16

Pandemic Influenza

OBJECTIVES

- Differentiate between seasonal and pandemic influenza.
- Identify proteins that change during genetic mutation of influenza viruses.
- Describe pharmaceutical options available to prevent influenza or reduce severity of disease.
- List the World Health Organization (WHO) phases of pandemic response.
- Explain the difference between the WHO pandemic phases and the US pandemic intervals.
- Describe how an outbreak peak curve can be compressed and what benefits are derived from compressing it.
- List what individuals can do to reduce the risk of influenza.
- Define nonpharmaceutical interventions and give examples.
- Summarize the types of activities local public health agencies should consider for each of the US pandemic intervals.
- Describe the limitations of a government response to a pandemic.

Introduction: The 1918 Influenza Pandemic and the Wickstrom Family

They were a young, adventurous, and hardworking couple with big plans ahead. Simon Wickstrom was 21 years old when he married Selma who was just 16. Simon had emigrated from Sweden to Minnesota, and in 1898 he built a farmhouse there for his new bride, not long before Selma gave birth to their first child, Ella. She was just 17 when their first child arrived. Many more children followed. Seven more arrived in the coming years, including Ralph, Lester, Carrie, Ted, Florence, Elmer, and Alvin (Fig. 16-1). It was a hard life filled with long days of difficult work. As their family grew, Selma had her older children, Ella and Ralph, to help with the chores.

November 1918 should have been a time for joyful celebration for families like the Wickstroms. The holidays were approaching and with the signing of the armistice ending World War I, peace was on the horizon. Though the “Great War” was ending, a new battle was emerging. It would eventually kill far more people than any war in history. The influenza pandemic of 1918–1919 became the worst influenza outbreak in modern history, infecting about one-third of the global population (Burnet and Clark, 1942; Frost, 1920). The case–fatality rate for most influenza pandemics is generally less than 0.1%. However, the 1918 influenza strain had case–fatality rates estimated to be greater than 2.5% (Marks and Beatty, 1976; Rosenau and Last, 1980). As a result, the global death estimates from this pandemic are about 50 million (Johnson and Mueller, 2002).

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FIGURE 16-1 Simon and Selma Wickstrom family (CDC, 2006a).

The influenza pandemic reached across every continent and caused devastating illnesses even in the most remote regions. The Wickstrom family of rural Minnesota was no exception. The infection swept through the family, sickening the parents and all eight children. Those who were less ill cared for the others. The eldest daughter, 19-year-old Ella, took care of her father and the other children, while her mother Selma and one of her brothers maintained the farm. In late November, 13-year-old Lester died, followed 5 days later by his 40-year-old father, Simon. The children were given little time to say goodbye to their brother and father. Their bodies were placed in wooden coffins and hastily buried by the local undertaker. Selma became a single mother at the age of 36. She and the surviving children, ranging in age from 1 to 19 years, were left to carry on in that chilling Minnesota winter (CDC, 2006a). These kinds of losses played out millions of times around the world in 1918 and 1919 and left countless legacies of suffering and courage, the depth and breadth of which will never be fully known.

Pandemic Definitions

Antibiotic (also antimicrobial) Drug developed from fungi, molds, and certain soil bacteria that destroys or prevents the growth of other disease-causing bacteria.

Antigenic drift Process in which the influenza virus undergoes normal genetic mutations. The amount of change can be subtle or dramatic, but eventually as drift occurs, a new variant strain becomes dominant. This process allows influenza viruses to change and reinfect people repeatedly through their lifetime and is the reason influenza virus strains in vaccine must be updated each year.

Antigenic shift Process in which the existing H (hemagglutinin) and N (neuraminidase) are replaced by significantly different H and Ns. These new H or H/N combinations are perceived by human immune systems as new, so most individuals do not have preexisting antibody protection to novel viral strains. This is one of the reasons pandemic viruses can have such a severe impact on the health of populations.

Antiviral Drug used to prevent or cure a disease caused by a virus by interfering with the ability of the virus to multiply or spread from cell to cell.

Asymptomatic Infected but presenting no symptoms of disease.

Avian influenza (also AI or bird flu) A highly contagious viral disease with up to 100% mortality in domestic fowl caused by influenza A virus subtypes H5 and H7 (see Hemagglutinin). Low-pathogenic AI causes few problems and is carried by many birds with no resulting problems. Highly pathogenic AI kills birds and if transmitted to humans, can also be fatal. There is little or no human immunity, however humans are rarely affected.

Community-based measures Activities to increase social distance that may include measures applied to whole neighborhoods, towns, or cities (eg, snow days, establishment of clinics, and community-wide quarantine).

Containment measures Measures taken to control disease exposure at specific sites or buildings that may include cancellation of public events (eg, concerts, sports events, and movies), closure of office buildings, apartment complexes, or schools, and closure of public transit systems. These measures can also involve restricting entrance to buildings or other sites (eg, requiring fever screening or use of face masks before entry).

Epidemic Disease occurring suddenly in humans in a community, region, or country in numbers clearly in excess of a typical presentation of the disease.

H5N1 Variant of avian influenza, which is a type of influenza virulent in birds. H5N1 was first identified in Italy in the early 1900s and is now known to exist worldwide. Both low and highly pathogenic variants exist in different regions of the world.

Hemagglutinin Important surface structure protein of the influenza virus. Hemagglutinin is an essential gene for the spread of the virus throughout the respiratory tract that enables the virus to attach itself to a cell in the respiratory system and penetrate it. Hemagglutinin is referred to as the "H" in influenza viruses (eg, H1N1). See also "Neuraminidase."

HPAI Highly pathogenic form of avian influenza. Avian flu viruses are classified based upon the severity of the illness and HPAI is extremely infectious among humans. The rapid spread of HPAI, with outbreaks occurring at the same time, is of growing concern for human health as well as for animal health. See also "LPAI."

Influenza Serious viral disease caused by influenza viruses that infect the respiratory tract.

Isolation State of physical separation and restriction of movement between persons or groups to prevent the spread of disease. Isolation measures can be undertaken in hospitals or homes, as well as in alternative facilities.

LPAI Low pathogenic form of avian influenza. Most avian flu strains are classified as LPAI and typically cause little to no clinical signs in infected birds. However, some LPAI virus strains are capable of mutating under field conditions into HPAI viruses. See HPAI.

Mutation Any alteration in a gene from its original natural state. This change may be disease causing or a benign, normal variant.

Neuraminidase Important surface structure protein of the influenza virus. Neuraminidase is an essential enzyme for the spread of the virus throughout the respiratory tract that enables the virus to escape the host cell and infect new cells. Neuraminidase is referred to as the "N" in influenza viruses (eg, H1N1). See also "Hemagglutinin."

