# 1918-1919 to 2018-2019: Influenza 100 years later

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## Purpose & Overview:

The purpose of this presentation is to review the historical and ongoing importance of influenza, to describe the viral structure and characteristics and how those contribute to defining characteristics of the annual epidemics and periodic pandemics, to review the signs, symptoms, the spectrum of illness and complications of the infection, to discuss the prevention strategies including the use of vaccine, hand hygiene and respiratory protection and to identify treatment and prophylaxis options in certain patient populations.

## Educational Objectives:

1. *Describe the characteristics of changes the virus undergoes to determine if we will have an epidemic or pandemic.*
2. *Understand the spectrum of illness caused by influenza infection including the complications.*
3. *List 3 important strategies to prevent influenza infection.*
4. *Recognize the real versus perceived adverse events associated with the influenza vaccine.*
5. *Describe the utility of hand hygiene and masks in preventing transmission of the influenza virus.*

## Overview and History:

Influenza viruses are responsible for significant morbidity, mortality and related economic costs. In the US alone, seasonal influenza causes an estimated average of 226,000 hospitalizations and 78,000 deaths every year.

Although the virus seems to have caused annual epidemics throughout human history, historical data on influenza are difficult to interpret, because the symptoms can be similar to those of other respiratory diseases. Hippocrates described influenza like illness noting its contagiousness and the cough as one of the primary manifestations back in 412 BC. The term influenza is traced to the 1357 epidemic of respiratory illness that occurred in Florence, Italy and was called *influenza di freddo* or "cold influence". In 1414, a Parisian epidemic of respiratory disease was thought to originate from the *vent puant et tout plein de froidure* or the "smelly and cold wind" contributing to the theory of miasma as the source of infectious diseases in the next few centuries. The infection likely spread from Europe to the Americas as early as the arrival of Christopher Columbus in 1493 as almost the entire indigenous population of the Antilles was killed by an epidemic resembling influenza.

Pandemic influenza is always caused by Influenza A, although the subtypes change shepherding a novel virus in an immune population. Each pandemic is defined by the pandemic severity index (PSI) which was developed in 2007 by the United States Department of Health and Human Services. The index considers case fatality ratio, projected number of US deaths and does not consider interventions.

The first convincing record of an influenza pandemic was of an outbreak in 1580, which began in Russia and spread to Africa and Europe. In Rome, over 8,000 people were killed, and several Spanish cities were almost wiped out. Pandemics continued sporadically throughout the 18$^{th}$ and 19$^{th}$ centuries, with the pandemic of 1830-1833 being particularly widespread; it inflected approximately a quarter of the people exposed. The best studied pandemics are those of the 19$^{th}$, 20$^{th}$ and 21$^{st}$ centuries, primarily the 21$^{st}$ century.

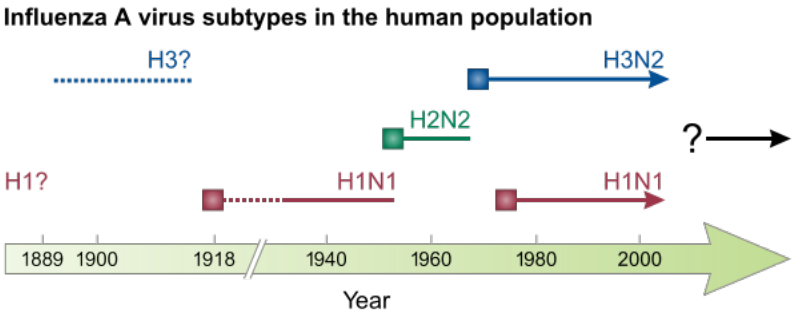
The **Asiatic/Russian Influenza Pandemic** occurred between October 1889 and December 1890, with additional waves between March and June 1891, November 1891 and June 1892, and over the winter of 1893–1894. The infection spread from St. Petersburg where it

was thought to originate to the United States. Ultimately over 1 million deaths occurred. The viral subtype responsible is thought to be either Influenza A subtype H2N2 or H3N8 based on serology studies.

| Modern Influenza Pandemic Characteristics* | | | | |
|---|---|---|---|---|
| **Name of pandemic** | **Deaths** | **Case fatality rate** | **Subtype involved** | **Pandemic Severity Index** |
| **1889–1890 Russian or Asiatic Influenza Pandemic** | 1 million | 0.15% | possibly H3N8 or H2N2 | Unknown |
| **1918-19 Spanish Influenza Pandemic** | 20 to 100 million | 2% | H1N1 | 5 |
| **1957-8 Asian Influenza Pandemic** | 1 to 2 million | 0.13% | H2N2 | 2 |
| **1968-9 Hong Kong Influenza Pandemic** | 0.75 to 1 million | <0.1% | H3N2 | 2 |
| **2009-10 H1N1 Influenza Pandemic** | 151,000 to 579,000 | 0.03% | H1N1/09 | 2 |

