CLINICAL REVIEW

Avian influenza: A review

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Purpose. A review of the avian influenza A/H5N1 virus, including human cases, viral transmission, clinical features, vaccines and antivirals, surveillance plans, infection control, and emergency response plans, is presented.

Summary. The World Health Organization (WHO) considers the avian influenza A/H5N1 virus a public health risk with pandemic potential. The next human influenza pandemic, if caused by the avian influenza A/H5N1 virus, is estimated to have a potential mortality rate of more than a hundred million. Outbreaks in poultry have been associated with human transmission. WHO has documented 258 confirmed human infections with a mortality rate greater than 50%. Bird-to-human transmission of the avian influenza virus is likely by the oral–fecal route. The most effective defense against an influenza pandemic would be a directed vaccine to elicit a specific immune response toward the strain or strains of the influenza virus. However, until there is an influenza pandemic, there is no evidence that vaccines or antivirals used in the treatment or prevention of such an outbreak would decrease morbidity or mortality. Surveillance of the bird and human populations for the highly pathogenic H5N1 is being conducted. Infection-control measures and an emergency response plan are discussed.

Conclusion. Avian influenza virus A/H5N1 is a public health threat that has the potential to cause serious illness and death in humans. Understanding its pathology, transmission, clinical features, and pharmacologic treatments and preparing for the prevention and management of its outbreak will help avoid its potentially devastating consequences.

Index terms: Antivirals; Epidemiology; Immunization; Infection control; Influenza; Influenza vaccines; Mortality; Vaccines

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The avian influenza A/H5N1 virus has the potential to cause devastating effects to agricultural poultry flocks and humans. Initially confined to Southeast Asia, the virus has now migrated to the Middle East, Europe, and former Soviet Union satellites. Outbreaks in poultry, primarily chickens and ducks, have been associated with human transmission. The World Health Organization (WHO) has documented 258 confirmed human infections with a mortality rate greater than 50%.[1] WHO considers the avian influenza A/H5N1 virus a public health risk with pandemic potential and recommends that all nations develop a national influenza preparedness plan.[2] The U.S. government has proposed a federal response, the Pandemic Influenza Plan.[3,4]

The next human influenza pandemic, if caused by the avian influenza A/H5N1 virus, is estimated to have a potential mortality rate greater than a hundred million.[5,6] The mathematical model estimates are based on the facts that humans have little or no immunity to the antigens of the influenza A/H5N1 virus and that the mortality rate so far has been approximately 57% for the cases that have been admitted to hospitals and reported to WHO.[1] The number of human cases that may present to health care facilities is expected to far exceed bed capacity and resources for treatment.

Background

The influenza A virus is in the family *Orthomyxoviridae*, a group of single-stranded, negative-sense ribonucleic acid (RNA) viruses, with a segmented genome. By definition, negative-sense RNA is viral RNA that has a base sequence complementary to that of messenger RNA (mRNA). The viral RNA must first be transcribed by RNA transcriptase to mRNA (positive sense), which in turn serves as a template for protein synthesis.[7] There are eight RNA segments in the influenza A virus,[8]

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containing genome encoding 11 viral proteins: the polymerase proteins (PB1, PB2, PA, PB1-F2), nucleocapsid proteins, hemagglutinin (HA), neuraminidase (NA), matrix proteins (M1, M2), and nonstructural proteins (NS1, NS2) (Figure 1).[9]

Naming conventions for influenza viruses follow a standard nomenclature and include the influenza type, place of isolation, strain designation, and year of isolation. For example, A/Hong Kong/156/97 would be interpreted as influenza type A, isolated in Hong Kong, strain 156, isolated in 1997.[7] Further classification is based on the hemagglutinin and neuraminidase antigens. There are 16 hemagglutinin and 9 neuraminidase antigenic types that serve as the basis for subtype classification of the influenza A viruses.[8,10] Viral attachment and entry into the host cell are mediated by hemagglutinin by binding to sialic acid receptors at the cell surface. Hemagglutinin is also responsible for neutralization of host antibodies. Neuraminidase catalyzes the cleavage of virus particles from the sialic acid sites on the host cell, thus increasing virions for further receptor binding and spread of the virus within the host.[7,8]

The specific hemagglutinin attachment and binding unique to a species may in part explain the species barrier between avian and human influenza viruses.[7,8] Human viruses bind preferentially to sialic acid receptors with galactose α-2-6 linkages in the respiratory epithelial cells, whereas avian viruses bind to sialic acid receptors with galactose α-2-3 linkages in the intestinal epithelial cells. Pig tracheal epithelium includes both α-2-3 and α-2-6 linkages and may serve as a host for coinfection and mixing of viruses; thus, it is the possible source of new virus types. Human respiratory epithelium with both α-2-3 and α-2-6 linkages also allows human infection by avian influenza viruses.[7,8] Mutations that occur in the influenza A/H5N1 virus that cause amino acid changes can induce antigenic protein alterations that affect host specificity for cell binding and may lead to more efficient transmission to humans.[11-13]

Antigenic alterations occur frequently in influenza hemagglutinin and neuraminidase antigenic sites and are the mechanism for virus adaptation to the host and survival. When these antigenic variations are relatively small, they are referred to as antigenic drift, and when they are large, they are referred to as antigenic shift.

Antigenic drift occurs frequently, usually every year to every few years, and includes minor antigenic changes in the hemagglutinin or neuraminidase antigenic sites due to accumulated amino acid changes.[11-13] The virus responds to the selective pressure of the host and generates different antigenic variants that avoid antibody neutralization. Because of antigenic drift, the influenza vaccine composition is changed each year.

Antigenic shift refers to a major change in the hemagglutinin or neuraminidase antigens that infect the host—a new virus to which a susceptible host population has no immunity.[11-13] The mechanism for this change may be caused by a reassortment or recombination of the eight gene segments, such as recombining gene segments from avian and human influenza isolates that produce a new hemagglutinin and neuraminidase combination, by adaptation via an intermediate host, such as a pig, or by direct introduction of one species-specific influenza virus to another species such as from a bird to a human (Figure 2).[7,8] Influenza pandemics may occur as a result of

Figure 1. Influenza A virus cross section.[9] HA = hemagglutinin, M, M_1, M_2 = matrix protein, NA = neuraminidase, NP = nucleocapsid protein, NS = nonstructural protein, NS_2 = nonstructural protein, PB1, PB2, PA = polymerase proteins.

