CONCISE COMMUNICATION

Risk of Influenza A (H5N1) Infection among Health Care Workers Exposed to Patients with Influenza A (H5N1), Hong Kong

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The first outbreak of avian influenza A (H5N1) occurred among humans in Hong Kong in 1997. To estimate the risk of person-to-person transmission, a retrospective cohort study was conducted to compare the prevalence of H5N1 antibody among health care workers (HCWs) exposed to H5N1 case-patients with the prevalence among nonexposed HCWs. Information on H5N1 case-patient and poultry exposures and blood samples for H5N1-specific antibody testing were collected. Eight (3.7%) of 217 exposed and 2 (0.7%) of 309 nonexposed HCWs were H5N1 seropositive (P = .01). The difference remained significant after controlling for poultry exposure (P = .01). This study presents the first epidemiologic evidence that H5N1 viruses were transmitted from patients to HCWs. Human-to-human transmission of avian influenza may increase the chances for the emergence of a novel influenza virus with pandemic potential.

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In 1997, 18 human cases of influenza A (H5N1) illness occurred in Hong Kong, coincident with outbreaks of highly pathogenic avian influenza A (H5N1) among domestic poultry [1, 2]. Human H5N1 infections raised concerns about the pandemic potential of this subtype, because only H1, H2, or H3 hemagglutinin subtypes had previously been known to cause outbreaks in humans, and human populations have little or no preexisting antibody to H5N1 [3, 4, 5]. The only prior culture-confirmed cases of naturally acquired human disease linked to avian influenza viruses were 2 unrelated cases of H7N7-associated conjunctivitis [6, 7]. A 1983–1984 study by Bean et al. of workers involved in the depopulation of H5N2-infected poultry in the United States did not find any evidence of human infection [8].

The key question related to the pandemic potential of the H5N1 virus was whether or not it could be transmitted from person to person. Low levels of human transmission may lead to adaptation of the virus to humans through the accumulation of point mutations or through reassortment with a human influenza virus. All recognized case-patients were hospitalized; however, undetected asymptomatic infections or mildly symptomatic H5N1 infections may also have occurred. We investigated whether health care workers (HCWs) exposed to H5N1-infected patients were at risk of H5N1 infection.

Methods

Study Design

We conducted a retrospective seroprevalence study among 3 groups of HCWs in Hong Kong. Each group consisted of HCWs who were exposed to ≥ 1 H5N1 case patients and HCWs with no known exposure but with patient care responsibilities similar to
those of the exposed HCWs. Participants completed questionnaires and donated blood samples for H5N1-specific antibody testing.

Definitions

Exposed HCWs. An HCW was considered to be exposed to an H5N1 case patient if he or she worked on a ward where a potentially infectious case patient was hospitalized.

Nonexposed HCWs. An HCW was considered to be nonexposed if he or she had not worked on a ward where a potentially infectious H5N1 case patient was hospitalized.

Infectious period. An H5N1-infected patient was considered to be potentially infectious to HCWs from the day of admission through 14 days after illness onset or until a repeat viral culture was negative [9].

Temporally-related illness. A respiratory illness that began 1–4 days after exposure to a potentially infectious H5N1 case patient was considered to be a temporally related illness [3].

HCW Exposure Groups

Group A. Group A consisted of nonexposed HCWs and HCWs who had been exposed to a 54-year-old man who was admitted to the hospital on his 6th day of illness with bilateral pneumonia. He died on the 12th day of illness, prior to the diagnosis of H5N1 infection. Standard infection-control procedures had been followed; however, because the determination of H5N1 infection was not made until the day after death, additional droplet precautions, such as wearing masks, gloves, and gowns when within 3 feet of the patient, were not initiated [10].

Group B. Group B consisted of nonexposed HCWs and HCWs who had been exposed to a 13-year-old girl hospitalized on the 6th day of her illness with bilateral pneumonia. On the 14th day of illness, H5N1 infection was diagnosed, and droplet precautions were initiated. She died on the 31st day of illness.

Group C. Group C included nonexposed HCWs and HCWs who were exposed to at least 1 of 3 children admitted to the same general pediatric ward. All 3 children had mild, uncomplicated H5N1-associated respiratory illnesses. The first child was a 2-year-old boy who was hospitalized on the second day of his illness and remained hospitalized for 2 days. He was discharged before the diagnosis of H5N1. The second child, a 5-year-old girl hospitalized on her fourth day of illness, was admitted for 1.5 days and then transferred to a respiratory isolation room when she was given a diagnosis of H5N1. The third child, a 2-year-old male cousin of the second child, was admitted directly to a respiratory isolation room on the second day of his illness.

