

Avian Influenza: What the family practitioner should know

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Introduction

Human immunity to influenza A virus depends on the specific subtype. Mortality after exposure to subtypes commonly causing human infection is low (approximately 0.1%). Other subtypes are specifically adapted to cause disease in birds. These subtypes are known as 'avian influenza'. Under certain circumstances avian influenza can also be transmitted to humans, causing a severe infection known as highly pathogenic avian influenza (HPAI), with a mortality currently exceeding 50%.

Avian influenza occurs naturally in wild and domesticated birds, especially migratory waterfowl, where the virus is carried in their intestines. Infected birds shed the virus in saliva, nasal secretions and feces and susceptible birds become infected on contact with these secretions.

Several cases of avian influenza in humans have occurred since 1997. Humans may become infected after contact with infected poultry, infected animals e.g. pigs or contaminated surfaces. Symptoms vary from flu-like symptoms (fever, myalgia, cough, rhinorrhea, sore throat, vomiting and watery diarrhea) to viral pneumonia and acute respiratory distress. Almost all patients with HPAI have clinically apparent pneumonia.

The epidemiology of human infection with influenza virus

Subtypes of the influenza virus differ, based upon glycoproteins on the surface of the virus i.e. the haemagglutinin (HA) protein and the neuraminidase (NA) protein. Although

there are sixteen different HA subtypes and nine different NA subtypes for influenza A virus, only a few commonly infect humans, i.e. subtypes H1N1, H1N2, H3N2¹.

Minor mutations called '*antigenic drifts*' due to poor RNA copying may occur in subtypes of human influenza virus, which cause the virus to be less recognizable to the human immune system. These mutations are responsible for outbreaks or epidemics in populations. Pandemics are caused when subtypes from different species of virus re-assort genetic material and merge. These more dramatic genetic rearrangements are called '*antigenic shifts*' and are responsible for a change in genotype, creating new subtypes with new combinations of proteins on the surface of the virus. Populations have no previous exposure to these new subtypes and therefore have had no opportunity to develop immunity against them. Antigenic shift probably occurs when humans live in close proximity to domestic poultry and pigs. Pigs are susceptible to both avian and mammalian influenza A viruses and can serve as a host for recombination of genetic influenza material, resulting in a new subtype able to infect humans². Once a pandemic influenza virus has spread it normally becomes established in the population and subsequently circulates as seasonal epidemics of influenza.

The history of influenza pandemics

Several pandemics have claimed millions of lives during the last

century³. The most significant of these were the following:

1918-19 "*Spanish flu*" subtype H1N1. 675 000 Deaths occurred in the USA and approximately 400 million infections and 30 - 50 million deaths occurred worldwide.

1957-58 "*Asian flu*" subtype H2N2, was first identified in China early in 1957 and subsequently spread to the USA by the middle of 1957, where approximately 70 000 people died.

1968-69 "*Hong Kong flu*" subtype H3N2, caused about 34 000 deaths in the USA.

Since 1997 three prominent avian influenza A subtypes have affected humans⁴ but the H5N1 subtype is cause for particular concern because⁵:

- It mutates rapidly
- It can acquire genes from viruses infecting other animal species
- It is highly pathogenic and can cause severe disease in humans
- Birds that survive this infection excrete H5N1 for at least 10 days, orally and in feces facilitating further spread
- If more humans become infected over time, humans infected with both human and avian influenza may cause the emergence of a novel subtype easily transmissible in the human population

The next pandemic

Outbreaks of influenza A (H5N1), a subtype not previously associated with human disease, occurred among poultry in eight countries in Asia during 2003-5⁶. Currently 25 countries are affected including Austria, France, Germany, Bosnia Herzegovina and

Nigeria⁷. Human infections with this subtype were subsequently reported in Thailand, Vietnam, Cambodia, China, Turkey and Iraq. Indonesia has also confirmed 26 cases, 19 of which were fatal⁸, confirming that this subtype has managed to cross over to human hosts.