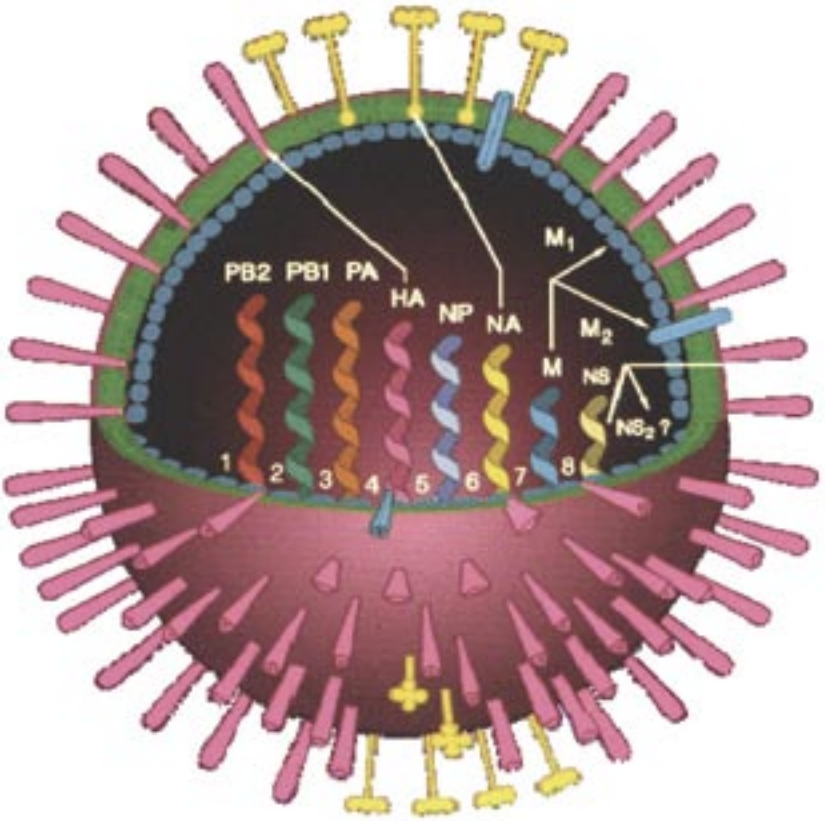
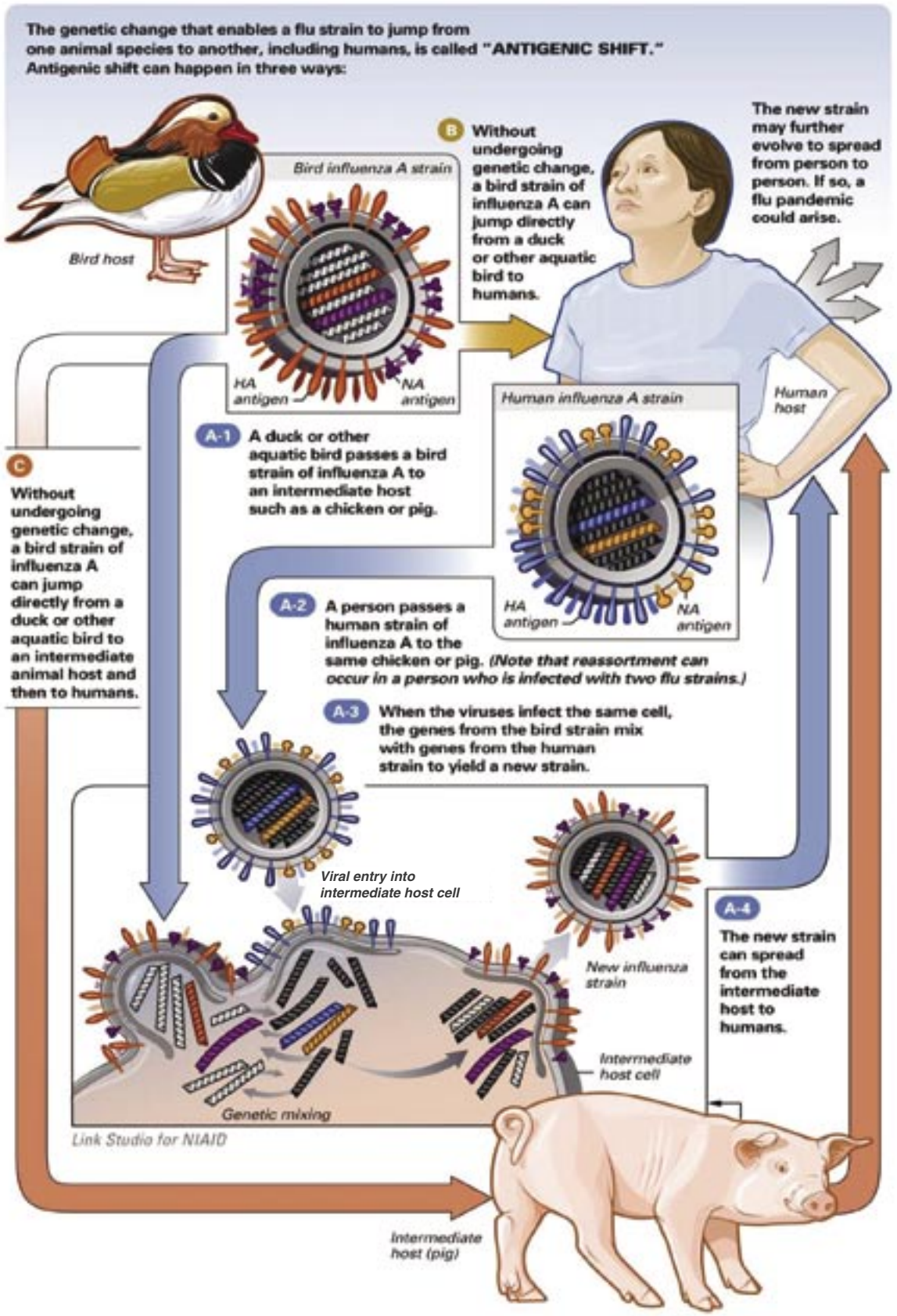


Figure 2. Antigenic shift.[14]



antigenic shifts or antigenic drifts if the mutation of the virus leads to efficient human-to-human transmission.

The complete genotype of the H1N1 influenza virus, which was responsible for the 1918 influenza pandemic (Spanish influenza), has been recreated.[15,16] Specimens obtained from World War I solders and an Alaskan native (Inuit) woman preserved in the Alaskan permafrost provided viral samples that were used for genetic sequencing.[16,17] Researchers identified the 1918 pandemic influenza virus as an avian-like virus that adapted to humans.[15,18] The other two most recent influenza pandemics of 1957 (Asian influenza) with H2N2 and of 1968 (Hong Kong influenza) with H3N2 were human–avian reassortments.[15] Amino acid changes identified in the H1N1 virus from 1918 have been found in the highly pathogenic H5N1 and H7N7 avian influenza strains that caused human fatalities, and these changes may contribute to viral replication and pathogenicity.[15]

The 1918 influenza pandemic caused an estimated 40–60 million deaths, possibly 100 million, and 500,000–675,000 in the United States.[19,20] The majority of the deaths in the 1918 pandemic occurred in the young between the second and fourth decades of life.[19,20] The virulence and lethality of the 1918 virus were theorized to be due to several factors: the preferred binding of the virus in the human respiratory epithelial cells, the adaptation that may have occurred in an intermediate host such as a pig, the enhanced cytokine and chemokine activation, and the lack of humoral immunity in the human host. A review of antibody neutralization assays from persons who lived through the 1918 pandemic indicates that those individuals had a significant amount of antibody to the H1N1 antigen to neutralize viral activity, and generations since have exhibited minimal or limited neutralization activity.[21]

Scientists theorized that one reason the 1918 pandemic was so severe was the ability of the virus to elicit a cytokine storm.[21] Induction of this cytokine storm by the H5N1 virus was recently demonstrated in a mouse model. Researchers developed techniques involving reverse genetics with complementary DNA to study the 1918 virus.[22] Kobasa and colleagues[21] used these techniques to manufacture a 1918-like live virus. Mice inoculated intranasally with this replicated virus developed infection in the entire lung with inflammatory cell infiltration and hemorrhagic findings, similar to the presentation of many victims of the 1918 pandemic. The virus's hemagglutinin protein preferentially recognized sialic acid receptors with galactose α-2-6 linkage found in respiratory epithelium. The severity of the inflammatory response correlated with high levels of macrophage-derived cytokines, namely interleukin (IL) 1β, IL-2, IL-6, IL-8, granulocyte colony stimulating factor, monocyte chemotactic protein 1, macrophage inflammatory protein (MIP) 1β, MIP-2, and MIP-3α. The investigators were able to determine that the virulence of the 1918 virus was associated with the hemagglutinin protein and the cytokine and hyperimmune response, not neuraminidase.[21] This study provided an understanding of the 1918 pandemic influenza from a genetic perspective and a biological response, as well as the historical interpandemic periods before and after. It is imperative to understand the 1918 and other pandemics for preparation for future avian influenza pandemics.

