Chapter 131: Influenza

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UPDATE SUMMARY

Update Summary

May 26, 2023

The following section was updated:

- Minor edits were made to self-assessment questions to improve clarity.
- Links to relevant sections in the text were added to self-assessment answers.

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 43, Influenza.

KEY CONCEPTS

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1. Influenza is a viral illness associated with high mortality and high hospitalization rates among persons older than 65 years. Aging of the population is contributing to an increased disease burden in the United States.

2. Seasonal influenza epidemics are the result of viral antigenic drift, which is why the influenza vaccine is changed on a yearly basis. Antigenic drift forms the foundation of the recommendation for annual influenza vaccination.

3. The acquisition of a new hemagglutinin and/or neuraminidase by the influenza virus is called *antigenic shift*, which results in a novel influenza virus that has the potential to cause a pandemic.

4. The primary route of influenza transmission is person-to-person via inhalation of respiratory droplets, and transmission can occur for as long as the infected person is shedding virus from the respiratory tract.

5. Clinical diagnosis of influenza is difficult. Classic signs and symptoms include abrupt onset of fever, muscle pain, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms usually resolve within 1 week of presentation.

6. In the United States, the primary mechanism of influenza prevention is annual vaccination. Vaccination not only prevents influenza illness and influenza-related hospitalizations and deaths but may also decrease healthcare resource use and the overall cost to society.

7. The inactivated influenza vaccine (IIV) and the live-attenuated influenza vaccine (LAIV) are commercially available for prevention of seasonal influenza. Both vaccines contain influenza A subtypes H3N2 and H1N1, and influenza B virus, which are initially grown in hens' eggs.

8. Antiviral drugs for prophylaxis of influenza should be considered adjuncts to vaccine and are not replacements for annual vaccination.

9. If used, antiviral drugs should be started within 48 hours of symptom onset to maximize effectiveness.

10. Neuraminidase inhibitors (oseltamivir, zanamivir, and peramivir) and cap-dependent endonuclease inhibitor (baloxavir) have activity against both influenza A and influenza B viruses. Although the adamantanes inherently have activity against influenza A H1N1 viruses, they are no longer used clinically due to overwhelming viral resistance.

BEYOND THE BOOK

BEYOND THE BOOK

Complete the influenza vaccine table

Approved Influenza Vaccines for Different Age Groups—United States

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Thimerosal Mercury Content (µg Hg/0.5-mL dose)	Age Group	Number of Doses
aIIV4						
IIV4 High Dose						
IIV4						
IIV4						
ccIIV4						
RIV4						
LAIV4						

INTRODUCTION

Influenza causes significant morbidity and mortality, particularly among young children and the elderly. The Centers for Disease Control and Prevention (CDC) estimates that influenza has resulted in 9 to 45 million illnesses, 140,000 to 810,000 hospitalizations, and 12,000 to 61,000 deaths annually since 2010.[1,2] Globally, influenza causes nearly 650,000 deaths each year, with the highest burden among children younger than 5 years and adults 75 years and older.[3] More people die of influenza than of any other vaccine-preventable illness. Significant societal consequences associated with influenza include visits to physicians' offices and emergency departments and days lost from school and/or work. The societal costs associated with influenza are more than $10 billion in healthcare costs and $16.3 billion in indirect costs.[4]

Vaccination is the primary mechanism of influenza prevention in the United States. The antiviral armamentarium for treatment and prophylaxis of influenza is limited, which further emphasizes the importance of prevention with vaccination and appropriate use of infection control measures during outbreaks. Research toward the development of novel antivirals and vaccines is needed for effective control of seasonal epidemics and for pandemic preparedness.

ETIOLOGY AND EPIDEMIOLOGY

1 Influenza infection can occur at any time during the year with the highest rates of influenza-associated illness during the winter months. The highest rate of infection occurs in children, but severe illness, hospitalization, and death occur most commonly among those older than 65 years, young children (younger than 2 years), and those with underlying medical conditions, including pregnancy and cardiopulmonary disorders, which increase their risk of complications from influenza. The seasonal influenza epidemics has resulted in an estimated 9.3 to 49 million influenza-related illnesses, 4.3 to 16.6 million healthcare visits, and between 12,000 and 79,000 deaths annually since 2010.[4] During 2019 to 2020 influenza season alone, influenza resulted in 39 to 56 million illnesses; 18 to 26 million medical visits; 410,000 to 740,000 hospitalizations, and 24,000 to 62,000 deaths.[5]

Influenza-associated illness was three times higher among children aged 0 to 4 years compared with those aged 5 to 17 years.[6] Similarly, influenza-associated illness rates among persons 65 years or older were nine times higher than those aged 18 to 49 years, and two times higher among those aged 50 to 64 years.[6] Furthermore, influenza-related hospitalization was highest among individuals age 65 years or older; 327 per 100,000 population.

Influenza activity was unusually low throughout the 2020 to 2021 influenza season both in the United States and globally, despite high levels of testing.[7] Between September 28, 2020, and May 22, 2021, in the United States, 0.2% of respiratory specimens tested by US clinical laboratories were positive for an influenza virus compared with 26.2% and 30.3% at the last three seasons. The low level of influenza activity at 0.8 per 100,000 population during this past season contributed to dramatically fewer influenza illnesses, hospitalizations, and deaths compared with previous seasons. Only one pediatric influenza death was reported during the 2020 to 2021 season compared to 37 (during 2011-2012) and 199 (during 2019-2020). COVID-19 mitigation measures, such as wearing face masks, staying home, hand washing, school closures, reduced travel, increased ventilation of indoor spaces, and physical distancing, have contributed to the decline in 2020 to 2021 influenza incidence, hospitalizations, and deaths.[7] Influenza vaccination may also contributed to reduced illness during the 2020 to 2021 season; however, vaccine intake was not different compared to previous seasons.[8,9]

Vaccination coverage with ≥1 dose of flu vaccine was 58% among children aged 6 months to 17 years, while vaccination coverage among adults ≥18 years was 55%.[8-10] Vaccine coverage was highest among individuals aged 65 years or older (80%). Overall vaccine effectiveness was low at 39% (39% among individuals 65 years or older and 34% for children younger than 9 years).[11] Influenza vaccine effectiveness in 2020 to 2021 was not estimated due to low influenza virus circulation during the 2020 to 2021 influenza season. Deaths associated with influenza often result from secondary bacterial pneumonia, primary viral pneumonia, and/or exacerbation of underlying comorbidities.[12]

Influenza Viruses A, B, and C

Influenza virus types A, B, and C are members of the Orthomyxoviridae family and affect many species, including humans, pigs, horses, and birds. Influenza A and B viruses are the two types that cause disease in humans. Influenza A viruses are responsible for the regular, seasonal epidemics of the flu, whereas influenza B viruses are typically associated with sporadic outbreaks, particularly among residents of long-term care facilities. Influenza A viruses are further categorized into different subtypes based on changes in two surface antigens—hemagglutinin and neuraminidase (NA). Influenza B viruses are not categorized into subtypes.

Hemagglutinin allows the influenza virus to enter host cells by attaching to sialic acid receptors and is the major antigen to which antibodies are directed on exposure.[13] NA allows the release of new viral particles from host cells by catalyzing the cleavage of linkages to sialic acid.[14]

Sixteen hemagglutinin subtypes (H1-H16) and nine NA subtypes (N1-N9) of influenza A have been isolated from birds. However, the only influenza A subtypes that have circulated among humans since the 1918 pandemic (see Antigenic Drift and Antigenic Shift) are H1 to H3 and N1 and N2.[13] The primary subtypes of influenza A that have been circulating among humans for the past three decades are H3N2 and H1N1.

Antigenic Drift and Antigenic Shift

2 Immunity to influenza virus occurs as a result of the development of antibody directed at the surface antigens, particularly hemagglutinin. However, immunity to one influenza subtype does not offer protection against other subtypes or types of influenza. Moreover, immunity to one antigenic variant of a subtype of influenza may not confer protection against other antigenic variants. Antigenic variants are created by point mutations in the surface antigens of a particular subtype, resulting in small changes in the hemagglutinin and/or NA molecules, which is called *antigenic drift*. Antigenic drift is the basis for seasonal epidemics of influenza, the reason for changes in the annual influenza vaccine, and the rationale behind the recommendation for annual vaccination.

3 Antigenic shift occurs when the influenza virus acquires a new hemagglutinin and/or NA via genetic reassortment rather than point mutations.[13] Most likely, the genetic reassortment occurs when an animal that supports the growth of multiple subtypes of influenza, such as a pig, is concurrently infected with two subtypes of the influenza virus. Conversely, antigenic shift may occur directly from avian strains that have gained competency in the human host. Antigenic shift results in the emergence of a novel influenza virus and carries the potential of causing a pandemic. However, novelty alone is insufficient to cause an influenza pandemic; the virus must be able to replicate in humans, spread person-to-person, and affect a susceptible

population.[13] Immunity to one subtype of influenza does not confer protection against other subtypes or types.

