# Influenza Prevention, Testing, and Treatment

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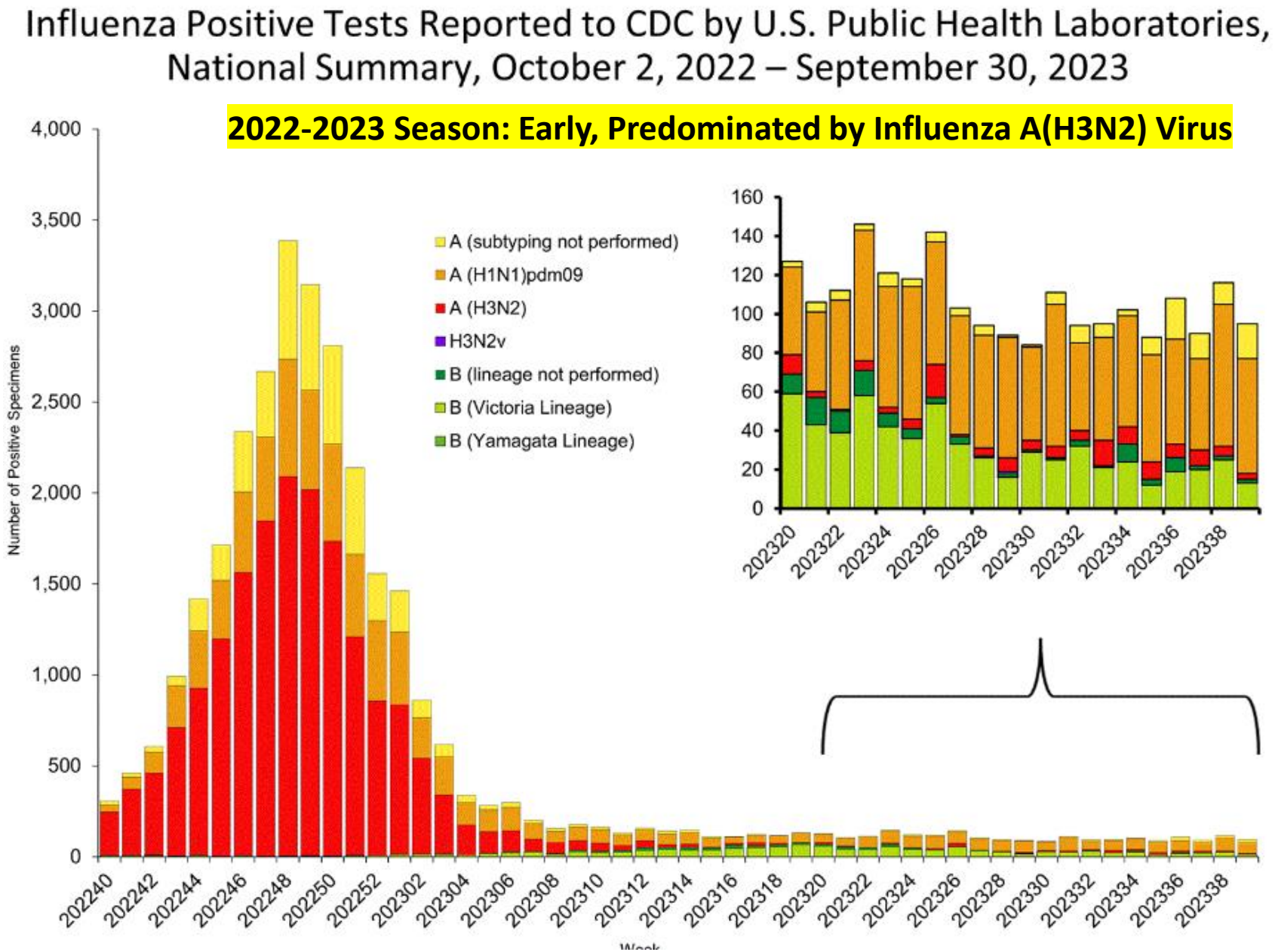
# Disclosures

