2022-2023 Seasonal Influenza Testing and Treatment During the COVID-19 Pandemic

Clinician Outreach and Communication Activity (COCA) Call

Tuesday, November 15, 2022

Free Continuing Education

- Free continuing education is offered for this webinar.
- Instructions on how to earn continuing education will be provided at the end of the call.

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- In compliance with continuing education requirements, all planners and presenters must disclose all financial relationships, in any amount, with ineligible companies over the previous 24 months as well as any use of unlabeled product(s) or products under investigational use.

- CDC, our planners, and presenters wish to disclose they have no financial relationship(s) with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

- Content will not include any discussion of the unlabeled use of a product or a product under investigational use with the exception of Dr. Tim Uyeki's discussion of antiviral medications for hospitalized patients that are FDA-approved for outpatients.

- CDC did not accept financial or in-kind support from ineligible companies for this continuing education activity.

Objectives

At the conclusion of today's session, the participant will be able to accomplish the following:

1. Discuss background on influenza tests and antivirals for treatment of influenza.

2. Review influenza testing guidance for patients with acute respiratory illness for the 2022-2023 season, including during community co-circulation of influenza viruses and SARS-CoV-2.

3. Describe antiviral treatment recommendations for patients with suspected or confirmed influenza for the 2022-2023 season, including during community co-circulation of influenza viruses and SARS-CoV-2.

To Ask a Question

- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov

Today's Presenter

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Tim Uyeki, MD, MPH, MPP
Influenza Division, CDC

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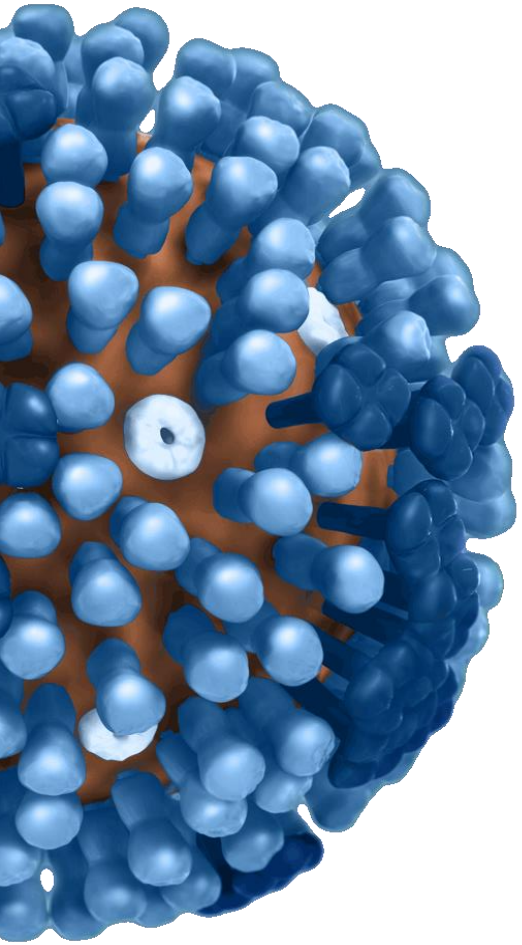
Overview

