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Review

Continuing Education

Influenza and Influenza Vaccine: A Review

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Influenza is a highly contagious, deadly virus, killing nearly half a million people yearly worldwide. The classic symptoms of influenza are fever, fatigue, cough, and body aches. In the outpatient setting, diagnosis can be made by clinical presentation with optional confirmatory diagnostic testing. Antiviral medications should be initiated as soon as possible, preferably within 24 hours of initiation of symptoms. The primary preventive measure against influenza is vaccination, which is recommended for all people 6 months of age or older, including pregnant and postpartum women, unless the individual has a contraindication. Vaccination should occur at the beginning of flu season, which typically begins in October. It takes approximately 14 days after vaccination for a healthy adult to reach peak antibody protection. There are challenges associated with vaccine composition and vaccine uptake. It takes approximately 6 to 8 months to identify and predict which influenza strains to include in the upcoming season's vaccine. During this time, the influenza virus may undergo *antigenic drift*, that is, mutating to avoid a host immune response. Antigenic drift makes the vaccine less effective in some seasons. The influenza virus occasionally undergoes *antigenic shift*, in which it changes to a novel virus, creating potential for a pandemic. There are also barriers to vaccine uptake, including lack of or limited access to care and misconceptions about receiving the vaccine. Interventions that improve access to and uptake of the influenza vaccine must be initiated, targeting multiple levels, including health care policy, patients, health care systems, and the health care team. This article reviews information about influenza identification, management, and prevention.

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INTRODUCTION

Influenza, also known as the flu, is a highly contagious respiratory illness caused by a number of RNA influenza viruses that can infect humans. Complications from influenza can cause significant morbidity and mortality.[1] Globally, as many as 500,000 people die annually from complications related to influenza. Since 2010, the Centers for Disease Control and Prevention (CDC) estimates seasonal influenza infection has resulted in 9.3 to 45 million cases, 140,000 to 810,000 hospitalizations, and 12,000 to 61,000 deaths annually in the United States.[1] For those who contract the infection, the risk of complications and symptom severity can be reduced with antiviral medications if taken as soon as possible, preferably within 24 to 72 hours of onset of symptoms.[2]

Most influenza infections can be prevented with the annual influenza vaccine.[2,3] Primary care clinicians, including midwives and advanced practice registered nurses, are ideally positioned to recommend vaccination for all persons over the age of 6 months, unless contraindicated, and to recognize, diagnose, and manage influenza infection soon after exposure to reduce chances of complications that contribute to this high morbidity and mortality rate. This article provides clinicians with information about influenza identification, management, and prevention. Some of the challenges involved in improving uptake of the influenza vaccine and preventing seasonal influenza epidemics are presented. Influenza in the context of the current severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) pandemic is also discussed.

EPIDEMIOLOGY OF INFLUENZA INFECTION

The seasonal incidence of symptomatic influenza among all residents in the United States is approximately 8%, ranging from 3% to 11% depending on the season.[4] In the United States and all countries in the Northern Hemisphere, influenza season typically occurs as early as late October and lasts until May. Some influenza seasons are more virulent than others. The severity of influenza any particular year is dependent upon the propagation and characterizations of the circulating influenza viruses, the availability and uptake of effective vaccines specific to current circulating strains, the host immune response, and the presence of an individual's comorbidities.[5] The CDC classifies the severity of an influenza season by monitoring and calculating 3 key influenza indicators, which are (1) outpatient visits for influenza-like illness, (2) influenza-associated hospitalizations, and (3) influenza/pneumonia-related deaths.[5]

Race and ethnicity-related disparities in the risk of influenza infection and influenza vaccination uptake exist. The literature suggests that differences in risk of contracting influenza infection may be related to varying levels of exposure (eg, group living conditions like dormitories, correctional facilities, or nursing care facilities), limited or no access to health care, and higher susceptibility to severe infection because of exacerbation of other preexisting health conditions.[6]

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Quick Points

- Influenza viruses cause significant morbidity and mortality yearly.
- Influenza viruses are constantly changing, making it challenging to predict which strains to include in the yearly, upcoming influenza vaccine.
- It is recommended that all individuals aged at least 6 months receive a yearly influenza vaccine unless contraindicated.
- Interventions that target health care providers, patients, and health care systems improve uptake of the influenza vaccine in people.