- None

# Overview

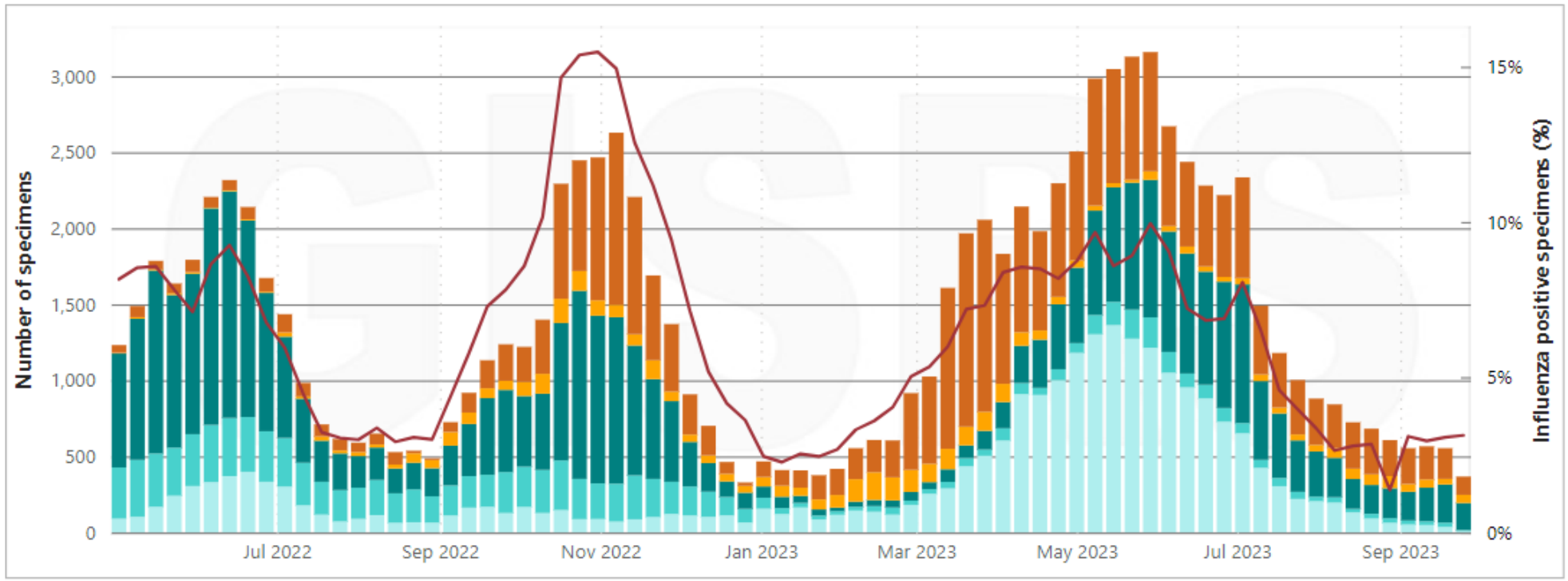
- Recent influenza activity
- Influenza disease burden
- Prevention - Influenza vaccines
- Clinical characteristics
- Clinical management
  - Influenza Tests
  - Antiviral Treatment

