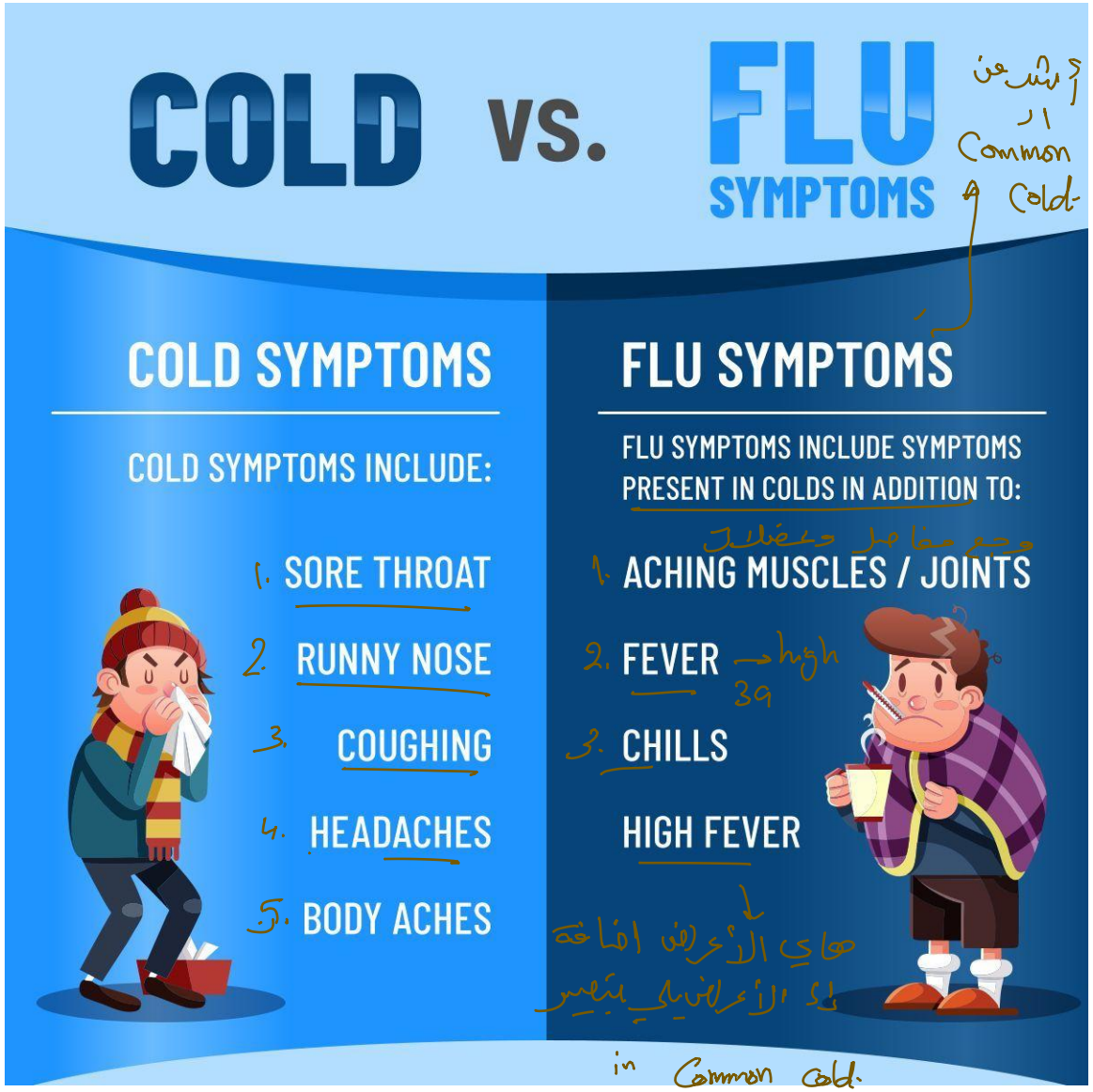
Influenza Virus Infection

↳ viral infection.