American Indians, Alaska Natives, and African Americans are at highest risk of developing serious complications from the flu.[6,7] It is believed that this is the result of US health disparities in chronic illnesses that preexist in these populations. Furthermore, non-Hispanic Black adults have a lower rate of vaccination uptake than other adult groups living in the United States, including non-Hispanic whites, Hispanics, and Asian Americans.[8,9]

Influenza in the Context of the SARS-CoV-2 Pandemic

There is emerging evidence that coinfection of influenza with coronavirus disease 2019 (COVID-19) (the illness caused by SARS-CoV-2) is rare; however, individuals with both infections may be at higher risk of poor health outcomes.[10,11] It is plausible that the careful use of social distancing, face covering, and handwashing used for COVID-19 prevention may also mitigate transmission of influenza.

Symptoms experienced by individuals with a respiratory illness are often similar, making it difficult for clinicians to differentiate the diagnosis. Table 1 compares and contrasts symptoms of 4 upper respiratory illnesses, including influenza, COVID-19, the common cold, and seasonal allergies. In addition, an algorithm that may be helpful for clinicians to triage symptoms of influenza or COVID-19 can be found at https://www.cdc.gov/flu/professionals/antivirals/office-evaluation.htm. It is especially critical for health care providers to recommend influenza vaccination because of risks associated with coinfections and to not further burden health care systems that are already strained because of the SARS-CoV-2 pandemic.[12]

THE INFLUENZA VIRUS

Three types of influenza viruses have been identified that infect humans: types A, B, and C. Type A influenza virus, which can infect humans and animals (eg, bovine, equine, and avian) is the most virulent and is most likely the culprit that can give rise to epidemics and pandemics. Influenza A is subclassified into 2 groups based on 2 virus surface proteins, hemagglutinin (HA) and neuraminidase (NA). There are 18 HAs and 11 NAs, which can combine to yield many varying subtypes or strains (eg, H1N1, H5N1).[2,13] Slower to mutate, type B influenza virus does not typically cause as severe disease as does type A and is more commonly seen in children, long-term care facilities, college campuses, and military camps.[13] Influenza C virus generally causes mild illness and therefore has not been linked to human influenza epidemics.[14]

Mutations of the Influenza Virus

Table 2 presents definitions of common terminology used to describe viral behavior with regard to antigenic potential. Genes in the various strains of type A influenza viruses continuously mutate to change the surface proteins, allowing the virus to avoid the host's immune response. This process, known as *antigenic variation*, enables the virus to avoid recognition, thus becoming more virulent by evading one's previously acquired immune response. If the mutation is gradual and minimal, the host (person) may be able to spark an immune response through production of antibodies. This gradual change over time is termed *antigenic drift*.[2] On occasion, a type A influenza virus subtype can cross over to another species and cause illness. An example is avian influenza A viruses, which can cross to humans directly through contaminated environments or through an intermediate host such as a pig. This ability to jump species allows genetic mixing or reassortment to occur and creates a new or novel influenza A virus.[15,16] A novel virus may spread quickly and infect many humans because most have little or no immunity protection, creating potential for a pandemic.[15,16] The process by which a novel virus is created is termed *antigenic shift*.[2]

INFLUENZA INFECTION

It is essential, especially from a public health perspective, that health care clinicians recognize how influenza is transmitted in order to counsel individuals about how to prevent spread of the infection throughout the community. The majority of individuals who seek care for flu-like symptoms have uncomplicated influenza that is self-limiting, and full recovery can be expected.[17] However, some individuals can have complications that result in severe disease and death. Clinicians must recognize signs and symptoms of infection and know how to diagnosis it quickly so as to provide timely treatment. The best time to prevent or reduce viral replication with antiviral medications is within 24 hours of symptoms first appearing.[2]

Transmission and Incubation

Influenza viruses are predominantly spread by large-particle respiratory droplets (particles ≥5 microns) through sneezing, coughing, and speaking. Droplets generally travel 6 feet or less. The virus may also be transmitted by indirect contact such as hand contamination to mucous membranes. If

