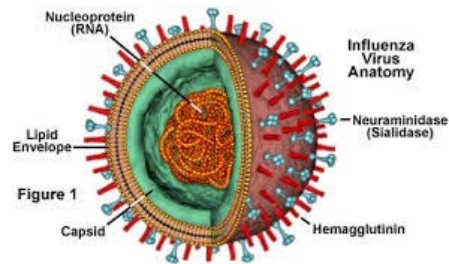


Influenza



Influenza (flu) is a contagious respiratory illness caused by influenza viruses that infect the nose, throat, and lungs. It can cause mild to severe illness. Serious outcomes of flu infection can result in hospitalization or death. Some people, such as older people, young children, and people with certain health conditions, are at high risk for serious complications.

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

- Fever or feeling feverish/chills
- Cough
- Sore throat
- Runny or stuffy nose
- Muscle or body aches
- Headaches
- Fatigue
- Some people may have vomiting and diarrhea, though this is more common in children than adult.



Most experts believe that flu viruses spread mainly by droplets made when people with the flu cough, sneeze or talk. These droplets land in the mouths or noses of people who are nearby. Less often, a person might also get the flu by touching a surface or object that has the flu virus on it and then touching their own mouth, eyes or possibly their nose.

You may be able to pass on the flu to someone else before knowing you are sick, as well as while you are sick. Most healthy adults may be able to infect others beginning 1 day before symptoms develop and up to 5 to 7 days after becoming sick. Children may pass the virus for longer than 7 days. Symptoms start 1 to 4 days after the virus enters the body. Some people, especially young children and people with weakened immune systems, might be able to infect others for an even longer time. That means that you may be able to pass on the flu to someone else before you know you are sick, as well as while you are sick. Some people can be infected with the flu virus, but have no symptoms. During this time, those persons may still spread the virus to others.

What is the difference between a cold and the flu? The flu and the common cold are both respiratory illnesses but they are caused by different viruses. Because these two types of illnesses have similar flu-like symptoms, it can be difficult to tell the difference between them based on symptoms alone. In general, the flu is worse than the common cold, and symptoms such as fever, body aches, extreme tiredness, and dry cough are more common and intense. Colds are usually milder

than the flu. People with colds are more likely to have a runny or stuffy nose. Colds generally do not result in serious health problems, such as pneumonia, bacterial infections, or hospitalization. Because colds and flu share many symptoms, it can be difficult (or even impossible) to tell the difference between them based on symptoms alone. Special tests that usually must be done within the first days of illness can be carried out, when needed to tell if a person has the flu. In general, the flu is worse than the common cold, and symptoms such as fever, body aches, extreme tiredness, and dry cough are more common and intense. Colds are usually milder than the flu. People with colds are more likely to have a runny or stuffy nose. Colds generally do not result in serious health problems, such as pneumonia, bacterial infections, or hospitalization.

The flu is unpredictable and how severe it is can vary widely from one season to the next depending on many things, including:

- What flu viruses are spreading
- How much flu vaccine is available
- When vaccine is available
- How many people get vaccinated, and
- How well the flu vaccine is matched to flu viruses that are causing illness.

Certain people are at greater risk for serious complications if they get the flu. This includes older people, young children, pregnant women and people with certain health conditions. Health conditions such as, asthma, diabetes, heart disease, and people who live in close quarters like nursing homes or prisons.

There are three types of influenza viruses: A, B and C. Human influenza A and B viruses cause seasonal epidemics of disease almost every winter in the United States. The emergence of a new and very different influenza virus to infect people can cause an influenza pandemic. Influenza type C infections cause a mild respiratory illness and are not thought to cause epidemics.

Influenza A viruses are divided into subtypes based on two proteins on the surface of the virus: the hemagglutinin (H) and the neuraminidase (N). There are

17 different hemagglutinin subtypes and 10 different neuraminidase subtypes. Influenza A viruses can be further broken down into different strains. Current subtypes of influenza A viruses found in people are influenza A (H1N1) and influenza (H3N2) viruses. In the Spring of 2009, a new influenza A (H1N1) virus emerged to cause illness in people. This virus was very different from regular human influenza A (H1N1) viruses and the new virus caused the first influenza pandemic in more than 40 years. That virus (often called “2009 H1N1”) has now mostly replaced the H1N1 virus that was previously circulating in humans.

Influenza B viruses are not divided into subtypes, but can be further broken down into different strains. The CDC follows an internationally accepted convention for influenza viruses. This convention was accepted by the World Health Organization in 1979 and published in February 1980 in the Bulletin of World Health Organizations. The approach uses the following components:

1. The antigenic type (e.g., A,B,C)
2. The host of origin (e.g., swine, equine, chicken, etc. For human-origin viruses, no host of origin designation is given.)
3. Geographical origin (e.g., Denver, Taiwan, etc.)
4. Strain number (e.g., 15, 7, etc.)
5. Year of isolation (e.g., 57, 2009, etc.)
6. For influenza A viruses, the hemagglutinin and neuraminidase description in parentheses (e.g., (H1N1), (H5N1))

For example:

- A/duck/Alberta/35/76 (H1N1) for a virus from duck origin
- A/Perth/16/2009 (H3N2) for a virus from human origin

Influenza A (H1N1), A (H3N2), and influenza B viruses are included in each year’s influenza vaccine. Getting a flu vaccination can protect against flu viruses that are the same or related to the viruses in the vaccine. Information about this season’s vaccine can be found at [Preventing Seasonal Flu with Vaccination \(/flu/protect/vaccine/index.htm\)](http://www.cdc.gov/flu/protect/vaccine/index.htm). The seasonal flu vaccine does not protect against influenza C viruses. In addition, flu vaccines will NOT protect against

infection and illness caused by other viruses that can also cause influenza-like symptoms. There are many other non flu viruses that can result in influenza-like illness (ILI) that spread during the flu season.

Influenza viruses can change in two different ways. One is called “antigenic drift.” These are small changes in the virus that happen continually over time. Antigenic drift produces new virus strains that may not be recognized by the body’s immune system. This process works as follows: a person infected with a particular flu virus strain develops antibodies against that virus. As newer virus strains appear, the antibodies against the older strains no longer recognize the “newer” virus, and re_infection can occur. This is one of the main reasons why people can get the flu more than one time. In most years, one or two of the three virus strains in the influenza vaccine are updated to keep up with the changes in the circulating flu viruses. So, people who want to be protected from the flu need to get a flu shot every year.

The other type of change is called “antigenic shift.” Antigenic shift is an abrupt, major change in the influenza A viruses, resulting in new hemagglutinin and/or new hemagglutinin and neuraminidase proteins in influenza viruses that infect humans. Shift results in a new influenza A subtype or a virus with a hemagglutinin or a hemagglutinin and neuraminidase combination that has emerged from an animal population that is so different from the same subtype in humans that most people do not have immunity to the new (e.g. novel) virus. Such a “shift” occurred in the spring of 2009, when a new H1N1 virus with a new combination of genes emerged to infect people and quickly spread, causing a pandemic. When shift happens, most people have little or no protection against the new virus. While influenza viruses are changing by antigenic drift all the time, antigenic shift happens only occasionally. Type A viruses undergo both kinds of change; influenza type B viruses change only by the more gradual process of antigenic drift.

People with the flu can spread it to others up to about 6 feet away. Most experts think that flu viruses are spread mainly by droplets made when people with the flu cough, sneeze or talk. These droplets can land in the mouths or noses of

people who are nearby or possibly be inhaled into the lungs. Think of this next time you are chatting with a “close talker.” Less often, a person might also get the flu by touching a surface or object that has the flu virus on it and then touching their own mouth or nose.

To avoid this, people should stay away from sick people and stay home if sick. This is extra important to us as health care providers. We do not want to infect our patients. It is also important to wash hands often with soap and water. If soap and water are not available, use an alcohol-based hand rub. Linens, eating utensils, and dishes belonging to those who are sick should not be shared without washing thoroughly first. Eating utensils can be washed either in a dishwasher or by hand with water and soap and do not need to be cleaned separately. Further, frequently touched surfaces should be cleaned and disinfected at home, work and school, especially if someone is ill.

A number of flu tests are available to detect influenza viruses. The most common are called “rapid influenza diagnostic tests.” These tests can provide results in 30 minutes or less. Unfortunately, the ability of these tests to detect the flu can vary greatly. Therefore, you could still have the flu, even though your rapid test result is negative. In addition to rapid tests, there are several more accurate and sensitive flu tests available that must be performed in specialized laboratories, such as those found in hospitals or state public health laboratories. All of these require that a health care provider swipe the inside of your nose or the back of your throat with a swab and then send the swab for testing. These tests do not require a blood sample.

If you have flu-like symptoms, will your health care provider test you for the flu? Not necessarily. Most people with flu symptoms do not require testing because the test results usually do not change how you are treated. The health care provider may diagnose you with flu based on symptoms and their clinical judgment or they may choose to use an influenza diagnostic test. During an outbreak of respiratory illness, testing for flu can help determine if flu viruses are the cause of the outbreak. Flu testing can also be helpful for some people with

suspected flu who are pregnant or have a weakened immune system, and for whom a diagnosis of flu can help their doctor make decisions about their care.



The influenza vaccination is an annual vaccination using a vaccine specific for a given year to protect against the highly variable influenza virus. Each seasonal influenza vaccine contains antigens representing three (trivalent vaccine) or four (quadrivalent vaccine) influenza virus strains: one influenza type A subtype H1N1 virus strain, one influenza type A subtype H3N2 virus strain, and either one or two influenza type B virus strains. Influenza vaccines may be administered as an injection, also known as the dreaded “flu shot”, or as a nasal spray.