Human cases

Human cases of avian influenza virus A/H5N1 were first reported in 1997 in Hong Kong, where avian-to-human transmission resulted in 18 cases of human infection and six deaths.[8,23] Again in Hong Kong, in 2003, there were 2 reported cases of human infection and one death. Hong Kong's response to control these outbreaks was to cull and slaughter millions of chickens. In December 2003, an outbreak of A/H5N1 occurred among poultry in South Korea and then afterward in Vietnam, Japan, Thailand, Laos, Cambodia, China, Indonesia, and Malaysia. From December 2003 through 2005, WHO documented three waves of avian-to-human transmission during these avian outbreaks involving 133 cases and 68 deaths in Vietnam, Thailand, Cambodia, Indonesia, and China: from December 26, 2003, to March 10, 2004; from July 19, 2004, to October 8, 2004; and from December 16, 2004, to August 5, 2005.[8] In the third and ongoing wave, cases continue to occur and the geographic distribution has increased to areas north and west of China, with avian influenza infections in areas of western China, Mongolia, Russia, Kazakstan, Turkey, Romania, Egypt, Iraq, Iran, Nigeria, India, Pakistan, and most of Southern, Central, and Eastern Europe, including France, Switzerland, Germany, Denmark, and Austria.[24] As of November 13, 2006, the cumulative number of confirmed human A/H5N1 cases reported to WHO was 258, with 153 deaths. The human cases were reported in 10 countries: Vietnam, Thailand, Cambodia, Indonesia, China, Turkey, Iraq, Azerbaijan, Egypt, and Djibouti.[1,25]

Gene reassortments have occurred in the A/H5N1 virus collected from ducks and chickens, aquatic and terrestrial flocks, in Southeast Asia. In 2001, six genotypes resulted from gene reassortment: A, B, C, D, E, and X_0. After 2002, eight more genotypes were detected: V, W, X_1, X_2, X_3, Y, Z, and Z^+. The Z genotype, which is now the dominant genotype, has a 5-amino-acid deletion in the NS1 protein and a 20-amino-acid deletion in the NA stalk, which may allow viral adaptation to land-based fowl. The first human cases reported in Thailand, Indonesia, and Vietnam had the Z genotype configuration,

except they lacked the NA stalk deletion; thus, the configuration was designated Z^+.[26]

Viral transmission

Avian influenza virus spreads through the oral–fecal route of transmission and water contamination through aquatic birds such as ducks, geese (bar-headed goose), great black-headed gulls, brown-headed gulls, and swans.[27] The 1997 Hong Kong H5N1 outbreak was postulated to have arisen from fecal contamination of water by migratory birds to ducks, then chickens acquired the virus with establishment in domestic flocks.[28] Bird-to-human transmission is also likely by the oral–fecal route. WHO reports evidence of bird-to-human transmission of A/H5N1 in 9 of 29 poultry cullers who tested seropositive to the virus in the 1997 Hong Kong H5N1 outbreak. In addition, an estimated 10% of poultry-market workers were also seropositive. Possible environment-to-human transmission and limited, nonsustained human-to-human transmission have occurred.[23] Probable human-to-human transmission was reported in Thailand from an 11-year-old girl to her mother and an aunt, who exhibited initial symptoms of fever within 3 and 7 days, respectively, of exposure to the child.[29] The duration of exposure to the child was 16–18 hours for the mother and 12–13 hours for the aunt. The child developed progressive respiratory distress, hypoxia, right lower-lobe consolidation, lymphopenia, thrombocytopenia, and shock syndrome. She died 6 days after the onset of initial symptoms of fever, cough, and sore throat. The mother exhibited similar symptoms and died 13 days from the time of exposure. The aunt was hospitalized 12 days after exposure with pneumonia and left lower-lobe consolidation. The aunt received oseltamivir and was discharged after 18 days in the hospital. Both mother and aunt had H5N1 detected by reverse-transcription polymerase chain reaction (RT-PCR); the child was the only likely exposure.

During the 1997 Hong Kong outbreak, only 6 of 51 household contacts and 8 of 21 health care workers were seropositive to the H5N1 virus.[23] Similar serologic studies during the 2004 outbreaks in Thailand and Vietnam have not demonstrated evidence of seropositivity in household contacts or health care workers. Evidence suggests that the risk of nosocomial transmission to health care workers has been low, even when appropriate isolation procedures were not followed.[30,31]

Viral transmission to other mammals, felines, has been reported. Two tigers and two leopards died from H5N1 infection; the source of transmission was presumed to be from eating colonized or infected dead, raw chickens.[32] In another report, 147 tiger deaths were attributed to H5N1.[33] These tigers either died from causes directly related to the infection or were euthanized because of illness. In a zoo population of 441 tigers, horizontal (tiger-to-tiger) transmission was probable. Clinical findings in these felines included leukopenia, thrombocytopenia, elevated transaminases, fever, respiratory distress, lung congestion and hemorrhaging, and serosanguinous nasal discharge with some cases of neurologic symptoms, similar to clinical findings in humans. The virus has also been found in domestic cats.[34] In February 2006, the first case in a domestic cat was reported in Germany and also in a stone marten, a nocturnal predatory mammal.[35,36]

The spread and lethality of the virus to the felines suggest a degree of adaptation and raise concerns of efficient transmission in other mammals. Virus virulence may increase by a single mutation, as was demonstrated in the PB2 protein that increased the lethality in mice.[37] Other studies involving both mice and ferrets demonstrated similar findings of increased virulence, using H5N1 isolates from birds and humans from 1997–2004. These investigators demonstrated with the ferret model that the human isolates from 2004 were more virulent than the human isolates from 1997 and the avian isolates from 2003–2004.[38]

Clinical features

The human cases of influenza A/H5N1 are based on WHO reports, which identify only laboratory-confirmed cases.[1] A report from the WHO writing committee summarized the clinical characteristics and manifestations of the initial human influenza A/H5N1 cases from Hong Kong in 1997 and cases in Southeast Asia in 2004 on the basis of the descriptions and information available from hospitalized patients.[23] This report included the 18 cases of the 1997 Hong Kong outbreak and 41 cases in the 2004 Southeast Asia outbreak (Thailand, Vietnam, Cambodia). The majority of hospitalized patients, greater than or equal to 70%, had exposure to ill poultry. Onset of illness to presentation or to hospitalization ranged from one to eight days with a median of three days in the 1997 Hong Kong outbreak, six days in the Vietnamese patients from 2004, and eight days in the Cambodian patients from 2004. The median age of patients ranged from 9.5 to 22 years, and the age range was 1 to 60 years.[23] Virtually all patients presented with fever (94–100%), cough (67–100%), shortness of breath (61–100%), and lower-respiratory-tract symptoms. Pulmonary infiltrates were present in 61% of 18 patients in the 1997 Hong Kong outbreak and 100% of the 41 hospitalized patients from the 2004 outbreak. Most patients also had initial symptoms of an influenza-like illness, although headache, myalgias, diarrhea, sore throat, and rhinorrhea were reported with greater variability. Sputum production was also variable but sometimes bloody.[39] Lower-respiratory-tract symptoms and mani-

festations were usually found at presentation. In addition, 50–80% of patients had lymphopenia, and 61–83% had elevated transaminases. Thrombocytopenia occurred in a large percentage of the patients, but this finding was variable, ranging from 33% to 80%. Progression to respiratory failure occurred in 70–100% of the subset of cases from 2004, but in only 44% of the 1997 cases. Pulmonary radiographic changes included diffuse, bilateral infiltrates with manifestations of acute respiratory distress syndrome. In a separate report of cases in Thailand, dyspnea and radiographic abnormalities (evidence of pneumonia) developed in a median of 5 days (range, 1–16 days) and a median of 7 days (range, 3–17 days), respectively. In this group of 12 patients, leukocyte, lymphocyte, and platelet counts were depressed in the 8 patients who died as compared with those who survived.[40]

Along with broad-spectrum antibiotics, corticosteroids, and antivirals, patients were treated with amantadine in 56% of the cases in 1997 and oseltamivir in 61% of the cases in 2004.[23,40] The overall mortality was 64%; the mortality ranged from 33% in the 1997 Hong Kong outbreak to 100% (four patients) in Cambodia in 2004. The overall mortality of the 2004 Southeast Asia outbreak was 78%.[23] The differences in clinical presentation and mortality are evidence of the changing pathogenicity as the virus undergoes antigenic drift and antigenic shift.