Questionnaires

We collected information on age, sex, occupation, smoking, chronic diseases, recent travel, respiratory illnesses, and exposure to case patients. Because poultry exposure was considered the other primary risk factor for H5N1 infection, HCWs were asked whether they had contact with ill poultry or poultry that died of an illness, shopped at a market that sold live poultry, or had freshly butchered or live poultry in their home between 1 January 1997 and the date of questionnaire administration for groups A and B and between 1 November 1997 through the date of questionnaire administration for group C [11]. Participants were also asked whether they had ever butchered poultry themselves or had ever lived on a poultry farm. A positive response to any one of these was considered to be indicative of poultry exposure.

Serologic Testing

Blood samples were collected from exposed and nonexposed HCWs a median of 14 days (range, 11–51) and 11 days (range, 11–19), respectively, after the date of last possible exposure in group A, a median of 18 days (range, 13–26) and 11 days (range, 10–24), respectively, for group B, and a median of 12 days (range, 11–28) and 15 days (range, 11–20), respectively, for group C. Serum was separated from blood and stored at −20°C until tested for antibody against H5N1.

Eighty-nine percent of exposed HCWs also had paired acute and convalescent postexposure blood samples available for testing. Blood samples were collected from exposed HCWs by hospital infection-control staff after case patients were identified as H5N1-positive. Exposed HCWs without a sample collected >10 days after the last possible exposure to a case patient were excluded from the analysis.

All sera were tested by an H5N1 virus-specific microneutralization assay by use of A/Hong Kong/156/97 (H5N1) at the Centers for Disease Control and Prevention (CDC) and A/duck/Singapore/-Q/F119-3/97 (H5N3) at the Department of Health Government Virus Unit, Hong Kong [12]. Any serum sample with an antibody titer ≥80 in 2 separate tests conducted at 1 or both facilities was confirmed by a Western blot assay at CDC by use of a highly purified baculovirus-expressed hemagglutinin protein from A/Hong Kong/156/97 virus (Protein Sciences, Meridian, CT) and serum diluted 1 : 100. Samples that were positive by both microneutralization and Western blot assays were considered to be positive for anti-H5 antibody. For adults aged >60 years, the sensitivity and specificity of the combined tests are 80% and 96%, respectively. Adults aged ≥60 years were excluded from the analysis because the H5N1 microneutralization and H5 Western blot assays are less specific for this age group [12].

Statistical Analysis

Differences between proportions were tested by use of the Pearson χ² statistic. When expected values for cells fell below 5, Fisher’s exact test was used. The Mantel-Haenszel summary χ² statistic was used for stratified analyses. Differences in age were tested by use of the Wilcoxon rank sum test [13]. In age-stratified analysis, age groups of <35, 35–44, and >44 years of age were used. A P value <.05 was considered statistically significant.

Results

Description of study participants. The 217 exposed and 309 nonexposed HCWs who participated in the investigation did not differ by age, presence of chronic medical conditions, occupation, or poultry exposure but did differ by sex, with a
higher percentage of females in the exposed group. Group A also had a higher percentage of females in the exposed group (table 1).

Serologic results. For all study participants combined, 8 (3.7%) of 217 exposed and 2 (1%) of 309 nonexposed HCWs were positive for H5 antibody (P = .01; table 1). This difference remained significant after stratifying by age group (P = .01), poultry exposure (P = .01), and sex (P = .01). Among exposed persons, having a temporally related respiratory illness was not associated with being seropositive.

In group A, 5 (5%) of 96 exposed HCWs and 1 (1%) of 201 nonexposed HCWs were H5 antibody positive (P = .01). Among the 96 exposed HCWs, seropositive persons more likely to have bathed the case patient (3/12 vs. 2/84, P = .01) or changed the case patient’s bed linens (3/19 vs. 2/77, P = .05), compared with seronegative exposed HCWs. No other H5-associated risk factors were identified among either group A or group B exposed HCWs.

Of the 10 antibody-positive persons, 6 were from group A and 4 were from group B. None of the group C participants were seropositive. Eight reported case-patient exposure, 6 reported poultry exposure, and 1 reported no history of exposure to either a case patient or poultry (table 2). Two antibody-positive HCWs with paired serum samples seroconverted. Both were exposed to a case patient, and neither reported poultry exposure. One of the 2 HCWs was asymptomatic, while the other reported a temporally related respiratory illness 2 days after exposure to the case patient. A viral culture specimen collected 9–10 days after this HCW became ill was negative.