# Low Influenza Activity, U.S. Current Season (to date)

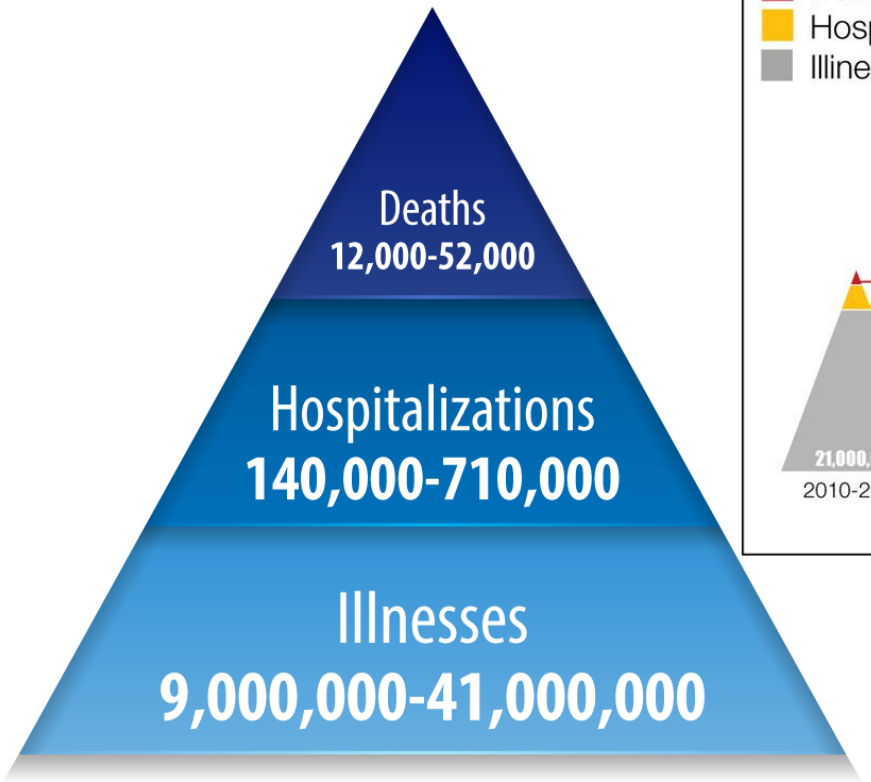


# Influenza Activity, Southern Hemisphere 2023

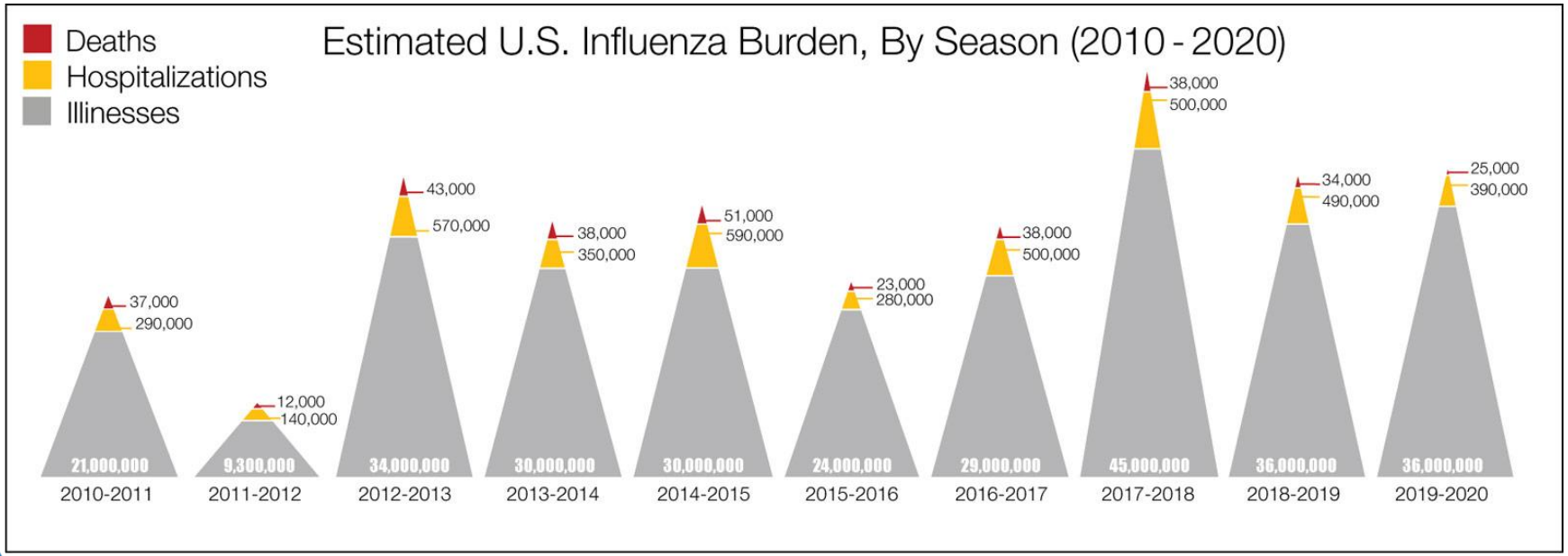
**2023 Season: Generally predominated by Influenza A(H1N1)pdm09 Virus**



