Flu 2020

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Course Summary

2018 was the 100th anniversary of one of the largest and most devastating flu pandemics in modern history in which more people died than in all of World War I. This course describes the current and historical impact of influenza, seasonal and pandemic. It includes influenza epidemiology, virus types and subtypes, how influenza viruses drift and shift, and a review of the worldwide impact of the 1918–1919 flu pandemic. We also discuss the goal of universal vaccination, diagnosis, and treatment, and the composition of the 2020 influenza vaccines.

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Course Objectives

When you finish this course you will be able to:

- 1. Describe the annual global incidence of seasonal flu worldwide.
- 2. State 2 characteristics each of influenza A, B, and C.
- 3. Define antigenic drift and antigenic shift.
- 4. Describe 3 characteristics of pandemic influenza.
- 5. Identify the 5 "classic" clinical features of seasonal influenza.
- 6. State the vaccination rate goal for healthcare providers under Healthy People 2020.
- 7. Describe 3 reasons why healthcare providers refuse or fail to receive a seasonal influenza vaccination.
- 8. Summarize the purpose of antiviral medications in the treatment of flu.
- 9. State the 5 key influenza prevention strategies that should be practiced in all long-term care settings.
- 10. Describe the 4 types of trivalent inactivated influenza vaccine that are approved for the 2019–2020 season.
- 11. Explain the makeup of the 2019–2020 influenza vaccine.

The Scourge of Influenza

During the recent severe 2017–2018 influenza season, vaccination is. . . estimated to have prevented 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8,000 deaths, despite an overall estimated vaccine effectiveness of 38% (Grohskopf et al., 2019).

Influenza is one of the deadliest viruses in the world, yet we take for granted that we are protected from its ill effects. We are deathly afraid of other viral infections, any of which kill only a fraction of the people that die each year from influenza. Yet many of us skip our annual flu shots, giving various excuses for forgoing the vaccine. This is despite the fact that the impact of influenza is enormous estimated to be about 1 *billion* cases worldwide with death in nearly half a million people.



The 2017–2018 influenza season was severe, with high levels of outpatient clinic and emergency department (ED) visits for influenza-like illness (ILI), high influenza-related hospitalization rates, and elevated and geographically widespread influenza activity for an extended period. In 2017 the Centers for Disease and Prevention (CDC) began using new methodology to classify seasonal severity and applied the methodology to the 2003–2004 through 2016–2017 seasons. The 2017–2018 season was the first season to be classified as high severity across all age groups (CDC, 2019q).

The 2018–2019 influenza season was of moderate severity and differed from recent seasons in that there were two waves of influenza A activity of similar magnitude. It was also longer than recent seasons with activity at or above baseline for 21 consecutive weeks. Overall, hospitalization rates were below those of the previous season, but rates for children under 17 years of age were similar to the previous year (Xu et al., 2019).

Influenza is a clever virus—it shifts, drifts, and adapts, every so often mutating into a virus to which humans have little or no immunity. When this happens, a pandemic can occur, as in 1918 when a devastating influenza pandemic killed *tens of millions* of people throughout the world. Some of us lost grandparents, aunts, or uncles to the 1918 pandemic. All influenza A pandemics since that time, and almost all cases of influenza A worldwide, have been caused by descendants of the 1918 H1N1 virus (Taubenberger & Morens, 2006).



One hundred years ago the 1918 influenza pandemic devastated entire communities and took an estimated 675,000 American lives. It was the most severe pandemic in recent history, sweeping the globe quickly and killing more than 50 million people. Source: CDC.

Online Resource

Video: 1918 Pandemic (1:31)

https://www.cdc.gov/flu/pandemic-resources/1918-commemoration/index.htm

Even if you are not familiar with the 1918 pandemic, you may be aware of the 2009 H1N1 pandemic—the first global influenza pandemic in more than forty years. It was caused by the emergence of a novel* H1N1 influenza strain that reminded us just how serious an influenza pandemic can be. By the time the World Health Organization (WHO) declared the pandemic officially over in August 2010, the CDC estimated that 43 to 89 million people in the United States had become infected and more than 12,000 had died. It is estimated that worldwide between 151,700 and 575,400 people died from 2009 H1N1 virus infection during the first year the virus circulated (CDC, 2018d).

***Novel**: New (novel) influenza viruses are different from those currently circulating. This can include highly pathogenic influenza A viruses (H1N1, H5N1, H7N3, and H7N9).

Influenza experts believe that another influenza pandemic will occur—likely caused by an influenza subtype to which there is little or no pre-existing immunity in the human population. Even though the H1N1 pandemic of 2009 is officially over, the H1N1 virus continues to circulate as a seasonal virus and is expected to do so for several years. Fortunately, most (although not all) countries have developed influenza vaccines that protect against the H1N1 virus.

Influenza Virus Types and Subtypes

There are three kinds of influenza: A, B, and C. Influenza B and C aren't much to worry about, at most causing minor illness. The influenza A viruses, by contrast, are highly variable and so have the potential to outwit the human immune system and cause a pandemic.

Henry Nicholls Pandemic Influenza: The Inside Story

It is helpful to understand a little bit about the influenza virus—the different types, how they are named, and how they mutate. The more you know, the better you will be able to protect your patients, friends, and family members from catching the flu.

Influenza viruses are categorized and named by **type**. There are three types of influenza viruses— A, B, and C. Type is determined by the material within the nucleus of the virus.



Left: The influenza virus. Copyright Zygote Media Group. Used with Permission. Right: Structure of the influenza virion. The hemagglutinin (HA) and neuraminidase (NA) proteins are shown on the surface of the particle. The viral RNAs that make up the genome are shown as red coils inside the particle and bound to ribonuclear proteins (RNPs). Source: NIH, public domain.

The nomenclature used to describe a specific influenza virus was established by the World Health Organization in 1980 and is expressed in this order:

- 1. Virus type,
- 2. Geographic site where the virus was first isolated,
- 3. Strain or lineage number,
- 4. Year of isolation, and

 Virus protein antigen subtype described by letter and number, H1 to H16 and N1 to N9 (CDC, 2015PB)

For example, the 2009 H1N1 pandemic influenza virus was named as follows:

A/California/04/2009 (H1N1)

This is translated as: Influenza type A, isolated first in California, lineage (strain) number 04, year 2009, and type H1N1.

In the image below, a Fujian influenza virus that circulated in 2002 was named as follows:

A/Fujian/411/2002 (H3N2)

This is translated as: Influenza type A, first isolated in Fujian (a province on the Southeast coast of mainland China), lineage number 411, year 2002, type H3N2.

Influenza Virus Nomenclature



Influenza virus nomenclature (for a Fujian flu virus). Source: Wikipedia.org

The Fujian H3N2 influenza of 2002 caused an unusually severe 2003–2004 flu season, partly because it spread rapidly and partly because the vaccine for that season had already been formulated when the Fujian H3N2 virus was identified.

Type A Influenza and Its Subtypes

Type A influenza viruses are divided into **subtypes**, based on the presence of two glycoproteins on the surface of the virus. These glycoproteins are called **hemagglutinin (HA)** and **neuraminidase (NA)**. About 18 hemagglutinins have been identified, although generally, only H1, H2, and H3 are found in human influenza viruses. There are more than 100 types of neuraminidase, but only N1 and N2 have been positively linked to influenza epidemics in humans.

AN INFLUENZA VIRUS





Ribonucleoprotein

The above image shows the features of an influenza virus, including the surface proteins hemagglutinin (HA) and neuraminidase (NA). Following influenza infection or receipt of the influenza vaccine, the body's immune system develops antibodies that recognize and bind to "antigenic sites," which are regions found on an influenza virus's surface proteins. By binding to these antigenic sites, antibodies neutralize flu viruses and prevent them from causing further infection. Source: CDC.

Hemagglutinin and neuraminidase are also called **antigens**, substances that, when introduced into the body, stimulate the production of an antibody. Currently, there are two subtypes of influenza A viruses found circulating among human populations: influenza A (H1N1) and influenza A (H3N2).

Wild Birds Provide the Usual Reservoirs

A **reservoir** is the place where a pathogen lives and survives. For all subtypes of influenza A viruses, wild birds are the primary natural reservoir and are thought to be the source of influenza A viruses in all other animals. Influenza A viruses are found in many different animals, including ducks, chickens, pigs, whales, horses, and seals.

Most influenza viruses cause asymptomatic or mild infection in birds; however, clinical signs in birds vary greatly depending on the virus. Infection with certain avian influenza A viruses (for example, some H5 and H7 viruses) can cause widespread, severe disease and death among some species of birds (CDC, 2018a). In 2013 the ability to quickly identify the reservoir of a novel avian influenza A (H7N9) virus helped Chinese officials contain what started as an outbreak of "pneumonia of unknown cause" in the eastern coastal province of Zhejiang, China. During the outbreak, there were 135 confirmed human infections with H7N9, the vast majority during the month of April. Many of the people infected with H7N9 reported contact with poultry. By August 2013, 45 people had died (Chen et al., 2013). The H7N9 virus had previously been detected in birds but had never been seen in humans or any other animals prior to this outbreak.

Annual epidemics of sporadic human infections with Asianlineage avian influenza A (H7N9) virus ("Asian H7N9") in China have been reported since March 2013. In late 2016, China experienced its fifth epidemic of Asian H7N9 human infections. This was the largest annual epidemic to date. As of September 13, 2017, the World Health Organization reported 764 human infections with Asian H7N9 virus during the fifth epidemic. During epidemics one through four, about 40% of people confirmed with Asian H7N9 virus infection died (CDC, 2018a).



Zhejiang province, China (in red). Shanghai, a city with a population of 24 million, is located on the northern tip of Zhejiang province. Source: Uwe Dedering, Wikipedia Commons.

Genetic Evolution of H7N9 Virus in China, 2013



The eight genes of the H7N9 virus are closely related to avian influenza viruses found in domestic ducks, wild birds, and domestic poultry in Asia. The virus likely emerged from "reassortment," a process in which two or more influenza viruses co-infect a single host and exchange genes. This can result in the creation of a new influenza virus. Source: CDC, 2014.

Type A Influenza Viruses Circulate in Pigs

Pigs are susceptible to avian, human, and swine flu viruses and can potentially be infected with influenza viruses from different species at the same time. If this happens, it is possible for the genes of these viruses to mix (**reassort**) and create a new virus.

Influenza viruses that normally circulate in pigs are called "variant" viruses when they are found in people and denoted with a letter "v." H3N2v viruses from the 2009 H1N1 pandemic virus were first detected in people in 2011 and were responsible for a multi-state outbreak in the summer of 2012 that resulted in 306 cases, including 16 hospitalizations and 1 fatality (CDC, 2019j).

Most cases of H3N2v identified during 2012 were associated with exposure to pigs at agricultural fairs. Many fairs have swine barns where pigs from different places come in close contact with each other and with people. These venues may allow the spread of influenza viruses both among pigs and between pigs and people. Infected pigs can spread influenza viruses even if they are not symptomatic. Although instances of limited person-to-person spread of this virus have been identified in the past, sustained or community-wide transmission of H3N2v has not occurred (CDC, 2019j).

Type B Influenza

Influenza type B viruses are separated into two genetic lineages (B/Yamagata and B/Victoria). They are not classified by subtype like influenza A viruses. Influenza B viruses from both the Yamagata and Victoria lineages have co-circulated in most recent influenza seasons. The trivalent influenza vaccines available in recent seasons have contained one influenza B virus, representing only the Yamagata lineage. The quadrivalent vaccine for 2019–2020 will contain both the Yamagata and Victoria lineages (CDC, 2019f).

Influenza type B viruses are usually found only in humans, and can cause morbidity and mortality among humans, but in general are associated with less severe epidemics than influenza A viruses. Although influenza type B viruses can cause human *epidemics*, they have not caused *pandemics*. Influenza B viruses undergo genetic changes less rapidly than influenza A viruses.

