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Influenza and avian flu

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The history of influenza can be traced back to at least 1679, with a description of the illness stated by Thomas Sydenham. The influenza virus has the capability to mutate, thus allowing this virus to maintain its place in the population for long periods of time. Contracting an influenza infection does not offer permanent immunity to its host as one might see with other diseases such as smallpox, where permanent immunity is conferred. Influenza needs large populations to continue, and the most susceptible individuals are children who have not been exposed. Influenza has a rate of mortality ranging from 1% to 20%. While 1% may give the impression of a small amount, a worldwide outbreak results in a rather significant number. These deaths are usually a result of primary viral or secondary bacterial pneumonia.

The influenza pandemic of 1918 is one historical example of the devastation an outbreak could cause. Named the Spanish influenza (H1N1), it is believed to have started on North American soil. Further evidence proposes that the Spanish flu originated in the United States

and was carried by soldiers to Europe during World War I. The pandemic affected healthy young adults with an unprecedented mortality rate. More than 20 million people died from the 1918 Spanish flu. This was more than all the casualties of World War I. The United States alone reported more than a half a million deaths.

Since that time, there have been two other pandemic influenzas, which both occurred in the 20th century. The Asian flu (H2N2) in 1957-1958, with 70,000 deaths in the United States, and the Hong Kong flu (H3N2), which caused 34,000 deaths in the United States. Influenza A (H3N2) still circulates today. The influenza virus was definitively identified in 1933 as the cause of influenza. This illness remains a major cause of mortality, with more people dying

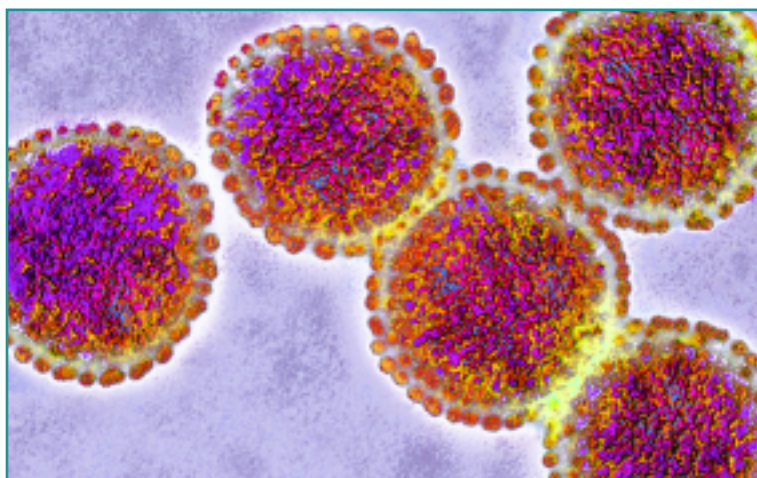


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GOAL:

To enhance pharmacists' understanding of influenza, avian influenza, and the treatments available

CREDIT:

This lesson provides two hours of CE credit and requires a passing grade of 70%.*

OBJECTIVES:

Upon completion of this article, the pharmacist should be able to:

- ✓ Determine the impact the influenza virus may have on the population
- ✓ Describe the difference between an antigenic drift and an antigenic shift
- ✓ Identify ways in which the avian flu may infect humans
- ✓ Explain nonpharmacologic measures to prevent influenza and avian influenza
- ✓ Discuss appropriate use of the medications currently available for the treatment and prevention of influenza

*To receive credit you must score 70% or higher on the quiz and complete the evaluation. Upon successful completion, the University of Florida College of Pharmacy will mail Statements of Credit for written quizzes within 10 working days. Participants completing the program on-line may print a Statement of Credit after successfully completing the program.

young adults with a high rate of mortality. The first step to a pandemic is the development of an *antigenic shift* causing a major change in the virus. The virus must then have the capability to spread readily among humans. Once the pandemic is established, there will be many waves of disease around the major outbreak. The occurrence of an influenza pandemic may be only a matter of time and may have a significant impact on the United States alone. A pandemic will last longer than other public health emergencies. Healthcare workers and emergency personnel will suffer a reduction in numbers because they will be exposed to the virus in the community and in healthcare settings. Resources could be limited, and a vaccine will take several months to manufacture, leaving people unvaccinated in the early stages of the pandemic.

