Avian Influenza A (H5N1) Infection in Humans

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5

**INCIDENCE**

The occurrence of human influenza A (H5N1) in Southeast Asia (Table 1) has paralleled large outbreaks of avian influenza A (H5N1), although the avian epidemics in 2004 and 2005 have only rarely led to disease in humans. The largest number of cases has occurred in Vietnam, particularly during the third, ongoing wave, and the first human death was recently reported in Indonesia. The frequencies of human infection have not been determined, and seroprevalence studies are urgently needed. The expanding geographic distribution of avian influenza A (H5N1) infections, with recent outbreaks in Kazakhstan, Mongolia, and Russia, indicates that more human populations are at risk.

**TRANSMISSION**

Human influenza is transmitted by inhalation of infectious droplets and droplet nuclei, by direct contact, and perhaps, by indirect (fomite) contact, with self-inoculation onto the upper respiratory tract or conjunctival mucosa. The relative efficiency of the different routes of transmission has not been defined. For human influenza A (H5N1) infections, evidence is consistent with bird-to-human, possibly environment-to-human, and limited, nonsustained human-to-human transmission to date.

**ANIMAL TO HUMAN**

In 1997, exposure to live poultry within a week before the onset of illness was associated with disease in humans, whereas there was no significant risk related to eating or preparing poultry products or exposure to persons with influenza A (H5N1) disease. Exposure to ill poultry and butchering of birds were associated with seropositivity for influenza A (H5N1) (Table 2). Recently, most patients have had a history of direct contact with poultry (Table 3), although not those who were involved in mass culling of poultry. Plucking and preparing of diseased birds; handling fighting cocks; playing with poultry, particularly asymptomatic infected ducks; and consumption of duck’s blood or possibly undercooked poultry have all been implicated. Transmission to felids has been observed by feeding raw infected chickens to tigers and leopards in zoos in

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**References**

1. Because many critical questions remain, modifications of these recommendations are likely.
2. The occurrence of human influenza A (H5N1) in Southeast Asia (Table 1) has paralleled large outbreaks of avian influenza A (H5N1), although the avian epidemics in 2004 and 2005 have only rarely led to disease in humans. The largest number of cases has occurred in Vietnam, particularly during the third, ongoing wave, and the first human death was recently reported in Indonesia. The frequencies of human infection have not been determined, and seroprevalence studies are urgently needed. The expanding geographic distribution of avian influenza A (H5N1) infections, with recent outbreaks in Kazakhstan, Mongolia, and Russia, indicates that more human populations are at risk.
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Thailand and to domestic cats under experimental conditions. Transmission between felids has been found under such conditions. Some infections may be initiated by pharyngeal or gastrointestinal inoculation of virus.

**Human to Human**

Human-to-human transmission of influenza A (H5N1) has been suggested in several household clusters and in one case of apparent child-to-mother transmission (Table 3). Intimate contact without the use of precautions was implicated, and so far no case of human-to-human transmission by small-particle aerosols has been identified. In 1997, human-to-human transmission did not apparently occur through social contact, and serologic studies of exposed health care workers indicated that transmission was inefficient.

### Table 1. Cumulative Number of Virologically Confirmed Cases of Avian Influenza A (H5N1) in Humans Reported to the WHO since 2003.

<table>
<thead>
<tr>
<th>Date of Onset</th>
<th>Vietnam</th>
<th>Thailand</th>
<th>Cambodia</th>
<th>Indonesia</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Cases</td>
<td>No. of Deaths</td>
<td>No. of Cases</td>
<td>No. of Deaths</td>
<td>No. of Cases</td>
</tr>
<tr>
<td>December 26, 2003, to March 10, 2004</td>
<td>23</td>
<td>16</td>
<td>12</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>July 19, 2004, to October 8, 2004</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>December 16, 2004, to August 5, 2005†</td>
<td>63</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>40</td>
<td>17</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

* Additional details are available at www.who.int/csr/disease/avian_influenza/country/cases_table_2005_08_05/en/print.
† Cases continue to occur. The total number of cases includes fatal ones. This list does not include the 18 patients, 6 of whom died, identified in Hong Kong in 1997 or the 2 patients, 1 of whom died, identified in Fujian Province, China, in 2003.

### Table 2. Serologic and Clinical Characteristics of Avian Influenza A (H5N1) Infection among Contacts of Patients or Infected Animals.