According to the WHO 170 laboratory confirmed cases of HPAI have been identified with 92 deaths by 20/02/2006⁸, exceeding a mortality of 50%. Although the majority of cases occurred due to infected poultry contact, human to human transmission may also have occurred, although spread have not continued beyond one person. Because these viruses do not commonly infect humans there is no immune protection against them, and if the virus mutates further to acquire the ability to spread from human to human, we may be faced with the next influenza pandemic. According to the WHO a global influenza pandemic could claim between 5 million and 150 million lives depending on what preventative steps are taken.

Diagnosis, treatment and prevention of serious infections with influenza virus

The management of serious influenza infection and prevention of the spread of this disease relies on early diagnosis, specific antiviral drugs, vaccines and infection control measures.

Laboratory diagnosis: The clinical diagnosis can be confirmed with virus culture done at certain reference laboratories. Alternative techniques to make a laboratory diagnosis of the disease and specific viral subtypes include molecular techniques such as polymerase chain reactions (PCR), immunofluorescence using monoclonal antibody to H5N1 or enzyme linked immunosorbent assay (ELISA) and immunofluorescent antibody (IFAT) for detection of specific antibodies. Appropriate samples to send to the laboratory include nasal, throat or nasopharyngeal swabs or aspirates, bronchoalveolar lavages or lungbiopsy. All samples should be

sent to the laboratory in viral transport medium. Serological tests can also be performed on acute and convalescent sera.

Antiviral drugs used for the treatment of influenza includes amantadine, rimantadine, oseltamivir (Tamiflu) and zanamivir (Relenza). Influenza strains may become resistant to any of these drugs and the 2004 influenza A (H5N1) virus identified in human patients in Asia, is resistant to both amantidine and rimantadine⁴. Patients with avian influenza should be treated with a neuraminidase inhibitor such as oseltamivir 75 mg 2x/d for 5 days. Treatment should start as early in the clinical course as possible. Amantidine and rimantidine should not be used because of resistance associated with the H5N1 virus. Resistance of H5N1 to oseltamivir has already been described in Vietnam⁹ and Japan, complicating treatment. Antimicrobials may be needed to cover for secondary bacterial infection.

Oseltamivir has recently been registered by the MCC in South Africa as a drug indicated for the prevention and treatment of HPAI.

Vaccines: Two problems are associated with a H5N1 vaccine. Since people have never been exposed to H5N1, a primer vaccine would have to be given followed by a second dose a month later. Because of this two-dose regimen, immunity would take about 6 weeks to develop, giving the virus a bigger window to infect even immunized persons. Secondly, a higher vaccine dose as for other types of influenza is needed to elicit an immune response, placing a strain on manufacturer's ability to produce enough vaccine. There is currently no vaccine against the H5N1 subtype but development is under way and several different vaccines have been produced for clinical testing (Sanofi-Aventis, Chiron Corp., Glaxo-SmithKline all plan clinical trials in 2006). The global capacity for vaccine production is about 300 million doses and at least four to six months will be needed to produce a

new vaccine capable of conferring protection against a new subtype.

Infection control: Infection control will be of paramount importance in containing a possible pandemic, and the following guidelines are proposed:

- Isolate the patient in a single room or cohort confirmed or suspected cases. Negative pressure room would be preferred
- Standard droplet and contact precautions, with specific emphasis on the importance of hand washing
- Patient visitors or Health Care Workers (HCW) should wear a high efficiency mask (N-95), gown, face shield or goggles, gloves, and boots or shoe covers³
- Limit the number of HCWs who have contact with the patient, and they should not look after other patients
- HCWs who had potential unprotected contact with droplets should be considered for post exposure prophylaxis with oseltamivir 75 mg/d for 7 days
- Infection control procedures should stay in place for 7 days after resolution of fever

Conclusion

An avian influenza pandemic might have devastating consequences for the world population. Culling of infected domestic poultry, isolation and appropriate treatment of infected patients, the institution of sound infection control measures and the development of an effective vaccine will be the cornerstones of containment of such an event. ☹

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