Spanish Influenza of 1918

The influenza pandemic of 1918 was the most significant infectious disease outbreak known to humans, causing approximately 40 to 50 million deaths in a year, with more than 500,000 deaths occurring in the United States.[14] The pandemic originated in China, but occurred almost concurrently in Europe, Asia, and North America.[14]

The 1918 pandemic was caused by a particularly virulent influenza A H1N1 virus, which was entirely of avian origin.[14] In contrast to the other pandemics of the 20th century, the 1918 pandemic resulted in an unusual mortality pattern. The mortality peaked for those younger than 4 years, those between the ages of 25 and 35 years, and those older than 65 years, which resulted in a W-shaped mortality curve, as opposed to the U- or J-shaped curve typically associated with influenza.[11] Over half of the deaths occurred in persons aged 20 to 40 years. The death toll associated with this pandemic culminated in an almost 10-year drop in the life expectancy of the population at the time.[14]

Asian Influenza of 1957

The Asian flu pandemic began when a new H2 subtype of influenza A surfaced in Hunan province in China in 1957.[13] The virus formed from coinfection with an avian H2N2 virus and a human H1N1 virus in a common host, possibly a pig or a human. The H2N2 virus quickly spread to Japan, South America, the United States, New Zealand, and Europe, resulting in 1 to 2 million deaths worldwide, with 70,000 deaths occurring in the United States.[15] Unlike the Spanish influenza of 1918, the mortality curve for the Asian influenza pandemic was U- or J-shaped, with infants and elderly being most affected.

Hong Kong Influenza of 1968

The H2N2 virus of the Asian influenza circulated in the human population until 1968, when a new H3 subtype emerged in China and Hong Kong following genetic reassortment with the H2N2 virus.[13] The H3N2 virus quickly spread to the United States and later to Europe. This pandemic caused more than 30,000 deaths in the United States and 0.5 to 2 million deaths worldwide. The lower morbidity and mortality associated with the Hong Kong influenza may be explained by previous exposure of the population to the N2 subtype, and the availability of antibiotics for the management of secondary bacterial pneumonia. Similar to the Asian influenza of 1957, the mortality curve for the Hong Kong influenza pandemic was U- or J-shaped, primarily affecting infants and elderly.

Avian Influenza

Influenza viruses are in circulation in southern China during all months of the year.[13] Given this fact and the close proximity of dense populations of people, pigs, and wild and domestic birds, this area proves ideal for the emergence of new influenza viruses via genetic reassortment (antigenic shift) such as avian influenza. Avian influenza infections have been reported with A(H5N1), A(H5N6), A(H7N9), A(H9N2), A(H6N1), and A(H7N4) in China.[16]

The first report of human infection with the avian H5N1 virus occurred in 1997 in Hong Kong.[16] The virus reemerged in 2003 as an antigenically and genetically different virus that has spread widely through wild and domestic bird populations in Asia, Africa, and Europe as well as infecting humans in several countries.[17] From 2003 to 2021, 863 cases and 456 deaths caused by H5N1 infection have been reported. The overall case fatality was 53%.

The novel avian influenza H7N9 virus infection was first reported in humans in 2013, in China.[18] Since then, 1,568 laboratory-confirmed cases of human infection have been reported, including 615 deaths.[17] The majority of avian H7N9 human infection cases have been among those with recent exposure to live poultry or potentially contaminated environments, especially markets where live birds are sold.[18] The overall case fatality was 39%.

In December 2014, the first case of novel avian influenza H5N6 human infection was reported in China,[17] and to date, 25 laboratory-confirmed human cases of avian influenza A(H5N6) virus infection, including six deaths, were reported to the World Health Organization (WHO) from China.[16,17]

The spread of avian influenza viruses from person to person is rare and has been limited, inefficient, and unsustained.[15-18] The precise mode of

transmission is unknown, but most cases have occurred as a result of contact with poultry, contaminated environment, and prolonged personal contact.[16] Cases of transmission via aerosolization have not been reported.[16,17] Clinical presentation includes high fever and influenza-like illness, and watery diarrhea without blood may occur up to 1 week prior to respiratory symptoms.[15] Almost all patients have clinically apparent pneumonia. Progression to death, most commonly as a consequence of respiratory failure, occurs at a mean of 9 to 10 days after the onset of illness.[19] The NA inhibitors (oseltamivir, peramivir, and zanamivir) and cap-dependent endonuclease inhibitor (baloxavir marboxil) have activity against influenza A and B viruses (including H1N1), although higher doses of NA inhibitors may be needed for efficacy.[19-21] Two inactivated monovalent influenza vaccines, nonadjuvanted[22] and adjuvanted[23] influenza H5N1 vaccine and an H7N9[24] virus vaccine, are available for vaccination of persons 6 months and older. They are only available to government agencies and for stockpiles.[16] The recommended dose of the nonadjuvanted vaccine is two 1-mL injections given intramuscularly 28 days apart (range, 21-35 days) if 18 to 64 years old,[22] while the nonadjuvanted vaccine dose is two 0.5-mL injections given 21 days apart if adjuvanted vaccine if 18 to 64 years old, or two 0.25-mL injection given 21 days apart if 6 months to 17 years.[23] Individuals at high risk, for example, those who work with poultry and H5N1 poultry outbreak responders, are encouraged to receive annual seasonal influenza vaccine to minimize the risk of coinfection with human and avian influenza A viruses. The potential for avian viruses H5N1 and H7N9 to cause a pandemic is of concern as it could spread more quickly than pandemics of the past because of the mobility of people in today's world.

A severe pandemic, like that of 1918, could cause more than 10 million hospitalizations and more than 2 million deaths, whereas a moderate pandemic, like those of 1957 and 1968, could result in more than 1 million hospitalizations and more than 650,000 deaths in the United States alone.[25-27]

Swine Influenza of 2009

An outbreak of a novel influenza A H1N1 (formerly swine-origin influenza virus [SOIV]) was initially detected in Mexico in March 2009 and subsequently in the United States in April 2009 in California and Texas.[28] The virus then spread throughout North America, Europe, Asia, and subsequently worldwide, prompting the WHO on June 11, 2009, to declare phase 6, indicating widespread human infection, for the influenza pandemic.[29] Since 1998, triple reassortant swine influenza A (H1) viruses, containing genes from swine, avian, and human lineages, have circulated among swine in the United States.[15,28]

The virus, now formally known as influenza A(H1N1) pdm09, has become the predominant influenza A H1N1 in circulation, effectively replacing traditional seasonal influenza A (H1N1).

Several characteristics of the novel influenza A H1N1 outbreak differ from those of a typical seasonal influenza outbreak. Symptomatology associated with the novel influenza includes fever (94%), cough (92%), sore throat (66%), diarrhea (25%), and vomiting (25%).[28,30] An estimated 43 to 89 million cases of 2009 H1N1 occurred between April 2009 and April 2010 with a median of 274,000 hospitalizations. Globally, up to 575,000 H1N1-related deaths were reported; however, this may represent an underestimation of true disease burden.[27,29] The majority of the cases occurred in otherwise healthy children and adults younger than 65 years of age including pregnant women, with the highest incidence reported among those aged 18 to 64 years.[29] Contrary to seasonal influenza, where about 60% of hospitalizations and 90% of deaths occur in people older than or equal to 65 years, approximately 90% and 87% of 2009 H1N1-related hospitalizations and deaths, respectively, occurred in people younger than 65 years. However, like seasonal influenza, people with underlying health conditions had greater risk of hospitalizations and death. Among those who were deceased due to novel H1N1 infection, the median age was ~40 years and 59% of deaths (respiratory and cardiovascular) occurred in Southeast Asia and Africa.[29] The wide spread of 2009 novel influenza was attributed to extensive global trade and travel, such that the virus was detected in 122 countries in 6 weeks as opposed to 6 months with previous pandemics.[27]

Variant Influenza A (H3N2v) 2012

H3N2v is a nonhuman influenza virus that normally circulates in pigs and that has infected humans.[31] In 2011, the US Centers for Disease Control and Prevention (CDC) reported the first case of an influenza infection due to influenza A H3N2 variant virus (H3N2v).[31] Since then, 430 cases have been documented from 17 states resulting in 34 hospitalizations and low mortality.[32] The H3N2v is considered a variant virus because it is different from influenza A viruses circulating among humans. The H3N2v virus contains genes from avian, swine, and human viruses and the M gene from the 2009

H1N1 pandemic virus (A[H1N1]pdm09).[31,32] The virus spreads more readily from pigs to people than other variant viruses, but has limited person-to-person transmission. The main risk factor for infection with the virus based on evaluation of available cases is exposure to pigs, mostly at agricultural fairs.[32] Since the virus is related to human flu viruses from the 1990s, most adults have some immunity against it.[31] Hence, most cases to date have occurred in children, who have little immunity against this virus.[29,32]

The symptoms and severity of H3N2v have mostly been mild and similar to those of seasonal influenza (fever, cough, sore throat, body aches, etc.), but like seasonal influenza, serious illness with H3N2v infection is possible.[29] Vaccination remains key to preventing H3N2v infection. Additionally, the CDC has encouraged people at high risk of influenza complications to stay away from swine barns at fairs.[32] People who are at high risk of serious complications from influenza, including H3N2v virus infection, are children younger than 5 years, people aged 65 years or older, pregnant women, body mass index of 40 or higher, age less than 19 years of age on long-term aspirin- or salicylate-containing drugs, chronic care facility residents, and people with certain chronic medical conditions (asthma, cystic fibrosis, chronic obstructive pulmonary disease, diabetes, heart disease, stroke, sickle cell, kidney and liver disorders, inherited metabolic disorders, immunocompromised, and neurologic or neurodevelopmental conditions).[33] The treatment of H3N2v virus infection is similar to that of seasonal influenza. NA inhibitors and cap-dependent endonuclease inhibitors are the mainstay of treatment. The adamantanes should not be used due to high resistance.

PATHOGENESIS

4 The route of influenza transmission is person-to-person via inhalation of respiratory droplets, which can occur when an infected person coughs or sneezes.[30,34] Transmission may also occur if a person touches an object contaminated with respiratory secretions and then touches his or her mucus membranes. The incubation period for influenza ranges between 1 and 7 days, with an average of 2 days.[34] Transmission can occur for as long as the infected person is shedding virus from the respiratory tract. Adults are considered infectious within 1 day before until 7 days after onset of illness. Children, especially younger children, might potentially be infectious for longer periods (more than 10 days).[35,36] Viral shedding can persist for weeks to months in severely immunocompromised people.