<table>
<thead>
<tr>
<th>Group</th>
<th>Location</th>
<th>Year</th>
<th>Assay Method†</th>
<th>No. Tested</th>
<th>No. (%) Positive</th>
<th>Comment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household contacts</td>
<td>Hong Kong</td>
<td>1997</td>
<td>MN, ELISA, WB</td>
<td>51</td>
<td>6 (12)</td>
<td>Concurrent exposure to poultry in 5 of 6 positive household contacts; 0 of 9 non-household contacts positive</td>
<td>Katz et al.8</td>
</tr>
<tr>
<td>Tour group contacts</td>
<td></td>
<td></td>
<td></td>
<td>26</td>
<td>1 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Workplace contacts</td>
<td></td>
<td></td>
<td></td>
<td>47</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry cullers</td>
<td>Hong Kong</td>
<td>1997</td>
<td>MN, WB</td>
<td>293</td>
<td>9 (3)</td>
<td>Seroconversion in 1 with mild acute respiratory illness</td>
<td>Bridges et al.7</td>
</tr>
<tr>
<td>Poultry-market workers</td>
<td>Hong Kong</td>
<td>1997</td>
<td>MN, WB</td>
<td>1525</td>
<td>— (estimated 10%)</td>
<td>Most asymptomatic</td>
<td>Bridges et al.7</td>
</tr>
<tr>
<td>Health care workers with contact</td>
<td>Hong Kong</td>
<td>1997</td>
<td>MN, WB</td>
<td>217</td>
<td>8 (4)‡</td>
<td>Seroconversion in 2; most asymptomatic</td>
<td>Buxton Bridges et al.7</td>
</tr>
<tr>
<td>Household contacts§</td>
<td>Vietnam</td>
<td>2004</td>
<td>MN</td>
<td>51</td>
<td>0</td>
<td>0 of 83 controls positive</td>
<td></td>
</tr>
<tr>
<td>Contacts of sick poultry§</td>
<td>Vietnam</td>
<td>2004</td>
<td>MN</td>
<td>25</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care workers with contact§</td>
<td>Vietnam</td>
<td>2004</td>
<td>MN, RT-PCR</td>
<td>83</td>
<td>0</td>
<td>2 with suspected illness (not confirmed)</td>
<td>Liem et al.10</td>
</tr>
<tr>
<td>Health care workers with contact§</td>
<td>Vietnam</td>
<td>2004</td>
<td>Clinical only</td>
<td>60</td>
<td>0</td>
<td>No recognized illness</td>
<td>Schultsz et al.11</td>
</tr>
<tr>
<td>Health care workers with contact§</td>
<td>Thailand</td>
<td>2004</td>
<td>Clinical only</td>
<td>54</td>
<td>0</td>
<td>No recognized illness</td>
<td></td>
</tr>
<tr>
<td>Poultry cullers§</td>
<td>Indonesia</td>
<td>2005</td>
<td>MN</td>
<td>79</td>
<td>1 (1)</td>
<td>Asymptomatic</td>
<td>Apisarnthanarak et al.12</td>
</tr>
</tbody>
</table>

* Some serologic surveys of apparent human-to-human transmission may have been confounded by concurrent exposure to ill poultry.
† MN denotes identification of serum antibody against influenza A (H5N1) by microneutralization, ELISA enzyme-linked immunosorbent assay, WB detection of influenza A (H5)–specific bands by Western blotting, and RT-PCR reverse-transcriptase–polymerase-chain-reaction assay for viral RNA.
‡ P=0.01 for the comparison with 2 of 309 health care workers without contact (0.6 percent).
§ Data are from the WHO Meeting on Case Management and Research on Human Influenza A (H5) held in Hanoi, May 10 through 12, 2005.
surveys in Vietnam and Thailand have not found evidence of asymptomatic infections among contacts (Table 2). Recently, intensified surveillance of contacts of patients by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay has led to the detection of mild cases, more infections in older adults, and an increased number and duration of clusters in families in northern Vietnam, findings suggesting that the local virus strains may be adapting to humans. However, epidemiologic and virologic studies are needed to confirm these findings. To date, the risk of nosocomial transmission to health care workers has been low, even when appropriate isolation measures were not used (Table 2). However, one case of severe illness was reported in a nurse exposed to an infected patient in Vietnam.