Table 1. Comparing and Contrasting Symptoms of Influenza, COVID-19, Common Cold, and Seasonal Allergies

Upper Respiratory Illness Symptoms	Influenza	COVID-19	Common Cold	Seasonal Allergies
Cough	Present	Present, dry	Present (mild to moderate)	Present (mild)
Fever with or without chills	Present	Present	Rare	Absent
Fatigue	Present	Present	Some	Absent
General malaise	Present	Present	Present	Absent
Shortness of breath or difficulty breathing	Present	Present	Absent	Absent
Sore throat	Present	Uncommon	Present	Some
Congestion or runny nose	Present	Present	Present	Present
Headache	Present	Present	Rare	Present
Joint pain	Present	Not reported	Absent	Absent
Myalgia	Present	Present	Absent	Absent
Ocular symptoms (itchy, red, swollen, eyes)	Absent	Absent	Present	Present
Rhinorrhea	Absent	Not reported	Present	Present
Sneezing	Absent	Not reported	Present	Present
Earaches	Absent	Not reported	Some	Present
New loss of taste or smell	Absent	Present	Absent	Absent
Nausea and/or vomiting	Rare	Some	Absent	Absent
Diarrhea	Rare	Some	Absent	Absent
Confusion	Absent	Some	Absent	Absent

Sources: Dykewicz et al,[45] Eccles,[46] Jiang et al.

Table 2. Definitions of Common Terminology Used to Describe Viral Behavior

Terminology	Definition
Virulence	The capacity of a pathogen, like a virus, to overcome the body's defenses against illness
Antigens	Molecular structures on the surface of viruses that are capable of triggering an immune response (antibody production)
Antibody	High molecular proteins that are produced after exposure to an antigen (naturally or by vaccination) and act specifically against the antigen through an immune response
Antigenic properties	Describes the antibody or immune response triggered by the antigens on a specific virus
Antigenic variation	The ability of an antigen (eg, virus) to alter their surface proteins to avoid a host immune response
Antigenic characterization	An analysis of a virus's antigenic properties to assess how related it is to another virus
Antigenic drift	Gradual, small changes (mutations) in the genes of a virus resulting in changes in the surface proteins of the virus
Antigenic shift	An abrupt, major change (mutation) in a virus resulting in a new (novel) virus that may lead to a pandemic
Epidemic	An increased, often sudden, spread of a disease above normally expected levels in a geographic population
Pandemic	A large epidemic that has spread over several countries or continents worldwide

Source: Centers for Disease Control and Prevention.[36]

a susceptible person touches a contaminated surface such as a phone, countertop, keyboard, door handle, or another individual's contaminated hand and then places their hand on or near their nose, mouth, or eyes, the virus can be transmitted.[13] Viral transmission has also been implicated via the airborne route (particles ≤5 microns that remains suspended in air) through aerosolization of droplets that can occur with singing, shouting, and specific medical procedures.[18,19] Influenza viruses can remain infectious on surfaces other than the body for extended periods of time, often days to weeks.[20]

Once an individual is exposed to an influenza virus, it typically takes about 2 days for symptoms of the infection to present, but the incubation period can range from 1 to 4 days. Some people may be contagious 1 to 2 days before they exhibit symptoms and are infectious for 5 to 7 days afterward. The average time people are contagious is 6 days; however, they may be contagious longer if immunocompromised.[2,13]

Signs and Symptoms, Complications

Exhibition of symptoms is usually abrupt; symptoms are listed in Table 1. Typically, people with mild to moderate illness will recover within 2 weeks; however, some individuals will develop severe illness that lasts much longer. The most common complications from influenza infection are pneumonia (either viral or bacterial), bronchitis, sinus infections, ear infections, and worsening of preexisting chronic health problems.[13] People classified as high risk of developing complications from influenza include individuals who are 65 years or older or less than 5 years of age, immunocompromised, pregnant, within 2 weeks of giving birth, or living in group settings (eg, dormitories, military barracks, nursing homes), and individuals who have preexisting chronic illnesses (eg, asthma, congestive heart failure, and diabetes) or obesity.[2,17]