Type C Influenza

Influenza type C is less common and less studied than influenza A and B. It can cause illness in humans and pigs, and it is thought that most people are exposed to influenza C during childhood. The influenza C virus lacks the multiple subtypes (hemagglutinin and neuraminidase) found in influenza A, which limits its ability to mutate. Influenza C is thought to be unlikely to cause a pandemic, although localized epidemics have occurred. As with type B influenza viruses, type C influenza viruses are not classified according to subtype.

Ту	pes of Influenza Virus
Influenza type	Characteristics
Туре А	Causes moderate to severe illnessOccurs in all age groupsAffects humans and other animals
Туре В	Causes milder disease than type AAffects primarily childrenOccurs in humans only
Туре С	Reported rarely in humansNo epidemics

Drifting and Shifting

To successfully infect a person, the influenza virus must develop ways to evade a person's immune system. Viruses do this through evolutionary processes called antigenic **drift** and antigenic **shift**. Influenza type A viruses undergo both kinds of changes, while influenza type B and C viruses change only by the gradual process of antigenic drift.

Antigenic Drift: Continual Small Changes

Antigenic drift involves continual small changes or mutations to a virus's surface antigens (HA or NA). Think of a small boat drifting across the ocean or clouds drifting across the sky. These changes produce new viral strains that are fairly closely related to one another and may be recognized by the immune system (sometimes called "cross-protection"). Changes due to antigenic drift can nevertheless accumulate over time, straining the ability of a person's immune system to recognize the new virus.



Like clouds drifting across the sky, antigenic drift involves small, continual changes to a virus's surface antigens. Source: Wikipedia Commons.

In most years, one or two of the virus strains in the influenza vaccine are updated to keep up with the changes in the circulating flu viruses. Changes in viruses due to antigenic drift can cause widespread infection because the protection that remains from past exposures to similar viruses is incomplete. Drift occurs in all three types of influenza virus (A, B, C).

Antigenic Shift, a Major, Abrupt Change

Antigenic shift is a major, abrupt change in one or both surface antigens (HA or NA). Shift occurs at varying intervals and likely is the result of **reassortment** (the exchange of a gene segment) between influenza A viruses, usually those that affect humans and birds.

Antigenic shift results in a new influenza A subtype that is so different from previous subtypes in humans that most people do not have immunity to the new virus. An antigenic shift can lead to a worldwide pandemic if the virus is efficiently transmitted from person to person.

An example of a "shift" occurred in the spring of 2009, when a novel H1N1 virus with a new combination of genes (from American pigs, Eurasian pigs, birds, and humans) emerged in people and quickly spread, causing a pandemic. Since the late nineteenth century, four occurrences of antigenic shift have led to major influenza pandemics.

Although influenza viruses constantly and gradually change by antigenic drift, antigenic shift happens only occasionally. When a

Like this lightning storm near New Boston, Texas, antigenic shift involves major, abrupt changes in surface antigens (HA or NA). Source: Griffinstorm, Wikipedia Commons.

type A virus undergoes both kinds of changes, it is capable of evading host immunity, with profound implications for epidemiology and control. This is the main reason why seasonal influenza vaccines are updated frequently, to maintain protection in risk groups against currently circulating strains (Arinaminpathy & Grenfell, 2010).

Influenz	za Virus: Antigenic Changes
Antigenic drift	 minor, continual changes, same subtype
	 caused by point mutations in gene
	 may result in epidemic
Antigenic shift	 major, abrupt changes, new subtype
	 caused by exchange of gene segments
	 may result in pandemic

Antigenic Drift and Shift of Influenza Strains



Antigenic drift vs. shift. Antigenic drift creates influenza viruses with slightly modified antigens, while antigenic shift generates viruses with entirely new antigens (shown in red). Source: Wikipedia Commons and USDA.

Online Resource

Inflenza: Get the (Antigenic) Drift—Video (2:52)

https://www.youtube.com/watch?v=ug-M1nIhfIA

The 2009 H1N1 Flu Pandemic—Quadruple Reassortment

The 2009 influenza A (H1N1) virus was a new flu virus that caused illness worldwide in March and April of 2009. This virus was originally referred to as "swine flu" because laboratory testing showed that many of the genes in this new virus were very similar to influenza viruses that normally occur in pigs in North America. Further study, however, showed that this new virus was very different from the one that formerly circulated in North American pigs. It has two genes from flu viruses that have circulated in pigs in Europe and Asia, plus bird (avian) genes and human genes. Scientists call this a **quadruple reassortant virus** (CDC, 2010).

Pandemic Influenza

Influenza occurs in two distinct patterns: pandemic and seasonal. Pandemic influenza results from the emergence of a new influenza A virus to which the population possesses little or no immunity and that can occur at any time of year. Seasonal influenza is usually caused by influenza A or B viruses and generally occurs each year during a specific time of the year.

While outbreaks of influenza may be traced as far back as 412 B.C.E., the first **pandemic**, or worldwide epidemic, that clearly fits the description of influenza occurred in 1580. It began in Asia and spread to most of the rest of the world, affecting nearly all of Europe in just six weeks. At least four influenza pandemics occurred in the nineteenth century, followed by three more in the twentieth century and one in this century.

In the twentieth century, the most devastating example of a new influenza subtype emerging in the human population occurred in 1918. The virus contained a subtype 1 hemagglutinin protein (H1) and a subtype 1 neuraminidase protein (N1). After the 1918 pandemic, H1N1 variants circulated for 39 years before being replaced by an H2N2 virus in 1957. The H2N2 virus was prevalent for only 11 years until 1968, when it was replaced by an H3N2 virus (Palese & Wang, 2011). In 2009, a new strain of H1N1 influenza emerged and caused a worldwide pandemic in which an estimated 280,000 people died.





(A) H1N1 indicates virus with hemagglutinin subtype 1 and neuraminidase subtype
1. H2N2 and H3N2 indicate viruses with hemagglutinin subtype 2 and
neuraminidase subtype 2 and hemagglutinin subtype 3 and neuraminidase subtype
2, respectively. pH1N1 indicates the novel swine origin virus first isolated in 2009.
(B) Antibody response in the human population, which the authors propose to have
contributed to the elimination of existing seasonal influenza virus strains. Source:
Palese & Wang, 2011.

How Influenza Pandemics Occur–Video (3:23)

How Influenza Pandemics Occur

http://www.youtube.com/watch?v=DdFCx8jbesQ

The Mother of All Pandemics: 1918–1919

The influenza pandemic of 1918–1919 killed more people than the Great War, known today as World War I, at somewhere between 20 and 40 million people. It has been cited as the most devastating epidemic in recorded world history. More people died of influenza in a single year than in the four years of the Black Death Bubonic Plague from 1347 to 1351. Known as "Spanish Flu" or "La Grippe," the influenza of 1918–1919 was a global disaster.

Molly Billings, 2005 *The Influenza Pandemic of 1918*

The 1918 influenza pandemic, caused by an H1N1 influenza subtype came on suddenly in March of 1918 and spread rapidly throughout the world. In the United States the first reports came from public health officials in Haskell County, Kansas, who reported "18 cases of influenza of a severe type." By June the virus had spread from the United States to Europe, where it quickly moved from the military to the civilian population. From there, the disease circled the globe—to Asia, Africa, South America, and, back again, to North America.

The effect of the influenza epidemic was so severe that the average lifespan in the United States was depressed by 10 years (Billings, 2005). The "Spanish influenza" of 1918 is estimated to have hit nearly a third of the world's population. Conditions at the end of World War I likely contributed to the mortality (Nicholls, 2006).

The 1918 pandemic occurred in three waves. The first wave was seen when mild influenza erupted in the late spring and summer of 1918. The second wave occurred with an outbreak of severe influenza in the fall of 1918 and the final wave hit in the spring of 1919. A physician stationed at Fort Devens, outside Boston, reported in late September 1918: This epidemic started about four weeks ago, and has developed so rapidly that the camp is demoralized and all ordinary work is held up till it has passed. . . . These men start with what appears to be an ordinary attack of La Grippe or Influenza, and when brought to the Hosp. they very rapidly develop the most viscous type of Pneumonia that has ever been seen. Two hours after admission they have the Mahogany spots over the cheek bones, and a few hours later you can begin to see the Cyanosis extending from their ears and spreading all over the face, until it is hard to distinguish the coloured men from the white. It is only a matter of a few hours then until death comes, and it is simply a struggle for air until they suffocate. It is horrible. One can stand it to see one, two, or twenty men die, but to see these poor devils dropping like flies sort of gets on your nerves. We have been averaging about 100 deaths per day, and still keeping it up. There is no doubt in my mind that there is a new mixed infection here, but what I don't know.



Influenza Ward During the 1918–1919 Epidemic

Source: Office of the Public Health Service Historian.

Few Tools to Fight the Pandemic

[Material in this section is from HHS, 2009 unless otherwise cited.]

Unfortunately, few tools were available to either prevent the spread of influenza or treat patients during the 1918–1919 pandemic. A variety of remedies were tried, many of which could be found in local drugstores. **Patent medicines** (medicines whose ingredients were secret and trademarked) were still in widespread use in 1918. Among these medicines, Vicks Vapo-Rub, atropine capsules (belladonna), and a host of other treatments were especially common. In terms of curing or treating influenza symptoms, these remedies did little to nothing (HHS, 2009).

Patent Medicine Label

At the time, most physicians believed that influenza was caused by a bacillus. Nevertheless, many practitioners resorted to treatments derived from older medical theories. These treatments included causing patients to sweat by wrapping them in blankets or cupping them to remove excess blood (HHS, 2009). People were also encouraged to wear masks, which had little effect.

Because patients experienced symptoms not traditionally associated with influenza, physicians found the disease especially difficult to diagnose in 1918. In the early stages of the pandemic, many physicians and scientists even claimed that influenza patients were suffering from cholera or bubonic plague, not influenza (HHS, 2009).

During the fall of 1918, researchers from the Public Health Service began looking for a vaccine. They were joined by researchers in many other countries. These researchers developed a range of vaccines that were then tested in communities all over the world. None of these vaccines proved effective. While researchers placed their hope in vaccines, many politicians and physicians came to believe that the spread of the disease could be contained by quarantines and bans on public gatherings (HHS, 2009).

Across the United States, cities and counties began to require or recommend that citizens wear gauze masks. Unfortunately, while masks are highly effective at preventing diseases that are caused by bacteria, they are less effective in providing



Drug advertisers routinely promised quick and painless cures. Source: National Library of Medicine.

People Wearing Masks to Ward Off the Flu



Drug advertisers routinely promised quick and painless cures. Source: National Library of Medicine.

protection against viral diseases. As a result, even in communities where the wearing of masks was mandatory, influenza could not be contained. Public officials also sought to limit influenza by banning spitting in public places and demanding that those who sneezed covered their mouths.

Red Cross Volunteers in Boston, Massachusetts, 1918



Massachusetts had been drained of physicians and nurses due to calls for military service, and no longer had enough personnel to meet the civilian demand for healthcare during the 1918 flu pandemic. Governor McCall asked every able-bodied person across the state with medical training to offer their aid in fighting the epidemic. Boston Red Cross volunteers assembled gauze influenza masks for use at hard-hit, Camp Devens in Massachusetts. Source: CDC Historical Image Gallery.

Early Symptoms, Recovery, and Relapse

During the 1918 pandemic, early symptoms included a temperature in the range of 102°F to 104°F. Patients experienced a sore throat, exhaustion, headache, aching limbs, bloodshot eyes, a cough, and occasionally a violent nosebleed. Some also suffered from digestive symptoms such as vomiting or diarrhea. Many patients who experienced these symptoms made a full recovery, only to suffer a relapse. Their temperatures, which had fallen, rose again and they now experienced serious respiratory problems. In some cases, these patients also experienced massive pulmonary hemorrhage. After death, pathologists found these victims to have swollen lungs and oversized spleens (HHS, 2009).

The Spanish Influenza



Chart showing mortality from the 1918 influenza pandemic in the United States and Europe, peaking in October and November 1918 and again in February and March of 1919. Source: Courtesy of the National Museum of Health and Medicine.

Origin of the 1918 Pandemic Strain

The 1918 pandemic strain of influenza is thought to have originated in China in a rare genetic shift of the influenza virus. The recombination of its surface proteins created a virus novel to almost everyone (Billings, 2005).

