an interim set of practical guidance designed for use in Europe. This draft has already benefited considerably from comments on earlier drafts from members of ECDC's Advisory Forum and their specialist colleagues.

## Types of Prophylaxis

Two forms of prophylaxis against AIs with oseltamivir have been proposed:

1. **Pre-exposure** – when there is a foreseen or continuing risk of exposure to a highly pathogenic avian influenza, especially H5N1

2. **Post-exposure** – when there has been a possible or certain exposure (sometimes described as early treatment but here called post-exposure prophylaxis).

This advice will mostly deal with the second case – post-exposure prophylaxis. It will not deal with treatment and care of individual patients when there is proven or strongly suspected infection

## General criteria

**Post-exposure prophylaxis** should be used only when confirmed or strongly suspected cases of highly pathogenic avian influenza (HPAI) including H5N1 occur in birds, animals and humans. There is little justification for using pre or post exposure prophylaxis where the avian influenza is known to be of low pathogenicity for birds (LPAI). When outbreaks of seeming LPAI occur a local risk assessment should be undertaken taking national specialist advice. Though there has been occasional cases of LPAI viruses infecting humans the of low pathogenicity to date these have been sporadic and always mild. People who are exposed need to be made aware of this possibility and what to do should they develop symptom. Such cases should then be treated with antivirals.

When dealing with known or suspected HPAI, post-exposure prophylaxis should be started as early as possible. For those occupationally exposed post-exposure or pre-exposure prophylaxis is **not** an alternative to good use of personal protective equipment. Post-exposure prophylaxis should be given as soon as possible. It is not required if the last exposure occurred more than 7 days previously.

People who are exposed need to be aware of the risks, what the symptoms of infection are in humans and what to do in the unlikely event that they develop such symptoms. Written materials are a huge advantage and have been developed by some countries.

## Specific Circumstances

Thirteen situations are listed below, with a note on the global experience so far and the actions that would recommended by ECDC.

'Global Experience – no cases' means no confirmed cases of H5N1 infection have been reported in humans where this exposure situation is considered to be the most likely source of infection. However, human cases can be associated with multiple exposures and therefore it should not be concluded that there is absolutely no risk via this route.

There have also been instances where other Avian Influenza viruses that are seemingly sometimes more transmissible to humans have caused human infections. Different types of Avian Influenzas viruses do not behave identically and that is why ECDC emphasizes the importance of local risk assessments around each outbreak or incident.

At times decisions will have to be taken on the basis of partial information and the precautionary principle followed. For example if it is known that an Avian Influenza is involved, that people have been exposed but that its not yet clear if this is H5N1 or even a Highly Pathogenic Virus. In that case it can be wise to assume it's a HPAI, start people on prophylaxis and review the situation when more laboratory testing is undertaken.

Specialist ECDC staff are happy to advise on these public health decisions and can be contacted urgently via the ECDC Duty Officer (+46 841047878).

Comments on this interim guidance is welcomed and should be directed to influenza@ecdc.eu.int

