# In the name of **Allah** the compassionate and the merciful

Influenza virus treatment and prevention

Dr.h. mazaherpour

- Influenza is an acute, febrile illness caused by infection with influenza type A or B virus that occurs in outbreaks of varying severity almost every winter in temperate climates, and year-round in tropical climates. The most common clinical manifestations are fever, malaise, and cough.
- Influenza virus has been causing recurrent epidemics of febrile respiratory disease every 1 to 3 years for at least the past 400 years.

- The greatest pandemic in recorded history occurred in 1918–1919 when, during three “waves” of influenza, 21 million deaths were recorded worldwide, among them 549,000 in the United States.
- Influenza viruses belong to the family Orthomyxoviridae and are classified into three distinct types: influenza A, influenza B, and influenza C virus.
- Influenza A viruses are further divided into subtypes based on the hemagglutinin (H, or HA) and neuraminidase (N, or NA) antigens (e.g., H1N1 or H3N2)

## TABLE 165.3 Differences Among Influenza A, B, and C Viruses

| | INFLUENZA A | INFLUENZA B | INFLUENZA C |
|---|---|---|---|
| Genetics | 8 gene segments | 8 gene segments | 7 gene segments |
| Structure | 10 viral proteins<br>M2 unique | 11 viral proteins<br>NB unique | 9 viral proteins<br>HEF unique |
| Natural host range | Humans, swine, equine, birds, marine mammals[a] | Humans only | Humans and swine |
| Epidemiology | Antigenic shift and drift | Antigenic drift only; two main lineages cocirculate | Antigenic drift only; multiple variants |
| Clinical manifestations | May cause large pandemics with significant mortality in young persons | Severe disease generally confined to older adults or persons at high risk; pandemics not seen | Mild disease without seasonality |

[a]Influenza A viruses have also been isolated from mink, dogs, and cats.

## TABLE 165.1 Antiviral Chemotherapy and Chemoprophylaxis for Influenza

| INDICATION | DRUG | ROUTE | DOSAGE |
|---|---|---|---|
| Influenza A and B: treatment | Oseltamivir | Oral | Adults: 75 mg bid ×5 days<br>Children aged 1–12 yr: 30–75 mg bid, depending on weight,[a] ×5 days |
| | Zanamivir | Inhaled orally | Adults and children aged ≥7 yr: 10 mg bid ×5 days |
| | Peramivir | Intravenous | Adult: 600 mg IV once<br>Children 2–12 yr: 12 mg/kg once |
| | Baloxavir | Oral | Adults: 80 mg PO once<br>Children ≥12 yr and <80 kg: 40 mg PO once |
| Influenza A: treatment | Amantadine[b] | Oral | Adults: 100 mg qd or bid ×5–7 days<br>Children aged 1–9 yr: 5 mg/kg/day (maximum, 150 mg/day) ×5–7 days |
| | Rimantadine[b] | Oral | 100 mg qd or bid ×5–7 days in adults |
| Influenza A and B: prophylaxis | Oseltamivir | Oral | Adults: 75 mg/day<br>Children aged ≥1 yr: 30–75 mg/day, depending on weight[a] |
| | Zanamivir | Inhaled orally | Adults and children aged ≥5 yr: 10 mg/day |
| | Peramivir | Intravenous | Not FDA approved for prophylaxis |
| Influenza A: prophylaxis | Amantadine[b] or rimantadine[b] | Oral | Adults: 200 mg/day<br>Children aged 1–9 yr: 5 mg/kg/day (maximum, 150 mg/day) |

- The HA is the viral attachment protein, and the receptor binding site is located in the globular head of the molecule. The viral NA is an enzyme that catalyzes the removal of terminal sialic acids (*N*-acetyl neuraminic acid) from sialic acid–containing glycoproteins.
- At least 16 highly divergent, antigenically distinct HAs have been described in influenza A viruses (H1 to H16), in addition to at least nine distinct NAs (N1 to N9)

- Although influenza B viruses have a similar structure, they do not exhibit the same type of antigenic and genetic variation in the HA and NA, and therefore do not have subtypes. However, since 2001, two antigenically distinct lineages of influenza B viruses, termed the “Victoria” lineage and the “Yamagata” lineage, have cocirculated in humans.