In the late 1990s, researchers found isolates of the 1918 pandemic virus in the formalin-fixed, paraffin-embedded lungs of an American serviceman. They subsequently retrieved further samples of this deadly virus from a second soldier, and also from a flu victim exhumed from a frosty mass grave in Alaska. The genetic sequencing of the 1918 HIN1 virus was completed in 2005 (Nicholls, 2006).

The sequencing of the 1918 pandemic strain resulted in a key finding. Each segment is more similar to avian viruses than to segments from any human strains. This suggests that the virus did not emerge through reassortment of genetic material but evolved directly via mutation from an avian virus (Nicholls, 2006).

Lung Tissue from Influenza Patient



In the end, more than 50 million people throughout the world died as a result of the influenza pandemic. An estimated 675,000 people died in the United States. More people died from influenza than died during World War I.

Lung from deceased influenza patient similar to that used to extract RNA from the 1918 killer strain. Source: Courtesy of the National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, D.C.

Online Resource

We Heard the Bells-1918 Flu Pandemic: Video (8 min)

http://www.flu.gov/video/2010/01/we-heard-the-bells.html

Seasonal Influenza

Seasonal influenza differs from pandemic influenza in that it occurs each year, typically during a specific time of the year. Seasonal flu generally causes less illness because the population has some immunity left over from previous, similar influenza strains. In the Northern Hemisphere, winter is the time for seasonal influenza, but the exact timing and duration of influenza seasons vary. While influenza outbreaks can happen as early as October, activity usually peaks in January or later.

The United States 2017–2018 influenza season was a high-severity season with high levels of outpatient clinic and ED visits for influenza-like illness, high influenza-related hospitalization rates, and elevated and geographically widespread influenza activity across the country for an extended period (Garten et al., 2018).

The "peak month of flu activity" is the month with the highest percentage of respiratory specimens testing positive for influenza virus infection during that influenza season. During this 36-year period, flu activity most often peaked in February (15 seasons), followed by December (7 seasons), March (6 seasons), and January (6 seasons) (CDC, 2018b).

Influenza activity in the United States during the 2018–2019 season (September 30, 2018–May 18, 2019) was considered to be of moderate severity. Nationally, influenza-like illness (ILI) activity began increasing in November 2018, peaked during mid-February 2019, and returned to below baseline in mid-April; the season lasted 21 weeks, making it the longest season in 10 years (Xu et al., 2019).

Influenza A viruses predominated, with very little influenza B activity. Two waves of influenza A were notable during this extended season: influenza A(H1N1) viruses from October 2018 to mid-February 2019 and influenza A(H3N2) viruses from February through May 2019 (see below charts). The number of influenza B viruses reported was low compared with previous seasons, accounting for only 4% of influenza viruses. Compared with the 2017–2018 influenza season, rates of hospitalization last season were lower for adults, but were similar for children (Xu et al., 2019).



Chart shows two waves of flu activity for 2018–2019. Source: CDC. https://www.cdc.gov/mmwr/volumes/68/wr/mm6824a3.htm?s_cid=mm6824a3_w



Chart shows flu activity for several recent years. Source: CDC. https://www.cdc.gov/mmwr/volumes/68/wr/mm6824a3.htm?s_cid=mm6824a3_w

Seasonal Influenza Clinical Features

[Material from this section from CDC 2019, CDC 2015, PB].

Influenza is a contagious respiratory illness caused by influenza viruses. It can cause mild to severe illness resulting in hospitalization or even death. "Classic" influenza is characterized by the abrupt onset of fever, myalgia, sore throat, nonproductive cough, and headache. The fever is usually 101°F to 102°F and accompanied by prostration (bedridden) (CDC, 2019, 2015PB).

The onset of fever is often so abrupt that the exact hour is recalled by the patient. Myalgias mainly affect the back muscles. Cough is believed to be a result of tracheal epithelial destruction. Additional symptoms may include runny nose, headache, substernal chest burning, and ocular symptoms such as eye pain and sensitivity to light (CDC, 2019, 2015PB).

The incubation period for influenza is usually 2 days, but can vary from 1 to 4 days. The severity of illness depends on whether the immune system has been exposed to related virus variants. Somewhat surprisingly, only about 50% of infected people will develop the classic clinical symptoms of influenza (CDC, 2019, 2015PB).

Systemic symptoms and fever usually last from 2 to 3 days, rarely more than 5 days. They may be decreased by such medications as aspirin* or acetaminophen. Recovery is usually rapid, but some patients may have lingering depression and lack of strength or energy for several weeks (CDC, 2019, 2015PB).

*Aspirin should NOT be used for infants, children, or teenagers because they may be at risk for contracting Reye syndrome following an influenza infection.

Symptoms of the Flu

People who have the flu often feel some or all of these symptoms:

- Fever* or feeling feverish, chills
- Cough
- Sore throat
- Runny or stuffy nose
- Muscle or body aches
- Headaches
- Fatigue
- Vomiting and diarrhea—more common in children than adults

* Not everyone with flu will have a fever.

Complications

[Material from this section from CDC 2019, CDC 2015, PB].

The most frequent complication associated with influenza is pneumonia, especially secondary bacterial pneumonia (eg, *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus*). Primary influenza viral pneumonia is an uncommon complication but has a high fatality rate. Reye syndrome is a complication that occurs almost exclusively in children taking aspirin, primarily in association with influenza B (or varicella zoster), and presents with severe vomiting and confusion, which may progress to coma due to swelling of the brain (CDC, 2019, 2015PB).

Other complications can include myocarditis and worsening of chronic bronchitis and other chronic pulmonary diseases. People with congestive heart failure may have a worsening of the condition triggered by the flu. Death is reported in less than 1 per 1,000 cases. The majority of deaths occur among individuals 65 years of age and older (CDC, 2019, 2015PB).

If vaccine supply is limited, vaccination efforts should focus on:

- Children 6 months to 4 years
- Adults 50 years and older
- Women who are or will be pregnant during influenza season
- Residents of nursing homes and other chronic-care facilities
- Those who are morbidly obese (body-mass index is 40 or greater)
- Healthcare personnel
- American Indians and Alaskan Natives
- People with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, neurologic, hematologic, or metabolic disorders (including diabetes mellitus)
- People who have a weakened immune system or those that are immunosuppressed (including immunosuppression caused by medications or HIV)
- Children 6 months through 18 years of age and receiving long-term aspirin therapy and who therefore might be at risk for experiencing Reye syndrome after influenza virus infection
- Household contacts and caregivers of children younger than 5 years of age and adults 50 years of age or older, with particular emphasis on vaccinating contacts of children aged younger than 6 months
- Household contacts and caregivers of people with medical conditions that put them at higher risk for severe complications from influenza (CDC, 2019, 2015PB)

Transmission

Influenza is primarily a community-based infection that is transmitted in households and community settings. In humans, influenza is primarily transmitted from person to person via large virus-laden droplets (particles more than 5 microns in diameter) that are generated when infected individuals cough or sneeze. These large droplets can then settle on the mucosal surfaces of the upper respiratory tracts of susceptible people who are nearby (within 3 feet).

Cone-Shaped Dispersion of Sneeze Particles



This photograph captures a sneeze in progress, revealing the plume of salivary droplets as they are expelled in a large cone-shaped array from this man's open mouth, thereby dramatically illustrating the reason for covering your mouth when coughing or sneezing, in order to protect others from germ exposure. Source: James Gathany, CDC PHIL, 2009.

Transmission can also occur through direct or indirect contact with respiratory secretions, such as when touching surfaces contaminated with influenza virus and then touching the eyes, nose, or mouth. Adults can transmit influenza from the day before symptom onset to approximately 5 days after symptoms begin. Children can transmit influenza to others for 10 or more days.

Healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 to 7 days after becoming sick. Some people, especially young children and people with weakened immune systems, might be able to infect others for an even longer time.

A German study yielded information about how and when influenza spreads within a group of people. In the study involving 180 participants, evidence of **pre-symptomatic** shedding of the influenza virus was observed in 30% of samples 1 day prior to the onset of symptoms. Shedding of virus was greatest on days 1 to 3 of illness (Suess et al., 2012).

Other findings included:

- Quantity of virus shed appeared to be the same for asymptomatic and symptomatic infected subjects
- Those infected with influenza B exhibited the highest viral shedding load
- Antiviral therapy induced a milder clinical course and faster illness resolution but had no effect on viral shedding
- Vaccinated and unvaccinated patients did not differ in terms of clinical course and shedding
- Viable viral shedding, as measured by viral culture, did not persist as long as PCR positivity (Suess et al., 2012)

Watch this fascinating 3-minute video showing how influenza is transmitted and replicated.

Flu Attack!	How A	Virus	Invades	Your	Body	(3:39)
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https://www.youtube.com/watch?v=Rpj0emEGShQ

The Goal of Universal Vaccination

It has been well-established that influenza vaccination reduces influenza-associated illness. CDC estimates that tens of thousands of hospitalizations are *averted* because of vaccination each year and that vaccination prevents millions of influenza-related illnesses. This is despite that fact that fewer than half of those over the age of 6 months are vaccinated each year. Higher vaccination rates almost certainly would prevent a substantial number of additional cases and hospitalizations.





The estimated number of flu illnesses prevented by flu vaccination during the 2017–2018 season: 7 million, about the population of New York City.

In the United States, goals for improving influenza vaccination rates are outlined in Healthy People 2020 (see table below). Since 2010 CDC has recommended that all people 6 months of age and older receive annual influenza vaccination. Despite substantial gains in the number of people vaccinated each year, we have yet to come close to the goal of universal influenza vaccination.

Flu Vaccination Coverage Among Adults by Age Group and Season,



Source: CDC.

The College of Physicians of Philadelphia provides a fascinating look at the issues associated with vaccines on their History of Vaccines website (http://www.historyofvaccines.org/). It is well worth the time to look over this website and explore "the ways in which vaccines, toxoids, and passive immunization work, how they have been developed, and the role they have played in the improvement of human health."

Vaccination Rates Among Adults

During the 2017–2018 season, flu vaccination coverage among adults was 37.1%, a decrease of 6.2% from the previous flu season. As in past years, people continued to get flu vaccinations through the winter and into spring. By the end of the 2017–2018 season, vaccine coverage for adults was approximately 8 percentage points higher than early-season estimates.

Early-season 2018–19 estimates show an increase in flu vaccination coverage among adults compared to the previous season. However, vaccination coverage varied by age group and state (CDC, 2018f).

Early and End of Season Flu Vaccination Coverage Among Adults, United States, 2014–November 2018



Source: CDC.

Flu vaccination coverage for the 2017–2018 season was lower for every age group compared to the previous year. For all adult age groups, flu vaccination rates were at their lowest levels compared with the seven previous seasons. There was large between-state variability in flu coverage among adults, ranging from 29.2% in Louisiana to 46.3% in West Virginia (CDC, 2018f).

Early findings show an increase in 2018-2019 flu vaccinations. Among children aged 6 months–17 years there was an increase of 6.8 percentage points to 45.6%, compared with the same time period the prior year. Flu vaccination coverage among adults aged \geq 18 years increased by 6.4 percentage points to 44.9%. Coverage increased for children aged 6 months–12 years and among all adult age groups. Interpretation of these results should take into account limitations of the surveys, including reliance on self-report of vaccination status and decreasing response rates (CDC, 2018f).

Low vaccination rates have also been noted in Europe, where surveys from five countries have shown consistently low coverage in the general population. During the 2009 H1N1 pandemic, vaccination campaigns were adopted in many countries; however, low acceptance of a vaccine or uptake rates against pandemic influenza were reported in many studies (25% among health workers in Beijing, 17% among a French adult population, and 8.9% among pregnant women in Turkey) (Wu et al., 2013).

Vaccination Rates Decline as Clinic Day Progresses

A retrospective, quality-improvement study of 11 primary care practices at the University of Pennsylvania Health System from September 1, 2014, to March 31, 2017 yielded interesting results. Researchers found that influenza vaccination rates significantly declined as the clinic day progressed.

