REVIEW ARTICLE

CURRENT CONCEPTS

Avian Influenza A (H5N1) Infection in Humans

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

The writing committee consisted of the following: John H. Beigel, M.D., National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md.; Jeremy Farrar, D.Phil., Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; Aye Maung Han, M.B., B.S., Department of Child Health, Institute of Medicine, Yangon, Myanmar; Frederick G. Hayden, M.D. (rapporteur), University of Virginia, Charlottesville; Randy Hyer, M.D., World Health Organization, Geneva; Menno D. de Jong, M.D., Ph.D., Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; Sorasak Lochindarat, M.D., Queen Sirikit National Institute of Child Health, Bangkok, Thailand; Nguyen Thi Kim Tien, M.D., Ph.D., Pasteur Institute, Ho Chi Minh City, Vietnam; Nguyen Tran Hien, M.D., Ph.D., National Institute of Hygiene and Epidemiology, Hanoi; Tran Tinh Hien, M.D., Ph.D., Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam; Angus Nicoll, M.Sc., Health Protection Agency, London; Sok Touch, M.D., Ministry of Health, Phnom Penh, Cambodia; and Kwok-Yung Yuen, M.D., University of Hong Kong, Hong Kong SAR, China. Address reprint requests to Dr. Hayden at the Department of Internal Medicine, P.O. Box 800473, University of Virginia Health Sciences Center, Charlottesville, VA 22908, or at fgh@virginia.edu.

N Engl J Med 2005;353:1374-85.

An unprecedented epizootic avian influenza A (H5N1) virus that is highly pathogenic has crossed the species barrier in Asia to cause many human fatalities and poses an increasing pandemic threat. This summary describes the features of human infection with influenza A (H5N1) and reviews recommendations for prevention and clinical management presented in part at the recent World Health Organization (WHO) Meeting on Case Management and Research on Human Influenza A/H5, which was held in Hanoi, May 10 through 12, 2005.[1] Because many critical questions remain, modifications of these recommendations are likely.

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 Kazakstan, Mongolia, and Russia, indicates that more human populations are at risk.[2,3]

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.[4,5] 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.[6] Exposure to ill poultry and butchering of birds were associated with seropositivity for influenza A (H5N1)[7] (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

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

Date of Onset	Vietnam		Thailand		Cambodia		Indonesia		Total	
	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths	No. of Cases	No. of Deaths
December 26, 2003, to March 10, 2004	23	16	12	8	0	0	0	0	35	24
July 19, 2004, to October 8, 2004	4	4	5	4	0	0	0	0	9	8
December 16, 2004, to August 5, 2005†	63	20	0	0	4	4	1	1	68	25
Total	90	40	17	12	4	4	1	1	112	57

* 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.*

Group	Location	Year	Assay Method†	No. Tested	No. (%) Positive	Comment	Reference
Household contacts Tour group contacts Workplace contacts	Hong Kong	1997	MN, ELISA, WB	51 26 47	6 (12) 1 (4) 0	Concurrent exposure to poultry in 5 of 6 positive household contacts; 0 of 9 nonhousehold contacts positive	Katz et al.[8]
Poultry cullers	Hong Kong	1997	MN, WB	293	9 (3)	Seroconversion in 1 with mild acute respiratory illness	Bridges et al.[7]
Poultry-market workers	Hong Kong	1997	MN, WB	1525	— (estimated 10%)	Most asymptomatic	Bridges et al.[7]
Health care workers with contact	Hong Kong	1997	MN, WB	217	8 (4)‡	Seroconversion in 2; most asymptomatic	Buxton Bridges et al.[9]
Household contacts§	Vietnam	2004	MN	51	0	0 of 83 controls positive	
Contacts of sick poultry§	Vietnam	2004	MN	25	0	—	
Health care workers with contact	Vietnam	2004	MN	83	0	2 with suspected illness (not confirmed)	Liem et al.[10]
Health care workers with contact	Vietnam	2004	MN, RT-PCR	60	0	No recognized illness	Schultsz et al.[11]
Health care workers with contact§	Thailand	2004	Clinical only	54	0	No recognized illness	
Health care workers with contact	Thailand	2004	Clinical only	35	0	No fever or influenza-like illness	Apisarnthanarak et al.[12]
Poultry cullers§	Indonesia	2005	MN	79	1 (1)	Asymptomatic	

* 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.