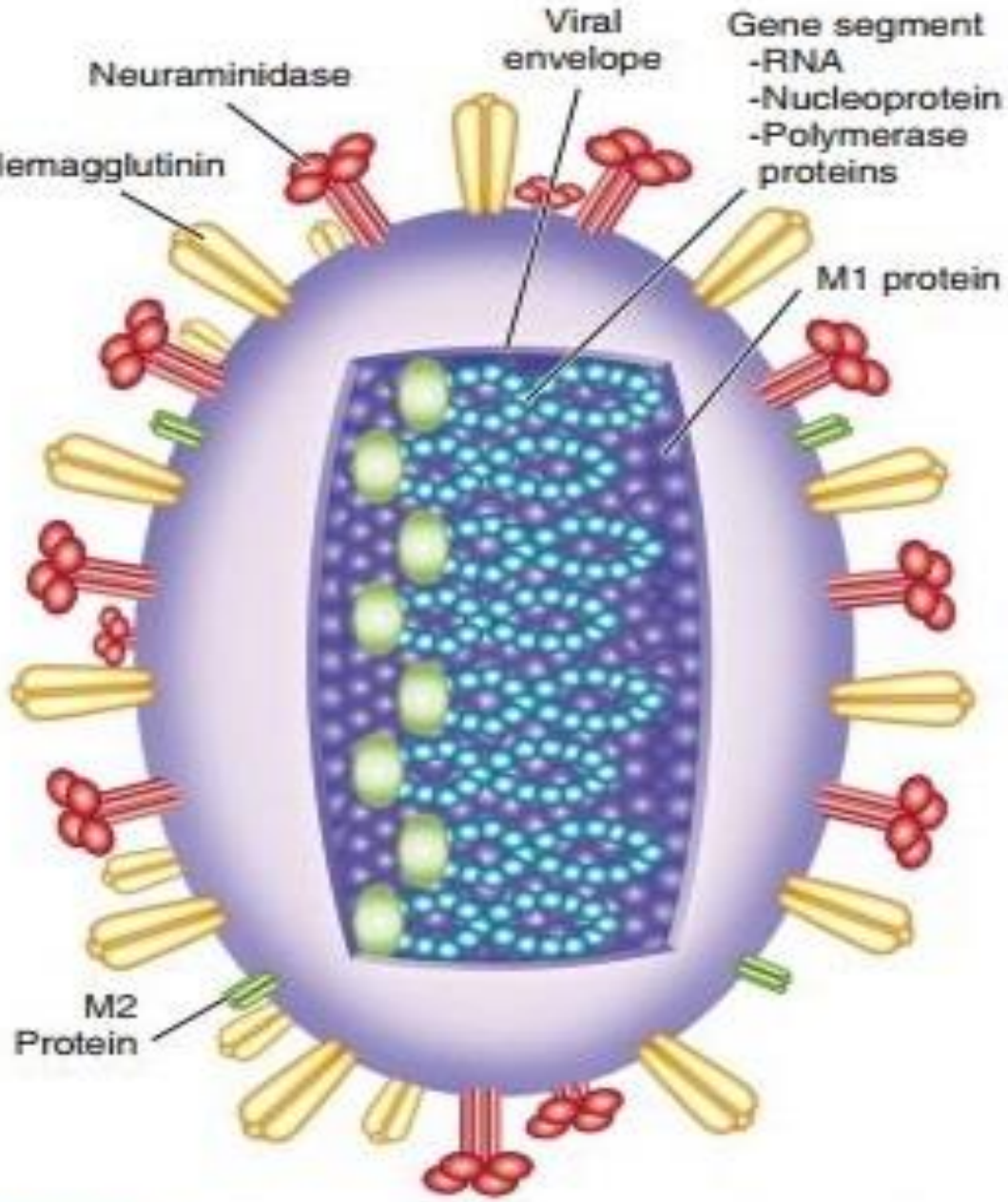



**FIG. 165.2** Schematic model of an influenza A virus.

- Attack rates are generally highest in the young, whereas mortality is generally highest among older adults. In some studies, up to three-fourths of all influenza-related deaths occur in those older than 65.

- Excess morbidity and mortality are also high in those with certain high-risk medical conditions, including adults and children with cardiovascular and pulmonary conditions such as asthma, or those requiring regular medical care because of chronic metabolic disease, renal dysfunction, hemoglobinopathies, or immunodefciency, and in individuals with neurologic conditions that compromise the handling of respiratory secretions.