Offering an "active choice" intervention in which medical assistants were prompted to make decisions on whether to template vaccinations orders in patients' electronic health record for clinicians to review was associated with a significant increase in vaccination rates. Importantly, the active choice intervention was associated with a significant increase in influenza vaccination rates that were similar in magnitude throughout the day.

Source: Kim et al., 2018.

Vaccination Rates Among Children

Influenza-associated deaths in children (less than 18 years) were added as a nationally notifiable condition in 2004. Of particular interest, for children in the United States, influenza vaccination rates are fairly high in young children but decrease with increasing age:

- 6–23 months: 76.3%
- 2-4 years: 66.2%
- 5-12 years: 59.9%
- 13–17 years: 48.8% (Black et al., 2017)

CDC analyzed data from the National Immunization Survey—Flu to estimate flu vaccination coverage for the U.S. population of children 6 months through 17 years during the 2018–2019 flu season. Receipt of flu vaccination was determined by parental report. Vaccination coverage varied by state and age group.

Estimates of flu vaccination coverage as of mid-November 2018 for children aged 6 months to 17 years was 45.6%, an increase of 6.8 percentage points compared with the same time period during the previous year (Xu et al., 2019).

During the 2018–2019 flu season, 116 laboratory-confirmed influenza-associated pediatric deaths (ages 2 months–17 years) were reported. Twenty-two percent of the deaths were associated with influenza A(H3N2) infection, 37% with influenza A(H1N1), 34% with an influenza A virus for which no subtyping was performed, 7% with an influenza B virus, and 1% with an influenza virus for which the type was not determined. The mean age of the pediatric deaths reported this season was 6.1 years and 66% of those children died after admission to the hospital. Among the 104 children with a known medical history, 51% had at least one underlying medical condition recognized by the Advisory Committee on Immunization Practices (ACIP) as placing them at high risk for influenza-related complications (Xu et al., 2019).

Among the 89 children who were eligible for influenza vaccination (age \geq 6 months at date of onset) and for whom vaccination status was known, 34% had received at least 1 dose of influenza vaccine before illness onset (25 of the children were fully vaccinated according to 2018 ACIP recommendations, and five had received 1 of 2 recommended doses) (Xu et al., 2019).



Early and End of Season Flu Vaccination Coverage Among Children, United States, 2014–November 2018

Source: CDC.

Vaccination Rates Among Healthcare Workers

The overall influenza vaccination coverage estimate among healthcare personnel was 78.4% during the 2017–2018 influenza season, a 15% increase since the 2010–2011 season, but similar to coverage during the previous four seasons. As in past seasons, the highest coverage was associated with workplace vaccination requirements. Reported coverage was consistently higher among healthcare personnel working in hospital settings than among those working in other settings; healthcare personnel working in hospital settings were also the most likely to report workplace vaccination requirements (Black et al., 2018).

Influenza vaccination coverage was higher among healthcare personnel with vaccination available at or promoted in their workplace than among those without any type of employer promotion of vaccination; however, coverage achieved through vaccine availability and promotion was still suboptimal in the absence of requirements. Neither vaccination coverage nor prevalence of employer vaccination requirements or promotion differed in the 2017–2018 season compared with the previous season, despite the severity of the 2017–2018 influenza season (Black et al., 2018).

Influenza vaccination coverage among healthcare personnel working in long-term care settings, the majority of whom work as assistants and aides, continues to be consistently lower than that among healthcare personnel working in all other healthcare settings. Influenza vaccination among healthcare personnel in long-term care settings is especially important because influenza vaccine efficacy is generally lowest among elders, who are at increased risk for severe disease (Black et al., 2018). In contrast to healthcare personnel working in hospitals, a much lower proportion of survey respondents working in long-term care settings reported having a requirement for vaccination, and 23.5% reported that their employer did not require, make available on-site at no cost, or promote vaccination in any way. Implementing workplace vaccination programs that have been successful in increasing coverage in hospital settings, including vaccination requirements, could increase coverage in long-term care and other settings with historically lower vaccination coverage (Black et al., 2018).

Did You Know. . .

Workplace vaccination programs that have been successful in increasing coverage in hospital settings could be implemented in long-term care and other settings with lower vaccination coverage.

Employers can use the long-term care **web-based toolkit** developed by CDC and the National Vaccine Program Office to access resources, strategies, and educational materials for increasing influenza vaccination among healthcare personnel in long-term care settings (Black et al., 2017).

These low rates are certainly at least partly related to high staff turnover; it is not uncommon for a long-term facility's staff to turn over completely every few years. Newly hired managers may not adhere to existing policies related to vaccinations, or they may decide to discard such policies and implement new ones (AHRQ, 2014).



Source: Morbidity and Mortality Weekly Report, 2018.

Vaccination Rates by Healthcare Occupation

[Material in this section from Black et a., 2017 unless otherwise cited.]

During the 2016–2017 season (earliest available statistics), flu vaccination coverage was highest among physicians (95.8%) and lowest among assistants and aides (69.1%), and highest overall among healthcare personnel who were required by their employer to be vaccinated (96.7%).

Among healthcare personnel working in settings where vaccination was neither required, promoted, nor offered onsite, vaccination coverage continued to be low (45.8%). An increased percentage of healthcare personnel reporting a vaccination requirement or onsite vaccination availability compared with earlier influenza seasons might have contributed to the overall increase in vaccination coverage during the past seven influenza seasons.

Vaccination Rates by Healthcare Setting

Not surprisingly, vaccination rates among healthcare providers vary by work setting. During the 2016–2017 season, vaccination coverage continued to be higher among healthcare personnel working in hospitals (92.3%) and lower among healthcare personnel working in ambulatory (76.1%) and long-term care settings (68%).

Coverage was highest among physicians, nurse practitioners/physician assistants, nurses, pharmacists, and healthcare personnel working in hospital settings. Coverage was lowest among assistants and aides and personnel working in long-term care settings. Employer vaccination requirements and offering vaccination at the workplace at no cost were associated with higher vaccination coverage.

Why is it so important to increase vaccination rates among healthcare personnel?

Because of their close proximity to sick patients, healthcare providers are more likely to get influenza *and to pass it on*, with more significant consequences than for any other group of workers. Paradoxically, when a healthcare provider gets sick, several studies have shown that more than 75% continue to work despite being infected with influenza (Riphagen-Dalhuisen et al., 2013).

A recent study conducted among nursing home workers in France suggest low rates of influenza vaccination there as well. Management and working environment appear to play a strong role and the authors suggest that: "To overcome vaccine 'hesitancy,' specific communication tools may be required to be adapted to the various NH professionals to improve influenza prevention" (Elias et al., 2017).

Refusing or Accepting the Flu Vaccine

Each year, we must decide whether to get vaccinated against the flu. Many of us get the vaccine without a second thought, while a significant percentage of Americans either choose not to get vaccinated or simply never get around to it.

Vaccine Hesitancy

For many individuals, the health benefits associated with vaccination is not a sufficient reason to embrace vaccination wholeheartedly. They doubt the benefits of vaccines, worry over their safety, and question the need for them, an attitude referred to as **vaccine hesitancy**. An attitude of hesitancy differs from an action of vaccine refusal. Even those who are vaccinated can harbor hesitancy toward certain aspects of vaccination (Yaqub et al., 2014).

While coverage rates are helpful for identifying those who reject, it does little to help us understand hesitant attitudes, their origins, and how to change them. Maintaining high coverage rates helps to ensure that vaccination benefits are delivered widely, but the very act of delivering wide-scale vaccination can make vaccines "victims of their own success." As the ravages of disease become less familiar to people, it may become more challenging to articulate the desirability of vaccination (Yaqub et al., 2014).

Reasons for Refusing the Flu Vaccine

It is certainly reasonable to ask why so many people, both in and out of healthcare, decide **not** to get vaccinated against influenza each year. Studies that investigate why a segment of the population does not accept vaccination have highlighted lack of knowledge, misperceptions, and distrust of vaccines. Ironically, another reason cited is a low perceived risk because the incidence has declined as a result of vaccination programs (Herzog et al., 2013).

Surveys in Europe and the United States have found that low seasonal vaccination coverage rates are influenced by inadequate (or no) recommendation by general practitioners, poor public awareness of influenza and influenza vaccines, a lack of proactive reminder systems, and a fear of needles (Blank et al., 2012).

Examining misconceptions about vaccination provides some context about why many people forgo the influenza vaccine each year:

- Fear that the immune system will be "overloaded" by vaccines, especially in children.
- The belief that many common diseases have disappeared and it is no longer necessary to vaccinate against them.
- The belief that more vaccinated than unvaccinated people get sick.
- The belief that hygiene and better nutrition are responsible for the reduction in disease rates, not vaccination.
- The belief that natural immunity is better than vaccine-acquired immunity. (The College of Physicians of Philadelphia, 2016)

When looking at the reasons why a significant percentage of healthcare providers in the United States say they do not intend to get a seasonal flu vaccine, the most commonly reported reason was that **they do not think the flu vaccine works**. Other reasons included thinking they do not need a flu vaccine, fear of getting sick, fear of side effects from vaccination, being allergic to the vaccine, and thinking that flu vaccination is not good for you.

Main Reason Reported for Not Getting the Flu Vaccine Among Healthcare Personnel Not Planning to Get One in 2016-2017 Internet Panel Survey, November 2016, USA I may experience side effects or get sick from the vaccine (n = 76) 23.9 I don't think that fluvaccines work (n = 81) 20.5



I do not need the vaccination (n = 56)

Source: CDC, 2016.

Recently, researchers from the European Centre for Disease Prevention and Control (ECDC) analyzed the results of a study conducted by vaccine producers, which looked at the costs and benefits of influenza vaccination. Cautioning that the data on vaccine coverage, disease burden, and health costs are imprecise, the analysts nevertheless agreed that it is important to understand the reasons for low vaccine coverage in the 27 European countries included in the study (Ciancio & Rezza, 2014). The reasons for low vaccine coverage echo many of the findings in earlier studies:

60

15.0

- 1. Vaccine hesitancy in healthcare workers and in the population
- 2. Lack of confidence in vaccine effectiveness and safety
- 3. Complex vaccine recommendations
- Short vaccine delivery window 4.
- 5. Lack of resources

Reasons for Accepting the Flu Vaccine

When I first started work as a nurse, I never got a flu shot. If I got the flu, I went to work even though I was sick. One year I got the flu shot on a Friday morning and was sick as a dog by the evening. Now I know that I already had the flu when I got the shot back then I blamed it on the vaccine and didn't get a shot for several more years. One year I got the flu, missed several days of work, and coughed my lungs out for almost two weeks. After that I thought, this is ridiculous, the flu vaccine will stop all of this. It was a no-brainer. Now I get a shot every year.

ER Nurse, California, 2018

There are many good reasons for healthcare workers to get a flu vaccine, not least of which is they are less likely to become ill themselves and much less likely to pass the virus on to their patients *and families*. Among healthcare personnel who received the flu vaccine in 2016, protecting themselves from flu was the most common reason reported for receiving the flu vaccination. Employer requirement for flu vaccination was the second most commonly reported reason why vaccinated healthcare providers decided to get the flu vaccination (CDC, 2016).

Main Reason Reported for Getting the Flu Vaccine Among Healthcare Personnel (n=1,378) Internet Panel Survey, November 2016, USA



Source: CDC, 2016.

During the 2009–2010 H1N1 influenza pandemic in France, Germany, and Mexico, the most common reason given to be vaccinated for A/H1N1 pandemic influenza was a physician's advice or recommendation. In the United States, media advertising was the most important motivating factor, although a physician's advice was nearly as important (Blank et al., 2012).