**Environment to Human**

Given the survival of influenza A (H5N1) in the environment, several other modes of transmission are theoretically possible. Oral ingestion of contaminated water during swimming and direct intranasal or conjunctival inoculation during exposure to

<table>
<thead>
<tr>
<th>Table 3. Presentation and Outcomes among Patients with Confirmed Avian Influenza A (H5N1).</th>
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</thead>
<tbody>
<tr>
<td><strong>Outcome or Measure</strong></td>
</tr>
<tr>
<td>Age — yr</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
</tr>
<tr>
<td>Time from last presumed exposure to onset of illness — days</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>No. of family clusters</td>
</tr>
<tr>
<td>Patients with exposure to ill poultry — no./total no. (%)</td>
</tr>
<tr>
<td>visited poultry markets</td>
</tr>
<tr>
<td>Time from onset of illness to presentation or hospitalization — days</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Clinical presentation — no./total no. (%)</td>
</tr>
<tr>
<td>Fever (temperature &gt;38°C)</td>
</tr>
<tr>
<td>Headache</td>
</tr>
<tr>
<td>Myalgia</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Cough§</td>
</tr>
<tr>
<td>Sputum</td>
</tr>
<tr>
<td>Sore throat</td>
</tr>
<tr>
<td>Rhinorrhea</td>
</tr>
<tr>
<td>Shortness of breath§</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
</tr>
<tr>
<td>Lymphopenia¶</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Increased aminotransferase levels</td>
</tr>
</tbody>
</table>
water are other potential modes, as is contamination of hands from infected fomites and subsequent self-inoculation. The widespread use of untreated poultry feces as fertilizer is another possible risk factor.

**Clinical Features**

The clinical spectrum of influenza A (H5N1) in humans is based on descriptions of hospitalized patients. The frequencies of milder illnesses, subclinical infections, and atypical presentations (e.g., encephalopathy and gastroenteritis) have not been determined, but case reports\(^{12,21,22}\) indicate that each occurs. Most patients have been previously healthy young children or adults (Table 3).

**Incubation**

The incubation period of avian influenza A (H5N1) may be longer than for other known human influenza. In 1997, most cases occurred within two to four days after exposure\(^{13}\); recent reports\(^{15,16}\) indicate similar intervals but with ranges of up to eight days (Table 3). The case-to-case intervals in household clusters have generally been 2 to 5 days, but the upper limit has been 8 to 17 days, possibly owing to unrecognized exposure to infected animals or environmental sources.
INITIAL SYMPTOMS
Most patients have initial symptoms of high fever (typically a temperature of more than 38°C) and an influenza-like illness with lower respiratory tract symptoms* (Table 3). Upper respiratory tract symptoms are present only sometimes. Unlike patients with infections caused by avian influenza A (H7) viruses,23 patients with avian influenza A (H5N1) rarely have conjunctivitis. Diarrhea, vomiting, abdominal pain, pleuritic pain, and bleeding from the nose and gums have also been reported early in the course of illness in some patients.14-16.24 Watery diarrhea without blood or inflammatory changes appears to be more common than in influenza due to human viruses25 and may precede respiratory manifestations by up to one week.12 One report described two patients who presented with an encephalopathic illness and diarrhea without apparent respiratory symptoms.22

CLINICAL COURSE
Lower respiratory tract manifestations develop early in the course of illness and are usually found at presentation (Table 3). In one series, dyspnea developed a median of 5 days after the onset of illness (range, 1 to 16).15 Respiratory distress, tachypnea, and inspiratory crackles are common. Sputum production is variable and sometimes bloody. Almost all patients have clinically apparent pneumonia; radiographic changes include diffuse, multifocal, or patchy infiltrates; interstitial infiltrates; and segmental or lobular consolidation with air bronchograms. Radiographic abnormalities were present a median of 7 days after the onset of fever in one study (range, 3 to 17).15 In Ho Chi Minh City, Vietnam, multifocal consolidation involving at least two zones was the most common abnormality among patients at the time of admission. Pleural effusions are uncommon. Limited microbiologic data indicate that this process is a primary viral pneumonia, usually without bacterial suprainfection at the time of hospitalization.

Progression to respiratory failure has been associated with diffuse, bilateral, ground-glass infiltrates and manifestations of the acute respiratory distress syndrome (ARDS). In Thailand,15 the median time from the onset of illness to ARDS was 6 days (range, 4 to 13). Multiorgan failure with signs of renal dysfunction and sometimes cardiac compromise, including cardiac dilatation and supraventricular tachyarrhythmias, has been common.14-16.24 Other complications have included ventilator-associated pneumonia, pulmonary hemorrhage, pneumothorax, pancytopenia, Reye’s syndrome, and sepsis syndrome without documented bacteremia.

