

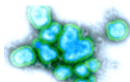
INFLUENZA

Dr.M.Jafarzadeh Infectious disease specialist



Influenza

- Is a disease caused by influenza viruses that infect the respiratory system of many animals, birds and humans.
- Human influenza is a highly contagious disease and is usually spread by a person's cough and sneeze .
- This disease is different from the common cold.

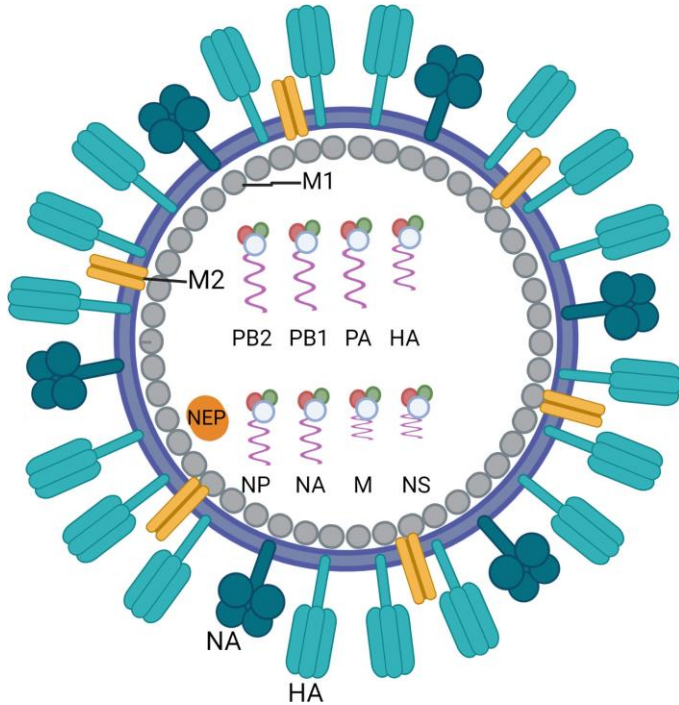


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The term influenza

- represents both a clinically defined respiratory illness accompanied by systemic symptoms of fever, malaise, and myalgia .
- Although this term is sometimes used more generally to denote any viral respiratory illness, many features distinguish influenza from these other illnesses, most particularly its systemic symptoms, its propensity to cause sharply peaked winter epidemics, and its capacity to spread rapidly among close contacts.



- **A.** Humans and animals , public health problems , pandemic risk with this type .
- **B.** Cause of seasonal epidemics .
- **C.** Can infect both humans and pigs , generally causes moderate illness .
- **D.** It primarily infects cattle .