The pathogenesis of influenza in humans is not well understood. The severity of the infection is determined by the balance between viral replication and the host immune response. Severe illness is likely a result of both a lack of ability of host defense mechanisms to inhibit viral replication and an overproduction of cytokines leading to tissue damage in the host.[16,30]

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Diagnosis of Influenza

General

- The clinical diagnosis of influenza can be difficult because the presentation is similar to a number of other respiratory illnesses. The sensitivity of clinical diagnosis ranges from 40% for children to 70% for adults and largely depends on the relative prevalence of influenza and other respiratory viruses circulating in a community.[34-36]
- The clinical course and outcome are affected by age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, and the degree of preexisting immunity.[36]
- Complications of influenza may include exacerbation of underlying comorbidities, primary viral pneumonia, secondary bacterial pneumonia or other respiratory illnesses (eg, sinusitis, bronchitis, otitis), encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome.[33,36]

Signs and Symptoms

- 5 Classic signs and symptoms of influenza include rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.[21,30,36]
- Nausea, vomiting, and otitis media are also commonly reported in children.[35]
- Signs and symptoms typically resolve in approximately 3 to 7 days, although cough and malaise may persist for more than 2 weeks.
- Primary viral pneumonia, occurring predominantly in pregnant women and those with underlying cardiovascular disease, usually begins with fever and dry cough, which changes to a productive cough of bloody sputum. This rapidly progresses to dyspnea, hypoxemia, and cyanosis with radiologic evidence of bilateral interstitial infiltrates.[36]
- Secondary bacterial pneumonia is usually seen in individuals with underlying pulmonary disorders and presents during the early stages of defervescence from the influenza infection. These patients usually present with fever, productive cough, and radiologic evidence of consolidation.[36]

Laboratory Tests

- Complete blood count and chemistry panels should be obtained to assess the overall status of the patient.
- The gold standard for diagnosis of influenza is reverse-transcription polymerase chain reaction (RT-PCR) or viral culture, which can provide information on the specific strain and subtype. Viral culture has a high sensitivity but can take as long as a week to develop, limiting the clinical relevance of the results.[36,37]

Other Diagnostic Tests

- Cultures of potential sites of infection should be obtained if coinfection, superinfection, or secondary infection is suspected.
- Chest radiograph should be obtained if pneumonia is suspected.

Influenza Diagnostic Tests

Influenza molecular assays

Rapid influenza molecular assays (RIMAs) detect influenza viral RNA in upper respiratory tract specimens utilizing different nucleic acid amplification technologies (NAATs). They have high sensitivity (90%-95%) and high specificity (55%-99%), depending on the virus type, compared with RT-PCR

assays.[38] FDA-cleared RIMAs are available for point of care (POC) use that produce results in approximately 15 to 30 minutes.

RT-PCR (real time or multiplex) is a nucleic acid amplification test that can identify the presence of influenza viral RNA or nucleic acids in respiratory specimens with high sensitivity and specificity. It is the most sensitive, specific, and versatile diagnostic test for influenza.[37] Results are available in approximately 45 minutes to several hours (1-6 hours) depending upon the assay, and are frequently used as a confirmatory test.

Rapid influenza diagnostic tests (RIDTs)

RIDTs use enzyme immunoassay (EIA) technology to provide results within 10 to 15 minutes and may have utility in community- and hospital-based outpatient settings because of their rapid processing times. RIDTs allow for differentiation of influenza viruses A and B but none of the RIDTs provide any information about influenza A virus subtypes. Sensitivities for RIDTs range are low often yielding false-negative results, while specificities are high compared with RT-PCR or viral culture.[37,38] For this reason, RIDTs are not recommended for use in hospitalized patients with suspected influenza, and RIMAs are preferred in outpatient settings since CLIA-waived tests are available for POC use.

Immunofluorescence assays (IFAs)

IFAs are antigen detection assays that generally require use of a fluorescent microscope to produce results in approximately 2 to 4 hours with moderate sensitivity and high specificity. One rapid IFA is an RIDT and utilizes an analyzer device to produce results in approximately 15 minutes.[37]

Viral culture

Culture allows for extensive antigenic and genetic characterization of influenza viruses. However, viral culture results do not yield timely results to inform clinical management. Shell-vial tissue culture results may take 1 to 3 days, while traditional tissue-cell viral culture results may take 3 to 10 days.

Serologic testing

Routine serological testing for influenza requires paired acute and convalescent sera, does not provide timely results to help with clinical decision making, is only available at a limited number of public health or research laboratories and is not generally recommended, except for research and public health investigations.

Specimen Collection

Upper respiratory tract specimens should be collected from outpatients for influenza testing as soon after illness onset as possible, preferably within 4 days of symptom onset to increase detection of influenza viruses. Nasopharyngeal specimens are preferred over other upper respiratory tract specimens. If nasopharyngeal specimens are not available, nasal and throat swab specimens should be collected and combined together for influenza testing over single specimens from either site (particularly over throat swabs). Collect endotracheal aspirate or bronchoalveolar lavage fluid specimens from hospitalized patients with respiratory failure receiving mechanical ventilation, including patients with negative influenza testing results on upper respiratory tract specimens, for influenza testing.

PREVENTION

The best means to decrease the morbidity and mortality associated with influenza is to prevent infection through vaccination.[34,35] Appropriate infection control measures, such as hand hygiene, basic respiratory etiquette (eg, cover your cough, throw tissues away), and contact avoidance, are important in preventing the spread of influenza. Additionally, chemoprophylaxis is useful in certain situations.

Vaccination

6 The primary means of influenza prevention used in the United States is annual vaccination. Vaccination can help prevent hospitalization and death among those at high risk, decrease influenza-like illness, decrease visits to physicians' offices and emergency rooms, decrease otitis media in children, and prevent school and/or work absenteeism. Annual vaccination is recommended for all persons aged 6 months or older and caregivers (eg, parents, teachers, babysitters, nannies) of children younger than 6 months. Vaccination is also recommended for those who live with and/or care for people who are at high risk, including household contacts and healthcare workers.

The ideal time for all influenza vaccination is during October or November to allow for the development and maintenance of immunity during the peak of the influenza season.[34,35] Table 131-1 lists the vaccination coverage rates and goals for various patient populations. Provider recommendation and offer of vaccination was associated with significantly higher vaccine uptake among adults 18 years and older (67%), compared to providers who only recommended but did not offer (48%), and those who neither recommended nor offered (32%).[39] If vaccination rates improved to the Healthy People goal of 70% for all age groups, another 4.6 million illnesses, 2.2 million medical visits, and 65,844 hospitalizations could have been prevented during the 2020 to 2021 influenza season.[10] Vaccine efficacy is highest when influenza virus in circulation is well matched with strains in the vaccine. Mismatched seasons have occurred, and were associated with reduced influenza vaccine uptake and severe influenza infection. TIV (vaccine efficacy 52% vs matched 65%) and LAIV (vaccine efficacy 54% vs matched 83%) provide cross protection against nonmatching circulating strains.[40]

TABLE 131-1

Influenza Vaccination Rates and Goals by Patient Population

Patient Population	Vaccination Coverage (%) 2020-2021	Vaccination Coverage National Goal (2030) (%)
Children aged 6 months to 17 years	58	70
Persons aged 18 years or older	55	70
Nursing home residents	72 (2019-2020)	90
Pregnant women	61	80
Healthcare workers	90 (2018-2019)	90

Data from References 8-10.

7 The two vaccine types available for prevention of seasonal influenza are the inactivated influenza vaccine (IIV) and the live attenuated influenza vaccine (LAIV).[34] IIV is available as trivalent (IIV3) and quadrivalent (IIV4) formulations, while LAIV is a quadrivalent formulation. Both vaccines contain two influenza A subtypes (H3N2 and H1N1) and two influenza B viruses; the specific strains included in the vaccine each year change based on antigenic drift. The viruses used for both vaccines are initially grown in embryonated hens' eggs, which explains the precautionary measures for vaccination of persons with a severe allergic reaction to eggs.[34] Two other vaccines are produced using non-egg based technologies, recombinant quadrivalent vaccine [RIV4 (Flublok® Quadrivalent)] and cell-culture quadrivalent vaccine [ccIIV4 (Flucelvax Quadrivalent®)], and are safe if the patient has egg allergy. The Advisory Committee on Immunization Practices (ACIP) has made the following recommendations regarding the vaccinations of persons with reports of egg allergy: (1) for persons with a history of severe allergic reaction (eg, anaphylaxis) to any egg-based IIV or LAIV of any valency, the provider can consider administering ccIIV4 or RIV4; (2) for persons with a history of severe allergic reaction (eg, anaphylaxis) to any ccIIV of any valency, the provider can consider administering RIV4; and (3) for persons with a history of severe allergic reaction (eg, anaphylaxis) to any RIV of any valency, the provider can consider administering ccIIV4. Providers can also consider consulting with an allergist to help determine which vaccine component is responsible for the allergic reaction.[34] The CDC encourages individuals to use the Vaccine Adverse Event Reporting System to aide in collecting and analyzing adverse events following influenza vaccinations.[31]