MORTALITY
The fatality rate among hospitalized patients has been high (Table 3), although the overall rate is probably much lower.21 In contrast to 1997, when most deaths occurred among patients older than 13 years of age, recent avian influenza A (H5N1) infections have caused high rates of death among infants and young children. The case fatality rate was 89 percent among those younger than 15 years of age in Thailand. Death has occurred an average of 9 or 10 days after the onset of illness (range, 6 to 30).15,16 and most patients have died of progressive respiratory failure.

LABORATORY FINDINGS
Common laboratory findings have been leukopenia, particularly lymphopenia; mild-to-moderate thrombocytopenia; and slightly or moderately elevated aminotransferase levels (Table 3). Marked hyperglycemia, perhaps related to corticosteroid use, and elevated creatinine levels also occur.19 In Thailand,15 an increased risk of death was associated with decreased leukocyte, platelet, and particularly, lymphocyte counts at the time of admission.

VIROLOGIC DIAGNOSIS
Antemortem diagnosis of influenza A (H5N1) has been confirmed by viral isolation, the detection of H5-specific RNA, or both methods. Unlike human influenza A infection,26 avian influenza A (H5N1) infection may be associated with a higher frequency of virus detection and higher viral RNA levels in pharyngeal than in nasal samples. In Vietnam, the interval from the onset of illness to the detection of viral RNA in throat-swab samples ranged from 2 to 15 days (median, 5.5), and the viral loads in pharyngeal swabs 4 to 8 days after the onset of illness were at least 10 times as high among patients with influenza A (H5N1) as among those with influenza A (H3N2) or (H1N1). Earlier studies in Hong Kong also found low viral loads in nasopharyngeal samples.27 Commercial rapid antigen tests are less sensitive in detecting influenza A (H5N1) infections than are RT-PCR assays.15 In Thailand, the results of rapid antigen testing were positive in only 4 of 11 patients with culture-positive influenza A (H5N1) (36 percent) 4 to 18 days after the onset of illness.
MANAGEMENT

Most hospitalized patients with avian influenza A (H5N1) have required ventilatory support within 48 hours after admission,15,16 as well as intensive care for multigorgan failure and sometimes hypotension. In addition to empirical treatment with broad-spectrum antibiotics, antiviral agents, alone or with corticosteroids, have been used in most patients (Table 3), although their effects have not been rigorously assessed. The institution of these interventions late in the course of the disease has not been associated with an apparent decrease in the overall mortality rate, although early initiation of antiviral agents appears to be beneficial.1,15,16 Cultivable virus generally disappears within two or three days after the initiation of oseltamivir among survivors, but clinical progression despite early therapy with oseltamivir and a lack of reductions in pharyngeal viral load have been described in patients who have died.

PATHOGENESIS

CHARACTERIZATION OF VIRUS

Studies of isolates of avian influenza A (H5N1) from patients in 1997 revealed that virulence factors included the highly cleavable hemagglutinin that can be activated by multiple cellular proteases, a specific substitution in the polymerase basic protein 2 (Glue27Lys) that enhances replication,28,29 and a substitution in nonstructural protein 1 (Asp92Glu) that confers increased resistance to inhibition by interferons and tumor necrosis factor α (TNF-α) in vitro and prolonged replication in swine,30 as well as greater elaboration of cytokines, particularly TNF-α, in human macrophages exposed to the virus.31 Since 1997, studies of influenza A (H5N1) indicate that these viruses continue to evolve, with changes in antigenicity35,36 and internal gene constellations; an expanded host range in avian species37,38 and the ability to infect felids;37,38 enhanced pathogenicity in experimentally infected mice and ferrets, in which they cause systemic infections39,40; and increased environmental stability.

Phylogenetic analyses indicate that the Z genotype has become dominant33 and that the virus has evolved into two distinct clades, one encompassing isolates from Cambodia, Laos, Malaysia, Thailand, and Vietnam and the other isolates from China, Indonesia, Japan, and South Korea.21 Recently, a separate cluster of isolates has appeared in northern Vietnam and Thailand, which includes variable changes near the receptor-binding site and one fewer arginine residue in the polybasic cleavage site of the hemagglutinin. However, the importance of these genetic and biologic changes with respect to human epidemiology or virulence is uncertain.