Yearly flu vaccination should begin soon after the flu vaccine is available, and ideally by October. However, getting vaccinated even later can be protective, as long as the flu viruses are circulating. While seasonal influenza outbreaks can happen as early as October, most of the time influenza activity peaks in January or later. Since it takes about two weeks after vaccination for antibodies to develop in the body that protect against influenza virus infection, it is best that people get vaccinated so they are protected before influenza begins spreading in their community.

Can a flu shot give you the flu? **No, a flu shot cannot cause flu illness.** Flu vaccines that are administered with a needle are currently made in two ways: the

vaccine is made either with a) with no flu vaccine viruses that have been inactivated and are therefore not infectious, or b) with no flu vaccine viruses at all (which is the case for recombinant influenza vaccine). The most common side effect from the influenza shot are soreness, redness, tenderness or swelling where the shot was given. Low grade fever, headache and muscle aches also may occur. In randomized blinded studies, where some people get inactivated flu shots and others get salt – water shots, the only differences in symptoms was increased soreness in the arm and redness at the injection site among people who got the flu shot. There were no differences in terms of body aches, fever, cough, runny nose or sore throat.

There are several reasons why someone might get a flu-like illness, even after they have been vaccinated against the flu.

1. One reason is that some people can become ill from other respiratory viruses besides the flu such as rhinoviruses, which are associated with the common cold, cause symptoms similar to the flu, and also spread and cause illness during the flu season. The flu vaccine only protects against influenza viruses, not other viruses.
2. Another explanation is that it is possible to be exposed to influenza viruses, which cause the flu, shortly before getting vaccinated or during the two-week period after vaccination that it takes the body to develop immune protection. This exposure may result in a person becoming ill with flu before protection from the vaccine takes effect.
3. A third reason why some people may experience flu like symptoms despite getting vaccinated is that they may have been exposed to a flu virus that is very different from the viruses the vaccine is designed to protect against. The ability of a flu vaccine to protect a person depends largely on the similarity or “match” between the viruses selected to make the vaccine and those spreading and causing illness. There are many different flu viruses that spread and cause illness among people.
4. A final explanation for experiencing flu-like symptoms after vaccination is that unfortunately, the flu vaccine doesn’t always provide adequate

protection against the flu. This is more likely to occur among people that have weakened immunity systems or people age 65 and older.

The United States Centers for Disease Control and Prevention recommend that everyone over the ages of 6 months should receive the seasonal influenza vaccine. Vaccination campaigns usually focus on people who are at risk of serious complications if they catch the flu, such as the elderly and people living with chronic illness or those with weakened immune systems, as well as health care workers.

The CDC has clearly stated that everyone who is at least 6 months of age should get the flu vaccine each season. This recommendation has been placed since February 24, 2010 when CDC's Advisory Committee on Immunization Practices (ACIP) voted for "universal" flu vaccination in the United States to expand protection against the flu to more people.

While everyone should get a flu vaccine this season, it's especially important for some people to get vaccinated.

Those people include the following:

- People who are at high risk of developing serious complications (like pneumonia) if they get sick with the flu.
- People who have certain medical conditions including asthma, diabetes, and chronic lung disease.
- Pregnant women
- People younger than 5 years (and especially those younger than 2), and people 65 years and older.
- People who live with or care for others who are at high risk of developing serious complications, such as:
 - Household contacts and caregivers of people with certain medical conditions including asthma, diabetes, and chronic lung disease.
 - Household contacts and caregivers of infants less than 6 months old.
 - Health care personnel.

- A complete list is available at [People Who Are at High Risk of Developing Flu-Related Complications \(/flu/about/disease/high_risk.htm\)](http://www.cdc.gov/flu/about/disease/high_risk.htm).

Most flu vaccines provide significant protection against the virus. Despite somewhat limited research, the safety of flu vaccines is reassuring; there is no evidence that they can cause serious harm, and no reason for serious side effects to be a concern.

According to the CDC, getting the flu vaccine is the best way to protect yourself against the flu and to help prevent its spread throughout the community. The flu vaccine can also reduce the severity of the flu even if a person contracts a strain of the flu that the vaccine did not contain.

An influenza epidemic emerges during the flu season each winter. There are two flu seasons annually, corresponding to the occurrence of winter in the Northern and Southern Hemispheres (winter in one hemisphere is at the same time as summer in the other).

Although difficult to assess, these annual epidemics are thought to result in between three and five million cases of severe illness and between 250,000 and 500,000 deaths every year around the world. Tens of thousands of Americans die in a typical flu season, but there are notable variations from year to year. In 2010 the Centers for Disease Control and Prevention (CDC) in the United States changed the way it reports the 30-year estimates for deaths from influenza. They are reported as a range from a low of about 3,000 deaths to a high of 49,000 per year over the past 30 years.

The majority of influenza-caused deaths in the industrialized world occur in adults aged 65 and over. A review at the National Institute of Allergy and Infectious Diseases (NIAID) division of the National Institutes of Health (NIH) in 2010 concluded that “Seasonal influenza causes more than 200,000 hospitalizations and 41,000 deaths in the U.S. each year, and is the seventh leading cause of death in the U.S.” The average total economic costs caused by the annual influenza outbreak in the U.S. have been estimated at over \$80 billion dollars.

The number of annual influenza-related hospitalizations is many times the number of deaths. “The high costs of hospitalizing young children for influenza creates a significant economic burden in the United States, underscoring the importance of preventive flu shots for children and the people with whom they have regular contact.” The CDC has projected that a total of 38 million days of school were missed by American students due to the flu.

The influenza vaccine has been demonstrated to prevent disease and death, both in numerous controlled studies and in painstaking reviews of these studies. The CDC reports that studies demonstrate that vaccination is a cost-effective counter-measure to seasonal outbreaks of influenza.

According to the research published in July 2011, vaccination against influenza is also thought to be important for members of high-risk groups who would be likely to suffer complications from influenza, for example pregnant women and children and teenagers from six months to 18 years of age;

- In raising the upper age limit to 18 years, the aim is to reduce both the time children and parents lose from visits to pediatricians and missing school and the need for antibiotics for complications.
- An added expected benefit would be indirect: reducing the number of influenza cases among parents and other household members, and possibly spread to the general community.

In one study of the elderly, flu vaccines cut the risk of death from influenza in half, and reduced the chance of hospitalization by more than a quarter.

For healthy, working adults, influenza vaccines can provide moderate protection against virologically confirmed influenza, but such protection is greatly reduced or absent in some seasons. Evidence for protection in adults aged 65 years or older is lacking. New vaccines with improved clinical efficacy and effectiveness are needed to further reduce influenza-related morbidity and mortality.

Influenza vaccination has been shown highly effective in health care workers (HCW), with minimal adverse effects. In a study of 40 matched nursing homes,

staff influenza vaccination rates were 69.9% in the vaccination arm versus 31.8% in the control arm. The vaccinated staff experienced a 42% reduction in sick leave from work ($P=.03$). A review of 18 studies likewise found a strong net benefit to health care workers. Of these eighteen HCW studies, only two also assessed the relationship of patient mortality relative to staff influenza vaccine uptake; both found that higher rates of health care worker vaccination correlated with reduced patient deaths. An analysis of data and patient population health in New Mexico's 75 long-term care facilities nursing homes found that as vaccination rates of health care personnel with direct patient contact rose from 51 to 75 percent, the chances of a flu outbreak among patients in that facility went down by 87 percent. The New Mexico study showed that vaccinating health care personnel provided more protection to residents than vaccinating the residents themselves. In a 2010 survey of United States healthcare workers, 63.5% reported that they received the flu vaccine during the 2010-11 season, an increase from 61.9% reported the previous season. Health professionals with direct patient contact had higher vaccination uptake.

It is important to note that the flu vaccine takes about two weeks to build up enough antibodies to protect against the flu (thus making the vaccinated person protected against the disease), and that the vaccine does not protect against every strain of the flu.

Vaccination of school-age children has a strong protective effect on the adults and elderly with whom the children are in contact. Children born to mothers who received the flu vaccination while pregnant are strongly protected from having to be hospitalized with the flu. "The effectiveness of influenza vaccine given to mothers during pregnancy in preventing hospitalization among their infants, adjusted for potential confounders, was 91.5%."

IN 2006, the United States began recommending influenza vaccinations for preschoolers, but Canada did not follow suit until 2010, "thereby creating a natural experiment to evaluate the effect of the policy in the United States." Studying the period from 2006 recommendation by the US and until 2010 when the Canadian recommendation to vaccinate preschoolers was initiated, a

Canadian study compared the proportion of pediatric emergency room visits that were for influenza-like illnesses at a Boston children's hospital and at a Montreal children's hospital over the course of several flu seasons. The study found that following the 2006 recommendation, the proportion of ER visits for influenza-like illness among 2-to 4-year-olds declined in Boston relative to the proportion of ER visits for influenza-like illness among 2-to 4-year-olds in Montreal.

In another six-year observational study, vaccination of children aged six months through five years was found to prevent illness in more than half.