| Setting | Type of Contact | Global Experience | Required additional actions | ECDC Advice on prophylaxis |
|---|---|---|---|---|
| Exposure to wild birds | 1. Physical contact with a healthy wild bird in an area where H5N1 in birds has been demonstrated or is strongly suspected | No human H5N1 case | | No case for offering prophylaxis. |
| | 2. Physical contact with a sick or dead wild bird in an area where H5N1 in birds has not yet been demonstrated | No H5N1 human case | Joint risk assessment by local veterinary and human authority. If appropriate, laboratory investigation of the bird. | No rationale for offering prophylaxis. |
| | 3. Physical contact with a sick or dead* wild bird in an area where H5N1 in birds has been demonstrated or is strongly suspected | Some H5N1 human cases following significant exposure | Rapid laboratory investigation of the bird. Joint risk assessment by local veterinary and health authorities. | Usually no rationale for offering post-exposure prophylaxis unless there is high risk exposure (e.g. preparing bird for cooking, feather plucking etc. |
| | 4. Physical contact with a sick or dead wild bird that is later verified to be infected with H5N1 | Some H5N1 human cases following significant exposure | Undertake rapid joint risk assessment by local veterinary and health authorities. | Consider offering post-exposure prophylaxis depending on level of exposure. |
| Exposure to domestic poultry | 5. Physical contact with healthy domestic poultry in an area were H5N1 is not yet suspected or verified in domestic poultry | No H5N1 human cases | | No case for offering prophylaxis. |
| | 6. Physical contact with healthy domestic poultry in an area were H5N1 is strongly suspected or verified in domestic poultry | Some H5N1 cases in affected countries where the exact risky contact with sick poultry can be unclear. However the exposure has to be significant e.g. slaughtering poultry | Undertake a rapid joint risk assessment by local veterinary and health authorities. | Only consider post-exposure prophylaxis if there is a significant exposure and the poultry are likely to have been infected themselves |
| | 7. Physical contact with (or being within one meter of) sick or dead domestic poultry strongly suspected or verified as having H5N1 and no PPE has been used | Human H5N1 cases in a number of countries | Undertake a rapid joint risk assessment by local veterinary and health authorities. | Urgently give post-exposure prophylaxis to all household members who have had contact with or have been within 1 meter of the poultry in the past week. |

| Setting | Type of Contact | Global experience | Required additional actions | ECDC Advice on prophylaxis |
|---|---|---|---|---|
| **Household and Social Contacts** | 8. Close household member of a verified or strongly suspected case of human H5N1 | Human H5N1 cases in a number of countries, probably because of shared exposure though there have also been some human to human transmissions. | Undertake a rapid joint risk assessment by local veterinary and health authorities. | **Strongly recommend giving post-exposure prophylaxis and urgently – these people are most at risk.** |
| | 9. Non-household social contact of verified or strongly suspected case of human H5N1 | No H5N1 human cases | | No case for offering prophylaxis. |
| **Occupational Exposure** | 10. Laboratory staff analysing samples for suspect or proven H5N1or another HPAI | No H5N1 human cases | Undertake a rapid joint risk assessment by local veterinary and health authorities if there has been a significant breach in procedures.. | Only offer prophylaxis if there has been a clear break of good laboratory practice. |
| | 11. Health care staff exposed to a patient verified or strongly suspected to have with H5N1 or another HPAI | One human H5N1 case in 1997 in Hong Kong | Undertake a rapid joint risk assessment by local veterinary and health authorities if there has been a significant breach in procedures | Offer prophylaxis, and always if there is failure of protective procedures and use of personal protective equipment (PPE) |
| | 12. Culling or poultry working staff exposed to a bird verified or strongly suspected to be with H5N1 or another HPAI including those using PPE | No H5N1 cases world-wide but this happened with other HPAIs (notably H7N7 in the Netherlands) | Undertake a rapid joint risk assessment by local veterinary and health authorities. | Offer pre-exposure prophylaxis, and post-exposure if not given in advance |
| | 13. Veterinary staff exposed to birds with confirmed or strongly suspected H5N1 or another HPAI | No H5N1 cases world wide but one happened with another HPAI (type H7N7 in the Netherlands – causing one fatality in a vet) | Undertake a rapid joint risk assessment by local veterinary and health authorities. | Offer pre-exposure prophylaxis, and post-exposure if not given in advance. |

