

# Influenza: A Comprehensive Review

## Faculty

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## Faculty Disclosure

Contributing faculty, Elizabeth T. Murane, PHN, BSN, MA, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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## Division Planner Disclosure

The division planner has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

## Audience

This course is designed for dental professionals to facilitate an understanding of influenza and their role in its prevention.

## Accreditation

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### **Disclosure Statement**

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### **Course Objective**

The purpose of this course is to help healthcare professionals understand the burden of influenza on their patients and their community. Information will be included to help healthcare professionals accept the importance of influenza vaccine in lessening the impact of the disease on their patients, preventing complications and hospitalizations, and saving healthcare dollars. Manufacture, side effects, effectiveness, storage and administration of the vaccine will be discussed. Guidelines on distinguishing influenza from influenza-like illnesses, especially those that could be used as biological weapons, will be provided. This course will also focus on the concern about avian influenza and the expected influenza pandemic.

### **Learning Objectives**

*Upon completion of this course, you should be able to:*

1. Articulate the burden influenza has on the community.
2. Explain the types of influenza viruses, including the H and N designations.
3. Describe the symptoms and transmission of influenza.
4. Distinguish between influenza and influenza-like illnesses.
5. Identify complications of influenza.
6. Articulate the effectiveness and importance of the influenza vaccines.
7. Implement a system to increase vaccine administration to vulnerable patients.
8. Describe the best method of hand hygiene and the significance of handwashing.
9. Explain ways of protecting against influenza.
10. List the current antiviral medications available and their use.
11. Teach family members how to care for people with the flu, including interventions for non-English proficient patients and caregivers.
12. Identify the significance of avian and swine influenza.
13. Articulate methods to decrease the impact of avian influenza.
14. Describe plans for coping with an influenza pandemic.



Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

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## INTRODUCTION

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Influenza is a disease that is often accepted as “a part of life.” While considered bothersome, it is not perceived to be a “serious” disease. However, new diseases, such as Sudden Acute Respiratory Syndrome (SARS), make headlines because of hospitalizations and fatalities. Much effort and money is expended to contain or find a way to prevent new diseases like SARS but little notice is given to the fact that in the United States, influenza and pneumonia hospitalize more than 100,000 people and cause an average of 36,000 deaths each year. In 2003, these diseases cost more than \$12 billion. Ten percent of the cost is due to medical expenses and 90% is in lost production. The pain and suffering caused by influenza is not considered when discussing costs [1]. Large amounts of time, energy and money will be spent to find a vaccine against SARS while the flu vaccine, though not perfect, is markedly underused. “Influenza and pneumonia will continue to be our leading infectious disease killer even after the full arrival of West Nile Virus or SARS” [2].

In 2001, pneumonia/influenza was listed as one of the top 10 causes of death in all age groups, except for children less than one year of age. As the cause of death, pneumonia/influenza ranked sixth in children 1 to 4 years of age, seventh in those 5 to 9 years of age, and ninth in youths 10 to 19 years of age. When all age groupings were combined, pneumonia/influenza ranked seventh as a leading cause of death ahead of Alzheimer’s disease, nephritis, and septicemia (8th, 9th and 10th, respectively). Influenza is the only communicable disease still listed as a leading cause of death in the U.S. [3]. The CDC provides information on adult mortality using data from 1999–2004, and influenza/pneumonia continue to be the seventh leading cause of death, ahead of Alzheimer’s disease, kidney disease, and suicide [92].

The reader should note that the use of “influenza” in this course refers to the specific definition, which is respiratory illness with fever and not to gastroenteritis with nausea, vomiting and/or diarrhea.

Influenza is a highly infectious viral illness occurring in winter months (October to March) in temperate climates north of the equator. In the United States, “flu season” usually begins in November, peaks in late December or January, and is basically over in March. However, as in 2003, earlier outbreaks in October can also occur and peak activity may continue as late as March. Surveillance conducted by the CDC of laboratories and outpatient facilities in 2005–2006 showed that all regions of the United States had similar patterns of influenza and all peaked the end of February and beginning of March [93].

Because it takes two weeks to develop the immunity provided by the flu vaccine, most campaigns to immunize the population occur from the middle of October through November. However, immunization through December and early January is encouraged for those who were not vaccinated earlier. Persons of any age with chronic conditions that increase their risk of complications from influenza should be immunized as early as September.

All age groups are susceptible to influenza, but children have the highest infection rate. Rates of serious illness and death are higher among those who are 65 years of age and older with medical conditions that place them at increased risk for complications from influenza. Approximately 90% of the 36,000 annual fatalities resulting from influenza occur in those who are 65 years of age or older. However, in 2003 much media attention was directed to the 143 nationwide fatalities among children. Sadly, only 4% of those children had received the influenza vaccine [1; 4]. In subsequent years, there have been fewer influenza-related pediatric deaths. Between October 2005 and June 2006, 41 child deaths in the United States were influenza-related [93].

The seriousness of influenza is unrecognized by the public or the media and often by the medical profession. One study reported that increasing the annual percentage of adults receiving the influenza vaccine from 37% to 90% would save 12,000 lives each year [128].

## HISTORY

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The term “influenza” originated in Italy sometime in the 15th century from an epidemic that was attributed to the “influence of the stars.” In 1580, there was a worldwide epidemic that, from written description, was most likely caused by the influenza virus. Several other pandemics have occurred throughout the centuries. The most famous of these pandemics, the “Spanish flu,” occurred for 10 months in 1918–1919, and resulted in an estimated 21 million deaths worldwide, with approximately 500,000 of these deaths in the United States [1]. Other more recent pandemics include the “Asian flu” (1957), “Hong Kong flu” (1968) and the “Swine flu” (1976).

Influenza A and B are the two virus types that cause the disease in humans. Influenza A virus was first isolated in 1933 by Smith, Andrews, and Laidlaw in ferrets. In 1936, influenza B virus was isolated by Francis. Swine influenza viruses (closely related to human influenza viruses) were isolated in 1930 [5]. In that same decade researchers discovered that influenza virus could be grown in embryonated chicken eggs. These discoveries led to the development of inactivated (killed) vaccines [1].

For many years, the proposed influenza epicenter has been thought to be Southeast Asia. Farming practices there bring pigs, fowl, and people into close contact, allowing swine, avian, and human flu viruses to mix. The cycle is thought to be birds to pigs to humans. Now it is clear that this cycle can occur any place in the world where there is the domestication of animals [5].

## INFLUENZA VIRUS

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### INFLUENZA VIRUS TYPES

Influenza belongs to the orthomyxovirus family and consists of a single-stranded, helically-shaped, RNA virus. There are three types of influenza viruses designated A, B and C. The differentiation is made by the type of proteins within the nucleus, specifically antigenic properties in their internal nucleocapsid and matrix proteins. The individual types have different effects on the humans who become infected.

Influenza type A is the virus that causes moderate to severe illness in all human age groups and is highly infectious, with an attack rate of 10% to 20%. It also causes influenza in pigs, birds, and other animals. There are several subtypes of influenza A.

Influenza type B generally causes milder disease. It primarily affects children but has also caused outbreaks in military camps and occasionally in long-term care facilities. It does not cause illness in animals and birds and, as a result, tends to be more stable with less antigenic change. Subtypes have not been defined for influenza B.

Influenza type C is rarely ever reported probably because any disease it causes is usually subclinical or mild. It does not affect animals and birds.

Because type A influenza virus causes more severe illness and also occurs in animal and birds, this course will focus on influenza A.

### INFLUENZA A SUBTYPES AND ANTIGENIC SHIFT

Influenza A subtypes are defined by the occurrence of the glycoproteins hemagglutinin (H) and neuraminidase (N), which are surface antigens on the virus. The hemagglutinins H1, H2, and H3 are involved in attaching the virus to cells. The neuraminidases N1 and N2 are involved in helping the virus penetrate the cell. There are 15 different subtypes of hemagglutinins and 9 different subtypes of neuraminidases leading to several possible combinations, which are indicated in the

name of the virus (H1N2, H2N3, etc.) Many combinations of the various hemagglutinin and neuraminidase antigen subtypes are possible. However, H1N1, H1N2, H2N2 and H3N2 have historically occurred in humans.

Pigs predominantly suffer from three of the same subtypes of influenza. Historically, they have not been infected by the H2N2 subtype. Wild waterfowl, in contrast, appear to acquire all influenza A subtypes. An additional difference is that the virus causes respiratory illness in humans, pigs and other mammals but infects the gastrointestinal tract in wild birds without causing disease. However, the virus is shed in the bird droppings, leading to the contamination of water supplies, barnyards, farms, fields and animal food supplies.

The genes of influenza viruses are carried on eight separate segments of ribonucleic acid (RNA) rather than on one long single molecule. This means that if two or more subtypes of influenza virus infect the same cell in a host, these viruses can exchange RNA segments during replication and create viruses with new gene combinations. This reconstruction is called “antigenic shift.” It often occurs in pigs and is the source of influenza epidemics because the human population has little immunity to the new subtype that results.

In comparison, “antigenic drift” is a slight change in a particular subtype that does not result in a new subtype but does influence the choice of the particular influenza viral subtypes for the annual influenza vaccine. Depending on the degree of antigenic drift, immunity developed to one virus may be adequate to protect against the related virus. In other situations, the drift has resulted in enough change that there is little protection.

In the past, the influenza subtypes present in birds did not directly infect humans. A different host was usually required to complete the reconstruction from an avian subtype to a subtype capable of infecting humans. This host has been the pig, which can be infected with avian, human, and swine influenza viruses. A possible scenario is that the food or water supply of the pig is contaminated by bird

feces containing a subtype or subtypes of influenza A. The pig also acquires different influenza subtypes from other pigs and/or humans. Reconstruction of the viral RNA occurs in the pig host, thus infecting other pigs. Farm workers catch the new subtype from the pigs and develop highly contagious influenza because they do not have immunity against this new subtype. Thus, a new influenza strain has been launched [5]. It is possible that reconstruction could occur in a person who acquires a strain from a bird and also has a human strain. Realignment of H and N in the person’s cells would result in a new strain. This new strain can become a pandemic if there is very little to no immunity in the human population and there is efficient, effective transmission from person to person [1].

Major pandemics of 1889–1891, 1918–1920, 1957–1958, and 1968–1969 have resulted from antigenic shifts. Characteristics of a pandemic are high attack rates in all age groups and a high mortality rate. Historically, pandemics have moved along trade routes with rapidity of spread matching available transportation methods [1]. Rapid movement of people around the world by aircraft, and fewer border restrictions by partners such as the European Union, allow new influenza subtypes to spread more quickly. However, cooperation between the World Health Organization (WHO), the Centers for Disease Control and Prevention in the United States (CDC), and the Centers for Disease Control in the European Union, which is currently being developed, will hopefully alert the population and contribute to slowing the spread of the virus. Also, minimizing the transmission of influenza virus from any of the hosts to any of the other hosts (birds, pigs, humans) will decrease the antigenic shift and lessen the development of new subtypes to which the population has not developed immunity [5].

Research has shown that work-related travel rates affect the spread of influenza more than geographical distance or air travel [94]. Based on 30 years of weekly data, influenza imported into a state with many inflows and outflows of workers, such as California, spreads much faster than if it enters a

less-connected state, such as Wyoming. Epidemics also tend to start and spread from more populated states. This information is especially important in the event of the appearance of a new virus, to which most of the population is susceptible. It usually takes 5 to 7 weeks for annual influenza disease to spread across the continent. However, if a new strain originates in a highly connected state, it would spread to all states within 2 to 4 weeks. The study also revealed that adults, not children, are responsible for the transmission of influenza across regions because they travel farther and more frequently. One proposed intervention is to limit interregional travel to slow the spread [94].

### VIRUS NAMING

The name of each influenza virus is developed following this formula [1]:

|  |        |
|--|--------|
| Virus type (A or B)  | A/     |
| Geographic origin (place where virus was first isolated)                                 | Wuhan/ |
| Strain number  | 395/   |
| Year of isolation  | 95/    |
| Virus subtype – based on combination of hemagglutinin (H) and neuraminidase (N) antigens | (H3N2) |

This was the principal virus isolated in the United States during most of the 1997–1998 influenza season.

Thus A/New Caledonia/20/99/ (H1N1) would be read influenza A, which was first isolated in New Caledonia, strain number 20, isolated in 1999, with hemagglutinin subtype 1 antigen and neuraminidase subtype 1 antigen.

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## INFLUENZA DISEASE

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A brief definition for influenza is “respiratory illness with fever.” This is a quick way for healthcare providers who are participating in the annual surveillance of influenza activity to categorize each of their patients. Approximately 1000 sentinel medical practitioners in the United States (U.S. Influenza Sentinel Provider Surveillance System) participate in providing statistics about the number of “respiratory illness with fever” cases that have been seen each week. These figures are collected weekly by designated local health departments and reported to the CDC by the corresponding state health department. The CDC compiles these figures and publishes them in the *Morbidity and Mortality Weekly Report (MMWR)*. They are also available at <http://www.cdc.gov/flu/weekly/fluactivity.htm>.

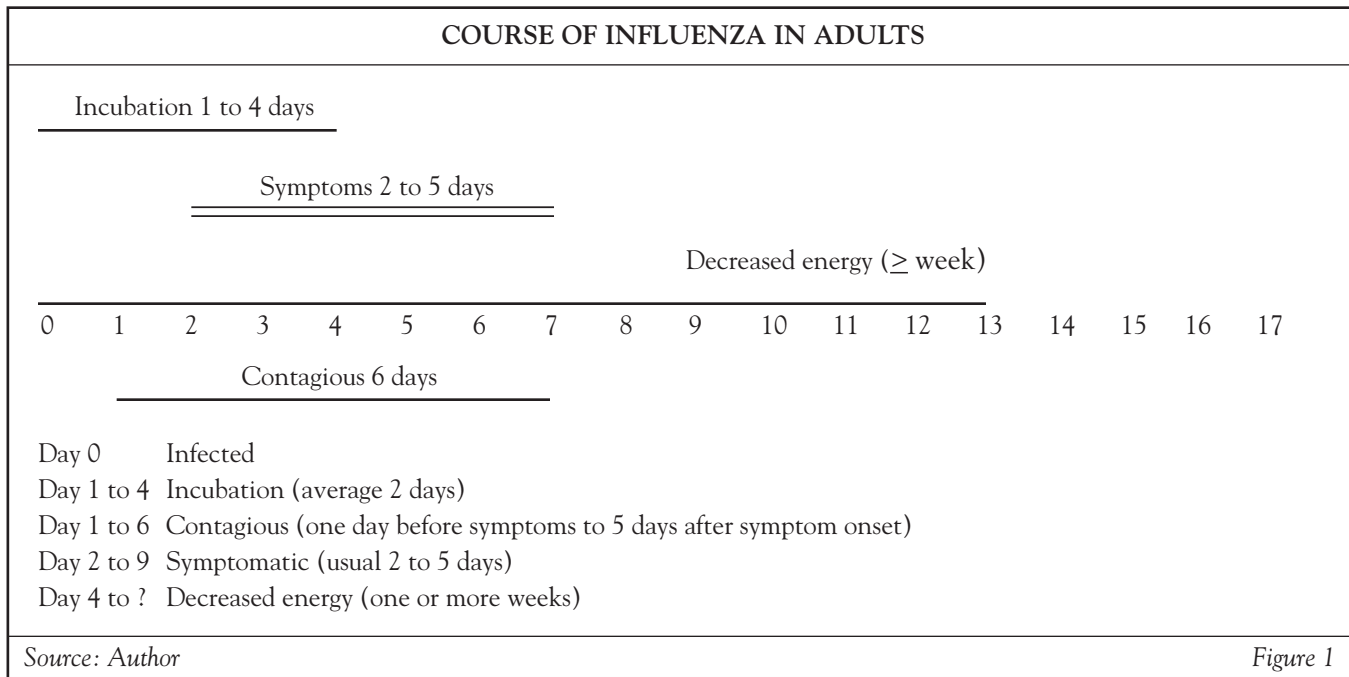
Obviously, the figures give a current view and contribute to a historical picture of influenza activity for that week. Monitoring and analyzing these figures also alerts medical professionals to changes in patterns. Any change in the historical pattern is especially important in early detection of a biological change, whether introduced naturally or by terrorist activity. Several biological agents that could be used by a terrorist first manifest their presence with flu-like symptoms.

### SYMPTOMS AND SIGNS

Uncomplicated influenza is characterized by an abrupt onset of:

- Constitutional symptoms: fever, chills, myalgia, headache, severe and persistent malaise, eye pain, light sensitivity, and substernal burning in the chest.
- Respiratory symptoms: nonproductive cough, sore throat, and rhinitis.

Initially, there are more constitutional than respiratory symptoms. If there are no complications, the chest is usually clear to auscultation.



Children may also experience any of the accompanying effects of fever, such as listlessness, irritability, anorexia, and convulsions. In addition, otitis media, nausea, vomiting, and diarrhea are frequently reported in children with influenza [6]. Pneumonia and encephalopathy are serious complications in children with influenza [7].

Elderly patients may exhibit confusion in addition to other symptoms.

The patient with influenza usually appears febrile and fatigued with hot, moist skin, a flushed face and red watery eyes. More than half of the patients infected with the influenza virus will have nasal discharge with obstruction and pharyngeal redness. Younger patients may have nontender cervical lymphadenopathy [8].

Influenza onset is so abrupt that many patients can pinpoint the hour in which they became ill. This is an important feature that helps distinguish influenza from other diseases with flu-like symptoms. The fever is generally 101 to 102 degrees F (38.3 to 39 degrees C). Children may run higher fevers. Patients may complain of body aches. Myalgia often localizes in the back muscles. These systemic symptoms usually last from 2 to 3 days and may persist as long as 5 days. Most systemic

symptoms respond to antipyretics and analgesics. It is important to remember that any medications containing aspirin should **never** be used in children or teenagers because of the risk of Reye's syndrome [1]. This will be discussed in more detail.

Uncomplicated influenza is generally a self-limiting disease. Recovery is usually rapid, but most patients experience a decrease in strength or energy for a week or more after recovery (**Figure 1**).

## TRANSMISSION

Influenza is **highly contagious**, with an attack rate of 10% to 20% from the day before symptoms begin through approximately 5 days after onset in adults. It is spread from person to person through coughing and sneezing by the infected individual. Influenza can be spread by the airborne route, which means that a person coughing in the room can transmit the virus to others in the room without close personal contact. This is in contrast to droplet transmission in which heavier particles (droplets) are transmitted to those with close contact (less than 3 to 6 feet depending on the organism). Droplet transmission also probably occurs in influenza. Airborne transmission is especially significant in congregate situations like institutions, daycare facilities, airplanes, and cruise ships [9].

As noted, the influenza virus may be transmitted between humans and pigs. More than 25 examples of transmission from pigs to humans have been documented in the medical literature [5]. It is assumed that many more undocumented cases occur in individuals who work with swine. Usually, this swine-human connection is missed because the flu seasons in both pigs and people overlap. However, this connection should not be minimized. Its influence in antigenic drift or shift and the introduction of new subtypes is important to traditional transmission patterns.

Contaminated hands are a frequent source of transmission and infection. Contagious individuals cough or sneeze into their hands and deposit virus on whatever they touch. Or, they cough the virus into the air, which settles on objects in the area. Others handle these objects and then touch their eyes, nose or mouth and are infected. Following an incubation period of 1 to 4 days (average 2 days), the individual develops symptoms. Another major factor in the spread of influenza is that it is transmitted to others before individuals even realize that they are sick [95].

Children are another source of infection, as they can be contagious for 10 or more days. In addition, young children can shed virus for up to 6 days before illness onset [6]. This is one reason to discourage the practice of kissing babies and children on the mouth.

### DIAGNOSTIC TESTS FOR INFLUENZA

Obviously, an accurate diagnosis of influenza on the basis of symptoms alone is difficult. The quickest way to decide if the patient has influenza, or some other disease, is to use a rapid diagnostic test for influenza. However, medical practitioners should be aware that false negative and false positive results do occur. Within 3 to 4 days after onset of influenza, the virus can be found from throat and/or nasopharyngeal swabs. Highest viral shedding occurs during the first 4 days of illness. Nasopharyngeal specimens generally are more accurate. There are several rapid diagnostic tests available, and these tests can usually detect the influenza virus

within 30 minutes [6]. The specimen to collect and the information provided by the results vary according to the test being used. These various rapid diagnostic tests for influenza A are 65% to 81% accurate. The accuracy rate depends on the particular rapid diagnostic test used and collection of the specimen at the optimum time [10]. Other factors that may improve the accuracy of these tests include knowledge that influenza is circulating in the community and obtaining the specimen from a patient within the first four days of illness [96]. The package insert should always be consulted as to the percentage of inaccurate results for the specific test. The rapid diagnostic test, therefore, can leave the medical practitioner with the need to base decisions about diagnosis and treatment on his or her clinical judgment [10]. Recent immunization with intramuscular (IM) influenza vaccine will not affect a rapid diagnostic test. However, intranasal vaccine will affect any serology test [11]. Not all patients with influenza symptoms require a rapid diagnostic test. They should be done only if the results will help with the diagnosis and/or influence treatment decisions [96].