# Estimated Influenza Disease Burden




Estimated Influenza Disease Burden 2010 - 2020




- **Seasonal influenza epidemics vary in severity**

**2022-2023 (preliminary estimates)**:

* 26-50 million illnesses
* 12-24 million medical visits
* 290,000 to 670,000 hospitalizations
* 17,000 to 98,000 deaths

*https://www.cdc.gov/flu/about/burden/index.html; https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm*

# Influenza Vaccines Available (U.S. 2023-2024)

**Table 1: Inactivated Influenza Vaccines (IIV4s) and Recombinant Influenza Vaccine (RIV4)**

| Trade name<br>*Manufacturer* | Available presentations | Approved age indications | Volume per dose by age group |
|---|---|---|---|
| **Quadrivalent IIVs (IIV4s)—Standard-dose—Egg-based (15 µg HA per virus component in 0.5 mL; 7.5 µg HA per virus component in 0.25 mL)** | | | |
| Afluria Quadrivalent<br>*Seqirus* | 0.5 mL prefilled syringe<br>5.0 mL multidose vial* | ≥3 yrs†<br>≥6 mos (needle/syringe)†<br>18 through 64 yrs (jet injector) | ≥3 yrs—0.5 mL†<br>6 through 35 mos—0.25 mL† |
| Fluarix Quadrivalent<br>*GlaxoSmithKline* | 0.5 mL prefilled syringe | ≥6 mos | ≥6 mos—0.5 mL |
| FluLaval Quadrivalent<br>*GlaxoSmithKline* | 0.5 mL prefilled syringe | ≥6 mos | ≥6 mos—0.5 mL |
| Fluzone Quadrivalent<br>*Sanofi Pasteur* | 0.5 mL prefilled syringe<br>0.5 mL single-dose vial<br>5.0 mL multidose vial* | ≥6 mos§<br>≥6 mos§<br>≥6 mos§ | ≥3 yrs—0.5 mL§<br>6 through 35 mos—0.25 mL ***or*** 0.5 mL§ |
| **Quadrivalent IIV (ccIIV4)—Standard-dose—Cell culture-based (15 µg HA per virus component in 0.5 mL)** | | | |
| Flucelvax Quadrivalent<br>*Seqirus* | 0.5 mL prefilled syringe<br>5.0 mL multidose vial* | ≥6 mos<br>≥6 mos | ≥6 mos —0.5 mL |
| **Quadrivalent IIV (HD-IIV4)—High-dose—Egg-based (60 µg HA per virus component in 0.7 mL)** | | | |
| Fluzone High-Dose Quadrivalent<br>*Sanofi Pasteur* | 0.7 mL prefilled syringe | ≥65 yrs | ≥65 yrs—0.7 mL |
| **Adjuvanted quadrivalent IIV4 (aIIV4)—Standard-dose with MF59 adjuvant—Egg-based (15 µg HA per virus component in 0.5 mL)** | | | |
| Fluad Quadrivalent<br>*Seqirus* | 0.5 mL prefilled syringe | ≥65 yrs | ≥65 yrs—0.5 mL |
| **Quadrivalent RIV (RIV4)—Recombinant HA (45 µg HA per virus component in 0.5 mL)** | | | |
| Flublok Quadrivalent<br>*Sanofi Pasteur* | 0.5 mL prefilled syringe | ≥18 yrs | ≥18 yrs—0.5 mL |