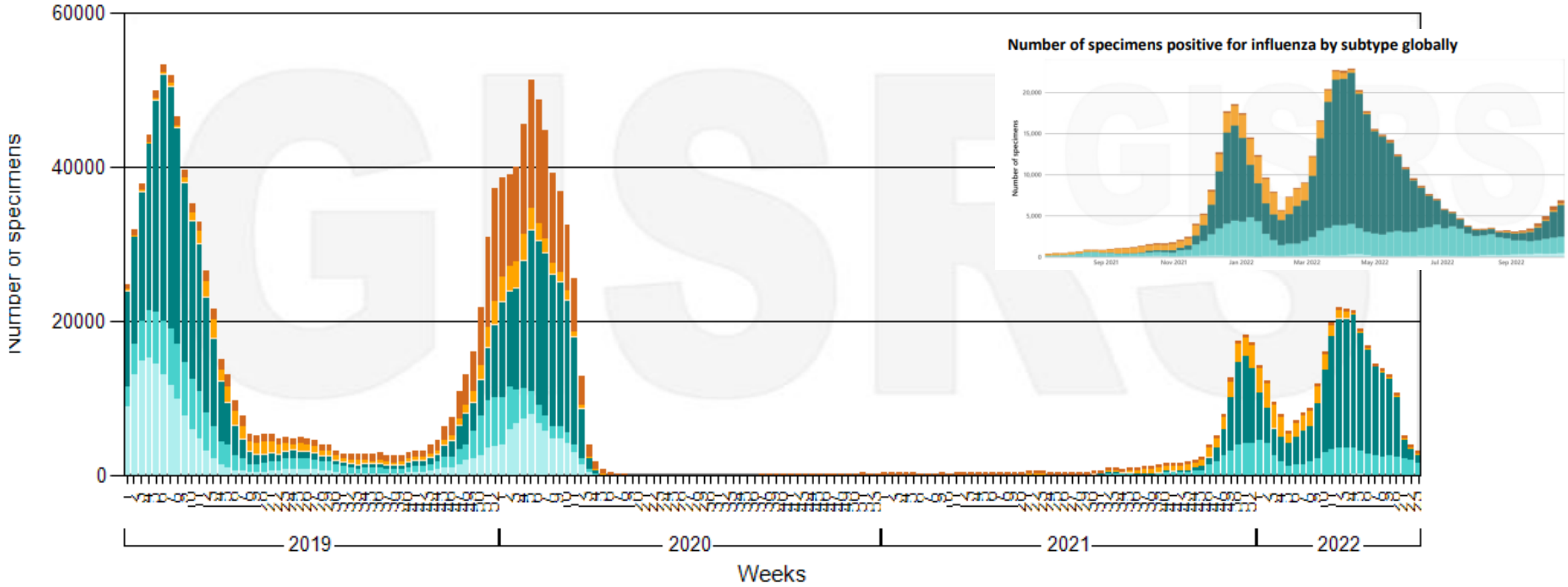
- 2021-2022 influenza activity; current 2022-2023 season
- Influenza disease burden
- Influenza vaccination 2022-2023 season
- Influenza testing
- Antiviral treatment of influenza