Thailand[17,18] and to domestic cats under experimental conditions.[19] 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[16] and in one case of apparent child-to-mother transmission (Table 3).[20] 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,[8] and serologic studies of exposed health care workers indicated that transmission was inefficient[9] (Table 2). Serologic

Table 3. Presentation and Outcomes among Patients with Confirmed Avian Influenza A (H5N1).*

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Age — yr					
Median	9.5	14	13.7†	19.4†	22
Range	1–60	2–58	5–24	6–35	8–28
Male sex — no. (%)	8 (44)	9 (53)	6 (60)	3 (30)	1 (25)
Time from last presumed exposure to onset of illness — days					
Median	NS	4	3	NS	NS
Range		2–8	2–4		
No. of family clusters		1	2	1	1
Patients with exposure to ill poultry — no./total no. (%)	11/16 (70) visited poultry markets	14/17 (82)	8/9 (89)	6/6 (100) Status of 4 unknown	3/4 (75)
Time from onset of illness to presentation or hospitalization — days					
Median	3	NS	6	6	8‡
Range	1–7		3–8	4–7	5–8
Clinical presentation — no./total no. (%)					
Fever (temperature >38°C)	17/18 (94)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Headache	4/18 (22)	NS	NS	1/10 (10)	4/4 (100)
Myalgia	2/18 (11)	9/17 (53)	0	2/10 (20)	NS
Diarrhea	3/18 (17)	7/17 (41)	7/10 (70)	NS	2/4 (50)
Abdominal pain	3/18 (17)	4/17 (24)	NS	NS	2/4 (50)
Vomiting	6/18 (33)	4/17 (24)	NS	1/10 (10)	0
Cough§	12/18 (67)	16/17 (94)	10/10 (100)	10/10 (100)	4/4 (100)
Sputum	NS	13/17 (76)	5/10 (50)	3/10 (30)	NS
Sore throat	4/12 (33)	12/17 (71)	0	0	1/4 (25)
Rhinorrhea	7/12 (58)	9/17 (53)	0	0	NS
Shortness of breath§	1/18 (6)	13/17 (76)	10/10 (100)	10/10 (100)	NS
Pulmonary infiltrates	11/18 (61)	17/17 (100)	10/10 (100)	10/10 (100)	4/4 (100)
Lymphopenia¶	11/18 (61)	7/12 (58)	NS	8/10 (80)	1/2 (50)
Thrombocytopenia	NS	4/12 (33)	NS	8/10 (80)	1/2 (50)
Increased aminotransferase levels	11/18 (61)	8/12 (67)	5/6 (83)	7/10 (70)	NS

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,[21] 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[10,11] (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 3. (Continued.)

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Hospital course — no. (%)					
Respiratory failure	8 (44)	13 (76)	9 (90)	7 (70)	4 (100)
Cardiac failure	NS	7 (41)	NS	0	NS
Renal dysfunction	4 (22)	5 (29)	1 (10)	2 (20)	NS
Antiviral therapy‖					
Amantadine	10 (56)	0	0	0	NS
Ribavirin	1 (6)	0	2 (20)	0	
Oseltamivir	0	10 (59)	5 (50)	10 (100)	
Corticosteroids**	5 (28)	8 (47)	7 (70)	5 (50)	NS
Inotropic agents	NS	8 (47)	2 (20)	NS	
Time from onset of illness to death — days					
Median	23	12	9	12.8†	8
Range	8–29	9–30	4–17	4–21	6–10
Deaths — no. (%)	6 (33)	12 (71)	8 (80)	8 (80)	4 (100)