Febrile seizures can occur when a child is sick with the influenza virus or other childhood illnesses that may cause fever. Febrile means "having a fever." A seizure is a convulsion or fit of uncontrolled body movements. A "febrile seizure" refers to a seizure/convulsion in a child associated with a fever. In children younger than 5 years old, having a fever for any reason (illness, vaccination, etc.) can bring on a febrile seizure. During a febrile seizure, a child often has spasms or jerking movements - large or small - and may lose consciousness. Febrile seizures usually last only a minute or two, and do not cause any permanent neurological damage. They are most common with body temperatures reaching 102 degrees or higher, but also can occur at lower body temperature or when a fever is going down. Therefore, febrile seizures are commonly seen during the cold and flu season in the United States. However, several studies of children in the United States have been conducted to see if there is an increased risk for febrile seizures following receipt of season flu vaccines. One study evaluated more than 45,000 children aged 6 months through 23 months of age who received influenza vaccines from 1991 through 2003 and did not find an association with seizures. In addition, there was no indication that seasonal flu vaccines or the 2009 H1N1 flu vaccines used in the United States during the 2009-2010 flu season were associated with an increased risk of febrile seizures.

On a separate note, during the 2010-2011 influenza season, CDC and the Food and Drug Administration (FDA) conducted monitoring for febrile seizures after influenza vaccination because of reports of an increased risk for fever and febrile seizures in young children in Australia associated with a 2010 Southern

Hemisphere vaccine produced by CSL Biotherapies (up to nine febrile seizures per 1,000 doses). Because of the findings in Australia, the U.S. ACIP does not recommend the U.S. – licensed CSL Biotherapies trivalent inactivated vaccine (Afluria) for children younger than 9 years.

In another study, CDC studied the health care visit records of more than 200,000 vaccinated children 6 months through 4 years of age through its [Vaccine Safety Datalink](#) project during the entire 2010-2011 influenza season. The analyses found that febrile seizures following inactivated influenza vaccine and pneumococcal conjugate (PCV13) vaccines given to this age group did occur, but were rare. The febrile seizures were most common in children ages 12 through 23 months when the two vaccines were given during the same health care visit. In this group, about one additional febrile seizure occurred among every 2,000 to 3,000 children vaccinated. After evaluating the data and taking into consideration benefits and risks of vaccination. After evaluating the data and taking into consideration benefits and risks of vaccination, the Advisory Committee on Immunization Practices (ACIP) has determined that no charges are recommended for the use of trivalent inactivated vaccine or PCV12 vaccines.

Febrile seizures are fairly common during childhood. About 2% to 5% of young children will have at least one febrile seizure, most febrile seizures occur in children between 6 months and 5 years of age. A child who has already had a febrile seizure is more likely to have another one. Also if a member of a child's immediate family (a brother, sister, or parent) has had febrile seizures, that child is more likely to have a febrile seizure. Nearly all children who have a febrile seizure recover quickly and are healthy afterward with no lasting effects. However, febrile seizures often result in a visit to an emergency room and can be very frightening for parents and caregivers.

About 1-in-3 children who have one febrile seizure will have at least one more febrile seizure during childhood. Most children (greater than 90%) who have a seizure will not develop epilepsy. Genetic predisposition (i.e., family history) and other factors such as cerebral palsy, delayed development, or other neurological abnormalities increase a child's risk for developing epilepsy after a febrile seizure.

In general, febrile seizures cannot be prevented. Some health care providers recommend aspirin-free fever-reducing medications to make the child more comfortable. Medicines, such as acetaminophen and ibuprofen can lower fevers in children. However, these medications have not been shown to prevent febrile seizures. To avoid choking, children should not be given medication or anything else by mouth during a seizure.

Vaccinations against the flu are directed at populations at a higher risk for infection, such as the elderly and the children. It is suggested that adults older than 50 years are at risk and should get vaccinated.

The flu vaccination may lead to side effects such as runny nose and sore throat, which can last for up to several days. Egg allergy may also be a concern, since flu vaccines are typically made using eggs, however research into egg-allergy and influenza vaccination has led some advisory groups to recommend vaccine delivery protocols for egg allergic persons. On January 17, 2013, the U.S. FDA approved Flublok, a faster-turnaround influenza vaccine which is the first grown in insect cells instead of eggs. It will be available in the 2013-14 season for people age 18-49, and avoids the problem with egg allergies.

Some injection-based flu vaccines intended for adults in the United States contain thiomersal (also known as thimerosal), a mercury-based preservative. Thimerosal is a mercury-based preservative that has been used for decades in the United States in multi-dose vials of some vaccines to prevent the growth of germs, bacteria and fungi, that can contaminate them. Despite some controversy in the media, the World Health Organization's Global Advisory Committee on Vaccine Safety has concluded that there is no evidence of toxicity from thiomersal in vaccines and no reason on grounds of safety to change to more-expensive single-dose administration.

Numerous studies have found no association between thimerosal exposure and autism. CDC places a high priority on vaccine safety, surveillance, and research. CDC is aware that the presence of the preservative thimerosal in vaccines and allegations of a relationship to autism have raised public concerns. These concerns have made decisions surrounding vaccinations confusing and difficult for

some people. Since 2001, no new vaccine licensed by FDA for use in children has contained thimerosal as a preservative and all vaccines routinely recommended by CDC for children younger than 6 years of age have been thimerosal-free, or contain only trace amounts of thimerosal, except for some formulations of the influenza vaccine. Unfortunately, reductions in the numbers of children identified with autism have not been observed indicating that the cause of autism is not related to a single exposure such as thimerosal. The federal government is committed to ensuring the safety of vaccines. This is achieved by FDA oversight of rigorous pre-licensure trials and post-licensure monitoring by CDC and FDA. This commitment stems from scientific, medical and personal dedication.

Although Guillain-Barre syndrome had been feared as a complication of vaccination, the CDC states that most studies on modern influenza vaccines have seen no link with Guillain-Barre. Getting infected by influenza itself increases both the risk of death (up to 1 in 10,000) and increases the risk of developing Guillain-Barre syndrome to a much higher level than the highest level of suspected vaccine involvement (approx. 10 times higher by 2009 estimates).

Guillain-Barre syndrome (GBS) is a rare disorder in which a person's own immune system damages their nerve cells, causing muscle weakness and sometimes paralysis. GBS can cause symptoms that last for a few weeks. Most people recover fully from GBS, but some people have permanent damage. In very rare cases, people have died of GBS, usually from difficulty breathing. In the United States, for example, as estimated 3,000 to 6,000 people develop GBS each year on average, whether or not they received a vaccination. Many things can cause GBS; about two thirds of people who develop GBS symptoms do so several days or weeks after they have been sick with diarrhea or a respiratory illness. Infection with the bacterium *Campylobacter jejuni* is one of the most common risk factors for GBS. People also can develop GBS after having the flu or other infections (such as cytomegalovirus and Epstein Barr virus). On very rare occasions, they may develop GBS in the days or weeks after getting a vaccination.

Anyone can develop GBS; however, it is more common among older adults. The incidence of GBS increases with age, and people older than 50 years of age are at greatest risk for developing GBS. GBS is rare. Medical events occur regardless of vaccination, and background rates are used to assess vaccine safety by comparing the expected rate of disease or death to the actual or observed rate in any given timeframe. The background rate for GBS in the U.S. is about 80 to 160 cases of GBS each week, regardless of vaccination.

In 1976 there was a small increased risk of GBS following vaccination with an influenza vaccine made to protect against a swine flu virus. The increased risk was approximately 1 additional case of GBS per 100,000 people who got the swine flu vaccine. The Institute of Medicine (IOM) conducted a thorough scientific review of this issue in 2003 and concluded that people who received the 1976 swine influenza vaccine had an increased risk for developing GBS. Scientists have multiple theories on why this increased risk may have occurred, but the exact reason for this association remains unknown.

A review has concluded that the 2009 H1N1 (“swine flu”) vaccine has a safety profile similar to that of a seasonal vaccine. Although one review gives an incidence of about one case per million vaccinations, a large study in China, reported in *The New England Journal of Medicine* covering close to 100 million doses of vaccine against the 2009 H1N1 “swine flu” found only eleven cases of Guillain-Barre syndrome, (0.1 per million doses) total incidence in persons vaccinated, actually lower than the normal rate of the disease in China, and no other notable side effects; “The risk-benefit ratio, which is that vaccines and everything in medicine is about, is overwhelmingly in favor of vaccinations.” Several studies have identified an increased incidence of narcolepsy among recipients of the pandemic H1N1 influenza AS03-adjuvanted vaccine, efforts to identify a mechanism for this suggests that narcolepsy is autoimmune, and that the H1N1 vaccine may mimic hypocretin, serving as a trigger.

A vaccine is assessed by its efficacy; the extent to which it reduced risk of disease under controlled conditions, and its effectiveness, the observed reduction in risk after the vaccine is put into use. In the case of influenza, effectiveness is

expected to be lower than the efficacy because it is measured using the rates of influenza-like illness, which is not always caused by influenza. Influenza vaccines generally show high efficacy, as measured by the antibody production induced in animal models or vaccinated people, or most rigorously, by immunizing healthy adult volunteers and then challenging them with virulent influenza virus. However, studies on the effectiveness of flu vaccines in the real world are uniquely difficult; vaccines may be imperfectly matched, virus prevalence varies widely between years, and influenza is often confused with other influenza-like illnesses. However, in most years (16 of the 19 years before 2007), the flu vaccine strains have been a good match for the circulating strains, and even a mismatched vaccine can often provide cross-protection.