Influenza Vaccination Programs

Influenza vaccination programs in healthcare facilities are most successful when they are multifaceted. Successful programs focus on the following:

- Full, visible leadership support with the expectation for vaccination fully and clearly communicated to all healthcare personnel
- Provision of adequate resources and support for the healthcare personnel vaccination program
- Inclusion of all practices necessary to reduce the spread of influenza in healthcare settings, including patient isolation, use of personal protective equipment, applying hand and respiratory hygiene and cough etiquette, and restriction of ill visitors and ill healthcare personnel (NVAC, 2013)

In one innovative program initiated by the University of Pittsburgh Medical Center, 14 long-term care facilities ceded control of vaccination-related policies and processes to a regional pharmacy. The facilities worked collaboratively with the pharmacy to implement and enforce standardized policies and processes to boost influenza vaccination rates among facility workers. This policy change significantly increased worker vaccination rates in participating facilities, enabling all facilities to reach the Healthy People 2010 goal of vaccinating 60% of workers in long-term care settings and several facilities to exceed the Healthy People 2020 goal of vaccinating 90% (AHRQ, 2014).

When receiving the influenza vaccine is a condition for employment, vaccination rates can approach 100%. During the 2010–2011 influenza season, CDC found that approximately 13% of healthcare personnel reported that their employers required influenza vaccination as a condition of employment. Among this group, vaccination coverage was 98.1%, compared with 58.3% among those without an employer requirement (NVAC, 2013).

A national survey of acute care hospitals found that 55.6% of the hospitals surveyed had implemented an institutional requirement, but that vaccination coverage rates increased most significantly in hospitals that also enforced consequences for vaccine refusal. Consequences ranged in severity from mandatory masking to employee termination for noncompliance (NVAC, 2013).

Diagnosis and Treatment of Influenza

During the influenza season, when flu is circulating within the community, most people who get the flu will experience self-limiting symptoms. However, severe disease can occur in older adults, in those with underlying medical conditions, and in the very young.

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community (CDC, 2019, 2015PB).

Early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because certain bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, bacterial infections can occur as a complication of influenza.

The Infectious Disease Society of America states that antiviral treatment should start as soon as possible for adults and children



An interactive quiz to test your flu knowledge: http://www.cdc.gov/flu/freeresources/w

with documented or suspected influenza, irrespective of influenza vaccination history, who meet

the following criteria (Uyeki et al., 2018):

- Persons of any age who are hospitalized with influenza, regardless of duration of illness.
- Outpatients of any age with severe or progressive illness, regardless of the duration of illness.
- Outpatients with chronic medical conditions and immunocompromised patients.
- Children younger than 2 years and adults \geq 65 years.
- Pregnant women and those within 2 weeks postpartum.

Antiviral treatment should be *considered* for adults and children who are not at high risk of influenza complications, with documented or suspected influenza, irrespective of influenza vaccination history, who are

- Outpatients with up to 2 days illness onset before presentation.
- Symptomatic household contacts of persons at high risk of developing complications from influenza, especially those who are severely immunocompromised.
- Symptomatic healthcare providers of patients at high risk of developing complications from influenza, especially those who are severely immunocompromised (Uyeki et al., 2018)

Although summer influenza activity in the United States typically is low, influenza cases and outbreaks can occur during summer months. Clinicians should remain vigilant in considering influenza in the differential diagnosis of summer respiratory illnesses. Testing for seasonal influenza viruses and monitoring for novel influenza A virus infections should continue year-round (Xu et al., 2019).

Healthcare providers also are reminded to consider novel influenza virus infections in persons with influenza-like illness and swine or poultry exposure or with severe acute respiratory infection after travel to areas where avian influenza viruses have been detected. Providers should alert the local public health department if novel influenza virus infection is suspected.

Influenza should be suspected in ill travelers returning from countries with ongoing influenza activity. Suspected variant influenza infections should be referred to state public health departments for testing (Xu et al., 2019).

Annual influenza vaccination is recommended for all persons aged ≥ 6 months and remains the most effective way to prevent influenza illness. Treatment as soon as possible with influenza antiviral medications is recommended for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who require hospitalization; or who are at high risk for influenza-associated complications, including adults ≥ 65 years. Providers should not rely on less sensitive assays such as rapid antigen detection influenza diagnostic tests to inform treatment decisions. (Xu et al., 2019).

Laboratory Diagnosis

The diagnosis of influenza is usually suspected on the basis of characteristic clinical findings, particularly if influenza has been reported in the community. Virus can be isolated from throat and nasopharyngeal swabs obtained within 3 days of onset of illness. Culture is performed by inoculation of chick embryos or certain cell cultures that support viral replication. A minimum of 48 hours is required to demonstrate virus, and 1 to 2 additional days to identify the virus type. Culture is helpful in defining the etiology of local epidemics, but not in individual case management (CDC, 2019, 2015PB).

Serologic confirmation of influenza requires demonstration of a significant rise in influenza immunoglobulin G (IgG). The acute-phase specimen should be taken less than 5 days from onset, and a convalescent specimen taken 10 to 21 days (preferably 21 days) following onset. Complement fixation (CF) and hemagglutination inhibition (HI) are the serologic tests most commonly used. The key test is HI, which depends on the ability of the virus to agglutinate erythrocytes and inhibition of this process by specific antibody. Diagnosis requires at least a fourfold rise in antibody titer (CDC, 2019, 2015PB).

Rapid diagnostic testing for influenza antigen is available, but because these tests fail to detect many patients with influenza, CDC recommends antiviral treatment with **oseltamivir** or **zanamivir** as early as possible for patients with confirmed or suspected influenza who have severe, complicated, or progressive illness; who require hospitalization; or who are at greater risk for serious influenza-related complications (CDC, 2019PB).

Antiviral Agents

Influenza antiviral prescription drugs can be used to treat influenza or to prevent influenza. In the United States, five antiviral agents are licensed for preventing or treating influenza. A sixth "prodrug" (Xoflusa) was approved by the FDA on October 24, 2018:

Neuraminidase Inhibitors

- 1. Inhaled Zanamivir (trade name Relenza)
- 2. Oral oseltamivir (available as a generic version or under the trade name Tamiflu)
- 3. Intravenous Peramivir (trade name Rapivab)

Adamantanes

- 4. Amantadine
- 5. Rimantadine

Influenza virus replication inhibitor

6. Baloxavir marboxil (trade name Xofluza) (CDC, 2018h)

Antiviral agents for influenza are an adjunct to vaccine and are not a substitute for vaccine. Vaccination remains the principal means for preventing influenza-related morbidity and mortality (CDC, 2019, 2015PB).

Neuraminidase Inhibitors

Three chemically-related antiviral medications known as neuraminidase inhibitors block the viral neuraminidase enzyme and have activity against both influenza A and B viruses: oral **oseltamivir phosphate** (available as a generic version or under the trade name Tamiflu), inhaled **zanamivir** (trade name Relenza), and intravenous **peramivir** (trade name Rapivab). (CDC, 2019r).

Adamantanes (Amantadine and Rimantadine)

Amantadine and rimantadine are antiviral drugs in a class of medications known as adamantanes. These medications are active against influenza A viruses, but not influenza B viruses (CDC, 2019a).

As in recent past seasons, there continues to be high levels of resistance (>99%) to adamantanes among circulating influenza A(H3N2) and influenza A(H1N1) viruses. Therefore, amantadine and rimantadine are not recommended for antiviral treatment or chemoprophylaxis of currently circulating influenza A viruses (CDC, 2019a).

Xoflusa

The newest antiviral is oral **baloxavir marboxil** (trade name Xoflusa), which is active against both influenza A and B viruses, but has a different mechanism of action than neuraminidase inhibitors. Baloxavir is an endonuclease inhibitor that interferes with viral RNA transcription and blocks virus replication (CDC, 2019r).

Baloxavir was approved by the FDA in October of 2018. It is not recommended for pregnant women, breastfeeding mothers, outpatients with complicated or progressive illness, or hospitalized patients, because there is no information about its use in these patients (CDC, 2019a).

FDA Approved Antivirals for 2019–2020

There are four influenza antiviral medications approved by the U.S. Food and Drug Administration (FDA) for use in the United States during the (2019–2020) influenza season:

- Oseltamivir phosphate (available as a generic version or under the trade name **Tamiflu**, is available as a pill or liquid suspension. Both are FDA approved for early treatment of flu in people 14 days and older.
- Zanamivir (trade name Relenza) is a powder that is inhaled and approved for early treatment of flu in people 7 years and older. It is not recommended for people with breathing problems like asthma or COPD.
- Peramivir (trade name **Rapivab**) is given intravenously by a health care provider and approved for early treatment of flu in people 2 years and older.
- Baloxavir marboxil (trade name Xoflusa) is a pill given as a single dose by mouth that is approved for early treatment of flu in people 12 years and older (CDC, 2019r).

Duration of treatment with antiviral drugs varies depending on the antiviral drug prescribed. Oseltamivir and zanamivir are usually prescribed to be taken twice daily for 5 days, although people hospitalized with flu may need antiviral treatment for longer than 5 days. Peramivir is given one time intravenously over a period of 15 to 30 minutes. Baloxavir is given as a single oral dose (CDC, 2019a).

Infection Control and Prevention

Traditionally, influenza viruses have been thought to spread from person to person primarily through large-particle respiratory droplet transmission (eg, when an infected person coughs or sneezes near a susceptible person). Transmission via large-particle droplets requires close contact between source and recipient persons, because droplets generally travel only short distances (approximately 6 feet or less) through the air. Indirect contact transmission via hand transfer of influenza virus from virus-contaminated surfaces or objects to mucosal surfaces of the face (eg, nose, mouth) may also occur (CDC, 2018e).

Airborne transmission via small particle aerosols in the vicinity of the infectious individual may also occur; however, the relative contribution of the different modes of influenza transmission is unclear. Airborne transmission over longer distances, such as from one patient room to another, has not been documented and is thought not to occur. All respiratory secretions and bodily fluids, including diarrheal stools, of patients with influenza are considered to be potentially infectious; however, the risk may vary by strain. Detection of influenza virus in blood or stool in influenza infected patients is very uncommon (CDC, 2018e).

In Healthcare Settings

Healthcare settings include, but are not limited to, acute-care hospitals; long-term care facilities, such as nursing homes and skilled nursing facilities; physicians' offices; urgent-care centers, outpatient clinics; and home healthcare (CDC, 2018e).

Preventing transmission of influenza within a healthcare setting requires a multi-faceted approach. Spread of influenza virus can occur among patients, healthcare personnel, and visitors; in addition, healthcare personnel may acquire influenza from people in their household or community(CDC, 2018e).

Core infection prevention strategies include:

- Promote and administer seasonal influenza vaccine
- Implement respiratory hygiene and cough etiquette
- Appropriate management of ill healthcare personnel
- Adherence to infection control precautions for all patient-care activities and aerosolgenerating procedures
- Implementation of environmental and engineering infection control measures (CDC, 2018e).

Successful implementation of many, if not all, of these strategies is dependent on the presence of clear administrative policies and organizational leadership that promote and facilitate adherence to these recommendations among the various people within the healthcare setting, including patients, visitors, and healthcare personnel (CDC, 2018e).

In Long-Term Care Facilities

Long-term care facilities are institutions, such as nursing homes and skilled nursing facilities, which provide healthcare to people (including children) who are unable to manage independently in the community. This care may represent custodial or chronic care management or short-term rehabilitative services (CDC, 2019i).

Influenza can be introduced into a long-term care facility by newly admitted residents, healthcare workers, or visitors. Spread of influenza can occur between and among residents, healthcare providers, and visitors. Residents of long-term care facilities can experience severe and fatal illness during influenza outbreaks (CDC, 2019i).

As in any healthcare setting, key prevention strategies in long-term care settings include:

- 1. Annual vaccination
- 2. Testing
- **3.** Infection control
- 4. Antiviral treatment
- 5. Antiviral chemoprophylaxis (CDC, 2019i)

If possible, all residents should receive trivalent inactivated influenza vaccine (TIV) annually before influenza season. In the majority of seasons, TIV will become available to long-term care facilities beginning in September, and influenza vaccination should begin as soon as vaccine is available. Informed consent is required to implement a standing order for vaccination, but this does not necessarily mean a signed consent must be present (CDC, 2019i).

Since October 2005 the Centers for Medicare and Medicaid Services (CMS) has required nursing homes participating in Medicare and Medicaid programs to offer all residents influenza and pneumococcal vaccines and to document the results. Each resident is to be vaccinated unless contraindicated medically, the resident or legal representative refuses vaccination, or the vaccine is not available (CDC, 2019).