Culture of the virus takes a minimum of 48 hours. Another 1 to 2 days are needed to identify the virus type. Viral culture can take as long as 10 days to complete. Obviously, these tests provide information as to the virus responsible for the illness but are not practical for individual case management. Knowing the virus or viruses responsible, however, allows more accurate planning for vaccine preparations. This information also helps evaluate the effectiveness of the formulation used in the current vaccine [1].

There are several ways that the influenza diagnosis can be confirmed:

- Rapid test
- Viral culture
- Direct fluorescent antibody
- Reverse transcriptase polymerase chain reaction
- Immunohistochemical analysis of tissues collected during autopsy

- Paired serology (comparison of antibody levels during acute and convalescent—2 to 3 weeks later—phases). Antibodies in the convalescent specimen should be at least 4 times greater than in the acute specimen to confirm influenza [11; 12].

For more information on available tests, please refer to the CDC's website at [www.cdc.gov/flu](http://www.cdc.gov/flu). Monitoring the status of influenza circulating in the community through the information provided by the CDC can also assist the practitioner in the diagnosis [96].

## INFLUENZA-LIKE ILLNESSES

Making the correct diagnosis when a patient presents with flu-like symptoms is becoming more critical. Many of the diseases that result from biological agents that might be used by terrorists initially resemble influenza. This section will discuss some clinical observations of influenza and the common cold, SARS, anthrax, brucellosis, pneumonic plague, smallpox, and tularemia. Hopefully, this discussion will increase the "suspicion index" of health practitioners, so they seek additional information when a patient presents with symptoms of the flu, such as respiratory complaints, fever, malaise, and

myalgia. By no means is the information meant to provide a practitioner with all he or she needs in making a diagnosis. The purpose of the discussion below is to highlight the importance of making a careful observation of the patient and obtaining an accurate history of the illness.

## INFLUENZA COMPARED TO THE COMMON COLD

Because both influenza and the common cold are caused by viruses that affect the respiratory tract, distinguishing between them is important. Adults rarely develop fever with a cold (coryza) but usually have a fever of 101 to 102 degrees F (38.3 to 39 degrees C) with the flu. Headaches, muscle aches, and extreme exhaustion are mild or nonexistent with a cold but are usual and severe with the flu. The prodromal signs of sneezing, runny nose, and sore throat signal that a cold is developing and may be present for one or more days before onset. These symptoms may occur with influenza but usually occur concurrently with the sudden onset rather than signaling an approaching illness. The flu develops suddenly, without warning. Like influenza, a cold may have a dry (nonproductive) cough. Some use a "rule of thumb" to distinguish between a cold, in which symptoms are from the neck up, and influenza, which is systemic (**Table 1**).

| INFLUENZA COMPARED TO COMMON COLD |                       |                |
|-----------------------------------|-----------------------|----------------|
| Clinical Presentation             | Influenza             | Common Cold    |
| Prodrome                          | None                  | 1 or more days |
| Onset                             | Sudden                | Gradual        |
| Fever                             | 101 to 102 degrees F. | Rare in adults |
| Headache                          | May be severe         | Rare           |
| Myalgia                           | Usual, often severe   | Mild           |
| Extreme exhaustion                | Usual                 | Never          |
| Tiredness/weakness                | May last >2 weeks     | Mild           |
| Sore throat                       | Common                | Often          |
| Sneezing                          | Occasionally          | Usual          |
| Rhinitis                          | Occasionally          | Usual          |
| Cough                             | Usual, nonproductive  | Mild hacking   |
| Source: Author                    |                       | Table 1        |

| INFLUENZA COMPARED TO SARS |                               |   |
|----------------------------|-------------------------------|---|
| Clinical Presentation      | Influenza                     | SARS  |
| Fever                      | 101 to 102 degrees F. or more | >100.4 degrees F.                                     |
| Chills                     | Usual, but no rigor           | With rigor  |
| Headache                   | May be severe                 | Sometimes   |
| Myalgia                    | Usual, often severe           | Sometimes   |
| Extreme exhaustion         | Usual                         | Not usually   |
| Malaise                    | Usual                         | Sometimes   |
| Cough                      | Dry, at onset                 | Dry, starts day 3 to 7                                |
| Dyspnea                    | Rare                          | Common, starts day 3 to 7                             |
| Progression                | Improves after 5 to 7 days    | Slowly worsens, severe in second week                 |
| Chest x-ray                | Normal                        | Initially normal, rapid progress to bilateral disease |
| Source: Author             |                               | Table 2   |

**INFLUENZA COMPARED TO SARS**

Sudden Acute Respiratory Syndrome associated with coronavirus (SARS-CoV) was first reported in Mainland China in February 2003. The incubation period is commonly 2 to 7 days, but can be as long as 10 days. It almost always begins with a fever greater than 100.4 degrees F (38 degrees C). The fever is usually accompanied by chills and rigor and sometimes headache, malaise, and myalgias. Initially, there may be only mild respiratory symptoms. After 3 to 7 days, the lower respiratory phase begins with a dry cough and dyspnea. The illness becomes more severe in the second week at which time a chest x-ray often reveals bilateral disease. Up to 10% to 20% of patients will progress to ventilatory failure. The estimated overall case fatality rate is 9.6%. It is greater than 50% in those older than 65 years of age. This high fatality rate is probably influenced by the presence of other chronic complicating conditions. Chronic conditions also lead to a higher case fatality rate in those older than 65 years of age with influenza [14].

In deciding between influenza and SARS, the degree of fever is too similar to be distinguishing and both exhibit chills. In SARS, the chills may be more severe with rigor. The incubation period is much longer for SARS than influenza but is rarely helpful because one does not know when incuba-

tion began. Respiratory symptoms accompany the onset of influenza. However, in SARS, respiratory symptoms initially are mild and develop 3 to 7 days after onset. A cough develops sooner in influenza and usually there is no dyspnea. The chest x-ray of a patient with influenza, or early in SARS, is usually normal. However, SARS progresses rapidly, so there are usually generalized, patchy, interstitial infiltrates on chest x-ray. The patient with influenza generally starts to improve after 5 to 7 days, but with SARS continues to deteriorate slowly until the patient becomes severely ill in the second week (Table 2).

In order to precisely discuss a disease so that all involved will be defining and reporting it the same way, a “case definition” is developed. Usually a case definition includes symptoms, contributing circumstances, and laboratory findings. A case definition will describe the disease as suspect, probable or confirmed, and give the criteria for each of these levels.

A suspect case of SARS, designated as SARS Report Under Investigation (SARS-RUI), must have 3 characteristics:

1. Fever  $\geq 100.4$  degrees F ( $\geq 38$  degrees C)
2. One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, dyspnea, hypoxia)

3. Within last 10 days before onset (contributing circumstance):  
 Travel to area with community transmission, OR  
 Close contact to someone with suspected SARS, OR  
 Employment as a healthcare worker with recent direct patient contact.

A probable case of SARS must have the following:

All of the above characteristics and:

1. Radiographic evidence of pneumonia or acute respiratory distress syndrome (ARDS), OR  
 Autopsy evidence without other explanation.

A confirmed case of SARS is based on:

1. A positive antibody titer >28 days after symptom onset.

Polymerase chain reaction (PCR) tests may also be done. A negative PCR test does not rule out SARS, as less than 50% of specimens are positive for virus RNA by PCR in the first week. The SARS coronavirus may also be isolated. However, in December 2003, the CDC decided that the results of the antibody titer would be the confirmatory evidence for the diagnosis of SARS for investigative and statistical purposes.

Some case definitions are included in this course for quick reference, to enumerate important information, to guide as to what laboratory tests are important, and to help allay some frustration.

Obviously, treatment is started long before a confirmed diagnosis of SARS is obtained, so the case definition is used as a statistical and epidemiological diagnosis. Unfortunately, no effective treatment for SARS has been found as yet. Currently, all therapy is supportive; antipyretics, fluids, rest, and respiratory support [14]. Early recognition of a case of SARS is extremely important to anyone caring for the patient because lapses in protective techniques and poor hand washing are often the rule rather than the exception.

Practitioners must decide, for each patient, whether it is influenza or perhaps SARS. One area in which there is little overlap concerns travel to a region or contact with a person from a community in which SARS is known to exist. Each influenza patient should quickly be asked if they have done any such traveling or had contact with anyone from such a community in the last 10 days before they became ill. Dyspnea in uncomplicated influenza rarely occurs, so such a symptom should be a warning that complications or other disease is present. Disease worsening after a week is another warning sign that something other than influenza is involved.

Because respiratory illnesses can be highly contagious, all healthcare professionals should be aware of the danger to their own health and take the proper personal protective precautions (mask, gloves, eye protection) and practice good hand-washing when in contact with a patient exhibiting respiratory illness with fever. Initially, transmission of the coronavirus implicated in SARS was considered to be by droplets. This required close contact for transmission. Droplet transmission is a major method by which the disease is spread. But a study published in the *New England Journal of Medicine* April 22, 2004 shows that airborne transmission is also likely [14]. Personnel involved in aerosol-generating procedures, such as intubation or suctioning, should pay close attention to protective precautions. Ideally, such procedures would only be done in negative pressure rooms. It appears that SARS patients are most contagious at the height of their symptoms; generally this is in the second week of the illness. In addition, there are “superspreaders” who have accounted for many secondary cases for unknown reasons. As a result, any healthcare worker in contact with a suspected case of SARS should have sealed eye protection, gown, gloves, and properly fitting N95 mask for all patient contact. The importance of good hand hygiene cannot be overstressed because the eyes, nose, and mouth appear to be the portals of entry. The eyes, nose, and mouth are places that hands often unconsciously touch [13].

| INFLUENZA COMPARED TO INHALATION ANTHRAX |                     |             |
|--|---------------------|-------------|
| Clinical Presentation                    | Influenza           | Anthrax     |
| Incubation                               | 1 to 4 days         | 1 to 7 days |
| Fever                                    | Yes                 | Yes         |
| Rhinitis, nasal congestion               | Some                | Rare        |
| Cough                                    | Dry                 | Mild        |
| Myalgia                                  | Usual, often severe | Yes         |
| Tiredness/weakness                       | May last >2 weeks   | Yes         |
| Nausea/vomiting                          | No                  | Sometimes   |
| Profound sweats                          | No                  | Yes         |
| Dyspnea                                  | No                  | Usual       |
| Hypoxia                                  | No                  | Usual       |
| Chest x-ray                              | Normal              | Abnormal    |
| 1 week after onset                       | Improving           | Worsening   |
| Source: Author                           |                     | Table 3     |

### INFLUENZA COMPARED TO INHALATION ANTHRAX

Anthrax is an illness caused by the bacteria *Bacillus anthracis*. It occurs in three forms in humans: cutaneous, inhalation, and intestinal. Because cutaneous and intestinal anthrax do not present with flu-like symptoms, this course will not discuss these two forms of anthrax. Following an incubation period of 1 to 7 days (usually 2 to 5 days), inhalation anthrax initially exhibits influenza-like symptoms of fever, fatigue, and cough [15]. There may be profound sweats. In rare cases, anthrax will present with rhinorrhea, but usually there is no nasal congestion. Myalgia and malaise are common. Some patients may have nausea and vomiting. All experience dyspnea and hypoxia. Untreated inhalation anthrax will always have an abnormal x-ray with mediastinal widening. Prognosis is poor once mediastinal widening occurs. X-rays earlier in the disease progression are also often abnormal, frequently with pleural effusion but rarely with infiltrates. Distinguishing anthrax from influenza is critical because early antibiotic treatment in anthrax is essential (**Table 3**).

A careful history is also important to distinguish between influenza and inhalation anthrax. Because anthrax is a progressively worsening disease, onset may be more gradual than in influenza. Can the patient indicate a set point in time when they started to feel ill? *Bacillus anthracis* spores can occur on farms, so it is important to find out the patient's occupation or if there was a recent visit to a farm or contact with farm animals, such as cattle, swine, or horses. Healthcare professionals should be aware that person-to-person transmission of anthrax has not been shown to occur. If a patient can point to a person from whom the disease was acquired, it probably is not anthrax [16].

The 1996 case definition developed by the CDC for inhalation anthrax is an illness with acute onset characterized clinically by:

- a brief prodrome resembling a viral respiratory illness,
- followed by development of hypoxia and dyspnea,
- with radiographic evidence of mediastinal widening.

| INFLUENZA COMPARED TO BRUCELLOSIS |                |             |
|-----------------------------------|----------------|-------------|
| Clinical Presentation             | Influenza      | Brucellosis |
| Onset                             | Sudden         | Insidious   |
| Fever                             | Yes            | Yes         |
| Headache                          | May be severe  | Yes         |
| Myalgia                           | Usual, in back | Generalized |
| Extreme exhaustion                | Usual          | Common      |
| Cough                             | Dry            | None        |
| Night sweats                      | No             | Yes         |
| Arthralgia                        | No             | Yes         |
| Anorexia/weight loss              | No             | Yes         |
| Source: Author                    |                | Table 4     |

Laboratory confirmation is:

1. Isolation of *Bacillus anthracis* from a clinical specimen (sputum or blood), OR
2. Anthrax electrophoretic immunotransblot (EITB) reaction to the protective antigen and/or lethal factor bands in one or more serum samples obtained after onset of symptoms, OR
3. Demonstration of *Bacillus anthracis* in a clinical specimen by immunofluorescence.

A confirmed case of inhalation anthrax is a clinically compatible case that is laboratory confirmed [17].

## INFLUENZA COMPARED TO BRUCELLOSIS

Although there are no respiratory symptoms with brucellosis, there are several common symptoms with influenza. Brucellosis is caused by *Brucella* species, a gram-negative coccobacillus. *Brucella abortus* is found in cattle, *B. suis* in pigs, *B. melitensis* in sheep and goats, *B. canis* in dogs. The incubation period is 5 to 60 days. Onset of symptoms can be insidious or sudden. Like influenza, brucellosis is characterized by fever, extreme exhaustion, headache, and generalized aching. There is arthralgia that could be confused with the myalgia of influenza, especially if the patient cannot distinguish between muscle aches and joint pain. However, brucellosis also causes symptoms such as night sweats, anorexia

and weight loss that do not accompany influenza (**Table 4**).

A confirmed case of brucellosis has the above clinical picture with laboratory isolation of *Brucella* spp. or demonstration by immunofluorescence in a clinical specimen (blood, serum, bone marrow, spleen or liver) [18].

Other factors that help to decide between influenza and brucellosis include:

- Does the patient have contact with farm animals?
- Does the patient consume unpasteurized milk or unpasteurized milk products?

## INFLUENZA COMPARED TO PNEUMONIC PLAGUE

Plague is caused by the bacteria *Yersinia pestis*, which infects animals and humans. It is found in rodents and their fleas in many areas around the world. It is endemic in mountainous areas of California. *Y. pestis* can infect various systems, leading to four clinical types of plague:

- Bubonic plague – in the lymph nodes resulting in “buboes”
- Septicemic plague – in the blood without “buboes”
- Pneumonic plague – in the lungs
- Pharyngeal plague – in the pharynx and cervical lymph nodes

| INFLUENZA COMPARED TO PNEUMONIC PLAGUE |                          |                          |
|--|--------------------------|--------------------------|
| Clinical Presentation                  | Influenza                | Pneumonic Plague         |
| Onset                                  | Sudden                   | Sudden                   |
| Fever                                  | 101 to 102 degrees F.    | Yes                      |
| Headache                               | May be severe            | Yes                      |
| Tiredness/weakness                     | May last >2 weeks        | Yes                      |
| Cough                                  | Dry                      | Productive               |
| Chest x-ray                            | Normal                   | Abnormal                 |
| Progression                            | Improving in 5 to 7 days | Worsening in 2 to 4 days |
| Source: Author                         |                          | Table 5                  |

Again, this course will only contrast influenza with primary pneumonic plague because of the initial similarity in presentation. Pneumonic plague can also occur secondary to dissemination of bubonic plague.

The incubation period for primary pneumonic plague is 1 to 6 days. The first symptoms are fever, headache, weakness, and a cough that produces bloody or watery sputum (**Table 5**). The disease, if untreated, progresses rapidly in 2 to 4 days, leading to septic shock and death. Transmission is through respiratory droplets and sputum from animals or humans with pneumonic plague. Transmission by the bite of infected fleas occurs in the other types of plague. Only pneumonic plague can be transmitted from person to person.

Unfortunately, *Y. pestis* can also be “weaponized” and intentionally released by terrorists to be inhaled by those exposed. Because the disease progresses quickly, early accurate diagnosis and treatment is essential. Several antibiotics are effective [19].

A cough producing watery or bloody sputum and an abnormal chest x-ray are indications that the patient probably does not have influenza. In addition, influenza tends to develop symptoms suddenly and then levels off until improvement occurs. Pneumonic plague has a sudden onset, but the patient’s condition worsens in 2 to 4 days. The patient should be placed in a negative pressure room. Everyone entering the room should be gowned, gloved, and masked. Clinical specimens should be collected before antibiotics are started.

A case of plague is confirmed if *Y. pestis* is isolated from a clinical specimen, or there is a fourfold or greater change in the serum antibody titer to *Y. pestis* F1 antigen.

#### INFLUENZA COMPARED TO SMALLPOX PRODROME

Smallpox is transmitted through droplets. Droplets containing the *variola* virus can be transmitted through face-to-face contact while talking, singing, coughing, or sneezing. There is no transmission of the virus during the 7 to 17 day (usual 10 to 12 days) incubation period. The prodromal period for smallpox is from 1 to 4 days. At the end of the prodrome, the patient starts to transmit the virus and continues to do so until the last scab from the rash has fallen off. Once the rash appears, influenza no longer is a possible diagnosis. However, during the prodromal day(s) influenza and smallpox have several similar symptoms. Both diseases have a sudden onset with fever, headache, back pain, and extreme exhaustion. While the fever in adults with influenza is 101 to 102 degrees F (38.3 to 39 degrees C), the fever ranges from 101 to 105 degrees F (38.5 to 40.6 degrees C) in smallpox. Headaches in smallpox are often described as “splitting.” The exhaustion in smallpox is so great as to be described as “prostration.” Chills are common to both diseases. About half of the patients with smallpox will vomit. Vomiting is rare with influenza. There is no cough with smallpox. Other symptoms that occur in the prodrome to smallpox but not in influenza are delirium, abdominal colic, diarrhea, and convulsions [20] (**Table 6**).

| INFLUENZA COMPARED TO SMALLPOX PRODROME |                       |                       |
|---|-----------------------|-----------------------|
| Clinical Presentation                   | Influenza             | Smallpox Prodrome     |
| Onset                                   | Sudden                | Sudden                |
| Fever                                   | 101 to 102 degrees F. | 101 to 105 degrees F. |
| Chills                                  | Usual                 | 60%                   |
| Headache                                | Usual, severe         | Usual, 'splitting'    |
| Myalgia                                 | Usual, in back        | Usual, in back        |
| Extreme exhaustion                      | Usual                 | Prostration           |
| Cough                                   | Usual, dry            | None                  |
| Vomiting                                | Rare                  | 50%                   |
| Delirium                                | None                  | 15%                   |
| Abdominal Colic                         | None                  | 13%                   |
| Diarrhea                                | No                    | 10%                   |
| Convulsions                             | No                    | 7%                    |

Source: Author Table 6

| INFLUENZA COMPARED TO TULAREMIA |                   |                      |
|---------------------------------|-------------------|----------------------|
| Clinical Presentation           | Influenza         | Tularemia            |
| Onset                           | Sudden            | Sudden               |
| Fever                           | Yes               | Yes                  |
| Chills                          | Yes               | Yes                  |
| Headache                        | Yes               | Yes                  |
| Myalgia                         | Yes               | Yes                  |
| Extreme exhaustion              | Usual             | No                   |
| Cough                           | Dry               | Dry                  |
| Tiredness/weakness              | May last >2 weeks | Progressive weakness |
| Diarrhea                        | No                | Yes                  |
| Joint pain                      | No                | Yes                  |

Source: Author Table 7

### INFLUENZA COMPARED TO TULAREMIA

Tularemia occurs naturally in all U.S. states except Hawaii. In the ten years from 1990 to 2000, the heaviest concentration of cases has been in the middle of the United States, especially in Missouri and Arkansas. Cases are reported throughout the year but occur most during May to August (not "flu season").