General Principles:

- ✓ Influenza is an acute febrile respiratory viral illness, readily transmissible and associated with outbreaks of varying severity during the winter months and with high mortality and high hospitalization rates.
  - ↳ in immunocompromized patient / elderly / childrens / with other comorbidities
  - عادة تحدث في الشتاء ولكن ممكن تصير أي وقت في السنة
- ✓ Seasonal influenza epidemics causes nearly 650,000 deaths each year globally, with the highest burden among children younger than 5 years and adults 75 years and older. (1) (2)
- ✓ Clinical presentation is similar to a number of other respiratory illnesses.
  - → Diagnosis based on clinical presentation.



أكثر شدة من Common Cold.

هاي الأعراض إضافة لكل الأعراض اللي بتصير in Common cold.

- ✓ Severe illness in:
  - older than age 65 years
  - young children (< 2 years old)
  - underlying medical conditions (pregnancy and cardiopulmonary disorders)

- ✓ Incubation period 1 to 7 days. Adults are infectious from the day before their symptoms begin through 7 days after the onset of illness.
- ✓ Children can be infectious for longer than 10 days after the onset of illness.
- ✓ Influenza A and B viruses are the two types that cause disease in humans.
- ✓ Influenza A viruses are further categorized into different subtypes based on changes in two surface antigens—hemagglutinin and neuraminidase (NA).
- ✓ Influenza B viruses are not categorized into subtypes.
- ✓ Primary subtypes of influenza A (circulating among humans for the past 3 decades) are H3N2 & H1N1.

Influenza prevention

1 - Infection control measures (hand hygiene, basic respiratory etiquette (cover your cough and throw tissues away)

2 - Contact avoidance

3 - Annual vaccination is recommended for:

1. All persons age 6 months or older

2. Caregivers (eg, parents, teachers, babysitters) of children less than 6 months of age

3. People who live with and/or care for people who are at high risk, including household contacts and healthcare workers.

4. Pregnant women regardless of trimester (vaccination with IIV but not with LAIV).

5. Immunocompromised hosts should receive annual influenza vaccination (IIV but not LAIV)

- Vaccine should be administered under the supervision of a health care provider who is able to recognize and manage severe allergic conditions (inpatient or outpatient medical setting).

- Ideal time: October/November (sufficient antibody titers after vaccination takes ~2 weeks).

- The specific strains included in the vaccine each year change based on antigenic drift.

- LAIV should not be administered until 48 hours after influenza antiviral therapy has stopped, and influenza antiviral drugs should not be administered for 2 weeks after the administration of LAIV because the antiviral drugs inhibit influenza virus replication.

Postexposure prophylaxis

- For seasonal prophylaxis and persons exposed to a household contact who were diagnosed with influenza.

- Antiviral drugs available for prophylaxis of influenza should be considered adjuncts but are not replacements for annual vaccination.

- Oseltamivir and zanamivir are effective prophylactic agents against influenza.

- Prophylaxis should be considered during influenza season for the following groups of patients:

  1. Persons at high risk of serious illness and/or complications who cannot be vaccinated.

  2. Persons at high risk of serious illness and/or complications who are vaccinated after influenza activity has begun in their community.

3. • Persons with severe immune deficiency or who may have an inadequate response to vaccination (e.g., advanced HIV disease, persons receiving immunosuppressive medications)- continued for the duration that influenza viruses are circulating in the community during influenza season.

4. • After exposure to an infectious person (prophylaxis continued for 10 days after last exposure)