* Data from Hong Kong are from Yuen et al.[13] and Chan,[14] data on Thailand are from Chotpitayasunondh et al.,[15] data on Vietnam are from Hien et al.,[16] or data were presented at the WHO Consultation. NS denotes not stated.
† The median was unavailable, and the mean is given.
‡ Some patients had multiple outpatient illness visits before hospitalization.
§ In Hong Kong, shortness of breath later developed in 11 of 18 patients (61 percent) during hospitalization. In Thailand, all patients had cough and shortness of breath at hospitalization.
¶ In Vietnam, the median lymphocyte count was 700 per cubic millimeter (range, 250 to 1100), and the median leukocyte count was 2100 per cubic millimeter (range, 1200 to 3400).[16] In Thailand, the mean leukocyte count was 4900 per cubic millimeter (range, 1200 to 13,600),[15] and the lymphocyte count was 1453 per cubic millimeter (range, 454 to 3400).
‖ In Thailand, 7 of 10 patients given oseltamivir died a mean of 11 days after the onset of symptoms (range, 5 to 22 days), as compared with 5 of 7 untreated patients. Oseltamivir was used in conventional doses (75 mg orally, twice daily for 5 to 10 days with a weight-based dose reduction in children) in the majority of recipients. In Vietnam, one of five recipients of oseltamivir recovered, as compared with one of five untreated patients.[16] The use of relatively low doses of oral ribavirin in two patients was not associated with obvious effectiveness.
** Initial patients in Vietnam received methylprednisolone (5 mg per kilogram of body weight per day or 1 to 2 mg per kilogram) for one to four days[16]; subsequent patients in Ho Chi Minh City received dexamethasone at 0.4 mg per kilogram per day for five days in a randomized trial. In Thailand, methylprednisolone (2 mg per kilogram per day) was administered for two to five days.

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 influenzas. 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[1] (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 viruses[25] 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.[16] 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 multiorgan 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 (Glu627Lys) 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)[32-34] indicate that these viruses continue to evolve, with changes in antigenicity[35,36] and internal gene constellations; an expanded host range in avian species[37,38] and the ability to infect felids[17,18]; enhanced pathogenicity in experimentally infected mice and ferrets, in which they cause systemic infections[39,40]; and increased environmental stability.

Phylogenetic analyses indicate that the Z genotype has become dominant[33] 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 patients,[42] and in the patients in 2003, elevated levels of the chemokines interferon-inducible protein 10, monocyte chemoattractant protein 1, and monokine induced by interferon-γ were found three to eight days after the onset of illness.[27] 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 avian influenza A who died as among healthy controls. Such responses may be responsible in part for the sepsis syndrome, ARDS, and multiorgan failure observed in many patients.

Among survivors, specific humoral immune responses to influenza A (H5N1) are detectable by microneutralization 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 severe pulmonary injury with histopathological changes of diffuse alveolar damage,[27,41,42] consistent with findings in other reports of pneumonia due to human influenza virus.[43] 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 fibroblasts. Infection of type II pneumocytes occurs.[41,42] 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.[13,15,27,42] 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 considered in all patients with severe acute respiratory 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 recognition of cases is confounded by the nonspecificity of the initial clinical manifestations and high background rates of acute respiratory illnesses from other causes. In addition, the possibility of influenza A (H5N1) warrants consideration in patients presenting with serious unexplained illness (e.g., encephalopathy or diarrhea) in areas with known influenza A (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 sensitivity depends heavily on the primers and assay method used. Laboratory confirmation of influenza A (H5N1) requires one or more of the following: a positive viral culture, a positive PCR assay for influenza A (H5N1) RNA, a positive immunofluorescence test for antigen with the use of monoclonal antibody against H5, and at least a fourfold rise in H5-specific antibody titer in paired serum samples.[44]

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 diagnostic testing, and antiviral therapy. If patients are discharged early, both the patients and their families require education on personal hygiene and infection-control measures (Table 5). Supportive care with provision of supplemental oxygen and ventilatory support is the foundation of management.[1] 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 pending the results of diagnostic laboratory testing. The optimal dose and duration of treatment with neuraminidase inhibitors are uncertain, and currently approved regimens likely represent the minimum required. These viruses are susceptible in

Table 4. Exposures That May Put a Person at Risk for Infection with Influenza A (H5N1).*

Countries and territories where influenza A (H5) viruses have been identified as a cause of illness in human or animal populations since October 1, 2003
During the 7 to 14 days before the onset of symptoms, one or more of the following:
Contact (within 1 m) with live or dead domestic fowl or wild birds or domestic ducks
Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
Unprotected contact (within touching or speaking distance) with a person for whom the diagnosis of influenza A (H5N1) is confirmed or being considered
Unprotected contact (within touching or speaking distance, 1 m) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
Occupational exposure†
Countries and territories where influenza A (H5) viruses have not been identified as a cause of illness in human or animal populations since October 1, 2003
During the 7 to 14 days before the onset of symptoms, close contact with an ill traveler from one of the areas with known influenza A (H5) activity, history of travel to a country or territory with reported avian influenza activity due to influenza A (H5N1) in the animal populations, or living in an area in which there are rumors of the death of domestic fowl, and one or more of the following:
Contact (within 1 m) with live or dead domestic fowl or wild birds in any setting or with domestic ducks
Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
Contact (within touching or speaking distance) with a patient with a confirmed case of influenza A (H5)
Contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
Occupational exposure†