The disease is caused by the bacteria *Francisella tularensis*, which is found in animals, especially

rodents and lagomorphs (rabbits and hares). *F. tularensis* is a gram-negative coccobacillus and is one of the organisms that could be used in a biological attack.

Onset of the symptoms is sudden. Fever, chills, headaches, muscle aches, and a dry cough are symptoms of tularemia as they are in influenza. Diarrhea, joint pain, and progressive weakness are common to tularemia but not to influenza (**Table 7**).

The incubation period for tularemia can be as long as 14 days, but it is usually 3 to 5 days. Person to person transmission has not been documented, so isolation of the patient is not needed. People acquire tularemia by being bitten by an infected tick or other insect, by handling the carcass of an infected animal, by consuming contaminated food or water, or by breathing in the organism.

Because there are several portals of entry for *F. tularensis*, various manifestations of the disease occur. Entry through an insect bite causes an ulceroglandular form. Ingestion of the organism results in painful pharyngitis and/or gastrointestinal disease. Inhalation may be followed by pneumonia accompanied by pleurisy. Obviously, the ulceroglandular and gastrointestinal forms of the disease would not be confused with influenza, but the pleuropulmonary tularemia initially could be thought to be influenza. Because the pleuropulmonary form has a high fatality rate from pneumonia and systemic infection, careful diagnosis is needed in order to start the appropriate antibiotics (streptomycin, gentamicin, tetracyclines) as soon as possible [21; 22].

### INFLUENZA COMPARED TO RICIN

Another possible biological weapon that can affect the respiratory system is the toxin ricin. Made from the waste left over in the processing of castor beans into castor oil, it can be in the form of a mist or powder that can be inhaled. It can also be made into pellets that can be dissolved. A 500-microgram dose (the size of the head of a pin), injected or inhaled, is fatal to an adult. Ricin enters the cells of a person's body and interferes with protein production, which leads to cell death.

A few hours (within 12 hours of exposure) after inhaling ricin, the victim develops a fever, cough, nausea, respiratory distress and tightness in the chest. Ricin is a poison, so there is no person-to-person transmission. There should be little confusion with influenza because of the respiratory distress and chest tightness. Other possible symptoms that may follow fairly rapidly are heavy sweating and pulmonary edema, cyanosis, hypotension, and respiratory failure. All treatment is supportive. It is important to get ricin off the body or out of the

body as quickly as possible. This includes removing the patient's clothing (never over the head) and washing the patient's body. Obviously, masks, gloves, and gowns should be worn while removing the clothing so that any ricin that could be released in the air will not be inhaled or get on the healthcare workers clothes. All clothing/gowns involved should be doubled bagged, marked as hazardous waste and disposed of properly. Hands should be scrupulously washed after the removal of gloves [23].

A natural occurring case of ricin poisoning is highly unlikely. Therefore, learning the patient's activities and whereabouts in the last 24 hours is extremely important. Any intentional release of ricin in the air will lead to more victims and probably to more contacts (in person or by telephone) from the "worried well" (those who are not ill, but are very concerned). See **Appendix 1** for suggestions for how to "shelter in place" for those in the area in which the ricin was released [24].

### INDEX OF SUSPICION

So far the focus of this course has been on the symptoms of influenza that are common to the initial symptoms in diseases caused by organisms that can be used in biological warfare. The purpose is to raise the suspicion index of all medical personnel. In the real world, in which healthcare professionals work, there is rarely enough time to complete the essentials. In such situations it is natural to see respiratory illness with a fever and quickly conclude it is influenza. Logically, the medical community—both hospital emergency departments and medical doctors' offices and clinics—will be on the front lines of any terrorist attack using a biological agent. The quicker the correct agent is identified, and the proper authorities are notified (public health and law enforcement), the quicker a coordinated response can be set in action and the impact on the population can be lessened. In addition, public health departments can advise as to which specimens to collect, how to collect them, and where to send them. Public health officials can also provide information on any prophylaxis for those who have been exposed, including the healthcare providers. Actually, California law specifies that

anthrax, plague, smallpox, and tularemia are to be reported within 1 hour by telephone and followed by a written report within 1 day. Other states may have similar reporting requirements. Considering the seriousness, significance, and possible source of these diseases, it is imperative to get all the resources involved as quickly as possible. Anyone reading this course should immediately find out the phone number of the appropriate person to contact at the local public health department and post this number in a prominent place. All staff should be informed of this number and where it can be found quickly. Since the September 11, 2001 attack, many more public health departments have a method to contact them at any time. Public health officials can help in case investigation, contact tracing, patient and public education, and provide other forms of assistance. It is also the responsibility of the local public health department to contact the state health department and, in the case of suspected terrorist activity, the FBI.

## INFLUENZA AND OTHER FLU-LIKE ILLNESSES

There are many other illnesses that initially look like influenza. For discussion and consideration in making a diagnosis, these diseases are sometimes grouped into influenza-like illnesses (ILI). Adults will average 1 to 3 ILI a year. Children can average 3 to 6 ILI in a year. The common cold is one of these, but the differences between influenza and colds have been discussed above. Other bacteria that cause ILI are *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, and *Legionella pneumophila*. In addition, respiratory syncytial virus (RSV) has similar symptoms. None of these ILI are significant as biological agents to be used by a terrorist. However, they are a significant source of disease and should be considered when deciding if a patient has influenza or something else. Because bacterial diseases are treatable with antibiotics, but influenza is not, an accurate diagnosis is important. Much of the overuse of antibiotics occurs when patients request them for any illness or when careful diagnosis is not made between viral and bacterial diseases.

It may be helpful to consider the time of year in which the diagnosis is being made. Generally, pneumococcal disease peaks in the winter as does influenza and RSV. Mycoplasma and legionellosis are more common during the summer and fall. Rhinoviruses and parainfluenza virus peak during the fall and spring. Adenoviruses circulate throughout the year [25]. Information on the presence of influenza, and predominant strains in the community, can usually be found out from the surveillance system maintained by the local health department [6].

Other information to consider is that, in healthy individuals, influenza is a self-limiting disease that strikes suddenly with most of its fury, maintains that level of illness for 3 to 5 days, and then shows improvement even though the aftereffects of weakness and tiredness may persist for a week or more. In most other ILI diseases the patient's condition continues to worsen.

These last two considerations are not meant to figure in the diagnosis but just to guide thinking about the patient's illness. For instance, if a greater than usual number of cases of ILI are being seen and it is the wrong time of year for influenza, another disease or a terrorist attack should be considered.

Some studies have been conducted on the use of clinical definitions for influenza-like illness. The results were:

- Fever, cough, and acute onset accurately predict influenza 30% of the time in nonhospitalized older patients
- Fever, cough and illness of <7 days in hospitalized older patients with chronic cardiopulmonary disease accurately predict influenza 73% of the time
- Fever, but not cough, in vaccinated older persons with chronic lung disease was 54% specific for influenza [10].

## COMPLICATIONS OF INFLUENZA

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Complications of influenza leading to hospitalizations and death are greater in persons 65 years of age and older, in young children, in pregnant women in the second and third trimester, and in persons of any age with underlying medical conditions. Preliminary laboratory data for the 2003–2004 influenza season indicated that 143 children less than 18 years of age had influenza-related deaths in spite of the fact that 45% of these children did not have underlying medical conditions. Of these deaths, 58 (41%) were children less than 2 years of age [6].

### PNEUMONIA

The major complication of influenza is pneumonia, which can be either bacterial or viral. In the leading causes of death, influenza and pneumonia are listed together. The mortality from pneumonia following influenza is highest in the elderly and in patients with chronic underlying diseases, such as heart, lung, and renal conditions. However, generally in a pandemic, 50% of the deaths from the complication of pneumonia occur in those less than 65 years of age [8].

Bacterial pneumonia secondary to influenza is usually caused by *Streptococcus pneumoniae* (50%) or *Staphylococcus aureus* (20%). The development of pneumonia may occur because of the damage to the tracheobronchial epithelium, which leads to impaired mucociliary clearance of organisms. The failure to clear organisms by the cilia leads to infection of the lung parenchyma [8].

Viral pneumonia is also a complication that can occur with influenza. If the causative organism is the same as the influenza virus, the patient is said to have primary pneumonia, which can be fatal. Obviously, other viruses can also infect the patient's lungs. In addition, the patient can have both viral pneumonia and bacterial pneumonia simultaneously.

Signs that the patient has developed pneumonia are:

- Symptoms continue after the expected 5 to 7 days
- Symptoms worsen after the patient has started to improve
- Fever returns and is higher than with the initial illness
- Dyspnea
- Productive cough
- Abnormal x-ray (pulmonary infiltrates)
- Rales on auscultation [8]

### REYE'S SYNDROME

An unfortunate complication of influenza in patients younger than 18 years of age is Reye's syndrome. Much education has been given to parents regarding the danger of giving aspirin to anyone less than 18 years of age with a fever. This education has led to a decrease in Reye's Syndrome. Unfortunately, acetylsalicylic acid or salicylic acid is a component in some over-the-counter preparations and may be unintentionally given to a child with a fever. Influenza virus, especially influenza A virus, and varicella (chicken pox) interact with acetylsalicylic acid to produce Reye's Syndrome. Symptoms are nausea and vomiting, decreased consciousness and/or convulsions caused by cerebral edema, hypoglycemia, and liver failure. Parents must be reminded to read the labels of all medications and that aspirin is listed as acetylsalicylic acid [8].

### MYOSITIS AND RHABDOMYOLYSIS

Myositis (inflammation of muscle tissue) and rhabdomyolysis (involving striated muscle tissue) can be complications of influenza. These complications occur most often in children and are manifested by extreme muscle tenderness, especially in the legs. Myoglobulinuria may lead to renal failure in these patients. Serum creatinine phosphokinase (CPK) is markedly increased [8].

### STAPHYLOCOCCUS AUREUS SUPERINFECTION

Influenza can be complicated by *Staphylococcus aureus*, leading to pneumonia as discussed above. Superinfection with *S. aureus* leading to

bacteremia, endocarditis, or epidural abscess can also occur following influenza. Influenza B and *S. aureus* have led to toxic shock.

### CARDIAC COMPLICATIONS

Other less common complications from influenza are myocarditis (inflammation of the cardiac tissues), and pericarditis (inflammation of the pericardial lining). A study conducted in Russia from 1993 to 2000 showed that the peak number of deaths from acute heart attacks and chronic heart disease coincided with the height of the influenza epidemic [110].

### PULMONARY COMPLICATIONS

Besides the more common complication of bacterial or viral pneumonia, influenza can lead to the worsening of chronic bronchitis and other chronic pulmonary diseases.

### CENTRAL NERVOUS SYSTEM COMPLICATIONS

Encephalitis, postencephalitic Parkinson's disease, transverse myelitis, Guillain-Barré syndrome and possibly amyotrophic lateral sclerosis have followed cases of influenza. There has been research suggesting that cases of Parkinson's disease resulted from the "Spanish flu" pandemic of 1918–1919 [84; 85; 86; 87; 88; 89].

Any person with a serious medical condition can be placed in jeopardy by influenza, not only from the complications listed above, but also from exacerbation of the underlying condition [8].

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## INFLUENZA VACCINE

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Influenza vaccine is the primary preventative measure against the virus. It is efficacious in preventing influenza. Among those at higher risk, it lessens the severity of the illness, decreases complications, reduces hospitalizations, and lowers the fatality rate. It is disappointing that a vaccine with such benefits and few side effects is not used more widely.

### HIGH RISK GROUPS THAT SHOULD RECEIVE THE INFLUENZA VACCINE

*Persons 65 years of age and older* have the highest fatality and hospitalization rate from influenza and its complications. Of the 36,000 annual deaths, 90% of them occur in those 65 years of age and older. In addition, 57% of the hospitalizations are in this age bracket [6].

*Persons 50 to 64 years of age* are also considered to be a high-risk group for influenza because many of the people in this age bracket have chronic diseases (29% in 2002). People in this age group often do not receive the vaccine because the publicity about the need to receive the vaccine has tended to focus on those than 65 years of age and older. In addition, Medicare pays for the vaccine after the person reaches 65 years of age [6]. Therefore, those individuals who fall into this age group may be disinclined to receive the vaccine.

*Persons with chronic health problems who are 6 months of age or older* are at high risk for complications from influenza or exacerbation of their condition. Such chronic conditions include:

- Cardiac disease, such as congestive heart failure
- Pulmonary disease, such as chronic obstructive pulmonary disease, cystic fibrosis, or asthma
- Renal disease
- Diabetes and other metabolic diseases
- Anemia and blood disorders, such as sickle cell disease

*Persons with compromised immune systems* from any cause—HIV/AIDS, autoimmune conditions, cancer, long-term steroid treatment, and medications—should receive the inactivated vaccine. Because the vaccine is inactivated (killed), it can and should be given to immunosuppressed people. However, because of the depressed immune system of this group of people, the expected antibody response may not be obtained. Those HIV-infected patients with minimal AIDS-related symptoms and high CD4 T-lymphocyte cell counts have

been shown to develop substantial antibody titers against influenza. For those with more advanced HIV disease and low CD4 T-cell counts, the vaccine might not induce protective antibody titers and a second dose has not been shown to increase the titer. Some studies have shown that there is a temporary (2 to 4 week) increase in replication of HIV-1 after receiving the influenza vaccine. However, other studies have not demonstrated this increase nor has progression of HIV disease been shown to occur following the administration of the influenza vaccine. Each immunocompromised individual must be evaluated before the vaccine is administered because an increase in plasma HIV levels and/or a decrease in CD4 count has been transient in most, but not all, cases of those receiving the influenza vaccine [33].

*Persons with conditions or diseases that may compromise respiratory function or increase the risk of aspiration should also be vaccinated against influenza to prevent any possible complications or damage.*

*All healthcare providers should receive the influenza vaccine annually. Additionally, healthcare facilities are encouraged to make available the vaccine to its workers. In its 2007–2008 recommendations, the Advisory Committee on Immunization Practices (ACIP) encouraged healthcare facilities to obtain a signed declination form from healthcare workers who refuse influenza vaccination [105].*

*Persons who reside in skilled nursing facilities (nursing homes) or other chronic care facilities are at high risk for influenza-related problems because of their weakened physical state and close living arrangements.*

*Persons 6 months to 18 years of age on long-term aspirin therapy should be immunized against influenza because of the interaction of the influenza virus and aspirin that can lead to Reye's Syndrome.*

*Pregnant women in the second or third trimester have the same complication and hospitalization rate from influenza as persons with chronic diseases and, therefore, should receive the vaccine. Basi-*

*cally, this would include women who will deliver from the beginning of October through the end of May. However, there are some recommendations that a woman should not receive the influenza vaccine before the 14th week of gestation. There is a coincidental association of spontaneous abortion, which is common in the first trimester. Also, many practitioners avoid any exposure to vaccines during the first trimester. However, no adverse fetal effects have been associated with influenza immunization [6; 26].*

*All children 6 to 59 months of age, especially children 6 to 23 months of age, even without any chronic conditions, should receive the annual influenza immunization because they are at a substantially increased risk for influenza-related hospitalizations. Many of the hospitalizations are due to dehydration that can occur rapidly in a child who has a fever and will not drink fluids. The hospitalization rate in this age group matches the hospitalization rate for other groups at high risk for complications and death from influenza. At this point, these higher hospitalization rates cannot be totally assigned to influenza because respiratory syncytial viruses (RSV) circulate at the same time. Since 2003, the Vaccine for Children (VFC) program will cover the cost of the influenza vaccine for all eligible children 6 to 23 months of age and all eligible children 2 to 18 years of age who are household contacts of a child 0 to 23 months of age [6]. The Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) published the "Recommended childhood and adolescent immunization schedule – United States, July – December 2004" on April 30, 2004. This schedule now includes a recommended yearly influenza immunization for all children 6 to 23 months of age. It continues the recommendation that children with chronic conditions from 2 to 18 years of age also receive an annual influenza immunization [6].*



The American Academy of Pediatrics recommends influenza immunization of healthy children between 6 and 24 months of age.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=4860](http://www.guidelines.gov/summary/summary.aspx?doc_id=4860).

Last accessed October 19, 2007.)

**Level of Evidence:** II-3 (Evidence obtained from multiple time series with or without the intervention, or dramatic results in uncontrolled experiments)

Media attention in the 2003–2004 influenza season focused on the number of children who expired because of influenza and/or its complications. There were 58 deaths (40.6%) in children younger than 2 years of age. In children 2 to 17 years of age, there were no underlying medical conditions in 65 deaths (45% of total deaths) [6; 33].

In the past, influenza-related deaths in children have not been on the list of deaths that should be reported. When it became apparent that a significant number of such deaths was occurring, the CDC requested that all influenza-related deaths of children less than 18 years of age be reported to the appropriate state health department. Any postmortem tissue specimens collected or autopsy reports that were completed were also asked to be sent to the CDC [12]. Without data from previous years, it is not known if the number of deaths of children during the 2003–2004 flu season was within normal parameters, above or below the number of deaths in previous years.

Data from the 2004 National Health Interview Survey indicated that only 42% of healthcare workers were immunized against influenza, in spite of the fact that vaccination reduced work absenteeism and resulted in fewer deaths among nursing home residents [96]. Reasons that workers go to work when ill include a sense of altruism, no paid personal or family sick leave, or pressure to work. Studies have also shown that ill workers account for as much as 60% of corporate healthcare costs. To respond to these situations, many companies are now offering free influenza vaccinations and expanding telecommuting options [107].

The public continues to follow the example of their healthcare providers. Although approximately 218 million Americans could have benefited from the influenza vaccine in the 2007–2008 flu season, millions of unused doses were destroyed [106]. To emphasize the importance of flu vaccinations, the CDC promoted the first National Influenza Vaccination Week November 27 to December 3, 2006 [108].

## OTHER GROUPS ADVISED TO RECEIVE THE INFLUENZA VACCINE

Basically, this includes anyone who has contact with those at risk of complications, hospitalization, or death from influenza. This contact could be through living or caregiving arrangements. This would include those with patient contact in acute and chronic care facilities, in doctors' offices or clinics, in emergency rooms, and in-home care providers. Family members of infants, from newborns to 23 months of age, are advised to protect their child/sibling by being immunized. This is especially critical for infants younger than 6 months of age for whom no current influenza vaccine is licensed. In addition, influenza vaccine should be given to all household members, including children, and caregivers of persons whose medical condition puts them at risk for severe complications if they contract influenza.

Many businesses recognize the economic impact from absenteeism due to influenza and make arrangements for their employees to receive the vaccine. Persons who provide essential services, such as law enforcement and firefighters, also should be immunized. This is especially important in a pandemic situation. Students living in dormitories should receive the vaccine in order to avoid disruption of their studies.

Travelers should be evaluated for influenza immunization when "travel shots" are being recommended. Influenza in temperate climates occurs in the winter months (October through March in the Northern hemisphere; April through September in the Southern hemisphere). It occurs year-round in tropical climates. People taking a cruise could be infected with influenza at any time of the year

because many of the service crew are from tropical areas, and a cruise ship is a closed community. This helps to assist in the spread of the virus [26].

Although it has been mentioned above, the need for healthcare workers to be immunized against influenza cannot be overemphasized. All healthcare workers should receive the influenza vaccine. Not only does it protect the patient, but it also protects the healthcare worker. Healthcare workers who have been immunized tend to remember to advise their patients to get the immunization. This can strengthen the advice by example and can also provide anecdotal reassurance about the pain or side effects experienced. Studies have shown that residents in long-term care facilities have fewer deaths from influenza when their caregivers have been immunized against influenza [6].

Obviously, the vaccine should be given to anyone who desires it, especially in school-aged children. However, in times of vaccine shortage or slow production, high-risk groups and their close contacts should receive the vaccine first, then when more vaccine becomes available, others should be immunized.