## The Evidence Base - Relevant Published Information:

### H5N1 transmission to Humans

1. Brett A. S., Zuger A. The Run on Tamiflu — Should Physicians Prescribe on Demand?
   N Engl J Med 2005; 353:2636-2637,
   http://content.nejm.org/cgi/reprint/353/25/2636.pdf
2. Elbers ARW, Fabri THF, de Vries TS et al. The highly pathogenic avian influenza A (H7N7) virus epidemic in the Netherlands in 2003. Avian Dis 2004; 48: 691-705
3. Hayden F, Croisier A. Transmission of Avian Influenza Viruses to and between Humans. J Infect Dis. 2005;192:1311-1314.
4. Liem NT, World Health Organization International Avian Influenza Investigation Team V, Lim W. Lack of H5N1 avian influenza transmission to hospital employees, Hanoi, 2004. Emerging Infectious Diseases 2005; 11(2):210-215
5. Moscona A. Neuraminidase inhibitors for influenza. NEJM 2005; 353: 1163-73. http://content.nejm.org/cgi/reprint/353/13/1363.pdf
6. Perdue ML, Swayne DE. Public health risk from avian influenza viruses. Avian Diseases 2005; 49: 317-327 2005
7. Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5. Avian Influenza A (H5N1) Infection in Humans. NEJM 2005; 353:1374-1385. http://content.nejm.org/cgi/reprint/353/13/1374.pdf
8. WER – Eurosurveillance article on Azerbaijan (in press)
9. WHO Time Line on Avian Influenza
   http://www.who.int/csr/disease/avian_influenza/timeline.pdf

### Transmission of other Avian Influenza Viruses to Humans

10. Puzelli S, Di Trani L, Fabiani C, Campitelli L, De Marco MA, Capua I, Aguilera JF, Zambon M, Donatelli I. Serological analysis of serum samples from humans exposed to avian H7 influenza viruses in Italy between 1999 and 2003. J Infect Dis. 2005 Oct 15;192(8):1318-22. Epub 2005 Sep 12
11. 2 Tweed SA, Skowronski DM, David ST, Larder A, Petric M, Lees M, et al. Human illness from avian influenza H7N3, British Columbia. Emerg Infect Dis [serial on the Internet]. 2004 Dec Available from
    http://www.cdc.gov/ncidod/EID/vol10no12/04-0961.htm
12. Kurtz J, Manvell J, Banks J. Avian influenza virus isolated from a woman with conjunctivitis. Lancet 1996; 348: 901-2.
13. Koopmans M, Wilbrink B, Conyn M, Natrop G, van der Nat H, Vennema H, Meijer A, van Steenbergen J, Fouchier R, Osterhaus A, Bosman A. Transmission of H7N7 avian influenza A virus to human beings during a large outbreak in

commercial poultry farms in the Netherlands. Lancet. 2004 Feb Feb 21;363(9409):587-93

14. Du Ry van Beest Holle M, Meijer A, Koopmans M, de Jager C. Human-to-human transmission of avian influenza A/H7N7, The Netherlands, 2003. Euro Surveill. 2005 Dec 1;10(12) http://www.eurosurveillance.org/em/v10n12/1012-222.asp
15. Fouchier RA, Schneeberger PM, Rozendaal FW, Broekman JM, Kemink SA, Munster V, Kuiken T, Rimmelzwaan GF, Schutten M, Van Doornum GJ, Koch G, Bosman A, Koopmans M, Osterhaus AD. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci U S A. 2004 Feb 3;101(5):1356-61. Epub 2004 Jan 26.

**Annex Treatment Doses:**

**Recommended Oseltamivir Dosage and Treatment if it is decided to give post exposure prophylaxis**

Adult prophylaxis: 75 mg per day for 10 days

Paediatric dosage (not licensed for use under one year):

| Weight | Dosage (prophylaxis) |
|---|---|
| Under 15 kg | 30 mg daily |
| 15 to 23 kg | 45 mg daily |
| 24 to 39 kg | 60 mg daily |
| 40 kg and over | 75mg daily |

When there has been significant exposure serological testing is recommended to determine whether or not people have not been infected, but this is to build up the global experience. Serological testing for H5N1 is a specialist subject and should only be embarqued upon after consultation with one of the specialised laboratories is required. These can be approached through National Influenza Centre's.

If a person exposed develops symptoms suggestive of infection with H5N1 then they need to be handed over for urgent clinical assessment by specialists who are likely to offer treatment which is at a higher dose than for prophylaxis. A person starting on the prophylactic dose moves over to clinical care and treatment dose if they develop symptoms.