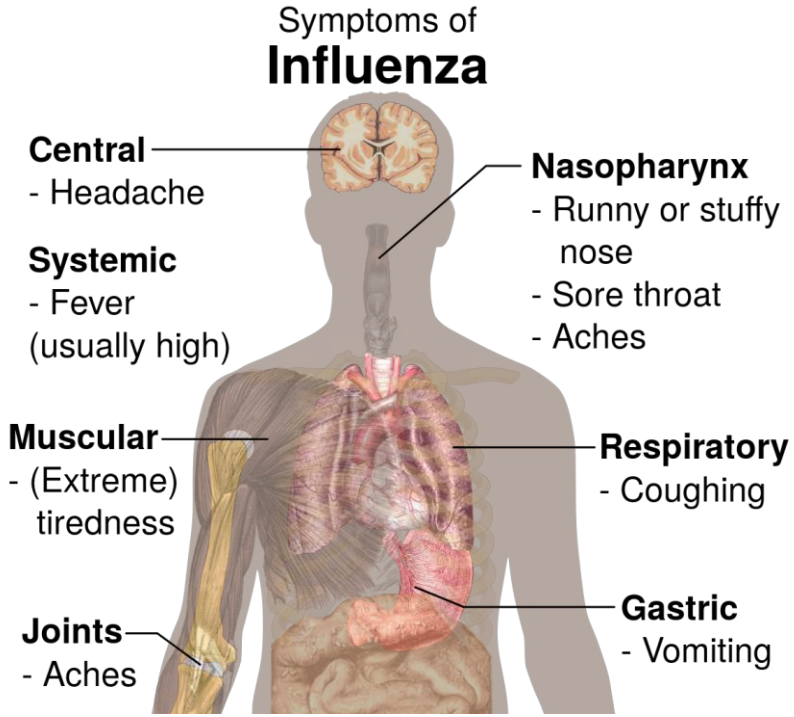
5. • Long-term care facility residents, regardless of vaccination status, when an outbreak has occurred in the institution.

Diagnosis:

- إذا الشخص يلي أخذ ال vaccine انصاب بـ influenza ولسا ما صار له أعراض أسبوعين بجسمه بمشي على ال antiviral أسبوعين.
- وعادةً غلب ال vaccine بده يكون inactivated.

✓ Clinical Presentation:

- Influenza virus causes an acute, self-limited febrile illness associated with rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.
- Nausea, vomiting, and otitis media are also commonly reported in children.
- Signs and symptoms typically resolve in 3 to 7 days. Cough & malaise may persist for > 2 weeks.



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CLINICAL PRESENTATION: Diagnosis of Influenza

General

- The clinical diagnosis of influenza can be difficult because the presentation is similar to a number of other respiratory illnesses. The sensitivity of clinical diagnosis ranges from 40% for children to 70% for adults and largely depends on the relative prevalence of influenza and other respiratory viruses circulating in a community.[34–36]
- The clinical course and outcome are affected by age, immunocompetence, viral characteristics, smoking, comorbidities, pregnancy, and the degree of preexisting immunity.[36]
- Complications of influenza may include exacerbation of underlying comorbidities, primary viral pneumonia, secondary bacterial pneumonia or other respiratory illnesses (eg, sinusitis, bronchitis, otitis), encephalopathy, transverse myelitis, myositis, myocarditis, pericarditis, and Reye's syndrome.[33,36]

لـ التهاب الـ spinal cord

Signs and Symptoms

- 5 Classic signs and symptoms of influenza include rapid onset of fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.[21,30,36]
- Nausea, vomiting, and otitis media are also commonly reported in children.[35]
- Signs and symptoms typically resolve in approximately 3 to 7 days, although cough and malaise may persist for more than 2 weeks.
- Primary viral pneumonia, occurring predominantly in pregnant women and those with underlying cardiovascular disease, usually begins with fever and dry cough, which changes to a productive cough of bloody sputum. This rapidly progresses to dyspnea, hypoxemia, and cyanosis with radiologic evidence of bilateral interstitial infiltrates.[36]
- Secondary bacterial pneumonia is usually seen in individuals with underlying pulmonary disorders and presents during the early stages of defervescence from the influenza infection. These patients usually present with fever, productive cough, and radiologic evidence of consolidation.[36]

Laboratory Tests

- Complete blood count and chemistry panels should be obtained to assess the overall status of the patient.
- The gold standard for diagnosis of influenza is reverse-transcription polymerase chain reaction (RT-PCR) or viral culture, which can provide information on the specific strain and subtype. Viral culture has a high sensitivity but can take as long as a week to develop, limiting the clinical relevance of the results.[36,37]

Other Diagnostic Tests

- Cultures of potential sites of infection should be obtained if coinfection, superinfection, or secondary infection is suspected.
- Chest radiograph should be obtained if pneumonia is suspected.

✓ Diagnostic Testing:

depending on clinical signs and symptoms

- The sensitivity of clinical diagnosis ranges from 40% for children to 70% for adults and largely depends on the relative prevalence of influenza and other circulating respiratory viruses.