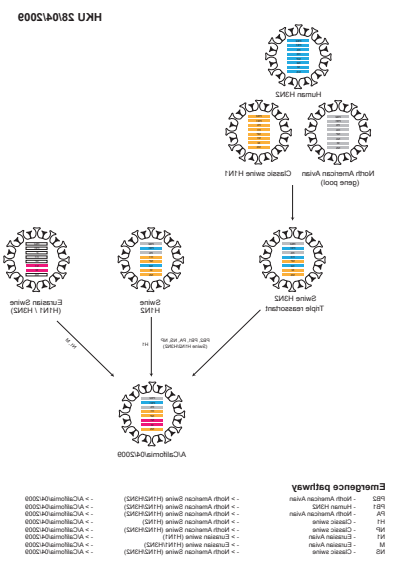
*table adapted from Wikipedia

The **Spanish Influenza Pandemic** of 1918-1919 is considered the "mother" of all medical pandemics and caused between 50 and 100 million deaths worldwide — approximately 600,000 of which were in the United States (11 times greater than the number of American casualties during World War I). This pandemic was caused by a particularly deadly H1N1 subtype that caused cytokine storms and was notable in the high mortality in young children, adolescents and young adults. Unique to this pandemic was the lower mortality in the elderly. Some authors dispute that this strain was more virulent and subscribe the high case fatality ratio to malnourishment, overcrowding and poor hygiene. This pandemic dropped the life expectancy in the US by 12 years.



The **Asian (1957-8) and Hong Kong (1968-9) Influenza Pandemics** were less severe than the 1918 pandemic and were unique in that the virus had been discovered and vaccine was developed as a prevention strategy. The Asian pandemic originated in China in early 1956, and lasted through 1958. It is believed to have originated in water

fowl and to have combined with human viruses. Mortality in the US was about 69,800 and worldwide deaths between one to four million. The subtype of the Asian pandemic was H2N2. This influenza subtype further shifted to an H3N2 strain and was associated with a milder pandemic that originated in Hong Kong occurring between 1968 and 1969. This later pandemic was associated with a lower case-fatality rate. Approximately 34,000 deaths were recorded in the US.



The **2009 H1N1 Pandemic** occurred between early 2009 to late 2010 and was caused by a novel H1N1 influenza virus. This subtype was unique and resulted from a previous triple reassortment of bird, swine and human influenza viruses that further combined with a Eurasian pig influenza virus. This pandemic infected 11-21% of the global population, and 151,000-579,000 died. Unlike most strains of influenza, H1N1 did not affect adults older than 60 years disproportionately. This strain is currently circulating worldwide.

Proposed quaternary reassortment of the H3N2, swine H1N1 and avian strains that lead to the pandemic H1N1 virus

## Virus

There are 4 antigenically distinct types of influenza viruses **A**, **B**, **C**, and **D** of which A, B, and C cause human infections. Influenza A viruses affects humans, birds and mammals and is the only virus associated with pandemic influenza. Influenza B uniquely affects humans. Influenza C is rare in humans and usually associated with mild or asymptomatic infection and influenza D is a bovine virus. These viruses compose the viral family, **Orthomyxoviridae**.

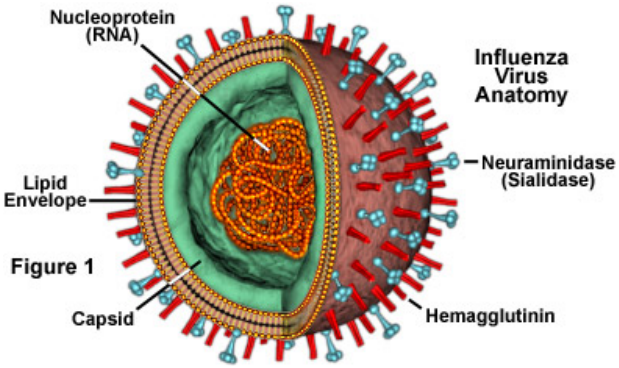
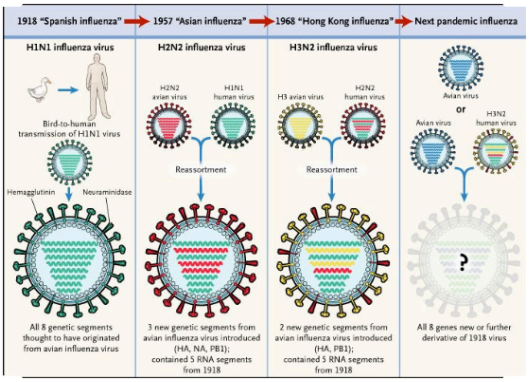


Figure 1

The influenza virion is a single-stranded, segmented RNA enveloped virus that derives its lipid bilayer from the plasma membrane of a host cell. The envelop is embedded with glycoprotein spikes, **hemagglutinin (HA)**, a trimeric glycoprotein that facilitates attachment of the virus to a host cell and **neuraminidase (NA)**, which facilitates the release from the host cell of newly produced virus particles. The inner side of the envelop is an antigenic matrix protein lining and the envelope is the influenza genome, which for influenza A and B is organized into eight pieces of single-stranded RNA.