Trivalent and Quadrivalent Influenza Vaccine

7 Intramuscular IIV is FDA-approved for use in people aged 6 months and older regardless of their immune status. For adults and older children, the deltoid is the preferred injection site. Infants and younger children should be vaccinated in the anterolateral thigh. Several commercial products are available and are approved for different age groups (Table 131-2). IIV is made with killed viruses, meaning it cannot cause signs and symptoms of influenza-like illness (Table 131-3). Age and immune status can affect the efficacy of IIV as can the similarity of the vaccine to the viruses in circulation. Fluzone quadrivalent may be given to children aged 6 to35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or

the other dose volume for this age group. Persons aged ≥3 years should receive 0.5-mL dose volume.[34] Flucelvax® quadrivalent vaccine use has been expanded to include those aged 6 months and older, and is reformulated without egg protein.[34]

TABLE 131-2

Approved Influenza Vaccines for Different Age Groups—United States, 2021-2022 Season

Vaccine	Trade Name	Manufacturer	Dose/Presentation	Thimerosal Mercury Content (µg Hg/0.5 mL dose)	Age Group	Number of Doses
Quadrivalent IIV (IIV4)						
IIV4	Afluria Quadrivalent	Seqirus	0.25-mL prefilled syringe 0.5-mL prefilled syringe 5-mL multidose vial	0 0 24.5	≥6-35 months ≥3 years ≥6 months (needle/syringe) or 18-64 years via jet injector	1 or 2[a] 1 or 2[a] 1 or 2[a]
IIV4	Fluarix Quadrivalent	GlaxoSmithKline	0.5-mL prefilled syringe	0	≥6 months	1 or 2[a]
IIV4	FluLaval Quadrivalent	GlaxoSmithKline	0.5-mL prefilled syringe 5-mL multidose vial	0 <25	≥6 months ≥6 months	1 or 2[a]
IIV4	Fluzone Quadrivalent[b]	Sanofi Pasteur	0.25-mL prefilled syringe 0.5-mL prefilled syringe 0.5-mL single-dose vial 5-mL multi-dose vial	0 0 0 25	≥6-35 months ≥6 months ≥6 months ≥6 months	1 or 2[a] 1 or 2[a] 1 or 2[a] 1 or 2[a]
Quadrivalent IIV high dose (IIV4-HD)						
aIIV4 high dose	Fluad Quadrivalent	Seqirus	0.5-mL prefilled syringe	0	≥65 years	1
IIV4 high dose	Fluzone HD Quadrivalent	Sanofi Pasteur	0.7-mL prefilled syringe	0	≥65 years	1
Cell culture-based quadrivalent IIV (ccIIV4)						
ccIIV4	Flucelvax Quadrivalent	Seqirus	0.5-mL prefilled syringe 5-mL multidose vial	0 25	≥ 6 months ≥ 6 months	1 or 2[a] 1 or 2[a]
Recombinant quadrivalent IIV (RIV4)						

RIV4	Flublok Quadrivalent	Sanofi Pasteur	0.5-mL prefilled syringe	0	≥18 years	1
LAIV quadrivalent (LAIV4)						
LAIV	FluMist Quadrivalent	AstraZeneca	0.2-mL sprayer	0	2-49 years	1 or 2[c]

[a]Two doses administered at least 4 weeks apart are recommended for children aged 6 months to less than 9 years who are receiving influenza vaccine for the first time or received one dose in the first year of vaccination during the previous influenza season.

[b]Fluzone quadrivalent may be given to children aged 6 to 35 months as either 0.25 mL per dose or 0.5 mL per dose. No preference is expressed for one or the other dose volume for this age group. Persons aged ≥3 years should receive 0.5-mL dose volume.

[c]Two doses administered 4 weeks apart are recommended for children aged 2 years to less than 9 years who are receiving influenza vaccine for the first time.

IIV, inactivated influenza vaccine; aIIV4, adjuvanted inactivated influenza vaccine, quadrivalent, high dose; IIV4, inactivated influenza quadrivalent vaccine; IIV4-HD, inactivated influenza quadrivalent vaccine – high dose; ccIIV4, cell culture-based quadrivalent influenza vaccine; RIV4, recombinant quadrivalent influenza vaccine; LAIV, live-attenuated influenza vaccine.

Note:

- IIVs and RIV4 may be administered concomitantly or sequentially with other inactivated vaccines or live vaccines. LAIV4 may be given simultaneously with other live or inactivated vaccines. However, after administration of a live vaccine (such as LAIV4), at least 4 weeks should elapse before another live vaccine is administered.
- Influenza antiviral medications might reduce the effectiveness of LAIV4 if given within 48 hours before to 14 days after administration of LAIV4. Persons who receive influenza antiviral medications within this period of LAIV4 vaccination can be revaccinated with another appropriate influenza vaccine (eg, IIV or RIV4).

Data from References 34 and 35.

TABLE 131-3

Comparison of Inactivated Influenza Vaccine (IIV) and Live-Attenuated Influenza Vaccine (LAIV)

Characteristic	IIV (IIV3/IIV4)	LAIV
Age groups approved for use	≥6 months	2-49 years
Immune status requirements	Immunocompetent or immunocompromised	Immunocompetent
Viral properties	Inactivated (killed) influenza A (H3N2), A (H1N1), and B viruses	Live-attenuated influenza A (H3N2), A (H1N1), and B viruses
Route of administration	Intramuscular	Intranasal
Immune system response	High serum IgG antibody response	Lower IgG response and high serum IgA mucosal response

Data from References 34 and 35.

In children aged between 6 and 24 months, a 2-year randomized study of intramuscular IIV3 exhibited 89% seroconversion and efficacy of 66% in year 1 and 7% in year 2 versus culture-confirmed influenza.[41] In children aged between 2 and 15 years, the efficacy of IIV3 was 91% and 77% against culture-confirmed influenza A H1N1 and H3N2, respectively. IIVs reduced the risk of influenza and influenza-like illness (ILI) in children.[42] To prevent one case of influenza, five children would need to be vaccinated, and to prevent one case of ILI, 12 children would need to be vaccinated. Therefore, vaccinating children could prevent influenza-related mortality and may also lead to fewer parents taking time off work. Two doses of IIVs are important for children under the age of 9 years, supporting the rationale for the recommendation of a booster dose of IIV at least 4 weeks after the initial dose in children between 6 months and less than 9 years of age if no previous vaccination (see Table 131-2).[34]

IIV is also effective in adult populations under and older than the age of 65 years. Intramuscular IIVs demonstrated a reduction in influenza, ILI, hospitalization, and work absenteeism in healthy adults aged 16 to 65 years.[43] Seventy-one adults would need to be vaccinated to prevent one influenza case, and 29 adults need to be vaccinated to prevent one ILI. In pregnant women, IIVs efficacy was 50% (number needed to vaccinate, NNV 55), and 49% in infants up to 24 weeks (NNV 56).

Adults older than the age of 65 years benefit from influenza vaccination, including prevention of complications, decreased risk of influenza-related hospitalization, and death.[44] However, people in this population may not generate a strong antibody response to the vaccine and may remain susceptible to infection. In patients older than the age of 60 years who do not reside in a long-term care facility, IIV efficacy was 58% against influenza illness.[45] Although the efficacy against influenza illness for those living in long-term care facilities is between 30% and 40%, the vaccine is 50% to 60% effective in preventing influenza-related hospitalization or pneumonia and 80% effective in preventing influenza-related death.[45]

Fluzone HD trivalent induced higher immune response compared with standard IIV3 and offered better protection than SD-IIV3 for persons aged 65 years or older. Fluzone HD prevented 24% more cases of influenza caused by any circulating influenza strain and 51% more cases of influenza caused by strains similar to those contained in the vaccine compared to standard trivalent vaccine. Compared to IIV3, Fluzone HD trivalent would avert 195,958 cases of influenza, 22,567 influenza-related hospitalizations, 5,423 influenza-related deaths, and generate 29,023 more Quality Adjusted Life Years among US seniors.[46] Fluzone HD quadrivalent or Fluad quadrivalent vaccine are preferred vaccines for use in adult patients 65 years and older.[35]

The most frequent adverse effect associated with IIV is soreness at the injection site that lasts for less than 48 hours. IIV may cause fever and malaise in those who have not previously been exposed to the viral antigens in the vaccine.[34] Allergic-type reactions (hives, systemic anaphylaxis) rarely occur after influenza vaccination and are likely a result of a reaction to residual egg protein in the vaccine.

The 1976 swine influenza vaccine was linked to a rise in the incidence of Guillain-Barré syndrome (GBS), and this has propagated the belief that IIV may cause GBS.[47] However, there is insufficient evidence to establish causality. Although several studies have failed to establish a relationship between influenza vaccination and increased frequency of GBS, some studies have demonstrated a small but significant increase in GBS following influenza vaccination.[47] Therefore, vaccination should be avoided in persons who are not at high risk for influenza complications and who have experienced GBS within 6 weeks of receiving a previous influenza vaccine.[34] The potential benefits of influenza vaccination in terms of prevention of severe illness, hospitalization, and mortality significantly outweigh the risks of GBS, and vaccination is recommended for all groups previously discussed.

The multidose vials and a few of the single-dose preparations of intramuscular IIV contain trace to small amounts of a preservative, thimerosal, which is a mercury-containing compound (see Table 131-2). Some individuals are concerned about thimerosal exposure, particularly among children, because of the unfounded belief that thimerosal exposure is linked to the development of autism. No scientifically persuasive evidence exists to suggest harm from thimerosal exposure from a vaccine. Conversely, accumulating evidence reports the lack of harm from such exposure.[48,49] Thus, similar to GBS, the potential benefits of influenza vaccination in terms of prevention of severe illness, hospitalization, and mortality significantly outweigh the theoretical risk associated with thimerosal exposure, and vaccination is recommended for all groups previously discussed. However, to maximize the public health benefit and placate concerned individuals, thimerosal-free vaccine is available (see Table 131-2).