Diagnosis

Diagnosis of influenza is primarily clinical and based on the signs and symptoms. Laboratory confirmation of influenza is possible if needed. The Infectious Diseases Society of America (IDSA) provides guidelines for clinicians including when laboratory confirmation is suggested and which test to order.[17] Laboratory confirmation is suggested in the outpatient setting only if testing will influence clinical management, meaning avoidance of unnecessary antibiotics, additional health care visits, and/or treatment with influenza antiviral medications. During influenza season, laboratory testing is suggested for patients who are at high risk of influenza complications and present to an outpatient setting with one of the following: (1) influenza-like symptoms (with or without fever), (2) pneumonia, (3) nonspecific respiratory illness, or 4) exacerbation of chronic health conditions (eg, asthma or chronic pulmonary obstructive disorder). For patients who are not high risk of influenza complications, testing is considered if they present with flu-like illness, pneumonia, or nonspecific respiratory illness and if use of unnecessary antibiotics, further diagnostic testing, and time in the emergency department may be avoided. Another factor to consider is if chemoprophylaxis with influenza antiviral agents may be needed for individuals living in homes with others who are deemed at high risk of influenza complications.[17] Individuals who are hospitalized during influenza season and have or develop acute respiratory illness (with or without fever) should be tested as well.[17] Prompt treatment should occur especially if influenza is circulating in the home or community.[2] For all individuals reporting upper respiratory symptoms, the health care provider should inquire about a recent positive history of fever, cough, body aches, headaches, sore throat, runny nose, chills, and/or fatigue. A full set of vital signs including a pulse oximetry reading should be obtained. All of these can be done via telehealth using applications on smart phones.[21]

Laboratory testing for influenza should preferably be inexpensive, highly sensitive for detecting influenza virus, and provide results quickly. Having access to rapid testing enables health care providers to initiate antiviral therapy quickly.[22] There are several different types of laboratory tests to detect influenza virus. IDSA provides recommendations for choosing the best test based on assessment in the outpatient or inpatient setting. In the outpatient setting, rapid molecular assays (eg, nucleic acid amplification tests) are recommended over rapid influenza diagnostic tests (RIDTs) to improve detection rates.[17] Rapid molecular assays, which detect genetic material of the virus, are obtained via a nasopharyngeal (NP) swab. Results are available in 15 to 20 minutes and have a high sensitivity rate of 90% to 95% for detecting influenza.[17]

RIDTs detect influenza virus antigens and are collected via NP swab, nasal aspirates, swabs, or washes. These tests can provide a result in 10 to 15 minutes and are reported as either positive or negative. However, RIDTs have a relatively low sensitivity rate of 50% to 70% and high specificity rate of greater than 90%; thus, they can produce more false negative results than false positive results.[22] Therefore, a negative result does not absolutely rule out influenza infection, and the clinician should consider confirming a negative result with a molecular assay.[13,17]

In hospitalized patients, reverse-transcription polymerase chain reaction (RT-PCR) or other molecular assays are recommended for diagnosis of influenza. A multiplex RT-PCR assay that targets a panel of respiratory pathogens is used for immunocompromised patients in addition to nonimmunocompromised patients if results may influence care (eg, reduce testing or decrease antibiotic use). Immunofluorescence assays for virus antigen detection or RIDTs should not be used to diagnose influenza in hospitalized patients when more sensitive molecular assays are available. If one of the less sensitive tests is used, follow up with a RT-PCR or other molecular assay to confirm all negative results. Viral cultures should not be used as the initial test to diagnose influenza because they take too long to generate a result and clinical management is delayed. However, viral cultures may be considered to confirm a negative result for RIDTs or immunofluorescence assays. Lastly, serologic testing for the diagnosis of influenza is not recommended because results from a single serum specimen cannot be reliably interpreted.[17]