*Grohskopf et al. MMWR August 25, 2023*

# ACIP Influenza Vaccine Recommendations 2023-2024

- Annual influenza vaccination recommended for all persons ≥6 months
  - Optimal timing: **Now** (and as long as influenza viruses are circulating)
- All influenza vaccines are **quadrivalent**
- Preferential recommendation for persons aged **≥65 years**
  - **High-dose, recombinant, or adjuvanted vaccine**
- **All persons aged ≥6 months with egg allergy should be vaccinated**
  - No additional safety measures; "All vaccines should be administered in settings in which personnel and equipment needed for rapid recognition and treatment of acute hypersensitivity reactions are available."
    - Previous severe allergic reaction to egg-based vaccine (inactivated or LAIV) or cell culture vaccine or recombinant vaccine is a contraindication to that vaccine

*Grohskopf et al. MMWR August 25, 2023*

# Influenza Vaccine Co-administration

- Coadministration of vaccines in general (if eligibility and timing criteria are met) is considered best practice
- **Coadministration of COVID-19 vaccine and influenza vaccine is recommended** (if eligibility and timing criteria are met)

# Southern Hemisphere Influenza Vaccine Effectiveness, 2023 (Argentina, Brazil, Chile, Paraguay, Uruguay)

Interim Effectiveness Estimates of 2023 Southern Hemisphere Influenza Vaccines in Preventing Influenza-Associated Hospitalizations — REVELAC–i Network, March–July 2023

- Adjusted interim influenza VE against hospitalization for severe acute respiratory infection with influenza viruses = **51.9%** (95% CI: 39.2-62%)
  - VE = **70.2%** among young children (generally aged <6 years)
  - VE = **37.6%** among older adults (≥60 years or ≥65 years)
  - Predominant virus: influenza A(H1N1)pdm09 virus (VE = 55.2%; 95% CI: 41.8-65.5%

*Fowlkes et al. MMWR 2023*

# Symptomatic Influenza Virus Infection

## Uncomplicated Influenza

**Table 2. Signs and Symptoms of Uncomplicated Influenza[a]**

| General | Head, Eyes, Ears, Nose, Throat | Neuromuscular | Gastrointestinal[b] | Pulmonary |
|---|---|---|---|---|
| Fever[c,d] | Headache | Myalgia, arthralgia | Abdominal pain | Nonproductive cough |
| Chills | Nasal congestion[d] | Weakness | Vomiting | Pleuritic chest pain |
| Malaise | Rhinorrhea[d] | Chest pain | Diarrhea[d] | |
| Fatigue | Sore throat/hoarseness | | | |

Adapted from Jani AA, Uyeki TM. Chapter 46. Influenza. In: Emergency management of infectious diseases. 2nd ed. Chin RL, ed. Cambridge, UK: Cambridge University Press, 2018.

[a]Abrupt onset of respiratory and systematic signs and symptoms, with or without fever.

[b]Gastrointestinal symptoms vary with age: Diarrhea is more common among infants, young children, and school-aged children; abdominal pain may be present among school-aged children; vomiting may be present among adults.

[c]Fever can be age-specific: High fever or fever alone may be the only sign in infants and young children; fever may be absent or low grade in infants and the elderly.

[d]Fever, nasal congestion, rhinorrhea, and diarrhea may be present among infants and young children.