There are three types of influenza viruses: A, B, and C. Influenza C causes mild illness without causing epidemics or pandemics. These viruses are from the family *Orthomyxoviridae* and are single-strand RNA respiratory viruses. The focus of this article will be on influenza A and B. Influenza A can infect people, birds, pigs, horses, and other animals, with wild birds as the natural host. Influenza A has two subtypes that are named based on the surface antigens hemagglutinin (HA) and neuraminidase (NA). Hemagglutination is responsible for the attachment and infection of the epithelial cells, and NA plays a role in releasing influenza viruses from infected cells. There are 15 different HA subtypes and nine NA subtypes. Currently, only three HA subtypes and two NA subtypes have been linked to epidemics. Influenza is identified by its surface proteins, for example H1N2 has the subtype HA 1 protein and NA 2 protein. Before the cause of the pandemics was known, they were named based on what was concluded as the point of origin. For example, the pandemic of 1889 was called the Russian flu.

Influenza A is the most severe influenza, causing pandemics and the highest morbidity and mortality rates. Influenza B is found only in humans, and, although it is less severe, it has a clinical presentation similar to that of influenza A. Influenza B is more common in children and young adults and may cause severe illness in the elderly. Influenza B does not have subtypes and may cause epidemics but not pandemics.

Both influenza A and B are further classified as strains. These strains change and replace older strains because of an antigenic change called an *antigenic drift*. Previous antibody protection obtained from other viruses or vaccines may not provide protection from the new strains. This contributes to the survival of influenza in the community and its ability to infect humans and others.

in short periods of time than with any other infectious disease.

Influenza outbreaks can be epidemic or pandemic. An epidemic occurs when the influenza is confined to a specific location, such as a city or country. They have a typical pattern and begin suddenly and peak within two to three weeks. These outbreaks will last five to six weeks. A *herald wave* will mark the end of the influenza epidemic that season. The herald wave is a short spike of new cases of influenza caused by a new strain. This wave may be a predictor of the predominant strain for the next influenza season.

Pandemics are more severe and rapidly involve all parts of the world. The occurrence of a pandemic is not predictable, and its interval will vary. The general population will not have immunity to this virus because it is a new subtype of influenza A that has never circulated among the population or has not spread in many years. Influenza pandemics greatly affect healthy

The changes that occur to the virus involve the two surface proteins HA and NA. These changes may be minor or major and are called antigenic drift or shift, respectively. An antigenic drift, or a small change, can occur gradually over a year to a few years. The change in the virus may be with the HA protein, NA protein, or both. When a person contracts influenza, the body begins to make antibodies that do not completely reduce the effect of the virus, allowing the virus to make amino acid changes in one or more of the five major antigenic sites on the HA molecule. Immunologic selection occurs, and the new virus strain takes the place of the previous strain. There is less information on how NA protein changes occur, but they are believed to follow a similar process. After a new subtype appears, a drift usually occurs less frequently. New variants will appear at an increased rate as the end of an era nears.

Major changes are called antigenic shifts and are frequently the prelude to a pandemic. The change is abrupt, with an alteration in the HA protein or both HA and NA protein that humans have not been exposed to for numerous years. Immunity increases in the population, which then makes drift more possible, and, after 10 to 30 years of different variants circulating, the conditions are again favorable for the development of a new virus subtype resulting in a new pandemic. The rise of a new pandemic has the attention of everyone and is a topic of extreme interest because of its potential for high mortality. The suggested explanation for the origin has three features: the virus has a segmented genome, the pandemic occurs only with influenza A viruses, and influenza A viruses and not other viruses have a vast genetic diversity in animals.

There are two proposed mechanisms by which avian viruses break the boundaries and cause interspecies transmission. One suggestion is that there is a reshuffling between the avian viruses and human viruses. To facilitate the reshuffling, there would need to be a third species that can contract both the avian and human viruses. Pigs meet these criteria. New pandemics often arise in the Far East where humans, pigs, and aquatic fowl live in close proximity, making this theory attrac-

tive. The second mechanism involves a direct change to the human host. This is facilitated by the transmission of the virus from the pig. The pig contracts the avian virus, and the receptor specificity evolves to a more mammalian type. Although this is supported by the 1918 Spanish flu, thought to be a swine influenza A flu directly introduced into humans, this type of event is rare.