### **GROUPS WHO SHOULD NOT RECEIVE THE INFLUENZA VACCINE**

*Persons with a severe allergic reaction to eggs* should not be given the influenza vaccine. A person with a severe hypersensitivity to eggs may develop an anaphylactic reaction (sudden sense of great uneasiness or anxiety, pounding headache, hypotension, urticaria, dyspnea). The vaccine is grown in eggs, and although it goes through a purification process, a small amount of egg protein remains. This minute amount could trigger a reaction in those who are severely allergic to eggs. A dislike for eggs or mild gastrointestinal symptoms following ingestion of eggs is not a contraindication for the influenza vaccine. Usually, asking a person receiving the influenza vaccine for the first time if they can eat eggs without a problem is a quick screening tool and an adequate precaution. New vaccines are under development that eliminate the need to utilize eggs to grow the vaccine, which will eliminate this concern in the future.

*Persons with acute respiratory or other active infections or illnesses* should be advised to wait until they have recovered to receive the vaccine.

*Persons with a history of Guillain-Barré syndrome (GBS)* are more prone to another episode of this syndrome. Because GBS is such a rare condition, it is impossible to know if the influenza vaccine is involved in its occurrence. During the swine flu epidemic (1976), there was an increase of GBS in those who had received the vaccine. However, an increased incidence of GBS following administration of other influenza vaccine formulations since has not been documented. According to the package insert for *Fluzone*, for patients who have recovered from GBS, it is better to err on the side of caution and avoid giving them the influenza vaccine until more information is available [26]. The *Epidemiology and Prevention of Vaccine-Preventable Diseases*, known as the “Pink Book,” states that persons who have developed GBS within 6 weeks of receiving the influenza vaccine would be wise to avoid a subsequent flu shot. However, the recommendations of the ACIP are that recovered GBS persons with risk factors that increase their vulnerability to the complications of influenza should receive the vaccine because the risk of complications is greater than the risk of a recurrence of GBS [1].

*Persons with an allergic reaction to dry natural latex rubber* should be evaluated before being given the vaccine because the stopper in the vial contains dry natural latex rubber [28].

Note: Influenza immunization is NOT contraindicated in breastfeeding mothers. In fact, it should be encouraged because she could give her vulnerable infant influenza if she gets the disease. She could also be liable to a decreased milk supply because of decreased fluid intake and fever, and would have the added burden of infant care and breastfeeding while experiencing exhaustion and other flu symptoms.

## MANUFACTURE OF THE VACCINE

Because of antigenic drift, each year the Advisory Committee on Immunization Practices (ACIP) and the Food and Drug Administration (FDA) must decide which influenza strains to include in the formulation of the year's vaccine. Because the formulation changes each year to provide protection against the expected circulating strains, an annual influenza immunization is needed. Obviously, the point is to include the strains that will be expected to spread around the world. There are two type A strains included in the formulation because type A influenza strains are usually those that lead to more complications, hospitalizations, and deaths. The third strain included is always a type B. In the 2003–2004 influenza season, the expected dominant strain killed the embryonated egg where the virus is grown due to the virulence of the strain [7]. A virus that was close to the expected circulating strain was chosen instead. However, the match was not close enough to the circulating strain for the vaccine to be as effective as it usually is. To the credit of the ACIP, this was only the second mismatch in 15 years [27; 28]. Sometimes antibodies produced against one strain can overcome another strain, but the strains must be closely related. Antibodies produced by the strains in the 2003–2004 formulation were not close enough to the dominant circulating strain to destroy it, so people who had received the vaccine still developed influenza. In fact, the choice of which strains to include is based on the current knowledge as to which will be the most virulent strains in circulation. Due to the fact that there are only 3 strains in the vaccine and multiple influenza strains, people who are vaccinated can still develop illness from a strain of influenza virus that was not included in the vaccine.

Another extremely significant factor in the choice of a strain is the ability to grow the strain so that the vaccine can be produced in millions of doses. When the vaccine is delayed in distribution it is often due to the fact that one particular strain would not reproduce well or quickly enough. As noted, some strains kill the culture medium.

The current production of influenza vaccine involves the following steps:

1. The three chosen strains of influenza virus are incubated in fertilized chicken eggs.
2. Fluids containing the virus are harvested.
3. The virus is inactivated (killed) by formaldehyde.
4. The virus is concentrated.
5. The virus is chemically disrupted to produce a "split-virus." (All influenza vaccine used in the United States is split-virus).
6. Further purification of the virus by chemical means is done.
7. The virus is suspended in sodium phosphate-buffered isotonic sodium chloride solution.
8. Each dose of vaccine contains 45 micrograms of hemagglutinin in each 0.5 cc dose. There are 15 micrograms of hemagglutinin from each strain in the vaccine.
9. No antibiotics are used in the preparation of influenza vaccine [26].

Thimerosal is a preservative used in multi-dose vials to inhibit bacterial growth that might occur because of multiple introductions of needles to withdraw individual doses. It is a compound containing 49.6% mercury. Because of the allegation that thimerosal is connected to conditions such as autism, and the fact that there have been warnings to avoid fish that has a high mercury content, thimerosal has been removed from most childhood vaccines. Vaccines without thimerosal are packaged in single dose vials. However, thimerosal is still used in multi-dose vials (5 cc or 10 dose vials) and single-dose prefilled syringes of influenza vaccine. There are 25 micrograms of mercury in each 0.5 cc dose of vaccine. One should note that there have been no studies proving any link between mercury poisoning and autism. Thimerosal is made from ethyl mercury, which is different from methyl mercury, the compound named in the government warning about consumption of or exposure to mercury [28]. Some influenza vaccine without thimerosal is made each year and should be used for those who

have a severe allergic reaction to thimerosal. But thimerosal-free vaccine is harder to produce, so it is less common and more expensive [32].

The formulations for the 2008–2009 influenza season were A/Brisbane/59/2007 (H1N1), A/Brisbane/10/2007 (H3N2), and B/Florida/4/2006 [33].

Current production methods have been used for decades and do not apply some of the modern technology available in the production of vaccines against other organisms, such as Hepatitis A or Hepatitis B. Influenza vaccine currently is incubated in fertilized chicken eggs. It takes one egg to produce one dose. More than 80 million doses are made for annual distribution in the United States alone. The number of chickens and eggs needed for this production is almost beyond comprehension. Also sobering is the thought of what would happen if one or more of the major flocks used for producing the eggs for the vaccine became infected with an avian influenza, which would require destruction of the flock(s).

Another issue involved is the amount of time required to produce the vaccine. Currently, it takes around 6 to 8 months for the annual influenza vaccine production. Any new strain of influenza could circulate around the world much faster than the vaccine could currently be produced, resulting in a pandemic. Some experimentation is being conducted on faster ways to produce the vaccine. Some companies are experimenting with caterpillar cells to incubate the virus. Experiments have indicated that the vaccine can be produced more quickly and it would be available to protect people against emerging strains. Phase I trials indicated that the new vaccine is safe. In a clinical trial of 400 elderly people, the vaccine produced using caterpillar cells stimulated the production of nearly twice the number of antibodies as the vaccine produced using eggs. In addition, there were no adverse effects. Phase II trials in 400 elderly participants showed that 97% developed antibodies if the highest dose of the vaccine was used [29; 30].

Another approach being explored in influenza vaccine production is to genetically engineer cells to replicate continuously. Such a process would lead to faster production and a more consistent vaccine [31]. Research is also being conducted regarding the ability to take a virus and add a gene that will encode either a hemagglutinin or a neuraminidase from the influenza virus. Clinical trials have shown that a vaccine produced using this process is well-tolerated and immunogenic. This process could decrease production time by 1 to 2 months [130].

Other experimentation is being done using DNA-based approaches to develop a broadly protective vaccine that utilizes influenza virus proteins from multiple strains. Several companies are working to develop new ways to grow the antigens that cause the immune system to fight infection [130].

Using the reverse genetics method, in which genomes of the influenza viruses are manipulated in order to transfer genes between viral strains, seed viruses for vaccine manufacture can be rapidly generated. In addition, highly pathogenic influenza viruses can be altered so that they are safer for vaccine manufacturers to handle [130].

Another method of vaccine development, cell culture, has been well tolerated and has successfully led to antibody development in trials. Some research has shown that vaccines developed based on cell culture have been efficacious against all strains of influenza A, including H5N1 [130]. Using cell-based vaccines creates a more consistent manufacturing process and could reduce production time to 9 to 12 weeks. Although there are some side effects from cell-based vaccines, including headaches and injection site reactions, they appear to have a similar tolerability profile to egg-based vaccines [99].

ACAM-FLU-A, a universal flu vaccine that could protect against all A strains, is entering phase 1 trials to determine its safety, tolerability, and effectiveness [100]. Another vaccine made from individual viral proteins rather than whole virus particles has also shown adequate immunogenicity in trials. The manufacturer hopes to apply for US licensing in 2008 and, if granted, could begin production in 2011 [100].

The National Institutes of Health has provided a grant of \$9 million over 5 years to research ways to improve the effectiveness of influenza vaccine. A vaccine additive that will boost the body's immune response to the flu vaccine is being researched. If effective, this additive could result in less flu vaccine being required to effect adequate immunity, which would be especially important in areas or times when limited supplies of vaccine are initially available [101]. In another area, one small study has been conducted that indicates that mild exercise before having a flu shot may make the vaccine more effective. Lifting weights before a flu shot increased antibody response in women, but reduced the response in men. However, the cell-mediated response in men was increased by weight lifting. The researchers suggest that exercise increases the number of immune cells in muscle tissues, which in turn increases activity in the lymph nodes and creating a more efficient immune response [98; 102].

## HANDLING AND STORAGE OF THE VACCINE

The following information pertains to the egg-based vaccine in use at this time. As is the case for all vaccines, the package insert should be consulted for proper handling and storage in order to preserve its effectiveness. Influenza vaccine should be stored at a temperature of 35 to 46 degrees F (2 to 8 degrees C). When being transported, it should be in insulated containers with cold packs. The vaccine should not be directly in contact with the cold packs nor should it be placed anywhere in a refrigerator where it can be frozen. **Freezing destroys the effectiveness** of influenza vaccine. The vaccine can tolerate being out of the refrigerator while an influenza clinic is being prepared or conducted. However, only enough vaccine for the first half hour should be taken from the refrigerator at a time. When immunizing individual patients in an office setting, the vaccine vial should be returned to the refrigerator as soon as the dose has been withdrawn.

It is important that the temperature of the vaccine storage refrigerator be checked and recorded each morning before starting to dispense immunizations and each evening before leaving for the day. Older refrigerators can develop cold spots where items can freeze, or they do not maintain a constant temperature. All inactivated vaccines, like influenza vaccine, are destroyed by freezing. Large bottles of water should be kept in the refrigerator at all times to help maintain an even temperature and to preserve cold longer in case of a power outage. Live vaccines, such as chicken pox and oral polio (no longer used in the U.S.), must be kept frozen. Vaccine should **never** be stored on the shelves in the door as the temperature there is erratic [34].

Available vaccines for the 2007–2008 flu season were Fluarix, FluMist, Fluvirin, Fluzone, Afluria, and FluLaval. Children younger than four years of age should not receive Fluvirin, Afluria, or FluLaval because they have not been proven to be effective for this population [97].

## ADMINISTERING THE VACCINE

The influenza vaccine being discussed is for intramuscular (IM) use only. The intranasal preparation will be discussed later in the course. The IM vaccine is for all people 6 months of age or older. In order to assure that the vaccine is given IM, it is necessary to use needles of the proper length. Vaccine that is administered subcutaneously because of improper technique or a needle that is too short is ineffective.

The recommended site for children older than 3 years of age and adults is the deltoid muscle. A 1-inch needle will reach the deltoid in most children and adults. Some patients with large arms will need a 1.5-inch needle. One should be careful to make sure the patient's sleeve can go high enough so that the needle can be inserted in the middle of the arm about an inch and a half below the top of the shoulder. Usually the firmness of the deltoid can be felt in that area. In patients who are very thin, it is wise to squeeze the deltoid between your thumb and finger to avoid hitting the bone.

Administration of the vaccine distal in the deltoid is more painful. The posterior portion of the arm should not be used.

In children younger than 3 years of age, the deltoid is usually not big enough to administer the vaccine. The *vastus lateralis* muscle should be used. This is the muscle on the outer aspect of the child's thigh and can usually be palpated. At times, when the infant kicks, the outline of the muscle can be seen. Two secrets to administering an injection to a child are to have the child properly and quickly restrained. An assistant, either the parent or a helper, should position the child so that the leg or arm where the injection will be given will not move. The upper body, the leg not being used for the shot, and the foot of the leg being used should be held tightly by the parent. Young children 3 years of age and older should sit sideways on the parent's lap so the child's legs can be clamped between the parent's knees. The arm that will not be used for the injection should go around the parent's waist and be clamped under the parent's arm. The hand of the arm being used for the injection should be held by the parent. The person giving the vaccination should have all injections prepared so that they can be administered quickly. It is also good to distract the older child by having them blow, count, or see how loudly they can say "ouch" [34].

Children should receive split-virus vaccine. This is not a problem in the United States as all vaccines are split-virus. Because influenza vaccine comes in multiple dose vials, a small amount of thimerosal is in the vaccine. For parents who are unwilling to accept the current studies showing no connection between thimerosal and autism, thimerosal-free preparations are available [6; 26].

Flumist and Fluarix do not contain thimerosal. The additional two vaccines in use are available with reduced thimerosal. Information on the amount of thimerosal present in each vaccine dose is available at <http://www.fda.gov/cber/vaccine/thimerosal.htm#t3> or <http://www.vaccinesafety.edu/thi-table.htm> [97].

Children younger than 9 years of age receiving influenza vaccine for the first time must receive two doses, one month apart. The dose for a child is age-related. Children from 6 to 35 months of age should be given 0.25 ml administered IM with a 1-inch needle in the outer aspect of the thigh. If it is the first time the child has received a flu shot, a second 0.25 ml dose IM should be given one month later. In subsequent years, the child will need to receive only one influenza vaccine each year. Children 3 years of age and older should be given 0.5 ml IM using a 1-inch needle in the deltoid. Children who are 3 to 8 years of age receiving influenza vaccine for the first time will need a second vaccine in a month. These second doses in those not previously immunized against influenza are given to maximize a satisfactory antibody response to all 3 antigens in the vaccine. Preferably both doses should be given before December [6; 28; 36]. Late-season immunization is acceptable and should be encouraged for those who have not received the vaccine [105]. Note: Inhalation preparations of influenza vaccine are not currently licensed for administration in children less than 5 years of age or for children with chronic underlying medical conditions. (It is also not indicated for those 50 years of age or older.)

As an inactivated vaccine, influenza can be administered with other vaccines if required. Separate needles and separate sites should always be used. In fact, for patients 65 years of age or older who have never received the immunization against pneumococcal disease, that vaccine should be given at the same visit. This is also an excellent time to check on the status of the patient's tetanus immunization. Tetanus vaccine must be given every 10 years, a fact that is often forgotten in adults, especially older individuals. Recent cases of tetanus have occurred in heroin users because the amount of heating in the preparation of black tar heroin is not adequate to kill the tetanus spores. Older people can contract tetanus when working in their gardens with manure products and receive a small puncture wound, which provides entrance to the tetanus organism.

All patients or their parent/guardian must receive the Vaccine Information Statement (VIS) appropriate to the vaccine being administered. The patient signs that he or she has read the VIS. The record the patient signs must contain the date that the VIS was provided to the patient. Many people think they are signing permission for the vaccine to be given. Actually, they are signing that they have read the VIS [35].

Children younger than 18 years of age should not be given any vaccines without a parent/guardian present. Grandparents frequently bring children to immunization clinics. A written permission from the child's parent/guardian should be presented to the staff before the vaccine is administered.

### **SIDE EFFECTS OF THE INFLUENZA VACCINE**

The most common side effect following influenza immunization is a local reaction—soreness, redness, or induration at the injection site—that occurs in 15% to 20% of the recipients. Generally, these effects last only a day or two. Some people (<1%) experience fever, chills, malaise and myalgias usually within 6 to 12 hours. This effect often is in those receiving the vaccine for the first time. As with the local reaction, these systemic reactions last only 1 to 2 days.

In a comparative study with a placebo, the systemic reactions occurred as often with the placebo as with the influenza injection. Neurological reactions to influenza do occur but they are rare [6].

A certain percentage of people will be incubating an influenza virus when they receive the influenza injection. When they have symptoms of influenza in a day or two, they are certain it is the result of the flu shot. Healthcare workers should try to reassure their patients that the vaccine could not be responsible because the virus in it is dead.

Immediate severe allergic reactions can occur after administration of influenza vaccine. These reactions are probably due to hypersensitivity to a component of the vaccine, usually it is a severe egg allergy. As noted, this concern may be eliminated as new technologies become available. All patients

receiving the influenza vaccine, especially for the first time, should be carefully screened for severe egg allergy. If a person has a severe allergic reaction to thimerosal, a thimerosal-free (Flumist or Fluarix) vaccine should be used. For those allergic to eggs but who have factors that increase their risk of complications from influenza infection, protocols to vaccinate them are available. A sheet with the symptoms of anaphylaxis and the dosage of therapeutic epinephrine should be posted near the preloaded epinephrine syringe and should be readily available and its whereabouts known to all staff. In addition, crushable packets of ammonia should be available in any area in which immunizations will be administered. It should be noted that anaphylactic reactions are extremely rare. Patients, especially teenagers, may faint and the crushed ammonia passed quickly under the nose is enough to revive them. Never ignore a patient who verbalizes fear of shots or mentions that they have fainted in the past. Make sure such a patient is seated, or lying down if in an exam room. Reassure the patient and administer the vaccine as quickly as possible. Position your body in such a way as to be able to support the patient if they are sitting and begin to faint. Taking time to carefully screen a patient for allergies to the components of the vaccine or other reactions to injections is always wise and saves time in the long run.

### **ADVERSE EVENTS**

Adverse events are any unusual conditions, such as fever, dizziness, behavior change, or serious allergic reactions, such as difficulty breathing, hoarseness or wheezing, hives, paleness, weakness, or tachycardia following influenza vaccine. Any such event should be reported to the provider of the flu shot and to the U.S. Department of Health and Human Services Vaccine Adverse Event Reporting System (VAERS). Any person can report an adverse event following the administration of any vaccine. Medical providers should report these events by calling 1-800-822-2463. Nonmedical providers and others should use 1-800-822-7967. A VAERS form will be sent or can be found on the internet at [www.vaers.org](http://www.vaers.org). Adverse events usually occur within 48 hours of vaccine administration. However,

Guillain-Barré syndrome may occur as long as 6 weeks after administration. The VAERS form will ask for detailed information on the vaccine, such as lot number, administration site, administrator, and date. Patients to whom influenza vaccine is administered should be instructed to call a physician if there is an adverse event. Careful investigation follows the receipt of a VAERS report [28; 37]. The provider is notified of the results of the investigation usually several months after the report was made. Therefore, it is wise to keep a copy of the report in the patient's file and a copy in a special file for VAERS reports. As the report is investigated, often the provider is contacted for clarification of or additional information.

### EFFECTIVENESS OF THE INFLUENZA VACCINE

The effectiveness of any vaccine depends upon the age and immunocompetence of the person receiving the vaccine. Most children and young adults receiving the vaccine have a good antibody response to the strains included in the vaccine and develop titers sufficient to protect them against those strains. For healthy adults younger than 65 years of age, if the vaccine strains match the circulating strains, illness will be prevented in 70% to 90% of those adults. In children, various studies have shown that children as young as 6 months of age develop antibodies. Children at high-risk to develop complications with influenza may have a lower antibody response than healthy children. Also, children receiving the vaccine in the second year exhibit lower attack rates. Otitis media rates are lowered in some studies but not in others. Overall, because the vaccine is beneficial to children in preventing disease and lowering hospitalization rates, the ACIP now recommends a yearly influenza immunization for all children 6 to 23 months of age and for children 2 to 18 years of age with chronic medical conditions [6].

In adults 60 years of age and older, who are not institutionalized, a randomized trial showed that the vaccine was 58% effective against influenza respiratory illness. Efficacy might be lower in those older than 70 years of age. However, the vaccine appears to be effective in preventing secondary

complications, hospitalization, and death among older adults, both those who are healthy and those with chronic medical conditions. Among non-institutionalized older adults, the vaccine prevented hospitalization for pneumonia and influenza 30% to 70% of the time. Among institutionalized older adults, the vaccine can be 50% to 60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death even though among this population it is only 30% to 40% effective in preventing illness [6]. Overall, in those 65 years of age and older, influenza immunizations have reduced hospitalization by 70% and death by 85% [36].