MANAGEMENT AND TREATMENT

Once the diagnosis of influenza is made, the clinician should counsel the individual about personal protective measures to prevent further spread of the illness in the home and community. Examples of effective personal protective measures are respiratory etiquette (covering mouth with elbow or tissue during coughing and sneezing), use of disposable tissues, proper hand hygiene (eg, soap and water and/or alcohol-based gel), and use of facemasks (eg, surgical or N95 respirators).[19,23] Instructions that alcohol, chlorine, hydrogen peroxide, soaps/detergents, and iodine-based antiseptics kill influenza viruses that are on surfaces should be provided.[24] Social distancing, self-quarantine, and other strategies to reduce airborne transmission of influenza must also be discussed. Improving room ventilation by opening a window and replacing the inside air with clean outdoor air may dilute the sick person's expiratory airborne aerosols to a lower concentration level, decreasing risk of transmission.[19] Air purifiers dilute particles in the air without actually filtering out the virus and therefore are not appropriate for use as a personal protective measure.[25] The patient should also be counseled about the use of acetaminophen or ibuprofen

Table 3. Food and Drug Administration–Approved Antiviral Influenza Medications

Drug, Generic (Brand)	Route	Use	Adult Dosage	Contraindications	Adverse Effects	Use in Pregnancy
Neuraminidase inhibitors						
Oseltamivir (Tamiflu) (preferred drug for influenza)	Oral	Treatment and chemoprophylaxis	75 mg twice daily for 5 d	None	N/V, headache, skin reactions, sporadic transient neuropsychiatric events	May use in pregnancy
Peramivir (Rapivab)	Intravenous	Treatment only	600 mg in a single dose	None	Diarrhea, skin reactions, sporadic transient neuropsychiatric events	Benefits must outweigh risk to take in pregnancy
Zanamivir (Relenza)	Inhaled	Treatment and chemoprophylaxis	10 mg twice daily for 5 d	People with underlying airway disease (eg, asthma, COPD); milk allergy	Risk of bronchospasm in people with underlying airway disease, headache, cough, dizziness, fever, chills, arthralgia, N/V, diarrhea, sinusitis, skin reactions, sporadic transient neuropsychiatric events	May use in pregnancy
CEN inhibitors						
Baloxavir marboxil (Xofluza)	Oral	Treatment only	40-79 kg (88-174 lb): 40 mg in a single dose ≥80 kg (≥175 mg): 80 mg in a single dose	none	Diarrhea, bronchitis, nasopharyngitis, headache, nausea	Avoid in pregnancy

Abbreviations: CEN, cap-dependent endonuclease; COPD, chronic obstructive pulmonary disease; N/V, nausea and vomiting.
Sources: Gaitonde et al,[2] Uyeki et al,[17] Moscona,[26] Savage.[27]

for fever and/or body aches. Lastly, the clinician should discuss antiviral medications and alternative or complementary therapies. All persons, including all health care providers, should be encouraged to self-isolate when symptomatic for influenza because isolation is one of the most effective methods of preventing transmission. Arranging coverage for job responsibilities requires cooperation and compassion.

Antiviral Medications

Antiviral medications can be prescribed for individuals infected with influenza.[15] IDSA recommends that antiviral medication is appropriate in high-risk patients with severe or worsening illness. High-risk groups include those who are aged less than 5 years or 65 years or older, women who are pregnant or postpartum within 2 weeks of birth, people with chronic illnesses, and people who are immunocompromised.[17] Four antiviral medications have been approved by the Food and Drug Administration (FDA) for the treatment of influenza, and information about these drugs is summarized in Table 3. They include (1) oseltamivir (Tamiflu), (2) peramivir (Rapivab), (3) baloxavir marboxil (Xofluza), and (4) zanamivir (Relenza).[2] These drugs are categorized according to their mechanism of action. The recommended first-line drugs, the neuraminidase inhibitors (oseltamivir, peramivir, and zanamivir) interfere with the

ability of the influenza virus to spread within the body by inhibiting viral replication.[26] The cap-dependent endonuclease inhibitor (baloxavir marboxil) is the newest antiviral, approved for use by the FDA in 2018, and it works by interfering with the ability of the influenza virus to multiply.[2] Replication of the influenza virus peaks between 24 and 72 hours after onset of illness; therefore, initiation of these antiviral medications should begin as soon as possible.[26] The oldest class of FDA-approved antiviral drugs is the adamantanes (amantadine hydrochloride and rimantadine hydrochloride). Both have traditionally been effective against type A influenza only. However, because of mutations, the influenza virus has become resistant to these 2 drugs, so they are no longer recommended by the CDC for therapy.[27]