Influenza viruses cause epidemics and pandemics. The relative size and impact result from antigenic variation, the immunity of the "herd" or population, and the relative virulence of the organism. Mutations in the antigenic structure of the influenza virus result in different influenza subtypes and strains. These subtypes are named according to the particular antigenic determinants of hemagglutinin (17 major types) and neuraminidase (11 major types) surface proteins. For example, influenza A H2N2 has the surface protein of hemagglutinin 2 and neuraminidase 2. Annual influenza A and B epidemics occur as a result in minor point mutations that occur within the genome without changes in the surface antigens. This process is called **antigenic drift**. Both A and B influenza viruses continually undergo antigenic drift, requiring reformulation of influenza vaccines each year so the vaccine covers new strains.



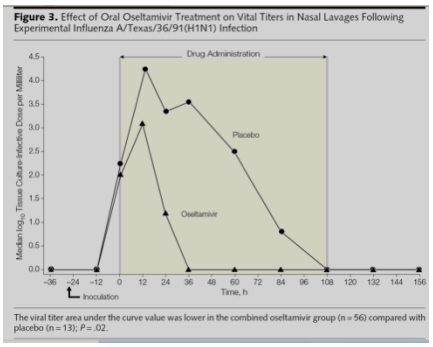

Influenza A also experiences **antigenic shift,** which is a sudden change and generally the result of reassortment of the viral genome resulting in a new subtype of influenza virus. This occurs occur when a cell becomes simultaneously infected by two different strains of type A influenza. In particular, the mixing of strains that can infect birds, swine, and humans has led to most antigenic shifts. These changes are not predictable and because they are sudden, the emergence of a new subtype of the virus leads to a population with limited immunity and can cause a global pandemic.

**Transmission:**

Influenza is transmitted among humans 3 ways: 1. Direct contact with infected individuals; 2. Contact with contaminated surfaces or objects; and 3. Inhalation of virus-laden droplets. Our understanding of influenza transmission is largely based on prospective household studies that assessed the transmission of influenza within families. About 30% of influenza transmission occurs in households. The proportion of children that attend daycare has markedly increased reaching nearly 60%. The average number of other individuals whom each infected individual will infect, in a population, which has no immunity to the infection, is 1.5-2 depending on the strain.

Influenza is primarily spread from person to person through coughing or sneezing. This transmission primarily occurs on large droplets that can travel 3-6 feet. There is limited data supporting airborne transmission primarily in the setting of procedures that aerosolize droplets such as nebulizer treatments. Contamination of mucosal surfaces (touching the eye with a contaminated finger) or touching contaminated surfaces is also suspected. Influenza A and B viruses survive on hard surfaces for 24-48 hours and on cloth, paper and tissues for up to 12 hours. The virus can survive on hands for up to 5 minutes after contamination of the hand. Previous animal-model studies demonstrated that low temperature and low relative humidity facilitate aerosol transmission of influenza infections. However, the relevance of those findings in humans is unclear.

Shedding of virus begins approximately 24 hours before symptom onset with maximal shedding for 4-5 days but it can extend up to 7.5 days. Virus can be recovered for longer periods with PCR than by viral culture. The use of antivirals (neuraminidase inhibitors) significantly decreases the duration of shedding.




Between 5-20% of the population develop influenza annually. Median incidence attack rates of influenza by age group are approximately 9.3% for children 0-17 years, 8.8% for adults 18-64 years, and 3.9% for adults 65 years and older. Among healthcare workers, the attack rate is higher and up to 23% (pre mandatory influenza vaccine) developed influenza annually. Importantly only 60% recall an influenza like illness, meaning up to 40% have minimal if any symptoms. Data from the H1N1 pandemic found that healthcare workers at the greatest risk of acquisition is among physicians and medical personnel (6.7%) with those in the adult and pediatric emergency rooms accounting for the highest acquisition, 29 and 24%, respectively.

## Signs, symptoms, spectrum of illness:

There is a wide spectrum of illness among those infected. While the virus is deposited in the respiratory tract yet lead to a systemic response. Typical signs and symptoms in adults include an **abrupt** onset of fever (> 37.8 $^{o}$C) that peaks within 24 hours, chills, headache, myalgia, nonproductive cough, sore throat, anorexia, and malaise. Malaise may be severe and last for several days, differentiating influenza infection from other common respiratory illnesses. Other symptoms may include substernal soreness, photophobia, and other ocular problems, and gastrointestinal distress, including nausea, abdominal pain, and diarrhea, although these symptoms are rarely prominent (except with H1N1). The severity of symptoms can range from asymptomatic at one extreme, to fatal pneumonia on the other. Children tend to experience similar symptoms, although abdominal symptoms and myalgia may occur more frequently. Their maximum temperatures may also be higher, prompting febrile convulsions. Gastrointestinal symptoms associated with influenza are sometimes experienced by children, but are less common among adults. The elderly may present with lassitude and confusion.