2021-2022 Season and Influenza Season Activity in 2022-2023

Global circulation of influenza viruses

Number of specimens positive for influenza by subtype



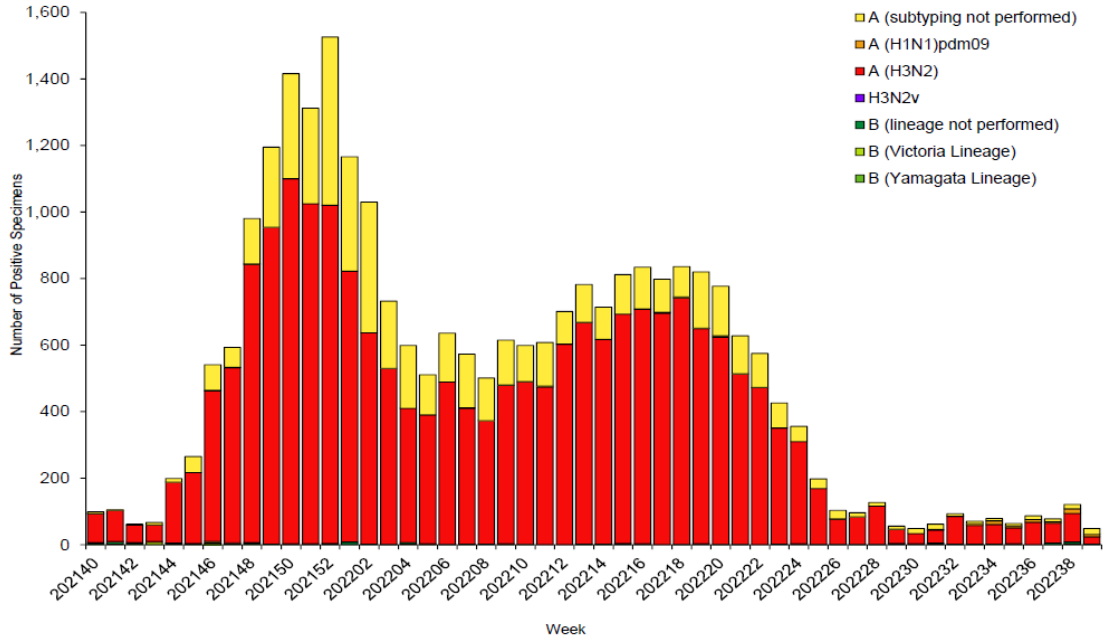
Data from: All sites

Data source: FluNet (www.who.int/flunet), GISRS

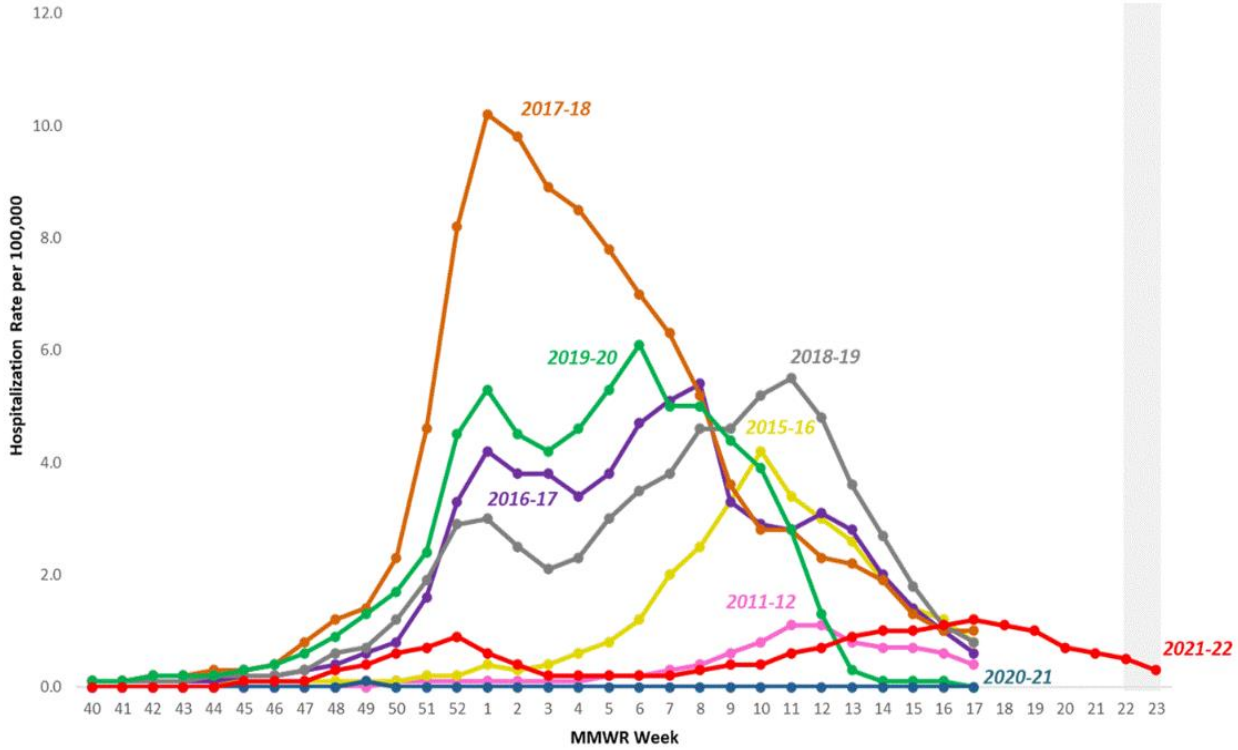
2021-2022 U.S. Influenza Season

- Compared to pre-COVID-19 pandemic seasons, 2021-2022 was a mild influenza season.
- Two peaks of influenza A(H3N2) activity occurred, extending to mid-June.

