CHAPTER 44

H1N1/Influenza

Christopher Grace

Influenza

p. 277

1. What is influenza?

Influenza is a respiratory illness caused by an RNA virus that comes in two forms that can infect humans: influenza A and influenza B. Although generally self-limited, influenza can cause significant morbidity and mortality, especially in those at risk (discussed later). Influenza is most common during the fall and winter months, due to increased indoor crowding and low humidity, though illness can continue through April and May in the Northern Hemisphere.

2. How are influenza a strains designated?

Influenza A is described by two surface glycoproteins: hemagglutinin (H) and neuraminidase (N). The hemagglutinin, of which there are 18 structurally different types,

crowding and low humidity, though illness can continue through April and May in the Northern Hemisphere.

2. How are influenza a strains designated?

Influenza A is described by two surface glycoproteins: hemagglutinin (H) and neuraminidase (N). The hemagglutinin, of which there are 18 structurally different types, allows attachment to host respiratory epithelium. The neuraminidase, of which there are 10 different types, acts as an enzyme facilitating release of newly replicated viruses from the infected cell. Humans are most often infected with influenza viruses having H1, H2, or H3 and N1 or N2.

The H and N terminology is also used to name the influenza stains spreading yearly. Generally each year there are one or two influenza A strains and an influenza B strain circulating. During the recent influenza seasons, the circulating strains included A H1N1, A H3N2, and two strains of influenza B.

3. What are the symptoms of influenza?

Influenza is an acute respiratory illness characterized by fever greater than 37.8°C (100°F) and cough. There may be associated sore throat, myalgias, arthralgias, fatigue, headache, nausea and vomiting, diarrhea, nasal congestion, and runny nose. The incubation period is generally 1 to 4 days. Not all patients have all these symptoms. Not all patients will

3. What are the symptoms of influenza?

Influenza is an acute respiratory illness characterized by fever greater than 37.8°C (100°F) and cough. There may be associated sore throat, myalgias, arthralgias, fatigue, headache, nausea and vomiting, diarrhea, nasal congestion, and runny nose. The incubation period is generally 1 to 4 days. Not all patients have all these symptoms. Not all patients will have a fever at the time of clinical assessment (though they may be able to give a history of chills or sweats). The degree of illness may vary from quite mild to very severe. Severe influenza can result in hospitalization, require intensive care treatment, and result in death. It is important to keep in mind that influenza may

- Cause an exacerbation of underlying chronic pulmonary or cardiac disease
- Present as a pneumonia with infiltrates on chest x-ray
- Be complicated by secondary bacterial infections
- Present with more severe illness with respiratory difficulty, confusion, and a "sepsis-like illness" and multiorgan failure
- Cause myocarditis, pericarditis, or trigger myocardial infarction

4. Who is at risk for more severe or complicated influenza?

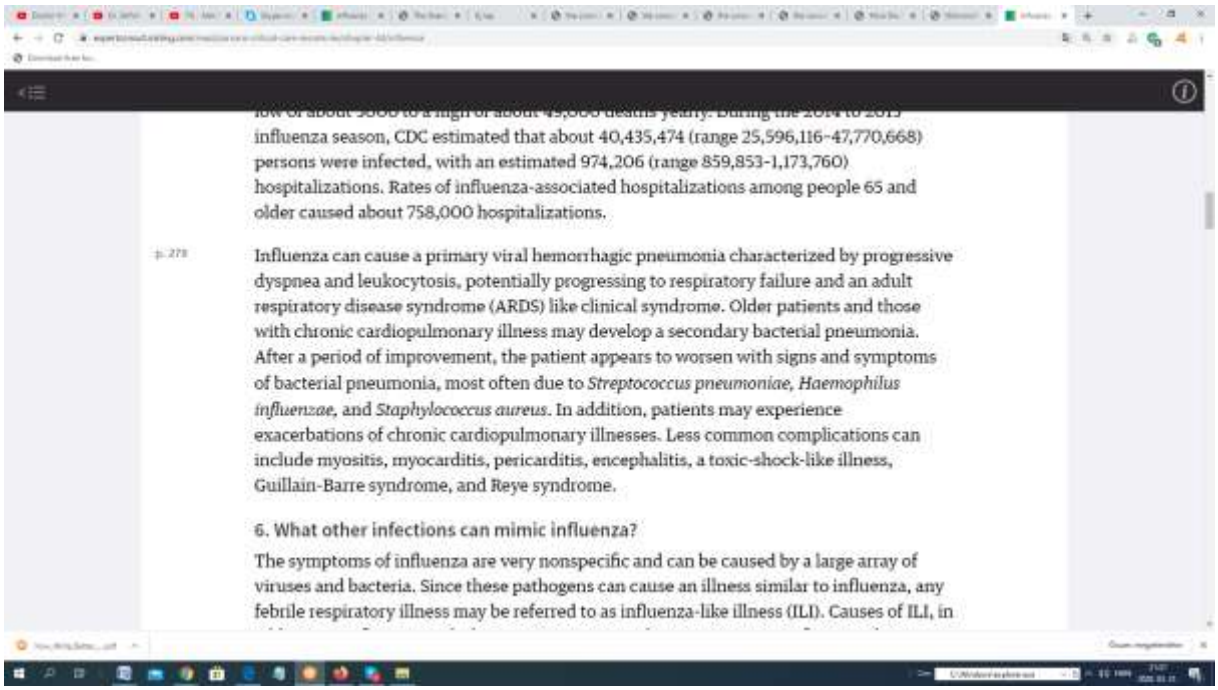
Influenza can be especially serious and life-threatening for patients with the risk factors listed here. These patients should be thoroughly assessed and consideration given to testing and treating during the influenza season.