PATTERNS OF VIRAL REPLICATION

The virologic course of human influenza A (H5N1) is incompletely characterized, but studies of hospitalized patients indicate that viral replication is prolonged. In 1997, virus could be detected in nasopharyngeal isolates for a median of 6.5 days (range, 1 to 16), and in Thailand, the interval from the onset of illness to the first positive culture ranged from 3 to 16 days. Nasopharyngeal replication is less than in human influenza,27 and studies of lower respiratory tract replication are needed. The majority of fecal samples tested have been positive for viral RNA (seven of nine), whereas urine samples were negative. The high frequency of diarrhea among affected patients and the detection of viral RNA in fecal samples, including infectious virus in one case,22 suggest that the virus replicates in the gastrointestinal tract. The findings in one autopsy confirmed this observation.41

Highly pathogenic influenza A (H5N1) viruses possess the polybasic amino acid sequence at the hemagglutinin-cleavage site that is associated with visceral dissemination in avian species. Invasive infection has been documented in mammals,28,29,39,40 and in humans, six of six serum specimens were positive for viral RNA four to nine days after the onset of illness. Infectious virus and RNA were detected in blood, cerebrospinal fluid, and feces in one patient.22 Whether feces or blood serves to transmit infection under some circumstances is unknown.

HOST IMMUNE RESPONSES

The relatively low frequencies of influenza A (H5N1) illness in humans despite widespread exposure to infected poultry indicate that the species barrier to acquisition of this avian virus is substantial. Clusters of cases in family members may be caused by common exposures, although the genetic factors that may affect a host’s susceptibility to disease warrant study.

The innate immune responses to influenza A (H5N1) may contribute to disease pathogenesis. In the 1997 outbreaks, elevated blood levels of interleukin-6, TNF-α, interferon-γ, and soluble inter-
leukin-2 receptor were observed in individual pa-
tients, and in the patients in 2003, elevated levels of the chemokines interferon-inducible protein 10, monocyte chemoattractant protein 1, and mono-
kine induced by interferon-γ were found three to eight days after the onset of illness. Recently, plasma levels of inflammatory mediators (interleukin-6, interleukin-8, interleukin-1β, and monocyte chemoattractant protein 1) were found to be higher among patients who died than among those who survived (Simmons C: personal communication), and the average levels of plasma interferon-α were about three times as high among patients with avi-
an influenza A who died as among healthy controls. Such responses may be responsible in part for the sepsis syndrome, ARDS, and multiorgan failure ob-
served in many patients.

Among survivors, specific humoral immune re-
sponses to influenza A (H5N1) are detectable by mi-
roneutralization assay 10 to 14 days after the onset of illness. Corticosteroid use may delay or blunt these responses.

PATHOLOGICAL FINDINGS

Limited postmortem analyses have documented se-
vere pulmonary injury with histopathological chang-
es of diffuse alveolar damage, consistent with findings in other reports of pneumonia due to human influenza virus. Changes include filling of the alveolar spaces with fibrinous exudates and red cells, hyaline-membrane formation, vascular congestion, infiltration of lymphocytes into the interstitial areas, and the proliferation of reactive fibro-
blasts. Infection of type II pneumocytes occurs. Antemortem biopsy of bone marrow specimens has shown reactive histiocytosis with hemophagocytosis in several patients, and lymphoid depletion and atypical lymphocytes have been noted in spleen and lymphoid tissues at autopsy. Centrilobular hepatic necrosis and acute tubular necrosis have been noted in several instances.

CASE DETECTION AND MANAGEMENT

The possibility of influenza A (H5N1) should be con-
sidered in all patients with severe acute respira-
tory illness in countries or territories with animal influenza A (H5N1), particularly in patients who have been exposed to poultry (Table 4). However, some outbreaks in poultry were recognized only after sentinel cases occurred in humans. Early recog-
nition of cases is confounded by the nonspecificity of the initial clinical manifestations and high back-
ground rates of acute respiratory illnesses from oth-
er causes. In addition, the possibility of influenza A (H5N1) warrants consideration in patients present-
ning with serious unexplained illness (e.g., enceph-
alopathy or diarrhea) in areas with known influen-
a virus (H5N1) activity in humans or animals.