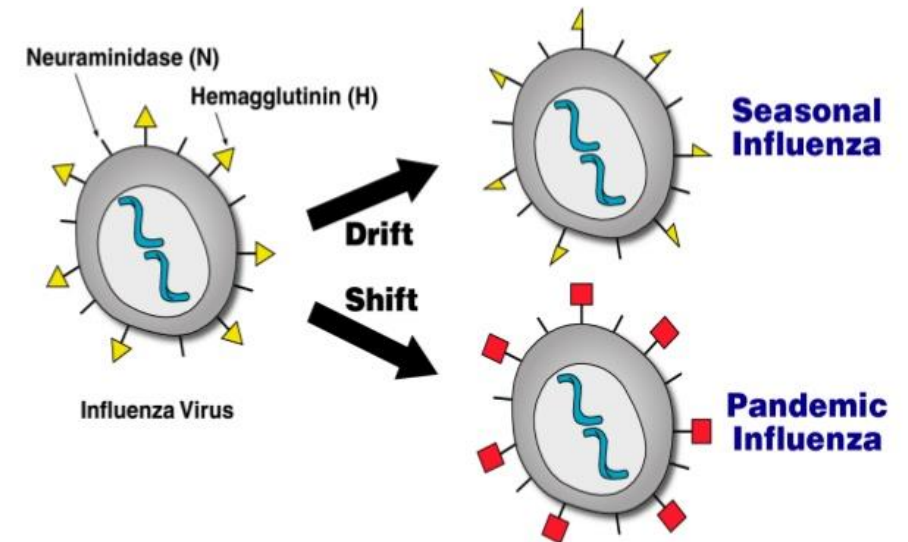


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- All influenza viruses are genetically unstable, and this issue raises the possibility of change and mutation changes occur over time.
- Small genetic changes in the composition of the influenza virus are called drift changes (small changes).
- On the other hand, the type A influenza virus, including the subspecies of different strains, can have genetic materials moved or rearranged and recombined during the process of rearrangement or mutation these changes are called shifts (big changes).
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Influenza: Antigenic Drift and Shift



Introduction

- Influenza type A virus is classified into different subspecies based on different compositions of its surface proteins (hemagglutinin and neuraminidase).
- So far, 18 subspecies of hemagglutinin and 11 subspecies of neuraminidase have been identified.
- Many subspecies have been identified in birds, and subspecies H17N10 and H18N11 have been identified only in bats.
- Depending on the primary host animal, type A influenza viruses can range from avian influenza types including A(H5N1), A(H7N9), A(H9N2), swine flu is classified as A(H1N1), A(H1N2), A(H3N2), or other types of animal flu.

Annual Global Incidence of Influenza Infection



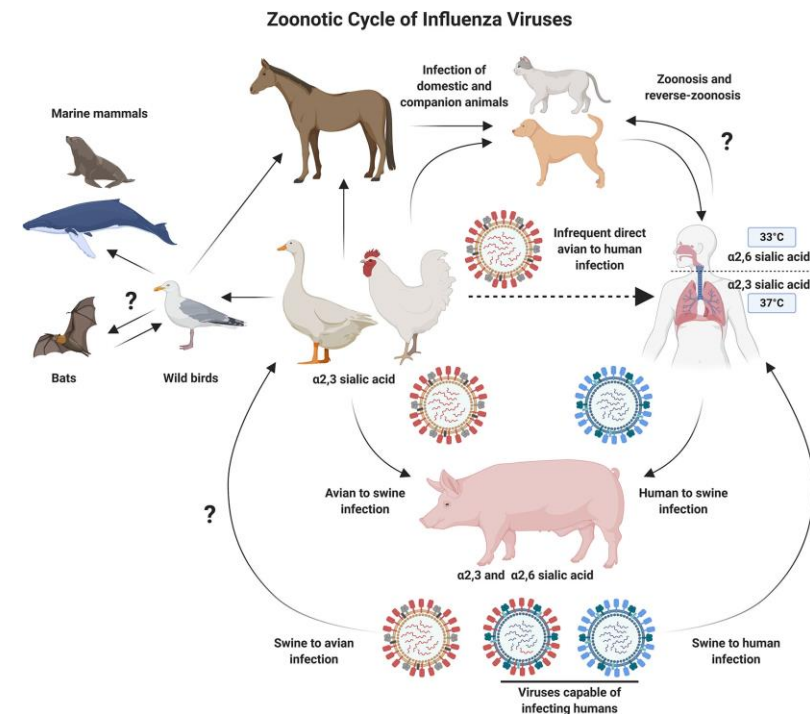
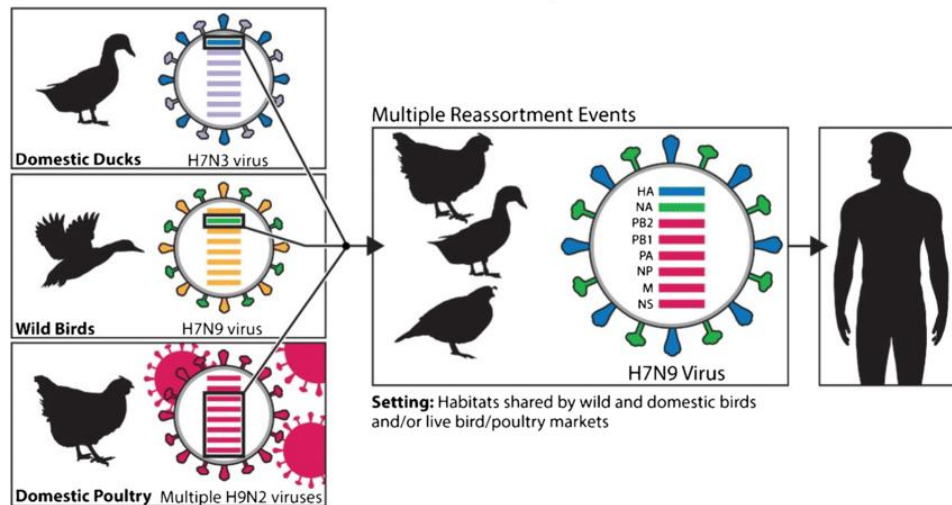
- In general, influenza occurs with an estimated annual incidence of 5-10% in adults and 20-30% in children.
- The resulting illness or disease can lead to hospitalization or death, especially in high-risk groups (children, the elderly, people with chronic diseases).
- Disease epidemics can lead to absenteeism in large work groups or schools and reduced production.

