Transmission of Avian Influenza Viruses to and between Humans

Frederick Hayden[1] and Alice Croisier[2]

[1]Health Sciences Center, University of Virginia, Charlottesville; [2]Global Influenza Programme, World Health Organization, Geneva, Switzerland

(See the article by Puzelli et al., on pages 1318–22.)

Reports of seropositivity for different avian influenza A viruses in exposed poultry workers, including the new findings reported by Puzelli et al. in this issue of the *Journal of Infectious Diseases* [1], and the recent instances of cross-species transmission that caused human disease [2] raise fundamental questions regarding the routes of transmission of avian viruses to and between humans, possible differences in transmission patterns between human and avian influenza viruses, and implications for prevention in those occupationally exposed to infected animals and also in health care, household, and community settings. Documentation of seropositivity for avian influenza viruses in farm workers is not a new finding [3], and previous studies have assessed human susceptibility by intranasal inoculation of selected avian influenza viruses [4]. However, the outbreak in Europe of H7N7 virus infection that led to many cases of conjunctivitis and 1 death resulting from viral pneumonia [5, 6], as well as the unprecedented epizootic caused by highly pathogenic avian influenza H5N1 virus in Southeast Asia, emphasize the importance of these issues.

One strength of the study by Puzelli et al. is the multiplicity of the serological tests used, which included a microneutralization assay with infectious virus, a hemagglutination inhibition (HI) assay, and a confirmatory Western blot analysis with purified H7 hemagglutinin to exclude the possibility of nonspecific cross-reactions with antibodies to human influenza viruses. Differential absorption with human influenza virus has also been utilized to confirm the presence of avian influenza virus–specific antibodies [7]. Such methods are essential to document seropositivity for an avian influenza virus, particularly when concerns about extensive transmission to humans are raised, as was reported elsewhere for H7N7 virus infection in The Netherlands [8]. The possibility that the latter virus caused widespread subclinical infections in poultry workers and household contacts—and, hence, manifested efficient human-to-human transmission—was raised by 1 study that used a modified HI assay to measure antibody [8]. Similarly, the recent report of asymptomatic infection by H5N1 virus in northern Vietnam, as determined by the detection of H5N1 RNA in household contacts, requires substantiation by confirmatory serological testing [9], although culture-confirmed H7N3 illnesses have occurred without an apparent detectable serologic response [10]. Even in those individuals with proven seropositivity for an avian influenza virus, it is uncertain whether they have been only exposed to antigen or are productively infected. The findings that seropositivity occurs in small numbers of poultry workers exposed during outbreaks of illness in poultry caused by some avian strains (H7N7, H7N3, and H5N1) but not others (H7N1 and H5N2) argue for actual infection and support the notion that some avian influenza viruses are more likely than others to infect humans [1]. Definitive evidence for active infection would include detection of virus or viral RNA at the time of exposure or illness. In any case, the recent reports of the apparently greater adaptation of H7N7 [7] and H5N1 [9] avian influenza viruses to humans than was previously recognized and the potential for reassortment during dual infection with a low or highly pathogenic avian influenza virus and a conventional human influenza virus mandate careful laboratory documentation involving multiple assays.

Transmission of human influenza virus occurs by inhalation of infectious droplets

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Reprints or correspondence: Dr. Frederick Hayden, University of Virginia Health Sciences Center, Hospital Dr., Private Clinics Bldg., Rm. 6557, Charlottesville, VA 22908 (fgh@virginia.edu).

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or airborne droplet nuclei and, perhaps, by indirect (fomite) contact followed by self-inoculation of the upper respiratory tract or conjunctival mucosa. The relative importance of these routes is debated, and there is evidence to support each of them, including transmission within health care facilities [11, 12], in human influenza. It is likely that each route contributes to transmission under appropriate circumstances and that the manifestations of illness, respiratory tract viral loads, and, perhaps, the type of infecting influenza virus influence the likelihood of transmission by a particular route. Of course, the use of measures to prevent infection, such as personal protective equipment (e.g., masks and eye protection), hand hygiene, and specific chemoprophylaxis or immunization modalities, by potentially exposed persons will alter the observed risks.

Transmission of avian influenza virus likely encompasses these routes, as well as others. Human conjunctiva [13] and ciliated nasal epithelial cells [14] contain cellular receptors that are recognized preferentially by the hemagglutinin of avian (α2,3 linkages between the terminal sialic acid residues and galactose), rather than human (α2,6 linkages), influenza viruses. The distribution of avian-type receptors in the lower airways and other tissues of humans requires study. However, it is particularly concerning that perhaps only 2 amino acid changes in the viral receptor binding site may be required to change the tropism of the H5 hemagglutinin from avian- to human-type receptors [15]. Clinically apparent infections due to avian influenza viruses of the H7 subtype typically cause conjunctivitis and demonstrate higher viral loads in the eye than in the pharynx [5, 6, 10]. The importance of the eye or nose as a site of initial infection and the importance of subsequent replication with non-H7 avian influenza viruses are unknown. In H5N1-infected patients, conjunctivitis has not been a feature, and rhinorrhea has been inconsistently reported. In contrast, the frequent occurrence of diarrhea and the detection of viral RNA in most fecal samples tested suggest that H5N1 virus may replicate in the human gastrointestinal tract and raise the question of whether human feces could be a source of transmission [16].