Influenza Positive Tests Reported to CDC by U.S. Public Health Laboratories, National Summary, October 3, 2021 – October 1, 2022



Weekly Rate of Hospital Admissions Reported to FluSurv-NET
(9% of United States population)

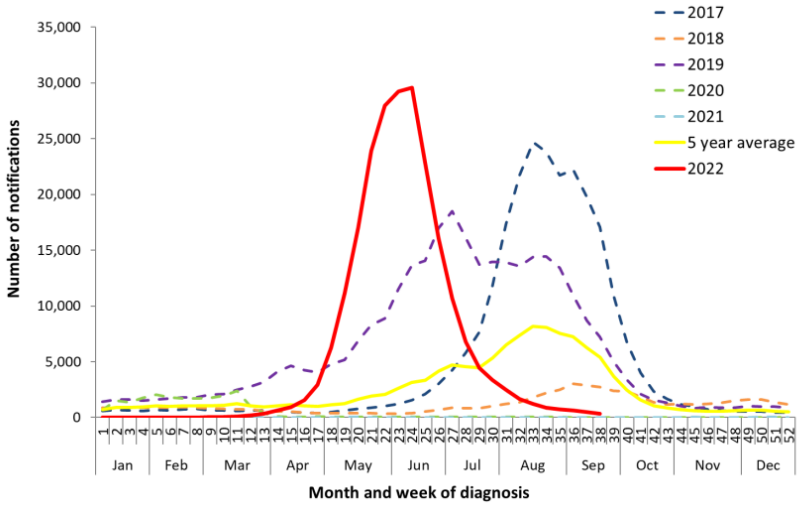


Overall cumulative hospitalization rate for the season: 17.2 per 100,000

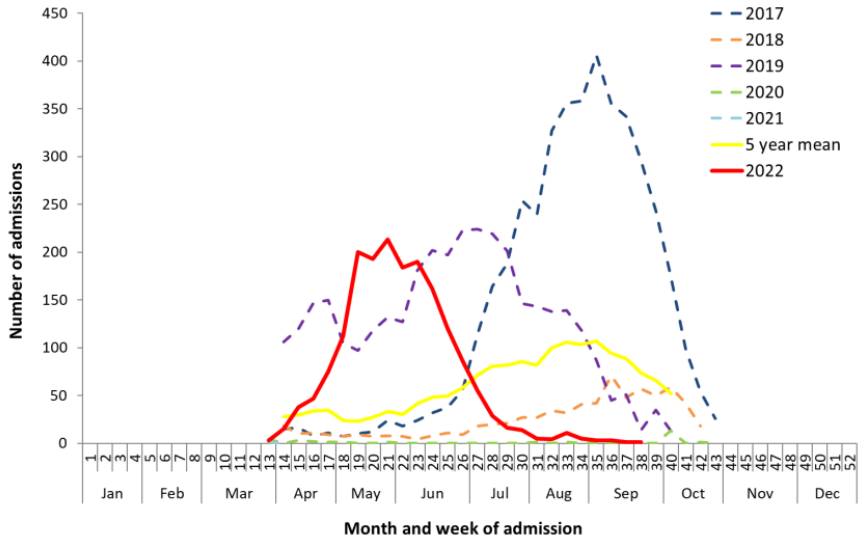
Weekly U.S. Influenza Surveillance Report | CDC