Nevertheless, multiple clinical trials of both live and inactivated influenza vaccines against seasonal influenza have been performed and their results pooled and analyzed in several 2012 meta-analyses. Studies on live vaccines have very limited data, but these preparations may be more effective than inactivated vaccines. The meta-analyses examined the efficacy and effectiveness of inactivated vaccines against seasonal influenza in adults, children, and the elderly. In adults, vaccines show a three-quarters reduction in risk of contracting influenza (4% influenza rate among the unvaccinated versus 1% among vaccinated persons) when the vaccine is perfectly matched to the virus and a one-half reduction (2% get the flu without vaccine versus 1% with the vaccine) when it is not, but no significant effect on the rate of hospitalization. However, the risk of serious complications from influenza is small in adults, so unless the effect from vaccination is large it might not have been detected. In children, vaccines again showed high efficacy, but low effectiveness in preventing “flu-like illness”. In children under the age of two, the data are extremely limited, but vaccination appeared to confer no measurable benefit. In the elderly, while many individual studies show effectiveness, the overall evidence is still insufficient evidence to draw clear conclusions on the effectiveness of vaccination, including a new high-dose flu vaccine formulated to provide a larger immune response. Available evidence indicated that the high-dose vaccine produces a stronger immune response, and a study designed to determine the effectiveness of Fluzone High-

Dose in preventing illness from influenza compared with Fluzone is expected to be completed in 2014-2015.

During an influenza pandemic, where a single strain of virus is responsible for illnesses, an effective vaccine could produce a large decrease in the number of cases and be highly effective in controlling an epidemic. However, such a vaccine would have to be produced and distributed rapidly to have maximum effect. Such distribution challenges may be met with good success. Overall, vaccines against the 2009 H1N1 influenza pandemic were found to be effective in a Scottish study.

A 2011 meta-study published in the journal *The Lancet*, "Efficacy and Effectiveness of Influenza Vaccines," analyzed 31 prior studies on the effectiveness of influenza vaccination trials conducted between 1967-2011. The analysis found that flu shots were efficacious 67 percent of the time; the populations that benefited the most were HIV-positive adults ages 18 to 55 (76 percent), healthy adults ages 18 to 46 (approximately 70 percent) and healthy children ages 6 to 24 months (66 percent).

The group most vulnerable to non-pandemic flu, the elderly, is also the least likely to benefit from the vaccine. There are multiple reasons behind this steep decline in vaccine efficacy, the most common of which are the declining immunological function and frailty associated with advanced age. In a non-pandemic year, a person in the United States aged 50-64 is nearly ten times more likely to die an influenza-associated death than a younger person, and a person over age 65 is over ten times more likely to die an influenza-associated death than the 50-64 group.

As mortality is also high among infants who contract influenza, the household contact and caregivers of infants should be vaccinated to reduce the risk of passing an influenza infection to the infant. Data from the years when Japan required annual flu vaccinations for school-aged children indicate that vaccinating children – the group most likely to catch and spread the disease – has a strikingly positive effect on reducing mortality among older people, due to herd immunity: one life saved for every 420 children who received the flu vaccine. However, a 2010 Cochrane review found that the same benefit did not extend to vaccinating

health care workers working with the elderly patients in long-term care facilities. In working adults, by contrast, Cochrane found that vaccination reduced both influenza symptoms and working days lost, without affecting transmission or influenza-related complications.

According to work published in 1973, 1983, and 2004, after vaccination against seasonal flu, antibody titres peak after typically two to four weeks. They decrease by about 50% over the next six months (the decrease is less for older adults), then remain stable for two to three years; protection without revaccination persists for at least three years for children and young adults.

It was previously thought that vaccination provided lifelong protection against specific strains. This is not totally untrue; a 2010 study found a significantly enhanced immune response against the 2009 pandemic H1N1 in study participants who had received vaccination against the swine flu in 1976. Also, a study, published in *Nature*, found that 90 years after the 1918 pandemic, survivors had antibody-producing cells that produced antibodies with “remarkable power to block 1918 flu virus infection in mice, proving that, even after nine decades after infection with this virus, survivors retain protection from it”. This immunity was a consequence of infection, not vaccination.

Flu vaccines are available either as

- TIV, QIV (injection or trivalent or quadrivalent, killed vaccine)
- LAIV, Q/LAIV (nasal spray of live attenuated influenza vaccine)

Vaccine	Trade name	Manufacturer	Age group
TIV	Fluzone	sanofi pasteur	≥6 mos
TIV	Fluvirin	Novartis Vaccine	≥4 yrs
TIV	Agriflu	Novartis Vaccine	≥18 yrs
TIV	Fluarix	GlaxosmithKline	≥3 yrs
TIV	FluLaval	ID Biomedical Corp. of Quebec, a subsidiary of GlaxoSmithKline	≥18 yrs
TIV	Afluria*	CSL Biotherapies	≥9 yrs
TIV High Dose	Fluzone High Dose	sanofi pasteur	≥65 yrs
LAIV	FluMist	Medimmune	2-49 yrs

*However, if no other age-appropriate, licensed inactivated seasonal influenza vaccine is available for a child aged 5 years through 8 years old who has a medical condition that increases their risk for influenza complications; providers may use Afluria. However, providers should discuss the benefits and risks of influenza vaccination with the parents or caregivers before administering Afluria.

TIV induces protection after injection (typically intramuscular, though subcutaneous and intradermal routes can also be protective) based on an immune response to the antigens present on the inactivated virus, while cold-adapted LAIV works by establishing infection in the nasal passages.

LAIV is not recommended for individuals under age 2 or over age 50, but might be comparatively more effective among children over age 2.

A study of military personnel showed that flu shots yielded less illness than nasal spray. This study was based on one of the largest head-to-head studies comparing LAIV and TIV. It was conducted by the U.S. Armed Forces Surveillance Center, on military personnel stationed in the U.S. during three flu seasons from 2004 through 2007. Investigators concluded that: "It may be prudent to use TIV in patients who were vaccinated at least once in the past 2 years, but LAIV against pandemic strains may be more protective than inactivated vaccines, because the population will probably lack preexisting immunity."

Annual season flu vaccination provides some protection against flu viruses that the vaccine was not designed for, including novel viruses. The CDC made the following statements in relation to the 2007-2008 vaccine: Antibodies made in response to vaccination with one strain of influenza viruses can provide protection against different, but related strains. A less-than-ideal match may result in reduced vaccine effectiveness against the variant viruses, but it still can provide enough protection to prevent or lessen illness severity and prevent flu-related complications. In addition, it is important to remember that the influenza vaccine contains three virus strains so the vaccine can also protect against the other two viruses. For these reasons, even during seasons when there is a less than ideal match, CDC continues to recommend influenza vaccination. This is particularly important for people at high risk for serious flu complications and their close contacts.

The cost-effectiveness of seasonal influenza has been widely evaluated for different groups and in different settings. In the elderly (aged over 65 years) the majority of published studies have found that vaccination is cost saving, with the cost savings associated with influenza vaccination (e.g. prevented health care

visits) outweighing the cost of vaccination. In older adults (aged 50-64 years), several published studies have found that influenza vaccination is likely to be cost-effective, however the results of these studies often found to be dependent on key assumptions used in the economic evaluations. The uncertainty in influenza cost-effectiveness models can partially be explained by the complexities involved in estimating the disease burden, as well as the seasonal variability in the circulating strains and the match of the vaccine. In healthy working adults (aged 18-49), a 2012 review found that vaccination was generally not cost-saving, with the suitability for funding being dependent on the willingness to pay to obtain the associated health benefits. In children, the majority of studies have found that influenza vaccination was cost-effective, however many of the studies included (indirect) productivity gains, which may not be given the same weight in all settings. Several studies have attempted to predict the cost-effectiveness of interventions (including pre-pandemic vaccination) to help protect against a future pandemic, however estimating the cost-effectiveness has been complicated by uncertainty as to the severity of the potential future pandemic and the efficacy of measures against it.

Various public health organizations, including the World Health Organization, have recommended that yearly influenza vaccination be routinely offered to patients at risk of complications of influenza and those individuals who live with or care for high-risk individuals, including:

- The elderly (UK recommendation is those age 65 or above)
- Patients with chronic lung disease (asthma, COPD, etc.)
- Patients with chronic heart diseases (congenital heart disease, chronic heart failure, ischaemic heart disease)
- Patients with chronic liver diseases (including cirrhosis)
- Patients with chronic renal disease (such as the nephritic syndrome)
- Patients who are immunosuppressed (those with HIV or who are receiving drugs to suppress the immune system such as chemotherapy and long-term steroids) and their household contacts

- People who live together in large numbers in an environment where influenza can spread rapidly, such as prisons, nursing homes, schools, and dormitories
- People who plan to attend or participate in a high profile important event with large numbers of people from various places (such as the Olympic Games, FIFA World Cup, and the World's Fair)
- People who are in the armed forces
- Healthcare workers (both to prevent sickness and to prevent spread to patients)
- Pregnant women. However, a 2009 review concluded that there was insufficient evidence to recommend routine use of trivalent influenza vaccine during the first trimester of pregnancy. Influenza vaccination during the flu season is part of recommendation for influenza vaccination of pregnant women in the United States

Both types of flu vaccines are contraindicated for those with severe allergies to egg proteins and people with a history of Guillain-Barre syndrome.

As of 2013, the UN World Health Organization recommends vaccination for, in order of priority:

1. Nursing-home residents (the elderly or disabled)
2. People with chronic medical conditions
3. Elderly individuals
4. Other groups such as pregnant women, health care workers, those with essential functions in society, as well as children from 6-24 months.