The diagnostic yield of different types of samples and virologic assays is not well defined. In contrast to infections with human influenza virus, throat samples may have better yields than nasal samples. Rapid antigen assays may help provide support for a diagnosis of influenza A infection, but they have poor negative predictive value and lack specificity for influenza A (H5N1). The detection of viral RNA in respiratory samples appears to offer the greatest sensitivity for early identification, but the sensi-
tivity depends heavily on the primers and assay method used. Laboratory confirmation of influenza A (H5N1) requires one or more of the follow-
ing: a positive viral culture, a positive PCR assay for influenza A (H5N1) RNA, a positive immuno-
fluorescence test for antigen with the use of monoclo-
al antibody against H5, and at least a fourfold rise in H5-specific antibody titer in paired serum samples.

HOSPITALIZATION

Whenever feasible while the numbers of affected persons are small, patients with suspected or proven influenza A (H5N1) should be hospitalized in isolation for clinical monitoring, appropriate diag-
nostic testing, and antiviral therapy. If patients are discharged early, both the patients and their famil-
ies require education on personal hygiene and in-
fecction-control measures (Table 5). Supportive care with provision of supplemental oxygen and venti-
latory support is the foundation of management.

Nebulizers and high—air flow oxygen masks have been implicated in the nosocomial spread of severe acute respiratory syndrome (SARS) and should be used only with strict airborne precautions.

ANTIVIRAL AGENTS

Patients with suspected influenza A (H5N1) should promptly receive a neuraminidase inhibitor pend-
ing the results of diagnostic laboratory testing. The optimal dose and duration of treatment with neuraminidase inhibitors are uncertain, and cur-
rently approved regimens likely represent the min-
imum required. These viruses are susceptible in
vitrto to oseltamivir and zanamivir. Oral oseltamivir and topical zanamivir are active in animal models of influenza A (H5N1). Recent murine studies indicate that as compared with an influenza A (H5N1) strain from 1997, the strain isolated in 2004 requires higher oseltamivir doses and more prolonged administration (eight days) to induce similar antiviral effects and survival rates. Inhaled zanamivir has not been studied in cases of influenza A (H5N1) in humans.

Early treatment will provide the greatest clinical benefit, although the use of therapy is reasonable when there is a likelihood of ongoing viral replication. Placebo-controlled clinical studies of oral oseltamivir and inhaled zanamivir comparing currently approved doses with doses that are twice as high found that the two doses had similar tolerability but no consistent difference in clinical or antiviral benefits in adults with uncomplicated human influenza. Although approved doses of oseltamivir (75 mg twice daily for five days in adults and weight-adjusted twice-daily doses for five days in children older than one year of age — twice-daily doses of 30 mg for those weighing 15 kg or less, 45 mg for those weighing more than 15 to 23 kg, 60 mg for those weighing more than 23 kg to 40 kg, and 75 mg for those weighing more than 40 kg) are reasonable for treating early, mild cases of influenza A (H5N1), higher doses (150 mg twice daily in adults) and treatment for 7 to 10 days are considerations in treating severe infections, but prospective studies are needed.

High-level antiviral resistance to oseltamivir results from the substitution of a single amino acid in N1 neuraminidase (His274Tyr). Such variants have been detected in up to 16 percent of children with human influenza A (H1N1) who have received oseltamivir. Not surprisingly, this resistant variant has been detected recently in several patients with influenza A (H5N1) who were treated with oseltamivir. Although less infectious in cell culture and in animals than susceptible parental virus, oseltamivir-resistant H1N1 variants are transmissible in ferrets. Such variants retain full suscepti-
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These summaries do not present formal WHO guidelines, although they contain content from WHO documents. The guidelines are adapted in part from the Centers for Disease Control and Prevention. NIOSH denotes National Institute for Occupational Safety and Health, and N-95 a non-oilproof respirator with at least 95 percent efficiency in filtering particles with a mean diameter of more than 3 µm. The duration of viral shedding in children younger than 12 years of age who have human influenza can last up to 21 days and also may be protracted in children and adults with avian influenza A (H5N1), so that infection-control precautions should be maintained for at least 7 days after the resolution of fever or possibly up to 21 days.