testing and treating during the influenza season.

- Pregnant women
- Children aged less than 5 years (especially <2 years)
- Patients with asthma, chronic lung, heart, liver, and kidney disease
- Immune-suppressed patients, including those with HIV, organ transplants, lymphoma and leukemia, receiving cancer chemotherapy or prolonged corticosteroids
- Neuromuscular disorders
- Obesity
- Residents of nursing homes and other chronic-care facilities
- Children and adolescents receiving long-term aspirin therapy (Reye syndrome)

5. What complications can occur from influenza?

Centers for Disease Control and Prevention (CDC) estimates that from the 1976 to 1977 season to the 2006 to 2007 flu season, flu-associated deaths ranged from an estimated low of about 3000 to a high of about 49,000 deaths yearly. During the 2014 to 2015 influenza season, CDC estimated that about 40,435,474 (range 25,596,116-47,770,668) persons were infected, with an estimated 974,206 (range 859,853-1,173,760) hospitalizations. Rates of influenza-associated hospitalizations among people 65 and older caused about 758,000 hospitalizations.



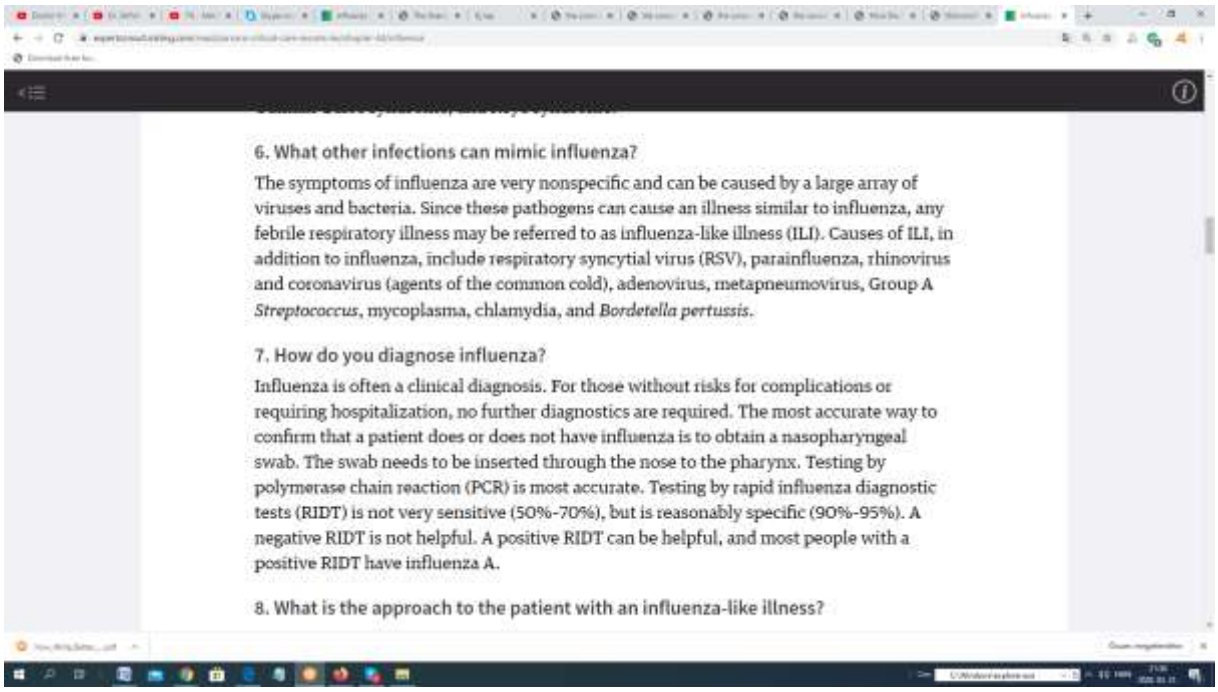
low of about 3000 to a high of about 49,000 deaths yearly. During the 2014 to 2015 influenza season, CDC estimated that about 40,435,474 (range 25,596,116-47,770,668) persons were infected, with an estimated 974,206 (range 859,853-1,173,760) hospitalizations. Rates of influenza-associated hospitalizations among people 65 and older caused about 758,000 hospitalizations.