- Diagnosis is usually made clinically during influenza season, with confirmation by nasopharyngeal swab for rapid antigen testing, PCR (higher sensitivity), or direct fluorescent antibody test and culture.

① ② ③

diagnosis test

Treatment:

✓ Treatment is usually symptomatic.

✓ Patients suffering from influenza should get adequate sleep and maintain a low level of activity.

✓ They should stay home from work and/or school in order to rest and prevent the spread of infection.

- ✓ Appropriate fluid intake should be maintained. Cough/throat lozenges, warm tea, or soup may help with symptom control (cough and sore throat).
- ✓ Antiviral medications may shorten the duration of illness but must be initiated within 24– 48 hours of the onset of symptoms to be effective in immunocompetent patients.
- ✓ Antiviral therapy should not be withheld from patients presenting > 48 hours after symptom onset requiring hospitalization or at high risk for complications.
  - The neuraminidase inhibitors (oseltamivir 75 mg PO q12h or zanamivir 10 mg inhaled q12h, each for 5 days, or peramivir, 600 mg single dose IV) are approved for the treatment of Influenza A and B.
  - M2 inhibitors (amantadine and rimantadine, each 100 mg PO q12h) are not recommended owing to high rates of resistance.

- Circulating strains change annually with varying resistance patterns to both classes of antivirals. Treatment decisions must be based on annual resistance data, available from the Centers for Disease Control and Prevention (CDC) (http:// www.cdc.gov).

✓ Vaccination is the most reliable prevention strategy.

✓ Annual vaccination is recommended for all individuals 6 months of age and older.

✓ Efficacy of vaccination varies annually from 50% to 90% depending on prevailing outbreak and circulating influenza strains.

TABLE 127-6 Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis—United States[33,34,53]

Drug	Adult Treatment	Adult Prophylaxis[a]	Pediatric Treatment	Pediatric Prophylaxis[a]
CAP-dependent endonuclease inhibitor				
Baloxavir[b,c]	12 yrs and older: 40 to <80 kg: One 40 mg dose >80 kg: One 80 mg dose	None	FDA approved and recommended for use in children 12 yrs or older weighing at least 40 kg. See adult dosage	None
Neuraminidase inhibitors				
Oseltamivir[d,e,f]	75-mg capsule twice daily x 5 days	75-mg capsule daily x 10 days	Term infants 0–8 months: 3 mg/kg/dose twice daily 9–11 months[g]: 3.5 mg/kg/dose twice daily or 3 mg/kg/dose twice daily ≥1 year: ≤15 kg: 30 mg twice daily >15–23 kg: 45 mg twice daily >23–40 kg: 60 mg twice daily >40 kg: 75 mg twice daily Duration: All for 5 days	Not recommended if <3 months 3-< 12 months, 3 mg/kg/dose daily 9–11 months, 3.5 mg/kg/dose daily ≥1 year: ≤15 kg: 30 mg daily >15–23 kg: 45 mg daily >23–40 kg: 60 mg daily >40 kg: 75 mg daily Duration: All for 10 days
Zanamivir	10 mg (2 of 5 mg inhalations) twice daily × 5 days	10 mg (2 of 5 mg inhalations) daily x 10 days	10 mg (2 of 5 mg inhalations) twice daily × 5 days for ≥7 years old	10 mg (2 of 5 mg inhalations) daily for ≥ 5 years old x 10 days
Peramivir[c,e]	13 yrs and older: One 600 mg dose via intravenous infusion for 15-30 minutes	None	2 to 12 yrs of age: One 12 mg/kg dose, up to 600 mg maximum, via intravenous infusion for a minimum of 15–30 minutes	None

Continued for Table 127-6

a If influenza vaccine is administered, prophylaxis can generally be stopped 14 days after vaccination for noninstitutionalized persons. When prophylaxis is being administered following an exposure, prophylaxis should be continued for 10 days after the last exposure. In persons at high risk for complications from influenza for whom vaccination is contraindicated or expected to be ineffective, chemoprophylaxis should be continued for the duration that influenza viruses are circulating in the community during influenza season.

