



The Clinical Newsletter
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***When is “when”?
An Avian Flu Pandemic Update***

In previous issues of *The Clinical Newsletter* we have said that it is not a matter of “if” but only a matter of “when” Avian A (H5N1) influenza becomes a pandemic. Much of what appears below is a summary of the information recently published or presented at the "Second World Health Organization (WHO) Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus" in March 2007 and summarized in *The New England Journal of Medicine* [358:261\(2008\)](#).

The predominant source of exposure in H5N1 cases is contact with infected poultry in the week before onset of illness. In cases involving no such contact, patients might have touched contaminated objects, fertilizer containing poultry feces, or have inhaled aerosolized infectious material.

Surveillance for cases of influenza H5N1 has focused on patients with severe illness, but milder illnesses in children, which are not pneumonic, occur. Limited seroepidemiologic studies conducted since 2003 involving villagers living with backyard poultry, workers in live-poultry markets, and health care workers suggest that asymptomatic or mild human influenza H5N1 virus infection is rare.

About a quarter of all human cases have occurred in clusters of 2 or more that were epidemiologically linked. More than 90 percent of the clusters have involved blood relatives, suggesting a possible genetic susceptibility to the infection. Most people in the clusters were probably infected through common exposure to poultry, but limited, nonsustained human-to-human transmission has probably occurred during very close, unprotected contact with a severely ill patient.

It is felt that changes in multiple viral genes, not just the hemagglutinin, are probably required to generate a potentially pandemic influenza H5N1 virus. To date all H5N1 flu strains that have infected humans have been of avian origin and similar to strains found locally in poultry and wild birds. So far no cases of influenza H5N1 illness have been identified among short-term travelers visiting countries affected by such outbreaks. What may be “needed” in order to produce a strain that is readily transmitted from human-to-human is genetic mixing of an avian and a human strain in a dually infected susceptible host such as a pig.

The report questions the "cytokine storm" theory: the proposition that the severe disease in H5N1 cases is a result of an overly intense immune response. It is suggested that the tissue damage probably results from the combined effects of unrestrained viral infection and inflammatory responses induced by the infection. Current understanding of the immune response to the infection is not adequate to guide efforts to treat the disease by modifying the immune response. Findings suggest that the initial infection may occur in either the upper or lower respiratory tract, although the latter may support more efficient replication.

WHO still advises against the routine use of corticosteroids in H5N1 patients. Corticosteroid therapy has not been effective, and prolonged or high-dose corticosteroids can lead to serious adverse events. The standard recommendation for early treatment is with oseltamivir (Tamiflu®). Doubling the oseltamivir dose and duration of treatment may be reasonable. Resistance to the drug has been seen in a few patients. Most of the viral isolates from Indonesia are fully resistant to amantadine and rimantadine. Some viral strains from other parts of Eurasia and Africa are usually susceptible to these drugs. [The CDC no longer recommends these two agents for seasonal influenza].

To date Indonesia has the highest reported number of human cases and the highest fatality rate (124 and 80.6% respectively as of 1/30/2008). The international case fatality rate is presently 61%, being highest among persons 10 to 19 years of

age and lowest among persons 50 years of age or older. About 15 to 20 percent of older adults have some antibodies to H5N1 and might respond to a single dose of vaccine. Whether preexisting immunity, differences in exposure, or other factors might contribute to the apparently lower frequency of infection and lethal illness among older adults is uncertain. However, a report at the Bangkok International Conference on Avian Influenza 2008 (January 23-25, 2008) demonstrated that animals that have previously been vaccinated against seasonal flu appear to respond far quicker to experimental H5N1 bird flu vaccines. Researchers found that ferrets that had been vaccinated against seasonal flu appeared to be more responsive when they were later administered the H5N1 vaccine. Another report showed that mice were protected from several strains of the virus when engineered human monoclonal antibodies to the H5N1 virus were mixed with antibody fragments taken from 9 blood donors with antigens from two H5N1 strains found in Viet Nam and Indonesia .

A study in the January 2008 issue of *Emerging Infectious Diseases* (14:121) showed that ordinary seasonal flu vaccines may provide a small amount of protection against bird flu. The study was among the first to support the idea that getting an annual flu shot may help people's bodies fight off the H5N1 virus. In the laboratory, they added H5N1 virus to the blood of volunteers and found that in some their antibodies acted against H5N1.

Decisions about pre-pandemic vaccination require complex risk-benefit and cost-benefit analyses because of likely effects on seasonal vaccine production and the chance that mass vaccinations would trigger adverse events (think swine flu vaccination). The fact that H5N1 hemagglutinin has evolved into several phylogenetically different epitopes requires that this must be considered in manufacturing an effective vaccine. Certain proprietary adjuvants seem to be highly effective in antigen sparing, i.e., reducing the amount of antigen needed to generate an immune response, and inducing cross-reactive antibody responses. However, the antibody levels needed for protection against the virus are unknown. The report stops short of endorsing pre-pandemic vaccination, i.e., giving an existing H5N1 vaccine before a pandemic in the hope that it will yield some protection against a later H5N1-based pandemic strain or will at least prime the immune system so that just one dose of a specific pandemic vaccine would be necessary. The durability of antibody responses is limited, but boosting with a homologous vaccine or one with viral antigen from another viral ancestor appears to be effective in persons who have received two priming doses.

The WHO chart of H5N1 viruses submitted in the past 5 years says 13 isolates were selected for development into vaccines. So far, 8 engineered viruses derived from these isolates, "suitable for vaccine development and production, are available for distribution".

Two other points to remember:

- ▶ Respiratory secretions and all bodily fluids, including feces, should be considered potentially infectious.
- ▶ Avian influenza A viruses are readily inactivated by a variety of chemical agents and physical conditions, including soaps, detergents, alcohols, and chlorination.

Clarification: in *The Clinical Newsletter* of January 2008 the statement "In at least one study in which LGG was administered to babies prenatally" was intended to convey that subjects consumed probiotic mixtures during their pregnancy.