Pandemic Worldwide outbreak of a disease in humans with case numbers clearly in excess of normal.

Pathogenic Causing or capable of causing disease.

Prepandemic vaccine Vaccine created to protect against currently circulating H5N1 avian influenza virus strains with the expectation it would provide at least some protection against new virus strains that might evolve.

Prophylactic Pharmaceutical or a procedure with properties capable of prevention or protection against a disease or condition (eg, vaccines, antibiotics).

Quarantine Time period of physical separation or restriction of movement decreed to control the spread of disease. Before the era of antibiotics, quarantine was one of the few available means of halting the spread of infectious disease. Quarantine is still used today as needed. Individuals may be quarantined at home or in designated facilities.

Seasonal flu Respiratory illness caused by the influenza virus transmitted from person to person. Most individuals have some immunity, and a vaccine is available. Seasonal flu is also known as the common flu or winter flu.

Virus One of the many simple, submicroscopic infectious agents of plants, animals, and bacteria that causes disease. Viruses consist essentially of a core of RNA or DNA surrounded by a protein coat. Unable to replicate without a host cell, viruses are typically not considered living organisms.

Widespread or community-wide quarantine Refers to the closing of community borders or the erection of a real or virtual barrier around a geographic area (a cordon sanitaire) with prohibition of travel into or out of the area.

Pandemic Influenza

Influenza, referred to as the flu, is a highly infectious respiratory disease caused by the influenza virus. It is a segmented, single-stranded, RNA virus that is part of the Orthomyxoviridae family (Fig. 16-2). The name influenza comes from the Italian form of the Latin word "influentia" as influenza illnesses were believed to result from occult "influences." The Orthomyxoviridae family name is derived from the Greek words "orthos," or straight, and "myxo," or mucus (International Committee on Taxonomy of Viruses, 2006). The name of a specific influenza strain is usually based on where it is initially discovered such as references to the geographic location (Hong Kong flu) or animal reservoir (bird flu).

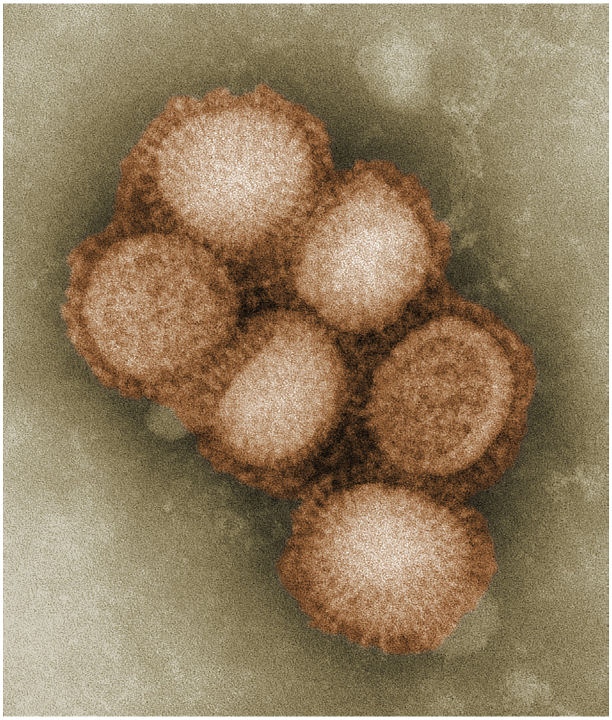


FIGURE 16-2 Negative-stained transmission electron micrograph depicts the ultrastructural details of a number of influenza virus particles, or "virions." *Centers for Disease Control and Prevention (CDC) Photograph by Cynthia Goldsmith.*

Human influenza viruses have their origin in animal reservoirs that adapt and pass from birds and swine directly or through other mammals. To cause a pandemic, three barriers must be overcome: the virus must be transmissible from animals to humans, the virus must be able to infect human cells, and there must be the ability to transmit the virus from human to humans. While these seem like formidable barriers, evidence of the many pandemics indicates these genetic changes are achievable if not common.

Influenza pandemics occur when a dramatic reassortment of the genetic structure of the virus makes it unrecognizable to the human immune system. Throughout the past century there were four pandemics: 1918, 1957, 1968, and 2009 (Cox and Subbarao, 2000). The severity of seasonal or pandemic influenza is caused by the genetic structure of the virus. There are three types of influenza viruses: A, B, and C. Influenza A is the most dangerous for humans and influenza C is the least dangerous. The specific structure of the influenza virus is expressed by the proteins it carries. Hemagglutinin proteins of the virus are the components that enable the virus to penetrate a foreign body. There are 16 different hemagglutinin proteins possible. Neuraminidase is another key protein of the virus. Neuraminidase has nine protein varieties. These two proteins are the defining factors for each strain of influenza and are the basis for the "H_N_" designation. For example, there have been concerns over H5N1 as a potential candidate for a future influenza pandemic. Another terminology used in discussing the various strains of viruses refers to the pathogenicity in animals. Influenza virus strains are referred to as being either low pathogenic or high pathogenic. For several years, a low-pathogenic avian influenza (LPAI) H5N1 strain has been present in North America, while there has been a highly pathogenic avian influenza (HPAI) H5N1 strain present in Asia (Badae et al., 2013; Inamasu et al., 2012; Manning, 2006).

Changes in a virus are caused by two types of mutations. Antigenic drift is a constant process of genetic change naturally occurring as a virus replicates itself. Small imperfections happen as copies are made causing a genetic drift, or slow process of change to occur. Occasionally, an antigenic shift occurs. This is a dramatic reassortment of the genetic structure of the virus when it is combined with other influenza strains and exchanges genetic material (Webster and Govorkova, 2006). Antigenic shift usually occurs in animals such as swine as they carry both human and animal strains of influenza virus and provide an ideal reservoir for various strains to mix and shift their genetic structure Reperant, et al., 2012.