Obviously, there is concern that a new pandemic will occur with a new virus or reemerging virus, but the observations in humans is that we are limited to the H1, H2, and H3 subtypes of HA and to the N1, N2, and possibly N8 of subtype NA, and there are limitations to the development of this new virus subtype. The recent outbreak in Hong Kong of H5N1 raises concerns about the possibility of this pandemic virus. The outbreak was of avian origin, but it seemed to be localized, and person-to-person transmission cannot be clearly proven. It could have been transmitted by a large number of infected birds. Even though this virus could have spread rapidly, it did not; although the possibility of these viruses fitting the right profile to become a pandemic is still a concern. We may not be able to predict the next pandemic, but planning is still in progress to prepare for such a horrific event.

Influenza illnesses typically occur during the winter

Table 1
Stages of a pandemic

Phases	Description
INTERPANDEMIC	
1	No new influenza virus subtype identified in humans; an influenza that has infected humans previously is present in animals; the risk of transmission to humans is thought to be low.
2	No new influenza in humans, but the circulating animal influenza has a high risk of causing human illness.
PANDEMIC ALERT PERIOD	
3	A new virus subtype causing human infection has been identified; no person-to-person transmission except rarely due to a close contact.
4	Person-to-person transmission occurs in small clusters and is highly localized; the virus may not be well adapted to humans.
5	Larger clusters of person-to-person transmission, but virus remains localized; increased adaptation to humans.
PANDEMIC PERIOD	
6	Elevated and consistent transmission exists in the general population.
Source: Adapted from www.cdc.gov/flu/avian/gen-info/pandemics.htm	

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months in the northern (October-April) and southern (May-September) hemispheres, except for the tropics, where they can occur year-round. The virus is spread through coughing and sneezing by the infected person. Its incubation period is usually one to four days, and adults can be infectious the day before the symptoms begin. Children can be infectious for up to 10 days and may shed virus several days before signs of illness. Virus may be shed for weeks to months in the immunocompromised. Children are the most susceptible to infection with influenza, but complications are highest among the elderly and patients with chronic diseases involving the pulmonary and cardiovascular systems. Other high-risk populations include immunosuppressed patients and those with diabetes who may suffer additional complications from influenza.

Influenza is characterized by a rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Children may also have nausea, vomiting, and otitis media. In severe cases, rhabdomyolysis, encephalitis, pneumonia, and toxic shock may occur. Influenza is most severe in patients who are in the second or third trimester of pregnancy and in the immunocompromised. Assessment of the patient is very important, as diseases such as meningitis, sepsis, and epiglottitis should be ruled out. In most people, the illness will resolve in three to seven days. Cough and fatigue may be present for two or more weeks, and patients with chronic illnesses may develop complica-

tions from contracting the flu. The risk of complications is the greatest in patients older than 65, children up to four years old, and those with underlying health problems. In the United States, approximately 150,000 people are hospitalized with influenza annually. Death is most common in the elderly and patients with chronic conditions and is uncommon in children with and without a chronic illness.

Every year, 500 million people around the world contract influenza. The estimated total healthcare costs contributed to influenza are around \$15 billion. The majority of the financial burden comes from indirect costs of lost productivity at work and school. Governments recognized that influenza was killing several thousands worldwide and tried to keep accurate records, asking their public health agencies to take charge of controlling epidemics and determining their cause. In general, influenza contributes to five to six days of restricted activity, up to four days of bed rest, and three days lost from work or school. Influenza reduces the productivity at work for adults and will reduce the level of independent living in the elderly.

Treatment

Practicing good hygiene and common sense can help prevent the spread of communicable diseases, including influenza. Unfortunately, hand washing is not as prevalent as it should be: A telephone survey conducted in 2005 revealed that only 32% of American adults

Table 2

Antiviral agents used in influenza treatment

Drug	Virus target	Dosage and treatment duration for adults	Precautions	Side effects
Amantadine	Influenza A	200 mg p.o. daily as single or divided dose; continue for 3-5 days, or 24-48 hours after symptoms resolve	Reduce dose in elderly, renal impaired, and those taking CNS medications; use cautiously in seizure disorders	CNS and GI symptoms
Rimantadine	Influenza A	100 mg p.o. twice daily for 5-7 days, or 24-48 hours after symptoms resolve	Reduce dose in elderly, severe renal/hepatic impairment; use cautiously in seizure disorders	CNS and GI symptoms
Oseltamivir	Influenza A & B	75 mg p.o. twice daily for 5 days	Reduce dose in renal impairment; has not been studied in patients with hepatic impairment	GI symptoms
Zanamivir	Influenza A & B	Two oral inhalations (one inhalation = one 5-mg blister) twice daily for 5 days	Use cautiously in underlying airway disease; has not been studied in patient with hepatic impairment	Bronchospasm in patients with asthma or COPD