A number of complications, such as the onset of bronchitis and pneumonia, can also occur in association with influenza and are especially common among the elderly, young children, and anyone with a suppressed immune system. Individuals at risk of serious complications include those aged over 65,

| Sign/Symptoms | Children | Adults | Elderly |
|---|---|---|---|
| Cough (nonproductive) | ++ | ++++ | +++ |
| Fever | +++ | +++ | + |
| Myalgia | + | + | + |
| Headache | ++ | ++ | + |
| Malaise | + | + | +++ |
| Sore throat | + | ++ | + |
| Rhinitis/nasal congestion | ++ | + | + |
| Abdominal pain/diarrhea | + | – | + |
| Nausea/vomiting | ++ | – | + |

++++ Most frequent sign/symptom; + Least frequent; – Not found

neurodevelopmental conditions, pregnant women (especially during the third trimester), children younger than 5 years, and those of any age with underlying medical conditions (asthma, diabetes, obesity, heart disease, renal, neurologic or liver disease or immunocompromised). Those using tobacco or who are Native Americans or Alaskan Natives and children or adolescents taking aspirin are also at increased risk. During the H1N1 pandemic, most complications occurred among previously healthy individuals, however, obesity and respiratory disease also emerged as important risk factors for complications. More than 70% of hospitalizations in the U.S. have been individuals with such underlying medical conditions.

In severe cases of primary influenza, patients generally begin to deteriorate around three to five days after symptom onset. The deterioration is rapid, with many patients progressing to respiratory failure within 24 hours, requiring intensive care. Pulmonary complications are common. Primary influenza pneumonia occurs most commonly in adults and may progress rapidly to acute lung injury requiring mechanical ventilation. Secondary bacterial infection is more common in children. *Staphylococcus aureus*, including methicillin-resistant strains and *Streptococcus pneumoniae* are common and important causes of secondary bacterial pneumonia among children and adults. Neuromuscular, cardiac complications Reyes syndrome and toxic shock are unusual but may occur.

The number of deaths related to influenza exceed those for breast and prostate cancer, suicide, and HIV.

**Groups at High Risk for Serious Influenza Complications**

- Children <5 years, but especially <2 years
- Adults ≥65 years of age
- Women who are pregnant or up to two weeks postpartum
- Residents of nursing homes and long-term care facilities
- Native Americans, including Alaska Natives
- People with medical conditions including:
  - Asthma
  - Neurologic and neurodevelopmental conditions (including disorders of the brain, spinal cord, and peripheral nerve and muscle such as cerebral palsy, epilepsy, stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, and spinal cord injury)
  - Chronic lung disease (eg, chronic obstructive pulmonary disease, cystic fibrosis)
  - Heart disease (eg, congenital heart disease, congestive heart failure, coronary artery disease)
  - Blood disorders (eg, sickle cell disease)
  - Endocrine disorders (eg, diabetes mellitus)
  - Kidney disorders
  - Liver disorders
  - Metabolic disorders (eg, inherited metabolic disorders and mitochondrial disorders)
  - Weakened immune system due to disease (eg, HIV, AIDS, cancer) or medication (eg, chemotherapy or radiation therapy, chronic glucocorticoids)
  - Children <19 years of age who are receiving long-term aspirin therapy
  - People with extreme obesity (body mass index [BMI] ≥40)

## Diagnosis:

The symptoms of influenza mimic those of many other respiratory viruses including parainfluenza, coronavirus, adenovirus and respiratory syncytial virus; hence, the confirmation of the diagnosis facilitates individual patient management, public health responses and surveillance efforts. The primary samples are obtained by a nasopharyngeal swab, nasal wash or combined throat and nasal

swabs. Samples that are obtained within 3 days of symptom onset have the highest yield (correlates with viral load).

Table 1 | **Advantages and disadvantages of influenza diagnostic tests**

| Diagnostic assay | Description | Advantages | Disadvantages |
|---|---|---|---|
| Virus culture | Virus detected by the appearance of cytopathic effect, HA assay or direct fluorescence antibody staining | • High specificity (>95%)[237]<br>• Enables characterization of novel viruses<br>• Enables surveillance of antiviral sensitivity and antigenic drift | • Slow (>3 days)<br>• Requires specialized skills and equipment<br>• Lower sensitivity than RT-PCR |
| RT-PCR | Primers to conserved genes can be used in combination with those for HA | • High specificity (>99%)[238]<br>• High sensitivity (>99%)[238]<br>• Can be multiplexed[238]<br>• Can be automated in relatively high throughput<br>• Moderately fast (hours)<br>• Can be used to simultaneously type and subtype viruses[239] | • Expensive<br>• More prone to false positive results (by nucleic acid contamination) than virus culture[238] |
| Rapid antigen test | Immunoassay detection of the presence of viral antigen in the sample | • Fast (15 min)<br>• Low cost<br>• Point of care<br>• Can detect both influenza A and influenza B | • Low sensitivity (70–50%)[240,241]<br>• Prone to false negative results[241] (96% negative predictive value)<br>• Cannot provide subtype information |
| Rapid molecular assay | Based on isothermal nucleic acid amplification; requires simple heat source and fluorescence detection | • Fast (15 min)<br>• High specificity (>99%)[240]<br>• Good sensitivity (66–100%)[240]<br>• Point of care | Expensive |

HA, haemagglutinin; RT-PCR, reverse transcription PCR.