p. 278

Influenza can cause a primary viral hemorrhagic pneumonia characterized by progressive dyspnea and leukocytosis, potentially progressing to respiratory failure and an adult respiratory disease syndrome (ARDS) like clinical syndrome. Older patients and those with chronic cardiopulmonary illness may develop a secondary bacterial pneumonia. After a period of improvement, the patient appears to worsen with signs and symptoms of bacterial pneumonia, most often due to *Streptococcus pneumoniae, Haemophilus influenzae,* and *Staphylococcus aureus*. In addition, patients may experience exacerbations of chronic cardiopulmonary illnesses. Less common complications can include myositis, myocarditis, pericarditis, encephalitis, a toxic-shock-like illness, Guillain-Barre syndrome, and Reye syndrome.

6. What other infections can mimic influenza?

The symptoms of influenza are very nonspecific and can be caused by a large array of viruses and bacteria. Since these pathogens can cause an illness similar to influenza, any febrile respiratory illness may be referred to as influenza-like illness (ILI). Causes of ILI, in



6. What other infections can mimic influenza?

The symptoms of influenza are very nonspecific and can be caused by a large array of viruses and bacteria. Since these pathogens can cause an illness similar to influenza, any febrile respiratory illness may be referred to as influenza-like illness (ILI). Causes of ILI, in addition to influenza, include respiratory syncytial virus (RSV), parainfluenza, rhinovirus and coronavirus (agents of the common cold), adenovirus, metapneumovirus, Group A *Streptococcus*, mycoplasma, chlamydia, and *Bordetella pertussis*.

7. How do you diagnose influenza?

Influenza is often a clinical diagnosis. For those without risks for complications or requiring hospitalization, no further diagnostics are required. The most accurate way to confirm that a patient does or does not have influenza is to obtain a nasopharyngeal swab. The swab needs to be inserted through the nose to the pharynx. Testing by polymerase chain reaction (PCR) is most accurate. Testing by rapid influenza diagnostic tests (RIDT) is not very sensitive (50%-70%), but is reasonably specific (90%-95%). A negative RIDT is not helpful. A positive RIDT can be helpful, and most people with a positive RIDT have influenza A.

8. What is the approach to the patient with an influenza-like illness?

positive RIDT have influenza A.

8. What is the approach to the patient with an influenza-like illness?

During the winter or flu season, a person with an ILI should be assumed to have influenza until proven otherwise; see the flow diagram provided (Fig. 44.1). The approach to the patient with ILI can progress in a stepwise manner. The patient should be assessed for the degree of illness and presence of risk factors for complications. Those with mild symptoms (no shortness of breath and ability to maintain hydration) and no risks for complications do not need further testing and can be treated symptomatically. Those with moderate symptoms (some shortness of breath, difficulty maintaining hydration, signs and symptoms of pneumonia) should be tested and treated with antiviral medications. Those with severe symptoms (respiratory distress, altered mental status) need immediate assessment in the emergency department. Pregnant women with influenza, especially those in the third trimester, have a high rate of complications and should be emergently assessed by obstetrics or in the emergency department (Fig. 44.1).

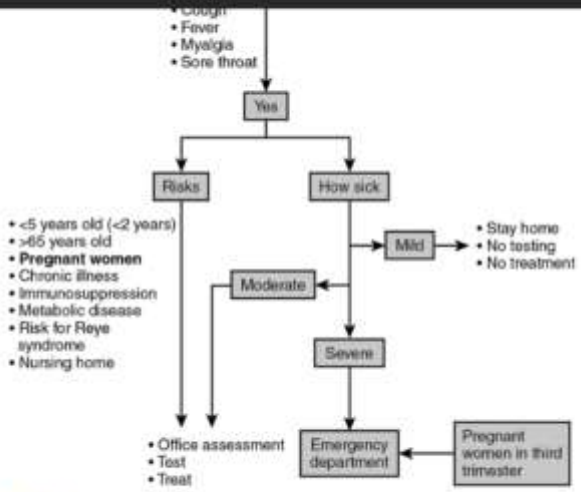


FIGURE 44-1 Approach to the patient with an influenza-like illness. When testing and t...

9. How do you treat influenza?

M2 channel blockers such as amantadine and rimantadine are not often used due to emergence of resistance and central nervous system toxicity. Neuraminidase inhibitors such as oseltamivir, zanamivir, and peramivir act by blocking the surface neuramidase (N). They are active against influenza A and B. Oseltamivir is oral and dosed at 75 mg twice daily for 5 days for treatment. Zanamivir is a oral spray (10 mg or two inhalations twice daily), has been approved for persons aged greater than or equal to 7 years, and is also given for 5 days. Peramivir is intravenous and can be used for persons unable to take oral or inhalational medications such as in the intensive care unit (ICU). It is given as a single 600 mg dose. Dosing of oseltamivir and peramivir must be modified for renal insufficiency. These agents have been shown to shorten the duration of influenza symptoms, but only modestly; if started within 48 hours of symptoms, the duration of the illness may be decreased by about 1 day. In the past, resistance has developed to the neuraminidase inhibitors but since 2009, 99% of influenza viral isolates have been susceptible.