The frequencies of milder or subclinical infections, or atypical presentations of the disease, are unknown. However, two pediatric cases in Vietnam, a nine-year-old girl and her four-year-old brother, presented with fever and watery diarrhea (greater than 10 episodes a day) to the hospital with progression to coma and death.[41] Death occurred five and seven days after the onset of symptoms for the sister and her brother, respectively. Samples from the throat, rectum, cerebrospinal fluid, and serum were obtained from the boy only and were confirmed as the H5N1 influenza virus. The confirmed and presumed (sister) cause of deaths was influenza encephalitis. In another case, a 39-year-old woman in Thailand presented to the hospital with a one-week history of fever, diarrhea, nausea, and vomiting, without respiratory symptoms. She was transferred to another institution with rapidly progressive pneumonia and died the next day.[42] These reports provide evidence to support inclusion of H5N1 influenza in the differential diagnosis when gastrointestinal and central nervous system illnesses are encountered and suggest the number of H5N1 cases may be greater than expected.

Mild cases of influenza-like illness may also be more prevalent. Recent data obtained from surveillance of greater than 45,000 inhabitants in nearly 12,000 households in FilaBavi, a rural area of Vietnam, during a three-month period in 2004 suggest that a mild form of the disease may be more common in humans than previously believed.[43] Individuals in this cohort were assessed for influenza-like symptoms, cough and fever or dyspnea, and exposure to poultry, including raising poultry in the household, commercial enterprises, poultry workers, poultry manure as fertilizer, and contact with sick or dead poultry. Contact with poultry was not associated with illness; however, direct contact with sick or dead poultry was a significant risk factor for influenza-like illness (odds ratio = 1.73). The investigators estimated that 650–750 cases of influenza-like illness could be attributed to direct contact with sick or dead poultry. Influenza-like illness was greatest in persons from 19 to 45 years of age. These are observational data, with no serologic confirmation testing or objective clinical data to confirm the influenza-like illness was indeed avian influenza. However, the investigators suggested that the relatively small numbers of severe H5N1 cases that have sought medical care at hospitals and have been reported likely overestimate the disease severity and case-fatality rates. Underserved populations, particularly in rural areas, have barriers to health care services and are likely to go undiagnosed and, therefore, unreported.

Pharmaceutical strategies: Vaccines and antivirals

The most effective defense against an influenza pandemic would be a directed vaccine to elicit a specific immune response toward the strain or strains of influenza virus. However, until there is an actual influenza pandemic, there is no evidence that vaccines or antivirals used in the treatment or prevention of such an outbreak will be effective in decreasing morbidity or mortality or for containing or delaying the spread of the pandemic. In addition, using current vaccine production methods, it is estimated that sufficient vaccine would not be available for approximately six months; this time frame would include the initial wave of the pandemic outbreak.[44]

Currently, the method of vaccine production relies on embryonated eggs, more than one egg for each vaccine dose. The world vaccine production resides primarily in Europe and the United States, and total capacity is less than one billion doses. However, because of the population being immunologically naive, a series of two vaccinations is likely, limiting the available vaccine to approximately 500 million people out of a world population of 6.5 billion. The H5N1 virus is lethal to embryonated eggs; thus, production of a vaccine to this virus will require alternative methods.[44] WHO is investigating whether a human vaccine may be produced in veterinary vaccine facilities. There are several requirement differences between human and animal vaccines,

including content and purity, and these will require review by the authorizing agencies of the world.[45]

Targeted use of vaccine and antivirals in high-risk populations or age-specified groups and infected patients is supported by evidence from clinical trials for human influenza disease (Table 1). Pharmacists will be responsible for procuring the appropriate antivirals and any vaccines that are available and will participate in immunization of the designated populations.

WHO has available several prototype H5N1 vaccine strains developed by recombinant methods. Many of these strains have been distributed to institutions and pharmaceutical companies for development and clinical trial study.[46] Investigational H5N1 vaccines manufactured by reverse genetics are prepared by removing or modifying the pathogenic genes of the specific viral strain and then inserting them into a relatively harmless influenza A virus to form a resorted virus suitable for seed strains.[47] An H5N1 investigational vaccine has been developed by Sanofi-Pasteur by the use of reverse genetics. Preliminary results of randomized clinical trials in the United States indicate that the vaccine elicited an immune response to suppress the virus in 117 of 450 participants, but at doses much greater (45 and 90 µg of hemagglutinin antigen) than other influenza vaccines. Only the highest does, 90 µg, elicited a neutralization antibody titer of 1:40 or more in >50% of the participants.[44,48] The results of this trial confirm the requirement for a two-dose vaccine series to attain the desired immunogenic response. Another candidate vaccine currently in clinical trials in the United States, sponsored by the National Institute of Allergy and Infectious Disease (NIAID), is an influenza A vaccine H9N2 (A/chicken/Hong Kong/G9/97 x A/Ann Arbor/6/60 ca), a cold-adapted, live, attenuated virus vaccine administered intranasally for the protection of humans against pandemic influenza viruses of the H9N2 subtype.[49]

Table 1.
Preventive Vaccination Strategies Against Influenza Pandemic[44]

Vaccine Strategies	Realities and Limitations
Mass vaccinations	Vaccine production cannot begin until a pandemic occurs and viral strain is identified; a vaccine will not be available for the initial wave of pandemic—6-mo lag time to availability Production capacity constraints secondary to limited available manufacturers and method of production Distribution, availability in areas of need, and administration require effective national plans
Targeted populations	As strain-specific vaccine is available, target high-priority groups (500 million out of a world population of 6.5 billion); should include essential personnel, health care workers, military, and government[64] Others should include care givers, those at high risk of death in the population on the basis of age groups, those with chronic diseases, and the healthy[64]
Targeted populations use current vaccines	Immunize more of the population in interpandemic years with current influenza vaccine for potential cross-protection against pandemic strain Develop H5N1 candidate vaccines and stockpile for use when conditions suggest there is a risk of a pandemic Before a pandemic, vaccinate the population where outbreaks are identified with an initial dose of H5N1 vaccine followed by a booster
Vaccine development and dosage	Developing vaccine using new and alternative technologies may require licensing and approval from the government drug agencies and intellectual property rights Low-dose monovalent vaccine should include the use of adjuvants to maximize yield of available vaccines Use the intradermal route of administration, which requires smaller dosages than the intramuscular route
Animal and bird vaccination	Culling of poultry is insufficient for containment United Nations Food and Agricultural Organization recommends vaccination of targeted poultry flocks Difficult to implement in countries with free-range poultry Cost : 2.5–5 cents per vaccination, but billions of vaccines required[84]

An initial pandemic wave will be identified when efficient human-to-human transmission occurs, and successive waves will be identified by periods of quiescence and then increases in case numbers and case severity. The 1918 pandemic was characterized by three successive waves, the second and third having a much higher frequency and greater severity of disease than the first wave.[5] With increased population densities and international travel, clearly defined periods between waves may not exist or may be very brief. The effect

of these factors on vaccination and antiviral production and distribution strategies must be considered as the pandemic unfolds.[44]

As vaccines will not be available for the initial pandemic wave, another option being promoted is the use of antiviral agents, specifically the neuraminidase inhibitors. The WHO pandemic response plan has recommended the stockpiling of antivirals to be used for prophylaxis, postexposure, and treatment in the occurrence of a pandemic to reduce the number of hospitalizations and deaths.[2]