Even if it is not influenza season, influenza testing should occur when any resident of a long-term care facility has signs and symptoms that could be due to influenza, and especially when two residents or more develop respiratory illness within 72 hours of each other. Because of the high risk of morbidity and mortality in older adults, daily active surveillance is recommended for respiratory illness among ill residents, healthcare personnel, and visitors to the facility (CDC, 2019i).

If influenza is already present in a long-term care facility, residents who are symptomatic should stay in their own rooms as much as possible. They should be restricted from participation in common activities and should have meals served in their rooms. If an outbreak is widespread, large-group activities should be limited and *all* meals should be offered in resident rooms. New admissions or transfers to wards with symptomatic residents should be avoided (CDC, 2019i).

A posted notice should alert visitors to the presence of influenza in a facility. The spread of influenza can be reduced by restricting visitation and excluding ill people from visiting the facility during an outbreak. During community outbreaks of influenza, children should also be restricted from visiting residents (CDC, 2019i).

Healthcare personnel with respiratory symptoms should be monitored and those with influenzalike symptoms should stay home until at least 24 hours after they no longer have a fever (CDC, 2019i).

Influenza Prevention Recommendations for Long-Term Care Facilities

- Residents with signs and symptoms of influenza-like illness should be tested for influenza.
- Residents being tested for other respiratory pathogens during non-influenza season periods should also be tested for influenza.
- Facilities should implement daily active surveillance for respiratory illness among ill residents, healthcare personnel, and visitors to the facility.
- Standard and Droplet Precautions should be used for all residents with suspected or confirmed influenza.
- Influenza antiviral treatment and chemoprophylaxis should be administered to residents and healthcare personnel according to current recommendations. Treatment should not wait for laboratory confirmation of influenza.
- Residents in the entire long-term care facility (not just currently impacted wards) should receive antiviral chemoprophylaxis as soon as an influenza outbreak is determined.
- Antiviral chemoprophylaxis can be considered or offered to unvaccinated personnel who provide care to people at high risk of complications.
- Drug-resistant viruses are a possibility and should be considered. (CDC, 2017)

Healthcare personnel who get vaccinated help to reduce the following:

- Transmission of influenza (to patients as well as their own family)
- Staff illness and absenteeism
- Influenza-related illness and death, especially among people at increased risk for severe influenza illness

(CDC, 2019i)

Influenza outbreaks in hospitals and long-term care facilities have been attributed to low influenza vaccination coverage among healthcare personnel. Higher vaccination levels among healthcare personnel have been associated with a lower risk of healthcare facility-associated influenza cases (CDC, 2019i).

Current ACIP Influenza Recommendations

To access the current (2019–2020) ACIP influenza recommendations please see:

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices, United States, 2019–2020 Influenza Season

Source: https://www.cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm.

Influenza Vaccines

A **vaccine** is a substance (an antigen) made from a virus or bacterium that triggers the body's immune system to develop antibodies. Substances are sometimes added to a vaccine to generate a stronger immune response so that less vaccine is needed for the body to recognize and fight the antigen. Influenza vaccines cause antibodies to develop about 2 weeks after vaccination.

Influenza vaccines are available in an inactivated form (IIV) and a live attenuated form (LAIV). Inactivated influenza vaccines have been available since the 1940s and have traditionally been administered intramuscularly or intradermally. Live attenuated vaccine was approved for use in the United States in 2003. Live attenuated influenza vaccines contain a version of the living microbe that has been weakened in the lab so it cannot cause disease.

Inactivated vaccines are produced by killing the disease-causing microbe in a virus or bacteria with chemicals, heat, or radiation. Inactivated vaccines are more stable and safer than live vaccines because the dead microbes cannot mutate back to their disease-causing state. However, most inactivated vaccines stimulate a weaker immune system response than do live vaccines (NAIAD, 2019b).





Influenza Vaccine Key Points		
Inactivated influenza vaccine (IIV)	Trivalent, quadrivalentAvailable since the 1940sIntramuscular or intradermal	
Live attenuated vaccine (LAIV)	QuadrivalentIntranasal	

Influenza Vaccine Production Technologies

In late February to early March—well before the new flu season begins—an FDA advisory committee reviews data about which flu viruses have caused disease in the past year, how the viruses are changing, and disease trends, so they can recommend the three or four flu strains to include in the trivalent and quadrivalent influenza vaccines for the United States in the upcoming flu season (FDA, 2019a). There are three different influenza vaccine production technologies approved by the FDA:

- Egg-based flu vaccine
- Cell-based flu vaccine
- Recombinant flu vaccine (2018c)

The most common way that flu vaccines are made is using an *egg-based* manufacturing process that has been used for more than 70 years. Egg-based vaccine manufacturing is used to make both inactivated (killed) vaccine used in the flu shot and live attenuated (weakened) vaccine used in the nasal spray flu vaccine (NIAID, 2019a).

Cell-based production of flu vaccines was approved by the FDA in 2012. Until recently, this production process began with egg-grown CVVs (candidate vaccine viruses). However, on August 31, 2016, the FDA issued an approval for **Seqirus**, the sole FDA-approved cell-based flu vaccine manufacturer in the United States, to use CVVs that are grown in animal cells. Cell culture technology has the potential for a faster start-up of the flu vaccine manufacturing process (NIAID, 2019b).

Recombinant technology for flu vaccines was approved for the U.S. market in 2013. It does not require an egg-grown vaccine virus and can be produced in a shorter amount of time than either egg-grown or cell-grown vaccine viruses.

Manufacturers using recombinant technology isolate a certain gene (the hemagglutinin or HA gene) from a naturally occurring (wild type) recommended vaccine virus. This HA gene is combined with portions of another virus that grows well in insect cells. It is then mixed with insect cells and allowed to replicate. The flu HA protein is then harvested from these cells and purified. Currently, recombinant flu vaccine is the only 100% egg-free vaccine on the U.S. market (CDC, 2018c).

The only influenza vaccine produced using recombinant technology is **Flublok Quadrivalent**. It has been licensed by the FDA for use in adults 18 years and older (CDC, 2018).

Trivalent Inactivated Vaccines (IIV3)

For years, flu vaccines were designed to protect against three different flu viruses (trivalent vaccines). Standard dose trivalent vaccines include an influenza A (H1N1) virus, an influenza A (H3N2) virus and one influenza B virus. Because there are two distinct lineages of influenza B viruses—Victoria and Yamagata—immunization against a single influenza B virus provides only limited cross protection against strains in the other lineage.

The standard dose trivalent shot (IIV3), is manufactured using virus grown in eggs. This shot (Afluria) can be given either with a needle (for people aged 5 years and older) or with a jet injector (or people aged 18 through 64 years only) (CDC, 2019p).

A three-component (trivalent) inactivated flu vaccine called Fluzone High-Dose is licensed specifically for people 65 years and older. Fluzone High-Dose contains four times the antigen of standard-dose inactivated influenza vaccines. The higher dose of antigen in the vaccine is intended to give older people a better immune response, and therefore, better protection against flu (CDC, 2019e).

The high-dose vaccine has been approved for use in the United States since 2009. Results of a clinical trial of more than 30,000 participants showed that adults 65 years and older who received the high-dose vaccine had 24% fewer influenza infections compared to those who received the standard dose flu vaccine (CDC, 2019m).

Fluzone

Fluzone, Fluzone High-Dose, Fluzone Intradermal Quadrivalent, and Fluzone Quadrivalent are all injectable vaccines. The intradermal flu vaccine is a shot that is injected into the skin instead of the muscle. The intradermal shot uses a much smaller needle than the regular flu shot, and it requires less antigen to be as effective as the regular flu shot. It may be used in adults 18 to 64 years of age.

Source: FDA, 2019b.

A trivalent flu shot made with adjuvant (**Fluad**) is approved for people 65 years and older. An adjuvant is an ingredient added to a vaccine to create a stronger immune response. The vaccine, FLUAD (allV3), was licensed in November 2015 and became available during the 2016–2017 flu season. It contains MF59 adjuvant, an oil-in-water emulsion of squalene oil. FLUAD is the first seasonal flu vaccine with adjuvant marketed in the United States. Squalene, a naturally occurring substance found in humans, animals, and plants, is highly purified for the vaccine manufacturing process (CDC, 2019b).

Quadrivalent Vaccines

The quadrivalent flu vaccine is designed to protect against four different flu viruses: two influenza A viruses and two influenza B viruses. Adding another B virus to the vaccine aims to give broader protection against circulating flu viruses (CDC, 2019n).

Standard-dose quadrivalent flu shots are manufactured using virus grown in eggs. These include Afluria Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, and Fluzone Quadrivalent. Different flu shots are approved for different age groups. There is a quadrivalent flu shot that can be given to children as young as 6 months of age. Other quadrivalent flu shots are approved for people 3 years and older (CDC, 2019n).

Most flu shots are given in the arm muscle with a needle. One quadrivalent flu shot (Afluria Quadrivalent) can be given either with a needle (for people aged 5 years and older) or with a jet injector (for people aged 18 through 64 years only) (CDC, 2019b).

A quadrivalent cell-based flu shot (Flucelvax Quadrivalent) containing virus grown in cell culture, is approved for people 4 years and older. A recombinant quadrivalent flu shot (Flublok Quadrivalent) is approved for people 18 years and older (CDC, 2019).

For more information on approved flu vaccines for the 2019–2020 flu season, as well as age indications for each vaccine, please see CDC's Table, *U.S. Influenza Vaccine Products for the 2019–2020) Season.*

https://www.cdc.gov/flu/professionals/vaccines.htm

2018 Flublok Recombinant Influenza Vaccine (RIV4)

In 2013 the U.S. Food and Drug Administration (FDA) announced its approval of Flublok, a trivalent inactivated influenza vaccine for the prevention of seasonal influenza in people 18 years and older. Flublok's manufacturing process has the potential for faster startup of vaccine manufacturing, which can be useful in the event of a pandemic or vaccine supply shortage, mainly because it is not dependent on an egg supply or limited by the selection of vaccine viruses that are adapted for growth in eggs. Also, this vaccine is suitable for vaccinating people with egg allergies because it is not made using eggs.

Flublok Quadrivalent (RIV4) is available for the 2019–2020 influenza season. RIV4 is indicated for persons aged \geq 18 years. RIV4 is manufactured without the use of influenza viruses; therefore, similarly to IIVs, no shedding of vaccine virus will occur. RIV4 is produced without the use of eggs, and thus is egg-free. No preference is expressed for RIV4 versus IIVs within specified indications. RIV4 is administered by intramuscular injection (Grohskopf et al., 2018), CDC, 2019o).

Live Attenuated Influenza Vaccine (LAIV)

Live attenuated influenza vaccine (LAIV) was approved for use in the United States in 2003. LAIV contains the same influenza viruses as inactivated influenza vaccines. It does not contain thimerosal or any other preservative.

LAIV is provided in a single-dose sprayer unit; half of the dose is sprayed into each nostril. The nasal spray flu vaccine contains attenuated (weakened) live viruses that will not cause influenza illness. The weakened viruses are cold-adapted, which means they are designed to only multiply at the cooler temperatures found within the nose. The viruses cannot infect the lungs or other areas where warmer temperatures exist.

During previous flu seasons (2016–2017 and 2017–2018), the Advisory Committee on Immunization Practices (ACIP) recommended that LAIV4 **not** be used because of concerns about low effectiveness against influenza A(H1N1)pdm09-like viruses circulating in the United States during the 2013–2014 and 2015–2016 seasons (Grohskopf et al., 2018).

For the 2019–2020 flu season, ACIP recommends any influenza vaccine that is appropriate for the recipient's age and health status, including inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live attenuated nasal spray influenza vaccine (LAIV4), with no preference expressed for any one vaccine over another (CDC, 2019l).

The nasal spray is approved for use in non-pregnant individuals, 2 years through 49 years of age. People with some medical conditions should not receive the nasal spray flu vaccine (CDC, 2019I). For more information, click here.