*Table from Kramer et al 2018*

The gold standard laboratory tests used for influenza are viral culture and reverse transcriptase PCR (RT-PCR). Cultures are critical to characterize novel viruses and to monitor for antiviral resistance and antigenic drift. Culture is used less commonly in clinical settings because it is time consuming, may delay the diagnosis and requires special equipment. RT-PCR has a high sensitivity and specificity (>99%) and is relatively quick in providing answers. Both methods require appropriate handling of samples to assure there is no degradation leading to false negative results. More recent technology including digital immunoassays and nuclei acid amplification tests have high sensitivities.

## Prevention:

***Vaccine:***

Within 15 years of the influenza virus being discovered (1930), a vaccine was available for the civilian population. Vaccination is the primary mode of prevention of influenza. The method for making vaccine has remained largely unchanged until recently. In the 1970's two changes instituted facilitated production by improving growth characteristics and by treating the virions with detergent to make the vaccine less reactogenic. Subsequently, manufactures have developed a cold adapted live attenuated influenza virus vaccine, developed vaccines using tissue culture based substrates or use recombinant DNA technologies. In addition, adjuvants have been added to enhance vaccine efficacy and high dose vaccines have been introduced. Influenza vaccine efficacy varies year to year, and at times can be low. The effectiveness of influenza vaccines varies annually and is based on circulating and vaccine strain match, the immunogenicity of vaccine strains, the virulence of circulating strains, subjects' prior exposure to the virus, and other relevant factors.

Overall, vaccine efficacy is estimated to be between 50-60% in adults with the efficacy closer to 83% in children (Osterholm 2011 & figure below). Data also show that the efficacy is higher among healthcare workers. Systematic reviews and meta-analysis of influenza vaccination effectiveness have looked at several outcomes. Among adult's influenza vaccination decreases the risk of influenza acquisition and leads to decreased in flu symptom severity and working days lost. Among patients with heart failure,

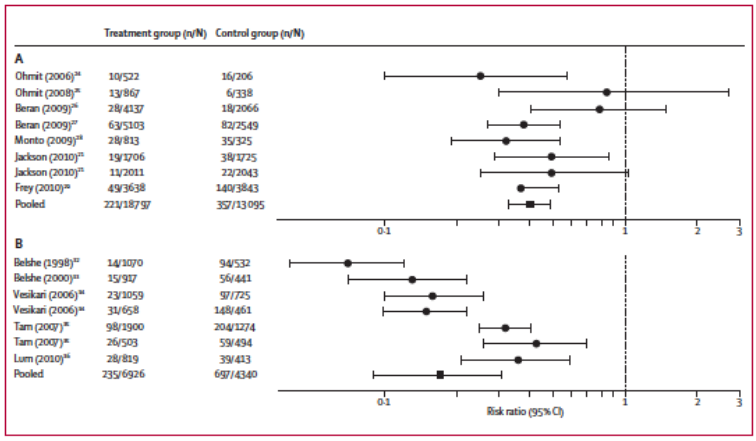



*Figure 2:* **Vaccine efficacy compared with placebo (Mantel-Haenszel random-effects model)**
(A) Trivalent inactivated influenza vaccine in adults aged 18–64 years. (B) Live attenuated influenza vaccine in children aged 6 months to 7 years. Studies were prospective (risk ratio) which are equivalent to case-control (odds ratio). n=cases of influenza. N=group size.

the risk of all-cause mortality was reduced (HR=0.69 95%CI 0.51-0.87) (Poudel 2019).

A variety of vaccine formulations is available for the clinician to administer; however, there is a lack of guidance on which vaccine is optimal and when to administer influenza vaccination for select populations. The vaccine is given annually and in general is tri- or quadri-valent, and includes two influenza A strains and one (for the trivalent formulation) or two (for the quadrivalent) influenza B strains. The vaccines are given **annually and are recommended for all over the age of 6 months of age**. The vaccine is strongly recommended for those in high-risk groups for severe influenza or complications of influenza.

Influenza vaccines are remarkably safe. Among vaccinees, local tenderness and pain is commonly reported, fever occurs in 5 -10 percent of children, and myalgias or fatigue are occasionally reported. The vaccine has not been linked to Guillain Barré syndrome (except in 1976 with the Swine flu vaccine). Generally, the vaccine can be given to those with egg allergies. The risk of anaphylaxis is extremely rare. In some cases, these individuals receive the recombinant vaccine formulations. Many vaccines are thimerosal free and those that are not have low levels of the compound.