Pharmaceuticals available in the antiviral armamentarium include the adamantanes (amantadine and rimantadine) and the neuraminidase inhibitors for treatment and prophylaxis of influenza. The adamantanes are effective toward influenza A viruses only, while the neuraminidase inhibitors are effective against both influenza A and B viruses. Recent evidence suggests that the adamantanes are not an appropriate empiric choice for influenza A treatment, as many H5N1 isolates tested from the 2004–05 Southeast Asia outbreak exhibited in vitro resistance to these compounds secondary to serine-to-asparagine amino acid substitution in the M2 protein.[11] In addition, testing by the Centers for Disease Control and Prevention (CDC) of the current 2005–06 human influenza A (H3N2) viruses has exhibited a resistance rate to the adamantanes in greater than 90% of isolates tested.[50] The significant change in resistance rates occurred in the Southeast Asia bird population with H5 strains (0% in 1979–83 to 31.1% in 2000–04), while resistance with H5 strains in North America remained at 0% during both periods, which suggests that the selection of resistance is occurring in bird populations.[42] Reports of amantadine treatment of poultry flocks in China, the availability of antiviral drugs in China and Russia without prescription, and the inclusion of nonprescription cold and influenza products to the regimen provide insight into the misuse of these antivirals and the selective pressure in the environment that promotes resistance. A global approach to restriction and control of antiviral agents is necessary and may reverse this resistance trend.[51]

Although significant resistance has occurred with the adamantanes, influenza virus susceptibility to the neuraminidase inhibitors has been maintained.[50] Testing of oseltamivir phosphate in mice infected with an H5N1 strain demonstrated activity and prevented death at doses ranging from 0.1 to 1 mg/kg/day.[52] The drug also prevented H5N1 influenza virus replication in the lungs and brains of the mice in doses ranging from 1 to 10 mg/kg/day. In addition, resistance did not occur after seven days of treatment. Zanamivir was also tested in a murine model against an H5N1 influenza strain and other avian influenza viruses that contained genes encoding H5N1-related proteins.[53] Mice were given an initial dose of zanamivir and four hours later were inoculated intranasally, followed by twice daily doses of zanamivir ranging from 1 to 100 mg/kg/day for five days. Zanamivir doses of 50 to 100 mg/kg/day prevented death, decreased viral replication into the lungs, and blocked the spread of the virus to the brain. Doses of <50 mg/kg/day were ineffective in managing the disease process. Development of resistance did not occur during the experimental treatments.[53]

Mutations, which cause amino acid changes in neuraminidase, the target of neuraminidase inhibitors oseltamivir and zanamivir, may impart drug resistance to one or both drugs.[11] In a series of eight patients from Vietnam with H5N1 infection treated with oseltamivir therapy 75 mg twice daily, there was 50% mortality. High-level resistance to oseltamivir occurred during treatment in two patients.[54] Resistance occurred secondary to a histidine to tyrosine substitution at position 274 of the NA protein. Both of the patients died of progressive pneumonia; there was an initial reduction in viral load, but it increased during or after completion of therapy. The survivors demonstrated a sustained reduction in viral load during and after therapy. In another report, the development of slight resistance to oseltamivir occurred during oseltamivir prophylaxis of 75 mg daily.[55] When the oseltamivir dose was increased to 75 mg twice daily, no virus was isolated. Selected oseltamivir-resistant and sensitive viral clones were all sensitive to zanamivir.

Dose-ranging studies of the neuraminidase inhibitors provide some information regarding tolerability at higher doses than those used for Food and Drug Administration (FDA)-approved indications. Zanamivir tolerability was described in a double-blind, placebo-controlled trial designed to determine the efficacy of zanamivir against a human influenza virus infection and the distribution of zanamivir in the respiratory mucosa. Zanamivir 600 mg twice daily administered intravenously for five days was compared with placebo infusion in 16 healthy male volunteers, 8 in each group. Four hours after the infusions, the participants were inoculated intranasally with an H1N1 human influenza virus. Zanamivir demonstrated protection against infection and reduction in symptoms, and it was detectable in nasal lavage samples. No participants withdrew from the study, and the only serious adverse effect in the zanamivir group was one upper-respiratory-tract infection that occurred 15 days after the final day of dosing. Hematology and chemistry laboratory panels showed no alterations.[56] Oseltamivir phosphate has also demonstrated good tolerability, with only minor gastrointestinal complaints of nausea and vomiting at doses up to 1000 mg/day for up to 7 days. Elderly patients >65 years of age had gastro-

intestinal events at mild to moderate intensity with doses of 200 mg twice daily, whereas the same effects were reported in the younger subjects only at 500 mg twice daily.[57]

If antivirals are theoretically deemed effective for use, the number of antivirals required needs to be determined. Estimates of antivirals necessary for national and worldwide stockpiles are based on mathematical models, which incorporate multiple variables identified from previous pandemics, namely the 1918, 1957, and 1968 influenza pandemics. These models include the clinical attack rate, the seropositivity of the population, hospitalization rates, age categories, risk categories, and mortality.[58-60] One model's estimates for antiviral courses needed were based on assumptions of treatment within 48 hours and a clinical attack rate of 25%.[58] This model estimates that an antiviral stockpile to cover 20–25% of the population would decrease hospitalizations by 50–70% and provide adequate treatment of patients with pandemic influenza based on current available data. The needed quantity of antivirals could be calculated from this model with an input of the clinical attack rate and the reproduction number of disease obtained from epidemiology and surveillance data. The quantity of antivirals could be reduced with selected targeting of age or risk categories, but with lesser effects on hospitalization rates. Clinical studies providing information on hospitalization, mortality, and development of resistance are needed to adequately test the model.[58]

A robust model for determining effectiveness of antivirals, prevaccination, and quarantine on the spread of influenza to a pandemic used multiple variables on the basis of exposures to the virus seen in a rural, population-dense (500,000) area of Southeast Asia.[59] Considerations of case contacts such as family, family clusters, schools, workplaces, casual contacts in markets, shops, and religious services were included in the model. In addition, variables of age groups, clinical attack rate, reproduction number of the disease, time to intervention, and type of targeted antiviral prophylaxis were included. The percentage of the population provided with targeted prophylaxis was also included with the virus reproduction number to predict prevention of the spread of the pandemic. Estimated courses of neuraminidase inhibitors needed to contain the influenza pandemic ranged from 120,000 to 1 million.[59]

One group of investigators has reported that there is a cost benefit to nations for stockpiling oseltamivir.[51] The mathematical model included assumptions on the effect of an influenza pandemic in the nation of Israel and included estimates of 25% of the population affected, physician visits, hospitalizations, deaths, and lost workdays. This model estimated that for every dollar spent on prophylaxis, an estimated savings of $2.44 for treatment of all cases, $2.49 for postexposure prophylaxis for all close contacts, and $3.68 for limited therapeutic use for high-risk patients would be realized.[51] The cost saving estimates were based in part on the price of oseltamivir bulk powder with a 10-year shelf life.[60] Obviously, the logistics of mass production of capsules from bulk powder in the case of a pandemic will be resource extensive and delay the availability of doses to the at-risk populations.

Adequate active ingredients and production capacity to produce the quantities of oseltamivir needed for a pandemic are required in order to effectively treat ill or exposed populations. Initially, Roche Pharmaceuticals indicated that an inadequate amount of active ingredient and a complex manufacturing process suggested that the demand would outpace supply if a worldwide pandemic occurred.[44] However, Roche has worked with WHO and has fulfilled orders for oseltamivir to 65 countries and has donated 5.125 million treatments to WHO for use where a pandemic may start.[61] In addition, Roche has increased oseltamivir production, granted sublicenses to an Indian company, and negotiated with a company in China to reach a target of 400 million treatment capacity by the end of 2006.[62] With targeted prophylaxis and treatment strategies, the number of necessary courses of the antiviral will be in the hundred of millions worldwide. In the United States alone, the government has requested 80 million treatment courses, a quantity sufficient for greater than 25% of the U.S. population, at a cost of $1.4 billion,[63] much of which will be borne by the states.[64]

Chemoprophylaxis strategies and recommendations are extensively described in the WHO pandemic influenza draft protocol for rapid response and containment.[65] Specific details on the oseltamivir global stockpile are also available. Oseltamivir will be packaged as individual boxes containing a strip pack of 10 capsules, or one patient treatment.