- Influenza-related death rates in nursing home residents with comorbid conditions are as high as 2.8% per year.
- Previous studies had identified an increased risk of hospitalization associated with influenza epidemics during pregnancy, especially in the second and third trimesters and in the immediate postpartum period
- Obesity also emerged as a risk factor for influenza morbidity and mortality during the 2009 pandemic that had not been recognized in previous seasonal epidemics or pandemics

- The first indicator of influenza activity was reports of increased numbers of children with febrile respiratory illness, followed by the occurrence of influenza-like illnesses among adults.
- During epidemics, attack rates in unvaccinated populations are estimated to be 10% to 20%, but rates as high as 40% to 50% have been reported.

# TABLE 165.6 Groups at Higher Risk for Influenza Complications

## Children and Adolescents at Higher Risk for Influenza Complications

Children younger than 4 years
Children with chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematologic, or metabolic (including diabetes mellitus) disorders
Children who are immunosuppressed, including children infected with human immunodeficiency virus and those taking immunosuppressive medications
Children with a condition that can compromise respiratory function or handling of respiratory secretions that can increase the risk for hypertension (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders)
Children who are receiving long-term aspirin therapy and who therefore might be at risk for developing Reye syndrome
Children who are residents of chronic-care facilities
Those who will be pregnant during the influenza season

## Adults at Higher Risk for Influenza-Related Complications

Persons aged 65 years or older
Women who will be pregnant during the influenza season
Persons with chronic pulmonary (including asthma), cardiovascular, renal, hepatic, hematologic, or metabolic disorders (including diabetes mellitus)
Persons who have immunosuppression (including immunosuppression due to medication or human immunodeficiency virus infection)
Persons with any condition that can compromise respiratory function or the handling of respiratory secretions or increase the risk of aspiration.
Persons with obesity, defined as a body mass index greater than 40
Residents of nursing homes and other chronic-care facilities

# Transmission

- Influenza viruses are transmitted from person to person via the respiratory route. Tree potential modes of transmission have been suggested.
- Coughing and sneezing could generate small-particle aerosols (<10 µm mass diameter) that can remain suspended in air for many hours and could transmit infection to individuals at a substantial distance.
- Larger particles or droplets will typically fall to the ground within 3 meters of the infected person and would be expected to infect individuals in direct contact.

- Finally, viral particles could land on surfaces, where influenza viruses remain infectious and could infect others through indirect contact.
- It has not been proven that these aerosols contain significant amounts of infectious virus, but experimental studies in humans have shown that very small amounts (approximately five infectious particles) may be sufficient to infect humans by the aerosol route.

- The risk of transmission of influenza A from the index case to other passengers was related to the amount of time passengers spent on the aircraft, and not on their seating proximity to the index case. Because most of the passengers did not have direct contact with the index case, airborne transmission appears to be likely.