Live-Attenuated Influenza Vaccine

7 LAIV is made with live, attenuated viruses and is approved for intranasal administration in healthy people between 2 and 49 years of age (see Table 131-3). Advantages of LAIV include its ease of administration, intranasal rather than intramuscular administration, and the potential induction of broad mucosal and systemic immune response.[34] The mucosal response occurs at the site of viral entry and may prevent infection before viral replication

occurs. LAIV is more expensive than IIV and is approved for use in a more limited population. Originally licensed as a trivalent vaccine, in 2012, the FDA approved FluMist® Quadrivalent vaccine (LAIV4) for influenza prevention in people aged 2 to 49 years.[34] FluMist® Quadrivalent vaccine which has replaced the trivalent vaccine contains four strains of the influenza viruses, two influenza A strains and two influenza B strains. The inclusion of a second B strain in the vaccine increases the likelihood of adequate protection against circulating influenza B strains.

Studies of FluMist® trivalent, in addition to three new clinical trials with the quadrivalent vaccine in 4,000 children (2-17 years) and adults (18-49 years) in the United States, provide supporting evidence on the efficacy and safety of FluMist® Quadrivalent.[50] Immune responses were similar between FluMist® Quadrivalent and FluMist® trivalent. LAIV4 recipients aged 2 to 5 years had 52.5% and 54.4% fewer cases of influenza illness against matched and mismatched strains, respectively, as compared with IIV3 recipients.[50]

Although LAIV4 is FDA-approved for adults younger than the age of 49 years, LAIV is effective in healthy adults aged between 18 and 64 years.[34] LAIV4 should not be used during pregnancy. Vaccination reduced the number of severe febrile illnesses by 18.8% and febrile upper respiratory tract illnesses by 23.6%.[50] Additionally, vaccination led to fewer days of illness, fewer days lost from work, fewer visits to healthcare providers, and decreased use of prescription antibiotics and nonprescription medications.[50]

Adverse reactions of LAIV are similar among those receiving FluMist® Quadrivalent and FluMist® trivalent. The adverse effects typically associated with LAIV administration include runny nose, congestion, sore throat, and headache. Because LAIV contains live, attenuated viruses, viral shedding may occur for several days following vaccination with LAIV, although this should not be equated with person-to-person transmission.[34] Additionally, because LAIV contains live, attenuated viruses, which carry a theoretical infection risk, LAIV should not be given to immunosuppressed patients or given by healthcare workers who are severely immunocompromised. Moreover, for the reasons discussed in IIV above, LAIV should not be administered to persons with a history of GBS or hypersensitivity to eggs. Vaccine effectiveness of LAIV was 45% against influenza A and B, with 25% protection against influenza A (H1N1) pdm09 compared with unvaccinated children.[34] LAIV is not recommended in several populations, including people older than 50 years and pregnant females, largely because the vaccine has not been studied extensively in these populations. However, many clinicians believe the use of LAIV in these populations is acceptable.[34,50]

Postexposure Prophylaxis

8 Antiviral drugs available for prophylaxis of influenza should be considered adjuncts but are not replacements for annual vaccination. Adamantanes are no longer recommended for prophylaxis or treatment in the United States because of widespread resistance among influenza viruses.[35,51] Neuraminidase (NA) inhibitor antiviral medications are approximately 70% to 90% effective in preventing influenza against susceptible influenza viruses and are useful adjuncts to influenza vaccination.[52] Peramivir is not approved for chemoprophylaxis; however, oseltamivir and zanamivir are effective prophylactic agents against influenza for preventing laboratory-confirmed influenza when used for seasonal prophylaxis (67% and 85% effective for zanamivir and oseltamivir, respectively) and preventing influenza illness among persons exposed to a household contact who was diagnosed with influenza (79%-81% and 68%-89% effective for zanamivir and oseltamivir, respectively). Additionally, oseltamivir was 92% effective against influenza, and also reduced associated complications when used as seasonal prophylaxis among immunized, institutionalized, elderly patients.[35,52] Zanamivir and oseltamivir are 79% to 81% and 68% to 89% effective, respectively, in preventing influenza illness among persons exposed to a household contact who was diagnosed with influenza.[34,51] In 2020, the FDA approved baloxavir for post-exposure prophylaxis of influenza in persons aged 12 years and older.[52] Baloxavir, when administered within 24 hours of the onset of symptoms in persons 12 years of age and older, reduced the risk of household transmission of influenza by 86% compared with placebo.[53] Prophylaxis was begun within 2 days after exposure. Oseltamivir is FDA-approved for chemoprophylaxis in individuals aged 1 year and older. However, the CDC, the American Academy of Pediatrics (AAP), and the Pediatric Infectious Diseases Society (PIDS) provide an expanded recommendation for chemoprophylaxis in those aged 3 months and older.[35,51] All of these agents remain active against all influenza viruses, including influenza A H3N2v. Table 131-4 lists dosing recommendations.

TABLE 131-4

Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis—United States

Drug	Adult Treatment	Adult Prophylaxis[a]	Pediatric Treatment	Pediatric Prophylaxis[a]
CAP-dependent endonuclease inhibitor				
Baloxavir[b,c]	12 yrs and older: 40 to <80 kg: One 40 mg dose >80 kg: One 80 mg dose	None	FDA approved and recommended for use in children aged 12 yrs or older weighing at least 40 kg. See adult dosage	None
Neurominidase inhibitors				
Oseltamivir[d,e,f]	75-mg capsule twice daily × 5 days	75-mg capsule daily × 10 days	Term infants 0-8 months: 3 mg/kg/dose twice daily 9-11 months[g]: 3.5 mg/kg/dose twice daily or 3 mg/kg/dose twice daily ≥1 year: ≤15 kg: 30 mg twice daily >15-23 kg: 45 mg twice daily >23-40 kg: 60 mg twice daily >40 kg: 75 mg twice daily Duration: All for 5 days	Not recommended if <3 months 3 to <12 months: 3 mg/kg/dose daily 9-11 months: 3.5 mg/kg/dose daily ≥1 year: ≤15 kg: 30 mg daily >15-23 kg: 45 mg daily >23-40 kg: 60 mg daily >40 kg: 75 mg daily Duration: All for 10 days
Zanamivir	10 mg (2 of 5 mg inhalations) twice daily × 5 days	10 mg (2 of 5 mg inhalations) daily × 10 days	10 mg (2 of 5 mg inhalations) twice daily × 5 days for ≥7 years old	10 mg (2 of 5 mg inhalations) daily for ≥5 years old × 10 days
Peramivir[c,e]	13 yrs and older: One 600 mg dose via intravenous infusion for 15-30 minutes	None	2 to 12 yrs of age: One 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for a minimum of 15-30 minutes	None

[a]If influenza vaccine is administered, prophylaxis can generally be stopped 14 days after vaccination for noninstitutionalized persons. When prophylaxis is being administered following an exposure, prophylaxis should be continued for 10 days after the last exposure. In persons at high risk for complications from influenza for whom vaccination is contraindicated or expected to be ineffective, chemoprophylaxis should be continued for the duration that influenza viruses are circulating in the community during influenza season.

[b]Time to peak = 4 hours. Food and cations (calcium, aluminum, magnesium, iron) can decrease peak concentration by 48%. Long half-life (79.1 hours) and is metabolized by UDP-glucuronosyltransferase (UGT1A3) and CYP3A4.

[c]For the treatment of uncomplicated influenza with oral baloxavir or intravenous peramivir, a single dose is recommended. Longer daily dosing (oral oseltamivir or intravenous peramivir) can be considered for patients who remain severely ill after 5 days of treatment.

[d]Oseltamivir dosing for preterm infants using their postmenstrual age (ie, gestational age + chronological age): <38 weeks: 1.0 mg/kg/dose twice daily; 38–40 weeks: 1.5 mg/kg/dose twice daily; >40 weeks: 3.0 mg/kg/dose twice daily.[32]

[e]In patients with renal insufficiency, the dose should be adjusted on the basis of creatinine clearance. See https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.[33,52]

[f]Some experts recommend 150 mg twice daily for severe illness in pregnant women. Optimal dosing for prophylaxis in pregnant women is unknown.[33]

[g]The American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily; CDC and US Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children aged 9 to 11 months.[32,54]

Note: Although amantadine and rimantadine have been used historically for the treatment and prophylaxis of influenza A viruses, due to high resistance, the CDC no longer recommends the use of these agents for the treatment and/or prophylaxis of influenza.

Data from References 35 and 52.

In those patients who did not receive the influenza vaccination and are receiving an antiviral drug for prevention of disease during the influenza season, the medication should optimally be taken for the entire duration of influenza activity in the community. The use of prophylaxis requires clinical judgment and depends on a variety of factors, but prophylaxis for seasonal influenza should be considered during influenza season for the following groups of patients after exposure to an infectious source[35,36,51]:

1. Persons at high risk of serious illness and/or complications who are exposed to an infectious person and cannot be vaccinated.
2. Persons at high risk of serious illness and/or complications who are vaccinated but exposed to an infectious person during the first 2 weeks following vaccination. The development of sufficient antibody titers after vaccination takes approximately 2 weeks.
3. Persons with severe immune deficiency or who may have an inadequate response to vaccination (eg, advanced human immunodeficiency virus [HIV] disease, persons receiving immunosuppressive medications), after exposure to an infectious person.
4. Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution.