Influenza Activity in Australia, 2022

Notifications of laboratory-confirmed influenza, Australia, 01 January 2017 to 25 September 2022



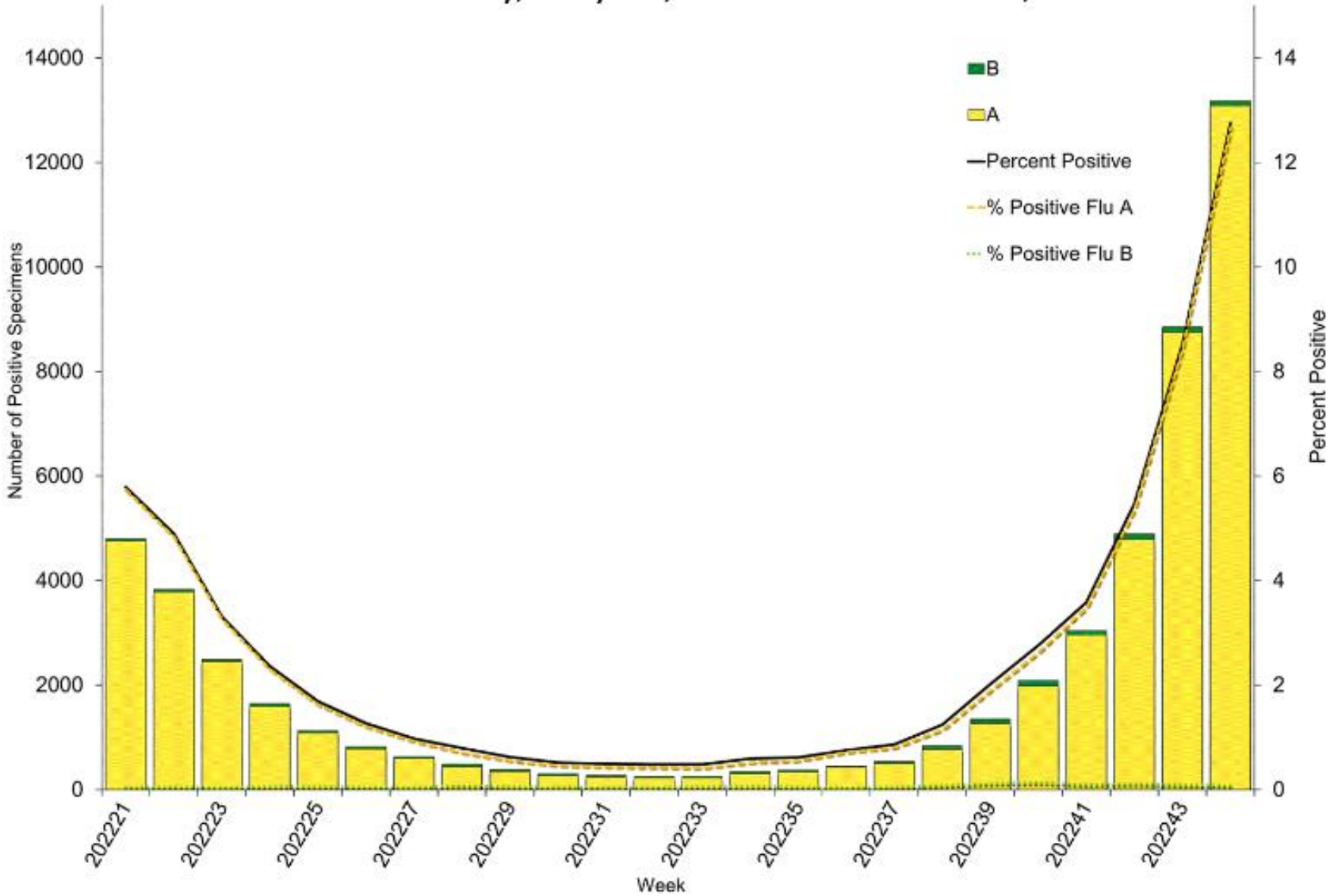
Number of influenza hospitalizations at sentinel hospitals in Australia, from April to October (2017-2022)