Health care workers are repeatedly designated as a targeted population for antivirals or oseltamivir prophylaxis or treatment. Stockpiling oseltamivir in hospitals for their workers and patients has been advocated. With the short onset of severe disease and the logistics of distributing a stockpiled drug from a distant location, the rapid availability of a drug at the site of patient care is prudent.[66]

With limited quantities of antivirals and vaccines, decisions regarding appropriate use of scarce resources will be critical, and global cooperation will be of paramount importance.[67] The rationing of scarce resources may require mandates to determine those who will receive antivirals or a vaccine. Public health workers, first responders, and health care workers will be priority groups. Ethical dilemmas will require decisions regarding at-risk populations

on the basis of the epidemiology of the pandemic that may differ from the groups previously viewed as having risk, such as the very young and very old. Instead, young adults in their second to fourth decades may be those that obtain resources. Other considerations include socioeconomic equity, globally as well as in the United States.[64]

In March of 2006, WHO published a document of advice on the use of oseltamivir.[68] In June of 2006, WHO published a document of advice guidelines for antiviral treatment and prophylaxis with risk categories and graded levels for recommendations.[69] This document recommends the use of oseltamivir, zanamivir, and the adamantanes in select high-risk populations. The document includes the dosing of oseltamivir, zanamivir, amantidine, and rimantidine for adults and children for the treatment and prophylaxis of influenza A virus on the basis of the experience in clinical trials and postmarketing use against human influenza (Tables 2 and 3).[70-75] The use of corticosteroids, immune globulin, and ribavirin was reviewed but not recommended for the treatment of avian influenza A/H5N1.[69]

There have been no clinical trials studying the effects of antivirals in the treatment of avian influenza A/H5N1. The evidence to suggest continued use of oseltamivir or other agents for H5N1 is from in vitro tissue culture testing, animal models demonstrating survival and suppression benefits, and a limited number of H5N1 human case reports in which oseltamivir treatment or prophylaxis occurred.[68,69] Currently,

Table 2.
Guidelines on Pharmacologic Management of Humans Infected with Avian Influenza A[68,69]

Management Type and Patient Population	Drug			
	Oseltamivir[a]	Zanamivir	Amantadine	Rimantadine
Treatment				
Adults and teenagers	Age ≥13 yr: 75 mg twice daily for 5 days (renal dosage adjustment)	10 mg twice daily for 5 days[b]	Age 10–65 yr: 100 mg twice daily for 5 days Age >65 yr: 100 mg daily for 5 days[c] Hemodialysis pts.: 200 mg every 7 days	Age ≥12 yr: 100 mg twice daily for 5 days[d]
Children	Age ≥1 yr: twice daily for 5 days[e] Weight ≤15 kg: 30 mg Weight >15–23 kg: 45 mg Weight >23–40 kg: 60 mg Weight >40 kg: 75 mg	Age ≥7 yr[f]: 10 mg twice daily for 5 days	Age 1–9 yr: 5 mg/kg/day in 2 divided doses—max. 150 mg for 5 days[g] Age 10–12 yr: 100 mg twice daily for 5 days	Age ≥12 yr: use adult treatment protocol[h]
Prevention				
Adults and teenagers	Age ≥13 yr: 75 mg once daily for 7–10 days after last known exposure[i]	10 mg once daily for 7–10 days after last known exposure[j]	Same as for treatment, except duration is 7–10 days after last known exposure	Age ≥10 yr: 100 mg twice daily for 7 days after last known exposure[d,k]
Children	Age 1–13 yr: once daily for 7–10 days after last known exposure[d] Weight ≤15 kg: 30 mg Weight >15–23 kg: 45 mg Weight >23–40 kg: 60 mg Weight >40 kg: 75 mg	Age ≥5 yr: 10 mg once daily for 7–10 days after last known exposure[a]	Same as for treatment, except duration is 7–10 days after last known exposure	Age <10 yr: 5 mg/kg/day in 2 divided doses—max. 150 mg Age ≥10 yr: see adult prevention

[a]A new warning concerning adverse effects of oseltamivir is found at www.fda.gov/Medwatch/safety/2006/safety06.htm#tamiflu.
[b]Oral inhalation—two inhalations by Diskhaler.
[c]Renal dose adjustment if creatinine clearance (CL_{cr}) <50 mL/min/1.73 m^2.
[d]Dose adjustment in elderly, renal failure (CL_{cr} <10 mL/min), or hepatic dysfunction: 100 mg daily.
[e]Suspension available.
[f]Not approved for use in children <7 years of age.
[g]Syrup available.
[h]Not approved for use in children <12 years of age.
[i]Prophylaxis up to eight weeks may be considered safe.
[j]Oral inhalation—two inhalations by Diskhaler; prophylaxis duration up to 28 days reported.
[k]Prophylaxis duration up to seven weeks reported.

Table 3.
Evidence Supporting the Use of Antiviral Agents[68,69,a]

Condition	Antiviral Agent	Strength of Evidence
Neuraminidase inhibitors available	Oseltamivir	Strong
	Zanamivir as an alternative	Weak
	Amantadine or rimantadine should not be used as first-line monotherapy	Strong
	Combination neuraminidase inhibitors and adamantanes[b]	Weak
Neuraminidase inhibitors not available	Amantadine or rimantadine as first-line monotherapy if local surveillance data indicate susceptible H5N1	Weak
High-risk exposure groups where neuraminidase inhibitors available	Prophylaxis with oseltamivir or alternative zanamivir	Strong
High-risk exposure groups where neuraminidase inhibitors not available	Possible prophylaxis with amantadine or rimantadine if H5N1 susceptible	Weak
	Do not administer during pregnancy	Strong
Moderate-risk exposure groups where neuraminidase inhibitors available	Possible prophylaxis with oseltamivir or alternative zanamivir	Weak
	Do not administer during pregnancy	Strong
Moderate-risk exposure groups where neuraminidase inhibitors not available	Possible prophylaxis with amantadine or rimantadine if H5N1 susceptible	Weak
Low-risk exposure groups	Prophylaxis with oseltamivir or alternative zanamivir should probably not be administered	Weak
	Amantadine or rimantadine should not be administered	Weak
	Do not administer during pregnancy	Strong
	Elderly and renally impaired persons should not receive amantadine or rimantadine	Strong

[a]Overall quality of evidence on which to base a summary assessment was very low for all antivirals.
[b]Consider only when susceptibility data are available and in the context of prospective data collection.

there is a study enrolling participants to compare standard-dose with high-dose oseltamivir (twice the standard dose) for the treatment of human and avian influenza.[76] Also, there is a proposed clinical trial to study the use of probenecid with oseltamivir; this trial has not yet begun enrollment.[77] The rationale for concomitant probenecid and oseltamivir therapy is that probenecid may reduce the renal clearance of oseltamivir by 50% with a corresponding doubling of plasma oseltamivir concentrations.[78]

Zanamivir is currently available and has been used to treat human influenza infections. The drug is now advocated for stockpile but as an alternative to oseltamivir, primarily because of the inhalation route of administration.[69] A neuraminidase inhibitor currently under investigation in clinical trials is peramivir. Peramivir was found to exhibit inhibitory effects against influenza viruses resistant to zanamivir and oseltamivir.[79] Biocryst Pharmaceuticals (Birmingham, Alabama) is developing i.v. and intramuscular formulations of the drug for application toward an influenza pandemic.[80] A Phase I dose-escalation study sponsored by the NIAID is under way to evaluate the i.v. formulation.