- **The global estimate of epidemics caused by influenza is about 3-5 million severe cases of the disease and about 250 thousand to 500 thousand deaths.**
- **Currently, the most effective way to prevent the disease and reduce the severity of the disease is vaccination and personal and social hygiene.**

- An influenza pandemic can occur when a new influenza virus acquires sufficient and stable human-to-human transmission ability and then spreads globally.
- So far, influenza pandemics have only been caused by new subspecies of type A virus because the human body is not immune to it and usually the resulting disease is very severe.

- Pandemic is not a one-stage event and disease stages occur in 2 or 3 time waves during 3 to 12 months of the year.
- The disease is expected to spread in all parts of the world by air travel (modern pandemic) in less than 3 months.
- Historical data shows the occurrence of all influenza pandemics with animal origin.

- Zoonotic (animal) influenza occurs when humans are infected by influenza viruses circulating in animals.
- Human infection is primarily caused by direct contact with an infected animal or contaminated environment.

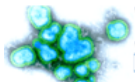


- The care definition of severe acute respiratory infections (SARI) in 2014 was initially used by the World Health Organization for infections caused by influenza.
- This definition is accepted to identify epidemics caused by dangerous respiratory infections.
- Many infectious viral acute respiratory diseases that have the ability to progress rapidly, such as covid-19, Middle East respiratory syndrome, Ebola, Nipah, have been curbed with this definition and the resulting strategy in the origin of the outbreak.

- On the other hand, the increase in international travel and global trade increases the need for intensified and integrated planning regarding the strengthening of diagnostic capacities and the identification and control of infectious diseases.
- Lessons learned from major health events, including outbreaks and epidemics of infectious diseases, show special attention to ONE HEALTH as a principle and HEALTH SECURITY as a basic pillar in planning.

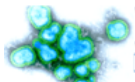
CLINICAL MANIFESTATIONS

- Influenza is primarily a respiratory illness causing cough, sore throat and rhinorrhea, or nasal congestion.
- The illness has a sudden onset and is epidemiologically linked to close contact with persons who have similar symptoms and often to community-wide respiratory illness.
- What distinguishes influenza from most other respiratory viral illnesses is the degree of accompanying fever, chills, fatigue, myalgia, and malaise.
- SARS-CoV-2 is the exceptional respiratory virus that also has a remarkable systemic component .
- Symptoms of influenza typically begin within 48–72 h of exposure.



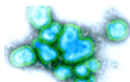
- **Respiratory symptoms,** particularly recurrent cough, persist well beyond the 2–5 days of systemic symptoms.
- There is a postinfectious delay in return to normal levels of activity.
- Pulmonary function is persistently decreased after acute influenza.
- Persons with a regular exercise routine (e.g., runners) note a decrease from their prior level of performance that typically lasts for a month or more.
- In the elderly, the respiratory presentation may be less prominent, but there is often a decline in baseline activity and a loss of appetite.