### COST-EFFECTIVENESS OF THE INFLUENZA VACCINE

In preventing illness among younger workers, the vaccine helps reduce economic losses caused by absenteeism. Decreasing hospitalization rates of healthy infants and toddlers, of older non-institutionalized and institutionalized adults and of persons with chronic conditions is cost-effective. Studies have demonstrated that physician visits are decreased 34% to 44%, there is a 25% decrease in antibiotic usage for secondary illness associated with influenza, and that there is a 32% to 45% decrease in lost workdays. These statistics led to a significant annual savings of healthcare dollars for each person who received influenza vaccine. In an era of escalating healthcare costs and increasing antibiotic resistance, these are important figures [6].

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### NASAL SPRAY INFLUENZA VACCINE

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FluMist, a new influenza vaccine, manufactured by MedImmune Vaccines, Inc., was approved in June, 2003. It is a live attenuated influenza vaccine (LAIV) sprayed into the nose. LAIV has been licensed only for healthy persons 2 to 49 years of age. LAIVs have been in development since the 1960s in the United States [6; 140].

LAIV preparations will contain the same 3 influenza strains (2 A and 1 B strain) as intramuscular injection vaccine. Both types of vaccine are prepared in eggs and must be administered annually. However,

LAIV contains live, but weakened, virus in contrast to IM vaccine where the virus has been killed. People with chronic health conditions should not be given the intranasal vaccine. Like traditional influenza vaccine, LAIV can be administered to family members or close contacts of high risk or immunosuppressed persons, it can be given at the same time with other vaccines—live and inactivated, and if not given at the same time, should be given 4 weeks after any other vaccine. Family members or close contacts of *severely* immunocompromised patients should **not** be given LAIV [6].

Because LAIV contains live virus, shipping and handling issues are more crucial. LAIV must be kept frozen, so it must not be stored in a self-defrosting freezer and requires special handling when shipped [34]. Again, practitioners are encouraged to check the package insert. In 2006, a formulation of LAIV that is stable when refrigerated became available, eliminating the necessity for freezing [97].

In animal studies and in adults and children, LAIV was shown to replicate in the mucosa of the nasopharynx. The viruses in LAIV replicate efficiently in temperatures between 25 to 38 degrees C (77 to 100.5 degrees F). This means that wild-virus replication is restricted because it is not cold-adapted like the viruses used in LAIV. It also means that LAIV does not replicate efficiently in the lower airways or lungs. As yet, it is not clear the exact protective mechanisms developed by LAIV but they seem to involve both serum and nasal secretory antibodies [6].

Several studies have been completed on the intranasal vaccine. A study of 185 elementary school students who received LAIV in Union Bridge, Maryland showed that the number of school days lost to influenza was decreased, the work days lost by the parents of those students were decreased, there were fewer trips to the doctor, and spending on influenza remedies was decreased by 50%. This was a comparative study between students who received LAIV and those who did not, conducted by the University of Maryland. There is some evidence that whole families had less influenza because the children did not bring home the infection [37; 38].

Dr. Robert B. Belshe, St Louis University and lead investigator for the FluMist pediatric trial, stated that LAIV may have a greater ability to produce a broader immunity than inactivated vaccine and also cover some of the antigenic drift strains. FluMist was 86% effective against the drifted A/H3N2 virus that produced influenza during the 2003–2004 flu season. The A/Fujian/411/2002 (H3N2)-like strain in the 2003–2004 IM vaccine preparation was not as effective because of the antigenic drift in the virus [39].

Studies have shown that LAIV is effective for children 1 to 5 years of age without a history of wheezing [103]. Researchers from medical schools in Missouri, Tennessee, California, and Finland found that children 6 months to 5 years of age had 55% fewer cases of influenza when protected by the nasal spray rather than the flu shot and were more likely to fight off strains that were not included in the formulation. However, in children younger than 12 months of age, there were slightly more hospitalization and episodes of wheezing in the group receiving the nasal spray. Asthmatic children 6 years of age and older did not have an increase in asthma attacks [103].

A different intranasal influenza vaccine marketed by Berna Biotech, used only in Switzerland in the 2000–2001 flu season, may be implicated in Bell's palsy. A study at the University of Zurich by Dr. Margot Mutsch reported that 27.2% of the 250 Bell's palsy patients had received the intranasal vaccine compared to 1.1% of the 722 control subjects. The vaccine is no longer in clinical use [40].

As noted, LAIV currently is not licensed for children younger than 2 years of age [140]. Trials done by Kaiser Permanente Vaccine Study Center in Oakland, California, suggest that, generally, intranasal influenza vaccine is safe for adolescents and children older than 3 years of age. In children 18 to 35 months of age, there was a four-fold increase in reactive airway disease [41].

In a partnership with MedImmune, Wyeth conducted clinical trials of FluMist with children who have a history of respiratory illness. In children 6 months to 6 years of age, FluMist was 53% more effective and in children 6 to 17 years of age 35% more effective than the IM influenza vaccine [42].

One factor that has dampened the enthusiasm for the intranasal vaccine is the cost. A single dose cost \$46 during the 2003–2004 flu season. Although, initially, MedImmune would lose money, the company is considering lowering the price to “the low \$20s” in order to build a consumer base. Hopefully, this will increase the use of LAIV and also increase usage among healthy people from 2 to 49 years of age, an age group that has not been immunized against influenza in great numbers in the past [43; 140]. Approximately 80% of the intranasal vaccine produced for the 2003–2004 flu season was unused and had to be destroyed [44].

An advantage of LAIV is that it seems to induce both mucosal and serum antibodies. It is easier to administer than an intramuscular injection, and it is preferred by some people.

### WHO SHOULD NOT RECEIVE LAIV

The following groups of people should not be given LAIV [6; 97; 140]:

- Anyone younger than 2 years of age or older than 49 years of age—it is currently not licensed for these ages
- Anyone with chronic underlying medical conditions, such as cardiac or pulmonary disease, diabetes, renal dysfunction, or a compromised immune system
- Children on long-term aspirin therapy
- Persons with a history of GBS
- Pregnant women
- Persons with hypersensitivity to any of the components of LAIV, including eggs
- Persons who have been on antiviral medications in the previous 48 hours
- Persons with a history of asthma or other reactive airway disease

The risk of acquiring influenza through the administration of LAIV is not known [6]. For increased safety, anyone administering LAIV should have been immunized against influenza at least two weeks earlier. Severely immunocompromised individuals should NOT administer LAIV because of the introduction of virus (even at low levels) into the environment during administration. However, other persons at high risk of complications from influenza, e.g., pregnant women, persons with asthma, and anyone older than 49 years of age, may administer LAIV. LAIV should not be given concurrently with other live-virus vaccines [97].

### ADMINISTRATION OF THE INTRANASAL INFLUENZA VACCINE

Intranasal influenza vaccine is supplied in prefilled single-use sprayers containing 0.5 ml of vaccine and must be stored at -15 degrees C (5 degrees F) or colder, unless the package insert indicates otherwise. Because frost-free refrigerators can cycle above this temperature, LAIV should not be stored in a frost-free refrigerator. It must be thawed before administration. This is done by holding the individual sprayer in the palm of the hand until it is thawed. It should be administered as soon as it is thawed. It can be thawed in the refrigerator and stored at 2 to 8 degrees C (35 to 45 degrees F) for  $\leq$ 24 hours. It should **not** be refrozen. Because the vaccine is so expensive, it is best to thaw it as needed. Half of the dose in the sprayer, approximately 0.25 ml, is sprayed into one nostril while the patient is sitting upright. The attached dose-divider clip is removed so the rest of the dose can be sprayed into the other nostril. The dose is **not** repeated if the person sneezes. Persons receiving LAIV should not take any antiviral medications for 2 weeks [6].

### SIDE EFFECTS OF LAIV

Several prelicensure clinical trials of approximately 28,000 doses to more than 20,000 subjects showed that there was no statistical difference in adverse events between LAIV recipients and placebo recipients.

Both children and adults note side effects of nasal congestion and headache. Children may also experience fever, vomiting, abdominal pain and myalgias. Many adults complain of sore throat. All of these side effects are statistically higher for those who received LAIV than the controls who received the placebo [6].

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## PROMOTING THE USE OF INFLUENZA VACCINE

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The Healthy People Year 2010 objectives are to [1]:

- Increase influenza vaccination levels to 60% or higher among high-risk groups
- Have 90% of residents in long-term care facilities receive the vaccine
- Reduce influenza-related deaths in those 65 years of age and older

Among non-Hispanic white people 65 years of age and older, the 60% objective has been exceeded to such an extent that the overall influenza vaccination rate for those 65 years of age and older is 66%. However, people of color have much lower rates. The influenza vaccine administration rate among whites is 70%, 52% among black elders, and 46% among Hispanics [36].

There are several other high-risk groups that have been listed above—persons of all ages with chronic medical conditions, infants 6 to 23 months of age, women in the second and third trimester of pregnancy during influenza season—that fall far short of the 60% influenza immunization rate. According to a study done by the National Foundation for Infectious Diseases and the National Coalition for Adult Immunization, only 29% of high-risk people, 18 to 64 years of age, were immunized against influenza during the 2000–2001 flu season [36].

## FACTORS INFLUENCING INFLUENZA IMMUNIZATION

One of the major factors influencing people with conditions that put them at high-risk for complications, hospitalization, and death from influenza is the **misconception that the flu shot will give**

**them the flu.** This misconception is fueled by the fact that, in such a large cohort receiving the influenza immunization, a certain percentage will already be incubating the flu. When the symptoms of influenza appear a day or so after getting the shot, the natural assumption is that the illness came from the shot. Some take the opposite view that the flu shot will protect them against colds so are disappointed the “the flu shot didn’t work” when they get a cold [2].

Another factor is that patients rely on their physician’s advice. Unfortunately, the physician may not specifically suggest that the patient get the influenza vaccine. This leads the patient to think it is not important or it would have been mentioned.

Cost may be a prohibitive factor for those too young for Medicare, which covers influenza and pneumococcal immunizations. A few people assume that the influenza immunization is effective for several years. Some feel that a healthy person should not take anything like a flu shot that might make them sick [2].

Others do not realize how effective the influenza vaccine is in preventing complications, hospitalizations, deaths, and actual prevention of influenza disease when the vaccine antigens correspond to the circulating antigens.

Probably one of the biggest factors affecting influenza immunization rates is the fact that influenza is so common—a true illustration of “familiarity breeds contempt.” Few are aware of the number of hospitalizations, deaths, and economic burden associated with influenza. Media attention focuses on deaths from SARS or other diseases while influenza kills far more each year.

## IMPROVING INFLUENZA VACCINE USAGE

### The Role of the Healthcare Provider

One of the major factors in increasing the number of administrations of influenza vaccine is the involvement of the medical practitioner providing care in a variety of settings—physicians’ offices, clinics, outpatient rehabilitation programs, or any place where there is contact between medical pro-

viders and their patients. The majority of flu shots given are administered by the person's personal healthcare provider [2]. In addition, studies have shown that 80% of people receiving the influenza immunization have been recommended to do so by their practitioner. For patients who were not told by their healthcare provider to get a flu shot, only 27% did so [45].

Studies have shown that as many as 75% of patients at high-risk for influenza or for death from a complication of influenza have seen a healthcare provider in the last year. One idea is to place a sticker on the front of the chart of any such high-risk patient so the influenza vaccine can be discussed at each visit and administered, as needed, if the visit occurs during the flu season.

Beginning in September, healthcare providers should offer the immunization to all high-risk patients, including children 6 months to 5 years of age. The CDC also recommends that the offer of the vaccine and its refusal be documented in the medical record [96].

A computer-generated list of high-risk patients who are not scheduled to be seen could also be developed. Reminders could be sent stating that the flu shot is due by phone, email or regular mail [1].

Educational efforts by public health departments through media and personnel could encourage high-risk people to ask their healthcare provider for the flu shot [2].

Medical providers should also be informed of the reimbursement for the vaccine and its administration by Medicare and Medicaid and instructed as to billing methods, especially roster billing.

Perhaps one of the most effective methods of encouraging a high-risk patient to receive the flu shot is the verbal recommendation of the patient's physician. One study showed that 80% of those who were not planning to get a flu shot received one because their physician told them to do so [45].

As with childhood immunizations, the perception of the healthcare provider as to the number of patients who receive the influenza vaccine is higher than statistics confirm. In one study, practitioners felt that 80% of their patients had received the influenza immunization, but a study of the patient records showed that only 15% had done so [45].

Patient reminders also increase the number of persons being immunized. Smaller practices can mail reminder post cards. Keeping a database or list of those patients who should receive these cards will lessen the staff time involved, especially if the database will print out addresses [45].



Provider reminders are recommended by the Task Force on Community Preventative Services on the basis of strong evidence of effectiveness in improving targeted influenza vaccination coverage among patients 65 years of age and older. Techniques by which reminders are delivered vary, from the use of notations in clients' charts, to attached chart prompt or stickers, to standardized checklists generated by the clinical staff or developed from computer databases and registries. ([http://www.guidelines.gov/summary/summary.aspx?view\\_id=1&doc\\_id=7081](http://www.guidelines.gov/summary/summary.aspx?view_id=1&doc_id=7081). Last accessed October 19, 2007.)

**Level of Evidence:** The body of evidence identified in the review included two studies of provider reminders focused on influenza vaccination, one study focused on pneumococcal vaccine, and four studies of both influenza and pneumococcal vaccination.

Beginning in September, emergency rooms and walk-in clinics should display posters and educational materials on the need for the flu shot, and provide the vaccine or information on where to obtain it [6].

Influenza immunization is recommended for all people who have contact with high-risk populations. Obviously, this includes all healthcare professionals. The immunization will lower worker absenteeism and transmission to vulnerable patients. However, only 38% to 42% of healthcare professionals receive an annual influenza immunization [6; 38; 96].

Those who supervise or manage other healthcare personnel should set an example for their staff and patients by making sure to get a flu shot each year. It seems that those who have received the vaccine are more aware of the need to inform the patients of the value of the flu shot and their example is an encouragement.

LAIV should not be used to immunize contacts of severely immunocompromised patients unless no contact for 7 days following receipt of LAIV can be assured [6]. At this time, there is no data that a healthcare professional immunized with LAIV has transmitted influenza to a patient. However, because LAIV has been recently introduced, it is best to err on the side of caution and use the IM vaccine to immunize those caring for immunocompromised individuals until more studies are available. Convenient access to the flu shot should be provided at the work site, free of charge, to encourage more healthcare professionals and allied personnel to get it [6].

### Standing Orders

Implementation of standing orders in acute care hospitals is another way to help increase influenza vaccine coverage. Patients who are hospitalized as flu season approaches, or during flu season, should have their records checked for chronic illness that is impacted by influenza and for influenza vaccine status. Those who have risk factors for complications and have not received the influenza immunization should receive the flu shot before discharge as covered by the standing order. Such standing orders would have to be developed and implemented by the medical board of the hospital. All medical personnel connected with the hospital should be made aware of the standing order and reminded by posters or other means during influenza season. A study of Medicare patients hospitalized during flu season showed that only 31.6% had received the flu vaccine before admission, 1.9% during admission, and 10.6% after admission [6].



According to the Advisory Committee on Immunization Practices (ACIP), strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs, should be implemented whenever feasible.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=10950](http://www.guidelines.gov/summary/summary.aspx?doc_id=10950).  
Last accessed October 19, 2007.)

**Level of Evidence:** Expert Opinion/Consensus Statement

In long-term care facilities, there should be a standing order for each patient to receive a flu shot in October. When a patient is admitted to the facility, the attending medical professional and family member(s) should be informed of the standing order. If there is a reason that the patient should not receive the influenza vaccine, the physician can so order or the family member can so request. All residents should be immunized on the same day, if possible, before flu season. Those admitted after this day should receive the vaccine upon admission [6]. One study showed that only 62% of residents in nursing homes received influenza immunization in spite of its demonstrated effectiveness in preventing complications, hospitalization and death in long-term care patients. Another study showed that if 80% or more of the residents in the facility were immunized against influenza, hospitalization from all causes was reduced regardless of the vaccination status of the individual resident [46].

As noted previously, another protective measure for residents of institutions is for the care providers to receive an influenza immunization.

Home healthcare agencies should also have protocols in place to immunize patients under their care during the flu season and to inform the in-home caregivers of their need to be immunized. Staff members with patient contact should also be immunized [6].

All healthcare providers of patients in hospitals, long-term care facilities, and home health agencies should be aware that the Centers for Medicare and Medicaid Services (CMS) has removed the physi-

cian signature requirement for the administration of influenza and pneumococcal vaccines to patients covered by Medicare and Medicaid [6].

### The Role of Community Agencies

Religious meeting places are a point of contact for many groups. Patient education materials can be included in the organization's bulletin. In some areas, the local public health department will provide an influenza immunization clinic in conjunction with a religious service.

Reminder posters and educational materials can also be displayed at banks, grocery stores, and community centers. These materials are available at the local public health department or on the CDC website.

Organizations, such as Lions, Kiwanis, Rotary and the American Association of Retired People (AARP), that are interested in controlling the cost of healthcare should be enlisted to help encourage their friends and neighbors to be immunized against influenza [45].

Many public health departments provide influenza immunizations in community settings, such as churches, community centers, meetings of minority groups, and malls—any place where a clinic can be temporarily set up for a few hours. Some even provide “drive-up clinics” where the person doesn't need to get out of the car to receive the flu shot. These clinics are especially helpful for a person who cannot wait in line or walk easily.

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## OTHER METHODS TO PREVENT INFLUENZA

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The primary and most effective way to prevent influenza is the vaccine. However, in the case where the antigens of the vaccine are not close enough to the circulating antigen, a shortage of vaccine, or a new strain has emerged and is circulating before the vaccine can be made and distributed, people will have to resort to other ways to protect themselves from infection.

## HANDWASHING

Good handwashing is difficult to practice, is rarely known or taught, and is one of the single most effective ways to prevent transmission of many diseases, including influenza. Everyone knows to wash their hands before eating and after using the restroom and have been doing so as long as can be remembered. However, few do little more than remove obvious dirt. Good handwashing involves removing the skin oils where the organism can remain even when the hands look clean. A quick pass under the water faucet and fast dry with the towel removes visible dirt but the oils and organisms remain.

To effectively remove the oils and organisms, the process should take at least 20 seconds—for children (and others)—the amount of time it takes to sing “Twinkle, Twinkle Little Star.” The hands should be soaped and rubbed vigorously for 15 seconds to create a good lather and to assure that all parts of each hand are soaped and rubbed well. Then the hands should be rinsed thoroughly and dried, preferably with a paper towel. The towel should be used to turn off the water and then properly thrown away. Such handwashing removes the oils that harbor the organisms. But 20 seconds is a long time in the busy life of a healthcare provider. If there is no visible dirt or contamination, a waterless hand sanitizer with at least 60% alcohol can be used between patients. However, nothing is as good as washing well with soap and water. Some mistakenly think that hot water must be used to kill the organisms. Water hot enough to kill organisms would be too hot to touch. Warm water mainly adds to comfort and hopefully encourages better washing technique. Careful attention to handwashing and cleansing may result in chapped skin so the medical professional must find the proper lotions to care for his/her hands [47].

## AVOID TOUCHING EYES, NOSE, OR MOUTH

The eyes, nose, and mouth are entryways for bacteria and viruses. Everyone tends to unconsciously touch their eyes, nose, and mouth when going about their activities. Because organisms are not visible, and

hand washing is often less than adequate, infection occurs. Though difficult, the person trying to prevent illness should make a conscious effort to avoid touching his/her face [48].

### **PROPER COVER FOR A COUGH OR SNEEZE**

Disposable paper tissues should be used to cover one's nose or mouth when coughing or sneezing. Hands will be contaminated with the offending virus or bacteria while covering. Ideally the hands would be cleaned with soap and water or alcohol-based hand cleaner after each cough or sneeze to prevent transfer of the organism to someone else. In reality, sneezes and coughs may often only be covered with a bare hand, which may not be washed immediately. Keeping tissues handy during cold and flu season is a good idea. Also, education of patients and children should include teaching them to cough and sneeze into their upper sleeve instead of into their hand. Covering a cough or sneeze is of primary importance however it is done [49]. Coughing, sneezing, or blowing nasal secretions into a cloth handkerchief results in maintaining a moist, viable culture that is then carried in the pocket or purse and can result in prolonged episodes of re-infection or transfer from cross-contamination.