Human Health Effects

Influenza symptoms typically include fever, muscle pain, runny nose, and cough. Those who die from seasonal influenza frequently have chronic medical conditions or weaker immune systems and die from secondary illnesses such as pneumonia. The primary differences during an influenza pandemic are the disease severity and the populations affected (see Table 16-1). Not only will the case–fatality ratio be excessive during a pandemic, but often those most severely affected are different demographically. In the 2009–2010 influenza A H1N1 pandemic, a study of 100 deaths revealed a high incidence of viral

Table 16-1 Differences Between Seasonal and Pandemic Influenza

Seasonal Influenza	Pandemic Influenza
Annual occurrence	Rare occurrence (several times per century)
Some natural human immunity	Little or no human immunity
Weak immune systems at increased risk	Those at increased risk have a strong immune system
Vaccine available before flu season	Vaccine not available for several months
Adequate antivirals for those at increased risk	Inadequate supply of antivirals for those at risk
Healthcare system is adequate to provide care	Healthcare system overwhelmed
Mild, non–life-threatening illness in most people	Severe, life-threatening illness in many more
Annual U.S. deaths in the tens of thousands	U.S. deaths in the hundreds of thousands
Does not normally close schools	School closures likely
Does not cause travel restrictions among the healthy	Travel restrictions likely
Mild impact on the economy and business continuity	Severe impact on the economy and business continuity

Adapted from the U.S. Department of Health and Human Services: www.pandemicflu.gov.

pneumonia and diffuse alveolar damage. These findings were similar to other findings in influenza outbreaks but different than "typical" seasonal influenza deaths (Sheih et al., 2010). There were also a higher incidence of deaths in patients with morbid obesity, pregnancy, and sleep apnea. Rather than populations with weaker immune systems having more severe illness, those with healthier immune systems can be more susceptible. When the human immune system is fighting an infection, cytokines are responsible for activating the immune functions and also stimulating production of more cytokines. It is a looped system that keeps the immune system balanced to fight illness effectively while minimizing damage to healthy cells. Some highly pathogenic strains of influenza produce a "cytokine storm" where cytokines and immune cells become hyperstimulated and damage the healthy cells of an infected respiratory tract. During the 1918 pandemic, many individuals between the ages of 18 and 40 with healthier immune systems had more severe illness due to cytokine stimulation. As the immune system began damaging the healthy cells of the respiratory tract, it led to acute respiratory distress syndrome (ARDS) (Kobasa et al., 2004; Osterholm, 2005). ARDS killed many within several days. Others succumbed over a longer period of time due to secondary bacterial infections of the lungs. These infections were ushered in by viral damage to the epithelial cells of the respiratory tract. Although the epithelial cells usually sweep the respiratory tract clean, as they are damaged by influenza viruses, bacteria from the mouth can make their way down the respiratory tract and cause secondary illnesses.

Because influenza is caused by a virus, there are only two pharmaceutical options. A vaccine can be used to prevent or reduce the severity of influenza (Figs. 16-3–16-6). Antiviral drugs can be used to reduce the severity and length of the illness. Antiviral drugs are often the initial focus of pandemic preparedness and response efforts because vaccine production requires access to the specific pathogenic organism FDA, 2008. Influenza viruses quickly mutate, making them evasive targets for vaccine development. Despite these historical limitations, a prepandemic H5N1 vaccine has been approved and is being

FIGURE 16-3 A single prefilled Fluzone® intradermal influenza virus vaccine syringe. *Centers for Disease Control and Prevention (CDC) photograph by Douglas Jordan, M.A.*

stockpiled. It is not known if the vaccine will offer enough protection or if a future H5N1 mutation could make the vaccine ineffective.

> *You might be asking too much if you're looking for one vaccine for every conceivable influenza. If you have one or two that cover the vast majority of isolates, I would not be ashamed to call that a universal vaccine.*
>
> *Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland (Talkington, 2009).*

If the current influenza vaccine production capacity is used to quickly make a new vaccine from a newly discovered influenza strain, the global influenza vaccine production capacity is about 500 million doses per year. The first shipments of vaccine to leave those facilities would take several months to develop. Some vaccine is cultured in eggs using a time-consuming process (Morse et al., 2006). This production schedule cannot be changed

FIGURE 16-4 A 5-ml vial containing the influenza virus vaccine, Fluzone®, distributed by Aventis Pasteur, USA. *Centers for Disease Control and Prevention (CDC) photograph by James Gathany.*

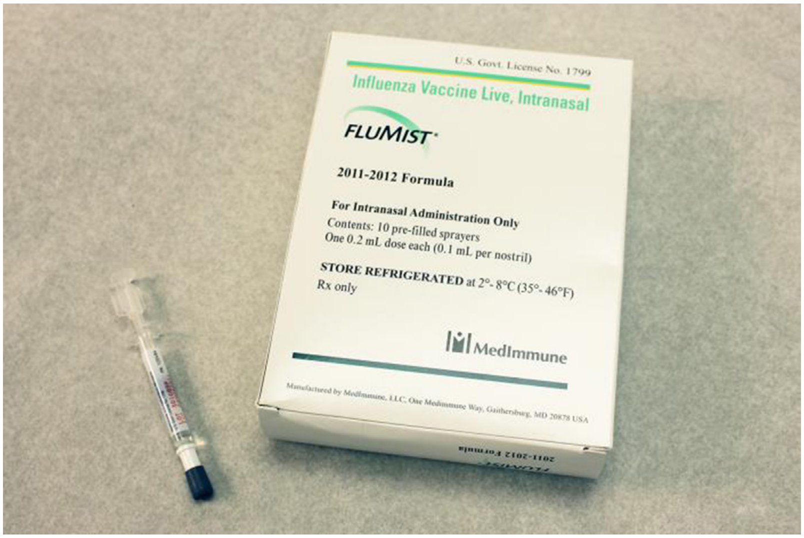


FIGURE 16-5 A box containing 10 prefilled FluMist® live attenuated intranasal vaccine (LAIV) sprayers, alongside of which was a single sprayer, which will be used to deliver the vaccine into the nasal cavity of the recipient. *Centers for Disease Control and Prevention (CDC) photograph by Douglas Jordan, M.A.*

FIGURE 16-6 Nurse administering a vaccination for a young boy. *Centers for Disease Control and Prevention (CDC) photograph by Judy Schmidt.*

using the current technologies and manufacturing approaches. Newer flu vaccine production methods include a cell-based approach approved in the United States by the Food and Drug Administration (FDA) in 2012. The first approved cell-culture flu vaccine was called Flucelvax. Instead of incubating eggs, vaccine viruses are cultured mammalian cells, purified and tested for use in vaccine. In most cases, to achieve necessary immunity with any inactivated virus, two doses are necessary to activate and sustain an immune response. The newest and fastest process uses recombinant technology. Approved in 2013 under the name, Flublok, the recombinant vaccine is one produced without using egg products or actual virus. Instead, Flublok uses an influenza virus protein made through genetic modification of a virus that infects insect cells. The virus produces an influenza protein that stimulates the immune response (FDA, 2015).

Vaccination rates following pandemic campaigns will vary. In multiple studies, several factors increased the likelihood of being vaccinated during the 2009 H1N1 pandemic: being a member of a priority group (healthcare worker, having children younger than 5 in the household, having a chronic condition with increased risk for complications from H1N1); having a history of seasonal flu vaccination and having a medical provider. Gilmour and Hofmann (2010) also found nearly three-quarters of those who had not been vaccinated reported they did not think it was necessary. Delays in vaccine distribution and delivery, relying on specialty care physicians for vaccinations (other than obstetricians) and a longer pandemic locally decreased vaccine rates (Davila-Payan et al., 2014). In the United States, vaccine rates were lower in some ethnic minorities because of fears of being used for experimentation. Public messaging must be culturally sensitive and multiple layers of communications strategies need to be applied in order to reach the most vulnerable populations.