Discussion

This study documents the first epidemiologic evidence that avian influenza A (H5N1) viruses can be transmitted from person to person and that asymptomatic H5N1 infections can occur. Exposure of HCWs to H5N1 case-patients was associated with having H5-specific antibody. In addition, the seroconversion of 2 exposed HCWs strongly suggested that H5N1 was transmitted from patients to HCWs. Of importance is the observation that exposed and unexposed HCWs reported no differences in poultry exposure, the other likely source of infection [11].

The overall seroprevalence of anti-H5 antibody among HCWs was low, confirming that transmission of the virus, whether from person to person or poultry to person, was uncommon in the study population. These results are consistent with those from the serologic investigation of persons exposed to the first case of human H5N1 illness in May 1997, in which 1 of 54 exposed HCWs were seropositive and none of 419 controls were seropositive [5].

Differences in the prevalence of H5 antibody among the HCW groups may be explained by differences in severity of illness among the groups’ case-patients and possibly by differences in the number of days from admission to diagnosis and in infection-control practices [14]. Groups A and B case-patients, the third and fourth documented human H5N1 infections, were critically ill but were not diagnosed with H5N1 until several days after hospital admission. Although influenza was suspected and viral cultures were collected on the day of admission, droplet precautions were not initiated until after H5N1 virus infection was confirmed. Shortly after these patients were given their diagnoses, H5-specific immunofluorescence rapid testing of clinical specimens became available in Hong Kong. Both case patients required complete care, necessitating close contact between HCW and patient. Indeed, in group A, bathing and changing the patient’s bed linens were activities associated with being seropositive. In contrast, 2 of the 3 group C case-

### Table 1. Characteristics of study participants by group and exposure to influenza A (H5N1)–infected case patients and results of H5N1-specific antibody testing.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group A</th>
<th>Group B</th>
<th>Group C</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposed (n = 96)</td>
<td>Nonexposed (n = 201)</td>
<td>Exposed (n = 82)</td>
<td>Nonexposed (n = 39)</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>30 (28)</td>
<td>30 (27)</td>
<td>.02</td>
<td>30 (27)</td>
</tr>
<tr>
<td>No. (%) female</td>
<td>72 (75)</td>
<td>172 (86)</td>
<td>.02</td>
<td>66 (80)</td>
</tr>
<tr>
<td>No. (%) with chronic medical condition(s) a</td>
<td>10 (10)</td>
<td>21 (10)</td>
<td>.9</td>
<td>4 (5)</td>
</tr>
<tr>
<td>No. (%) nurses or physicians b</td>
<td>66 (69)</td>
<td>156 (78)</td>
<td>.1</td>
<td>72 (88)</td>
</tr>
<tr>
<td>No. (%) with poultry exposure history</td>
<td>53 (55)</td>
<td>127 (63)</td>
<td>.2</td>
<td>50 (61)</td>
</tr>
<tr>
<td>No. (%) H5N1 antibody-positive</td>
<td>5 (5)</td>
<td>1 (5.5)</td>
<td>.01</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

a Chronic medical conditions included those considered by the Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention, to be associated with an increased risk of complications from influenza infection.

b Other HCWs were radiology, respiratory and physical therapy, and clerical and housekeeping staff.
patients were admitted to respiratory isolation rooms, and all 3 had mild disease. Studies on human influenza-virus infections have shown a close correlation between severity of illness and the quantity of virus recovered in respiratory specimens [14].

Serologic evidence of secondary H5N1 virus infection was not confirmed by viral isolation. Because influenza infection generally results in viral shedding for <7 days, it is not surprising that culture specimens collected after 9 days of illness from the symptomatic HCW were negative [9, 14]. In this population, in which preexisting H5N1 antibody was rare, serologic testing is the best possible indicator of infection when viral cultures are not available [3, 5]. While having paired serum collected at the same time from all exposed and nonexposed HCWs would have been ideal, this was not possible in an outbreak situation. However, the single samples collected from nonexposed persons were collected during the same time period as the late blood specimens from exposed HCWs. This provided both case-patient–exposed and –nonexposed HCWs with a similar amount of time for potential exposure to H5N1-infected poultry or persons in the community.

Our study has shown for the first time, based on the epidemiologic evidence and the seroconversion of 2 HCWs, that human-to-human transmission of H5N1 occurred. Although no human H5N1 infections have been detected since December 1997, influenza H5 viruses, along with other influenza A subtypes, continue to circulate among bird populations [3, 15]. With avian viruses now having demonstrated their ability to infect humans and pass from human to human, strengthening international surveillance for H5N1 and other influenza A subtypes among domestic and feral birds, as well as human populations, should be a public health priority.

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