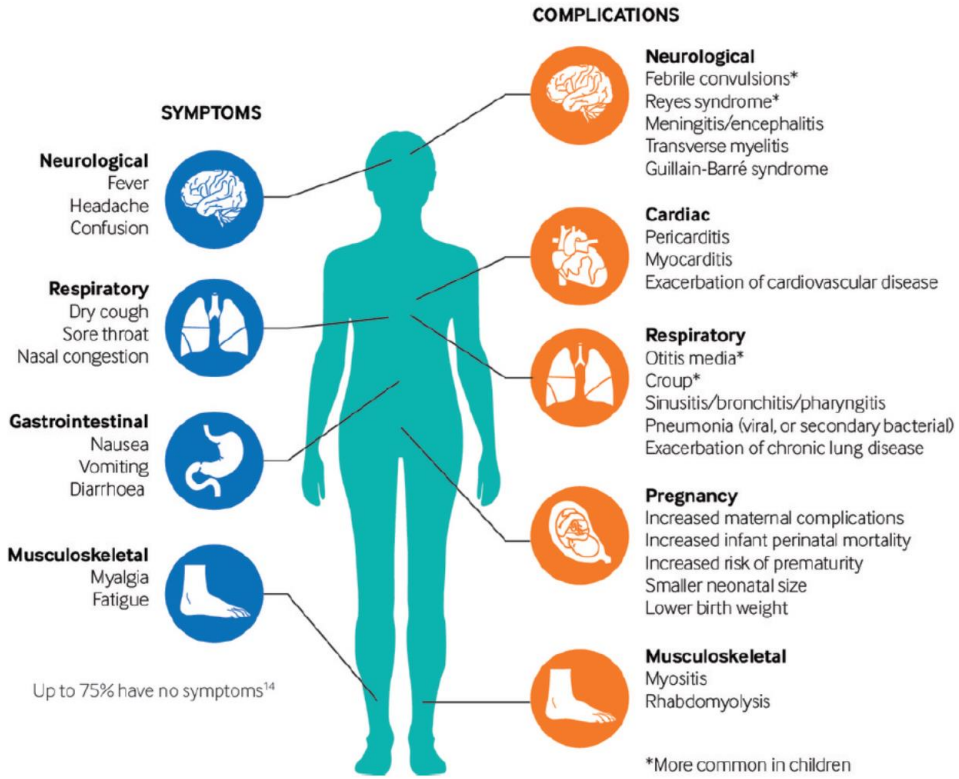
## Uncomplicated COVID-19

- Most common: Cough, chills, headache, fatigue, muscle aches, malaise (with/without fever)
- Less common: Difficulty breathing, chest pain, wheezing, nasal congestion or rhinorrhea, sore throat, reduced or loss of taste or smell, nausea, vomiting, diarrhea, abdominal pain, skin rashes, conjunctivitis

*Uyeki Clinical Infect Dis 2019; CDC Interim Clinical Guidance for Management of Patients with Confirmed Coronavirus Disease (COVID-19)*
*https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html*

# Influenza Complications

- **Moderate Illness**:
  - Otitis media in young children, sinusitis
  - Exacerbation of chronic disease
- **Severe to Critical Illness:**
  - **Exacerbation of chronic disease**
  - **Respiratory:** viral pneumonia, croup, status asthmaticus, bronchiolitis, tracheitis, ARDS
  - **Cardiac:** myocarditis, pericarditis, myocardial infarction
  - **Neurologic:** encephalopathy & encephalitis, cerebrovascular accident, Guillain-Barre syndrome (GBS), Acute Disseminated Encephalomyelitis (ADEM), Reye syndrome
  - **Bacterial co-infection:** invasive bacterial infection (pneumonia)
    - *Staphylococcus aureus* (MSSA, MRSA), *Streptococcus pneumoniae*, Group A *Strept*
  - **Musculoskeletal:** myositis, rhabdomyolysis
  - **Multi-organ failure** (respiratory, renal failure, septic shock)
  - **Healthcare-acquired infections** (e.g. bacterial or fungal ventilator-associated pneumonia)




*Ghebrehewet BMJ 2016*

# Groups at Increased Risk for Influenza Complications and Severe Illness

- **Children under 2 years and adults aged 65 years and older**
- **Persons with chronic medical conditions**, including pulmonary (including asthma) or cardiovascular (excluding isolated hypertension), renal, hepatic, neurologic (including persons who have had a stroke) and neurodevelopmental, hematologic, metabolic or endocrine disorders (including diabetes mellitus)
- **Persons who are immunocompromised**
- **Persons with extreme obesity (BMI ≥40)**
- **Children and adolescents who are receiving aspirin-or salicylate-containing medications** (who might be at risk for Reye syndrome after influenza virus infection)
- **Residents of nursing homes and other long-term care facilities**
- **Pregnant persons and people up to 2 weeks postpartum**
- **People from certain racial and ethnic minority groups, including non-Hispanic Black, Hispanic or Latino, and American Indian or Alaska Native persons**