### **AVOID PEOPLE WITH RESPIRATORY SYMPTOMS**

During cold and flu season, trips to the store, school, church, work place, etc. bring contact with those who are coughing and sneezing. If at all possible, avoid close contact. This is an excellent time to consciously work on keeping your hands away from your face. Good handwashing should be done as soon as possible after contact with someone exhibiting symptoms of respiratory illness. Help the immune system to overcome the organisms by getting enough rest, drinking 6 to 8 glasses of water a day, and eating fresh fruits and vegetables [50]. Healthcare providers can lessen the spread of influenza by utilizing proper cough etiquette, providing tissues and safe disposal, using rapid diagnostic tests and antiviral chemoprophylaxis for suspected flu in healthcare workers, and recommending that influenza sufferers stay home [96].

### **ANTIVIRAL MEDICATIONS AS PREVENTION**

Antiviral medications can also be used to prevent influenza. Three of the four antiviral drugs used to treat illness due to influenza can also be used to prevent it. Amantadine (Symmetrel) and rimantadine (Flumadine) have been approved for treatment and prevention but are not approved to be used in infants younger than one year of age. Oseltamivir (Tamiflu) is an effective treatment of uncomplicated acute illness due to influenza A and B viruses in adults and children older than one year of age, and it is approved as a preventative in persons 13 years of age and older. In 2007, the Japanese Ministry of Health, Labor and Welfare issued a warning that oseltamivir may cause psychiatric problems and suicide in patients 10 to 19 years of age [109]. This warning has been the subject of much controversy, and no such warning has been issued in the United States. Zanamivir (Relenza) is not approved for prophylaxis.

A physician's order is required to obtain any of the antivirals. In healthy adults amantadine and rimantadine have been demonstrated to prevent influenza A illness 70% to 90% of the time [6]. However, the increasing incidence of amantadine and rimantadine resistant strains of influenza in the United States has made these medications less effective [91].

Antiviral medications can make a person less contagious to others, so they are prescribed for contacts of people who are at high risk for complications from the flu. A subclinical infection may develop in a patient taking an antiviral. This allows the body to make antibodies against the virus. If unsuccessful in fully preventing clinical illness, the person should be less contagious. If any antiviral medication is to be totally effective, it must be taken as long as influenza is active in the community. Some studies indicate that taking an antiviral during peak influenza activity in a community is also effective. The less expensive single application vaccine is the best choice in preventing influenza in contacts of high-risk persons. However, in situations where the individual has a hypersensitivity to one of components of the vaccine, or

the needed 2 weeks to develop immunity are not available before contact, an antiviral medication can be used. Another reason to use an antiviral prophylaxis would be if the available vaccine does not match the circulating virus.

Antivirals are also used in closed environments, such as an institution or cruise ship, to control flu outbreaks. In such a case, it is best to combine the vaccine with an antiviral to provide protection for those exposed but have not developed illness until the vaccine can stimulate the immune system to make protective antibodies. This also avoids the protracted use of the antiviral medication. The antiviral will not interfere with the antibody response elicited by the vaccine [1; 6; 51].

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## ANTIVIRAL MEDICATIONS

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The antiviral medications, amantadine, rimantadine, zanamivir and oseltamivir, are also used to treat acute illness due to influenza. To be effective, any of these medications must be started within 48 hours of symptom onset. Generally, a course of one of these antivirals will reduce the illness by 1 to 2 days and will make the patient less contagious to others. These medications are effective only against influenza viruses and will not affect the common cold or other influenza-like illnesses of viral origin [6; 51; 52].

### AMANTADINE

Amantadine was approved as a treatment for uncomplicated respiratory tract illness caused by influenza in 1966. It belongs to a group of chemically related drugs called adamantanes (tricyclic amines) and is effective only against influenza A viruses. This drug is approved for use in patients one year of age or older. The dosage for patients 10 years of age and older, weighing 40 or more kilograms (88 or more pounds), is 200 mg daily, which can be administered in a single dose or 100 mg twice a day by mouth. A treatment course is for 3 to 5 days. A lower dose should be used in patients with renal impairment and they should be observed carefully for adverse reactions. For children less than 40 kg/88 lbs, the dose is 5 mg/kg/

day, not to exceed 50 mg/day. Children 1 through 9 years of age should be given 4.4–8.8 mg/kg/day not to exceed 150 mg/day. Anyone with untreated angle closure glaucoma should not take amantadine because of its anticholinergic effects that might cause mydriasis.

Side effects may be central nervous system (CNS) manifestations, such as nervousness, anxiety, trouble concentrating, insomnia, or confusion and occur in 13% of patients. Nausea and anorexia occur in approximately 1% to 3% [6]. The CNS side effects occur more frequently with amantadine than with its sister drug, rimantadine. Patients with long-term illnesses may have more serious side effects of delirium, hallucinations, agitation, and seizures. Side effects cease soon after the medication is discontinued. It takes about a week for the side effects to disappear in patients who must continue to take either amantadine or rimantadine. Amantadine is also used to treat parkinsonism and similar conditions. A drug history should be obtained.


Viruses that develop resistance to amantadine (usually after 2 to 3 days of therapy) are also resistant to rimantadine, and vice versa. The CDC completed extensive testing for drug resistance in the major influenza strains during the 2005–2006 influenza season. This research indicated that amantadine and rimantadine resistance had risen to the point of impaired effectiveness. For this reason, the CDC issued interim guidelines recommending against the use of amantadine or rimantadine for the treatment or prophylaxis of influenza A in the United States for the remainder of the 2005–2006 season [91]. The resistant strains currently do not appear to be more virulent or transmissible than susceptible viruses, but more research is needed [6; 10; 52; 53] (**Table 8**). Again, practitioners are encouraged to consult the package insert or the CDC for current recommendations.

### RIMANTADINE

Rimantadine, approved in 1993, is also in the adamantanes group. Therefore, it is also only effective against influenza A and may have the same side effects as listed under amantadine. CNS side effects occur less frequently with rimantadine (6%). Like

| COMPARISON OF ANTIVIRALS USED IN INFLUENZA |   |   |   |   |
|--|---|---|---|---|
|  | Amantadine  | Rimantadine   | Zanamivir   | Oseltamivir   |
| Type of antiviral                          | Adamantane  | Adamantane  | Neuraminidase inhibitor                                   | Neuraminidase inhibitor   |
| Effective for type                         | Influenza type A                                    | Influenza type A                                    | Influenza types A and B                                   | Influenza types A and B   |
| Route of administration                    | Oral  | Oral  | Inhaled   | Oral  |
| Age that can receive                       | 1 year of age and older<br>Treatment and prevention | 1 year of age and older<br>Treatment and prevention | Treatment: 7 years of age and older<br>Not for prevention | Treatment: 1 year of age and older<br>Prevention: 13 years of age and older |
| Action                                     | Decrease symptoms                                   | Decrease symptoms                                   | Decrease symptoms   | Decrease symptoms<br>Decrease antibiotic use                                |
| Side effects                               | CNS and GI symptoms                                 | CNS and GI symptoms<br>Fewer than amantadine        | <5% diarrhea, nausea, headache, cough                     | Nausea and vomiting   |
| Comparative cost                           | Cheapest  | Middle  | High  | High  |
| Sold as                                    | Symmetrel   | Flumadine   | Relenza   | Tamiflu   |
| <i>Source: Author</i>                      |   |   |   | <i>Table 8</i>  |

amantadine, nausea and anorexia occurred in 1% to 3% of the patients. Dosage for adults is 200 mg/day in divided doses of 100 mg, twice a day. If older patients experience CNS side effects, the dose should be decreased to 100 mg/day [6; 10; 52; 53]. At this time, rimantadine should not be used in the prophylaxis or treatment of influenza A.



The Advisory Committee on Immunization Practices (ACIP) recommends that, because antiviral testing results indicated high levels of resistance, neither amantadine nor rimantadine should be used for the treatment or chemoprophylaxis of influenza in the United States during the 2007-08 influenza season. Oseltamivir or zanamivir can be prescribed if antiviral treatment of influenza is indicated.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=10950](http://www.guidelines.gov/summary/summary.aspx?doc_id=10950).  
Last accessed October 19, 2007.)

**Level of Evidence:** Expert Opinion/Consensus Statement

## ZANAMIVIR

Zanamivir belongs to the antiviral group of neuraminidase inhibitors. It is effective against both influenza A and B and was approved in 1999 to treat uncomplicated illness due to influenza

virus in adults and children 7 years of age and older. As noted above, zanamivir is not approved to prevent influenza. The dosage is 10 mg twice a day by inhalation for 5 days. Doses should be 12 hours apart. Zanamivir can lead to a decrease in respiratory function and bronchospasm. It is not recommended for patients with asthma, obstructive pulmonary disease or other chronic lung diseases. Side effects include diarrhea, nausea, headache, dizziness, nasal infections, sinusitis, and bronchitis, but occur in less than 5% of patients. Some allergic responses of oropharyngeal or facial edema have also occurred [6; 10; 52; 53].

## OSELTAMIVIR

Oseltamivir also is a neuraminidase inhibitor and effective against both influenza A and B viruses. Like zanamivir, it was approved in 1999. It can be used as treatment in adults and children older than one year of age who have been symptomatic for no more than 2 days. It can also be used as a preventative in anyone 13 years of age or older. The dose is 75 mg twice a day by mouth for adults and for children and adolescents who weigh more than 40 kg/88lbs. Studies have shown that oseltamivir reduces the incidence of complications that may require antibiotics. Although the neuraminidase inhibitors promote a drug-resistant mutant of the virus, less resistance appears to occur with oseltamivir than with zanamivir. The reported side effects

with oseltamivir are nausea and vomiting which are lessened if the medication is taken with food [6; 10; 52; 53].

## ANTIVIRALS AS TREATMENT OF ACUTE ILLNESS RESULTING FROM INFLUENZA

All treatment with any of the 4 antivirals must begin within 48 hours of symptom onset to be effective. In most individuals without underlying medical conditions, influenza is a self-limiting disease. Recovery usually occurs after a week, although fatigue and malaise may persist two or more weeks. The decision to use an antiviral is influenced by the type of work the patient does. In an epidemic or pandemic, persons providing critical services should be treated because shortening their absence by one or two days is important. For other personnel, the decision should be based on the comparison between the wages that would be lost and the cost of the medication [52].

Some people may desire treatment because of upcoming plans or because they don't like to be sick. These individuals should be encouraged to obtain the annual influenza vaccine in the future, as disease that develops in spite of the vaccine is usually milder unless the vaccine strains do not match the circulating strains.

If an outbreak of influenza occurs in an institution, antiviral medications should be used for both treatment and prophylaxis [6].

For patients with underlying factors that put them at high-risk for complications, hospitalization, and/or death, an antiviral should be given if it is within 48 hours of symptom onset, and the condition, or current medications taken by the patient, do not interact adversely with the antiviral. Preventing hospitalization with an antiviral is cost-effective. Also, preventing the need for antibiotics in secondary bacterial infections is wise [6; 52].

At this time, studies of the effects the adamantanes on the fetus have only been done on animals where the high doses used were teratogenic and embryotoxic. Therefore, antivirals should only be used

with pregnant women when the potential risk of complications from influenza exceeds the potential risk from the antiviral [6].

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## CARE OF THE INFLUENZA PATIENT

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### AT HOME

Family members or friends should be located to care for the high-risk patient who lives alone. With enough community support (home health, neighbors, Meals-on-Wheels), a patient might be able to remain alone, but it would require careful planning and coordination among all involved. During an epidemic or a pandemic, it may be necessary to set up temporary facilities, such as a shelter for medically fragile patients, to provide care. A normally healthy adult living alone may only need help in the form of shopping.

Points in care of the patient include: careful observation, providing symptomatic relief, help with activities of daily living, helping the patient remain hydrated, and emotional support (**Appendix 2**).

### PREVENTIVE MEASURE FOR THE CAREGIVER

Attention must also be given to the person(s) caring for the influenza patient in the home to protect him/her from the disease. This would include influenza immunization, with or without an antiviral medication for two weeks, instruction on effective handwashing, wearing a mask when providing care or when the patient is coughing, getting adequate rest, consuming 5 or more fruits, fruit juices, and vegetables each day, and drinking 8 glasses of water a day (**Appendix 3**).

### SELF-CARE

Hopefully, no one reading this course will experience influenza because they will have obtained the immunization. However, should the reader develop influenza and not be at high-risk for complications, there are a few general steps to speed recovery and protect others [54].

- Consider obtaining an antiviral if flu is in the first or second day of illness
- Stay home to protect others from infection
- Get plenty of rest
- Drink plenty of liquids
- Do not drink alcohol or use tobacco products
- Consider over-the-counter medications to relieve the symptoms
- Cover coughs and sneezes
- Wash hands well and frequently, especially after coughing or sneezing

### OBSERVATIONS INDICATING URGENT MEDICAL HELP IS NEEDED

By keeping a written record of observations, a patient's subtle changes become more apparent, and the information will also help a physician. As discussed above, there are many diseases that initially present like influenza, or conditions that can be complicated by influenza, therefore each person with influenza should be watched. The patient with influenza usually starts to improve after a few days. Patients and/or caregivers should be given a list of symptoms that indicate when a physician should be notified (*Appendix 4*).

Any difficulty in breathing, a fever that is not responding to antipyretics, change in mental state, inability to maintain hydration, or worsening of symptoms should be reported to a physician, or the patient should be taken to the emergency room if a physician is unavailable.

The healthcare professional should review the following items with influenza patients or their family member(s), so a physician can be notified appropriately and promptly:

- High or prolonged fever
- Breathing: in children, may be fast or difficult with retractions, there may be cyanosis in adults, there may labored breathing or shortness of breath, pain or pressure in the chest

- Inadequate fluid intake—fewer wet diapers, darker urine (dehydration in small children with influenza is one of the more common reasons for hospitalization)
- Changes in mental status: hard to arouse, confusion, too irritable to be comforted
- Fainting or near-fainting, seizures
- Severe or persistent vomiting
- Worsening of a chronic disease
- Worsening of influenza symptoms, increasing weakness
- Any rash, jaundice
- Dry cough that becomes productive [54]

### THE INFLUENZA PATIENT IN THE HOSPITAL, MEDICAL OFFICE, OR CLINIC

Infection control procedures should be followed carefully as soon as any contact with an influenza patient occurs so that transmission can be prevented. In order to protect staff, posters prominently displayed or warning signs at the sign-in desk should request that the staff be informed if the patient has any respiratory symptoms.

Patient education posters on the flu, the vaccine, and on cough etiquette should be displayed in emergency rooms, waiting rooms, exam rooms, on elevators, and other appropriate traffic areas used by patients and visitors. Messages should be brief but clear. Pictures could also be included for children who cannot read or for non-English speakers.

As a result of the evolving racial and immigration demographics in the U.S., interaction with patients for whom English is not a native language is inevitable. Because patient education is such a vital aspect of the prevention and treatment of influenza, it is each practitioners' responsibility to ensure that information and instructions are explained in such a way that allows for patient understanding. When there is an obvious disconnect in the communication process between the practitioner and patient due to the patient's lack of proficiency in the English language, an interpreter is required.

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between clients/patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter.

All education materials should be provided in the major languages of the community.

Educational materials might include:

- Cough etiquette
  - Cover your cough.
  - Use a tissue.
  - Throw the tissue away in the wastebasket.
  - Wash your hands.
  - Tissues and wastebaskets should be easily accessed.
- Handwashing
  - Use soap.
  - Rub your hands well to make a good lather.
  - Rub your hands for 15 seconds.
  - Rinse well.
  - Dry with a paper towel.
  - Turn off water with a paper towel.
  - Throw the paper towel in the wastebasket.

If no facilities to wash hands are available, alcohol-based hand cleaner should be available.

When influenza is present in the community, patients who are coughing are given a mask and asked to sit in a separate area. If a separate area is not available, they should be at least 3 feet away from other people. Masks can be the surgical masks with ties or procedural masks with ear loops. They do not need to be respirator N95 masks.

Staff involved with patients who have respiratory symptoms with fever should follow droplet precautions as developed at their work place. For all patient contact, a mask (surgical or procedural) should be worn. Hands should be washed thoroughly following contact. During an epidemic, staff circulating between floors in the hospital should be limited [55].

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## AVIAN INFLUENZA

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In the past, the influenza viruses that are carried by birds, both domesticated and wild, rarely have infected humans. There is a natural barrier partly due to the fact that avian influenza (AI) viruses attach to receptors found on bird cells but not found on human cells. Human viruses prefer the receptors found in the human respiratory tract. Pigs have been the link between avian and human influenza viruses because they have receptors that avian, swine, and human influenza viruses use. Because pigs acquire all 3 types of viruses, reassortment/antigenic shift of the hemagglutinin and neuraminidase proteins occurs in the pig host, which then transmits the new strain to humans or other pigs [5]. There now exists evidence that avian influenza can spread directly to humans [83]. In 2004, areas of Asia experienced large-scale outbreaks of avian influenza, specifically the H5N1 virus, in poultry. The virus went on to infect humans, with a high mortality rate. The number of countries, people and animals affected by the virus reached unprecedented levels. In 2006, the CDC summarized the H5N1 outbreak. Wild birds and poultry had been infected in Asia, parts of Europe, the Middle East, and Africa. Human infections were continuing to be reported in China, Egypt, Indonesia, Azerbaijan, Cambodia, and Djibouti. There were some probable human-to-human transmissions of H5N1, but these were rare. As of June 2006, there had been 225 human cases of H5N1, with a continued fatality rate of approximately 50% [112]. The WHO has reported that there is a strong threat of a future pandemic of avian influenza and that preparedness is vital [90].



The Centers for Disease Control and Prevention (CDC) recommends that state and local health departments, hospitals, and clinicians enhance their efforts to identify patients who could be infected by influenza A (H5N1) virus and take infection-control precautions when influenza A (H5N1) is suspected.

([http://www.guidelines.gov/summary/summary.aspx?doc\\_id=4761](http://www.guidelines.gov/summary/summary.aspx?doc_id=4761). Last accessed October 19, 2007.)

**Level of Evidence:** Consensus Statement and/or Expert Opinion

Although influenza A viruses can infect all birds, domestic poultry flocks are more vulnerable to infections that can reach epidemic proportions. Generally, domesticated fowl transmit the virus in saliva, nasal secretions, and feces. However, it is thought that the fecal-oral route is the common way the virus is spread among flocks. Wild birds rarely become sick but are a source of infection through their droppings because they carry the virus in their intestines. Free-roaming domestic fowl are at more risk from wild bird droppings than housed flocks. Both food and water supplies can be contaminated by droppings or sharing with wild birds. At first it was thought that wild birds spread the virus from farm to farm, but further study indicated that people and equipment probably spread the virus to domesticated flocks [56; 57].

Avian influenza viruses are classified as low pathogenic and high pathogenic because of their genetic sequence and the resulting illness in birds. Low pathogenic AI has been detected in wild birds, mostly ducks, geese, and gulls, since 1975 [113]. Low pathogenic AI virus causes only ruffled feathers and a reduction in egg production. Fortunately, most AI viruses are low pathogenic, however, in 6 to 9 months, they can mutate to high pathogenic. High pathogenic AI viruses, first noted in 1878 in Italy, are highly contagious, spread rapidly, and are almost 100% fatal. Fowl can die the same day they first exhibit symptoms [58; 59; 113].

Whenever an AI virus infects a human directly, there is much concern. Humans rarely have any immunity to AI viruses. Medical resources around the world quickly mobilize when there is a case of avian influenza that skips reassortment in swine and directly infects a human. Fowl within a 2-mile (3-kilometer) radius of the source bird/flock are killed in order to contain the virus. An AI virus in humans usually produces upper respiratory disease and conjunctivitis. The infected humans and their contacts are watched closely for secondary transmission. For a pandemic to follow, these factors are needed:

- Humans do not have immunity to the virus
- Direct transmission from bird to human
- Sustainable transmission from human to human
- Movement of infected/contagious individuals to other geographic locations

Once a new pandemic influenza virus emerges, it generally circulates for many years [56; 58; 60].