# ANTIGENIC VARIATION

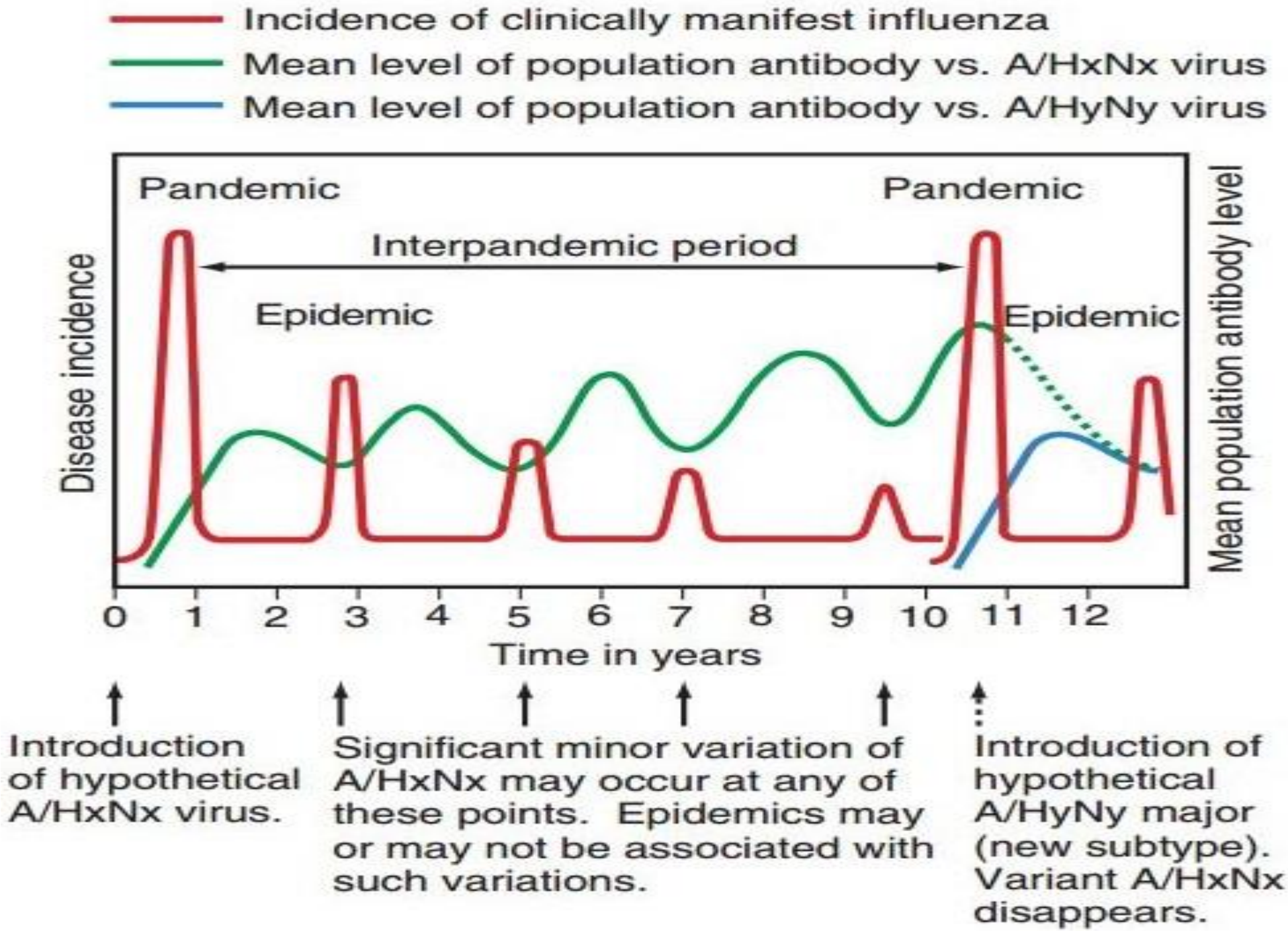
- One of the unique and most remarkable features of influenza virus is the frequency with which changes in antigenicity occur, collectively referred to as antigenic variation. The phenomenon of antigenic variation helps explain why influenza continues to be a major epidemic disease of humans.
- Antigenic variation involves principally the two external glycoproteins of the virus, HA and NA, and is referred to as antigenic drift or antigenic shift, depending on whether the variation is small or great.

# Antigenic Drift

- Antigenic drift refers to relatively minor antigenic changes that occur frequently within the HA and/or NA of the virus. Drift has been studied most intensively for the HA and is the result of gradual accumulation of amino-acid changes in one or more of the five identified major antigenic sites on the HA molecule

# Antigenic Shift

- At unpredictable intervals, influenza A viruses with more radical changes in the antigenicity of the HA and/or NA have emerged to cause widespread disease, or pandemics. These major antigenic changes are referred to as antigenic shifts, and result in viruses toward which the population has little or no prior immunity and is therefore highly susceptible


Incidence of clinically manifest influenza
Mean level of population antibody vs. A/HxNx virus
Mean level of population antibody vs. A/HyNy virus
Pandemic
Pandemic
Interpandemic period
Epidemic
Epidemic
Disease incidence
Mean population antibody level
0 1 2 3 4 5 6 7 8 9 10 11 12
Time in years
Introduction of hypothetical A/HxNx virus.
Significant minor variation of A/HxNx may occur at any of these points. Epidemics may or may not be associated with such variations.
Introduction of hypothetical A/HyNy major (new subtype). Variant A/HxNx disappears.