According to the CDC, the live attenuated virus (which comes in the form of the nasal spray in the US) should be avoided by:

- Children younger than 2 years
- Adults age 50 years and older
- People with a history of severe allergic reaction to any component of the vaccine or to a previous dose of any influenza vaccine.
- People with asthma

- Children or adolescents on long-term aspirin treatment
- Children and adults who have chronic pulmonary, cardiovascular, (except isolated hypertension), renal hepatic, neurologic/neuromuscular, hematologic, or metabolic disorders
- Children and adults who have immunosuppression (including immunosuppression caused by medications or by HIV)
- Pregnant women

In 2008, the National Advisory Committee on Immunization, the group that advises the Public Health Agency of Canada, recommended that everyone aged 2 to 64 years be encouraged to receive annual influenza vaccination, and children between the ages of six and 24 months, and their households contacts, should be considered a high priority for the flu vaccine. The NACI also recommends the flu vaccine for:

- People at high risk of influenza-related complications or hospitalization, including the morbidly obese, healthy pregnant women, children 6 to 59 months, the elderly, aboriginals, and people suffering from one of an itemized list of chronic health conditions
- People capable of transmitting influenza to those at high risk, including household contacts and healthcare workers
- People who provide essential community services
- Certain poultry workers

In the United States, “Routine influenza vaccination is recommended for all persons aged greater than 6 months” since 2010. Within its blanket recommendation for general vaccination in the United States, the Centers for Disease Control and Prevention (CDC), who began recommending the influenza vaccine to health care workers in 1981, emphasizes to clinicians the special urgency of vaccination for members of certain vulnerable groups, and their caregivers: Vaccination is especially important for people at higher risk of serious influenza complications or people who live with or care for people at higher risk for serious complications. In 2009, a new high-dose formulation of the standard influenza vaccine was approved. The Fluzone High Dose is specifically for people

65 and older; the difference is that it has four times the antigen dose of the Fluzone.

The U.S. Government requires hospitals to report worker vaccination rates. Some U.S. states and hundreds of U.S. hospitals require health-care workers to either get vaccinations or wear masks during flu season. These requirements occasionally engender union lawsuits on narrow collective bargaining grounds, but proponents note that courts have generally endorsed forced vaccination laws affecting the general population during disease outbreaks.

Vaccines have been formulated against several of the avian H5N1 influenza varieties. Vaccination of poultry against the ongoing H5N1 epizootic is widespread in certain countries. Some vaccines also exist for use in humans, and others are in testing, but none have been made available to civilian populations, nor produced in quantities sufficient to protect more than a tiny fraction of the Earth's population in the event of an H5N1 pandemic.

Each year, the CDC conducts studies to estimate how well the flu vaccine protects against having to go to the doctor because of a flu illness. In 2012-2013, CDC is publishing information about how well the flu vaccine is working in the United States at three different times during the season: the beginning, middle, and end of the flu season. (Note: For the 2013-2014 flu season CDC plans to publish a middle and end-of-season estimate, but not a beginning of season estimate. An early season estimate was done in 2012 as a result of the high levels of early season flu activity). CDC's estimates of the benefits of flu vaccine (also known as vaccine effectiveness or "VE" for short) are based on information CDC collects as the flu season progresses. Throughout the flu season, CDC collects data to determine how well the flu vaccine works in different age groups, and how well it works against the specific flu viruses that are spreading and causing illness. CDC's estimates of vaccine effectiveness can change over time as more information is collected. The CDC publishes estimates of vaccine effectiveness to help inform prevention and treatment decisions made by doctors and other health care practitioners during the flu season.

CDC's mid-season VE estimates were published on February 21, 2013, in a Morbidity and Mortality Weekly Report entitled: "Interim Adjusted Estimates of Seasonal Influenza Vaccine Effectiveness-United States, February 2013.

Overall, the VE estimate for protecting against having to go to the doctor because of the flu illness was 56% for all age groups (95% confidence interval: 47% to 63%). This VE estimate means that getting a flu vaccine in 2013 reduced the vaccinated population's risk of having to go to the doctor because of the flu by more than half. However, VE can vary across age groups and across different flu viruses, so CDC further analyzed the VE estimates to adjust for these factors. When broken down by different age groups, the VE against flu A and B viruses ranged from 27% in people 65 and older to 64% in children (aged 6 months to 17 years old).

When looking at the flu virus specific VE, effectiveness against flu A (H3N2) virus – which was the main virus spreading in 2013, it was estimated to be 47% (95% CI: 35% to 58%), while effectiveness against flu B was 67% (95%CI:51% to 78%) for all ages.

These results indicate that vaccination with the 2012-2013 flu season vaccine reduced the risk of flu-associated medical visits from flu A (H3N2) viruses by one half and from flu B viruses by two-thirds for most of the population. Overall, VE estimates

Suggest that the 2012-2013 flu vaccine has moderate effectiveness for most people against the flu viruses spreading in the United States, similar to previously published reports. The one exception to this was the VE among people 65 and older against flu A (H3N2) viruses, which was lower. The single point estimate for VE in this age group was 9% (95% CI:-84% to 55%). Note that because the confidence interval crossed zero for the 65 and older age group, this estimate is not statistically significant, and therefore, the results should be interpreted with caution. Overall, this estimate means that vaccine effectiveness was lower than expected in this age group against flu A (H3N2) viruses.

These overall vaccine effectiveness estimates are within the range expected during the flu seasons when most flu viruses spreading causing illness are like the viruses the flu vaccine is designed to protect against, which is the case of the 2013 season. Flu vaccination, even with moderate effectiveness of about 60%, can also reduce the following: flu-related illness, antibiotic use, time lost from work, hospitalizations, and deaths.

The early season results and the mid-season results published by the CDC are consistent with each other. The CDC published its early season flu vaccine effectiveness (VE) estimates on January 11, 2013. This estimate was preliminary, but it provided an overall look at how well the flu vaccine was working against all flu viruses in the United States across the whole population. Unlike the mid season VE estimate, this early season VE estimate did not look at how well the flu vaccine was working in different age groups or against specific subtypes of flu viruses. For the 2012 estimate, the CDC reported VE of 62% (95% CI: 51%-71%). CDC's mid-season VE estimates published in February included an additional 3 weeks of data collected during the peak of the flu season. These estimates were adjusted to control for characteristics of the study participants that can bias results. For example, CDC adjusted for the following characteristics: age, race/ethnicity, study site, self-rated health, and days from illness onset to enrollment in the study. Adjusting for these factors can change the overall estimate of VE, but it's reassuring that the CDC's early season VE estimate and mid-season estimate are not significantly different. The CDC's end of the season VE estimates will also adjust for medical conditions that are associated with increased risk of serious complications from the flu.

The CDC's study measured lower VE among people 65 and older against flu A in 2013 than it did among other age groups. However, VE against flu B was similar to what was seen in other age groups, while VE against flu A (H3N2) viruses in people 65 and older was significantly lower than in other age groups. One possible explanation for this is that some older people did not mount an effective immune response to the A (H3N2) virus component of the 2013 season's flu vaccine; however, it's not possible to say this for certain.

Despite the fact that flu vaccines can work less well in people who are 65 and older, there are many reasons why people in that age group should be vaccinated each year.

- First, people 65 and older are at higher risk of getting seriously ill, being hospitalized and dying from the flu.
- Second, while the effectiveness of the flu vaccine can be lower among older people, there are seasons when significant benefit can be observed in terms of averting illness that results in a doctor's visit. Even if the vaccine provides less protection in older adults than it might in younger people, some protection is better than no protection at all, especially in this high risk group.
- Third, current CDC studies look at how well the vaccine works in preventing flu illness that results in a doctor's visit or admission to a hospital. This is just one outcome. There are other studies that look at the effects of flu vaccination on hospitalization rates as well as looking at death as an outcome. For example, one study concluded that one death was prevented for every 4,000 people vaccinated against the flu.
- In frail elderly adults, hospitalizations can mark the beginning of a significant decline in overall health and mobility, potentially resulting in loss of the ability to live independently or to complete basic activities of daily living. While the protection elderly adults obtain from the flu vaccination can vary significantly, a yearly flu vaccination is still the best protection currently available against the flu.
- There are limited data to suggest that flu vaccination may reduce flu illness severity; so while someone who is vaccinated may still get infected, their illness may be milder.
- Fourth, it's important to remember that people who are 65 and older are a diverse group and often are different from one another in terms of their overall health, level of activity and mobility, and behavior when it comes to seeking medical care. This group includes people who are healthy and active and have responsive immune systems, as well as those who have underlying medical conditions that may weaken their immune system, and

therefore, their bodies' ability to respond to vaccination. Therefore, when evaluating the benefits of flu vaccination, it's important to look at a broader picture than what one study's finding can present. Although the flu vaccine is not perfect, the overall evidence supports the public health benefit of flu vaccination. Vaccination is particularly important for people 65 and older who are especially vulnerable to serious illness and death, despite the fact that the vaccine may not work as well in this group.

From September 30, 2012, to February 9, 2013, 64 flu-related deaths in children were reported to the CDC. Sixteen deaths in children were associated with flu A H3N2 virus infection, 19 deaths were associated with flu A virus infection that was not subtyped, and 29 deaths were associated with flu B virus infection.

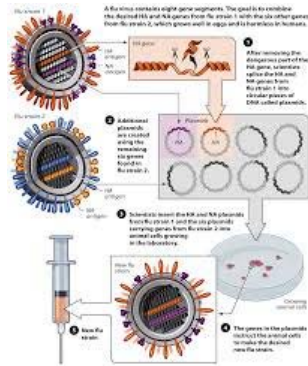
You should still get vaccinated even if you have already gotten sick with the flu. There are a couple of reasons why you should be vaccinated even if you have already been sick with symptoms of the flu this season. First, it's possible that your illness was not caused by a flu virus. There are other respiratory viruses circulating along with the flu that can have similar flu symptoms. The only way to know for sure that a flu virus is making you sick is to have a sample taken and tested in a laboratory. Second, even if you were sick with one flu virus, the seasonal flu vaccine protects against the three flu viruses that research suggests will be most common. This means the flu vaccine can offer protection against other flu viruses you haven't been exposed to you.