CNS = central nervous system; GI = gastrointestinal; COPD = chronic obstructive pulmonary disease

Source: Adapted from *American Family Physician*, 2004

admitted to washing their hands after coughing or sneezing. Covering the mouth and nose when coughing or sneezing and hand washing for 15 to 20 seconds with either soap and warm water or an alcohol-based hand sanitizer are simple ways to limit the spread of infection.

Updated recommendations for influenza prevention are published annually. The revised guidelines for the 2005 influenza season, published by the Advisory Committee on Immunization Practices (ACIP), recommend that the following groups receive the influenza vaccination in 2005: any persons at risk for influenza-related complications, which include persons age six to 23 months and 65 years or above, pregnant women in all trimesters, and persons with chronic medical conditions such as diabetes or asthma; persons aged 50 to 64, as this group is at increased risk for certain chronic conditions; and persons who care for or live with other persons at high risk. The evidence that the influenza vaccine prevents mortality is so strong, that health institutions are looking at ways to increase the vaccination rate of their employees, including consideration of mandating the vaccine. Although most vaccinations are given in October and November, flu vaccine may be given as early as September and at any time during the flu season if vaccine is available. Immune response against the flu peaks approximately two weeks after vaccination.

The strains included in the influenza vaccine are determined annually based on global surveillance activity of circulating flu strains. Coordinated by the World Health Organization (WHO), the monitoring network consists of Influenza Centers and WHO laboratories in 83 countries detecting trends in emerging virus strains. During the first few months of each year, the Food & Drug Administration, WHO, and the Centers for Disease Control & Prevention collaborate to determine the antigenic composition of the flu vaccine to be used for the next flu season. The influenza vaccine produced is a trivalent, inactivated vaccine. Each vaccine is composed of three strains (two influenza A and one influenza B). The live viral strains are killed during the manufacturing process, making them inactive and, therefore, reducing the risk of causing flu symptoms in people receiving the vaccine. Although the viral strains for the vaccine are chosen more than six months prior to the start of the influenza season, the vaccine covers the circulating flu strains approximately 90% of the time.

Certain patients may be eligible for influenza vaccination by the live, attenuated influenza vaccine (LAIV). LAIV is available as FluMist in the United States. The viral antigenic composition is identical to the tradition-

al vaccine; however, this vaccine is administered by intranasal actuation rather than by intramuscular injection. LAIV is approved for administration to healthy persons aged five to 49 who are not close contacts or family members of immunocompromised patients requiring a protective environment. Should there be a shortage of inactivated vaccine, it is recommended that LAIV be administered to those eligible to receive it, thus saving inactivated vaccine doses for those at highest risk. LAIV is more costly than the inactivated vaccine.

Both vaccines are cultured in egg; therefore, care must be taken to assess prospective persons for anaphylactic hypersensitivity to eggs. Contrary to popular belief, neither form of the influenza vaccine causes influenza, although an underlying respiratory illness can develop following vaccination. The adverse-event profiles of the vaccines are reflective of their different routes of administration. In patients receiving LAIV, runny nose, headache, and sore throat are common. Vaccination site soreness is the most frequent adverse effect of the inactivated virus, reported in up to 64% of patients. Fever, malaise, and myalgia can also occur. Guillain-Barré syndrome, a rare, but serious demyelinating nerve disease, has been reported following influenza vaccination (risk of one additional case/one million persons vaccinated).

There are four antiviral agents available in the United States for the treatment of uncomplicated influenza: rimantadine, amantadine, zanamivir (Relenza), and oseltamivir (TamiFlu). All but zanamivir are approved for influenza prevention as well. The efficacy of each agent has been studied alone against placebo, and all were studied in otherwise healthy adults. Therapeutic success of these agents is dependent on initiation of treatment within two days of symptom onset (within 40 hours for oseltamivir). Therefore, accurate and rapid diagnosis is essential. Rapid diagnostic tests are available for commercial use, though they should be used with caution because of the products' varied sensitivities and specificities. The point-of-care tests include ZymeTx Inc.'s ZstatFlu and the FLU OIA influenza tests. Larger studies must be conducted to look at the cost benefit of these tests in identifying influenza from other diagnoses. Viral culture is most reliable and should be used to confirm a negative test, especially if warranted by clinical symptoms.