Antiviral drugs are the most effective pharmaceutical options immediately available for managing an avian influenza pandemic (Schunemann et al., 2007). Although there are multiple drugs approved by the U.S. FDA for treatment and prevention of influenza, in recent years several strains of influenza show resistance to many previously prescribed antiviral drugs (CDC, 2006b). Using predictive modeling based on WHO criteria for a pandemic, Gani et al. (2005) suggests having antiviral access, through stockpiling or immediate commercial availability, with enough available to treat 25% of the population could reduce hospitalizations by 50–75%. In the 2009 influenza A (H1N1) pandemic, an assessment of the efficacy of antiviral use confirmed this, especially among the age group of 18–64 years (Atkins et al., 2011). Communities need to develop strategies for allocating antiviral medications when in short supply while awaiting development and distribution of strain-specific vaccine.

There is also an important role for antimicrobial drugs in pandemic influenza preparedness and response. Secondary bacterial infections are a common cause of death among those who die from influenza-related complications. In fact, about one-quarter of those who die from seasonal influenza are found with coinfections from bacterial infections as major factors in mortality (Bhat et al., 2005; Lim et al., 2001). It is important to determine the organism's susceptibility to the antimicrobial drug selected. It is also crucial to effectively triage those needing antimicrobial therapy so individuals with weak immune function receive priority treatment (Gupta et al., 2008).

Prevention and Preparedness

The WHO tracks seasonal influenza reports from around the world and analyzes data for anomalies that may signal the emergence of a novel influenza strain. Participating nations follow a set of international health regulations that include obligations to notify the WHO of any event that may constitute a public health emergency reaching the level of international concern. Nearly all nations have established processes for detecting and responding to emerging infectious disease threats. Influenza, however, receives more attention and resources than any other infectious disease threat given the potential for severe consequences associated with a novel pathogenic strain. Even the annual flu seasons have a tremendous global health impact. For example, over the past several decades the United States has experienced an increasing trend in the number of hospitalizations associated with seasonal influenza with the average number reaching over 200,000 per year (Thompson et al., 2004).

There are several measures that can be instituted to reduce the risk of influenza infection. These measures include both pharmaceutical and nonpharmaceutical interventions. The primary pharmaceutical measure for influenza is vaccination. As stated earlier, with an emerging pandemic influenza strain, a rapid, dramatic shift has occurred in the virus that will not allow sufficient time to incorporate the new strain into a vaccine before the pandemic is already spreading. There will likely be a delay of several months using the current vaccine production processes.

Public Messaging: Individual Influenza Prevention Tips

1. Get a flu shot every year. Even if the current vaccine does not protect specifically against avian influenza, it offers some protection against influenza and may reduce the overall disease severity during a pandemic.
2. Wash hands often with soap and water or use alcohol-based hand cleaner. Hand washing decreases risk for all sorts of illnesses including influenza.
3. Avoid touching your face. Touching your eyes, nose, and mouth may transfer virus from your hands and infect you with the virus.
4. Clean frequently touched surfaces often, including door handles, hand rails, cell phones, etc.
5. Cover your mouth when you cough or sneeze. Cough into your elbow and not your hand.
6. Stay away from those who are ill.
7. Avoid crowded congregate settings when there is illness in the community.
8. Stay home when ill and for at least 24 hours until after the fever is gone.
9. Avoid unnecessary travel when illness is prevalent. Take extra precautions when traveling.
10. Use antiviral medications, if your healthcare practitioner prescribes them, to decrease illness severity and to shorten the time you are sick. Antiviral medications can also prevent serious flu complications in those at high risk.

The CDC simplified these measures into a program called, *"Take 3" Actions to Fight the Flu*. It simplifies the 10 messages listed here into (Fig. 16-7):

1. Take time to get a flu vaccine.
2. Take everyday preventive actions to stop the spread of germs.
3. Take antiviral medications if your healthcare provider prescribes them.

FIGURE 16-7 "Take 3" Actions to Fight the Flu. A CDC influenza prevention education initiative. Available at: http://www.cdc.gov/flu/protect/preventing.htm. *Image courtesy of* www.Flu.gov, *a U.S. government website managed by the U.S. Department of Health and Human Services.*

In allocating scarce resources, antiviral medications may be used early in a pandemic for close contacts of initial cases and to contain disease clusters. Close contacts may include family members, friends, coworkers, healthcare providers, and fellow travelers on aircraft, buses, etc. The targeted use of antiviral medications can contain an outbreak or reduce individual and public health impact. The use of antiviral medications can also prevent cases in high-risk facilities such as long-term care or in well-defined regions such as military installations or school campuses. Strategies for use of antiviral medications for prevention and treatment may change during a pandemic. Early in the pandemic to a new region, it may be best to use antiviral medications to prevent infections. However, once influenza cases begin to spread across a community, priority antiviral allocation should be given to those with severe illness to improve their outcomes.

Nonpharmaceutical intervention measures offer the best or sometimes the only option for some regions. With billions of people at risk during a pandemic, there will not be adequate pharmaceutical measures to go around in the foreseeable future (WHO, 2005). There are several nonpharmaceutical interventions that offer the best prevention: hand washing, isolation, quarantine, and social distancing. The primary nonpharmaceutical intervention is hand washing. It is the most effective, most underrated measure to prevent illness. Isolation of those who are sick from those who are healthy is another fundamental nonpharmaceutical measure. Isolating sick patients in hospitals or at home should be undertaken with appropriate personal protective equipment if available. During a pandemic, hospitals may be full, and many who are able to care for themselves, or who have an adequate support system to provide care, should isolate themselves from others to reduce the risk of additional virus transmission. There are also those who are not yet ill but may have been exposed to the virus. These individuals may choose self-quarantine. Others with no illness or known exposure may choose social distancing by not attending social functions, limiting time in crowds, and/or wearing protective face masks. The concept is the same for all these prevention measures. In the context of prevention, the primary distinction between isolation, quarantine, and social distancing is the health status of the person taking action to stay away from others.

With the growing global threat of avian influenza, in fall 2005, the White House released the U.S. National Strategy for Pandemic Influenza. The U.S. approach remains essentially the same today with three steps:

1. Stopping, slowing, or otherwise limiting the spread of a pandemic to the United States
2. Limiting the domestic spread of a pandemic, and mitigating disease, suffering, and death
3. Sustaining infrastructure and mitigating impact to the economy and the functioning of society.