**TABLE 1. Influenza vaccines — United States, 2019–20 influenza season***

| Trade name (Manufacturer) | Presentation | Age indication | HA (IIVs and RIV4) or virus count (LAIV4) for each vaccine virus (per dose) | Route | Mercury (from thimerosal) (μg/0.5mL) |
|---|---|---|---|---|---|
| **IIV4—Standard Dose—Egg based†** | | | | | |
| Afluria Quadrivalent (Seqirus) | 0.25-mL PFS§ | 6 through 35 mos | 7.5 μg/0.25 mL§ | IM¶ | — |
| | 0.5-mL PFS§ | ≥3 yrs | 15 μg/0.5 mL§ | | — |
| | 5.0-mL MDV§ | ≥6 mos (needle/syringe) 18 through 64 yrs (jet injector) | | | 24.5 |
| Fluarix Quadrivalent (GlaxoSmithKline) | 0.5-mL PFS | ≥6 mos | 15 μg/0.5 mL | IM¶ | — |
| FluLaval Quadrivalent (GlaxoSmithKline) | 0.5-mL PFS | ≥6 mos | 15 μg/0.5 mL | IM¶ | — |
| | 5.0-mL MDV | ≥6 mos | | | <25 |
| Fluzone Quadrivalent (Sanofi Pasteur) | 0.25-mL PFS** | 6 through 35 mos | 7.5 μg/0.25 mL** | IM¶ | — |
| | 0.5-mL PFS** | ≥6 mos | 15 μg/0.5 mL** | | — |
| | 0.5-mL SDV** | ≥6 mos | | | — |
| | 5.0-mL MDV** | ≥6 mos | | | 25 |
| **IIV4—Standard Dose—Cell culture based (ccIIV4)** | | | | | |
| Flucelvax Quadrivalent (Seqirus) | 0.5-mL PFS | ≥4 yrs | 15 μg/0.5 mL | IM¶ | — |
| | 5.0-mL MDV | ≥4 yrs | | | 25 |
| **IIV3—High Dose—Egg based† (HD-IIV3)** | | | | | |
| Fluzone High-Dose (Sanofi Pasteur) | 0.5-mL PFS | ≥65 yrs | 60 μg/0.5 mL | IM¶ | — |
| **IIV3—Standard Dose—Egg based† with MF59 adjuvant (aIIV3)** | | | | | |
| Fluad (Seqirus) | 0.5-mL PFS | ≥65 yrs | 15 μg/0.5 mL | IM¶ | — |
| **RIV4—Recombinant HA** | | | | | |
| Flublok Quadrivalent (Sanofi Pasteur) | 0.5-mL PFS | ≥18 yrs | 45 μg/0.5 mL | IM¶ | — |
| **LAIV4—Egg based†** | | | | | |
| FluMist Quadrivalent (AstraZeneca) | 0.2-mL prefilled single-use intranasal sprayer | 2 through 49 yrs | $10^{6.5–7.5}$ fluorescent focus units/0.2 mL | NAS | — |

The current quadrivalent vaccine for the 2019-20 season includes the following viruses.

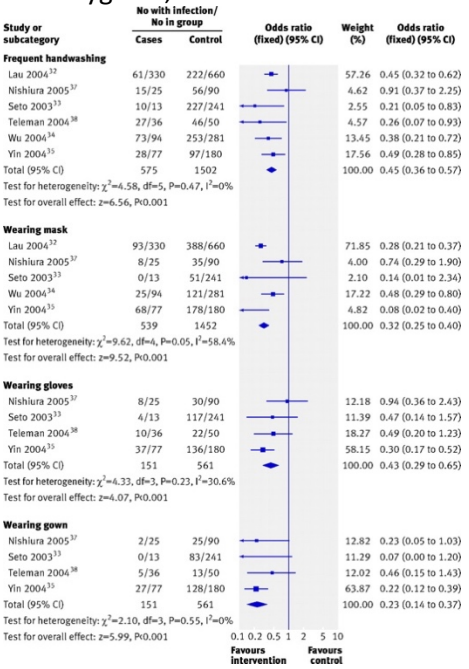
- A/Michigan/45/2015 (H1N1)pdm09-like virus.
- A/Singapore/INFIMH-16-0019/2016 (H3N2)-like virus.
- B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage).

- B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage).

Questions arise about the best vaccine formulations for different patient population. The area of most interest to internists is the high dose (HD) influenza vaccine formulations for individuals over 65. Three systematic reviews have summarized the findings. The HD formulation does provide enhanced immunogenicity to the virus and prevents influenza like infection (pooled OR 0.81 95% CI 0.71-0.91, 19.5% reduction) and influenza related hospitalizations (pooled OR 0.82 95%CI 0.74-0.92, 17% reduction) (Lee 2018). Other authors suggest the efficacy is higher and up to 24% (Wilkinson, 2017). This vaccine is associated with increased local adverse events including tenderness, erythema and induration (p=0.001, Chong 2018).

### *Nonpharmacologic prevention strategies:*

The mainstay of prevention strategy remains vaccine but there are other physician interventions such as hand hygiene, use of masks and other barriers (gowns and gloves) that have been assessed in the setting of respiratory infections. Most studies have been undertaken examining the impact of these interventions of several respiratory infections including influenza, coronaviruses (SARS and MERS-CoV) and respiratory syncytial virus simply because of the size of studies needed. However, these cost effective strategies can and do prevent transmission of respiratory viruses in the home, school and healthcare settings. Washing hands (soap and water or alcohol based hand rub) more than 10 times daily reduced respiratory virus acquisition by 55% (OR 0.45, 95%CI 0.36-0.57); wearing masks reduced acquisition of infection by 78% (OR 0.32, 95%CI 0.25-0.40) and N95 masks by 91% (OR=0.09; 95%CI 0.03-0.30), wearing gloves by 57% (OR 0.43, 95%CI 0.29-0.65), wearing gowns 77% (OR 0.23, 95%CI 0.14-0.37) and the bundle of hand hygiene, masks, gloves and gowns 91% (0.09, 95%CI 0.02-0.35) (Jefferson 2009). The combination was also effective in interrupting the spread of influenza.