*https://www.cdc.gov/flu/highrisk/index.htm*

# Influenza Tests Available in Clinical Settings

| Test | Method | Time to Results | Performance | Notes† |
|---|---|---|---|---|
| Rapid diagnostic test | Antigen detection | 10 min | Low to moderate sensitivity; high specificity | Negative results may not rule out influenza; most assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2 |
| Rapid molecular assay | Viral RNA detection | 15–30 min | Moderately high to high sensitivity; high specificity | Negative results may not rule out influenza; some assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2 |
| Immunofluorescence assay | Antigen detection | 2–4 h | Moderate sensitivity; high specificity | Negative results may not rule out influenza; requires trained laboratory personnel with fluorescent microscope in a clinical laboratory |
| Molecular assay | Viral RNA detection | 60–80 min for some assays; up to 4–6 h for others | High sensitivity; high specificity | Negative results may not rule out influenza; multiplex assays can identify and distinguish among influenza A, influenza B, and SARS-CoV-2 |

**Multiplex Antigen detection** 15 min
(Influenza A/B, SARS-CoV-2)

**Multiplex Viral RNA detection** 36-45 min
(Influenza A/B, SARS-CoV-2, RSV)

**Multiplex Viral RNA detection** ≥60 min
(Influenza A/B, SARS-CoV-2, RSV, other viral targets)

# What Influenza Tests Are Recommended?

- **Outpatients:**
  - **Rapid influenza molecular assays are recommended over rapid influenza antigen tests**
- **Hospitalized patients:**
  - **RT-PCR or other influenza molecular assays are recommended**
    - Rapid antigen detection tests and immunofluorescence assays are not recommended and should not be used unless molecular assays are not available
  - **Immunocompromised patients: Multiplex RT-PCR assays targeting a panel of respiratory pathogens, including influenza viruses are recommended**

- ***Do not order viral culture for initial or primary diagnosis of influenza***
- ***Do not order serology for influenza***
  - **Results from a single serum specimen cannot be reliably interpreted, and collection of paired acute and convalescent sera 2-3 weeks apart are needed; testing at specialized laboratories**

*Uyeki et al. IDSA 2018 Influenza Clinical Practice Guidelines CID 2019*

# Antivirals for Treatment of Influenza

## Four FDA-approved antivirals recommended:

- **All have demonstrated efficacy and are FDA-approved for early treatment (<2 days of illness onset) in outpatients with uncomplicated influenza**
- **Neuraminidase inhibitors (NAIs):**
  - **Oseltamivir** (oral, twice daily x 5 days)
  - **Zanamivir** (inhaled, twice daily x 5 days) [investigational IV zanamivir is not available]
  - **Peramivir** (intravenous: single dose)
- **Cap-dependent endonuclease inhibitor: Baloxavir marboxil** (oral: single dose)

| Antiviral Drug | Route of Administration | Recommended Ages for Treatment |
|---|---|---|
| Oseltamivir | Oral (twice daily x 5d) | All ages |
| Zanamivir | Inhaled (twice daily x 5d) | ≥7 years |
| Peramivir | Intravenous (single infusion) | ≥6 months |
| Baloxavir | Oral (single dose) | ≥5 years (otherwise healthy)<br>≥12 years (high-risk) |

*https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm*

# Antiviral Treatment

**Focus on prompt treatment of persons with severe disease and those at increased risk of influenza complications**

- **Antiviral treatment is recommended and has the greatest clinical benefit when started *as soon as possible* for patients with confirmed or suspected influenza who are:**
  - **Hospitalized*** (without waiting for testing results) **(oral/enteric oseltamivir)**
  - **Outpatients with complicated or progressive illness of any duration (oral oseltamivir)**
  - **Outpatients at high risk for influenza complications (oral oseltamivir or oral baloxavir)**