Most cases of human infection due to avian influenza viruses have involved close contact with infected poultry, particularly ill or dying chickens. During the outbreak in Hong Kong in 1997, 1 case-control study [17] found that exposure to live poultry within a week before the onset of illness was associated with human disease, but no significant risk was related to traveling, eating or preparing poultry products, or being exposed to persons with disease caused by H5N1 virus. Another study in Hong Kong [18] found that exposure to ill poultry and butchering of birds were associated with seropositivity for H5 avian influenza viruses. Four workers who culled infected birds in Japan [19] and 2 animal attendants who cared for infected tigers in Thailand [20] were found to have antibodies to H5N1 virus during the outbreaks in 2004; seroconversion indicating recent infection was found in only 1 of the Japanese workers. During the first wave of human infections in 2003–2004, a history of direct contact with poultry was found in 8 of 10 H5N1-infected patients in Vietnam [21] and with dead chickens in 8 of 12 H5N1-infected patients in Thailand [22], whereas no clinical cases of illness were noted in those involved in mass culling of poultry. It has been estimated that 12%–61% of rural Thai residents have regular contact with birds [22]. However, ~30% of H5N1-infected patients in Vietnam have not reported exposure to sick poultry [16], which leaves the issue open to speculations about more frequent human-to-human transmission than has been found. However, this finding might be biased, because retrospective notification of animal disease has important consequences in some countries.

Infection after consumption of fresh duck blood and undercooked poultry products has been suspected in some cases of illness. Indeed, transmission to felids was observed after experimental feeding of infected chickens to domestic cats [23], and feeding tigers raw infected chicken led to outbreaks of illness in Thai zoos, in which felid-to-felid transmissions were also implicated [20, 24]. Infected birds shed high concentrations of virus in feces [25]. Direct intranasal or conjunctival inoculation while swimming in contaminated water or, perhaps, inhalation or ingestion of water could have been potential modes of transmission to some H5N1-infected patients. As for human influenza, hand contamination from fomites and self-inoculation into the eye or upper respiratory tract remain possible modes.

Greater adaptation of avian influenza viruses to human hosts could alter the routes of transmission and increase the likelihood of human-to-human spread. In addition to sporadic bird-to-human and suspected environment-to-human transmission, human-to-human transmission of H5N1 avian virus has been implicated by epidemiological findings in several household clusters in which similar illnesses were reported in relatives [21] and in 1 well-documented situation in which there was child-to-mother and likely child-to-aunt transmission in Thailand [26]. These probable human-to-human transmissions involved close contact during the critical phase of illness and were inefficient without additional chains of transmission. Several household contacts also developed symptomatic H7N7 avian virus infections after exposure to ill family members in The Netherlands in 2003 [6]. However, in contrast to the studies of human influenza viruses [27], molecular epidemiological studies to rigorously establish human-to-human transmission of H5 avian viruses have not been completed. Cohort studies in 1997 found that human-to-human transmission might have occurred through close physical contact but not through social contact [28]. Intimate, face-to-face contact without the

use of measures to prevent infection was implicated in these circumstances, and no evidence to date indicates that there has been human-to-human transmission of H5N1 avian virus by small-particle aerosol exposure. Recent serosurveys in southern Vietnam and Thailand have not found evidence for inapparent infections in family contacts [16]. Although viral RNA was detected by polymerase chain reaction in swab samples from asymptomatic family contacts of ill patients in Vietnam in 2005, these infections remain to be confirmed by serological testing.

Nosocomial transmission of H5N1 virus to health care workers (HCWs) was found by serological assessment in Hong Kong in 1997 [29] and is suspected in a nurse exposed to an infected patient in Vietnam in 2005 [16]. To date, the risk of infection in health care settings appears low, even when appropriate isolation measures have not been used [7, 30, 31]. In 2004, no illness occurred in exposed HCWs or laboratory workers in Vietnam [21] or in 35 exposed and unprotected HCWs in Thailand [30]. No serological evidence of infection was present in 83 exposed and masked HCWs in Hanoi [7], and another study of 64 unprotected HCWs in Ho Chi Minh City found no illness or seroconversion [31]. However, given the potential threat and changing transmissibility of avian influenza viruses, isolation precautions within health care facilities should encompass the measures used for potentially pneumoenteric pathogens, such as severe acute respiratory syndrome–associated coronavirus [32].

In summary, observations made to date suggest that differences in the routes of transmission between human and avian influenza viruses exist. The multiple potential routes for the spread of avian influenza viruses, particularly H5N1, indicate that, in addition to protection for the respiratory tract and eyes, proper hand hygiene may be especially important in preventing infection. This applies also in emergency departments and clinics where patients with febrile illnesses who are from areas with documented H5N1 virus infections in poultry or people may be evaluated. In households in which illness has occurred, additional specific protective measures—that is, postexposure chemoprophylaxis with oseltamivir—would be advisable for known household contacts. In affected countries, public education regarding simple precautionary measures for food preparation, poultry handling, and avoidance of contaminated water are essential until effective human vaccines for H5N1 viruses become available.

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