Table 5. Strategies to Prevent Avian Influenza A (H5N1) in Humans in a Nonpandemic Setting.*

<table>
<thead>
<tr>
<th>Isolation precautions in health care facilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients should be treated with a combination of standard, contact, droplet, and airborne isolation precautions.†</td>
</tr>
<tr>
<td>Patients should be housed alone in a negative-pressure room, if available, or in a single room with the door closed.</td>
</tr>
<tr>
<td>If a single room is not available, patients should be housed in designated multibed rooms or wards. The beds should be at least 1 m apart and preferably separated by a physical barrier.</td>
</tr>
<tr>
<td>High-efficiency masks (NIOSH-certified N-95 or equivalent), long-sleeved cuffed gowns, face shield or eye goggles, and gloves are recommended for health care workers.</td>
</tr>
<tr>
<td>When feasible, limit the number of health care workers with direct contact with patient and limit access to the environment of patients. If possible, these health care workers should not look after other patients.</td>
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<tr>
<td>Restrict visitors to a minimum and give them proper personal protective equipment and instructions in its use.</td>
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<th>Health care worker exposures</th>
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<tr>
<td>Those caring for infected patients should monitor temperature twice daily and report any febrile event. If unwell for any reason, health care workers should not be involved in direct patient care. Health care workers with fever (temperature &gt;38°C) and patient contact should undergo appropriate diagnostic testing. If an alternative cause is not identified, they should be treated immediately with oseltamivir on the assumption of influenza infection.</td>
</tr>
<tr>
<td>Those who have had a possible exposure to infectious aerosols, secretions, or other body fluids or excretions because of a lapse in aseptic technique should be considered for postexposure chemoprophylaxis with oseltamivir at a suggested dose of 75 mg once daily for 7 to 10 days.</td>
</tr>
<tr>
<td>Health care workers involved in high-risk procedures (e.g., aerosol-generating procedures) should consider the need for preexposure prophylaxis.</td>
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<tr>
<th>Precautions for household and close contacts</th>
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<tr>
<td>Household contacts should use appropriate hand hygiene, should not share utensils, should avoid face-to-face contact with patients with suspected or proven cases, and should consider donning high-efficiency masks and eye protection.†</td>
</tr>
<tr>
<td>Contacts who have shared a defined setting (household, extended family, hospital or other residential institution, or military service) with a patient with proven or suspected avian influenza A (H5N1) infection should monitor their own temperature twice daily and check for symptoms for 7 days after their last exposure.</td>
</tr>
<tr>
<td>In such persons, postexposure prophylaxis with oseltamivir at a suggested dose for adults of 75 mg once daily for 7 to 10 days is advisable.</td>
</tr>
<tr>
<td>Household or close contacts should receive empirical antiviral treatment and undergo diagnostic testing if fever (temperature &gt;38°C) and cough, shortness of breath, diarrhea, or other systemic symptoms develop.</td>
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<th>Precautions for travelers*†</th>
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<tr>
<td>Travelers to areas with avian influenza activity should be immunized with the available trivalent human vaccine, preferably at least 2 weeks before traveling.</td>
</tr>
<tr>
<td>Travelers should avoid all direct contact with poultry, including chickens, ducks, or geese that appear to be well, and farms or live-animal markets with poultry, and should avoid touching surfaces contaminated with poultry feces or secretions.</td>
</tr>
<tr>
<td>Travelers should reduce possible exposure by practicing good hand hygiene with frequent hand washing or use of alcohol gels and by not ingesting undercooked eggs or foods from poultry.</td>
</tr>
<tr>
<td>Hand washing is important when handling raw poultry for cooking (e.g., during cooking classes).</td>
</tr>
<tr>
<td>Travelers should be advised to consult a health care provider if they become ill with fever and respiratory symptoms within 10 days of returning from an affected area.</td>
</tr>
</tbody>
</table>

* These summaries do not present formal WHO guidelines, although they contain content from WHO documents.† The guidelines are adapted in part from the Centers for Disease Control and Prevention. NIOSH denotes National Institute for Occupational Safety and Health, and N-95 a non-oilproof respirator with at least 95 percent efficiency in filtering particles with a mean diameter of more than 3 µm. The duration of viral shedding in children younger than 12 years of age who have human influenza can last up to 21 days and also may be protracted in children and adults with avian influenza A (H5N1), so that infection-control precautions should be maintained for at least 7 days after the resolution of fever or possibly up to 21 days.
bility to zanamivir and partial susceptibility to the investigational neuraminidase inhibitor peramivir in vitro.\(^{57,58}\)