Immunity

Immunity following administration of inactivated influenza vaccine is less than 1 year, due to waning of vaccine-induced antibodies and antigenic drift of circulating influenza viruses. Influenza vaccine efficacy varies by the similarity of the vaccine strain to circulating strains and the age and health of the recipient.

CDC conducts studies each year to determine how well the influenza vaccine protects against flu illness. While vaccine effectiveness (VE) can vary, recent studies show that flu vaccination reduces the risk of flu illness by between 40% and 60% among the overall population during seasons when most circulating flu viruses are well-matched to the flu vaccine. In general, current flu vaccines tend to work better against influenza B and influenza A(H1N1) viruses and offer lower protection against influenza A(H3N2) viruses (CDC, 2018f).

Antibody against one influenza virus type or subtype confers limited or no protection against another type or subtype. Frequent emergence of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and necessitates consideration for adjustment of vaccine viruses each season (Grohskopf et al., 2018).

Pregnant Women and Neonates

Both ACIP and the American College of Obstetricians and Gynecologists (ACOG) recommend that women who are or will be pregnant during influenza season receive an *inactivated* influenza vaccine as soon as it is available. Because pregnant women are at high risk of serious flu complications, **CDC recommends influenza vaccination during any trimester of pregnancy** (CDC, 2019c).

Influenza is more likely to cause severe illness in pregnant women than in women who are not pregnant, particularly during the second and third trimesters. Changes in the immune system, heart, and lungs during pregnancy make pregnant women (and women up to 2 weeks postpartum) more prone to severe illness from flu, including illness resulting in hospitalization. Flu also may be harmful for a pregnant woman's developing baby. A common flu symptom is fever, which may be associated with neural tube defects and other adverse outcomes for a developing baby (CDC, 2019c).

Numerous studies have shown that flu vaccination protects pregnant women during and after pregnancy and also protects babies from flu infection for several months after birth, before the child is old enough to be vaccinated (the mother passes antibodies on to the developing baby during her pregnancy) (CDC, 2019c).

Millions of flu vaccines have been given for decades, including to pregnant women. Numerous studies, including clinical trials and observational studies, and data from vaccine safety monitoring systems have demonstrated consistently the safety of influenza vaccination during pregnancy (CDC, 2019c).

Immunocompromised People

Immunocompromised states include a wide range of conditions. ACIP recommends that LAIV4 **not** be used for immunocompromised persons because of the uncertain but biologically plausible risk for disease attributable to the vaccine virus. In addition to potential safety issues, immune response to live or inactivated vaccines might be blunted in some clinical situations, such as for persons with congenital immune deficiencies, persons receiving cancer chemotherapy, and persons receiving immunosuppressive medications (Grohskopf et al., 2019).

The Infectious Diseases Society of America (IDSA) has published guidance for the selection and timing of vaccines for persons with specific immunocompromising conditions, including congenital immune disorders, stem cell and solid organ transplant, anatomic and functional asplenia, and therapeutic drug-induced immunosuppression, as well as for persons with cochlear implants or other conditions leading to persistent cerebrospinal fluid-oropharyngeal communication. Given the lack of safety data for LAIV in most of these populations, and the availability of alternative vaccines, IIV or RIV4 should be used instead of LAIV for these persons (Grohskopf et al., 2019).

High-Risk Households

Efforts should be made to vaccinate household and other close contacts of high-risk people. These include healthcare personnel, employees of long-term care facilities, and household contacts of high-risk people. These individuals may be younger and healthier and more likely to be protected from illness than are older adults. All healthcare providers should receive annual inactivated influenza vaccine (CDC, 2019, 2015PB).

Groups to be targeted include physicians, nurses, and other personnel in hospitals and outpatient settings who have contact with high-risk patients in all age groups, and providers of home care to high-risk people (CDC, 2019, 2015PB).

Older Adults

Because of the vulnerability of older adults to severe influenza illness, hospitalization, and death, efficacy and effectiveness of influenza vaccines among older adults is an area of active research. Recent comparative studies of vaccine efficacy/effectiveness against laboratory-confirmed influenza outcomes among older adults have focused on HD-IIV3 (Fluzone High-Dose), RIV4 (Flublok Quadrivalent), and aIIV3 (Fluad). Each of these three vaccines has been studied in comparison to a standard dose, unadjuvanted IIV (Grohskopf et al., 2019).

Although HD-IIV3 has been the most extensively studied, and evidence has accumulated for its superior efficacy and effectiveness compared with SD-IIV3 in this population, no preference is expressed for any one vaccine type. Vaccination should not be delayed if a specific product is not readily available. For persons aged \geq 65 years, any age-appropriate IIV formulation (standard-dose or high-dose, trivalent or quadrivalent, unadjuvanted or adjuvanted) or RIV4 are acceptable options (Grohskopf et al., 2019).

Makeup of 2019–2020 Influenza Vaccines

Each year, experts from CDC, World Health Organization (WHO), and other institutions study virus samples collected from around the world to identify the influenza viruses that are the most likely to cause illness during the upcoming flu season. This information is used to create a vaccine.

Because flu viruses are constantly changing, it is not possible to predict with certainty which types of viruses will predominate during a given season. Flu viruses can change from one season to the next and can even change within the course of one flu season. Experts must pick which viruses to include in the vaccine many months in advance in order for vaccine to be produced and delivered on time. Because of these factors, there is always the possibility of a less-than-optimal match between circulating viruses and the viruses in the vaccine.

The 2019–2020 U.S. trivalent influenza vaccines contain the following:

- an A/Brisbane/02/2018 (H1N1)-like virus
- an A/Kansas/14/2017 (H3N2)-like virus and
- a B/Colorado/06/2017-like virus (Victoria lineage). (Grohskopf et al., 2019)

The 2019–2020) U.S. quadrivalent vaccines contain the same three antigens listed above and an additional influenza B virus component, a B/Phuket/3073/2013–like virus (Yamagata lineage). Compared with the 2018–2019 season, the composition for 2019–2020 includes updates in the influenza A(H1N1) and influenza A(H3N2) components of the vaccine (Grohskopf et al., 2019).

For the 2019–2020 season, routine annual influenza vaccination of all people aged \geq 6 months without contraindications continues to be recommended. A licensed, recommended, and age-appropriate vaccine should be used (Grohskopf et al., 2019).

Two recent regulatory actions have been made for the 2019–2020 season:

In October 2018, the FDA approved an expanded age indication for Afluria Quadrivalent (IIV4). Previously licensed for persons aged ≥5 years, Afluria Quadrivalent (IIV4) is now licensed for persons aged ≥6 months. The dose volume is 0.25 mL per dose for children aged 6 through 35 months and 0.5 mL per dose for all persons aged ≥36 months (≥3 years) (Grohskopf et al., 2019).

Only Afluria Quadrivalent is expected to be available for the 2019–2020 season. The dosage is age dependent: the dose volume for children aged 6 through 35 months is 0.25 mL per dose and the dose volume for all persons aged \geq 36 months (\geq 3 years) is 0.5 mL per dose (Grohskopf et al., 2019).

In January 2019, the FDA approved a change in dose volume for Fluzone Quadrivalent (IIV4) from 0.25 mL to either 0.25 mL or 0.5 mL per dose for children aged 6 through 35 months. Children aged ≥36 months (≥3 years) and adults should receive 0.5 mL per dose (Grohskopf et al., 2019).

A quadrivalent live attenuated influenza nasal spray vaccine (LAIV4) made with attenuated (weakened) live flu viruses, is approved for use in people 2 years through 49 years of age. This vaccine is not recommended for use in pregnancy or for people with some specific medical conditions (CDC, 2019b).

For the 2019–2020 flu season, ACIP recommends annual influenza vaccination for everyone 6 months and older with any licensed, influenza vaccine that is appropriate for the recipient's age and health status, including inactivated influenza vaccine (IIV), recombinant influenza vaccine (RIV), or live attenuated nasal spray influenza vaccine (LAIV4), with no preference expressed for any one vaccine over another (CDC, 2019b).

People with egg allergies can receive any licensed, recommended, age-appropriate influenza vaccine (IIV, RIV4, or LAIV4) that is otherwise appropriate. People who have a history of severe egg allergy (those who have had any symptom other than hives after exposure to egg) should be vaccinated in a medical setting, and supervised by a healthcare provider who is able to recognize and manage severe allergic reactions (CDC, 2019b).

Balancing considerations regarding the unpredictability of timing of onset of the influenza season and concerns that vaccine-induced immunity might wane over the course of a season, it is recommended that vaccination should be offered by the end of October. Children aged 6 months through 8 years who require 2 doses should receive their first dose as soon as possible after vaccine becomes available, to allow the second dose (which must be administered \geq 4 weeks later) to be received by the end of October (Grohskopf et al., 2019).

Community vaccination programs, however, should balance maximizing likelihood of persistence of vaccine-induced protection through the season with avoiding missed opportunities to vaccinate or vaccinating after onset of influenza circulation occurs. No recommendation is made for revaccination later in the season of persons who have already been fully vaccinated (ie, providing a booster dose) (Grohskopf et al., 2019).

For a table of approved influenza vaccines for the 2019–2020 season, click here.

Giving an Influenza Vaccination via Needle



Source: United States Navy. Public domain.

Concluding Remarks

Influenza has been with us for a long time. More people died from influenza during the 1918–1919 influenza pandemic than died during World War I. Like all viruses, influenza is very good at finding ways to mutate and bypass our immune system defenses. We have been able to stay a step ahead by developing vaccines that stimulate our immune system to fight off these potentially deadly viruses.

Periodically however, influenza outsmarts us by mutating or shifting into a virus that our immune systems fail to recognize. When this happens, influenza pandemics can occur, as happened in 1918 with disastrous results. Although public health officials are rightly concerned about pandemics, seasonal influenza kills many thousands of people every year and many of these deaths can be prevented by getting a flu vaccination.

In past years CDC has emphasized the importance of increasing vaccination rates among high-risk groups, working toward a goal of universal vaccination. To that end, in 2010, in an attempt to simplify vaccination recommendations and increase vaccination rates, CDC issued guidelines stating all individuals aged 6 months or older should be vaccinated annually. This universal vaccination guideline reflects lessons learned from the 2009 H1N1 pandemic.

Despite these strong recommendations, more than half of the general public and about 25% of healthcare workers fail to get vaccinated against flu each year. The situation is particularly dire in long-term care settings, where some of our most vulnerable citizens are exposed to influenza by unvaccinated workers, visitors, and residents. Getting vaccinated each year protects high-risk populations from catching the flu from the people who are supposed to be helping and protecting them.

Vaccination is available in a live-attenuated (LAIV) and an inactivated (IIV) form. Knowing which one works best for you and your patients is important. The makeup of this year's influenza vaccine is based on information about which influenza viruses are circulating, how they are spreading, and how well the previous season's vaccine viruses protected against any that are being newly identified.

VE (vaccine effectiveness) data collected from children and adults enrolled in the U.S. Influenza Vaccine Effectiveness Network from Nov. 23, 2018 through Feb. 2, 2019 indicate that the flu vaccine reduced the risk of acute respiratory virus infection (ARI) by 46% (CDC, 2019h).

Children ages 6 months to 17 years who were vaccinated against flu last season reduced their risk of contracting influenza A(H1N1) illness by more than 62% and their risk for illness from all influenza types by 61%. For all ages, the CDC said VE against influenza caused by A(H1N1) virus infection was 46%, and VE against illness due to influenza A(H3N2) was 44% (CDC, 2019h).

For the 2019–2020 U.S. influenza season, providers may choose to administer any licensed, ageappropriate influenza vaccine (IIV, recombinant influenza vaccine, or LAIV4). LAIV4 is an option for those for whom it is otherwise appropriate. No preference is expressed for any influenza vaccine product (Grohskopf et al., 2019).

Vaccination should be offered as long as influenza viruses are circulating. To avoid missed opportunities for vaccination, providers should offer vaccination during routine healthcare visits and hospitalizations when vaccine is available.

Getting an annual influenza vaccine provides the best protection against influenza for virtually everyone.