Alternative and Complementary Therapies

Because of antigenic shifting when reassortment between different strains of influenza viruses render vaccines and antiviral medications less effective, it is important to discuss with patients alternative and complementary therapies. Patients can be counseled about taking supplemental vitamin D during the influenza season. Because vitamin D is known to have a broad spectrum of activity, including antimicrobial properties, counseling about its potential benefits cannot be excluded. The National Institutes of Health (NIH) recommends vitamin D supplementation of 600 units per day for people aged 1 to 70 years and 800 units per day for those older than 70 years. Vitamin D is needed not only for bone health but also for immune function and its anti-inflammatory properties.[28] People with frequent sunlight exposure often have adequate vitamin D levels to fight off infections, particularly in the summertime. However, during the winter months, many people do not have high enough levels for protection. The NIH has set the upper intake limit of vitamin D supplementation at 4000 units per day.[28] However, no studies have reported adverse effects of supplements with less than 10,000 units per day.[29] Doses greater than 50,000 units per day can raise serum concentrations, leading to hypercalcemia. Symptoms of vitamin D toxicity include nausea, vomiting, dehydration, weight loss, constipation, loss of appetite, lethargy, polyuria, polydipsia, renal dysfunction, and altered sensorium.[30] To prevent infection, Grant et al recommend that people at risk of influenza and/or COVID-19 consider taking 10,000 units vitamin D daily for a few weeks to rapidly raise vitamin D concentrations followed by 5000 units daily. People infected with influenza virus might need even higher doses of vitamin D.[29]

There are no national recommendations for melatonin supplementation against influenza. However, an in vivo study showed that melatonin, a hormone produced and secreted by the pineal gland, has antioxidant and anti-inflammatory properties and plays a role in immunoregulation.[31] Melatonin has been implicated in prevention and/or suppression of influenza infection.[31,32] It has a high safety profile, and supplemental doses as high as 500 mg daily may lessen infection severity and fatality associated with viral infections, including influenza and COVID-19.[32] This is especially true for people with preexisting health conditions associated with suppressed melatonin synthesis.[32] Therefore, health care providers may want to counsel individuals about potential beneficial effects of melatonin supplementation. Lastly, individuals can be counseled about increasing consumption of tea catechins (eg, green tea), which have the ability to inhibit viral absorption and enhance immunity.[33]

PREVENTION

Prevention of influenza can occur through vaccination and/or chemoprophylaxis. The choice of which option or use of both is based on the patient's risk category.

Vaccination

Vaccination is the primary preventive measure against influenza infection and should be offered during all routine health care visits and hospitalizations at any time during influenza season. Vaccine efficacy is about 60% in a good season, but if the vaccine does not match the current circulating strains of the virus, effectiveness can be as low as 10% to 20%.[34] The overall estimated effectiveness of influenza vaccines is 38%.[3] It is recommended that all people aged 6 months or older receive an annual influenza vaccination unless they have contraindications for the vaccine or any of its components.[3] Ideally, the vaccine should be administered before the end of October because it takes about 2 weeks from vaccination to immunization. However, immunity from vaccination wanes over time, so picking the ideal time to receive the vaccine can be challenging because one cannot predict when influenza outbreaks will peak during the season. Peak time for outbreak could occur early in the season (eg, October) or late in the season (eg, April or May). Therefore, if an individual receives a vaccine early in the season, they may have less protection if the virus peaks later in the season.[3] The vaccination can be given concurrently with other inactivated vaccines but should be administered in separate anatomic sites.[3]

The health care provider should review common adverse effects from influenza vaccination, which include pain and tenderness at the injection site, headache, fatigue, and muscle or joint pain. Individuals should be taught that adverse reactions to the influenza vaccine are rare but to notify their health care provider if they experience reactions such as urticaria, angioedema, or anaphylaxis. Anaphylaxis is extremely rare.[35]

Vaccine Development

The process of developing a yearly vaccine is lengthy. Every year, the CDC characterizes about 2000 influenza viruses antigenically to monitor for drift or shift and compares them with viruses included in the current influenza vaccine. This information provides an indication of the flu vaccine's ability to produce an immune response in individuals against current circulating influenza viruses.[36] In addition, antigenic characterization aids CDC experts in their recommendations for which viruses to include in the upcoming seasonal flu vaccine.[36]