- Antiviral treatment can be considered for any previously healthy, non-high-risk outpatient with confirmed or suspected influenza (e.g. with influenza-like illness) on the basis of clinical judgment, if treatment can be initiated within 48 hours of illness onset; including empiric treatment (e.g. in-person visit or via telemedicine) **(e.g. oral oseltamivir or oral baloxavir)**

**Based on observational studies*

# Meta-analyses of Oseltamivir Treatment RCTs in Outpatients

**Randomized Clinical Trials (RCTs) have shown that oseltamivir treatment has significant clinical benefit when started within 36-48 hours after illness onset versus placebo**

- Pooled meta-analysis of 5 RCTs in children (oseltamivir n=770 vs. placebo n=838)
  - **Powered for Mild Disease Outcomes: Treatment started within 48 hours of onset:**
    - **Reduced illness duration by 18 hours overall and by 30 hours in children without asthma** (-29.9 hours; 95% CI: -53.9 to -5.8 hours)
    - **Reduced risk of otitis media by 34%** (RR 0.66; 95% CI: 0.47-0.95)
- Pooled meta-analysis of 9 RCTs in adults (oseltamivir n=1565 vs. placebo n=1295)
  - **Powered for Mild Disease Outcomes: Treatment started within 36 hours of onset:**
    - **Reduced illness duration by 25.2 hours** (-25.2 hours; 95% CI: -36.2 to -16.0 hours)
    - **44% Reduced risk of lower respiratory tract complications occurring >48 hours after treatment requiring antibiotics** (RR: 0.56; 95% CI: 0.42 to 0.75; p=0.0001)

*Malosh Clinical Infect Dis 2018; Dobson Lancet 2015*

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- Pooled meta-analysis of 15 RCTs in persons ≥12 years (oseltamivir n=3443; not txed n=2852)
  - **Outcome of interest: Hospitalization**
    - **None of the included RCTs were powered for a severe outcome (e.g., hospitalization)**
    - **No association found between oseltamivir and risk of hospitalization for all 6295 participants (RR, 0.77; 95%CI, 0.47-1.27) or for ≥65 years (RR, 0.99; 95%CI, 0.19-5.13) or for patients at greater risk of hospitalization (RR, 0.90; 95%CI, 0.37-2.17).**
    - **Analysis was underpowered: would require 15,000 to 30,000 participants because the event rate for hospitalization in the control (untreated) study population was only 0.6%.**
    - **Inconclusive meta-analysis: An enormous RCT is needed of oseltamivir to reduce risk of severe influenza**

*Malosh Clinical Infect Dis 2018; Dobson Lancet 2015; Hanula JAMA Internal Medicine 2023*

# Influenza Clinical Management - Hospitalized Patients

- **Implement infection prevention and control measures**
  - Standard, droplet precautions
- **Start antiviral treatment as soon as possible**
  - Oseltamivir treatment

➢**Supportive care of complications**

- Secondary bacterial co-infection
- Respiratory failure, ARDS
- Sepsis
- Multi-organ failure (respiratory & renal)

# Trials of Influenza Therapies for Severe Influenza (in-progress)

***GAP: Therapeutics with demonstrated efficacy in clinical trials***

- **Antivirals in Hospitalized Influenza Patients**
  - Oseltamivir, Baloxavir (REMAP-CAP*, RECOVERY*)

- **Immunomodulators in Hospitalized Influenza Patients**
  - Low-dose corticosteroids (RECOVERY)
  - Dexamethasone (REMAP-CAP)
  - Hydrocortisone (REMAP-CAP)
  - IL-6 receptor blocker (Tocilizumab) (REMAP-CAP)
  - Janus kinase inhibitor (Baricitinib) (REMAP-CAP)

*Adaptive clinical trial platforms – allow multiple comparisons (non-placebo untreated standard of care comparator)

# Key Points

- Influenza vaccination is recommended for all persons aged ≥6 months
  - The time to get vaccinated is NOW!
- Influenza testing can guide clinical management when there is substantial co-circulation of other respiratory viruses
- Antiviral treatment of influenza is recommended as soon as possible for outpatients at increased risk for complications, and for hospitalized patients