* These summaries do not present formal WHO guidelines, although they contain content from WHO documents.[1]

† At-risk occupations include domestic-fowl worker, worker in a domestic-fowl processing plant, domestic-fowl culler (catching, bagging, or transporting birds or disposing of dead birds), worker in a live-animal market, chef working with live or recently killed domestic fowl, dealer or trader in pet birds, health care worker, and a worker in a laboratory processing samples possibly containing influenza A (H5N1) virus.

vitro to oseltamivir and zanamivir.[46,47] Oral oseltamivir[46] and topical zanamivir are active in animal models of influenza A (H5N1).[48,49] 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.[50] Inhaled zanamivir has not been studied in cases of influenza A (H5N1) in humans.

Early treatment will provide the greatest clinical benefit,[15] although the use of therapy is reasonable when there is a likelihood of ongoing viral replication. Placebo-controlled clinical studies of oral oseltamivir[51,52] and inhaled zanamivir[53] 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 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.[54] Not surprisingly, this resistant variant has been detected recently in several patients with influenza A (H5N1) who were treated with oseltamivir.[21] Although less infectious in cell culture and in animals than susceptible parental virus,[55] oseltamivir-resistant H1N1 variants are transmissible in ferrets.[56] Such variants retain full suscepti-

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

Isolation precautions in health care facilities
Patients should be treated with a combination of standard, contact, droplet, and airborne isolation precautions.†
Patients should be housed alone in a negative-pressure room, if available, or in a single room with the door closed.
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.
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.
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.
Restrict visitors to a minimum and give them proper personal protective equipment and instructions in its use.
Health care worker exposures
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 >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.
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.
Health care workers involved in high-risk procedures (e.g., aerosol-generating procedures) should consider the need for preexposure prophylaxis.
Precautions for household and close contacts
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.†
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.
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.
Household or close contacts should receive empirical antiviral treatment and undergo diagnostic testing if fever (temperature >38°C) and cough, shortness of breath, diarrhea, or other systemic symptoms develop.
Precautions for travelers[45]
Travelers to areas with avian influenza activity should be immunized with the available trivalent human vaccine, preferably at least 2 weeks before traveling.
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.
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.
Hand washing is important when handling raw poultry for cooking (e.g., during cooking classes).
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.

* These summaries do not present formal WHO guidelines, although they contain content from WHO documents.[1] The guidelines are adapted in part from the Centers for Disease Control and Prevention.[45] 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 postexposure 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), postexposure 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.

We are indebted to the National Institute of Allergy and Infectious Diseases and the Wellcome Trust for their collaborative support of the WHO meeting; to Drs. Klaus Stohr and Alice Croisier of the Global Influenza Program at the WHO, Geneva; and to Drs. Peter Horby and Monica Guardo and the staff of the WHO Country Offices, Vietnam, for organizing the WHO consultation and for support in the preparation of the manuscript; and to Diane Ramm for help in the preparation of the manuscript.