### Treatment and Prophylaxis:

All patients with influenza should receive supportive care, which can include antipyretics, fluids, and other appropriate care. The question is among those at risk for severe influenza and its complications who should and what therapy should they receive?

There are several **antiviral** treatment options available for these types of patients.

1. Neuraminidase inhibitors including oseltamivir, peramivir and zanamivir are active against influenza A and B.
2. Selective inhibitor of influenza cap dependent endonuclease or baloxavir is active against influenza A and B.
3. The adamantanes, amantadine and rimantadine are active against influenza A only.

Currently **adamantanes are not recommended** for use except in very selected situations because of the level of resistance among circulating influenza strains. Resistance to adamantanes among the 2009H1N1 and H3N2 strain was reported to be 100% in 2016 (Krammer 2018).

The **neuraminidase inhibitors** and **baloxavir** can shorten duration of symptoms to ~ 3 days, duration of viral shedding, and may decrease the risk of influenza complications, length of stay in hospital and influenza associated mortality. Oseltamivir has been shown to shorten the duration of influenza symptoms by 1 day and to reduce the duration of shedding. Some studies suggest that oseltamivir reduces illness severity and complications (lower respiratory tract infections), hospital admission and length of hospital stay. Data for zanamivir are similar to oseltamivir in terms of duration of symptoms, it has not been shown to decrease complications except for bronchitis and there are not data assessing its impact on hospital admission and length of stay. Peramivir is the newest neuraminidase that has been approved by the FDA and has been show to reduce symptoms. It was found to be non-inferior to oseltamivir in one clinical trial. The adverse events associated with agents are similar and include GI symptoms (most prominent with oseltamivir) and zanamivir may cause bronchospasm and should not be used in individuals with chronic or acute lung disease. Skin reactions and transient neuropsychiatric events are reported. These agents are best administered within 48 hours of symptom onset but should not be withheld in hospitalized and critically ill patients.

Indications for treatment per the Advisory Committee on Immunization Practices and the Infectious Diseases Society of America (IDSA) guidelines recommend prompt initiation of therapy and include the following groups:

1. Hospitalized patients with influenza regardless of duration prior to hospitalization
2. Outpatients with severe or progressive illness regardless of duration of symptoms
3. Outpatients who are at risk of influenza complications.

The IDSA further states that therapy can be considered in those with suspected or confirmed influenza who are not at high risk for complications irrespective of influenza vaccination if they are

1. Outpatients with illness onset < 48 hours to reduce the duration of illness. Those with symptoms >48 hours should not be treated;
2. Symptomatic outpatients who are household contacts of persons at high risk for influenza complications (including immunocompromised);
3. Symptomatic healthcare workers who routinely care for patients at high risk for influenza complications (including immunocompromised).

Interestingly some data do not suggest that administering these drugs to healthy adults with influenza alter the risk of complications and may not alter the course of disease. A recent study that randomized 558 participants, of which 501 had documented influenza found that oseltamivir decreased the shedding of virus from 57.2% in the placebo group to 45% in the oseltamivir group and did not significantly decrease the duration of symptoms (84 hours versus 79 hours, p=0.34) (Beigle 2019).

Choice of agent will depend on the clinical situation. In general, experts favor oral oseltamivir and inhaled zanamivir over intravenous peramivir. Oseltamivir is the preferred drug for severe influenza. Dosing is above and there is no data supporting increased dosing in severely ill or immunocompromised patients. Two randomized clinical trials have supported no differences in clinical or virologic outcomes with increased dosing.

Baloxivir is a novel agent that selectively inhibits influenza cap endonuclease and blocks the influenza proliferation by inhibiting RNA synthesis. It has been studied in patients over the age of 12 and shown to reduce the duration of symptoms by 27 hours (similar to neuraminidase inhibitors) and rapidly decreases viral shedding (more so than oseltamivir). The rapid emergence of resistance to the polymerase acidic protein variants with I38T/M/F substitutions conferred decreased susceptibility to

baloxavir and occurred in 2.2% and 9.8% of participants in the two clinical trials performed. The most common adverse effect was diarrhea.

Studies to date that have combined antivirals (triple combination antiviral drug (TCAD)) have not demonstrated superior outcomes in critically ill patients.

Other adjunct therapies have been studied will variable results. **Corticosteroids** have been tested in 10 studies involving 6,548 patient and the pooled analysis suggests that their use increased mortality (RR 1.75 95%CI 1.3-2.36), increased ICU stay and the secondary infection rate but not duration of mechanical ventilation (Ni 2019). Statins have been shown to decrease mortality in patients with influenza due to their proposed anti-inflammatory effect but these findings have not been confirmed in randomized clinical trials. A combination of clarithromycin and naproxen (2 days) with oseltamivir (5 days) and amoxicillin-clavulanate for CAP was tried and associated with a lower 30 and 90 day mortality and shorter length of hospital stay. Further investigation of this strategy is warranted.