- **On physical examination,** the patient with influenza appears ill and rheumy, with sweating, coughing, nonpurulent conjunctivitis, and diffuse pharyngeal erythema.
- With lower respiratory involvement, pulmonary examination typically reveals nonlocalizing scattered rales, rhonchi, and wheezes.
- When present, localized pulmonary findings suggest relatively complicated pneumonia with a bacterial component.
- Muscle pain may be elicited by pressure, particularly in the calves and thighs.
- There are rare gastrointestinal findings.
- No rash is associated with influenza.



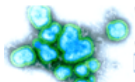
COMPLICATIONS

- Most persons who become ill with influenza virus infection recover without serious complications or sequelae.
- Complications of influenza occur most commonly in persons ≥ 65 years of age, young children, persons of all ages with underlying cardiopulmonary disease and immunosuppression, and women who are in the second or third trimester of pregnancy .



Respiratory Complications

- Pneumonia characterized by progressive air hunger, localized pulmonary findings on physical examination, and radiographic findings of diffuse infiltrates or consolidation is the most common complication of influenza.
- Pneumonia in influenza can be primary influenza viral pneumonia, secondary bacterial pneumonia, or mixed viral and bacterial pneumonia.
- Primary viral pneumonia is characterized by increasing dyspnea, persistent fever, and—in more severe cases—cyanosis.



- **Pathologically** , a marked inflammatory reaction in the alveolar septa is characterized by infiltration of monocytes , lymphocytes, and macrophages, with variable numbers of neutrophils.
- Destruction and hemorrhage are seen in the respiratory epithelium.
- Large amounts of virus can be recovered from the lungs.

- **In secondary bacterial pneumonia** or mixed viral and bacterial pneumonia, illness may be biphasic, with evidence of recovery from the primary influenza illness followed by recrudescence of fever and pulmonary symptoms.
- Localizing findings may be detected on pulmonary examination and/or x-ray.
- The development of secondary bacterial infection is not surprising, as influenza de-epithelializes the airways and destroys ciliary function, allowing bacterial contamination.

- **Another proposed mechanism** for bacterial/viral enhancement is the production by *Staphylococcus* and *Pseudomonas* of proteases that enhance cleavage of the influenza hemagglutinin and thereby facilitate viral replication.
- The risk of secondary bacterial disease is greatest in elderly patients and those with chronic obstructive pulmonary disease (COPD).

- **Some influenza strains** cause laryngotracheobronchitis bronchiolitis , or croup in children.
- Otitis media—a common accompaniment to influenza in children—may also be due to a combination of influenza virus and bacteria.

- **Extrapulmonary Complications** Although influenza is believed to spread only rarely beyond the respiratory epithelial cells , where unique endogenous proteases facilitate hemagglutinin cleavage and productive infection , this disease causes not only prominent systemic complaints but also a variety of extrapulmonary manifestations.

- **The most common extrapulmonary** manifestation of influenza is myositis, which is seen more often in influenza B and is characterized by severe muscle pain, elevated creatinine phosphokinase levels, and myoglobinuria that can lead to renal failure.
- The muscles are extremely tender to touch.
- Myo/pericarditis is seen less frequently.
- However, a consistent epidemiologic link exists between influenza epidemics and excess cardiovascular hospitalizations.

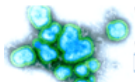
- **Neurologic involvement** , while rare, does occur following influenza infection.
- Influenza-associated encephalopathy or encephalitis is characterized by rapid progression within a few days of influenza infection.
- Transverse myelitis and Parkinsonian symptoms have been reported.
- Postinfectious acute demyelinating encephalomyelitis can follow influenza as well as other viral infections.
- The literature is mixed on the benefit and reliability of efforts to establish a polymerase chain reaction (PCR)–based diagnosis in this condition.

- MRI shows distinctive multifocal, symmetric brain lesions affecting the thalamus, brainstem tegmentum, cerebral periventricular white matter, and cerebellar medulla.
- Neurologic manifestations are more frequent in children as compared to adults.
- Children most commonly present with febrile seizures, increased seizure frequency among those with seizure disorders, or self-limited encephalopathy.
- More serious manifestations of meningitis, encephalitis, and focal brain lesions may occur, particularly in children with preexisting neurologic conditions .