REFERENCES

1. World Health Organization. WHO interim guidelines on clinical management of humans infected by influenza A(H5N1). February 20, 2004. (Accessed September 2, 2005, at http://www.who.int/csr/disease/avian_influenza/guidelines/Guidelines_Clinical%20Management_H5N1_rev.pdf.)
2. Liu J, Xiao H, Lei F, et al. Highly pathogenic H5N1 influenza virus infection in migratory birds. Science 2005;309:1206.
3. Chen H, Smith JD, Zhang SY, et al. Avian flu: H5N1 virus outbreak in migratory waterfowl. Nature 2005;436:191-2.
4. Salgado CD, Farr BM, Hall KK, Hayden FG. Influenza in the acute hospital setting. Lancet Infect Dis 2002;2:145-55. [Erratum, Lancet Infect Dis 2002;2:383.]
5. Bridges CB, Kuehnert MJ, Hall CB. Transmission of influenza: implications for control in health care settings. Clin Infect Dis 2003;37:1094-101.
6. Mounts AW, Kwong H, Izurieta HS, et al. Case-control study of risk factors for avian influenza A (H5N1) disease, Hong Kong, 1997. J Infect Dis 1999;180:505-8.
7. Bridges CB, Lim W, Hu-Primmer J, et al. Risk of influenza A (H5N1) infection among poultry workers, Hong Kong, 1997-1998. J Infect Dis 2002;185:1005-10.
8. Katz JM, Lim W, Bridges CB, et al. Antibody response in individuals infected with avian influenza A (H5N1) viruses and detection of anti-H5 antibody among household and social contacts. J Infect Dis 1999;180:1763-70.
9. Buxton Bridges C, Katz JM, Seto WH, et al. Risk of influenza A (H5N1) infection among health care workers exposed to patients with influenza A (H5N1), Hong Kong. J Infect Dis 2000;181:344-8.
10. Liem NT, World Health Organization International Avian Influenza Investigation Team, Vietnam, Lim W. Lack of H5N1 avian influenza transmission to hospital employees, Hanoi, 2004. Emerg Infect Dis 2005;11:210-5.
11. Schultsz C, Dong VC, Chau NVV, et al. Avian influenza H5N1 and healthcare workers. Emerg Infect Dis 2005;11:1158-9. (Also available at http://www.cdc.gov/ncidod/EID/vol11no07/05-0070.htm.)
12. Apisarnthanarak A, Kitphati R, Thongphubeth K, et al. Atypical avian influenza (H5N1). Emerg Infect Dis 2004;10:1321-4.
13. Yuen KY, Chan PK, Peiris M, et al. Clinical features and rapid viral diagnosis of human disease associated with avian influenza A H5N1 virus. Lancet 1998;351:467-71.
14. Chan PK. Outbreak of avian influenza A(H5N1) virus infection in Hong Kong in 1997. Clin Infect Dis 2002;34:Suppl 2:S58-S64.
15. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis 2005;11:201-9.
16. Hien TT, Liem NT, Dung NT, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med 2004;350:1179-88.
17. Keawcharoen J, Oraveerakul K, Kuiken T, et al. Avian influenza H5N1 in tigers and leopards. Emerg Infect Dis 2004;10:2189-91.
18. Thanawongnuwech R, Amonsin A, Tantilertcharoen R, et al. Probable tiger-to-tiger transmission of avian influenza H5N1. Emerg Infect Dis 2005;11:699-701.
19. Kuiken T, Rimmelzwaan G, van Riel D, et al. Avian H5N1 influenza in cats. Science 2004;306:241.
20. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). N Engl J Med 2005;352:333-40.
21. World Health Organization. WHO inter-country-consultation: influenza A/H5N1 in humans in Asia: Manila, Philippines, 6-7 May 2005. (Accessed September 2, 2005, at http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_7/en/.)
22. de Jong MD, Cam BV, Qui PT, et al. Fatal Avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med 2005;352:686-91.
23. Fouchier RAM, Schneeberger PM, Rozendaal FW, et al. Avian influenza A virus (H7N7) associated with human conjunctivitis and a fatal case of acute respiratory distress syndrome. Proc Natl Acad Sci U S A 2004;101:1356-61.
24. Tam JS. Influenza A (H5N1) in Hong Kong: an overview. Vaccine 2002;20:Suppl 2:S77-S81.
25. Nicholson KG. Human influenza. In: Nicholson KG, Webster RG, Hay AJ, eds. Textbook of influenza. Oxford, England: Blackwell Science, 1998:219-64.
26. Kaiser L, Briones MS, Hayden FG. Performance of virus isolation and Directigen Flu A to detect influenza A virus in experimental human infection. J Clin Virol 1999;14:191-7.
27. Peiris JS, Yu WC, Leung CW, et al. Re-emergence of fatal human influenza A subtype H5N1 disease. Lancet 2004;363:617-9.
28. Hatta M, Gao P, Halfmann P, Kawaoka Y. Molecular basis for high virulence of Hong Kong H5N1 influenza A viruses. Science 2001;293:1840-2.
29. Shinya K, Hamm S, Hatta M, Ito H, Ito T, Kawaoka Y. PB2 amino acid at position 627 affects replicative efficiency, but not cell tropism, of Hong Kong H5N1 influenza A viruses in mice. Virology 2004;320:258-66.
30. Seo SH, Hoffman E, Webster RG. Lethal H5N1 influenza viruses escape host anti-viral cytokine responses. Nat Med 2002;8:950-4.
31. Cheung CY, Poon LL, Lau AS, et al. Induction of proinflammatory cytokines in human macrophages by influenza A (H5N1) viruses: a mechanism for the unusual severity of human disease? Lancet 2002;360:1831-7.
32. Guan Y, Peiris JSM, Lipatov AS, et al. Emergence of multiple genotypes of H5N1 avian influenza viruses in Hong Kong SAR. Proc Natl Acad Sci U S A 2002;99:8950-5.
33. Li KS, Guan Y, Wang J, et al. Genesis of a highly pathogenic and potentially pandemic H5N1 influenza virus in eastern Asia. Nature 2004;430:209-13.
34. Avian influenza A (H5N1). Weekly Epidemiol Rec 2004;79(7):65-70. (Also available at http://www.who.int/wer/2004/en/wer7907.pdf.)
35. Sims LD, Ellis TM, Liu KK, et al. Avian influenza in Hong Kong 1997-2002. Avian Dis 2003;47:Suppl:832-8.
36. Horimoto T, Fukuda N, Iwatsuki-Horimoto K, et al. Antigenic differences between H5N1 human influenza viruses isolated in 1997 and 2003. J Vet Med Sci 2004;66:303-5.