10. How do you manage a patient admitted to the hospital with influenza-like illness?

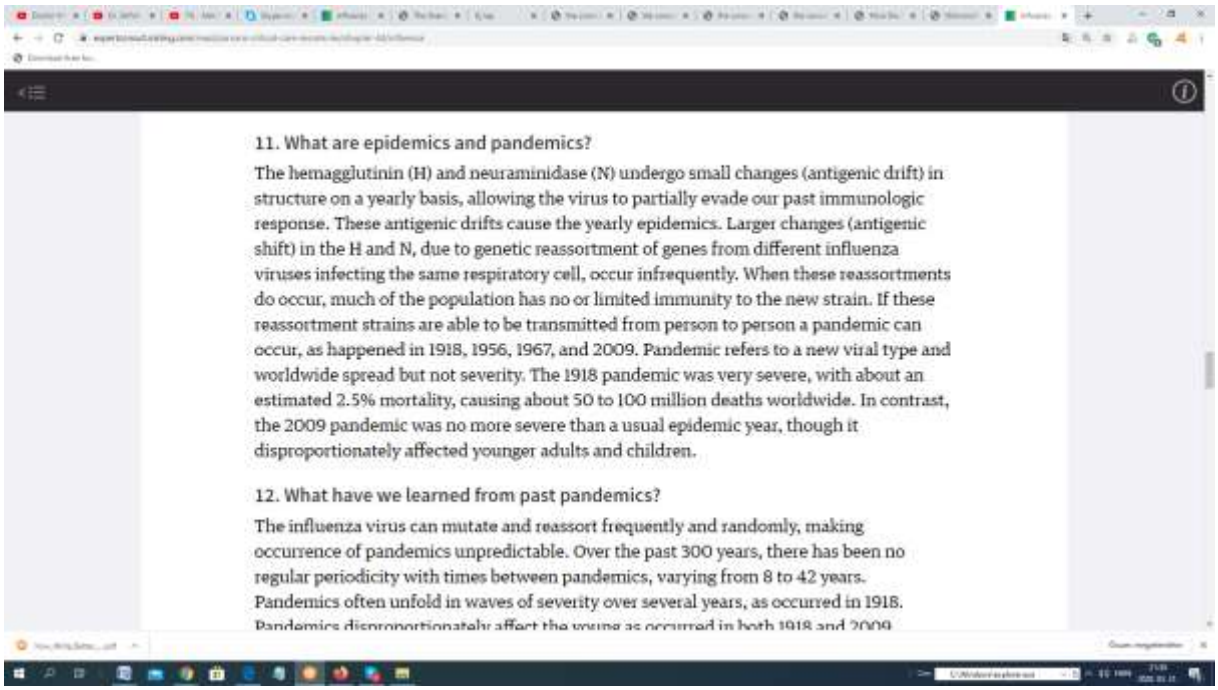
All patients with ILI during the fall/winter flu season admitted to the hospital should be

10. How do you manage a patient admitted to the hospital with influenza-like illness?

All patients with ILI during the fall/winter flu season admitted to the hospital should be presumed to have influenza until ruled out by nasopharyngeal PCR. Until that test result is back, they should be isolated in a private room, standard and droplet precautions instituted and treated with neuraminidase inhibitors. Consideration should be given to treating with antibiotics, such as ceftriaxone, to cover potential streptococcal, staphylococcal, and haemophilus superinfection. If the nasopharyngeal PCR returns negative, influenza treatment and isolation can be stopped. Keep in mind a negative RIDT does not rule out influenza.

11. What are epidemics and pandemics?

The hemagglutinin (H) and neuraminidase (N) undergo small changes (antigenic drift) in structure on a yearly basis, allowing the virus to partially evade our past immunologic response. These antigenic drifts cause the yearly epidemics. Larger changes (antigenic shift) in the H and N, due to genetic reassortment of genes from different influenza viruses infecting the same respiratory cell, occur infrequently. When these reassortments do occur, much of the population has no or limited immunity to the new strain. If these reassortment strains are able to be transmitted from person to person a pandemic can occur, as happened in 1918, 1956, 1967, and 2009. Pandemic refers to a new viral type and worldwide spread but not severity. The 1918 pandemic was very severe, with about an