# CLINICAL FINDINGS

- **Uncomplicated Influenza:** Typical uncomplicated influenza often begins with an abrupt onset of symptoms after an incubation period of 1 to 2 days. Many patients can pinpoint the hour of onset. Initially, systemic symptoms predominate, including feverishness, chilliness or frank shaking chills, headaches, myalgia, malaise, and anorexia. In more severe cases, prostration is observed. Usually, myalgia or headache is the most troublesome symptom, and the severity is related to the height of the fever.

- Severe pain in the eye muscles can be elicited by gazing laterally, and arthralgia but not frank arthritis is commonly observed. Other ocular symptoms include tearing and burning. The systemic symptoms usually persist for 3 days, the typical duration of fever. Respiratory symptoms, particularly a dry cough, severe pharyngeal pain, and nasal obstruction and discharge, are usually also present at the onset of illness but are overshadowed by the systemic symptoms.

- Cough is the most frequent and troublesome of these symptoms and may be accompanied by sub sternal discomfort or burning.
- Fever is the most important physical finding. The temperature usually rises rapidly to a peak of 100°F to 104°F, and occasionally to 106°F, within 12 hours of onset, concurrent with the development of systemic symptoms.

# Complications of Influenza

- Two manifestations of pneumonia associated with influenza are well recognized: primary influenza viral pneumonia and secondary bacterial infection.
- **Primary Influenza Viral Pneumonia:** The illness begins with a typical onset of influenza, followed by a rapid progression of fever, cough, dyspnea, and cyanosis. Physical examination and chest radiographs reveal bilateral findings consistent with the adult respiratory disease syndrome but no consolidation.

- Blood gas studies show marked hypoxia, Gram stain of the sputum fails to reveal significant bacteria, and bacterial culture yields sparse growth of normal flora, whereas viral cultures yield high titers of influenza A virus. Such patients do not respond to antibiotics, and mortality is high.
- **Secondary Bacterial Pneumonia:** The patient has a classic influenza illness followed by a period of improvement lasting usually 4 to 14 days.

- Recrudescence of fever is associated with symptoms and signs of bacterial pneumonia such as cough, sputum production, and an area of consolidation detected at physical examination and on a chest radiograph.
- The two pathogens that are currently most commonly associated with influenza are *Streptococcus pneumoniae* and *Staphylococcus aureus,* which is otherwise an uncommon cause of community-acquired pneumonia.

## TABLE 165.7 Comparative Features of Pulmonary Complications of Influenza

| | PRIMARY VIRAL PNEUMONIA | SECONDARY BACTERIAL PNEUMONIA | MIXED VIRAL AND BACTERIAL PNEUMONIA |
|---|---|---|---|
| Setting | Cardiovascular disease; pregnancy; young adult (pH1N1) | Adults and children | Any associated with A or B |
| Clinical history | Relentless progression from classic 3-day influenza | Improvement, then worsening after 3-day influenza | Features of both primary and secondary pneumonia |
| Physical examination | Bilateral findings, no consolidation | Consolidation | Consolidation |
| Sputum bacteriology | Normal flora | *Pneumococcus, Staphylococcus, Haemophilus influenzae* | *Pneumococcus, Staphylococcus, H. influenzae* |
| Chest radiography | Bilateral findings | Consolidation | Consolidation |
| Detection of influenza virus | Yes | Not always | Yes |
| Response to antibiotics | No | Yes | Often |
| Mortality | High | Variable | Variable |

# Non-pulmonary Complications

- **Myositis:** Myositis and myoglobinuria with tender leg muscles and elevated serum creatine phosphokinase (CPK) levels have been reported, mostly in children, but they can also occur in adults
- **Cardiac Complications:** Both myocarditis and pericarditis have been rarely associated with influenza A or B virus infection. Myocardial infarction may also be triggered by influenza infection, possibly as an effect of platelet aggregation. Studies have shown a substantially increased risk of myocardial infarction in the 7 days after hospitalization for influenza.