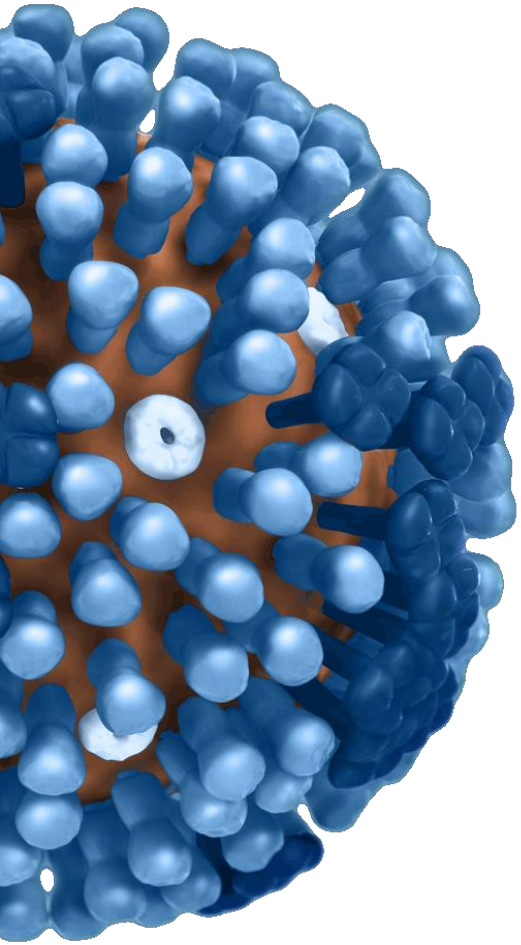
- Influenza activity in Australia was early and robust
  - ➢ Peaked 1-3 months earlier than historical seasons, but was a truncated season compared to historical trends
  - ➢ Influenza A(H3N2) virus predominated
- Rates were highest in younger age groups and comparable to 2019 season
- Mortality was lower compared to other influenza A(H3N2) seasons

Department of Health and Aged Care | Australian Influenza Surveillance Report and Activity Updates

Influenza Positive Tests Reported to CDC by U.S. Clinical Laboratories, National Summary, May 22, 2022 – November 5, 2022