These steps are generalizable to all nations and include delaying or stopping a pandemic before it reaches a point of entry, reducing the spread of illness and mitigating suffering and death, and sustaining society, critical infrastructure, and the economy. The strategy also defines three pillars on which these activities are sustained. They include preparedness and communications, surveillance and detection, and response and containment (HSC, 2005). With this strategic vision, pandemic preparedness funding and associated requirements began arriving in 2006 for state and local governments to initiate local plans and begin training and exercising for a pandemic. Although this vision seems relatively simple, the challenge rests in translating it into tangible preparedness activities that federal, state, and local governments can take to enhance future response. This must be accomplished in a setting that includes profound challenges for sustainment of critical infrastructure, limitations on the mobility of people and goods, and a strain on the global economy.

Pandemic Lessons Learned from the Past 100 Years

1. No two pandemics are alike. There are differences in mortality, severity, and patterns of spread.
2. The need for rapid hospital surge capacity is a common factor in all pandemics.
3. Pandemic viral strains are more lethal and often cause severe disease in unlikely age groups, such as young, healthy adults.
4. Pandemics occur in waves. Age groups and geographical areas not affected initially are more likely to be vulnerable in subsequent waves. Subsequent waves are often more severe.
5. Virological surveillance is often the key to alerting public health agencies to a coming pandemic by isolating and characterizing the virus, and making it available to vaccine manufacturers.
6. Over the centuries, most pandemics have originated in parts of Asia where dense populations of humans live in close proximity to ducks and pigs.
7. Historically, public health interventions delay international spread of pandemics, but do not stop them. Quarantine and travel restrictions have little effect on viral disease spread.
8. Delaying disease spread can flatten the epidemiological peak, thus distributing cases over a longer period of time. Having fewer people ill at a given time increases the likelihood medical and other essential services can be maintained and reduces patient surge capacity needs (Fig. 16-8).
9. The impact of vaccines on a pandemic remains to be demonstrated. In 1957, 1968, vaccine manufacturers responded with too little vaccine, too late into the disease spread to have an impact.

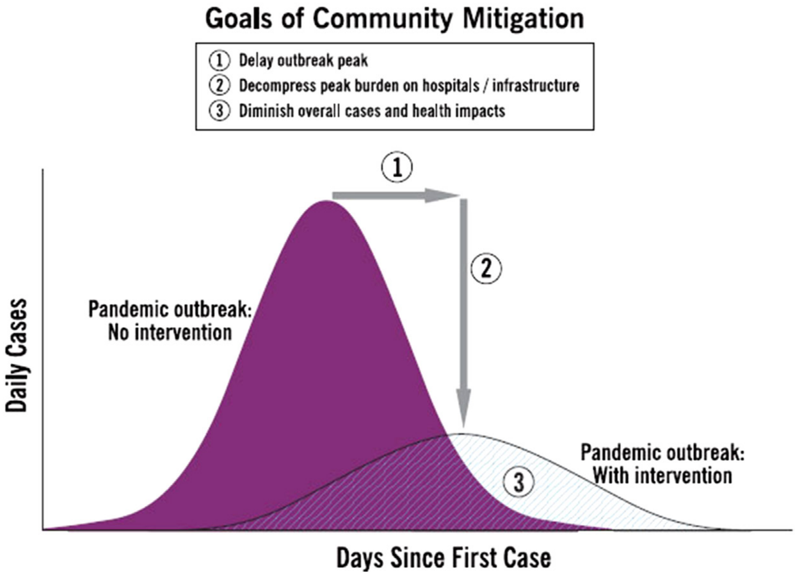


FIGURE 16-8 The goal of community mitigation measures during a pandemic is to compress the peak number of cases and keep the number of ill at any given time as manageable as possible. *U.S. Department of Health and Human Services, Community Strategy for Pandemic Influenza Mitigation (U.S. Department of Health and Human Services, 2007).*

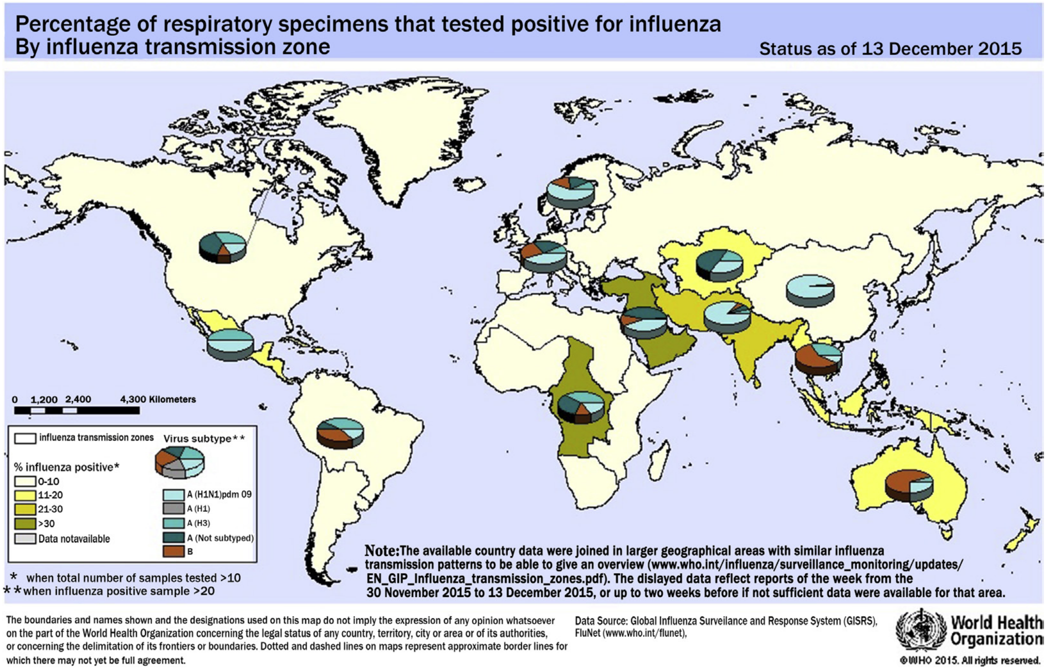
10. Countries with domestic manufacturing capacity will be the first to receive vaccines.

11. The tendency of pandemics to be more severe in later waves may extend the time before large supplies of vaccine are needed to prevent severe disease in high-risk populations.

12. Regions with good annual influenza vaccination programs have experience in the logistics of vaccine administration to at least some groups requiring priority protection during a pandemic.
Adapted from Avian influenza: Assessing the pandemic threat. World Health Organization, pp. 31–33. Available at: http://www.who.int/influenza/resources/documents/h5n1_assessing_pandemic_threat/en/.