Rimantadine and amantadine are approved in adults and children over one year of age for the prevention and treatment of influenza A only. They inhibit viral replication by blocking the uncoating of the virus particle within the host cell. In treatment, both drugs shorten the duration of fever by one day. For prophylaxis, amantadine was shown to be 61% effective and

rimantadine 72% effective in preventing influenza A, though rimantadine failed to reach statistical significance. Perhaps because of its ability to achieve higher concentrations in the respiratory mucosa at lower doses, rimantadine causes fewer central nervous system (CNS) side effects (dizziness, anxiety, and insomnia) than amantadine. For this reason, amantadine should be used cautiously in patients on concomitant CNS therapy. Both drugs should be dose-adjusted in the elderly, and amantadine should be dose-adjusted in patients with renal impairment. Both drugs are classified under Pregnancy Category C.

Oseltamivir and zanamivir were approved in 1999 and have activity against both influenza A and B. Oseltamivir is approved for prophylaxis in persons 13 years or older and for treatment of influenza in persons one year and older. Zanamivir is approved for treatment of influenza in persons seven years and older, although it has been shown to have similar effectiveness to oseltamivir in preventing influenza (zanamivir, 84%; oseltamivir, 82%). These agents work by selectively inhibiting the viral neuraminidase enzyme, thus preventing the spread of virus throughout the respiratory tract. Both agents reduce the duration of influenza-associated symptoms by about one day. The most common adverse effects reported during oseltamivir use are nausea and vomiting (~10%, higher among pediatric patients). Zanamivir is available only as a powdered inhalation. Although the adverse-effect profile of inhaled zanamivir is similar to that of a placebo inhaler, it is not recommended for use in patients with airway disease. Both drugs are listed under Pregnancy Category C.

Avian influenza

While most individuals are familiar with the risk of the human influenza virus and how it affects society, the media continue to attempt to educate the public on the avian influenza or "bird flu" as it is more commonly referred to recently. This virus, which continues to spark public concern, is believed to be related to our yearly recognized strains of influenza A. As the name states, this infection is derived from birds, as all influenza A types are believed to be. While the virus' origin resides in birds, this flu has also been noted to infect other animals such as horses, pigs, and other domestic animals. A few of these animal strains are believed to have mutated enough to cause outbreaks in humans.

It has been speculated that the current avian influenza A (H5N1) has been associated with multiple influenza pandemics in the past. This theory has been supported by the analysis of past influenza disease outbreaks. This avian strain was first identified in humans in 1997 in Hong Kong, having similar markers to a prior strain (H1N1) seen in North China in 1977, and was the strain identified as the cause of the 1950 influenza epidemic. Yet the historic connection with the most impact has been the proclamation that the 1918-1919 pandemic was a mutated avian strain that effortlessly infected humans directly, resulting in more than 20 million deaths. This pandemic precipitated the investigation of viral research with the goal of preventing future influenza devastation.

As noted above, in order to better understand this viral transition, scientists have classified viral subtypes based on the mutations of two viral surface proteins, HA and NA, in addition to a third group of proteins in the polymerase complex (PB1, PB2, and others). There are more than 15 different HA and nine NA subtypes that provide multiple combinations, all of which can be found in birds. These variations of the surface glycoproteins alter the virulence of the strain as well as provide a genetic tracking system for scientists to follow. The neuraminidase protein is the viral enzyme necessary to dissolve neuraminic acid, which is present in human mucus. The HA viral surface glycoprotein is involved in providing attachment to its host cell for cell entry. There has been a concern that if this glycoprotein mutates, the current H5N1 strain could gain a greater affinity for humans versus its current avian hosts. This transformation from primarily avian transmission to direct human-to-human transmission has scientists speculating how this could potentially occur.