It is possible to get sick with the flu even if you have been vaccinated (although you won't know for sure unless you get a positive flu test). This is possible for the following reasons:

- You may be exposed to a flu virus shortly before getting vaccinated or during the period that it takes the body to gain protection after getting vaccinated. This exposure may result in you becoming ill with the flu before the vaccine begins to protect you. (About 2 weeks after vaccination, antibodies that provide protection develop in the body).

- You may be exposed to a flu virus that is not included in the seasonal flu vaccine. There are many different flu viruses that circulate every year. The composition of the flu shot is reviewed each season and updated if needed to protect against the three viruses that research suggests will be most common. Characterization of flu viruses collected in 2013 indicated that most circulating viruses are like the vaccine viruses; however, there is a smaller percentage of viruses that the flu vaccine would not be expected to protect against.
- Unfortunately, some people can become infected with a flu virus the flu vaccine is designed to protect against despite get vaccinated. Protection provided by flu vaccination can vary widely, based in part on health and age factors of the person getting vaccinated. In general, the flu vaccine works best among healthy adults and older children. Some older people and people with certain chronic illnesses may develop less immunity after vaccination. While vaccination offers the best protection against flu infection, it's still possible that some people may become ill after being vaccinated. Lu vaccination is not a perfect tool, but it is the best tool currently at our disposal to prevent the flu.

The CDC has received reports of some people who were vaccinated against the flu becoming ill and testing positive for the flu. This occurs every season. The 2012-2013 flu season was an early season, with more flu activity reported in early weeks than was seen during recent previous flu seasons. There are, however, a number of reasons why people who got a flu vaccine may still get the flu every season. To estimate how well flu vaccines work each year, the CDC has been working with researchers at universities and hospitals since the 2004-2005 flu season conducting observational studies using laboratory-confirmed flu as the outcome.



How is the flu vaccine manufactured? The flu vaccine is usually grown by vaccine manufacturers in fertilized chicken eggs. In the Northern hemisphere, the manufacturing process begins following the announcement (typically in February) of the WHO recommended strains for the winter flu season. Three strains (representing an H1N1, an H3N2, and a B strain) of the flu are selected and chicken eggs inoculated separately, these monovalent harvests are then combined to make the trivalent vaccine.

As of November 2007, both the conventional injection and the nasal spray are manufactured using chicken eggs. The European Union has also approved Optaflu, a vaccine produced by Novartis using vats of animal cells. This technique is expected to be more scalable and avoid problems with eggs, such as allergic reactions and incompatibility with strains that affect avians like chickens. Research continues into the idea of a “universal” influenza vaccine that would not require tailoring to a particular strain, but would be effective against a broad variety of influenza viruses. However, no vaccine candidates had been announced by November 2007.

A DNA-based vaccination, which is hoped to be even faster to manufacture, is as of 2011 in clinical trials, determining safety and efficacy. On November 20, 2012, Novartis received DNA approval for the first cell-culture vaccine.

In a 2007 report, the global capability of approximately 826 million seasonal influenza vaccine doses (inactivated and live) was double the production of 413

million doses. In an aggressive scenario of producing pandemic influenza vaccines by 2013, only 2.8 billion courses could be produced in a six-month time frame. If all high-and upper-middle income countries sought vaccines for their entire populations in a pandemic, nearly 2 billion courses would be required. If China pursued this goal as well, more than 3 billion courses would be required to serve these populations. Vaccine research and development is ongoing to identify novel vaccine approaches that could produce much greater quantities of vaccine at a price that is affordable to the global population.

Methods of vaccine generation that bypass the need for eggs include the construction of influenza virus-like particles (VLP). VLP resemble viruses, but there is no need for inactivation, as they do not include viral coding elements, but merely present antigens in a similar manner to a virion. Some methods of producing VLP include cultures of *Spodoptera frugiperda* Sf9 insect cells and plant-based vaccine production (e.g., production in *Nicotiana benthamiana*). There is evidence that some VLPs elicit antibodies that recognize a broader panel of antigenically distinct viral isolates compared to other vaccines in the hemagglutination-inhibition assay (HIA).

The seasonal influenza vaccine is designed to protect against the influenza viruses research indicates are most likely to spread and cause illness among people during the upcoming flu season. Flu viruses are constantly changing, so the vaccine is updated each year based on which influenza viruses are making people sick, now those viruses are spreading, and how well the previous season's vaccine protects against those viruses.

More than 100 national influenza centers in over 100 countries conduct year-round surveillance for influenza. This involves receiving and testing thousands of influenza virus samples from patients with suspected flu illness. The laboratories send representative viruses to five World Health Organization (WHO) Collaborating Centers for Reference and Research on Influenza, which are located in the following places:

- Atlanta, Georgia USA (Centers for Disease Control and Prevention, CDC);

- London, United Kingdom (National Institute for Medical Research);
- Melbourne, Australia (Victoria Infectious Diseases Reference Laboratory);
- Tokyo, Japan (National Institute for Infectious Diseases); and
- Beijing, China (National Institute for Viral Disease Control and Prevention).

Each year, three strains are chosen for selection in that year's flu vaccination by the WHO Global Influenza Surveillance Network. The chosen strains are the H1N1, H3N2, and Type-B strains thought most likely to cause significant human suffering in the coming season. Starting with the 2012-2013 Northern Hemisphere influenza season (coincident with the approval of quadrivalent influenza vaccines), the WHO has also recommended a 2nd B-strain for use in quadrivalent vaccines. The World Health Organization coordinates the contents of the vaccine each year to contain the most likely strains of the virus to attack the next year.

On February 27, 2013, VRBAC met and approved for the United States the following WHO-recommended composition for the Northern Hemisphere 2013-2014 influenza vaccine.

- An A/California/9/2009(H1N1)pdm09-like virus;
- An A(H3N3) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011;
- A B/Massachusetts/2/2012-like(Yamagata lineage) virus.

The WHO Global Influenza Surveillance Network was established in 1952. The network comprises 4 WHO Collaborating Centers (WHO CCs) and 112 institutions in 83 countries, which are recognized by WHO as WHO National Influenza Centres (NICs). These NICs collect specimens in their country, perform primary virus isolation and preliminary antigenic characterization. They ship newly isolated strains to WHO CCs for high level antigenic and genetic analysis, the result of which forms the basis for WHO recommendations on the composition of influenza vaccine for the Northern and Southern Hemisphere each year.

The Global Influenza Surveillance Network's selection of viruses for the vaccine manufacturing process is based on its best estimate of which strains will

predominate the next year, amounting in the end to well-informed, but fallible guesswork.

Formal WHO recommendations first issued in 1973; beginning in 1999, there have been two recommendations per year, one for the northern hemisphere and the other for the southern hemisphere.

Recent WHO seasonal influenza vaccine composition recommendation:

2014 Southern Hemisphere influenza season

The composition of virus vaccines for use in the 2014 Southern Hemisphere influenza season recommended by the World Health Organization on September 26, 2013 was:

- An A/California/7/2009 (H1N1)pdm09-like virus;
- An A/Texas/50/2012 (H3N2)-like virus;
- A B/Massachusetts/2/2012-like virus.

It is recommended that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus.

2013-2014 Northern Hemisphere influenza season

The composition of virus vaccines for use in the 2013-2014 Northern Hemisphere influenza season recommended by the World Health Organization on February 20, 2013 was:

- An A/California/7/2009 (H1N1)pdm09-like virus;
- An A (H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 (WHO recommends A/Texas/50/2012 for the A(H3N2) vaccine component because of antigenic changes in earlier A/Victoria/361/2011-like vaccine viruses (such as IVR-165) resulting from adaptation to propagation in eggs)
- B/Massachusetts/2/2012-like virus.

WHO recommends that quadrivalent vaccines containing two influenza B viruses contain the above three viruses and a B/Brisbane/60/2008-like virus.

The H1N1 strain used in these compositions is the same strain used in the 2009 flu pandemic vaccine, now known as A(H1N1)odm09. As of December 2013, vaccine manufacturers estimate that 138-145 million doses of flu vaccine to be produced during the 2013-2014 Northern Hemisphere influenza season.

Every year, multiple manufacturers produce and market the influenza vaccination. Below is a list of the common vaccinations available.

- Flulaval – Distributed by GlaxoSmithKline and manufactured in Quebec City, QC, Canada.
- Afluria – Distributed by Merck and manufactured in Parkville, Victoria Australia.
- Fluarix – Distributed by GlaxoSmithKline and manufactured in Dresden, Germany.
- Fluvirin – Distributed by Novartis and manufactured in Liverpool, UK.
- Fluzone – Distributed by Sanofi Pasteur and manufactured in Swiftwater, PA 18370 USA.

Fluzone, Fluzone High-Dose, Fluzone Intradermal and Fluzone Quadrivalent are all injectable influenza vaccines made to protect against the flu strains most likely to cause illness for that particular flu season. Fluzone High-Dose vaccine contains four times the amount of antigen (the part of the vaccine that prompts the body to make antibody) contained in regular flu shots. The additional antigen is intended to create a stronger immune response (more antibodies) in the person getting the vaccine.

The intradermal flu vaccine is a shot that is injected into the skin instead of the muscle. The intradermal shot uses a 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 18-84 years of age.