https://www.cdc.gov/flu/weekly/index.htm



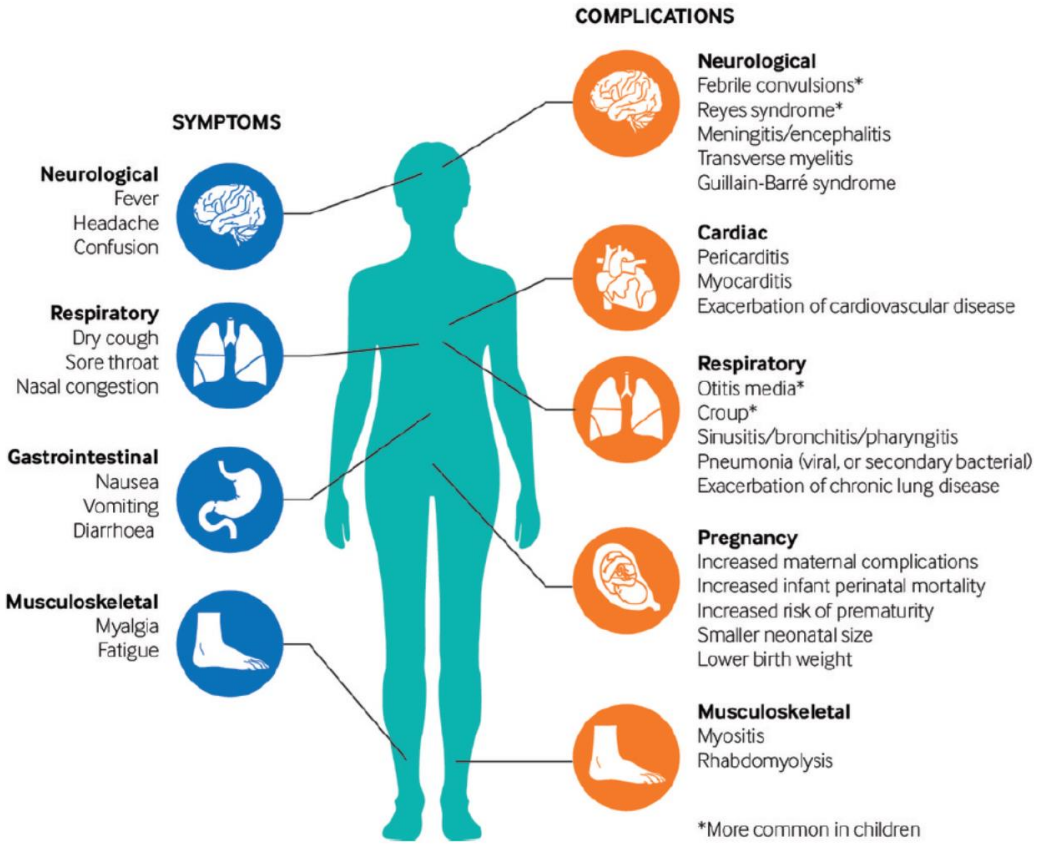
Influenza Disease Burden

Spectrum of Influenza Virus Infection

- Disease severity and clinical manifestations vary by age, host factors, immunity, influenza virus type/subtype
  - **Asymptomatic infection**
  - **Uncomplicated illness**
    - Upper respiratory tract illness
    - Fever may not be present (such as in elderly, immunosuppressed, others with uncomplicated influenza)
    - Typical: abrupt onset of fever, cough, chills, muscle aches, fatigue, headache, sore throat, runny nose
    - GI symptoms (more common in young children)
    - Infants can have fever alone, irritability, may not have respiratory symptoms
  - **Complicated illness**

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 (e.g. community-acquired pneumonia)
    - *Staphylococcus aureus* (MSSA, MRSA), *Streptococcus pneumoniae*, Group A *Strep*
  - **Musculoskeletal:** myositis, rhabdomyolysis
  - **Multi-organ failure** (respiratory, renal failure, septic shock)
  - **Healthcare-associated infections** (e.g. bacterial or fungal ventilator-associated pneumonia)