b Time to peak = 4 hours. Food and cations (calcium, aluminum, magnesium, iron) can decrease peak concentration by 48%. Long half-life (79.1 hours) and is metabolized by UDP-glucuronosyltransferase (UGT1A3) and CYP3A4.

c For the treatment of uncomplicated influenza with oral baloxavir or intravenous peramivir, a single dose is recommended. Longer daily dosing (oral oseltamivir or intravenous peramivir) can be considered for patients who remain severely ill after 5 days of treatment.

d Oseltamivir dosing for preterm infants using their postmenstrual age (i.e., gestational age + chronological age): <38 weeks: 1.0 mg/kg/dose twice daily; 38–40 weeks: 1.5 mg/ kg/dose twice daily; >40 weeks: 3.0 mg/kg/dose twice daily.

e In patients with renal insufficiency, the dose should be adjusted on the basis of creatinine clearance. See https://www.cdc.gov/flu/professionals/antivirals/summaryclinicians.htm.

f Some experts recommend 150 mg twice daily for severe illness in pregnant women. Optimal dosing for prophylaxis in pregnant women is unknown.

g The American Academy of Pediatrics recommends 3.5 mg/kg per dose twice daily; CDC and US Food and Drug Administration (FDA)–approved dosing is 3 mg/kg per dose twice daily for children aged 9–11 months.

Note: Although amantadine and rimantadine have been used historically for the treatment and prophylaxis of influenza A viruses, due to high resistance, the CDC no longer recommends the use of these agents for the treatment and/or prophylaxis of influenza

Just the red text is required

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UpToDate: Antiviral regimens for treatment and/or prophylaxis of seasonal influenza in adults (1/2)

Antiviral agent	Treatment dose	Prophylaxis dose	Contraindications
Oseltamivir*	75 mg orally twice daily for 5 days[¶]	75 mg orally once daily; usual duration 7 days*[Δ]	N/A
Zanamivir[◊§] (inhelation)	10 mg (two 5 mg inhalations) twice daily for 5 days	10 mg (two 5 mg inhalations) once daily; usual duration 7 days Bronchospasm لأنه بسبب	Zanamivir (inhaled) is contraindicated in patients with asthma or chronic obstructive pulmonary disease, and it should not be used for treatment of severe influenza (given limited data).
Peramivir* (IV)	600 mg intravenously as a single dose[¶¥]	N/A	Peramivir should be reserved for patients who cannot tolerate oral or inhaled agents. ← للأشخاص اللي ما تجربوا inhelation or oral يرجعوا medi cation.
Baloxavir[§‡]	40 kg to <80 kg: 40 mg orally as a single dose ≥80 kg: 80 mg orally as a single dose	Postexposure prophylaxis: same dose as for treatment, single dose[†] لا يستخدم	Baloxavir should not be used for treatment of severe influenza (given limited data), immunocompromised hosts (given concern for emergence of resistance), or pregnant patients (given limited data).

UpToDate: Antiviral regimens for treatment and/or prophylaxis of seasonal influenza in adults (2/2)

* Dose reduction of oseltamivir and peramivir is recommended for patients with renal impairment.

¶ For patients with ongoing symptoms of severe lower respiratory tract disease (particularly in the setting of immunosuppression), an extended duration of antiviral treatment (up to 10 days) may be reasonable, particularly in those who continue to have detectable viral RNA from a respiratory specimen after 5 days of antiviral treatment.

Δ Longer courses may be warranted in the setting of institutional outbreaks. Refer to UpToDate topic on prevention of seasonal influenza for further discussion.

◊ Zanamivir is administered via oral inhalation by using a plastic device included in the package; patients will benefit from instruction and demonstration of the correct use of the device.

§ During outbreaks caused by oseltamivir-resistant influenza virus, zanamivir or baloxavir may be used. It is important to assess the risk of oseltamivir-resistant influenza before selecting an antiviral drug; clinicians should review regional influenza surveillance data to determine which influenza types and subtypes are circulating, as well as resistance patterns. This information is available via the United States Centers for Disease Control and Prevention website.

¥ If peramivir is used for treatment of severe influenza, we favor administration for 5 days[5].

‡ Coadministration of baloxavir with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (eg, calcium, iron, magnesium, selenium, zinc) should be avoided.