- **Toxic Shock Syndrome:** In recent outbreaks of influenza A or B, a toxic shock–like syndrome has occurred in previously healthy children or adults, presumably because viral infection changed colonization and replication characteristics of the toxin-producing staphylococci
- **Central Nervous Complications:** Guillain-Barré syndrome (GBS) has been reported to occur after influenza A infection, as it has after numerous other infections, but no definite etiologic relationship has been established. In addition, cases of transverse myelitis and encephalitis have occurred rarely

# DIAGNOSIS

- **Clinical Diagnosis:** Most cases of influenza are diagnosed based on compatible clinical symptoms and seasonal epidemiology. In fact, several studies have shown that the accuracy of a clinical diagnosis in healthy adults in the setting of an influenza outbreak is as high as 80% to 90%.
- **Laboratory Diagnosis: Polymerase Chain Reaction–Based Tests**
  The most widely used method in clinical laboratories to detect influenza infection is PCR tests. PCR-based tests have the advantage of being potentially more sensitive than other available tests and allow detection in samples in which the virions have lost viability

- Improvements have been made in PCR techniques that have reduced the time to carry out assays in the laboratory to as little as 45 to 80 minutes.
- **Rapid Influenza Diagnostic Tests** The tests widely referred to as “rapid diagnostic” tests are based on immunologic detection of viral antigen in respiratory secretions. The reported sensitivities of each test in comparison to cell culture have ranged between 40% and 80%, and they are somewhat dependent on the nature of the samples tested and the patients from whom they were derived.

- **Virus Isolation:** Isolation of influenza virus in cell culture has historically been the definitive laboratory test to diagnose influenza infection. Virus can be isolated readily from nasal swab specimens, throat swab specimens, nasal washes, or combined nose and throat swab specimens, or sputum samples.

# PREVENTION

- Multiple forms of influenza vaccine are currently available both in the United States and elsewhere, including virion- or protein-based IIVs administered intramuscularly, and LAIVs administered intranasally. Both types of vaccines are thought to work primarily by inducing antibody against the viral hemagglutinin, although other mechanisms probably also play a role.

- **Egg-Grown Inactivated Influenza Vaccines (IIV-3, IIV-4):** The original influenza vaccine, which consisted of formalin-inactivated whole virions grown in embryonated chicken eggs, was demonstrated to have a protective efficacy of 70% in healthy adults. Treatment of the whole virus with solvents to create “split” vaccines, or with detergents to create “subunit” vaccines, resulted in a vaccine with fewer adverse reactions, particularly fever, than the whole-cell vaccine.

- **Cell Culture–Derived Inactivated Vaccine (ccIIV-4)** One strategy to avoid the problems associated with egg adaptation would be to produce the vaccine by propagating the viruses in mammalian cell culture.
- **Recombinant Hemagglutinin Expressed in Insect Cells (rIV-4)** Another alternative is to express the hemagglutinin using an appropriate expression system. The expression of proteins in insect cells using recombinant baculovirus expression vectors can be achieved rapidly and results in proteins with mammalian-like glycosylation.

- A recombinantly expressed hemagglutinin vaccine is currently licensed in the United States for ages 18 and above.
- **MF-59 Adjuvanted Inactivated Influenza Vaccine (aIIV-3)**
  Another approach to improving vaccine performance is the use of adjuvants, or immune stimulators designed to improve the response to a co-administered antigen. The squalene-based oil-in-water adjuvant MF59 has been shown to increase the immunogenicity of egg-derived influenza vaccine in older adults, and has been licensed in the United States and elsewhere in this age group.

- **Intranasal Live-Attenuated Influenza Vaccine (LAIV-4)** Live-attenuated vaccines have a long track record of success against a wide variety of viral diseases, such as smallpox, measles, polio, and others, in part because they generate a diverse immune response that mimics the immune response to the pathogen.

# Safety

- **Inactivated Vaccines**: The most common adverse events reported after immunization with IIV are tenderness and/or pain at the injection site. Most injection site reactions are mild and rarely interfere with daily activities. Systemic reactions after immunization of adults with inactivated vaccine are uncommon.
- Immediate hypersensitivity reactions (hives, wheezing, angioedema, or anaphylactic shock) after vaccination with inactivated vaccine can also occur, and vaccine is considered contraindicated for persons who experienced a previous anaphylactic reaction following vaccine administration.

- Guillain-Barré syndrome (GBS), an acute inflammatory demyelinating polyneuropathy, was associated with the 1976 swine influenza vaccination campaign, with an increased risk of approximately 1 per 100,000 vaccinees.
- Pregnancy is recognized as a risk factor for more severe influenza, and pregnant women are an important target group for immunization. Most studies of pregnancy outcomes have found no association between vaccination and adverse pregnancy outcomes, although relatively less information is available regarding first trimester vaccination.