The process of choosing which viruses to include involves several steps.[37] First, public health and clinical laboratories partner with the CDC to monitor current circulating strains of influenza. In February each year, the World Health

Organization (WHO) meets to predict which strains of influenza will be prevalent during the upcoming influenza season for the Northern Hemisphere. The WHO then makes recommendations to the FDA because the FDA has regulatory authority over vaccines in the United States. The FDA makes the final decision regarding which strains of the influenza virus will be included in the vaccine. Finally, this information is sent to manufacturers, who produce and market various vaccines.[37] It typically takes about 6 to 8 months from predicting and choosing which strains of type A influenza and type B influenza to include in the vaccine for the upcoming influenza season to distribution. The lengthy process allows time for antigenic drift variants to evolve that may be less matched to the chosen vaccine strains, creating a potential for severe epidemics.[2]

Types of Vaccines

Most vaccines are quadrivalent, meaning the vaccine stimulates the immune system to defend against 4 antigens, or 4 different strains of the influenza virus (2 influenza type A strains and 2 influenza type B strains). Selection of the appropriate vaccine is based on age, risk factors, and individual characteristics. For example, vaccines recommended for people who are 65 years or older are 4 times more potent than vaccines recommended for younger people.[2] Basically, 3 different production technologies are used to create vaccines, which include (1) egg-based vaccines (most common), (2) cell-based vaccines, and (3) live attenuated (weakened) vaccines.

Egg-Based Vaccines

Most manufacturers use eggs to grow the influenza virus during the development process. People with egg allergies no longer need to be observed for allergic reactions for 30 minutes after administration of the vaccine. However, the CDC provides additional guidance for health care clinicians, especially if the individual has a history of a severe egg allergy.[3]

Egg-based vaccines are either inactivated (dead viruses) or attenuated (weakened live viruses). Most inactivated influenza vaccines (IIVs) are quadrivalent, containing 2 type A influenza antigens (viruses) and 2 type B influenza antigens. Examples of quadrivalent IIVs are Afluria (Seqirus), Fluarix (GlaxoSmithKline), and Fluzone (Sanofi Pasteur). Two high-dose trivalent IIVs, Fluzone High-Dose (Sanofi Pasteur) and Fluad (Seqirus), are available and licensed for use in adults aged 65 years and older.[3]

Recombinant Vaccines

Recombinant influenza vaccines (RIVs) are produced using recombinant technology, which is the process that alters the genetic material to enhance desirable characteristics. Instead of using eggs, the cells are grown in cultured cells of mammalian origin.[2] The benefits of RIVs over egg-based vaccines are that they can be produced quicker should a pandemic or egg shortage occur and that mutations, which sometimes occur naturally in eggs, can be avoided. Flublok (Sanofi Pasteur) is the quadrivalent FDA-approved RIV.[3]

Attenuated Vaccines

The live, attenuated influenza vaccine, FluMist (AstraZeneca), which is administered via a nasal spray, is also quadrivalent.[3] This vaccine is egg-based and may be administered to anyone aged 2 to 49 years in the absence of contraindications.[3] Increased risk for Reye's syndrome has been noted in children who receive the live attenuated influenza vaccine and those who take salicylate-containing drugs (eg, aspirin). Therefore, people aged 2 to 17 years with contraindications should avoid the live attenuated influenza vaccine.[3] The CDC's Advisory Committee on Immunization Practices (ACIP) recommends that vaccine providers consider observing patients for 15 minutes after administration of the vaccine to decrease the risk of injury if dizziness occurs.[3]

Contraindications to Influenza Vaccine in Adults

Individuals with a history of acquiring Guillain-Barré syndrome within 6 weeks of a previous influenza vaccine should not receive another flu vaccine. Instead, consider using chemoprophylaxis with antiviral medications if they have been exposed to the flu. The influenza vaccine is contraindicated for individuals who have a history of a severe reaction (eg, anaphylaxis) to a previous influenza vaccine, regardless of the component suspected of being responsible for the reaction. Vaccination is not contraindicated for individuals with an egg allergy unless they had a severe reaction to the influenza vaccine previously. Live attenuated vaccines are contraindicated for pregnant women.[3,38]

Considerations in Prescribing an Influenza Vaccine

The ACIP has no preference for any one influenza vaccine over another for persons who do not have a specific contraindication.[3] Because IIVs and RIVs are suitable for all risk groups, including pregnant and postpartum individuals, the health care provider can chose which vaccine to stock in the primary care setting or prescribe from the pharmacy. It is good practice to have available, in the office, clinic, or pharmacy, a high-dose IIV recommended for individuals aged 65 years or older.