| ANTIVIRAL AGENT | ACTIVITY AGAINST | USE | RECOMMENDED FOR | ADULT DOSE/DURATION | ADVERSE EVENTS |
|---|---|---|---|---|---|
| **ORAL OSELTAMIVIR** | Influenza A and B | Treatment | Any age | 75mg PO BID X 5 days | **Adverse events**: nausea, vomiting, headache, rare serious skin reactions; sporadic, transient neuropsychiatric events |
| | | Chemo-prophylaxis | 3 months and older | 75mg PO QD* | |
| **INHALED ZANAMIVIR** | Influenza A and B | Treatment | 7 yrs. and older | 10mg inhalation BID X 5 days | **Adverse events**: risk of bronchospasm, sinusitis, and dizziness. Rare serious skin reactions and sporadic, transient neuropsychiatric events |
| | | Chemo-prophylaxis | 5 yrs. and older | 10mg inhalation QD* | |
| **INTRAVENOUS PERAMIVIR** | Influenza A and B | Treatment | 2 yrs. and older | 600mg dose IV X 1 (single dose) | **Adverse events**: diarrhea. Rare serious skin reactions and sporadic, transient neuropsychiatric events |
| **ORAL BALOXAVIR** | Influenza A and B | Treatment | 12 yrs. and older | 40mg X 1 (40-80 kg) (single dose) | **Adverse events**: Rapid antiviral resistance. |
| | | | | 80mg X 1 (≥80 kg) (single dose) | |

*duration of prophylaxis depends on the clinical situation

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# Influenza Vaccine Products for the 2019–2020 Influenza Season

| Manufacturer | Trade Name (vaccine abbreviation)[1] | How Supplied | Mercury Content (mcg Hg/0.5mL) | Age Range | CVX Code | Vaccine Product Billing Code[2] CPT |
|---|---|---|---|---|---|---|
| AstraZeneca | FluMist (LAIV4) | 0.2 mL (single-use nasal spray) | 0 | 2 through 49 years | 149 | 90672 |
| GlaxoSmithKline | Fluarix (IIV4) | 0.5 mL (single-dose syringe) | 0 | 6 months & older[3] | 150 | 90686 |
| | FluLaval (IIV4) | 0.5 mL (single-dose syringe) | 0 | 6 months & older[3] | 150 | 90686 |
| | | 5.0 mL (multi-dose vial) | <25 | 6 months & older[3] | 158 | 90688 |
| Sanofi Pasteur | Flublok (RIV4) | 0.5 mL (single-dose syringe) | 0 | 18 years & older | 185 | 90682 |
| | Fluzone (IIV4) | 0.25 mL (single-dose syringe) | 0 | 6 through 35 months[3] | 161 | 90685 |
| | | 0.5 mL (single-dose syringe) | 0 | 6 months & older[3] | 150 | 90686 |
| | | 0.5 mL (single-dose vial) | 0 | 6 months & older[3] | 150 | 90686 |
| | | 5.0 mL (multi-dose vial) | 25 | 6 through 35 months[3] | 158 | 90687 |
| | | 5.0 mL (multi-dose vial) | 25 | 3 years & older | 158 | 90688 |
| | Fluzone High-Dose (IIV3-HD) | 0.5 mL (single-dose syringe) | 0 | 65 years & older | 135 | 90662 |
| Seqirus | Afluria (IIV4) | 0.25 mL (single-dose syringe) | 0 | 6 through 35 months[3] | 161 | 90685 |
| | | 0.5 mL (single-dose syringe) | 0 | 3 years & older[3] | 150 | 90686 |
| | | 5.0 mL (multi-dose vial) | 24.5 | 6 through 35 months[3] | 158 | 90687 |
| | | 5.0 mL (multi-dose vial) | 24.5 | 3 years & older[4] | 158 | 90688 |
| | Fluad (aIIV3) | 0.5 mL (single-dose syringe) | 0 | 65 years & older | 168 | 90653 |
| | Flucelvax (ccIIV4) | 0.5 mL (single-dose syringe) | 0 | 4 years & older | 171 | 90674 |
| | | 5.0 mL (multi-dose vial) | 25 | 4 years & older | 186 | 90756 |

**NOTES**

1. IIV3/IIV4 = egg-based trivalent/quadrivalent inactivated influenza vaccine (injectable); where necessary to refer to cell culture-based vaccine, the prefix "cc" is used (e.g., ccIIV4); RIV4 = quadrivalent recombinant hemagglutinin influenza vaccine (injectable); aIIV3 = adjuvanted trivalent inactivated influenza vaccine.
2. An administration code should always be reported in addition to the vaccine product code. Note: Third party payers may have specific policies and guidelines that might require providing additional information on their claim forms.
3. Dosing for infants and children age 6 through 35 months:
   - Afluria 0.25 mL
   - Fluarix 0.5 mL
   - FluLaval 0.5 mL
   - Fluzone 0.25 mL or 0.5 mL
4. Afluria is approved by the Food and Drug Administration for intramuscular administration with the PharmaJet Stratis Needle-Free Injection System for persons age 18 through 64 years.

**Immunization Action Coalition** Saint Paul, Minnesota • 651-647-9009 • www.immunize.org • www.vaccineinformation.org | Technical content reviewed by the Centers for Disease Control and Prevention
www.immunize.org/catg.d/p4072.pdf • Item #P4072 (9/10/19)