Immediate Actions

One of the most critical actions that a public health system can take in preventing and responding to a pandemic is health surveillance and monitoring the incidence of influenza. Reporting influenza-like–illness (ILI) through direct reporting by healthcare providers or through healthcare system reporting can indicate surges in possible cases as well as identify circulating strains. This information can be used to rapidly deploy pharmaceutical interventions and implement social distancing actions. Healthcare providers can report ILI through the U.S. Influenza Sentinel Provider Surveillance Network where the total number of ILI is reported and a number of patient samples are tested for influenza virus for genetic typing. Syndromic surveillance systems such as Biosense and ESSENCE can indicate emergency department utilization for ILI and assist monitoring for impact. Viral surveillance can also indicate the incidence of antiviral resistance. The WHO collects influenza surveillance data and provides global information through its Global Influenza Surveillance and Response System (Fig. 16-9).


Percentage of respiratory specimens that tested positive for influenza
By influenza transmission zone
Status as of 13 December 2015

* when total number of samples tested >10
**when influenza positive sample >20

Note: The available country data were joined in larger geographical areas with similar influenza transmission patterns to be able to give an overview (www.who.int/influenza/surveillance_monitoring/updates/EN_GIP_Influenza_transmission_zones.pdf). The dislayed data reflect reports of the week from the 30 November 2015 to 13 December 2015, or up to two weeks before if not sufficient data were available for that area.

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: Global Influenza Surveilance and Response System (GISRS), FluNet (www.who.int/flunet),

World Health Organization

FIGURE 16-9 Sample WHO Influenza Summary Report. *Available at:* http://www.who.int/influenza/surveillance_monitoring/en/.

In 2013, the WHO updated their pandemic alert system from six phases (WHO, 2009) to four. These pandemic phases provide a global snapshot of a pandemic based upon the monitoring of virological, epidemiological, and clinical data. The phase determination is one of three pandemic preparedness and response tools used by the WHO to communicate and coordinate a pandemic response. The WHO director-general can also declare a Public Health Emergency of International Concern (PHEIC) or issue a Pandemic Declaration. Each of these declarations is accompanied by temporary recommendations or regulatory actions for member states (WHO, 2013).

1. Interpandemic: The period between pandemics where WHO and member states support preparedness activities and capacity development.

2. Alert: Issued when a new influenza subtype with pandemic potential is identified. Global influenza risk assessments are carried out according to international health regulations. Member states are asked to increase overall vigilance and initiate advisory groups and partner networks. Antiviral measures may be staged and prepared for use to control the introduction and spread of a novel virus.
3. Pandemic: Issued when a novel influenza strain spreads globally. Risk assessments are accomplished using virologic, epidemiologic, and clinical data. A pandemic is declared and responses are initiated by member states and supported by WHO based upon a global risk assessment.
4. Transition: Global risk drops, prompting stepdowns in global actions and response activities. Based upon ongoing global risk assessments, responses are scaled and consideration is given to modify or terminate the PHEIC.

The illustration below depicts how the WHO pandemic phases can transpire. It is a global picture so some nations can have no activity while others can have widespread cases before the WHO phase is elevated or dropped. The phases do not have a clean shift from one phase to the next. For example, the transition from the alert phase to the pandemic phase may not align perfectly with the global epidemiological curve. The scale is the "global average" of pandemic influenza cases (Fig. 16-10).

The CDC also updated the U.S. framework for pandemic influenza preparedness and response following the H1N1 pandemic. Updated guidance was released in 2014 (Holloway et al., 2014). The framework displays the progression of a pandemic with defined intervals triggering specific actions. This facilitates better federal, state, and local planning and enhances response coordination. The CDC framework has six defined intervals (Fig. 16-11):

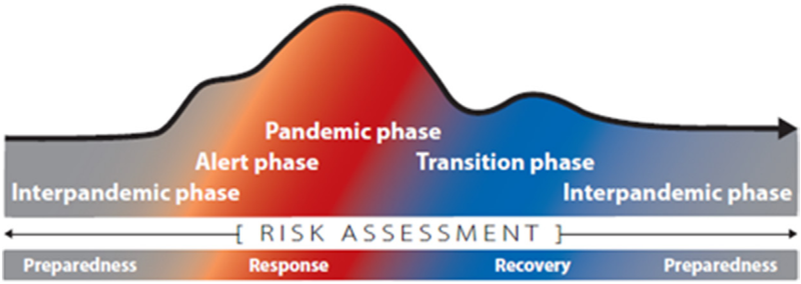


FIGURE 16-10 WHO pandemic phases (WHO, 2013).

1. Investigation Interval: A novel influenza virus with the potential to be a human health threat is identified and investigated anywhere in the world.

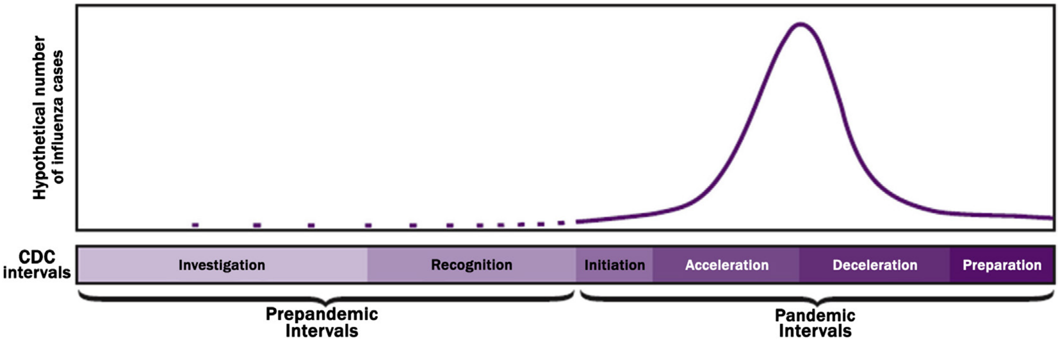


FIGURE 16-11 U.S. Preparedness and response framework for novel influenza A virus pandemics: CDC intervals (Holloway et al., 2014).

2. Recognition Interval: A novel influenza virus displays potential for ongoing human-to-human transmission. This may include increasing numbers or clusters of human cases.
3. Initiation Interval: The virus displays efficient and sustained human-to-human transmission. This is most apparent in institutional or family outbreak attack rates (>20%) and in the number of transmission generations (3 or more linked cases).
4. Acceleration Interval: Consistently increasing influenza cases demonstrating established disease transmission.
5. Deceleration Interval: Consistently decreasing influenza cases demonstrating the pandemic has passed its peak and is no longer accelerating.
6. Preparation Interval: Low numbers of influenza cases resulting in scaling back response activities, focusing on recovery and preparation for subsequent waves.