- **Guillain-Barré syndrome** can develop after influenza and was reported after a widespread influenza vaccination effort in the fall of 1976 that was undertaken in anticipation of a swine influenza epidemic (which never materialized).
- Until aspirin was recognized as a cofactor in its precipitation, Reye syndrome, an acute hepatic decompensation, was seen commonly in children and adolescents with influenza, particularly those infected with influenza B virus.
- Subsequently, the use of aspirin for fever control and symptom relief in children with viral infections was strongly discouraged, and Reye syndrome has virtually disappeared from clinical practice.

- **LABORATORY FINDINGS AND DIAGNOSIS**

- Influenza virus is most easily recovered from nasopharyngeal specimens.
- If nasopharyngeal specimens are not available, nasal and throat swab specimens should be collected and combined together for influenza testing over single specimens from either site.
- These samples are most effectively collected with a flocculated swab.



- The most useful clinical approach today is to use a PCR-based molecular probe that amplifies specific segments of the influenza genome.
- Not only is this the most sensitive and specific method; it also provides opportunities to identify the strain with some specificity. Testing by multiplex PCR can simultaneously identify multiple respiratory pathogens—an advantage in the ill hospitalized patient.

- **Serologic confirmation** of infection is also possible but requires paired serum samples, with the convalescent-phase sample obtained 2 weeks after infection.
- Mucosal antibody assays that are now being developed can detect strain-specific antibodies in paired mucosal specimens and yield insights into the importance of mucosal immunity in protection against influenza.
- Other laboratory tests are of limited value.
- Mild leukopenia is seen in influenza, and a white blood cell count above 15,000/ μ L suggests a secondary bacterial component in influenzal pneumonia.

- **DIFFERENTIAL DIAGNOSIS** Influenza may be diagnosed clinically based on an acute presentation of a febrile respiratory illness during high periods of influenza circulation.
- However, less common presentations of influenza, and cases occurring outside of peak influenza season, are frequently misdiagnosed on the basis of symptoms alone.
- Influenza symptoms and signs may overlap with symptoms of other respiratory viruses.
- Respiratory syncytial virus often co-circulates with influenza virus; it particularly affects the youngest children, causing bronchiolitis, but it can also infect the elderly, leading to an influenza-like nonspecific respiratory illness and a decline in mobility, nutrition, and pulmonary function, with resultant hospitalization.

- **Patients with COVID-19** have a wide range of symptoms reported, ranging from mild to severe illness. Many of these symptoms—fever, chills, cough, shortness of breath, fatigue, muscle aches, headaches, congestion, or runny nose—overlap with the symptoms of influenza.
- While new loss of taste (ageusia) or smell (anosmia) may distinguish COVID-19 from influenza, they are reported in the minority of infected persons.
- When SARS-CoV-2 and influenza viruses are cocirculating, clinicians should consider both viruses, as well as co-infection, in patients with acute respiratory illness symptoms.
- The similar clinical presentations reiterate the importance of testing in order to inform treatment decisions.

- **IMMUNIZATION** Vaccination is the best approach to prevent influenza.
- The vaccines currently available in the United States are increasing in number and diversity .
- These vaccines fall into two broad categories: parenterally administered inactivated influenza vaccines and intranasally administered live-attenuated influenza vaccines.
- Current vaccines are further classified based on production substrate (eggs, cell), antigen dose and valence (trivalent or quadrivalent), and the presence or absence of adjuvants.
- Current inactivated influenza vaccines are designed with the common goal to induce immunity to the hemagglutinin surface glycoprotein of the influenza virus.
- No effort is made to standardize the neuraminidase content.



- As the viral surface hemagglutinin undergoes frequent antigenic drift, the seasonal influenza vaccine is reformulated as often as twice annually to match the strains projected to circulate in the following influenza season.
- The decision about vaccine composition must be made approximately 10 months before the seasonal peak in influenza virus circulation.