Chemoprophylaxis

Although vaccination is the primary preventive measure for influenza, chemoprophylaxis with oseltamivir or zanamivir is a good alternative in specific circumstances when one has been exposed to the flu, especially for people in high-risk populations. Chemoprophylaxis should be considered if the vaccine and virus are mismatched as a result of antigenic shifting of the virus during the vaccine production or distribution process. In addition, chemoprophylaxis should be considered if there is a supply shortage of influenza vaccines. Vaccine shortages can be the result of egg shortages (eggs are needed for production of most vaccines) or due to a pandemic when the supply of vaccines may be reduced.[3] Table 3 contains information about oseltamivir and zanamivir.

PRECONCEPTION, PREGNANCY, POSTPARTUM, AND NEWBORN

Women who have influenza and are either pregnant or within the 2-week postpartum period are at increased risk of subsequent development of pneumonia. Influenza during pregnancy is associated with increased risk of additional medical visits, hospitalizations, intensive care unit admissions, and adverse perinatal and neonatal outcomes.[38] It is recommended by the CDC's ACIP, the American College of Nurse-Midwives, and the American College of Obstetricians and Gynecologists that all people aged 6 months and older receive an annual influenza vaccine and most importantly that women who are or will be pregnant (preconception) during flu season receive an IIV, preferably when it is available.[3,38] Women who are breast feeding may safely receive an IIV as well.[3] Live vaccines should be avoided during pregnancy.[38]

Newborns and infants less than 6 months of age with influenza have higher rates of severe influenza-related complications and higher mortality.[39] Women who receive the influenza vaccination during pregnancy can transfer their antibodies through the placenta to their fetus. The antibodies can protect the child up to 6 months of age, at which time it is recommended that the infant receive their own vaccine.[40] Vaccinating the parents and caregivers may reduce the transmission of influenza to newborns and infants who are too young to receive their own vaccinations. Lastly, it is recommended that women receive the tetanus toxoid, diphtheria toxoid, and acellular pertussis (Tdap) vaccine during pregnancy for the same reason as getting the influenza vaccination, to provide passive immunity (specifically pertussis). It is especially important to reduce the risk of corespiratory infections with influenza, COVID-19, and/or pertussis during infancy.[12]

IMPLICATIONS FOR CLINICAL PRACTICE

Approximately 45% of individuals receive a seasonal influenza vaccine, which falls short of the 80% goal set by the US Department of Health and Human Services Healthy People 2020 recommendations.[41] Midwives and other health care providers have the opportunity to make a positive impact on morbidity and mortality rates associated with influenza infection. Recommending vaccination and dispelling myths from a multilevel health care team is needed in addition to increasing access to the vaccine. By increasing access there will likely be a spike in the number of individuals receiving the vaccine. Barriers to influenza vaccine uptake include insufficient knowledge about the importance of vaccination, needle phobia, misconception that the vaccine will evoke active influenza infection, and concern about adverse effects.[42] Health care professionals should recognize these barriers and any others in order to dispel misconceptions.

Vaccination rates during pregnancy can be improved by: (1) bundled interventions that target health care providers (eg, standing orders, education, and provider feedback); (2) strategies that increase patient self-initiation and motivation to receive the vaccine; and (3) health care systems (eg, availability of free or low-cost vaccines, adequate supply of vaccines, multimedia educational campaigns).[39,43,44] Multilevel interventions orchestrated to include patients, health care clinicians, health care systems, and health care policy should be implemented. Ideally, all individuals will recognize the importance of vaccination, have access to the vaccines, and consent to uptake in order to reduce the unnecessary burden of morbidity and mortality created by seasonal influenza infections.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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