One proposed method might be through a "mixing vector" or in simpler terms an animal that could acquire both the "human influenza" as well as the avian strain of influenza. Then, just as we see occur with bacterial resistance, the viral strains could share genetic information resulting in genetic reassortment. This could result in a strain that, once acquired by a human, could be contracted by human-to-human transmission. Prior documentation of previous outbreaks has identified the particular strains of H5, H7, and H9 avian influenza to be more pathogenic for humans. More recently, as the research communi-



ty received more political pressure, Terrence Tumpey, senior microbiologist at CDC's Influenza Branch, and his colleagues used genetic techniques to recreate the 1918 influenza virus in their laboratory. The animal models developed from his recreated laboratory viral strain have provided more insight into the pathogenesis of this virus. This research stated that the virulence of this strain was no longer limited to the HA protein but now involved the NA protein as well. Mutations on this surface glycoprotein also affect transmission and severity of symptoms.

While a review of history revealed only 10 influenza A pandemics over the past 300 years, the identification of the current avian strain as an H5N1 has placed the scientific community on alert. An additional concern has also been recognized. Perhaps the number of avian influenza strains infecting humans is not accurate. The current number of avian infections documented may not be a true representation but just a subset of the more pathogenic strains identified. In this case, each time a human is infected with an avian strain, the risk of its mutation within the patient could place others at risk for future human-to-human transmission and a new pandemic.

Environmental transmission remains a concern, as the H5N1 virus has been able to use its hosts to transcend species. Water contamination is the primary mode of transmission between waterfowl, such as ducks, and other animals. This virus is spread from contact with the feces and respiratory secretions of infected animals, which can survive in the environment for up to six days and potentially as long as months given the right temperature and humidity. The majority of human viral transmission at the current time has been by viral droplets inhaled or directly inoculated into the eyes or upper respiratory tract during the handling of mainly live poultry. However, there have been a few reports of potential person-to-person transmission from patients to family caretakers described in case reports. These cases involved significant exposure to the ill patient and potentially their secretions or feces without any precautions.

It should be noted that the disease did not continue past the second human infection and identification of a potential predisposing genetic component has not been explored. Testing of other healthcare workers has identified a few asymptomatic cases with a seroconversion rate of approximately 3% following viral exposure, thus reducing the concern of nosocomial transmission at the present time. Of greater concern are the mobility of humans and the expansion of the poultry industry. These factors could allow an avian pathogenic strain a greater mode of transmission to those previously not

exposed to high-risk environments. Along with the new environment comes the increased risk of contaminated water from the infected species, which would serve as an additional reservoir.

Once a person has been exposed to the H5N1 influenza virus, the incubation period, which represents the time from viral exposure to development of symptoms, may be as short as two to four days. However, multiple cases have provided reports of symptoms not occurring for as long as eight days after exposure and, in rare cases, for as long as 17 days. The patient presenting after more than eight days should be evaluated for possible secondary environmental exposure rather than direct exposure. Common symptoms include a fever, acute rhinitis, conjunctivitis, and sore throat, as well as gastrointestinal tract and lower respiratory tract symptoms. The GI symptoms, which may present up to a week prior to the respiratory symptoms, tend to be vomiting, abdominal pain, and watery diarrhea without blood.

Respiratory tract symptoms are often the most revealing. In less virulent strains of influenza, particular host enzymes located in the upper respiratory tract must be present to allow viral replication to occur, thus limiting the human virus to this area in healthy individuals. Yet, this more virulent strain allows multiple enzymes to cleave the precursors of the HA surface glycoprotein, resulting in active viral particles. Without this previous enzyme location limitation, the H5N1 viral strain is no longer restricted to the upper respiratory tract but allows effective replication in the lower respiratory tract, resulting in extensive damage. As a result, a patient can present early in the infection with shortness of breath, potentially progressing within days to respiratory failure and adult respiratory distress syndrome. Most patients require mechanical ventilation to sustain their oxygen levels. Systemic involvement is common, as documented by identification of both virus and RNA in the blood and cerebral spinal fluid in addition to physical manifestations.

Multisystem organ failure often involves acute tubular necrosis and liver necrosis. In some cases, the patients developed encephalitis, cardiac complications, pneumothorax, and pancytopenia, as well as secondary bacterial infections involving sepsis. The overall mortality rate for persons infected with the H5N1 strain is currently approximately 70% for most outbreaks. While the rate of infection is greatest for younger healthier patients, the mortality has varied depending upon the strain. The rate is often greater for those under 13 years of age or for the older population.