LAIV should not be administered until 48 hours after influenza antiviral therapy has stopped, and influenza antiviral drugs should not be administered for 2 weeks after the administration of LAIV because the antiviral drugs inhibit influenza virus replication.[34,36] No contraindication exists for concomitant use of IIV and influenza antiviral drugs. If chemoprophylaxis is given, it should be administered as soon as possible after exposure, ideally no later than 48 hours after exposure.[36] Postexposure prophylaxis should not be given if >48 hours has elapsed since exposure, and full-dose empiric antiviral treatment should be initiated as soon as symptoms occur, if treatment is indicated. Duration of chemoprophylaxis in a non-outbreak setting is 7 days after the most recent exposure to a close contact with influenza.[36,51]

Pregnant Females and Immunocompromised Hosts

Pregnant females and immunocompromised hosts are special populations at increased risk of influenza complications and are also populations in whom careful consideration must be given in regard to prevention strategies.

Pregnant females, regardless of trimester, should receive annual influenza vaccination with IIV but not with LAIV.[34,36] No studies have demonstrated an increased incidence of adverse effects in mothers or their infants related or potentially related to IIV, but no such data exist for LAIV.[34] Receipt of an influenza vaccination reduced hospitalizations of pregnant females by about 40%.[55] Influenza vaccination of pregnant females reduced hospitalization of their infants by 92% during the first 6 months of life.[54] IIV is also safe for breastfeeding mothers. No data exist for LAIV and breastfeeding mothers, but caution is warranted because of the potential for viral shedding.[34]

Immunocompromised hosts should receive annual influenza vaccination with IIV but not with LAIV. IIV was 100% effective against laboratory-confirmed influenza in HIV-positive patients with no significant effect on viral load or CD4 cell count.[56] HIV-infected persons may benefit from vaccination with high-dose IIV3 due to greater immunogenicity compared to standard-dose vaccine (H1N1, seroprotection rate; 96% vs 87%).[56] In solid-organ transplant recipients high-dose IIV3 (compared with standard dose IIV) resulted in higher immunogenicity.[57] A two-dose vaccination strategy spaced 5 weeks apart in solid-organ transplant recipients elicited greater immune response compared to single dose.[58] Although this suggests a potential benefit from

a two-dose regimen, such a regimen is not recommended for solid-organ transplant recipients. Standard annual influenza vaccination and early antiviral therapy were shown to reduce influenza-related morbidity in transplant recipients (solid and hematopoietic).[59] Immune responses in patients receiving chemotherapy for either solid or hematologic tumors are lower (fourfold rise, 17%-52%) than in those who had completed chemotherapy (50%-83%) and healthy patients (67%-100%).[60] However, there was lower mortality- and infection-related outcomes with influenza vaccination of immunocompromised adults with cancer.[61]

Large clinical trials evaluating the use of influenza antivirals for prophylaxis are lacking in immunocompromised hosts. Viral shedding occurs for prolonged periods in this population and may promote the development of antiviral resistance, which has been documented with oseltamivir in immunocompromised patients.[35,36]

PATIENT CARE PROCESS

Patient Care Process for Influenza Infection Treatment

Collect

- Patient characteristics: age, occupation, travel, lifestyle, immune status, present and past medical history, allergies
- Medication history (include prescription, nonprescription, and other substances); vaccination history; pregnancy status
- Microbiologic results from rapid respiratory viral panel and secondary bacterial infection. Bacterial susceptibility tests when available (see Clinical Presentation: Diagnosis of Influenza)
- Laboratory results, major organ function (particularly, kidney and liver), lactate

Assess

- Assess for medication contraindications and drug interactions
- Determine severity of illness based on vital signs, acute organ dysfunction, and source control (or lack thereof) (see Clinical Presentation: Diagnosis of Influenza)
- Determine at-risk patients for secondary bacterial infection of the respiratory tract, patient's microbiologic history, previous antibiotic exposure, and response to current therapy (see Clinical Presentation: Diagnosis of Influenza)
- Determine if other conditions are present such as chronic lung disease likely to affect outcomes of infection
- Estimate creatinine clearance for drug dosing

Plan*

- Strongly recommend future influenza vaccine if no contraindication is present (Tables 131-2 and 131-3)
- Initiate treatment neuraminidase therapy—oral or inhaled or IV based on severity of illness (Table 131-4)
- Determine influenza treatment goals of therapy with monitoring parameters for each goal (see Goals of Therapy)
- Determine appropriate antibiotic therapy for secondary bacterial infection and monitoring plan
- Establish antimicrobial monitoring goals for efficacy (eg, resolution of infection, clearance of bacteria from blood cultures) and drug toxicity
- Check for drug interactions and dose adjustments based on end-organ function

Implement

- Initiate a neuraminidase inhibitor and continue for ~7 days after identification of illness onset in the last patient (prophylaxis for community outbreak) or 5 days (treatment) or establish a tentative stop date for severely ill patients
- If secondary bacterial infection is suspected, initiate empiric antimicrobial regimen, and deescalate antimicrobial therapy to more narrow-spectrum agents as appropriate based on response and microbiologic data
- Assess patient as needed for response to antiviral medications, and other treatments
- Use measures to minimize adverse events to medications and assess for occurrence of adverse events

Follow-up: Monitor and Evaluate

- Refer patient for other health, wellness, or follow-up services to their identified primary care provider or another provider (provide patient with documentation of referral)
- Determine if patient shows improvement in the signs and symptoms of infection within 48 hours after neuraminidase inhibitor is initiated
- Monitor for emergence of resistant virus
- Monitor for occurrence of secondary bacterial pneumonia

****Collaborate with patient, caregiver(s), and other healthcare professionals.***

TREATMENT

When prevention efforts fail or are not used, clinicians must turn to the agents available for treatment of influenza. Antiviral treatment options are limited, particularly in the face of resistance to the adamantanes and oseltamivir. The four primary goals of therapy of influenza are to control symptoms, prevent complications, decrease work and/or school absenteeism, and prevent the spread of infection.

General Approach to Treatment

In the era of pandemic preparedness and increasing resistance, early and definitive diagnosis of influenza is crucial. Antiviral drugs are most effective if started within 48 hours of the onset of illness. Moreover, the sooner the antiviral drugs are started after the onset of illness, the more effective they are. Antiviral drugs shorten the duration of illness and provide symptom control. Adjunct agents, such as acetaminophen for fever or an antihistamine for rhinitis, may be used concomitantly with the antiviral drugs.

Nonpharmacologic Therapy

Patients suffering from influenza should get adequate sleep and maintain a low level of activity. They should stay home from work and/or school to rest and prevent the spread of infection. Appropriate fluid intake should be maintained. Cough/throat lozenges, warm tea, or soup may help with symptom control (cough, sore throat).

Pharmacologic Therapy

The Cap-dependent endonuclease inhibitor, baloxavir and NA inhibitors, oseltamivir, zanamivir, and peramivir are the only antiviral drugs available for the treatment and prophylaxis of influenza.[51] Peramivir is the only intravenous formulation commercially available. The adamantanes (amantadine and rimantadine) are no longer recommended due to high resistance among influenza viruses. A limited discussion of adamantanes can be found in the following section, but the focus will be on oseltamivir, zanamivir, and peramivir.

Adamantanes

The adamantanes (amantadine and rimantadine) block the M2 ion channel, which is specific to influenza A viruses, and inhibit viral uncoating. Historically, the adamantanes were used for the treatment of seasonal influenza A H1N1, as they do not have activity against influenza A H3N2 or influenza B viruses. The novel influenza A H1N1 that emerged during the 2009 to 2010 influenza season, which has now replaced seasonal influenza A H1N1 as the predominant seasonal virus, was resistant to the adamantanes. Since 2009 more than 99% of influenza A H3N2 and H1N1pdm09 were resistant to adamantanes.[51] As a result, the CDC only recommends the use of NA inhibitors for the treatment and prophylaxis of influenza A, until susceptibility of adamantanes is reestablished among influenza A viruses. Resistance to adamantanes is often conferred by a single-point mutation, and this is problematic because it results in cross-resistance to the entire class.[36]

Cap-Dependent Endonuclease Inhibitor

Oral baloxavir marboxil is a Cap-dependent polymerase acidic endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication.[52] It is approved for use within 48 hours of illness onset, in people aged 12 years and older, for the treatment of acute, uncomplicated influenza in patients who are at high risk for developing serious influenza-related complications, for example, those with chronic conditions like asthma, heart disease, and diabetes. Avoid co-administration of baloxavir with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives or antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, or zinc).[52] When administered within 48 hours of symptom onset, baloxavir decreased duration of illness by 2.5 days. The safety and efficacy of baloxavir in patients less than 12 years of age or weighing less than 40 kg have not been established. Baloxavir is not recommended for use in pregnant women or breastfeeding mothers. Commonly reported events for baloxavir were diarrhea, bronchitis, nausea, nasopharyngitis, and increased liver enzymes.[52] The recommended doses are listed in Table 131-4.

Neuraminidase Inhibitors

Oseltamivir, zanamivir, and peramivir are NA inhibitors that have activity against both influenza A and influenza B viruses.[51] Without NA, release of the virus from infected cells is impaired, and, thus, viral replication is decreased. Although no randomized, placebo-controlled trials of antiviral treatment have been conducted in hospitalized influenza patients to establish the efficacy of NA inhibitors, a number of observational studies have reported clinical benefits of NA inhibitors in hospitalized patients, including reduction in duration of hospitalization and risk of death, including ICU patients.[62,63] When administered within 48 hours of the onset of illness, NA inhibitors may reduce the duration of illness by approximately 1 day versus placebo. Neuroaminidase inhibitors shortened symptom duration in adults by 0.5 to 1 day, and improved survival in hospitalized patients.[63] In children, NA inhibitor use resulted in shorter duration of illness and 34% lower risk of otitis media.[64] Treatment of children with laboratory-confirmed influenza with oseltamivir significantly reduced the duration of illness by 17.6 hours.[64] This has a significant effect on not only the quality of life for the patient but also the societal costs associated with influenza. The benefits of treatment are highly dependent on the timing of the initiation of treatment, with the ideal initiation period being within 12 hours of illness onset, up to 48 hours after onset of illness.[35,36,51] Debate still exists regarding the benefit of antiviral administration more than 48 hours after onset. Observational studies have reported a lower risk for severe outcomes with oral oseltamivir started as late as 4 and 5 days after onset of illness in critically ill patients with suspected or confirmed influenza.[65-67] Based upon the available observational data in hospitalized patients with influenza, including ICU patients, initiation of NA inhibitor treatment is recommended as soon as possible for hospitalized patients with suspected or confirmed influenza.