37. Sturm-Ramirez KM, Ellis T, Bousfield B, et al. Reemerging H5N1 influenza viruses in Hong Kong in 2002 are highly pathogenic to ducks. J Virol 2004;78:4892-901.
38. Perkins LE, Swayne DE. Pathogenicity of a Hong Kong-origin H5N1 highly pathogenic avian influenza virus for emus, geese, ducks, and pigeons. Avian Dis 2002;46:53-63.
39. Zitzow LA, Rowe T, Morken T, Shieh WJ, Zaki S, Katz JM. Pathogenesis of avian influenza A (H5N1) viruses in ferrets. J Virol 2002; 76:4420-9.
40. Govorkova EA, Rehg JE, Krauss S, et al. Lethality to ferrets of H5N1 influenza viruses isolated from humans and poultry in 2004. J Virol 2005;79:2191-8.
41. Uiprasertkul M, Puthavathana P, Sangsiriwut K, et al. Influenza A H5N1 replication sites in humans. Emerg Infect Dis 2005; 11:1036-41.
42. To KF, Chan PK, Chan KF, et al. Pathology of fatal human infection associated with avian influenza A H5N1 virus. J Med Virol 2001;63:242-6.
43. Guarner J, Shieh W-J, Dawson J, et al. Immunohistochemical and in situ hybridization studies of influenza A virus infection in human lungs. Am J Clin Pathol 2000;114: 227-33.
44. World Health Organization. Recommended laboratory tests to identify influenza A/H5 virus in specimens from patients with an influenza-like illness. 2005. (Accessed September 2, 2005, at http://www.who.int/csr/disease/avian_influenza/guidelines/avian_ labtests1.pdf.)
45. Centers for Disease Control and Prevention. Update: notice to travelers about avian influenza A (H5N1). July 29, 2005. (Accessed September 2, 2005, at http://www.cdc.gov/travel/other/avian_flu_ah5n1_031605.htm.)
46. Leneva IA, Roberts N, Govorkova EA, Goloubeva OG, Webster RG. The neuraminidase inhibitor GS4104 (oseltamivir phosphate) is efficacious against A/Hong Kong/156/97 (H5N1) and A/Hong Kong/1074/99 (H9N2) influenza viruses. Antiviral Res 2000; 48:101-15.
47. Govorkova EA, Leneva IA, Goloubeva OG, Bush K, Webster RG. Comparison of efficacies of RWJ-270201, zanamivir, and oseltamivir against H5N1, H9N2, and other avian influenza viruses. Antimicrob Agents Chemother 2001;45:2723-32.
48. Gubareva LV, McCullers JA, Bethell RC, Webster RG. Characterization of influenza A/HongKong/156/97 (H5N1) virus in a mouse model and protective effect of zanamivir on H5N1 infection in mice. J Infect Dis 1998;178:1592-6.
49. Leneva IA, Goloubeva O, Fenton RJ, Tisdale M, Webster RG. Efficacy of zanamivir against avian influenza A viruses that possess genes encoding H5N1 internal proteins and are pathogenic in mammals. Antimicrob Agents Chemother 2001;45:1216-24.
50. Yen HL, Monto AS, Webster RG, Govorkova EA. Virulence may determine the necessary duration and dosage of oseltamivir treatment for highly pathogenic A/Vietnam/1203/04 influenza virus in mice. J Infect Dis 2005;192:665-72.
51. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. JAMA 2000;283:1016-24.
52. Cooper NJ, Sutton AJ, Abrams KR, Wailoo A, Turner D, Nicholson KG. Effectiveness of neuraminidase inhibitors in treatment and prevention of influenza A and B: systematic review and meta-analyses of randomised controlled trials. BMJ 2003;326:1235.
53. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. J Infect Dis 1999;180:254-61.
54. Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. J Antimicrob Chemother 2005;55: Suppl 1:i5-i21.
55. Ives JAL, Carr JA, Mendel DB, et al. The H274Y mutation in the influenza A/H1N1 neuraminidase active site following oseltamivir phosphate treatment leaves virus severely compromised both in vitro and in vivo. Antiviral Res 2002;55:307-17.
56. Herlocher ML, Truscon R, Elias S, et al. Influenza viruses resistant to the antiviral drug oseltamivir: transmission studies in ferrets. J Infect Dis 2004;190:1627-30.
57. Wetherall NT, Trivedi T, Zeller J, et al. Evaluation of neuraminidase enzyme assays using different substrates to measure susceptibility of influenza virus clinical isolates to neuraminidase inhibitors: report of the neuraminidase inhibitor susceptibility network. J Clin Microbiol 2003;41:742-50.
58. Gubareva LV, Webster RG, Hayden FG. Comparison of the activities of zanamivir, oseltamivir, and RWJ-270201 against clinical isolates of influenza virus and neuraminidase inhibitor-resistant variants. Antimicrob Agents Chemother 2001;45:3403-8.
59. Madren LK, Shipman C Jr, Hayden FG. In vitro inhibitory effects of combinations of anti-influenza agents. Antivir Chem Chemother 1995;6:109-13.
60. Knight V, Gilbert BE. Ribavirin aerosol treatment of influenza. Infect Dis Clin North Am 1987;1:441-57.
61. Baron S, Isaacs A. Absence of interferon in lungs from fatal cases of influenza. Br Med J 1962;5270:18-20.
62. Treanor JJ, Wilkinson BE, Masseoud F, et al. Safety and immunogenicity of a recombinant hemagglutinin vaccine for H5 influenza in humans. Vaccine 2001;19:1732-7.
63. Nicholson KG, Colegate AE, Podda A, et al. Safety and antigenicity of non-adjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a randomised trial of two potential vaccines against H5N1 influenza. Lancet 2001;357:1937-43.
64. Stephenson I, Bugarini R, Nicholson KG, et al. Cross-reactivity to highly pathogenic avian influenza H5N1 viruses after vaccination with nonadjuvanted and MF59-adjuvanted influenza A/Duck/Singapore/97 (H5N3) vaccine: a potential priming strategy. J Infect Dis 2005;191:1210-5.
65. Webby RJ, Webster RG. Are we ready for pandemic influenza? Science 2003;302: 1519-22.
66. Webby RJ, Perez DR, Coleman JS, et al. Responsiveness to a pandemic alert: use of reverse genetics for rapid development of influenza vaccines. Lancet 2004;363:1099-103.
67. Altman LC. Avian flu drug works in first tests. New York Times. August 7, 2005.
68. Belshe RB, Mendelman PM, Treanor J, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenzavirus vaccine in children. N Engl J Med 1998;338: 1405-12.
69. Derrick JL, Gomersall CD. Protecting healthcare staff from severe acute respiratory syndrome: filtration capacity of multiple surgical masks. J Hosp Infect 2005;59:365-8.
70. Hayden FG, Belshe R, Villanueva C, et al. Management of influenza in households: a prospective, randomized comparison of oseltamivir treatment with or without post-exposure prophylaxis. J Infect Dis 2004;189: 440-9.
71. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. JAMA 2001;285:748-54.