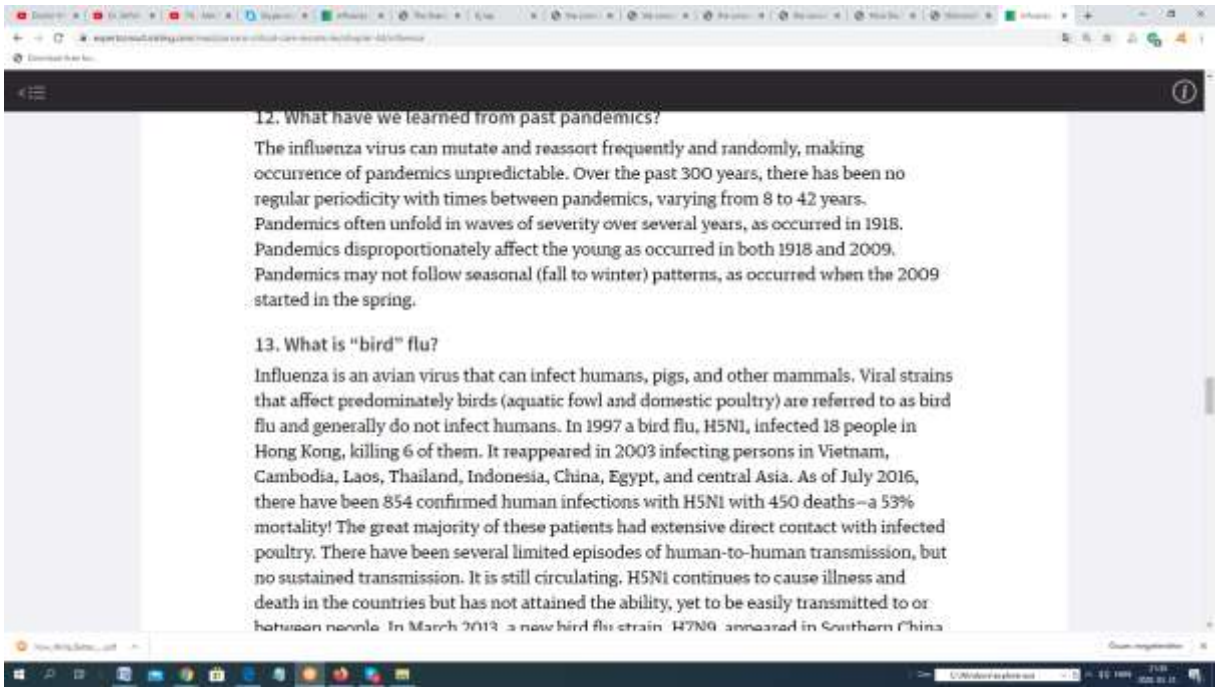


11. What are epidemics and pandemics?

The hemagglutinin (H) and neuraminidase (N) undergo small changes (antigenic drift) in structure on a yearly basis, allowing the virus to partially evade our past immunologic response. These antigenic drifts cause the yearly epidemics. Larger changes (antigenic shift) in the H and N, due to genetic reassortment of genes from different influenza viruses infecting the same respiratory cell, occur infrequently. When these reassortments do occur, much of the population has no or limited immunity to the new strain. If these reassortment strains are able to be transmitted from person to person a pandemic can occur, as happened in 1918, 1956, 1967, and 2009. Pandemic refers to a new viral type and worldwide spread but not severity. The 1918 pandemic was very severe, with about an estimated 2.5% mortality, causing about 50 to 100 million deaths worldwide. In contrast, the 2009 pandemic was no more severe than a usual epidemic year, though it disproportionately affected younger adults and children.

12. What have we learned from past pandemics?

The influenza virus can mutate and reassort frequently and randomly, making occurrence of pandemics unpredictable. Over the past 300 years, there has been no regular periodicity with times between pandemics, varying from 8 to 42 years. Pandemics often unfold in waves of severity over several years, as occurred in 1918. Pandemics disproportionately affect the young as occurred in both 1918 and 2009



12. What have we learned from past pandemics?

The influenza virus can mutate and reassort frequently and randomly, making occurrence of pandemics unpredictable. Over the past 300 years, there has been no regular periodicity with times between pandemics, varying from 8 to 42 years. Pandemics often unfold in waves of severity over several years, as occurred in 1918. Pandemics disproportionately affect the young as occurred in both 1918 and 2009. Pandemics may not follow seasonal (fall to winter) patterns, as occurred when the 2009 started in the spring.

13. What is "bird" flu?

Influenza is an avian virus that can infect humans, pigs, and other mammals. Viral strains that affect predominately birds (aquatic fowl and domestic poultry) are referred to as bird flu and generally do not infect humans. In 1997 a bird flu, H5N1, infected 18 people in Hong Kong, killing 6 of them. It reappeared in 2003 infecting persons in Vietnam, Cambodia, Laos, Thailand, Indonesia, China, Egypt, and central Asia. As of July 2016, there have been 854 confirmed human infections with H5N1 with 450 deaths—a 53% mortality! The great majority of these patients had extensive direct contact with infected poultry. There have been several limited episodes of human-to-human transmission, but no sustained transmission. It is still circulating. H5N1 continues to cause illness and death in the countries but has not attained the ability, yet to be easily transmitted to or between people. In March 2013, a new bird flu strain, H7N9, appeared in Southern China

started in the spring.