Human immune defenses become weaker with age, which places older people at greater risk of severe illness from influenza. Also, aging decreases the body's ability to have a good immune response after getting the influenza vaccine. A higher dose of antigen in the vaccine is supposed to give older people a better immune response, and therefore, better protection against the flu.

The safety profile of Fluzone High-Dose vaccine is similar to that of regular flu vaccines, although some adverse events (which are also reported after regular flu vaccines) were reported more frequently after vaccination with Fluzone High-Dose. The most common adverse events experienced during clinical studies were mild and temporary, fever and malaise. Most people had minimal or no adverse events after the Fluzone High-Dose vaccine. Fluzone High-Dose is approved for use in people 65 years of age and older. As with all flu vaccines, Fluzone High-Dose is **not** recommended for people who have had a severe reaction to the flu vaccine in the past.

Vaccines are used in both humans and nonhumans. Human vaccine is meant unless specifically identified as a veterinary, poultry or livestock vaccine.

The first influenza pandemic was recorded in 1580. However, the etiological cause of influenza, the orthomyxoviridae was discovered by the Medical Research Council (MRC) of the United Kingdom in 1933.

Known flu pandemics

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Name of pandemic	Date	Deaths	<u>Case fatality rate</u>	Subtype involved	<u>Pandemic severity index</u>
<u>1889–1890 flu pandemic</u> (Asiatic or Russian Flu) ^[136]	1889– 1890	1 million	0.15%	possibly <u>H3N8</u> or <u>H2N2</u>	NA
<u>1918 flu pandemic</u> (Spanish flu) ^[137]	1918– 1920	20 to 100 million	2%	<u>H1N1</u>	5
<u>Asian Flu</u>	1957– 1958	1 to 1.5 million	0.13%	<u>H2N2</u>	2
<u>Hong Kong Flu</u>	1968– 1969	0.75 to 1 million	<0.1%	<u>H3N2</u>	2
<u>Russian flu</u>	1977– 1978	no accurate count	N/A	<u>H1N1</u>	N/A
<u>2009 flu pandemic</u> ^{[138][139]}	2009– 2010	18,000	0.03%	<u>H1N1</u>	NA

The CDC carries out and supports flu research in an effort to reduce the health burden flu places on society and to promote improvements in human health. The CDC supports collaborative research projects with the World Health Organization (WHO), state, local, and federal government partners, academic institutions, and other international partners. In addition, the CDC also conducts its own public health research. Recent or ongoing areas of flu research by the CDC include the reconstruction and analysis of the 1918 pandemic flu viruses, laboratory studies, research into new vaccine development methods and vaccine effectiveness studies.

The so called “1918 virus” is the flu virus responsible for the 1918 pandemic that caused the death of an estimated 50 million people worldwide. An unusual feature of the 1918 pandemic was a high death rate among healthy adults 15-34 years of age. In fact, the 1918 pandemic virus was so virulent and deadly among healthy adults that it lowered the average life expectancy in the United States by more than 10 years. In contrast, most seasonal flu viruses-and the other two recorded pandemics of the 20th century-have caused higher death rates among the very young and the elderly.

Studying the 1918 virus by the CDC enables us to better understand pandemic flu viruses and allows us to improve capacity to protect against future pandemic flu viruses.

In the world wide Spanish flu pandemic of 1918, “Physicians tried everything they knew, everything they had ever heard of, from the ancient art of bleeding patients, to administering oxygen, to developing new vaccines and sera (chiefly against what we now call Hemophilus influenza – a name derived from the fact that it was originally considered the etiological agent – and several types of pneumococci). Only one therapeutic measure, transfusing blood from recovered patients to new victims, showed any hint of success.

In 1931, viral growth in embryonated hen’s eggs was reported by Ernest William Goodpasture and colleagues at Vanderbuil University. The work was extended to growth of influenza virus by several workers, including Thomas Frances, Wilson Smith and Macfarlane Burnet, leading to the first experimental influenza vaccines. In the 1940s, the US military developed the first approved inactivated vaccines for influenza, which were used in the Second World War. Hen’s eggs continued to be used to produce the virus used in influenza vaccines, but manufacturers made improvements in the purity of the virus by developing improved processes to remove egg proteins and to reduce systemic reactivity in cell cultures and influenza vaccines made from recombinant proteins have been approved, with plant-based influenza vaccines being tested in clinical trials.

According to the CDC: “Influenza vaccination is the primary method for preventing influenza and its severe complications. Vaccination is associated with reductions in influenza-related respiratory illness and physical visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults. Although influenza vaccines levels increased substantially during the 1990s, further improvements in vaccine coverage levels are needed.”

The egg-based technology (still in use as of 2005) for producing the influenza was created in the 1950s. In the U.S., the swine flu scare of 1976, President Gerald Ford was confronted with a potential swine flu pandemic. The vaccines program was rushed, yet plagued by delays and public relations problems. Meanwhile, maximum military containment efforts succeeded unexpectedly in confining the new strain to the single army base where it had originated. On that base a

number of soldiers fell severely ill, but only one died. The program was canceled, after about 24% of the population had received vaccinations. An excess in deaths of twenty-five over normal annual levels as well as 400 excess hospitalizations, both from Guillain-Barre syndrome, were estimated to have occurred from the vaccination program itself, illustrating that vaccine itself is not free of risks. The result has been cited to stroke lingering doubts about vaccination. In the end, however, even the maligned vaccine may have saved lives. A 2010 study found a significantly enhanced immune response against the 2009 pandemic H1N1 in study participants who had received vaccination against the swine flu in 1976.

Influenza research includes molecular virology, molecular evolution, pathogenesis, host immune responses, genomics, and epidemiology. These help in developing influenza countermeasures such as vaccines, therapies and diagnostic tools. Improved influenza countermeasures require basic research on how viruses enter cells, replicate, mutate, evolve into new strains and induce an immune response. The Influenza Genome Sequencing Project is creating a library of influenza sequences that will help us understand what make one strain more lethal than another, what genetic determinants most affect immunogenicity, and how the virus evolves over time. Solutions to limitations in current vaccine methods are being researched.

According to VaccineNewsDaily, a recent study published in Vaccines found that by providing a school located vaccination clinic, flu vaccination rates among children increased 13.2 percent when compared to children in schools without vaccination clinics. The vaccine can be lifesaving for children and less costly than a doctor's office visit.

The rapid development, production, and distribution of pandemic influenza vaccines could potentially save millions of lives during an influenza pandemic. Due to the short time frame between identification of a pandemic strain and need for vaccination, researchers are looking at novel technologies for vaccine production that could provide better "real-time" access and be produced more affordably, thereby increasing access for people living in low-and moderate-income countries, where an influenza pandemic may likely originate, such as live attenuated (egg-based or cell-based) technology and recombinant technologies (protein and virus-like particles). As of July 2010, more than 70 known clinical trials have been completed or are ongoing for pandemic influenza vaccines. In September 2009, the US Food and Drug Administration approved four vaccines

against the 2010 H1N1 influenza virus (the 2009 pandemic strain), and expected the initial vaccine lots to be available within the following month. A quadrivalent flu vaccine administered by nasal mist was approved by the U.S. Food and Drug Administration (FDA) in March 2012. Fluariz Quadrivalent was approved by the FDA in December 2012.

Many groups worldwide are pursuing development of a universal flu vaccine that does not require modification each year. Companies pursuing the vaccine as of 2009 and 2010 include BiodVax, Theraclone, Dynavax Technologies Corporation, VaxInnate, Crucell NV, Inovio Pharmaceuticals, and Immune Targeting Systems (ITS).

In 2008, Acambis announced work on a universal flu vaccine (ACAM-FLU-ATM) based on the less variable M2 protein component of the flu virus shell. The vaccine was tested in a human trial in the United States, where it was reported in 2008 to have developed antibodies against the flu virus in 90% of individuals; further human trials were planned.

In 2009, the Wistar Institute received a patent for using “a variety of peptides” in a flu vaccine, and announced it was seeking a corporate partner.

In 2010, the National Institute of Allergy and Infectious Diseases (NIAID) of the U.S. NIH announced a breakthrough; the effort targets the stem, which mutates less often than the head of the virus.

DNA vaccines, such as VGX-3400X (aimed at multiple H5N1 strains), contain DNA fragments (plasmids). Inovio’s SynCon DNA vaccines include H5N1 and H1N1 subtypes.

In July 2011, researchers created an antibody, which targets a protein found on the surface of all influenza A viruses called haemagglutinin. F16 is the only known antibody that binds (its neutralizing activity is controversial) to all 16 subtypes of the influenza A virus haemagglutinin and might be the lynchpin for a universal influenza vaccine. The subdomain of the haemagglutinin that is targeted by F16, namely the stalk domain, was actually used earlier as universal influenza virus vaccine by Peter Palese’s research group at Mount Sinai School of Medicine.

Some universal flu vaccines have started early stage clinical trials.

- BiondVax are targeting the less variable stalk of the haemagglutinin molecule with Multimeric -001. This is aimed at type A (inc H1N1) and Type B influenza and has started a phase IIa study.
- Dynavax have developed a vaccine N8295 based on two highly conserved antigens NP and M2e and their TLR 9 agonist, and started clinical trials in June 2010.
- ITS's fp01 includes 6 peptide antigens to highly conserved segment of the PA, PB1, PB2, NP & M1 proteins, and has started phase I trials.

Based on the results of animal studies, a universal flu vaccine may use a two-step vaccination strategy priming with a DNA-based HA vaccine followed by a second dose with an inactivated, attenuated, or adenovirus-vector-based vaccine.

Some people given a 2009 H1N1 flu vaccine have developed broadly protective antibodies, this raises hopes for a universal flu vaccine.