Oseltamivir treatment in adults and adolescents with documented influenza illness resulted in a 27% reduction in overall antibiotic use, a 55% reduction in lower respiratory tract complications (bronchitis, pneumonia), and a 59% reduction in hospitalizations.[68] Zanamivir treatment in adults and adolescents with influenza-like illness resulted in a 28% reduction in antibiotic use and a 40% reduction in lower respiratory tract complications.[69] The data in these studies largely come from healthy individuals rather than those at highest risk for complications associated with influenza. The impact of appropriate treatment in high-risk populations may be even greater than that documented to date.

Oseltamivir is FDA approved for treatment in those aged 14 days and older, zanamivir for treatment in those older than 7 years, and peramivir for those aged 2 years and older.[51] The CDC, the American Academy of Pediatrics (AAP), and the Pediatric Infectious Diseases Society (PIDS) provide an expanded recommendation for oseltamivir for treatment of infants younger than 14 days.[35,51] The recommended doses vary by agent and age (see Table 131-4). The recommended duration of treatment for both oseltamivir and zanamivir is 5 days, and one dose for 1 day for peramivir.

The FDA-approved single-dose peramivir injection (Rapivab®) for intravenous use for the treatment of acute uncomplicated influenza in people aged 2 years and older.[36,51] Peramivir is as effective as oseltamivir, without severe adverse events.[70,71] It is an effective option in patients who are unable to tolerate or absorb oral or enterically administered oseltamivir due to gastric stasis, malabsorption, or gastrointestinal bleeding. Enteric oseltamivir and intravenous peramivir had similar clinical benefits in hospitalized influenza patients.[70] The benefit of peramivir beyond 1 day has not been demonstrated. Intravenous peramivir at a dosage of 600 mg once daily (10 mg/kg once daily in children) for 5 days plus standard of care did not demonstrate a clinical benefit compared with placebo plus standard of care in hospitalized patients younger than 6 years.[72]

Neuropsychiatric complications consisting of delirium, seizures, hallucinations, and self-injury in pediatric patients (mostly from Japan) have been reported following treatment with oseltamivir, and peramivir. Since influenza itself can be associated with neuropsychiatric manifestations, a causal relationship between oseltamivir or peramivir and neuropsychiatric effects has not been delineated. However, the labels for oseltamivir and peramivir have been updated to include neuropsychiatric events as a precaution, and their occurrence with use of these agents should not be ignored.

Influenza resistance to the NA inhibitors has been documented but cross-resistance between the NA inhibitors has not.[21,51] Antiviral resistance remains relatively low. During the 2018 to 2019 influenza season, 99% of the tested A(H1N1) pdm09 viruses were susceptible to oseltamivir and peramivir, and 100% of the 2009 H1N1 viruses tested were susceptible to zanamivir; 100% of influenza A (H3N2) tested were susceptible to both oseltamivir and zanamivir; and 100% of influenza B viruses tested were susceptible to both oseltamivir and zanamivir.[21,51] Antiviral susceptibility testing of circulating viruses confirmed that seasonal influenza A H3N2 and variant influenza H3N2 maintain susceptibility to oseltamivir, peramivir, and zanamivir.[21] The burden of surveillance rests on clinicians to identify local patterns of influenza circulation to guide antiviral therapy.

Special Populations

There is inadequate data for the use of anti-influenza medications in special populations, such as immunocompromised hosts. Furthermore, there is limited data for use of influenza antivirals during pregnancy. The adamantanes are embryotoxic and teratogenic in rats, and limited case reports of adverse fetal outcomes following amantadine use in humans have been published. Oseltamivir and zanamivir have been used but lack solid safety clinical data in pregnant females. Pregnancy should not be considered a contraindication to oseltamivir or zanamivir use. Oseltamivir is preferred for the treatment of pregnant females because of its systemic activity; however, the drug of choice for chemoprophylaxis is not yet defined. Zanamivir may be preferred because of its limited systemic absorption, but respiratory complications need to be considered, especially in females with underlying respiratory diseases. Both the adamantanes and the NA inhibitors are excreted in breast milk and should be avoided by mothers who are breastfeeding their infants. More studies are needed in these populations who are at high risk for serious disease and complications from influenza.

PANDEMIC PREPAREDNESS

This chapter is not meant to provide an exhaustive review of the biology of influenza or pandemic preparedness. This topic is rapidly changing and interested readers are referred to the following Websites: *www.flu.gov*, *www.who.int/influenza/human_animal_interface/en/*, and *www.cdc.gov/h1n1flu*.

A vital component of pandemic preparedness is forethought—plans must be established for how to effectively triage large numbers of ill patients, prioritize and/or ration vaccine and antivirals, and communicate with the public through mass media during a period of severe labor shortage (a result

of stress and illness among healthcare workers) and supply shortfall (a result of societal and economic disruption).

EVALUATION OF THERAPEUTIC OUTCOMES

Patients should be monitored daily for resolution of signs and symptoms associated with influenza, such as fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. These signs and symptoms will typically resolve within approximately 1 week. If the patient continues to exhibit signs and symptoms of illness beyond 10 days or a worsening of symptoms after 7 days, a physician visit is warranted as this may be an indication of a secondary bacterial infection. Ideally, antiviral therapy should not be started until influenza is confirmed via the laboratory. However, therapy should be initiated within 48 hours of illness onset, emphasizing the need for rapid diagnosis. Repeat diagnostic tests to demonstrate clearance of the virus are not necessary.

ABBREVIATIONS

AAP	American Academy of Pediatrics
ACIP	Advisory Committee on Immunization Practices
CDC	US Centers for Disease Control and Prevention
DFA	direct fluorescence antibody
EIA	enzyme immunoassay
FDA	Food and Drug Administration
GBS	Guillain-Barré syndrome
GMTs	geometric mean titers
HIV	human immunodeficiency virus
IFA	indirect fluorescence antibody
IIV	inactivated influenza vaccine
IIV3	trivalent influenza vaccine
IIV4	quadrivalent influenza vaccine
LAIV	live-attenuated influenza vaccine
M	matrix
NA	neuraminidase
PIDS	Pediatric Infectious Diseases Society
POC	point of care
PRs	protection rates
RIDTs	Rapid Influenza Diagnostic Tests
RIMAs	rapid influenza molecular assays
RT-PCR	reverse-transcription polymerase chain reaction
SOIV	swine origin influenza virus
VE	vaccine efficacy
WHO	World Health Organization

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SELF-ASSESSMENT QUESTIONS

1. A 21-year-old, otherwise healthy college student presents to clinic with history of 4 days of fever, myalgia, dry cough, and malaise. She is diagnosed with influenza A infection. What would be the most appropriate recommendation for her?

   A. Oseltamivir 75 mg once daily for 5 days

   B. Maintenance of fluid intake, warm tea, and cough lozenges

   C. Oseltamivir 75 mg plus rimantadine 100 mg twice daily for 5 days

   D. Zanamivir 10 mg twice daily for 5 days plus maintenance of fluid intake, warm tea, and cough lozenges

2. Which of the following characteristics is *true* for the influenza B virus?

   A. Responsible for the seasonal epidemics of influenza

   B. Typically associated with sporadic outbreaks

   C. Categorized into subtypes based on hemagglutinin and neuraminidase

   D. Does not cause disease in humans

3. Which of the following statements is *true* regarding antigenic drift and antigenic shift?

   A. Antigenic shift occurs when point mutations in the surface antigens of a particular subtype create antigenic variants, resulting in small changes in the hemagglutinin and/or neuraminidase molecules.

   B. Antigenic drift occurs when the influenza virus acquires a new hemagglutinin and/or neuraminidase via genetic reassortment.

   C. Antigenic shift causes seasonal epidemics of influenza and is the rationale behind the recommendation for annual vaccination.

   D. Antigenic drift causes seasonal epidemics of influenza and is the rationale behind the recommendation for annual vaccination.

4. What elements are needed for an avian influenza pandemic to occur?

   A. Sustained transmission from human to human

   B. Direct transmission from bird to human

   C. An influenza virus against which humans have no immunity

   D. All of the above

5. The influenza virus can be transmitted person-to-person via which of the following mechanisms?

A. Influenza virus is not transmitted person-to-person.

B. Via inhalation of respiratory droplets after someone sneezes

C. Contact with an object contaminated with respiratory secretions, such as a used tissue

D. Both B and C could allow viral transmission.

6. How long after the onset of illness are children considered infectious?

A. 2 days

B. 5 days

C. 7 days

D. ≥10 days

7. Which of the following patients should not receive the live-attenuated influenza vaccine (LAIV)?

A. A 45-year-old male hemodialysis patient

B. A healthy 2-year-old girl

C. A 37-year-old female with HIV and a CD4 cell count of 150 cells/mm^3 (0.15×10^9/L)

D. A healthy 39-year-old accountant

8. A 52-year-old person presents with fever, malaise, nonproductive cough, and sore throat for the last 5 days. They are diagnosed with influenza. What other signs and symptoms of influenza would be classical for this patient?