The most sensitive and specific means of detection of the H5N1 influenza strain is by reverse transcrip-

tase polymerase chain reaction (RT-PCR) using respiratory specimens. Use of specimens from the lower respiratory tract have not been studied but would potentially provide an enhanced site for viral testing, as viral replication would be extensive. Stool specimens are a great source of viral identification, since the GI tract is also a primary location for viral replication. Blood work reveals significant reductions in lymphocytes as well as platelet counts. As seen with the standard disease processes involving the kidneys and liver, there will be increases in the creatinine and liver function test numbers.

Our most effective means of controlling the avian influenza at the current time is surveillance and infection control. The goal is to identify those individuals who are at risk for contracting the avian influenza and start treatment as soon as possible. When attempting to recognize those individuals who should receive possible treatment for H5N1, the time period of high suspicion should be between seven and 14 days prior to symptom onset. If these individuals have been exposed to domestic fowl, wild birds, or domestic ducks within a one-meter radius or have been within speaking radius of an infected individual (either confirmed or suspected), treatment should be started. Other high-risk populations include those who work with domestic fowl either in the food processing or sales and healthcare workers and laboratory workers.

Patients infected with the virus currently have limited treatment options with minimal treatment response. Amantadine and rimantadine are believed to be ineffective because of resistance that was identified in a prior 2004 H5N1 outbreak. The neuraminidase inhibitor oseltamivir has been shown to be of some potential benefit if started early in the course of infection, making it the only drug available for use in both prophylaxis and treatment. Any patient suspected of being exposed or infected should be started on oseltamivir while infection is being confirmed or ruled out. The dose and duration are still being evaluated for treatment as well as prophylaxis against this virus. Oseltamivir is being used for prophylaxis at a dose of 75 mg daily for seven to 14 days. The treatment dose, which is routinely 75 mg twice a day for treatment of human influenza, should be 150 mg twice daily for at least seven to 10 days, depending upon the severity.

Even with the elevated dose, there is a concern of the risk of drug resistance developing. This resistance can occur with a single mutation of the neuraminidase protein and has unfortunately already been seen in some H5N1 strains. The need for this drug in Asian countries has resulted in a discussion between Taiwan and the drug manufacturer of a potential break in patent law to

get production up to meet the necessary stockpile needed in these countries.

Steroids have been used to attempt to decrease the inflammatory response prevalent in this disease. Recent research has reported that this virus can trigger a cytokine inflammatory response 10 times that routinely seen with the human influenza. These cytokines, produced by the human immune response, are thought to be responsible for assisting in the resulting lung damage identified on autopsy in the victims of this disease and, potentially, the lymphopenia observed. However, to date, steroids have not been proven to bestow additional survival benefit.

Other medications under investigation for use in H5N1 influenza are zanamivir; peramivir, an investigational neuraminidase inhibitor; ribavirin; and interferon alfa. The most effective means of controlling this disease is still a possible vaccine, which is under investigation at the current time. An investigational vaccine called RD-3 is under study in Europe.

In addition to the treatment of symptomatic patients, precautions are necessary to protect those who may be exposed in healthcare facilities or by household contacts and traveling. In healthcare facilities, universal precautions and masks should be used to prevent infectious exposure. Patients should be placed in individual negative pressure rooms. If possible, the number of healthcare providers having access to the patient as well as the number of visitors should be limited. Providers with high exposure may consider oseltamivir 75 mg daily for seven to 10 days as prophylaxis. Household contacts should use proper hand-washing techniques and avoid face-to-face contact and sharing utensils. As above, the exposed individual may consider oseltamivir 75 mg daily for seven to 10 days as prophylaxis. If exposure does occur, twice-daily temperature checks should be done as well as monitoring for symptoms after day seven. If traveling, individuals should receive the trivalent human influenza vaccine two weeks prior to traveling, avoid direct contact with animals, use hand hygiene, and seek medical attention for any fever or symptoms.

Conclusion

Influenza is a devastating illness with significant emotional and economic impact. It is important to understand the impact of this illness and the steps to prevent and treat influenza. Influenza and avian influenza are related and most likely derived from birds. There are risks with both, especially to the very young and old, and proper hand washing and infection control are your best protection. The flu vaccine has also proven to significantly reduce the mortality of influenza.

Medications for both avian flu and influenza must be initiated as early as possible to prevent mortality.

A pharmacist can play a key role in the education of patients on proper hand washing and receiving the influenza vaccine. In several states, pharmacists have developed their own flu vaccine program in an effort to make vaccination more accessible to the public. The pharmacist should also be prepared to educate patients

on the medication therapy available to patients with these illnesses. This includes the proper use of the medication along with the adverse effects associated with the treatment.