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Post Test

Use the answer sheet following the test to record your answers.

- 1. Although the H1N1 influenza pandemic of 2009 has been declared officially over:
 - a. Public health officials are not concerned about another influenza outbreak
 - b. The H1N1 virus is expected to continue to circulate for many years
 - c. There is still no vaccine against this strain of influenza

d. So many people were infected by the H1N1 virus that it likely conferred herd immunity to the entire population

- 2. An antigen is:
 - a. The place where a pathogen lives and survives
 - b. A substance or microorganism that stimulates production of an antibody

c. A protective protein produced by the immune system in response to the presence of a foreign substance.

d. A type of antiviral drug approved for preventing or treating influenza

- 3. The primary natural reservoir of influenza type A viruses is:
 - a. Pigs
 - b. Humans and monkeys
 - c. Reptiles
 - d. Wild birds

4. Influenza type A viruses from birds, humans, and other pigs can circulate in pigs. This is important because:

- a. Humans can become infected with influenza by eating pork
- b. Wild pigs can transmit these viruses to wild birds
- c. It is possible for the genes of these viruses to mix (reassort) and create a new virus
- d. Mosquitoes that have bitten a pig can transmit these viruses to humans
- 5. Compared to influenza caused by type A viruses, type B influenza viruses:
 - a. Are found only in pigs
 - b. Are rarely reported in humans
 - c. Are the cause of most historical influenza pandemics
 - d. Cause milder disease than type A

6. Antigenic drift, continuous small changes in one or more surface antigens of the influenza A virus:

- a. Causes such gradual change in the virus that it is unrelated to major outbreaks of influenza
- b. May cause widespread infection because protection from past exposures is incomplete

c. Occurs because of the overuse of antibiotics, resulting in antibiotic-resistant strains of the virus

d. Happens because of mutations in immune system of the affected person

7. Antigenic shift, a major and abrupt change in influenza A viruses:

- a. Can lead to a worldwide pandemic
- b. Occurs regularly, making it relatively easy to adjust vaccines
- c. Only occurs every few centuries and has caused pandemics every time it has happened
- d. Has not occurred in the past hundred years.

8. Pandemic influenza:

a. Generally occurs each year during a specific time of the year

b. Results from the emergence of a novel bacterium to which the population possesses little or no immunity

c. Results from the emergence of a new influenza A virus to which the population possesses little or no immunity

- d. Occurred regularly in ancient times but has not occurred in modern times
- 9. The 1918 influenza pandemic, caused by an H1N1 influenza subtype:
 - a. Killed more people in 1 year than died in 4 years from the bubonic plague
 - b. Was particularly virulent in North America but caused only mild illness in Europe
 - c. Caused more deaths in hot climates and countries closer to the equator
 - d. Was contained effectively with prevention efforts such as hand hygiene and masking
- 10. Seasonal influenza differs from pandemic influenza in that:
 - a. The length of the season is unpredictable
 - b. It generally causes more illness than pandemic influenza
 - c. It spreads rapidly because there is little or no immunity to a new strain
 - d. It occurs each year, typically during a specific time of the year
- 11. The "classic" clinical symptoms of influenza:
 - a. Typically last for at least 1 to 2 months.
 - b. Include abrupt onset of fever, myalgia, sore throat, cough, and headache.

- c. Can be treated with antibiotics in infants, children, and teenagers
- d. Occur more often in adults than in children
- 12. The most frequent influenza complication is:
 - a. Meningitis that may occur up to 2 weeks after initial symptoms
 - b. Pneumonia, especially secondary bacterial pneumonia
 - c. Reye syndrome, especially in older adults taking aspirin
 - d. Myocarditis, especially in people with severe asthma
- 13. Transmission of influenza in humans:
 - a. Occurs from chronic carriers of the disease who don't know they are infected
 - b. Is primarily through the blood of an infected person
 - c. Can be through contact with fecal material of individuals who have symptomatic diarrhea

d. Occurs primarily person to person via large virus-laden droplets generated by cough or sneeze4

- 14. Although influenza vaccination rates are fairly high in young children:
 - a. Vaccination rates decrease with increasing age
 - b. Vaccination rates increase with increasing age
 - c. Vaccination rates are close to 100% in children aged 13 to 17 years
 - d. After 2 to 4 years, influenza vaccination is no longer needed

15. In long-term care facilities, one of the reasons that influenza vaccination rates are so low is that:

a. The CDC has failed to set realistic goals for vaccination

b. A high percentage of staff in long-term care are allergic to the egg products found in the influenza vaccine

c. Staff turnover is high, meaning workers and managers may not be familiar with existing vaccination policies

d. Increasing influenza vaccination rates has no effect on flu rates among residents.

- 16. Which work setting has the lowest vaccination rate among its healthcare employees:
 - a. Hospitals
 - b. University-based healthcare clinics
 - c. Physician's offices
 - d. Long-term care facilities

17. Among healthcare workers, the most common reason for not getting an influenza vaccine is:

- a. I may get sick from the vaccine
- b. I don't want a vaccination
- c. I'm protected by herd immunity
- d. I don't need a flu vaccination

18. Among the American public, vaccination rates are below the goals set by the CDC. The most common reasons given are:

- a. Lack of health insurance
- b. Belief that herd immunity will protect them from infection
- c. Fear of side effects and doubts about vaccine efficacy
- d. Belief that one influenza shot lasts for several years

19. Among healthcare providers, the most common reason for receiving an influenza vaccination is:

- a. To protect myself from the flu
- b. I want to protect my patients from getting the flu from me
- c. I want to protect my friends and family from getting the flu
- d. The flu vaccine was offered free of charge at my work

20. During flu season, you should consider that influenza may be present in infants and young children, regardless of vaccination status:

- a. If they are accompanied by an adult with respiratory symptoms
- b. Whether they have a fever or not
- c. If they have become chilled for any reason
- d. If they have a fever and no other signs or symptoms
- 21. Antiviral agents for influenza:
 - a. Were first used against the 2009 H1N1 influenza
 - b. May be used freely, as there are no problems with resistant viral strains
 - c. Are an adjunct to vaccine but not a substitute for vaccine
 - d. Are quickly replacing vaccines as the primary means to combat influenza
- 22. The influenza antiviral agents zanamivir and oseltamivir:
 - a. May be used instead of antibiotics for treatment of influenza
 - b. Have been shown to prevent influenza
 - c. Are not recommended because of documented resistance in isolates
 - d. Are active against influenza types A and B

23. Preventing the spread of flu in long-term care settings is a public health priority. Important prevention approaches include:

- a. Family education, isolation, and vaccination
- b. Classes on influenza, facemasks, and infection control
- c. Breathing treatments, hand hygiene, and antiviral prophylaxis
- d. Vaccination, testing, and infection control

24. Vaccines are:

a. Medicines that are used to treat infections caused by bacteria

b. Substances (an antigen) made from a virus or bacterium that trigger the body's immune system to develop antibodies

c. Genetically engineered proteins derived from human genes

d. The therapeutic delivery of nucleic acid polymers into a patient's cells as a drug to treat disease

25. Fluzone high-dose trivalent IIV (inactivated influenza vaccine), licensed specifically for people 65 years and older:

- a. Contains four times the antigen of standard-dose inactivated influenza vaccines
- b. Is also licensed for infants under the age of 6 months.
- c. Is not as effective as the trivalent vaccine
- d. Is really a quadrivalent vaccine because it is four times stronger that a trivalent vaccine

26. According to the CDC, during the 2019-2020 flu season, LAIV influenza vaccine:

- a. Must be followed up with two more vaccinations over two months
- b. Must be given only intramuscularly or subcutaneously
- c. Is an option for vaccination of persons for whom it is appropriate for the 2019-2020 season
- d. Is approved for administration to healthy, pregnant women.
- 27. Immunity following inactivated influenza vaccination (IIV) is less than 1 year because:
 - a. The pharmaceutical companies weaken the vaccine to ensure sales of vaccine each year
 - b. The immune system produces less vaccine-induced antibodies over time
 - c. Circulating influenza viruses change dramatically from year to year.
 - d. The amount of antigen in the vaccine is too low to last for very long
- 28. Older adults:
 - a. Should avoid getting the flu vaccine because it may cause them to get the flu
 - b. Should only receive a nasal vaccine to avoid urticaria

- c. Can be given any age-appropriate IIV formulation
- d. Are at significantly lower risk for contracting the flu than adults aged 18 to 49

29. For the 2019-2020 flu season:

a. It is recommended that flu vaccination wait until February 2018, which is the month of highest flu reports

b. The LAIV4 flu vaccine is not recommended by CDC

c. Routine annual flu vaccination of all people aged ≥ 6 months without contraindications continues to be recommended.

d. Routine annual flu vaccination is not recommended for people over the age of 65

Answer Sheet

Flu 2020

Name (Please print your name):

Date:

Passing score is 80%

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Course Evaluation

Please use this scale for your course evaluation. Items with asterisks * are required.

- 5 = Strongly agree
- 4 = Agree
- 3 = Neutral
- 2 = Disagree
- 1 = Strongly disagree

* Upon completion of the course, I was able to:

a. Describe the annual global incidence of seasonal flu worldwide.

 $\bigcirc 5 \bigcirc 4 \bigcirc 3 \oslash 2 \oslash 1$

b. State 2 characteristics each of influenza A, B, and C.

 $\bigcirc 5 \bigcirc 4 \oslash 3 \oslash 2 \oslash 1$

c. Define antigenic drift and antigenic shift.

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d. Describe 3 characteristics of pandemic influenza.

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e. Identify the 5 "classic" clinical features of seasonal influenza.

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- f. State the vaccination rate goal for healthcare providers under Healthy People 2020.
 5 4 3 2 1
- g. Describe 3 reasons why healthcare providers refuse or fail to receive a seasonal influenza vaccination.

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h. Summarize the purpose of antiviral medications in the treatment of flu.

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i. State the 5 key influenza prevention strategies that should be practiced in all long-term care settings.

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j. Describe the 4 types of trivalent inactivated influenza vaccine that are approved for the 2019– 2020 season.

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k. Explain the makeup of the 2019–2020 influenza vaccine.

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* The author(s) are knowledgeable about the subject matter.

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* The author(s) cited evidence that supported the material presented.

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* This course contained no discriminatory or prejudicial language.

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○ Yes ○ No
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* The course was free of commercial bias and product promotion.

○ Yes ○ No

* As a result of what you have learned, do you intend to make any changes in your practice?

○ Yes ○ No

If you answered Yes above, what changes do you intend to make? If you answered No, please explain why.

* Do you intend to return to ATrain for your ongoing CE needs?

 \odot Yes, within the next 30 days.

- Yes, during my next renewal cycle.
- Maybe, not sure.
- No, I only needed this one course.

* Would you recommend ATrain Education to a friend, co-worker, or colleague?

• Yes, definitely.

Possibly.

No, not at this time.

* What is your overall satsfaction with this learning activity?

 $\bigcirc 5 \bigcirc 4 \bigcirc 3 \bigcirc 2 \bigcirc 1$

* Navigating the ATrain Education website was:

- Easy.
- Somewhat easy.
- Not at all easy.

* How long did it take you to complete this course, posttest, and course evaluation?

- 60 minutes (or more) per contact hour
- 50-59 minutes per contact hour
- 0 40-49 minutes per contact hour
- 30-39 minutes per contact hour
- Less than 30 minutes per contact hour

I heard about ATrain Education from:

- Government or Department of Health website.
- State board or professional association.
- \odot Searching the Internet.
- \bigcirc A friend.
- An advertisement.
- I am a returning customer.
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- Other
- Social Media (FB, Twitter, LinkedIn, etc)

Please let us know your age group to help us meet your professional needs.

- 18 to 30
- 31 to 45
- 0 46+

I completed this course on:

- My own or a friend's computer.
- A computer at work.
- A library computer.
- A tablet.
- A cellphone.
- A paper copy of the course.

Please enter your comments or suggestions here:

Registration Form

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* Professional Credentials/Designations:		
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🛛 Yes 🛛 No

(If you request an email certificate we will not send a copy of the certificate by US Mail.)

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