A. Rhinitis

B. Nausea and vomiting

C. Otitis media

D. None of the above is classical signs and symptoms of influenza.

9. Which diagnostic test would be the *most* appropriate to use in the patient from #8 to provide a rapid result?

A. Rapid antigen test

B. Direct fluorescence antibody test

C. Viral culture

D. All of the above could be used in this patient for rapid diagnosis.

10. In which of the following patients would prophylaxis with an antiviral medication be appropriate?

A. A vaccinated (received 1 month ago) 74-year-old male resident of a long-term care facility with a current influenza outbreak

B. A 54-year-old female presenting to clinic to receive her influenza vaccination because she heard about several influenza cases in the community

C. An unvaccinated 34-year-old mother of three (healthy children aged 3, 6, and 9 years)

D. Prophylaxis with antiviral medication is appropriate in all of the above.

11. Which of the following is the most appropriate prophylactic regimen for the patient(s) requiring prophylaxis from #10?

    A. Rimantadine 200 mg once daily for the duration of influenza activity

    B. Zanamivir 10 mg twice daily for 5 days

    C. Oseltamivir 75 mg daily for up to a week after last documented influenza infection

    D. Zanamivir 10 mg twice daily for 2 days

12. Which of the following statements is *true*?

    A. Thimerosal-free vaccines are available because thimerosal causes autism.

    B. No thimerosal-free formulations of the influenza vaccine are available.

    C. No scientifically persuasive evidence exists to suggest harm from thimerosal exposure from a vaccine.

    D. The risks of using a thimerosal-containing vaccine outweigh the benefits of receiving the influenza vaccine.

13. Which of the following patients is *not* at high risk for complications or severe disease from seasonal influenza infection?

    A. A 28-year-old pregnant female at 34 weeks' gestation with no significant medical history

    B. A 47-year-old male with hypertension successfully managed with lisinopril

    C. An 82-year-old female residing in a nursing home

    D. A 12-year-old boy with asthma

14. Adamantane monotherapy would be most appropriate in which of the following situations?

    A. Prophylaxis for patients in a nursing home during an influenza A outbreak

    B. Prophylaxis for patients in a nursing home during an influenza B outbreak

    C. Treatment in a 58-year-old male presenting within 36 hours of the onset of illness

    D. Use of the adamantanes is not appropriate for monotherapy because of rapid development of resistance

15. What are the primary subtypes of influenza A that have been circulating among humans over the past 30 years?

    A. H3N2 and H1N1v

    B. H3N2 and H5N1

    C. H3N2 and H1N1

    D. H2N2 and H5N1

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Antivirals if used, should be started within 48 hours of symptom onset to maximize effectiveness. This patient is presenting with 4 days history of fever, etc. A is incorrect, because the oseltamivir dose is incorrect for treatment (see Table 131-4) and the patient is presenting outside the recommended treatment window. C is incorrect because rimantadine is no longer recommended for treatment or prophylaxis of influenza A. Although oseltamivir dose is correct, it is unknown of the benefit since it has been 4 days since symptom onset. Likewise, D is incorrect – symptom is greater than 48 hours onset.

2. **B.** B is correct as influenza B viruses are typically associated with sporadic outbreaks, particularly among residents of long-term care facilities. A is incorrect as that is the characteristics of influenza A as we have seen various variants with antigenic drift over the years. C is a characteristic of influenza A. Influenza B viruses do not have subtypes. D is incorrect, influenza B causes disease in humans and is included in seasonal influenza vaccine.

3. **D.** Seasonal influenza epidemics are the result of viral antigenic drift, which is why the influenza vaccine is changed on a yearly basis. (See section on "Prevention - Vaccination".) Antigenic drift forms the foundation of the recommendation for annual influenza vaccination. The acquisition of a new hemagglutinin and/or neuraminidase by the influenza virus is called antigenic shift, which results in a novel influenza virus that has the potential to cause a pandemic. A and B are incorrect as they do not describe Antigenic shift or Antigenic drift. C is incorrect – antigenic shift is the basis for pandemic when influenza A acquires hemagglutinin and/or neuraminidase leading to a novel virus. D is correct and describes antigenic drift phenomenon. See Key Concepts 2 and 3.

4. **D.** These are novel viruses that must be able to replicate in humans, spread person-to-person, and affect a susceptible population. The spread of avian influenza viruses from person-to-person is rare, and has been limited, inefficient, and unsustained. Therefore A, B, C all have to be present for a pandemic. D is the correct answer. See the Avian Influenza section and Key Concept 3.

5. **D.** A is incorrect because the spread of influenza is person-to-person. B and C are correct modes of transmission. Therefore, D is the correct answer.

6. **D.** Children, especially younger children, might potentially be infectious for longer periods (more than 10 days). Therefore A, B, C are incorrect. See the Influenza Pathogenesis section.

7. **C.** LAIV4 is FDA approved for adults younger than 49 years. LAIV4 should not be used during pregnancy. LAIV should not be given to immunosuppressed patients or given by healthcare workers who are severely immunocompromised. LAIV should not be administered to persons with a history of GBS or hypersensitivity to eggs. The ACIP recommends that anyone with a severe allergic reaction (eg, anaphylaxis) to any egg-based IIV or LAIV of any valency should receive non-egg-based influenza vaccine. A is incorrect because is a candidate for vaccine. B and D are candidates for LAIV vaccine. C is immunocompromised AIDS patient and should not receive LAIV vaccine due to theoretical infection risk. The patient also has hypersensitivity to eggs, although types and severity are unknown. See Table 131-3.

8. **A.** Classic signs and symptoms include abrupt onset of fever, muscle pain, headache, malaise, nonproductive cough, sore throat, and rhinitis. These are also symptoms to monitor for resolution of illness. A is correct, rhinitis is one of the cardinal symptoms. B and C are incorrect as they are not classic signs or symptoms. See Key Concept.

9. **B.** Rapid antigen test provides results within 10 to 15 minutes; however, do not provide any information about influenza A virus subtypes. Sensitivities for rapid antigen test range are low often yielding false-negative results. Rapid antigen test s not recommended for use in hospitalized patients with suspected influenza, and are not preferred in outpatient settings. Therefore, A is incorrect. C is incorrect because it does not yield timely results to inform clinical management. Shell-vial tissue culture results may take 1 to 3 days, while traditional tissue-cell viral culture results may take 3 to 10 days. D is incorrect because B is an appropriate test. B is correct and yields result in 1 to 4 hours. Immunofluorescence assays (IFAs) have moderate sensitivity and high specificity. See section on "Influenza Diagnostic Tests".

10. **A.** A is correct, because this person meets the definition of high risk (age and chronic care facility) where there is an outbreak. B is incorrect, as this is a healthy individual who is not considered high risk. C is incorrect because although they are unvaccinated they are not considered high risk (see section on "Postexposure Prophylaxis"). Prophylaxis for seasonal influenza should be considered during influenza season for the following groups of patients after exposure to an infectious source:

    1. Persons at high risk of serious illness and/or complications who are exposed to an infectious person and cannot be vaccinated.

    2. Persons at high risk of serious illness and/or complications who are vaccinated but exposed to an infectious person during the first 2 weeks following vaccination. The development of sufficient antibody titers after vaccination takes approximately 2 weeks.

    3. Persons with severe immune deficiency or who may have an inadequate response to vaccination (eg, advanced human immunodeficiency virus [HIV] disease, persons receiving immunosuppressive medications), after exposure to an infectious person.

4. Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution.

11. **C.** A is incorrect because it is an amantadine which are no longer effective. B is incorrect because dose and duration of zanamivir corresponds to treatment of influenza. D is incorrect because duration of prophylaxis therapy of 2 days and frequency of dosing is also incorrect for prophylaxis. Dosing frequency for prophylaxis is daily. C is correct – dose and frequency of dosing are appropriate and since this is an outbreak at chronic care facility, prophylaxis should be continued beyond 10 days until last documented influenza infection. See Table 131-4 for drug dosing.

12. **C.** A is incorrect because although thimerosal-free vaccines are available (rendering B also incorrect) it is not because thimerosal causes autism. No evidence has established causal effect of thimerosal and autism. D is incorrect because the preventive benefit of influenza vaccine outweigh any unfounded risk of autism from thimerosal in influenza vaccine. See section on "Trivalent and Quadrivalent Influenza Vaccine" for thimerosal discussion.

13. **B.** People who are at high risk of serious complications from influenza, including H3N2v virus infection, are: children younger than 5 years, people older than or equal to 65 years, pregnant women, body mass index of 40 or higher, age less than 19 years of age on long-term aspirin or salicylate containing drugs, chronic care facility residents, and people with certain chronic medical conditions (asthma, cystic fibrosis, chronic obstructive pulmonary disease, diabetes, heart disease, stroke, sickle cell, kidney and liver disorders, inherited metabolic disorders, immunocompromised, and neurologic or neurodevelopmental conditions). An age of 47 and diagnosis of hypertension do not qualify as high risk for influenza. See text on patients at high risk for complications or severe disease.

14. **D.** A, B, C are incorrect because adamantanes show >99% ineffectiveness against influenza A H1N1. Adamantanes do not have activity against influenza A H3N2 or influenza B viruses. Therefore, they may not be used for prophylaxis or treatment.

15. **C.** The correct answer is C. These influenza A subtypes and influenza B are the main targets for yearly influenza vaccine. A is incorrect since there is not a H1N1 variant in circulation. There is H3N2 variants. B and D are incorrect because H5N1 and H2N2 are not predominantly in circulation. H5N1 is Avian influenza and H2N2 is Asian influenza.