- Subsequently , the FDA , which has regulatory authority over vaccines in the United States, convenes an advisory committee that considers the recommendations of WHO, reviews and discusses similar data, and makes a final decision regarding vaccine virus composition of influenza vaccines licensed and marketed in the United States.
- This timing can result in a mismatch of vaccine composition with the viral strains that are actually prevalent in the upcoming season.
- Influenza vaccine is unique in being given seasonally in the months immediately preceding an outbreak in temperate climates.
- In the United States, vaccine is typically available starting in August or September .

- The currently available vaccines are all based on purified subunit inactivated virus produced in eggs, in tissue culture, or through a baculovirus-expressed hemagglutinin protein.
- They are all calibrated to hemagglutinin content. Depending on the vaccine, they are administered intramuscularly or intradermally.
- The recommendations for use, the approved age range of each product, the route of administration, and the anticipated side effects are published annually by the CDC

- A meta-analysis of randomized controlled trials of influenza vaccine efficacy over 12 influenza seasons showed inactivated influenza vaccines had a pooled efficacy of 59% (95% CI, 51%–67%) among those aged 18–65 years.

- Studies support that influenza vaccine mitigates disease severity.
- For example, observational studies in children support that influenza vaccination reduces intensive care unit hospitalizations and deaths by an estimated 74% and 65%, respectively.

- **Newer technologies have been developed to overcome some of the limitations of current vaccines.**
- **The first fully recombinant vaccine was approved by the FDA in 2017.**
- **Both recombinant and cell-based vaccines may overcome the egg-adaptation of vaccine strains that may contribute to diminished vaccine effectiveness.**
- **Oil-in-water adjuvanted vaccines and high-dose vaccines elicit greater immune responses than traditional inactivated influenza vaccines and are approved in the United States for persons ≥ 65 years of age.**
- **In most head-to-head comparisons, high-dose vaccines have shown superior effectiveness to standard dose. While evidence is more limited, select comparisons of recombinant and adjuvanted vaccines with standard vaccines likewise show improved effectiveness.**

- In head-to-head comparisons in pediatric populations in the 1990s, a live, attenuated, intranasally administered vaccine (LAIV) exhibited an efficacy exceeding that of injected inactivated vaccines.
- LAIV is a desirable option in children given the ease of intranasal administration and theoretical advantage of stimulating mucosal immunity by the topical route.
- However, in the 2014–2016 influenza seasons, LAIV had lower replicative fitness and no demonstrable efficacy assignable to the vaccine's H1N1 component. Consequently, advisory committees in the United States and elsewhere suspended the recommendations for use of LAIV until manufacturing improvements allowed reinstatement of recommendations for its use in 2018.
- Since that time, LAIV has performed comparably to inactivated influenza vaccines in annual effectiveness assessments.

- Inactivated influenza vaccines have been licensed for more than 60 years and have a robust safety and tolerability profile. While local reactions are most common following inactivated influenza vaccines, rare adverse events may occur.
- These include Guillain-Barré syndrome, identified in 1976 and less frequently during other years; oculorespiratory syndrome, first recognized in 2000; and febrile seizures first reported in young children in Australia in 2010.
- Adjuvanted vaccines in general cause more local pain and erythema than unadjuvanted vaccines.
- LAIVs have been associated with excess wheezing and hospitalizations in children younger than 2 years, and thus are not licensed for use in this age group.

- Vaccine-specific recommendations for use, the approved age range of each product, the route of administration, and the anticipated side effects are updated annually by the CDC .
- In the United States, routine annual influenza vaccination is recommended for all persons 6 months of age and older.
- No preferential recommendation is made for one influenza vaccine product over another for persons for whom more than one licensed, recommended, and appropriate product is available.
- Two doses of vaccine should be given to children < 9 years of age who are getting their first or second yearly vaccination.