## AVIAN INFLUENZA VIRUSES

The hemagglutinin antigens that historically have caused human influenza are H1, H2, and H3. Although all known hemagglutinin subtypes occur in birds, H5, H7, and H9 have been implicated more in recent outbreaks. Various combinations with the neuraminidase antigens occur. All of these AI viruses are type A as B and C do not infect birds. Some of the cases focused upon in recent years have included the following:

- H5N1 – Hong Kong, 1997, first documented human infection—18 hospitalized, 6 deaths, 1.5 million chickens culled
- H9N2 – Hong Kong, 1999, 2 mild cases in children, several in mainland China
- H7N2 – Virginia, 2002, 4.7 million chickens and turkeys killed
- H7N7 – Netherlands, 2003, 80 poultry workers, 3 family members infected (79 eye infections, 6 influenza-like), 1 veterinarian death due to acute respiratory distress syndrome and complications

H5N1 – Hong Kong/China, 2003, 2 ill, 1 death

H9N2 – Hong Kong, 2003, 1 case confirmed  
in a child

H5N1 – Asia, 2004–2005 (H5N1 had been  
found in Asian chickens April, 2003)  
[61]. As of August 2005: 112 confirmed  
cases, 57 deaths; too widespread to cull  
all fowl [90]

H7N3 – British Columbia, 2004

H5N2 – Taiwan, 2004, low pathogenic,  
no human illness

H7N2 – Delaware, 2004, no human illness

H5N2 – Texas, 2004, no human illness

H5N1 – Russia/Romania/Turkey/Azerbaijan,  
2006, some human illness, unknown  
deaths [111]

Fortunately, although in some of these outbreaks bird to human transmission did occur, human to human transmission has been extremely rare. Limited transmission possibly did occur between humans in the Netherlands, but no sustainable transmission occurred, so an epidemic or pandemic did not follow. There were 14 cases and 12 deaths (11 children) from H5N1 virus in Vietnam. The viruses isolated from those who expired in Vietnam were mostly resistant to amantadine and rimantadine. Studies are continuing as to the effectiveness of oseltamivir and zanamivir against H5N1 viruses. There is some evidence that the 2004 H5N1 virus in Asia is sensitive to oseltamivir [56; 57; 58; 61; 62; 63]. Most of these outbreaks were controlled by veterinarian officials or spontaneously died out. However, H1N1 continues to fulminate in poultry in Egypt and Nigeria [104].

## AVIAN INFLUENZA AND HUMANS

Most cases of avian influenza in humans have resulted from contact with infected poultry or contaminated surfaces. It is also possible that the virus becomes aerosolized and then lands on exposed surfaces of the mouth, nose, or eyes. Aerosolized virus could also be inhaled directly into the lungs. Eating poultry products has not been associated with the development of avian influenza. Influenza

viruses are destroyed by adequate heat. Because of the pathogens found in poultry, all patients should be reminded to cook all poultry, including eggs, thoroughly. Chicken should be cooked until the internal temperature reaches 180 degrees F. All utensils and surfaces that have come in contact with raw poultry should be washed well with soap and water immediately following use. A separate cutting board should be used to cut raw poultry. In order to retard bacterial or viral replication, all poultry products should be defrosted in the refrigerator, not at room temperature [61].

Some patients might become concerned about contaminated poultry products from other countries entering our food supply. Some countries will not permit poultry from countries in which there were confirmed human cases of AI in 2003 and 2004 to be imported. However, the risk of AI spreading through the global chicken industry is low because most chickens on the international market are killed and frozen or chilled. All documented transmission at this time has been from live birds [64].

Humans have no immunity to avian influenza A viruses, so illness tends to be severe and the fatality rate is high. Prevention is difficult because the viruses tend to be highly contagious. Because of the mobile nature of people and efficient, rapid transport, any virus can spread quickly around the world. The current manufacturing process of influenza vaccine requires several months. The elements are all in place for a pandemic.

On August 10, 2007, a team of scientists at the National Institute of Allergy and Infectious Diseases reported that they had developed a way to generate vaccines and therapeutic antibodies that could target constantly mutating influenza viruses, such as H5N1. The team focused on mutations that enable H5N1 hemagglutinin protein to better recognize and enter human cells and those mutations that will elicit antibodies. This information will enable researchers to consider how to design potential vaccines that will protect people from future emerging avian influenza virus mutants, possibly helping to contain a pandemic in its early stages [114].

In order to understand how influenza viruses mutate, researchers have been working to synthesize the hemagglutinin responsible for the 1918 influenza pandemic. The success of this endeavor was reported in 2004, and scientists have since discovered how subtle alterations enabled the virus to move from birds to people [117].

## **PREVENTING OR LESSENING THE EFFECTS OF A PANDEMIC**

### **Vaccine Development**

As with the development of all vaccines, the first step is to isolate the organism. In the case of avian influenza, various research centers and companies around the world are working to make a vaccine. The first step is to isolate the virus—specifically in 2004 the H5N1 influenza A virus. Next, the virus is dismantled so that the most virulent elements can be excluded. Then the virus is reassembled without those virulent elements, and attempts are made to produce it [64]. As noted, the virus has been isolated and the virulent elements have been identified to allow vaccine development to proceed. In 2006, a new recombinant H5N1 virus became available for distribution to companies interested in pandemic vaccine development [115]. In 2007, GlaxoSmithKline received a contract from the U.S. Department of Health and Human Services to manufacture 22.5 million doses of avian influenza vaccine in addition to the 5 million doses ordered in 2006 [127]. Currently, all influenza virus for vaccine production is grown in eggs, but some research is being conducted to find other media or other methods, such as splicing pieces of genetic code into other cells to mass produce the virus [65].

In April 2007, the FDA approved the first human vaccine for the avian influenza virus H5N1 [67]. This new vaccine is intended for individuals 18 to 64 years of age who could be at an increased risk of exposure to the H5N1 influenza virus. The vaccine is not available commercially, but rather has been purchased by the federal government to be distributed if necessary. The vaccine consists of two 1 ml IM doses given 21 to 35 days apart (optimum is 28 days). Note: there is thimerosal in

this vaccine [67; 116; 129]. Because this vaccine has been approved by the FDA and found to be safe and effective, it is no longer considered experimental. Therefore, it can be used during a pandemic without the time-consuming protocol and signed informed consent necessary for an experimental drug or vaccine [116].

### **Antiviral Stockpile**

Another plan is to gather a supply of effective antiviral medications to use not only to treat avian influenza but also to use as a preventative if a vaccine is not available. As discussed above, some testing of the four current antivirals available has been done with the H5N1 virus, which produced illness in Asia in 2004. So far, only oseltamivir was shown to be effective. More research is needed [57]. Some have suggested combining probenecid and oseltamivir to enhance effectiveness and to stretch limited oseltamivir supplies [118].

It is not known if other AI strains will be sensitive to oseltamivir or to any of the other antivirals. The suggestion is being made to stockpile antivirals so they would be available in a pandemic. Logically, it would make sense to include the effective antiviral medications in the Strategic National Stockpile, and use the same distribution system and overall protocol in managing them [68].

### **Increased Interaction Between Veterinary and Human Disease Experts**

Because of the rapid spread of avian influenza among flocks in Asia in the spring of 2004, the need for more involvement and communication between animal and human experts became apparent. Currently, there is no single system to monitor animal diseases around the world. No reporting of animal diseases is required by WHO. Human medical practitioners are not trained in the subtle indications of animal illnesses nor are they usually aware of early indications that an epidemic is developing. Veterinarian expertise is also needed to institute the best measures for containing the illness and limiting transmission not only to animals but to humans as well [69].

### Travelers

During the outbreaks of AI in poultry in Asia during 2003–04, people were not restricted from traveling to outbreak areas because of the limited transmission to humans. However, the following recommendations were sent to embassies and Americans living abroad:

- Practice frequent and careful handwashing with soap and water or with a hand cleanser if soap and water are unavailable.
- Avoid bird markets and poultry yards where AI is most likely to be transmitted.
- All poultry and eggs should be cooked well as influenza virus is destroyed by heat.
- Masks and other personal protective equipment in public areas are not recommended [70].

Travelers should be immunized with the current influenza vaccine against human influenza strains before traveling and should be reminded that winter, i.e., flu season, occurs in the Southern Hemisphere when the Northern Hemisphere is experiencing summer.

### Limiting Introduction of Avian Influenza to Other Countries

The CDC has developed guidelines for airline personnel with a suspected case of avian influenza on board an international flight originating in an area in which AI has been reported. General precautions of handwashing and covering coughs are, as always, important.

- As much as possible, airline staffs are to keep the sick person separated from close contact with others.
- A surgical or procedural mask should be provided to limit the amount of droplets coughed into the air. If the passenger can't wear the mask, anyone assisting him/her should be masked.
- Staff should teach the passenger cough etiquette if it is not being practiced.

- Disposable gloves are to be worn for any contact with body fluids and hands are to be washed well when gloves are removed.
- The captain is to report the illness to the nearest U.S. Quarantine Station if the aircraft is coming to the U.S. The Quarantine Station will coordinate appropriate medical assistance when the plane lands and will notify the appropriate CDC staff.

Should flight personnel or ground staff become ill and believe they have been exposed to AI, they should notify their employer. If they are away from home, they should obtain local medical help. On any visit to a medical practitioner, they should inform the staff of the possible exposure to AI [71].

### Limiting Continuing Disease and Transmission Among Fowl

The major way to limit disease and transmission among domesticated fowl is to destroy all diseased birds and their flock mates. Because the virus appears to be carried by people and machines, possibly on shoes and tires, to surrounding areas, the recommendation is that all fowl in a 2-mile (3-kilometer) radius of the diseased flock be culled. Obviously no shipping of live poultry from the infected areas should occur.

Those culling the flocks are vulnerable to infection because they will be dealing with diseased birds, exposed to their feces or to dust/dirt contaminated with the feces. Therefore, cullers must have personal protective equipment; coveralls or a surgical gown with long sleeves and an impermeable apron, heavy duty rubber gloves or disposable nitrile or vinyl gloves, rubber boots or disposable shoe covers, N95 respirator masks, and safety goggles. Frequent effective hand washing is important. All cullers should have received the current influenza vaccine so that they will not acquire the circulating influenza and provide an opportunity for reassortment with the AI strain. Cullers should be monitored by the local health department, and be provided information on the ways to prevent infection. They should be

instructed when to call the practitioner, and to always tell the practitioner that they have been exposed to avian influenza. Persons who are at high-risk for complications from influenza should not be employed as cullers. Medical personnel who have contact with cullers should make sure that the cullers have received the current influenza vaccine, understand the symptoms of the flu, realize that eye infections are common, and understand the importance of following the protective guidelines, including how to effectively wash their hands. The CDC also recommends that while the workers are involved with culling, they should receive an antiviral drug based on sensitivity testing of the offending virus. If this testing is not available, oseltamivir should be used [72; 73].

Those who disposed of the carcasses and those who are cleaning and disinfecting the environment where the flocks were housed are also at risk. The viruses can survive for varying periods of time depending upon the temperature and humidity. These viruses may survive for weeks in cool, moist environments. For personal protection, they should follow the same recommendations as the cullers [73].

All workers involved in eradication efforts should be monitored for one week after the last involvement with the diseased birds, or their environment, for respiratory symptoms, fever, and conjunctivitis. If they seek medical care, they should be instructed to tell the practitioner that they were working with birds that had avian influenza. Other than seeing the practitioner, all symptomatic personnel should stay home until their temperature has been normal for 24 hours. To protect their families, they should cover all coughs and dispose of the tissues safely, wash their hands well, and try to limit any face-to-face contact with others [73].

In handing environmental clean up, it is important to note that the virus is killed by heating to 56 degrees C/132.8 degrees F for 3 hours or 60 degrees C/140 degrees F for 30 minutes. Formalin and iodine compounds will also kill AI. When the temperature is cool, the virus can survive for 3 months in

contaminated manure. It can survive for 4 days at 22 degrees C/71.6 degrees F in water and for more than 30 days at 0 degrees C/32 degrees F [58].

The culling of millions of birds has an economic impact on the owners and countries in which the culling must be done. However, the more widespread the virus is in any country or countries, the more opportunity there is for transmission to humans. Each AI in a human increases the possibility that co-infection with a human influenza virus can occur leading to reassortment of the antigens and a new virulent influenza virus that can be transmitted person-to-person [58].

### **Limiting Transmission of Influenza by Medical Treatment**

If the patient is known to have, or suspected of having, respiratory avian influenza, they should be segregated in the waiting room, be provided with a surgical or procedural mask, be given tissues and a way to dispose them, and not be kept in the waiting room for an extended period.

A nasopharyngeal swab or aspirate should be collected and sent to the local public health laboratory. It is important to keep the local health authorities aware of any such suspected illness so that the full use of available resources can be made, if necessary. The specimen should then be forwarded to the state laboratory for reverse transcription—polymerase chain reaction (RT-PCR) for influenza A analysis and, if possible, for H1 and H3 analysis. Should the state not have the capacity to perform these tests, or if the tests are positive, the specimen should be sent to the CDC. Only a level 3+ laboratory should attempt to isolate the virus.

Blood should be collected and stored locally for an acute (within one week of symptom onset) and convalescent (after 3 weeks of symptom onset) specimen to test for avian influenza antibodies [61; 73].

Medical practitioners should also be alert to ask all patients with respiratory symptoms and fever if they have traveled to any area in which avian influenza is reported [74].

### Increase Detection and Surveillance Systems

Early detection is another way to handle AI so that proper containment procedures can be initiated as soon as possible. WHO is working to increase surveillance in countries around the world. Hopefully, all countries will be able to detect and acknowledge the presence of a disease before it becomes widespread and the death toll escalates [58].

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## SWINE INFLUENZA

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As discussed, pigs represent an important link in the interspecies transmission of influenza and in the creation of new virus types. In addition, swine influenza has the potential to cause significant disease in humans.

Swine influenza is usually caused by the H1N1 subtype, but other swine influenza A viruses do occur, including H1N2, H3N1, and H3N2 [132]. Pigs may become infected with more than one virus subtype simultaneously; in these cases, genes from the viruses may mix and create a new “reassortant” virus [131].

Among pigs, swine influenza is a highly contagious acute respiratory disease. In many countries, including the United States, swine populations are routinely vaccinated against the prevalent subtypes. Vaccination of pigs, while not sufficient to produce sterilizing immunity, can reduce the levels of virus shed by the animals and reduce the potential for human exposure and infection [131].

It is difficult to predict the potential impact of swine influenza in humans. Because most individuals, with the possible exception of those with regular contact with pigs, do not have immunity to these viruses, the potential for pandemic exists.

In April 2009, a novel influenza A (H1N1) virus of swine origin was detected in people in the United States [133]. In June 2009, WHO signaled that a global pandemic of novel influenza A (H1N1) was underway by raising the worldwide pandemic alert to its highest level, Phase 6 [133]. As of November 2009, the virus had become widespread in almost all states and was responsible for hundreds of deaths,

particularly among children, well before the usual peak influenza season [134]. The proportion of deaths attributed to pneumonia and influenza was above the epidemic threshold. As of October 2009, 99% of circulating influenza viruses in the United States were novel H1N1 influenza [135].

### DIAGNOSIS AND CLINICAL PRESENTATION

Unless it becomes a pandemic, swine influenza infection in humans generally goes undistinguished from typical human influenza as a result of the overlapping flu seasons and the relatively mild clinical presentation. The disease is diagnosed by analysis of a sputum sample collected in the first 4 to 5 days of illness, when an individual is most likely to be shedding the virus [132]. In the case of the 2009 novel H1N1 virus, the CDC recommends that clinicians test persons for the virus if they have an acute febrile respiratory illness or sepsis-like syndrome [136]. Patients who require hospitalization or who are at high risk for severe disease should be tested and treated first.

The symptoms of uncomplicated swine influenza infection in humans are similar to those seen with typical seasonal influenza and include fever, lethargy, lack of appetite, and cough. Swine influenza tends to have a low (1% to 4%) associated morbidity [131]. However, in some cases, patients may develop severe complications, such as exacerbation of existing medical conditions, pneumonia, respiratory decompensation, and even death.

It is believed that persons at greater risk for complications of seasonal influenza will also be at greater risk for complications associated with 2009 H1N1 flu. This includes [136]:

- Pregnant women
- Children younger than 5 years of age
- Persons 65 years of age or older
- Adults and children who have chronic disorders
- Adults and children who have immunosuppression
- Children and adolescents who are receiving long-term aspirin therapy

Unlike the seasonal flu, the median age for patient hospitalized due to H1N1 swine flu infection is 20 years of age, and the incidence is highest among patients younger than 4 years of age [137]. Only 5% of hospitalized H1N1 patients are 65 years of age or older; with seasonal flu, 60% of hospitalizations are for persons 65 years of age or older.

## TRANSMISSION

Swine influenza viruses are transmitted among pigs by contact (direct and indirect) and aerosols [131]. In general, humans contract the disease through exposure to infected pigs and/or their environment. Factors most strongly associated with swine influenza seropositivity include being a swine farm owner or a member of the farm owner's family, living on a swine farm, or entering a swine barn at least 4 days per week [5]. Consumption of pork products that have been properly handled and prepared has not been associated with contraction of the disease. The virus is destroyed at temperatures of 160°F/70°C [131; 132].

When a swine influenza virus does become a source of widespread human illness, the transmission patterns change. Instead of being mainly limited to swine contact, the virus will spread from human-to-human contact. According to the CDC, available data indicate that the 2009 H1N1 virus is transmitted in ways similar to other influenza viruses, primarily large-particle respiratory droplet transmission [136]. Because humans have little to no immunity to influenza viruses of swine origin, transmission may be common.

## TREATMENT AND PREVENTION

While most swine influenza cases are sufficiently mild to resolve spontaneously, antiviral medications may be used if treatment is indicated. The specifically recommended agents are determined based on clinical and epidemiological assessment of the virus. For example, in the case of the 2009 swine influenza outbreak in North America, the virus's susceptibility profile indicated that the preferred antivirals would be oseltamivir or zanamivir [131].

During the 2009 H1N1 pandemic, the CDC has recommended antiviral treatment for all persons with suspected or confirmed influenza requiring hospitalization [135]. In addition, early empiric treatment with oseltamivir or zanamivir should be considered for persons with suspected or confirmed influenza who are at higher risk for complications, including [135]:

- Children younger than 2 years of age
- Persons 65 years of age or older
- Pregnant women and women up to 2 weeks postpartum (including following pregnancy loss)
- Persons of any age with certain chronic medical or immunosuppressive conditions
- Persons younger than 19 years of age who are receiving long-term aspirin therapy

The recommended treatment for adult and adolescent patients is either 75 mg oseltamivir twice per day or 10 mg (two 5-mg inhalations) of zanamivir twice daily [135]. Children 7 years of age and older may be treated with the adult dose of zanamivir. However, calculating oseltamivir doses for children is more complicated and has been the source of medical errors [138]. It is important to note that while healthcare providers in the United States generally write prescriptions for liquid medicines in milliliters, oseltamivir is dosed in milligrams [138]. For children younger than 1 year of age, the oseltamivir dose is based on age. Infants younger than 3 months of age should be given 12 mg twice daily; infants 3 to 5 months of age should receive a dose of 20 mg twice daily [129]. Infants 6 to 11 months of age should receive a dose of 25 mg twice per day. For children between 1 and 12 years of age, dosage is based on weight [129; 135]:

- ≤15 kg (≤33 lbs): 30 mg twice daily
- >15 kg to 23 kg (>34 lbs to 51 lbs): 45 mg twice daily
- >23 kg to 40 kg (>52 lbs to 88 lbs): 60 mg twice daily
- >40 kg (>88 lbs): 75 mg twice daily

Treatment should continue for 5 days [135]. Pregnancy is not considered a contraindication to the use of oseltamivir or zanamivir.

### Vaccine

The CDC has identified five groups who should be given priority vaccines for the 2009 H1N1 virus [137]:

- Pregnant women
- Persons who live with or provide care for infants younger than 6 months of age
- Healthcare and emergency medical services personnel
- Children and young adults 6 months to 24 years of age
- Persons 25 to 64 years of age at higher risk for influenza-related complications

These patients should be vaccinated as soon as the vaccine is available. It is also important to note that 2 doses of the vaccine may be necessary for previously unvaccinated persons younger than 9 years of age, as young children typically have had limited exposure to influenza viruses and are not immunologically primed [137; 139]. At least one study has shown that a single injection is adequate when vaccinating pregnant women [139].