Like the WHO pandemic phases, these intervals provide a common reference for communicating the current pandemic risk level. With each increase in pandemic intervals, a variety of response measures are instituted. The intervals address the need for triggers. As events unfold leading up to a pandemic, it is essential to maintain a common frame of reference to understand when actions must be taken. There is no way to predict the timeframe for changes between the intervals. It may take days or years to move up or down from one interval to another. This variable timeline underscores the importance of coordinated pandemic preparedness planning. The six intervals do not run concurrently with the WHO phases (see Table 16-2). The intervals for U.S. government actions are based on the specific threat to the U.S. population.

Table 16-2 Preparedness and Response Framework for Novel Influenza A Virus Pandemics: A Crosswalk of the World Health Organization Phases and CDC Intervals, with Federal and State/Local Indicators (Holloway et al., 2014)

World Health Organization Phases	CDC Intervals	Federal Indicators for CDC Intervals	State/Local Indicators for CDC Intervals
Interpandemic phase: Period between influenza pandemics	**Investigation:** Investigation of novel influenza A infection in humans or animals	Identification of novel influenza A infection in humans or animals anywhere in the world with potential implications for human health	Identification of novel influenza A infection in humans or animals in the United States with potential implications for human health
Alert phase: Influenza caused by a new subtype has been identified in human			
	Recognition: Recognition of increased potential for ongoing transmission of a novel influenza A virus	Increasing number of human cases or clusters of novel influenza A infection anywhere in the world with virus characteristics, indicating increased potential for ongoing human-to-human transmission	Increasing number of human cases or clusters of novel influenza A infection in the United States with virus characteristics indicating increased potential for ongoing human-to-human transmission
Pandemic phase: Global spread of human influenza caused by a new subtype	**Initiation:** Initiation of a pandemic wave	Confirmation of human cases of a pandemic influenza virus anywhere in the world with demonstrated efficient and sustained human-to-human transmission	Confirmation of human cases of a pandemic influenza virus in the United States with demonstrated efficient and sustained human-to-human transmission
	Acceleration: Acceleration of a pandemic wave	Consistently increasing rate of pandemic influenza cases identified in the United States, indicating established transmission	Consistently increasing rate of pandemic influenza cases identified in the state, indicating established transmission
	Deceleration: Deceleration of a pandemic wave	Consistently decreasing rate of pandemic influenza cases in the United States	Consistently decreasing rate of pandemic influenza cases in the state
Transition phase: Reduction in global risk, reduction in response activities, or progression toward recovery actions	**Preparation:** Preparation for future pandemic waves	Low pandemic influenza activity but continued outbreaks possible in some jurisdictions	Low pandemic influenza activity but continued outbreaks possible in the state

Each interval triggers specific local activity. Many of the activities extend and build upon the efforts of previous intervals. These examples assume an existing pandemic preparedness program (CDC, 2014a). The listed activities are not intended to be exhaustive but rather to serve as general examples of local preparedness and response activities when transitioning to subsequent intervals over the course of a pandemic:

Investigation Interval

- Review and exercise response plans.
- Maintain and enhance influenza and respiratory virus surveillance systems.
- Investigate novel influenza infections in humans and animals.
- Report cases according to the Nationally Notifiable Diseases Surveillance System.
- Advise healthcare providers to promptly diagnose and treat influenza.

Recognition Interval

- Consider activation triggers for emergency operations centers.
- Enhanced influenza surveillance.
- Investigate and report cases.
- Confirm suspected cases at a public health laboratory.
- Prepare for nonpharmaceutical interventions.

Initiation Interval

- Consider activation of emergency operations centers and public health emergency declarations.
- Implement nonpharmaceutical interventions.
- Monitor surge demands in healthcare facilities.
- Implement mass vaccination campaigns.
- Disseminate risk communication messages.

Acceleration Interval

- Monitor the effectiveness of response.
- Transition surveillance from individual case confirmation to syndromic surveillance.
- Provide laboratory confirmation only as required for virologic surveillance.
- Activate and expand community mitigation measures.
- Continue mass vaccination campaigns.

Deceleration Interval

- Review response activities and scale them proportionate to the situation.
- Continue severe disease and syndromic surveillance.
- Assess need for community mitigation measures and plan for cessation.
- Initiate reduction or cessation of surge capacity strategies.
- Continue vaccinations as appropriate.

Preparation Interval

- Consider deactivation of emergency operations centers.
- Prepare for subsequent waves.

- Return to routine laboratory interpandemic virologic surveillance.
- Replenish stockpiles or caches.
- Continue to vaccinate.

Many preparedness and response activities undertaken by the U.S. during a future pandemic may be triggered by a CDC evaluation tool called the Influenza Risk Assessment Tool or IRAT. The IRAT uses 10 scientific measures of the risk for emergence of a novel influenza virus and its public health impact. Each of the 10 criteria is used in a scoring system to depict pandemic risk. This includes "low risk" with scores between 1 and 3, "moderate risk" with scores between 4 and 7, and "high risk" for scores between 8 and 10. These outcomes are reviewed and weighted according to the risks of emergence and public health impact (CDC, 2014b). These 10 criteria are grouped into three categories:

Properties of the Virus

1. Genomic variation: Genetic characteristics important for human infections and disease.
2. Receptor binding: Whether the preferred viral host is animal or human and the types of cells it infects (eg, cells and tissue in the nose verses those deep in the lungs).
3. Transmission in lab animals: Displayed through airborne or contact transmission in a lab setting.
4. Antiviral susceptibility/resistance: Effectiveness of treatment with antiviral drugs (eg, oseltamivir, zanamivir and M2 blockers).

Attributes of the Population

1. Existing population immunity: Susceptibility to infection and severity of illness based upon age, geographic area, or genetic factors.
2. Disease severity and pathogenesis: The severity of illness caused by a particular influenza virus in people and/or animals.
3. Antigenic relationship to vaccine candidates: How similar a novel influenza virus is compared to current or previously manufactured vaccine strains.

Ecology and Epidemiology

1. Global distribution in animals: How widespread an influenza virus is in animals (eg, limited area or from many different areas).
2. Infection in animal species: Animals impacted by the virus and the likelihood of human contact with them (eg, in wild birds or domestic birds).
3. Human infections: Whether human infections are occurring and under what circumstances (eg, human-to-human transmission or clusters of disease occurred verses transmission after direct and prolonged contact between humans and infected animals).

Once a pandemic begins to sweep across a community, it will likely overwhelm local acute care facilities and cause a ripple effect of patient surge that will strain services across a region, a state, and eventually the nation. To save as many lives as possible, the healthcare system must remain functional and delivering the best care possible under whatever conditions arise (Toner et al., 2006). The strategy to accomplish this is to institute community measures to delay and compress the outbreak peak (see Fig. 16-8). As interventions are instituted, some cases of illness will be delayed and others prevented. As a result, the cases in a given region can be spread over a longer period of time. Even though some who delay their illness eventually become ill, as the cases are spread over a more manageable timeframe, the peak number of cases will be more manageable for providers making it easier to sustain essential services.