References are available upon request.

Key reference: Centers for Disease Control & Prevention. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Reports* 2005; 54 (no. RR-8): 1-40.

TEST QUESTIONS

Write your answers on the answer form appearing on page 74 (photocopies of the answer form are acceptable) or on a separate sheet of paper. Mark the most appropriate answer.

- Which of the following statements is true?
 - Influenza confers permanent immunity.
 - Mortality from influenza ranges from 1% to 20%.
 - The pandemic of 1918 was the Russian flu.
 - The most susceptible patients are the elderly.
- An influenza outbreak peaks in:
 - One week
 - Five to six weeks
 - Two to three weeks
 - One month
- Which of the following statements is true?
 - Epidemics are outbreaks that occur worldwide, and pandemics are confined to a specific location.
 - Influenza B may cause a pandemic.
 - Epidemics are localized outbreaks, and pandemics are more severe, involving all parts of the world.
 - A pandemic has a shorter duration than an epidemic.
- Influenza A:
 - May affect only birds
 - May affect humans, birds, pigs, and other animals
 - Is the least severe influenza
 - Does not have subtypes
- The major alteration in the HA protein or the NA protein that may precede a pandemic is:
 - Antigenic drift
 - Epidemic
 - Subtype change
 - Antigenic shift
- Which two proteins are involved in antigenic shift and drift?
 - Hemagglutinin and neuraminidase
 - Matrix protein and neuraminidase
 - Polymerase complex and hemagglutinin
 - Matrix protein and hemagglutinin
- Which of the following is *not* a feature required for a new pandemic to occur?
 - The virus has a segmented genome.
 - An antigenic drift has occurred.
 - It occurs with influenza A viruses.
 - Influenza A has a large genetic diversity only in animals.
- For which of the following age groups is LAIV approved?
 - Six to 23 months
 - 24 months to five years
 - Five to 49 years
 - 50 years and older
- Immune response to flu vaccine reaches its peak in:
 - Two hours
 - Two days
 - Two weeks
 - Two months
- What is the pregnancy category for the antiviral agents used to prevent and treat influenza?
 - Category A
 - Category B
 - Category C
 - Category X
- Which drug used to treat influenza is available only as an inhalation?
 - Amantadine
 - Rimantadine
 - Oseltamivir
 - Zanamivir
- Which adverse effect is most commonly reported in patients receiving the inactivated flu vaccine?
 - Myalgia
 - Injection site soreness
 - Fever
- Nausea and vomiting are the most common adverse effects reported for:
 - Amantadine
 - Rimantadine
 - Oseltamivir
 - Zanamivir
- It is recommended that the antiviral influenza agents be taken within what time after symptom onset?
 - Two hours
 - Two days
 - Three days
 - Four days
- There have been confirmed cases of avian influenza by person-to-person transmission.
 - True
 - False
- What is the current mortality rate for infection with avian influenza (H5N1)?
 - 40%
 - 50%
 - 60%
 - 70%

TEST QUESTIONS

- 17.** One of the most distinguishing symptoms of avian influenza is:
 a. Fever
 b. Watery diarrhea with blood
 c. Lower respiratory tract pneumonia
 d. Rhinitis
- 18.** The current dosing recommendation for oseltamivir for someone with symptoms of avian influenza is:
 a. 75 mg daily
 b. 75 mg twice a day
 c. 150 mg daily
 d. 150 mg twice a day
- 19.** The current dosing recommendation for oseltamivir for healthcare workers who would like to use prophylaxis prior to extensive exposure to someone with avian influenza is:
 a. 75 mg daily
 b. 75 mg twice a day
 c. 150 mg daily
 d. 150 mg twice a day
- 20.** When traveling to an area where avian influenza can be found, how far in advance should you receive the trivalent human influenza vaccine?
 a. One week
 b. Two weeks
 c. Three weeks
 d. Four weeks

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	Strongly Agree	Agree	Disagree	Strongly Disagree
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ANSWER FORM

INFLUENZA AND AVIAN FLU

DECEMBER 12, 2005 012-999-05-260-HO1

Test questions start on preceding page

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|-----------------------|-----------------------|------------------------|------------------------|------------------------|
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| 3. a. b. c. d. | 7. a. b. c. d. | 11. a. b. c. d. | 15. a. b. | 19. a. b. c. d. |
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