Personal stockpiling of antivirals is strongly discouraged because of the risks of the development of resistance and the loss of a scarce and potentially lifesaving resource.[81] Obviously, physicians are discouraged from prescribing antivirals and pharmacists are discouraged from dispensing antivirals for other than appropriate indications. Pharmacists may be the first groups to identify unusually high volumes of prescription activities regarding antivirals and may consider reporting or be required to report this activity, depending on local emergency planning.

Surveillance and prevention

Birds. Since 2003, over 100 million domesticated birds, primarily chickens and ducks, have died from either avian influenza virus H5N1 or intentional culling to keep the virus from spreading.[82] Eliminating the poultry host stopped the 1997 Hong Kong avian influenza outbreak. In Thailand, culling of chickens was implemented late, but was helpful in controlling further disease spread; around 62 million birds died from either disease or culling. The estimated cost to the Thai economy was 0.39% of the national gross domestic product ($630 million U.S.).[83] Culling of poultry may be insufficient for containment. Vaccination of targeted poultry flocks has been rec-

ommended, but this may be difficult in countries with free-range poultry and low biosecurity. The cost per vaccination for domestic poultry is relatively inexpensive; however, the overall cost to vaccinate billions of birds is exponential and economically unfeasible.[84] In order to protect the American poultry industry, the U.S. Department of Agriculture (USDA) has been monitoring migratory birds in the Alaska flyway since 1998. Starting in 2000, USDA began monitoring migratory birds in the Atlantic flyway, and added monitoring of migratory birds in the Pacific flyway in the summer of 2005. At this time, all surveillance testing on these migratory birds has been negative for the highly pathogenic H5N1. This surveillance will provide early detection of H5N1 in wild migratory birds entering the United States via the flyways, thus enabling a swift response to protect the domestic poultry and human populations.[85-87]

Humans. While the use of antivirals or a vaccine will be of paramount importance in the management of a pandemic, there is no doubt that infection-control standards and practices will be the backbone to contain and prevent transmission of organisms. Infection control includes surveillance and epidemiology; prevention of transmission through hand hygiene, barrier protection, respiratory protection, and appropriate patient placement; and monitoring of health workers by the use of a daily self-monitoring assessment tool, the administration of prophylaxis to health care workers postexposure, and the use of work quarantines.

Currently, there is no A/H5N1 influenza activity in the United States. However, the WHO Pandemic Alert currently lists A/H5N1 as Level 3, since the virus has achieved two of the three requirements necessary for a pandemic[88]: (1) a new influenza A subtype that can infect humans, (2) causes serious illness or death, and (3) efficient human to human transmission (presently this has not been documented).

Current surveillance for human cases involves identifying potential exposure to A/H5N1 through recent travel to or from areas with known avian influenza activity. This information enables the health care team to determine appropriate isolation and quarantine and the level of personal protective equipment needed to protect themselves from an exposure event while providing care to the patient. Surveillance also enables health departments to track exposures and initiate quarantine and treatment (e.g., antivirals). Surveillance is to epidemiology as hand hygiene and respiratory etiquette are to infection control. Hand hygiene may consist of a hand washing using soap and water, alcohol-based hand gel, or hand wipes. Respiratory etiquette includes coughing or sneezing into a tissue or by covering the face with the elbow. This prevents contamination of the hands.

Continued surveillance and rapid identification tests for the virus strains causing disease are needed for containment efforts. An H5-specific RT-PCR can rapidly detect a virus in clinical specimens, and optimal recovery of an organism is obtained from a throat swab instead of a nasopharyngeal wash.[89] The United States improved the country's ability to monitor and identify cases of the highly pathogenic H5 influenza virus. In February 2006, FDA approved a rapid test for the Asian lineage of the H5 influenza strain, the Virus Real-Time Reverse Transcription Polymerase Chain Reaction Primer and Probe Set developed by CDC.[90] Testing will be limited to Laboratory Response Network-designated laboratories, approximately 140 laboratories in 50 states. The test will take approximately four hours to complete.[90]

CDC has recognized that the review of purchases or prescriptions of pharmaceutical classes may help identify unusual disease activity. Researchers in France have also suggested that surveillance of pharmaceutical sales may be useful to correlate treatment courses and diagnostic testing and clinical reporting of diseases.[91,92] In fact, the pharmaceutical industry may use these findings to determine production needs and to control a targeted agent in the market, as did Roche Pharmaceuticals when it limited the supply and purchases of oseltamavir in 2005.

Infection control

All too often the simplicity of hand hygiene is overlooked. In today's age of technology, hand hygiene does not have an appealing factor. However, hand hygiene, the turtle in the infection-control race, will win every time.

Coinciding with hand hygiene is barrier protection; this includes the use of gloves, gowns, and eye protection. The role of barrier protection is to prevent the exposure to a microorganism through either direct or indirect contact with mucosa, skin, or clothing where the people providing care have the potential to inadvertently inoculate themselves. The last, and most significant, piece of protective equipment for health care workers during a pandemic influenza outbreak will be respiratory protection equipment.

Normal seasonal human influenza is transmitted via large respiratory droplets, requiring anyone entering a patient's room to wear a surgical mask or a respirator when performing high-risk procedures (e.g., intubation, aerosol treatments, suction). In the presence of an influenza strain that is highly pathogenic and has the potential to cause a pandemic, CDC may require health care workers to wear an N-95 respirator or a positive air pressure respirator (PAPR) for all patient contacts. However, a large pandemic outbreak would rapidly deplete the supply of N-95 respirator masks and the availability of batteries

for PAPRs. This would leave health care workers with only one alternative for respiratory protection, the surgical mask, which may not be sufficient in the presence of procedures that generate aerosolized droplets.

CDC recommends patients with influenza be admitted to a negative pressure room if available. During a normal influenza seasonal outbreak, there may be insufficient negative pressure rooms, and it is recommended that patients be admitted to a private room or cohorted with other confirmed cases.[93] An influenza pandemic has the ability to generate surge capacity, which would rapidly deplete the availability of negative pressure rooms, private rooms, and semiprivate rooms. Therefore, the management of surge capacity requires the integration of hospitals, local and state public health agencies, and local and state government emergency response planners in order to be able to meet the needs of the community at large.

When a human case of influenza caused by a potential pandemic strain is suspected or confirmed in a local region, health care institutions will work with public health agencies in advising staff to begin a daily self-assessment. This self-assessment includes, but is not limited to, the self-reporting of fever, diarrhea, cough, body aches, and any influenza-like illness to the health care facility per policy. Simultaneously, health care workers who have had an exposure event will start antiviral prophylaxis to prevent development of disease. Local public health agencies in conjunction with state public health agencies and CDC will determine when or if to initiate quarantine procedures for health care workers.