> *If a severe pandemic materializes, all of society could pay a heavy price for decades of failing to create a rational system of healthcare that works for all of us.*
>
> *Irwin Redlener, Director of the National Center for Disaster Preparedness at Columbia University's Mailman School of Public Health (Kristof, 2009).*

Although there are a variety of community measures that can be taken during a pandemic to reduce the risk of exposure and subsequent cases of illness, a balance is needed when instituting interventions. No intervention is without some economic or social cost. If individuals are isolated or quarantined, and there is no support system in place to provide essentials such as groceries and prescriptions, or services such as child care for ill parents of small children, there can be social disruption in addition to extended health effects. Economic protection measures may need to be considered to allow those who are ill to work from home or at least to have some assurance taking sick days will not result in job loss. A variety of consequences must also be considered when closing schools and day care centers or when discouraging public gatherings. Children are at increased risk of influenza transmission in both preschool contacts and school-age contacts. Viboud et al. (2004) found there was also an increased risk in contacts exposed to preschool index patients and school-age index patients compared with those exposed to adult index cases. However, there are substantial economic and social outcomes to school-related measures. If children are not in school or day care, some parents will be unable to work. Parents are also likely to congregate children who have been kept out of school in order to have child care and to provide a diversion for the children, thereby negating the desired social distancing. If mass transit and congregate gatherings are discouraged, a variety of industries will suffer. Social distancing interventions may be important to public health but must be used judiciously. If the impact is seen as too severe, the political and social consequences may be too burdensome and the public may not comply. On the other hand, if interventions are established too late, they may be ineffective.

Nonpharmaceutical Intervention Examples

1. Isolation of the sick at home or in healthcare settings. Limiting visitors especially those from high-risk groups (young, elderly, and those with chronic illnesses).
2. Voluntary quarantine of households with confirmed or probable influenza.
3. Closure of daycares, K–12 schools, colleges, and congregate institutions. This should be followed by reducing child contacts through social distancing.
4. Social distancing of adults including cancellation of large gatherings and altered work schedules.

The challenges of managing a pandemic are immense, and the limitations of government response at all levels are known. The nongovernment resources from businesses, faith-based organizations, and others will certainly play a major role in a community pandemic response. Even communities with relatively broad preparedness participation from these organizations have rarely identified and characterized the resources and support these organizations can offer during an actual pandemic. It is also not known what policies may be instituted by these organizations to support or counter nonpharmaceutical interventions, such as implementation of sick leave benefits. It is difficult to effectively strategize with the substantial gaps existing in current planning assumptions. Involving these organizations in preparedness activities will be an important step in an effective pandemic response.

Recovery Challenges

It seems pandemic preparedness and response is so ominous and complex that when a WHO pandemic phase is reached, the planning stops. It is important to consider the post influenza pandemic scenarios and extend the process well beyond where many plans currently stop. For example, if there are significant fatalities within a certain demographic, special challenges for handling of human remains will emerge. If there are substantial numbers of adult losses, the secondary impact may be the loss of primary caregivers for children in some urban communities. If the losses are more among the working population, there are essential businesses and services that may be short-handed and unable to perform indispensable functions. This inoperability will result in a long-term economic ripple as production decreases, investment capital is diminished and further production is reduced. The healthcare sector is particularly vulnerable because healthcare workers will be repeatedly exposed. The system may suffer excessive losses, compromising the availability of staff or the standard of care. Even when the pandemic has resolved, critical infrastructure may take some time to fully recover. There are many unknowns in predicting what special challenges may result from a pandemic, making it critically important to push forward in the planning, training, and exercising of processes to include the recovery component addressing these possibilities. This should include consideration for a variety of scenarios as well as the mental/behavioral health impact and other resultant long-term issues.

Summary

Pandemic influenza has occurred at fairly regular intervals throughout history and will be repeated (Fig. 16-12). There are significant differences between each of these historical outbreaks and there will certainly be unique, unanticipated aspects to any future pandemic. Many gaps remain in preparedness activities and contemporary social changes may work against an optimal pandemic response. Influenza virus diversity and mutation proclivity inhibit efforts toward universal vaccine development or wholly effective antiviral medication. For over a decade, H5N1 influenza in the avian populations across multiple continents has been considered a possible precursor to a pandemic. While it is not

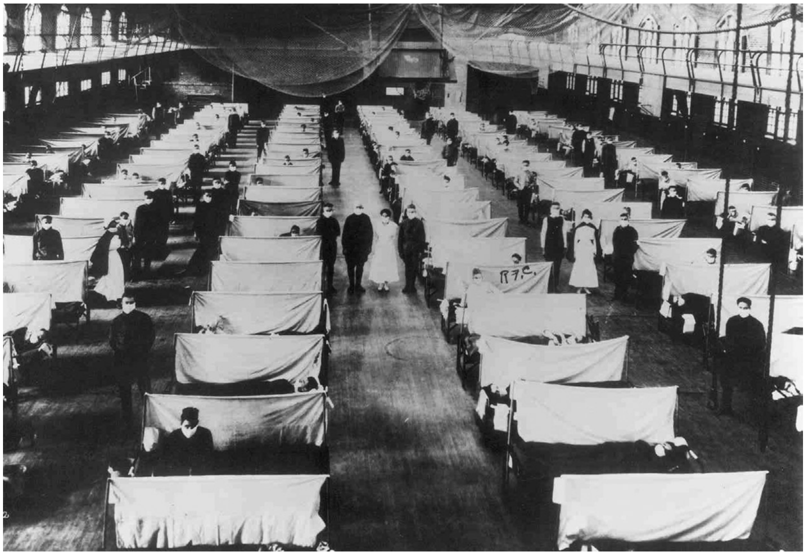


FIGURE 16-12 Mass care during the 1918 flu pandemic. *Department of Health and Human Services. Available at:* http://www.flu.gov/pandemic/history/1918/.

possible to predict that H5N1 will be next, it is certain another influenza virus will emerge, just as H1N1 did in 2009–10.

There are a number of positive factors regarding pandemic preparedness. Tremendous strides have been made in pharmaceuticals, critical care, and public health interventions. The WHO and public health organizations around the world are collaborating closely on monitoring the progress of H5N1 in both human and animal populations. Unprecedented international coordination will occur if and when the pandemic phase is elevated. In the United States, the recent investment in public health preparedness following the terrorist attacks of 2001 and more recent investments specifically in pandemic preparedness for H5N1 in 2006 and again for H1N1 in 2009 have filled several gaps in a public health infrastructure that had been eroding for decades.

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