13. What is "bird" flu?

Influenza is an avian virus that can infect humans, pigs, and other mammals. Viral strains that affect predominately birds (aquatic fowl and domestic poultry) are referred to as bird flu and generally do not infect humans. In 1997 a bird flu, H5N1, infected 18 people in Hong Kong, killing 6 of them. It reappeared in 2003 infecting persons in Vietnam, Cambodia, Laos, Thailand, Indonesia, China, Egypt, and central Asia. As of July 2016, there have been 854 confirmed human infections with H5N1 with 450 deaths—a 53% mortality! The great majority of these patients had extensive direct contact with infected poultry. There have been several limited episodes of human-to-human transmission, but no sustained transmission. It is still circulating. H5N1 continues to cause illness and death in the countries but has not attained the ability, yet to be easily transmitted to or between people. In March 2013, a new bird flu strain, H7N9, appeared in Southern China, most likely originating in the live animal markets in that area. As of February 2016, there have been 777 cases with 273 deaths, a 35% mortality. It is still circulating. Other strains of avian influenza, including highly pathogenic H5 strains, regularly affect domestic flocks in the United States, resulting in many millions of poultry deaths. In the United States, none of these strains have as yet infected humans.

p. 288

14. What was the pandemic of 2009?

During the 2009 to 2010 influenza season, a large change in the H and N structure occurred leaving much of the population, especially those less than 65 years old, with inadequate immunity. This new structure was the result of a reassortment of bird, swine, and human influenza strains. It appeared to start simultaneously in Southern California and Mexico in the spring of 2009 and spread rapidly worldwide with the World Health Organization declaring a pandemic on June 11, 2009. Young adults and children were particularly affected. In Argentina, for example, pediatric hospitalization rates doubled. Of hospitalized children, 19% were admitted to the ICU, 17% required mechanical ventilation, and 5% died. In the United States, 45% of patients admitted to the hospital were under age 18 years. Seventy-three percent of patients had at least one underlying condition including asthma, diabetes, heart, lung and neurological diseases, and pregnancy. Fortunately the 2009 pandemic caused a "mild" pandemic as compared with that in 1918. Many countries, including Australia, Spain, and the United States, had more ICU admissions, need for mechanical ventilation, and deaths. Those admitted to ICUs often had extensive multifocal pneumonias on chest x-ray. In one study of those admitted to the ICU, 36% had pulmonary emboli on chest computerized tomography. Early in the pandemic, Spain noted that 91% of the patients admitted to the ICU had primary viral pneumonia, 75% had multiorgan failure, 75% required mechanical ventilation, and 22% needed renal replacement therapy. In the Australia and New Zealand experience, one-third of mechanically ventilated patients were treated with

primary viral pneumonia, 75% had multiorgan failure, 75% required mechanical ventilation, and 22% needed renal replacement therapy. In the Australia and New Zealand experience, one-third of mechanically ventilated patients were treated with extracorporeal membrane oxygenation (ECMO), and 21% died. In Canadian experience, 81% of critically ill patients received mechanical ventilation for a median of 12 days. The 28-day mortality of these patients was 14.3%. Lung rescue therapies included neuromuscular blockade (28%), inhaled nitrous oxide (13.7%), high frequency oscillatory ventilation (11.9%), ECMO (4.2%), and prone positioning ventilation (3.0%). The 90-day mortality was 17.3%.

15. How should the patient admitted to the intensive care unit be managed?

Any patient admitted to the ICU with a respiratory illness during the influenza season should be presumed to have influenza, until proven otherwise by nasopharyngeal swab PCR. Patients may present with exacerbations of underlying cardiopulmonary diseases, primary viral pneumonia, and/or secondary bacterial pneumonias. All patients should be treated with a neuraminidase inhibitor and antibiotics. Antibacterial therapy should be directed toward primarily *S. pneumoniae*, *S. aureus*, and *H. influenzae*. Possible initial regiments may include ceftriaxone and vancomycin.

16. What infection control measures are needed?

Influenza is most often spread by large particle respiratory droplets created by patient