WHO has published interim infection-control guidelines for health care facilities, which can be accessed through the WHO website. These guidelines were amended on February 9, 2006, and contain recommendations for infection-control measures, barrier protection, and patient placement (Table 4 and Figure 3).[94]

Emergency response plan

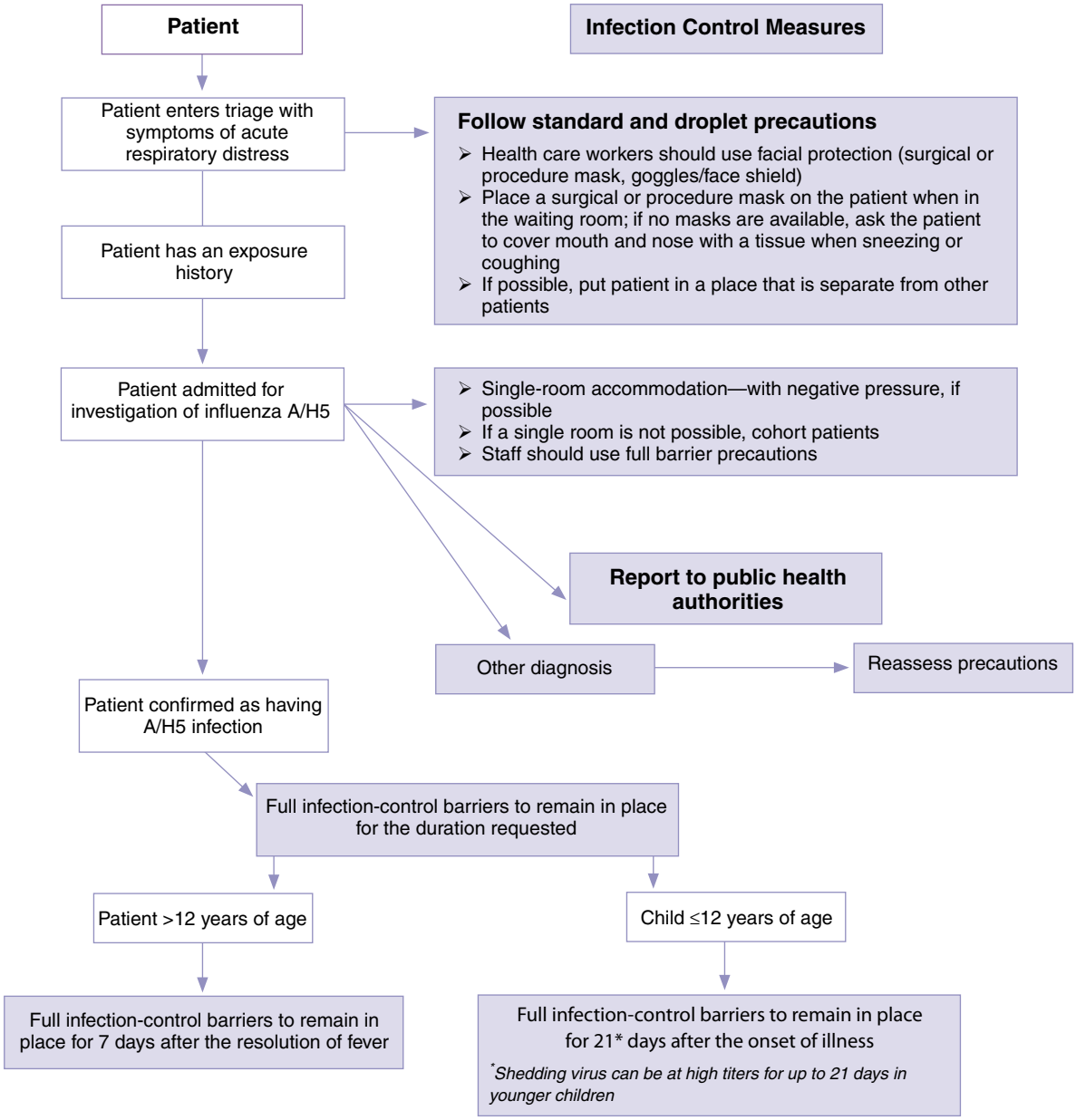
The most effective method for the management of pandemic influenza will be through the implementation of emergency response plans that include the activation of an incident command system, a continuity of operations plan, a memorandum of understanding with other health

Table 4.
Barrier Precaution Recommendations for Persons Providing Care for Patients with Respiratory Illness or Suspected or Confirmed Avian Influenza Infection[94]

Barrier Precaution	Point of Exposure			
	Close Contact (<1 m) with Pts. with Acute Febrile Respiratory Illness Who Have No Known AI Risk Factors[a]	Entry to AI Isolation Room or Area, No Anticipated Pt. Contact	Close Contact (<1 m) with AI Infected Pts. in or out of Isolation Room or Area	Performance of Aerosol-Generating Procedure on AI Pts.[b,c]
Hand hygiene[d]	Yes	Yes	Yes	Yes
Gloves	Not routinely	Risk assessment	Yes[e]	Yes
Apron	Not routinely	Risk assessment[f]	Not routinely[g]	Not routinely[g]
Gown	Not routinely	Risk assessment[f]	Yes[g]	Yes[g]
Hair cover	Not routinely	Not routinely	Not routinely	Yes
Surgical mask on health care worker	Yes	Not routinely[h]	Not routinely[h]	Not routinely[i]
Particulate respirator	Not routinely	Yes	Yes	Yes
Eye protection	Risk assessment	Risk assessment[j]	Yes	Yes
Surgical mask on patient	Yes	No	Not routinely[k]	No

[a]Bird exposure in regions with avian influenza (AI) infections in animals or exposure to AI-infected patients.
[b]Aerosol-generating procedures create aerosols of different sizes (large-particle and small-particle aerosols). Examples of aerosol-generating procedures include endotracheal intubation, aerosolized or nebulized medication administration, diagnostic sputum induction, bronchoscopy, airway suctioning, tracheostomy care, chest physiotherapy, nasopharyngeal aspiration, positive pressure ventilation via face mask, high-frequency oscillatory ventilation, and postmortem excision of lung tissue.
[c]Whenever possible, aerosol-generating procedures should be performed in negative pressure rooms, side rooms, or other closed single-patient areas with minimal staff present. Personal protective equipment should cover the torso, arms, hands, eyes, nose, and mouth.
[d]Standard precautions are the minimum level of precautions indicated for all patients at all times.
[e]Gloves should be worn in accordance with standard precautions. If glove demand is likely to exceed supply, glove use should always be prioritized for contact with blood and body fluids (ambidextrous nonsterile gloves) and contact with sterile sites (sterile gloves).
[f]Gloves and gowns or aprons should be worn during cleaning procedures.
[g]If splashing with blood or body fluids is anticipated and gowns that are not fluid-resistant are used, a waterproof apron should be worn over the gown.
[h]If particulate respirator is not available, use tightly fitting surgical mask.
[i]If particulate respirator is not available, use tightly fitting surgical mask and face shield.
[j]Use eye protection if close contact (<1 m) with patient is possible.
[k]Provide surgical mask for patient (if tolerated) when patient is outside of isolation room or area.

Figure 3. Initiation of avian influenza infection-control precautions in health care facilities.[94]



care institutions, a unified command with local public health and local government agencies, and the appropriate use of limited resources. An influenza pandemic plan should be included in a health care system's emergency preparedness plan. Institutional pharmaceutical caches of medications, including antivirals, to manage a threat before activation of the Strategic National Stockpile are advisable. Health-system pharmacists must be familiar with and knowledgeable of their national and state influenza pandemic plans to be prepared to fulfill their professional public health role.

Pharmacists are well positioned to play a major role in the prevention and treatment from a biological threat, including an influenza pandemic. Pharmacists are knowledgeable of disease states and appropriate medications and doses. Pharmacists may be recognized to assist in fulfilling an important surveillance role, in the form of their responsibilities in drug-use evaluations or review of sales of classes of pharmaceuticals. Pharmacists are already well positioned and will play an instrumental role in the deployment, distribution, and dispensing of the Strategic Na-

tional Stockpile. In addition, pharmacists can play an expanded public health role. The pharmacists' contributions should include patient triage and screening, obtaining medical and medication histories, recommending therapeutic interchange, education, prescribing (limited to some states), therapeutic management by interdisciplinary approved protocols, and immunization of designated populations.

An appendix provides websites that the pharmacist may find useful as sources for pandemic influenza planning.

Conclusion

Avian influenza A/H5N1 is a public health threat that has the potential to cause serious illness and death in humans. Understanding its pathology, transmission, clinical features, and pharmacologic treatments and preparing for the prevention and management of its outbreak will help avoid its potentially devastating consequences.

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Appendix—Sources for pandemic influenza planning

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