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## INFLUENZA PANDEMIC

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Should methods for containment of a new avian influenza virus fail, a worldwide epidemic or pandemic could follow. Because the population has no immunity to the new strain, millions of people could be infected and several million would probably die. The expected attack rate would be approximately 25% to 30% of the population. As a comparison, “seasonal” flu may affect 20% of the population [96]. The estimate is that there would be 20 to 47 million illnesses, 18 to 42 million outpatient visits, 314,000 to 734,000 hospitalizations, and 89,000 to 207,000 deaths in the United States. In a worst case scenario, the fatality rate would be approximately 2.5% of the total population, which would be a case-fatality rate matching the 1918 pandemic, the

most lethal pandemic according to available data from the past 300 years [96]. The duration of the outbreak in any given community is expected to be approximately 8 weeks, with the average duration of illness about 10 days [96]. The resulting strain on resources would be far more severe than any terrorist attack that is localized to one or a few areas and lasting from a few minutes to hours. However, planning for a bioterrorist attack and an influenza pandemic have many similarities, and each can enhance the other [75; 76].

The government has decided that it will not close our borders if pandemic flu occurs elsewhere. Challenges to closing the borders are numerous, and the disease will inevitably infect the United States regardless of border closures. In the event of a pandemic, attempts will be made to limit those who might be infected from entering the country [121].

Medical practitioners, emergency departments, and clinics, especially walk-in facilities, will be the first contacts in a pandemic. Having a high index of suspicion is vital to help slow the spread of the disease. Checking the CDC weekly influenza reports will help to clarify suspicions [96]. Experience during the 2004 SARS outbreak in Toronto showed that, once SARS was recognized, infection control measures worked well to protect the medical community and facilities. The public health infrastructure was active, strong and responsive, ensuring that public health in a major urban center was also protected [96].

The World Health Organization has defined 6 stages for a pandemic [77].

1. **Novel Virus Alert:** A new influenza virus is discovered in  $\geq 1$  humans.  
The population has little or no immunity to the virus.  
This may be a precursor to a pandemic.
2. **Pandemic Alert:** There is sustained person-to-person transmission.  
Multiple cases occur in the same geographic area.

3. **Pandemic Imminent:** There are unusually high rates of morbidity and mortality in widespread geographic areas.
4. **Pandemic:** Further spread involving multiple continents.
5. **“Second Wave”:** Pandemic appears to be ending. Second wave of cases occurs within several months.
6. **Pandemic Over:** Waves of cases cease. Virus joins those that cause seasonal epidemics.

The California Department of Health Services Influenza Response Guidelines gives the estimated percentages developed by the CDC as to the numbers of cases, doctor visits, hospitalizations, and deaths that would occur in an influenza pandemic. Local practitioners can use these estimates to discover the possible impact a pandemic would have in their area by multiplying local population by the suggested percentage [77]:

- Up to 35% of the population will become ill with influenza
- Up to 19% of the population will require outpatient visits
- Up to 0.4% of the population will require hospitalization
- Up to 0.1% of the population will die of influenza-related causes

The CDC has developed guidelines for public response in a pandemic situation. These stress that people should stay away from crowds, avoid close contact with anyone at work or school, stay home if they or anyone in the household is sick, wash hands frequently, practice covering all coughs and sneezes and disposing of tissues safely.

Many people think they will be protected in a crowd if they wear a mask, but there is little scientific data proving that masks protect against the flu. Industrial masks/N95 respirators should be considered for caregivers. N95 masks must fit closely (no air leaks) to be effective. Masks that become damp or wet cease to be protective. Proper disposal of a mask is imperative, as it has the potential to become a source of infection rather than protection [120].

## PLANNING FOR A PANDEMIC

In planning for the inevitable pandemic, five areas must be covered. These include: surveillance and laboratory issues, communication, community services, medical care, and vaccines and drugs. In September 2006, the California Department of Health Services developed the *Pandemic Influenza Preparedness and Response Plan* before the services of the Department were divided to create the California Public Health Department. The 2006 plan includes sections on pandemic influenza surveillance and epidemiology, laboratory testing capacity, healthcare planning, infection control in the healthcare setting, case management, vaccine programs, antiviral drug programs, community disease control and prevention, and risk communication. These sections cover the responsibilities of the medical community (health practitioners, hospitals, and clinics) and public health departments and include prevention and mitigation plans [121].

### Surveillance and Laboratory Issues

This area includes establishing global and local data collection systems in order to know expected disease rates in humans and animals so that an increase is recognized as quickly as possible. It also includes developing laboratory infrastructure and expertise to handle specimens correctly and accurately. The federal government has limited capabilities to detect and track outbreaks, as the nationwide surveillance system still requires considerable improvements [122].

### Communication

The second planning area is communication among all those who will be involved in a response on local, state, and federal levels. The Federal Emergency Management Agency (FEMA) requires that all planning for various hazards/disasters/terrorist acts follow the Incident Command System (ICS). This system provides a structure for the flow of information to the participants providing the response and back to those in authority. An influenza pandemic would require multiple agencies, organizations, and community groups to effectively respond, so in many areas, they would be under the local ICS.

In addition, communication includes accurate, frequent, concise, and timely information for the public by a primary spokesperson. Health experts should use interactions with media personnel to provide educational points about the transmission, prevention, and symptoms of influenza. Such points, referred to as “sound bites,” are brief, accurate, in common language, and important. Do not wait for the interviewer to ask the right question. Provide the message(s) you know that the public needs. Aim to educate with accurate information and be sure to correct false or misleading information.

Another area of communication is between individual healthcare providers and patients. Having patient educational materials prepared before the flu season will assist patients to remember what they have been told and increase their participation in preventing the flu, as well as caring for themselves or someone else with the flu. Some patient handouts are included in this course. Others can be found on the websites included at the end of the course. The Association for Professionals in Infection Control and Epidemiology (APIC) has also developed a pamphlet for business owners that lists steps that can be taken to protect employees and to help keep businesses operating in the case of an outbreak [119].

### **Community Services**

One of the facets of a pandemic is the social disruption because of the illness of so many employees. Therefore, the third area in any preparedness plan is maintenance of community services from healthcare providers, ambulance personnel, police, firemen, utility workers, and truckers—all the services that are called on daily to maintain life in our communities. This may involve providing vaccine first to healthcare professionals and those responsible for essential services in the community. Some services and work may need to be done via telecommuting so that more people can stay at home and lessen their exposure to the influenza virus. A priority list of those who should be vaccinated first in the event of a pandemic was expected in 2007.

### **Medical Care**

Medical care is the fourth area that will be heavily impacted in a pandemic. The local health officer in most jurisdictions has the legal authority to isolate those with symptoms and quarantine those who have been exposed, as needed, to slow the spread of the disease. Equipment and care may have to be prioritized. In a pandemic, multiple geographic areas are impacted, so obtaining help from another area probably won't be possible. Some hospitals, health departments and other medical facilities are developing lists of nurses, who are no longer practicing or are retired, who would be available to assist during a crisis if needed [78]. In the 2000–2001 flu season, Ontario, Canada offered influenza vaccine to all its residents to lessen the impact on the hospitals. But results of this program are not known [79].

If all available hospital beds in the area are in use, it may be necessary to set up a shelter for medically fragile people. Local health departments have plans and agreements with the American Red Cross and other organizations to establish shelters. Normally, these shelters are for people who have been displaced/evacuated because of a natural event (fire, flood, earthquake). A shelter for medically fragile people has additional equipment and staffing needs. Such a shelter would be for people who require help with medical treatment, such as wound care, medications, and IVs. People who are too sick to care for themselves and have no one to care for them would be appropriate referrals for a medically fragile shelter [80].

### **Vaccines and Drugs**

The final area to be addressed is the supply and delivery of vaccines and drugs. Currently, those with high-risk of complications from the flu are the first to receive the vaccine if a shortage is anticipated or production is slow. In a pandemic, the decision may be made that healthcare professionals and others providing essential services would be the first recipients of vaccine. Because the vaccine would be completely new to a person's immune system, it may be that two doses 30 days

apart will be needed to produce immunity, as is the current practice for children younger than 9 years of age receiving influenza vaccine for the first time [78; 81].

The objectives of planning are to reduce morbidity and mortality, to make sure essential services are available, to reduce the economic impact, and equitably distribute the resources [75].

### Nonpharmacologic Interventions

During the influenza pandemic in 1918, large public gatherings continued to be permitted in some areas, most notably in Philadelphia, which served to spread the epidemic and led to an excess death rate of 719 per 100,000. Cities that had enforced a shutdown of schools, churches, and other gatherings slowed the spread and experienced an excess death rate of 347 per 100,000. Quarantine, school closings and public meeting bans cut peak death rates 30% to 50% [123].

In 2007, the federal government established that, in the case of a severe influenza outbreak, schools should be closed for up to three months; sports events, movies, church and other public gatherings and events should be canceled; working hours should be staggered to decrease the number of commuters using public transportation at any one time; and the use of public transport should be discouraged [124]. Sick people and their families, even healthy members, should stay home 7 to 10 days. Issues of other gathering places, such as daycare centers and malls, will also need to be addressed. Parents should prevent their children from gathering. Measures of isolation (isolating ill patients) and quarantine (isolating exposed persons) will be used to slow the spread of influenza [126]. State borders and airports would not be closed because of the need to transport food and other supplies [124; 126].

In New York City, the plan emphasizes the importance of early detection. A monitoring system that tracks 60,000 pieces of information (i.e., ambulance runs, emergency room visits, and pharmacy sales) has been developed [125].

A cooperative research project between Azusa Pacific University in California and National Chung Sing University in Taiwan is researching traditional Chinese herbal treatments and their effects on influenza virus subunits to develop alternative treatments, especially for countries in which vaccines or pharmaceutical treatments will be unavailable in a pandemic [66].

### CHALLENGES OF A PANDEMIC

For medical care providers, an influenza epidemic provides many challenges. These would be compounded by the increased number of cases in a pandemic. A group in Los Angeles studied the impact on emergency departments and outpatient facilities during 7 influenza epidemics. Some of the lessons learned in order to better cope with an increased number of patients were that:

- Elective surgery should be reduced or eliminated.
- Facilities should work with licensing agencies, fire marshal, etc., to relax staff-patient ratios and/or bed capacity limitations.
- Additional staff resources for epidemics should be developed.
- Walk-in influenza clinics should be established to triage and treat patients at lower cost.
- Methods to identify additional equipment must be developed.

During the SARS outbreak, nurses at Stanford University Medical Center set up receiving areas to prescreen hundreds of patients before they entered the emergency department. Those with influenza-like illnesses were diverted to negative pressure rooms for further testing. Screening questions were used to triage the patients [82]. Included is a list of questions that could be asked of patients to provide extra information that may assist in a more rapid diagnosis (**Table 9**). These questions should be asked in the receiving area of the hospital, clinic, or office in order to minimize the introduction of highly contagious organisms.

**ASSESSMENT OF A PATIENT WITH INFLUENZA-LIKE ILLNESS**

These are a few suggestions that could be helpful in making a correct diagnosis when a patient presents with symptoms of influenza.

When asking a patient or family member when a symptom began, or other information that depends on recalling one's activities, it is helpful to have a calendar and to refer any symptom to some event that would be easily remembered; for example, "Your sister visited on Tuesday. Did you have the fever then?"

1. Is this the time of year when influenza is expected?
2. Has the patient done any traveling in the last 10 days? If any traveling, find out where so the practitioner can relate to any known SARS, avian flu, etc., in the area. Did he travel in an airplane or on a cruise ship?
3. Can the patient pinpoint an exact time when the illness began?
4. Has the patient had any contact with any farm animals, such as pigs, cows, chickens, turkeys, ducks or other birds recently?
5. In the last few days, has he been around anyone who is sick? If yes, find out who was sick, type of contact, when it was, symptoms of the person who was sick.
6. Is he getting sicker or feeling just as bad as when he first became ill? Or perhaps feeling a bit better?
7. Has he been in any place in the mountains? Did he notice any signs warning about plague? What did he do there—camp, hike, etc.?
8. Has the patient had any raw/unpasteurized milk to drink in the last month?
9. If ricin toxin is suspected, find out the patient's activities in the last 24 hours.

Source: Author

Table 9

This receiving area would also be a place where educational materials could be provided for the "worried well." In an office situation, it might be possible to set up a small table outside the office door to screen patients and distribute masks and educational materials. Some public health department plans include supplying public health staff to emergency rooms to help answer questions and educate the worried well, allowing the hospital staff to assist in the care of those critically ill.

**CONCLUSION**

Influenza, with its complication pneumonia, is the only infectious disease that remains as one of the top ten killers in the United States. An effective vaccine to prevent influenza has been available for decades but is underused by both ordinary citizens and healthcare professionals. As a result, the economic burden of influenza is billions of dollars, including the inefficient use of healthcare resources.

In the modern world, the threat of biological weapons has made the control of influenza imperative as many of the possible biological agents initially may be misdiagnosed as influenza because of similar symptoms. Added to the perils facing the world is the expected pandemic of influenza as the result of the introduction of an avian influenza virus to which humans have no immunity.

## GLOSSARY OF TERMS

**Antigenic drift:** Slight change in an influenza virus that helps that virus resist the immunity developed against it. Antigenic drift is a factor behind the need for an annual influenza vaccine.

**Antigenic shift:** Reassortment of RNA segments involving hemagglutinin and neuraminidase antigens from two different influenza A types in one host cell to create a new influenza type.

**Antiviral:** A medication that will kill or weaken a virus.

**Avian, or bird, influenza (AI):** Influenza caused by viruses that occur naturally among wild birds. The low pathogenic variety is common in birds and causes few problems. High pathogenic AI is deadly to domestic fowl and may be transmitted to humans, resulting in high morbidity and mortality rates due to lack of immunity.

**Case definition:** A standardized precise description of a disease to assist in accurate data collection. Generally, there are 3 levels in a case definition: suspect, probable, confirmed. Description for each level is particular to the disease being defined based on clinical symptoms and laboratory findings.

**Epidemic:** An increase in the expected number of cases of a particular disease. The amount of increase needed to declare an epidemic depends upon the disease involved. For example, three cases of *Neisseria meningitidis* with a common affiliation but no close contact within 3 months.

**Hemagglutinin:** A surface antigen on the influenza A virus indicated in the name of the virus by a capital H followed by the subtype number.

**Influenza:** Respiratory illness with fever.

**Isolation:** Separation of a person with a contagious disease from the public.

**Neuraminidase:** A surface antigen on the influenza A virus indicated in the name of the virus by a capital N followed by the subtype number.

**Quarantine:** Restriction of a well person who has been exposed to a known infectious organism.

**Pandemic:** Epidemic of a disease that is worldwide.

**Seasonal flu:** Respiratory illness with fever occurring during winter months for which most people have some immunity and there is an available vaccine. Transmitted from person to person.

**Split virus:** Chemical alteration of a virus for use in a vaccine. All influenza vaccine in the U.S. is split virus.

## WEBSITES

**For further current information on influenza:**

<http://www.cdc.gov/flu>

<http://www.who.int/csr/disease/influenza>

<http://www.cdc.gov/flu/weekly/fluactivity.htm>

<http://www.dhs.ca.gov>

<http://www.calph.ca.gov>

<http://www.astho.org>

<http://www.apic.org>

<http://www.niaid.nih.gov>

**National Immunization Program**

<http://www.cdc.gov/vaccines>

**National Network for  
Immunization Information**

<http://www.immunizationinfo.org>

**For information on reporting  
a vaccine adverse event**

<http://www.vaers.hhs.org>

**For information on shelters for medically  
fragile populations and the EMSA plan**

<http://www.emsa.ca.gov/dms2/toolkit.pdf>

## APPENDIX 1

### SHELTERING IN PLACE

To be used if there is a toxic chemical, a biological agent, or ionizing radiation in the air.

1. Everyone (people and pets) should get indoors immediately.
2. Shut and lock all doors and windows.
3. Turn off all fans, air conditioners, swamp coolers, and heating systems.
4. Close the damper on the fireplace if you have one.
5. Quickly gather a radio, disaster supplies, water, warm clothes and blankets if it is cold, books and games for the children.
6. Go into a room without a window if you have one.
7. Seal doors, exhaust fans, vents, and windows of the room with duct tape. Use wet towels if you don't have duct tape.
8. Listen to the radio for directions.
9. Stay in your shelter until told that it is safe to go out.

Source: *Author*

## APPENDIX 2

### HOME CARE OF AN INFLUENZA PATIENT

1. Monitor the patient for improvement or worsening of symptoms. Write down the date and time of all observations: temperature, coughing, sneezing, amount the patient has had to drink and eat.
2. Supportive care
  - Over-the-counter medicines that bring fever down (**no aspirin** in anyone less than 18 years of age)
  - Pain relievers—medications or carefully monitored heating pads
  - Back or leg rubs
  - Cough medications, as ordered and needed
  - Cool cloth to the head
  - Limited light in the room
  - An encouraging, positive but not overly exuberant attitude
3. Maintain the patient's fluid intake—water, juices, popsicles, ice cubes, tea or coffee, broths. Milk may be appealing to some patients.
4. Provide any foods that are appealing to the patient —however, fluid intake is more critical than solid food intake. It is not just “an old wives’ tale”—chicken soup, broth-based not cream-based, often is appealing.
5. Provide tissues and a disposal place that the patient can reach—wastebasket or paper bag pinned to the bed.
6. Assist the patient to the bathroom, if needed.
7. Continue any routine medications, if possible. Check with the doctor if the patient can't take or vomits the medications or if the medication needs to be taken with food and the patient isn't eating.
8. Persons on insulin should have their blood sugar carefully monitored—blood sugar may go up because of the disease process or go down because of poor food intake.
9. Keep the patient oriented as to time of day and date by telling him/her the time (and day, if needed) whenever they awaken. Napping can lead to disorientation especially in the elderly patient. Some patients may also need to be reminded where they are.
10. Provide a way for the patient to summon help—a bell, whistle, or some other method.

Source: *Author*

## APPENDIX 3

### CARING FOR YOURSELF TO PREVENT THE FLU

1. Get the flu shot.
2. Wash your hands frequently—use soap, make a good lather, rub lather all over your hands for 15 seconds, rinse well, dry with a paper towel or with your own towel at home. The process should take at least 20 seconds.
  - After shaking hands
  - After being around someone who is coughing/sneezing
  - After caring for someone who is sick
  - As soon as you get home
3. Avoid touching your mouth, nose, or eyes.
4. Wear a mask when you take care of someone with the flu.
5. Get 7 to 8 hours rest in 24 hours.
6. Drink at least 6 to 8 glasses of water each day. Sodas don't count.
  - If one is tiring of water, putting it in a colored glass helps.
  - Room temperature water is easier to drink in quantities.
7. Eat at least 5 or more servings of fruits and vegetables each day.
8. If caring for someone, get away from the house for a period of time each day.
  - Take a walk
  - Go to the store
9. Avoid alcohol and tobacco.

Source: Author

## APPENDIX 4 WHEN TO CALL THE DOCTOR

Phone Number \_\_\_\_\_

Usually the person with the flu gets very sick suddenly and stays very sick for a few days and then starts to feel better. The flu can cause other problems. Below is a list of symptoms and signs that the person needs help from the doctor.

As you take care of the person, write down the date and time when you take the temperature, or you notice a new sign or symptom. If you are having trouble getting the patient to drink fluids, write down the time the person had a drink and how much they drank.

### **Fever**

The temperature stays above 102 degrees F. in spite of the person taking medicine to bring the fever down.  
**Never give aspirin to anyone younger than 18 years of age.**

### **Breathing**

The person says or looks like they are having trouble breathing.  
The person is short of breath.  
The child is breathing very fast.  
The chest between the ribs or above the collar bone retracts when the child takes a breath.  
The person, especially if a child, looks a little blue.

### **Fluids**

The person won't drink water, juice, or any fluid or suck popsicles or ice.  
The baby has less than 6 wet diapers in 24 hours.  
The urine is very dark and there isn't much of it.  
If the skin on the forearm is pinched up, it slowly returns to normal.  
The eyes are sunken in and the mouth is dry.  
The person keeps vomiting or retching.

### **Changes in Mental State**

The person is hard to wake up.  
No matter what you try, the child/baby can't be comforted.  
The person is confused or seeing things.  
The person has fainted or nearly fainted.  
The person has a convulsion.

### **Change in Condition**

Any worsening of the flu symptoms—usually the person with the flu will start to feel better after 3 to 5 days.  
Any worsening of any health problem the person has—chest pain, swelling of the feet.

### **Rash**

May indicate an allergy to a medicine or a disease other than the flu.

Source: Author

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