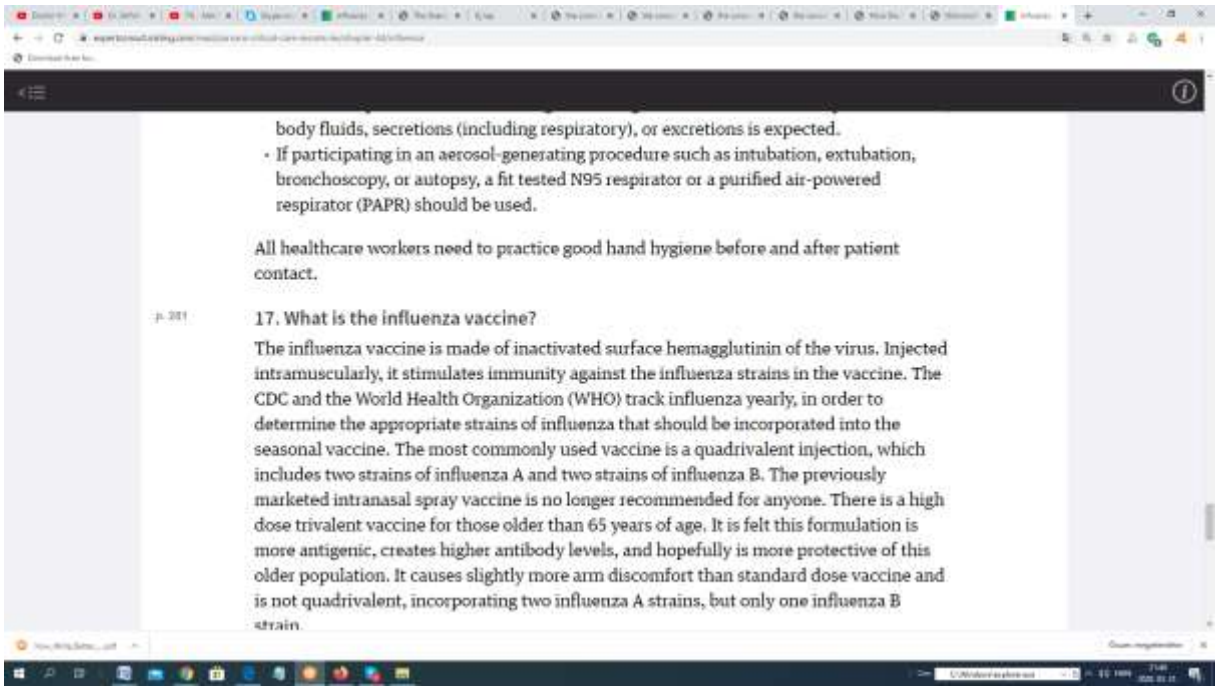
regiments may include ceftriaxone and vancomycin.

16. What infection control measures are needed?

Influenza is most often spread by large particle respiratory droplets created by patient coughing or sneezing. This mode of transmission generally requires close contact (3-6 feet), since these larger and heavier respiratory particles quickly fall out of the air. Hand contact with environmental surfaces contaminated with the virus can also transmit influenza when those hands come in contact with mucosal surfaces, such as touching your eye, nose, or mouth. There has been concern that influenza may be airborne transmitted by small particle aerosols, though it is not clear how much this mode of transmission contributes to community spread. For the office and hospital, the CDC recommend standard and droplet precautions that include:

- Placing the patient in a private room
- Persons entering the patient room wear a surgical mask
- Healthcare providers should wear gloves and gowns if contact with the patient's blood, body fluids, secretions (including respiratory), or excretions is expected.
- If participating in an aerosol-generating procedure such as intubation, extubation, bronchoscopy, or autopsy, a fit tested N95 respirator or a purified air-powered respirator (PAPR) should be used.

All healthcare workers need to practice good hand hygiene before and after patient



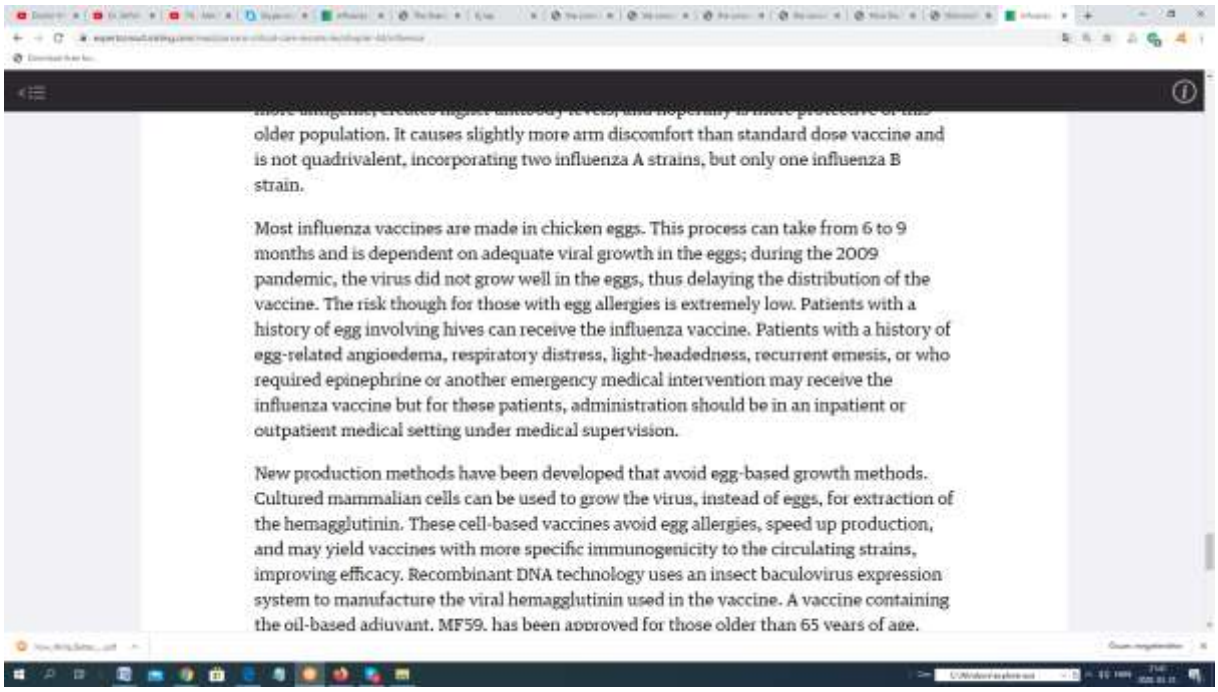
body fluids, secretions (including respiratory), or excretions is expected.
- If participating in an aerosol-generating procedure such as intubation, extubation, bronchoscopy, or autopsy, a fit tested N95 respirator or a purified air-powered respirator (PAPR) should be used.