- Influenza vaccine is currently considered safe in all trimesters
- **Live-Attenuated Vaccines:** Young children with advanced HIV infection may have difficulty clearing wild-type influenza virus from the respiratory tract, and there have been several reports of very prolonged virus shedding in highly immunosuppressed children with AIDS. However, because of the possibility of transmission, LAIV is not recommended for close contacts of individuals who have levels of immunocompromise that necessitate a protected environment.

# ANTIVIRAL AGENTS

- Five antiviral drugs in two classes are currently available for the prevention and treatment of influenza, and several more are in the advanced stages of development.

## TABLE 165.8 Antiviral Agents for Influenza

| | AMANTADINE[a] | RIMANTADINE[a] | ZANAMIVIR | OSELTAMIVIR | PERAMIVIR | BALOXAVIR |
|---|---|---|---|---|---|---|
| Protein target | M2 | M2 | Neuraminidase | Neuraminidase | Neuraminidase | Cap-dependent endonuclease |
| Activity | A only | A only | A and B | A and B | A and B | A and B |
| Side effects | CNS (13%)<br>GI (3%) | GI (6%)<br>GI (3%) | Bronchospasm | GI (9%) | GI (8%) | Diarrhea, bronchitis |
| Metabolism | None | Multiple (hepatic) | None | Hepatic | None | UGT1A3, CYP3A4 |
| Excretion | Renal | Renal + others | Renal | Renal (tubular secretion) | Renal | Fecal (80%): urine (15%) |
| Drug interactions | Antihistamines, anticholinergics | None | None | Probenecid (increased levels of oseltamivir) | — | Antacids and laxatives reduce concentration |
| Dose adjustments needed | ≥65 yr old<br>CrCl <50 mL/min | ≥65 yr old<br>CrCl <10 mL/min | None | CrCl <30 mL/min<br>Severe liver dysfunction | CrCl <30 mL/min | — |
| Contraindications | Acute-angle glaucoma | Severe liver dysfunction | Underlying airway disease | | | — |
| **FDA-Approved Indications** | | | | | | |
| Therapy | Adults and children aged ≥1 yr | Adults only | Adults and children aged ≥7 yr | Adults and children aged ≥2 wk | Adults who cannot take oral or inhaled medications | Adults and children ≥12 yr of age[b] |
| Prophylaxis | Yes | Yes | Adults and children aged ≥5 yr | Adults and children aged ≥1 yr | — | — |

- **M2 Inhibitors: Amantadine and Rimantadine**: Currently, all circulating influenza viruses are resistant to the M2 inhibitors amantadine and rimantadine. The M2 inhibitors amantadine and rimantadine are related primary symmetrical amines and are active against influenza A virus, but not influenza B or C virus, in a variety of cell culture systems and animal models.
- The most common side effects of amantadine are minor and reversible central nervous system (CNS) side effects such as insomnia, dizziness, and difficulty in concentrating.

- Resistance is the result of single point mutations in the membrane-spanning region of the M2 protein, and it confers complete cross-resistance between amantadine and rimantadine
- **Neuraminidase Inhibitors: Zanamivir, Oseltamivir, and Peramivir** The NIs act by inhibiting the functioning of the influenza virus NA. Oseltamivir is rapidly absorbed from the gastrointestinal tract and is converted in the liver by hepatic esterases to the active metabolite, oseltamivir carboxylate.

- Administration of the drug with food may improve tolerability without affecting drug levels.
- Zanamivir is not bioavailable by the oral route and must be administered topically to be effective. The standard dose is therefore two inhalations twice a day.
- Peramivir was initially studied as an orally active agent, but pharmacodynamic evaluation determined that oral absorption was not sufficient for this mode of administration. The drug is now licensed as an intravenous

- The major adverse effects reported for oseltamivir have been gastrointestinal upset, probably irritation due to rapid release of the drug in the stomach. Rates of nausea can be substantially reduced if the drug is taken with food. The most commonly reported adverse effects in individuals treated with zanamivir have been diarrhea, nausea, and nasal signs and symptoms, which have occurred at essentially the same rate as in placebo recipients. Peramivir has a similar safety profile in studies conducted to date

- Drug-resistant viruses were isolated infrequently from oseltamivir treated individuals in clinical trials, being seen in less than 2% of treated adults and detected in 5.6% of children.

# Thanks for your attention