On February 13, 2013, U.S. Food and Drug Administration (FDA) Chief Scientist Jesse Goodman predicted that a universal flu vaccine was still 5 to 10 years away. When asked about the prospects of a universal flu vaccine in a hearing before House Energy and Commerce Subcommittee on Oversight and Investigations, Goodman replied "Nature is very tricky and as this is a very craft virus, so I'd be very hesitant to predict....I think the earliest we'd begin to see something with clinical benefit might be 5 to 10 years.

Why does the CDC conduct research on bird flu viruses? Birds are the natural host to all known subtypes of influenza A viruses, and while bird flu viruses mainly infect birds, they can-and have-crossed the species barrier to infect humans. Rarely, bird flu viruses may develop the capacity to infect and spread among humans. Those viruses that can spread efficiently among humans may lead to a pandemic. Because bird flu viruses are an important source of potential new human flu viruses, the CDC seeks to learn more about these viruses and their properties, and how different bird flu subtypes and strains might affect humans.

Highly pathogenic avian influenza A (H5N1) viruses (Asian lineage) or so called "H5N1, " which began spreading in birds throughout Asia in 2003 and continue to

spread to other regions, now meet two of the three conditions necessary for a pandemic to occur:

1. These are new influenza viruses in people to which there is little or no human immunity, and
2. These viruses have infected humans and caused illness.

However, highly pathogenic H5N1 have not met the third condition for a pandemic: the viruses are not capable of easy and ongoing spread among humans.

Previous flu pandemics, particularly the 1918 pandemic, resulted in significant illness and death in humans. Again, because flu viruses change constantly, experts are concerned that highly pathogenic H5N1 viruses could develop to spread easily among people, causing a pandemic.

Of the few bird flu viruses that have crossed the species barrier to infect humans, highly pathogenic H5N1 virus have caused the largest number of detected cases of severe illness and death in humans. For this reason, CDC has focused considerable resources and time on monitoring H5N1 virus spread and monitoring changes in the virus, including the ability of influenza antiviral medications to work against H5N1 viruses.

CDC's Influenza Division is working to better understand bird flu viruses and their ability to infect and cause illness in mammals, including humans. Animal models have been developed in mice and ferrets to study how bird flu viruses infect and cause illness and to model how flu viruses may spread. In particular, the ferret model has been used to evaluate how H5N1 viruses might infect and cause illness in humans and other animals. Ferrets are useful in flu studies because their respiratory tract cells are similar to those of humans and are susceptible to similar types of viruses.

Yes, animals can get the flu. "Vaccination in the veterinary world purses four goals: (i) protection from clinical disease, (ii) protection from infection with virulent virus, (iii) protection from virus excretion, and (iv) serological differentiation of infected from vaccinated animals (so-called DIVA principle). In the field of influenza vaccination, neither commercially available nor experimentally tested vaccines have been shown so far to fulfill all of these requirements."

Horses with horse flu can run a fever, have a dry hacking cough, have a runny nose, and become depressed and reluctant to eat or drink from several days but usually recover in two to three weeks. "Vaccination schedules generally require a primary course of 2 doses, 3-6 weeks apart, followed by boosters at 6-12 month intervals. It is generally recognized that in many cases such schedules may not maintain protective levels of antibody and more frequent administration is advised in high-risk situations." It is a common requirement in the United Kingdom that horses be vaccinated against equine flu and a vaccination card must be produced; the International Federation for Equestrian Sports (FEI) requires vaccination every six months.

Poultry vaccines for bird flu are made on the cheap and are not filtered and purified like human vaccines to remove bits of bacteria or other viruses. They usually contain whole virus, not hemagglutinin as in most human flu vaccines. Purification to standards needed for humans is far more expensive than the original creation of the unpurified vaccine from eggs. There is no market for veterinary vaccines that are that expensive. Another difference between human and poultry vaccines is that poultry vaccines are injected with mineral oil, which induces a strong immune reaction but can cause inflammation and abscesses.

"Chicken vaccinators who have accidentally jabbed themselves have developed painful swollen fingers or even lost thumbs. Effectiveness may also be limited. Chicken vaccines are often only vaguely similar to circulating flu strains - some contain an H5N2 strain isolated in Mexico years ago. With a chicken, if you use a vaccine that's only 85 percent related, you'll get protection," Dr. Cardona said.

"In humans, you can get a single point mutation, and a vaccine that's 99.99 percent related won't protect you. They are weaker than human vaccines. Chickens are smaller and you only need to protect them for six weeks, because that's how long they live till you eat them," said Dr. John J. Treanor, a vaccine expert at the University of Rochester. "Human seasonal flu vaccines contain about 45 micrograms of antigen, while an experimental A (H5N1) vaccine contains 180. Chicken vaccines may contain less than 1 microgram. You have to be the agriculture department's Southeast Poultry Research Laboratory. Birds are more closely related to dinosaurs."

Researchers, led by Nicholas Savill of the University of Edinburgh in Scotland, used mathematical models to simulate the spread of H5N1 and concluded that at least

95 percent of birds need to be protected to prevent the virus spreading silently. In practice, it is difficult to protect more than 90 percent of a flock; protection levels achieved by a vaccine are usually much lower than this. The Food and Agriculture Organization of the United Nations has issued recommendations on the prevention and control of avian influenza in poultry, including the use of vaccination.

A filtered and purified Influenza A vaccine for humans is being developed and many countries have recommended it be stockpiled so if an Avian influenza pandemic starts jumping to humans, the vaccine can quickly be administered to avoid loss of life. Avian influenza is sometimes called avian flu, and commonly bird flu.

Swine origin influenza virus (SoIV) vaccines are extensively used in the swine industry in Europe and North America. Most swine flu vaccine manufacturers include an H1N1 and an H3N2 SoIV strains.

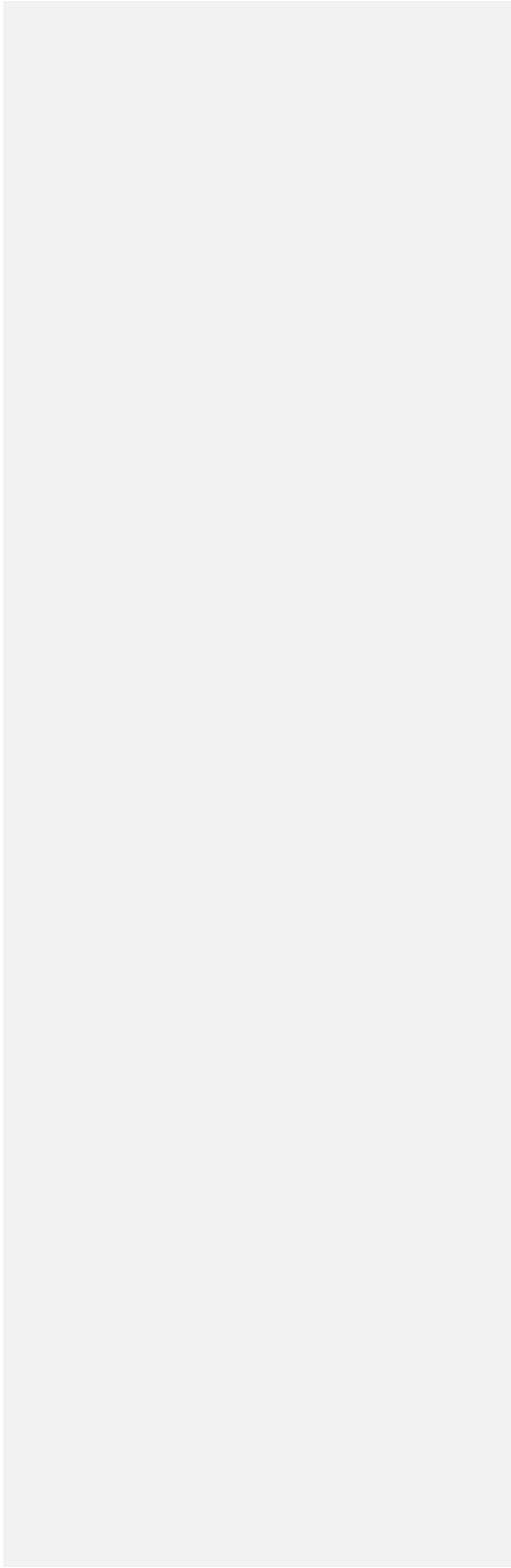
Swine influenza has been recognized as a greater problem since the outbreak in 1976. Evolution of the virus has resulted in inconsistent responses to traditional vaccines. Standards commercial swine origin flu vaccines are effective in controlling the problem when the virus strains match enough to have significant cross-protection and custom (autogenous) vaccines made from the specific viruses isolated are created and used in the more difficult cases.

SoIV vaccine manufacture Novartis paints this picture: "A strain of swine origin influenza virus (SoIV) called H3N2, first identified in the US in 1998, has brought exasperating production losses to swine producers. Sows go off feed for two or three days and run a fever up to 106 degrees. Mortality in a naïve herd can run as high as 15%."

In 2004, Influenza A virus subtype H3N8 was discovered to cause canine influenza. Because of the lack of previous exposure to this virus, dogs have no natural immunity to this virus. However, a vaccine is now available.

The bottom line for health care providers: Influenza is a contagious respiratory illness caused by the flu viruses. Approximately 5-20% of U.S. residents get the flu each year. As health professionals, it is vital that we stop the spread of the flu virus. We must recognize the signs of the flu and make sure to stay home to

alleviate spreading the flu to our patients. By getting vaccinated, you help protect yourself, your family at home, and your patients.



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