In contrast to isolates from the 1997 outbreak, recent human influenza A (H5N1) isolates are highly resistant to the M2 inhibitors amantadine and rimantadine, and consequently, these drugs do not have a therapeutic role. Agents of clinical investigational interest for treatment include zanamivir, peramivir, long-acting topical neuraminidase inhibitors, ribavirin,\(^{59,60}\) and possibly, interferon alfa.\(^{61}\)

**Immunomodulators**

Corticosteroids have been used frequently in treating patients with influenza A (H5N1), with uncertain effects. Among five patients given corticosteroids in 1997, two treated later in their course for the fibroproliferative phase of ARDS survived. In a randomized trial in Vietnam, all four patients given dexamethasone died. Interferon alfa possesses both antiviral and immunomodulatory activities, but appropriately controlled trials of immunomodulatory interventions are needed before routine use is recommended.

**Prevention**

**Immunization**

No influenza A (H5) vaccines are currently commercially available for humans. Earlier H5 vaccines were poorly immunogenic and required two doses of high hemagglutinin antigen content\(^{62}\) or the addition of MF59 adjuvant\(^{63}\) to generate neutralizing antibody responses. A third injection of adjuvanted 1997 H5 vaccine variably induced cross-reacting antibodies to human isolates from 2004.\(^{64}\) Reverse genetics has been used for the rapid generation of nonvirulent vaccine viruses from recent influenza A (H5) isolates,\(^{65,66}\) and several candidate vaccines are under study. One such inactivated vaccine with the use of a human H5N1 isolate from 2004 has been reported to be immunogenic at high hemagglutinin doses.\(^{67}\) Studies with approved adjuvants like alum are urgently needed. Live attenuated, cold-adapted intranasal vaccines are also under development. These are protective against human influenza after a single dose in young children.\(^{68}\)

**Hospital-infection control**

Influenza is a well-recognized nosocomial pathogen.\(^{4,5}\) Current recommendations are based on efforts to reduce transmission to health care workers and other patients in a nonpandemic situation and on the interventions used to contain SARS (Table 5).\(^{1}\) The efficiency of surgical masks, even multiple ones,\(^{69}\) is much less than that of N-95 masks, but they could be used if the latter are not available. Chemoprophylaxis with 75 mg of oseltamivir once daily for 7 to 10 days is warranted for persons who have had a possible unprotected exposure.\(^{70,71}\) The use of preexposure prophylaxis warrants consideration if evidence indicates that the influenza A (H5N1) strain is being transmitted from person to person with increased efficiency or if there is a likelihood of a high-risk exposure (e.g., an aerosol-generating procedure).

**Household and close contacts**

Household contacts of persons with confirmed cases of influenza A (H5N1) should receive post-exposure prophylaxis as described above. Contacts of a patient with proven or suspected virus should monitor their temperature and symptoms (Table 5). Although the risk of secondary transmission has appeared low to date, self-quarantine for a period of one week after the last exposure to an infected person is appropriate. If evidence indicates that person-to-person transmission may be occurring, quarantine of exposed contacts should be enforced. For others who have had an unprotected exposure to an infected person or to an environmental source (e.g., exposure to poultry) implicated in the transmission of influenza A (H5N1), post-exposure chemoprophylaxis as described above may be warranted.

**Conclusions**

Infected birds have been the primary source of influenza A (H5N1) infections in humans in Asia. Transmission between humans is very limited at present, but continued monitoring is required to identify any increase in viral adaptation to human hosts. Avian influenza A (H5N1) in humans differs in multiple ways from influenza due to human viruses, including the routes of transmission, clinical severity, pathogenesis, and perhaps, response to treatment. Case detection is confounded by the nonspecificity of initial manifestations of illness, so that detailed contact and travel histories and knowledge of viral activity in poultry are essential. Commercial rapid antigen tests are insensitive, and confirmatory diagnosis requires sophisticated laboratory support. Unlike human influenza, avian in-
fluenza A (H5N1) may have higher viral titers in the throat than in the nose, and hence, analysis of throat swabs or lower respiratory samples may offer more sensitive means of diagnosis. Recent human isolates are fully resistant to M2 inhibitors, and increased doses of oral oseltamivir may be warranted for the treatment of severe illness. Despite recent progress, knowledge of the epidemiology, natural history, and management of influenza A (H5N1) disease in humans is incomplete. There is an urgent need for more coordination in clinical and epidemiologic research among institutions in countries with cases of influenza A (H5N1) and internationally.

The views expressed in this article do not necessarily reflect those of the WHO or other meeting sponsors.

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