All healthcare workers need to practice good hand hygiene before and after patient contact.

p. 261

17. What is the influenza vaccine?

The influenza vaccine is made of inactivated surface hemagglutinin of the virus. Injected intramuscularly, it stimulates immunity against the influenza strains in the vaccine. The CDC and the World Health Organization (WHO) track influenza yearly, in order to determine the appropriate strains of influenza that should be incorporated into the seasonal vaccine. The most commonly used vaccine is a quadrivalent injection, which includes two strains of influenza A and two strains of influenza B. The previously marketed intranasal spray vaccine is no longer recommended for anyone. There is a high dose trivalent vaccine for those older than 65 years of age. It is felt this formulation is more antigenic, creates higher antibody levels, and hopefully is more protective of this older population. It causes slightly more arm discomfort than standard dose vaccine and is not quadrivalent, incorporating two influenza A strains, but only one influenza B strain.



older population. It causes slightly more arm discomfort than standard dose vaccine and is not quadrivalent, incorporating two influenza A strains, but only one influenza B strain.

Most influenza vaccines are made in chicken eggs. This process can take from 6 to 9 months and is dependent on adequate viral growth in the eggs; during the 2009 pandemic, the virus did not grow well in the eggs, thus delaying the distribution of the vaccine. The risk though for those with egg allergies is extremely low. Patients with a history of egg involving hives can receive the influenza vaccine. Patients with a history of egg-related angioedema, respiratory distress, light-headedness, recurrent emesis, or who required epinephrine or another emergency medical intervention may receive the influenza vaccine but for these patients, administration should be in an inpatient or outpatient medical setting under medical supervision.

New production methods have been developed that avoid egg-based growth methods. Cultured mammalian cells can be used to grow the virus, instead of eggs, for extraction of the hemagglutinin. These cell-based vaccines avoid egg allergies, speed up production, and may yield vaccines with more specific immunogenicity to the circulating strains, improving efficacy. Recombinant DNA technology uses an insect baculovirus expression system to manufacture the viral hemagglutinin used in the vaccine. A vaccine containing the oil-based adjuvant, MF59, has been approved for those older than 65 years of age.

Cultured mammalian cells can be used to grow the virus, instead of eggs, for extraction of the hemagglutinin. These cell-based vaccines avoid egg allergies, speed up production, and may yield vaccines with more specific immunogenicity to the circulating strains, improving efficacy. Recombinant DNA technology uses an insect baculovirus expression system to manufacture the viral hemagglutinin used in the vaccine. A vaccine containing the oil-based adjuvant, MF59, has been approved for those older than 65 years of age. The mammalian cell-based, recombinant, and adjuvant technologies produce only trivalent vaccines.

Among adults aged 18 to 65 years, a 2012 meta-analysis found that the efficacy of the injection trivalent vaccine against confirmed influenza was 59% (95% CI = 51–67). For those older than 65 years of age, the vaccine is generally less protective. The influenza vaccine has reduced children's risk of pediatric ICU admissions due to influenza by 74%. For persons 50 years and older who received the influenza vaccine, their risk of hospitalization for influenza has been reduced by 57%.

18. Who should get the influenza vaccine?

The CDC recommends that all persons older than 6 months of age get yearly vaccinations. This is especially true for those at high risk for complications of influenza as outlined previously. All healthcare workers need to be vaccinated yearly, so as to remain healthy and not risk spreading influenza to the more vulnerable patients.

18. Who should get the influenza vaccine?

The CDC recommends that all persons older than 6 months of age get yearly vaccinations. This is especially true for those at high risk for complications of influenza as outlined previously. All healthcare workers need to be vaccinated yearly, so as to remain healthy and not risk spreading influenza to the more vulnerable patients.

KEY POINTS: H1N1/INFLUENZA ✓

1. Can cause severe respiratory illness requiring ICU care
2. May exacerbate underlying cardiopulmonary conditions
3. All patients admitted to hospital for presumed influenza should be treated with antiviral medications
4. Secondary bacterial pneumonias may develop and should be looked for and treated
5. All persons aged greater than 6 months should be vaccinated yearly

Bibliography