† Baloxavir is US Food and Drug Administration approved for postexposure prophylaxis but not for pre-exposure prophylaxis.

Evaluation of therapeutic outcomes

- Patients should be monitored daily for resolution of signs and symptoms associated with influenza, such as fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis.

➢ These signs and symptoms will typically resolve within approximately 1 week.

➢ If the patient continues to exhibit signs and symptoms of illness beyond 10 days or a worsening of symptoms after 7 days, a physician visit is warranted as this may be an indication of a secondary bacterial infection. Ideally, antiviral therapy should not be started until influenza is confirmed via the laboratory.

✓ Therapy should be initiated within 48 hours of illness onset, emphasizing the need for rapid diagnosis.

↳ symptoms onset

✓ Repeat diagnostic tests to demonstrate clearance of the virus are not necessary.

Patient Care Process for Influenza Infection Treatment

Collect

- Patient characteristics: age, occupation, travel, lifestyle, immune status, present and past medical history, allergies
- Medication history (include prescription, nonprescription, and other substances); vaccination history; pregnancy status
- Microbiologic results from rapid respiratory viral panel and secondary bacterial infection. Bacterial susceptibility tests when available (see Clinical Presentation: Diagnosis of Influenza)
- Laboratory results, major organ function (particularly, kidney and liver), lactate

Assess

- Assess for medication contraindications and drug interactions
- Determine severity of illness based on vital signs, acute organ dysfunction, and source control (or lack thereof) (see Clinical Presentation: Diagnosis of Influenza)
- Determine at-risk patients for secondary bacterial infection of the respiratory tract, patient's microbiologic history, previous antibiotic

exposure, and response to current therapy (see Clinical Presentation: Diagnosis of Influenza)

- Determine if other conditions are present such as chronic lung disease likely to affect outcomes of infection
- Estimate creatinine clearance for drug dosing

Plan*

- Strongly recommend future influenza vaccine if no contraindication is present (Tables 131-2 and 131-3)
- Initiate treatment neuraminidase therapy—oral or inhaled or IV based on severity of illness (Table 131-4)
- Determine influenza treatment goals of therapy with monitoring parameters for each goal (see Goals of Therapy)
- Determine appropriate antibiotic therapy for secondary bacterial infection and monitoring plan
- Establish antimicrobial monitoring goals for efficacy (eg, resolution of infection, clearance of bacteria from blood cultures) and drug toxicity
- Check for drug interactions and dose adjustments based on end-organ function

Implement

- Initiate a neuraminidase inhibitor and continue for ~7 days after identification of illness onset in the last patient (prophylaxis for community outbreak) or 5 days (treatment) or establish a tentative stop date for severely ill patients
- If secondary bacterial infection is suspected, initiate empiric antimicrobial regimen, and deescalate antimicrobial therapy to more narrow-spectrum agents as appropriate based on response and microbiologic data
- Assess patient as needed for response to antiviral medications, and other treatments
- Use measures to minimize adverse events to medications and assess for occurrence of adverse events

Follow-up: Monitor and Evaluate

- Refer patient for other health, wellness, or follow-up services to their identified primary care provider or another provider (provide patient with documentation of referral)
- Determine if patient shows improvement in the signs and symptoms of infection within 48 hours after neuraminidase inhibitor is initiated
- Monitor for emergence of resistant virus.
- Monitor for occurrence of secondary bacterial pneumonia

** Collaborate with patient, caregiver(s), and other healthcare professionals.*

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Complications:

- ✓ People at greater risk of complications are:
  - Adults > 65 years old
  - residents of nursing homes and other long-term care facilities
  - pregnant women (and those up to 2 weeks postpartum)
  - patients with chronic medical conditions (e.g., pulmonary disease, cardiovascular disease, active malignancy, diabetes mellitus, chronic renal insufficiency, chronic liver disease, immunosuppression including HIV and transplantation, morbid obesity)

- ✓ Influenza pneumonia and secondary bacterial pneumonia, typically due to S. aureus, are the most common complications of influenza infection.

- ✓ Viral antigenic drift and shift can cause emergence of strains with enhanced virulence or the potential for pandemic spread, requiring modified therapy or heightened infection control measures.