- In general, influenza vaccine is not recommended for persons with a history of severe allergic reaction to the vaccine or to components other than egg.
- Manufacturer package inserts and updated CDC guidance should be consulted for information on contraindications and precautions for individual influenza vaccines, including specific guidance for persons with a history of egg allergy.
- A history of Guillain-Barré syndrome within 6 weeks of a previous dose of influenza vaccine is considered a precaution for the use of all influenza vaccines.

- **Antiviral therapy** for influenza has been limited by the paucity of available drugs, the short duration of symptoms in uncomplicated influenza, and the changing patterns of drug resistance in influenza viral strains.
- In the past, influenza A infection could be treated with the M-2 channel blockers amantadine and rimantadine.
- Widespread resistance has currently relegated these compounds to historical interest only .

- Neuraminidase inhibitors have been the mainstay for treatment of influenza A and B viruses for many years.
- As their name implies, these drugs inhibit the influenza neuraminidase and thus limit the egress of influenza virus from an infected cell.
- They are most effective in patients whose influenza illness is recognized early and confirmed by rapid diagnostic testing or on the basis of clinical and epidemiologic evidence.

- In experimental trials, these drugs hasten the resolution of symptoms if given within 48 h of infection.
- There are indications for their use both prophylactically—either throughout the season or, when a case is recognized in a close contact, in the short term—and therapeutically.
- The anticipated effect of early administration is the resolution of symptoms 1–2 days sooner than without treatment.
- The use of neuraminidase inhibitors is recommended for complicated influenza infections in hospitalized patients in the absence of formal proof of efficacy and when diagnosis may have been delayed.

- All the available neuraminidase inhibitors carry a risk of development of resistance, particularly with prolonged administration (e.g., to an immunodeficient individual with persistent recovery of influenza virus).
- Resistance to neuraminidase inhibitors is not widespread among currently circulating influenza A or B strains, but its development has been demonstrated in the laboratory, and clinical resistance could influence the utility of these drugs.

- The defined risk groups who can benefit from neuraminidase inhibitors include children < 2 years of age, adults > 65 years of age, patients with chronic conditions, immunosuppressed individuals, pregnant women, women who have delivered infants ≤ 2 weeks previously, patients <19 years old who are receiving long-term aspirin treatment, Native Americans (including Alaska Natives), morbidly obese individuals, and residents of nursing homes or chronic-care facilities.
- This list resembles that of candidates whose vaccination is a high priority (Table 200-2).
- Use of neuraminidase inhibitors should be considered in selected high-risk cases despite a history of vaccination.

- The available neuraminidase inhibitors are oral oseltamivir, nasal-spray zanamivir, and intravenous peramivir.
- Oseltamivir, which is most widely used, is an orally absorbed drug that is converted to its active component, oseltamivir carboxylate, in the liver.
- Gastrointestinal symptoms, especially nausea, may accompany the administration of oseltamivir.
- Because zanamivir is not orally bioavailable, it is given as an inhaled dry powder dispersed through a Diskhaler device.

- The usual duration of therapy with either oral oseltamivir or intranasal zanamivir is 5 days, with twice-a-day dosing.
- Oseltamivir is preferred for treatment of pregnant women and is approved for treatment at any age, beginning at 14 days of life in infants.
- Poor oral intake or absorption is a contraindication to the use of oseltamivir, although this drug can also be given by oro/nasal tube.
- Asthma and COPD are relative contraindications to the use of intranasal zanamivir; this agent is approved for treatment in persons 7 years and older.

- For hospitalized patients with suspected or confirmed influenza, initiation of antiviral treatment with oral or enterically administered oseltamivir is recommended as soon as possible.
- For patients who cannot tolerate or absorb oral or enterically administered oseltamivir, the use of a single infusion of intravenous peramivir should be considered. Peramivir is licensed for individuals ≥ 2 years of age.

A purple rectangular tag with a hole on the left side is placed on a rustic wooden surface. A thin, light-colored string is looped through the hole. Three white daisies with yellow centers are scattered around the tag: one in the foreground to the right, and two in the background, slightly out of focus. The text 'Thank you!' is written in a black, cursive script on the tag.

Thank
you!