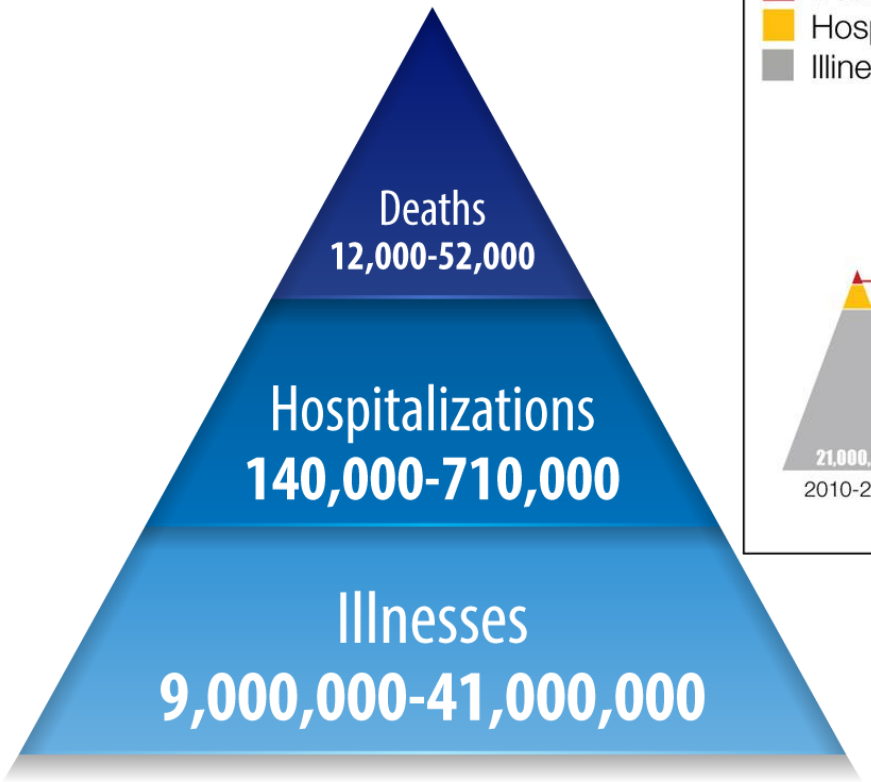


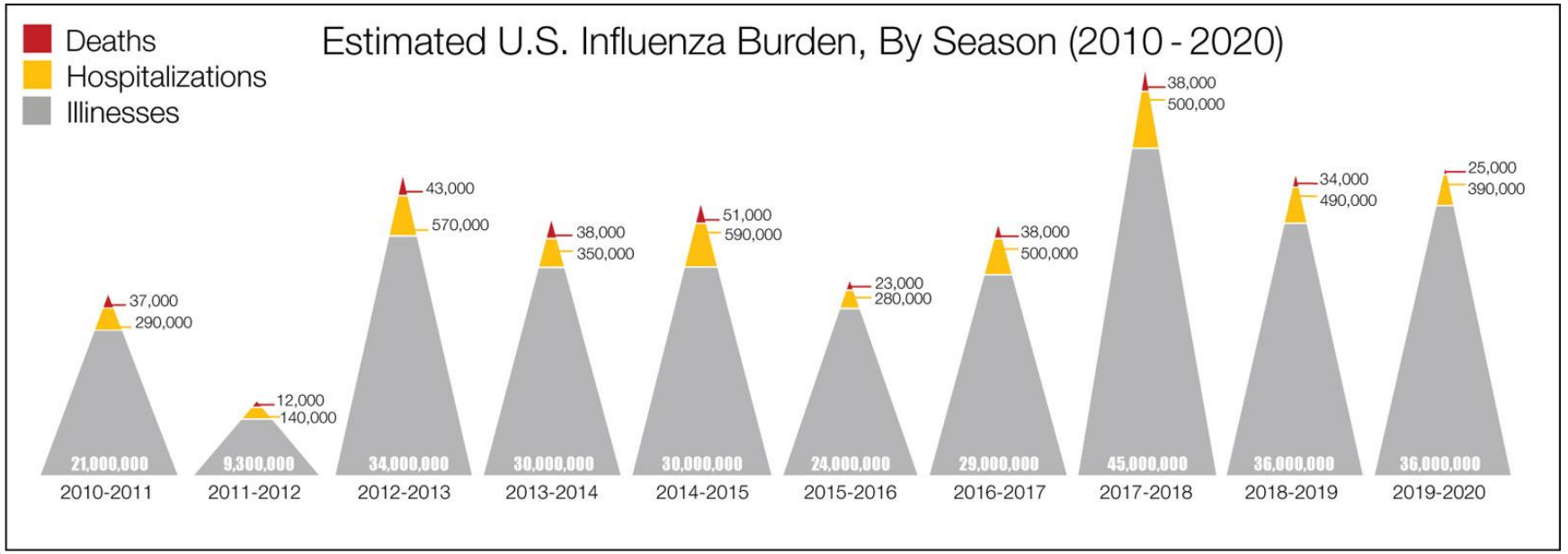
Ghebrehewet S et al., BMJ 2016

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**

Estimated Influenza Disease Burden





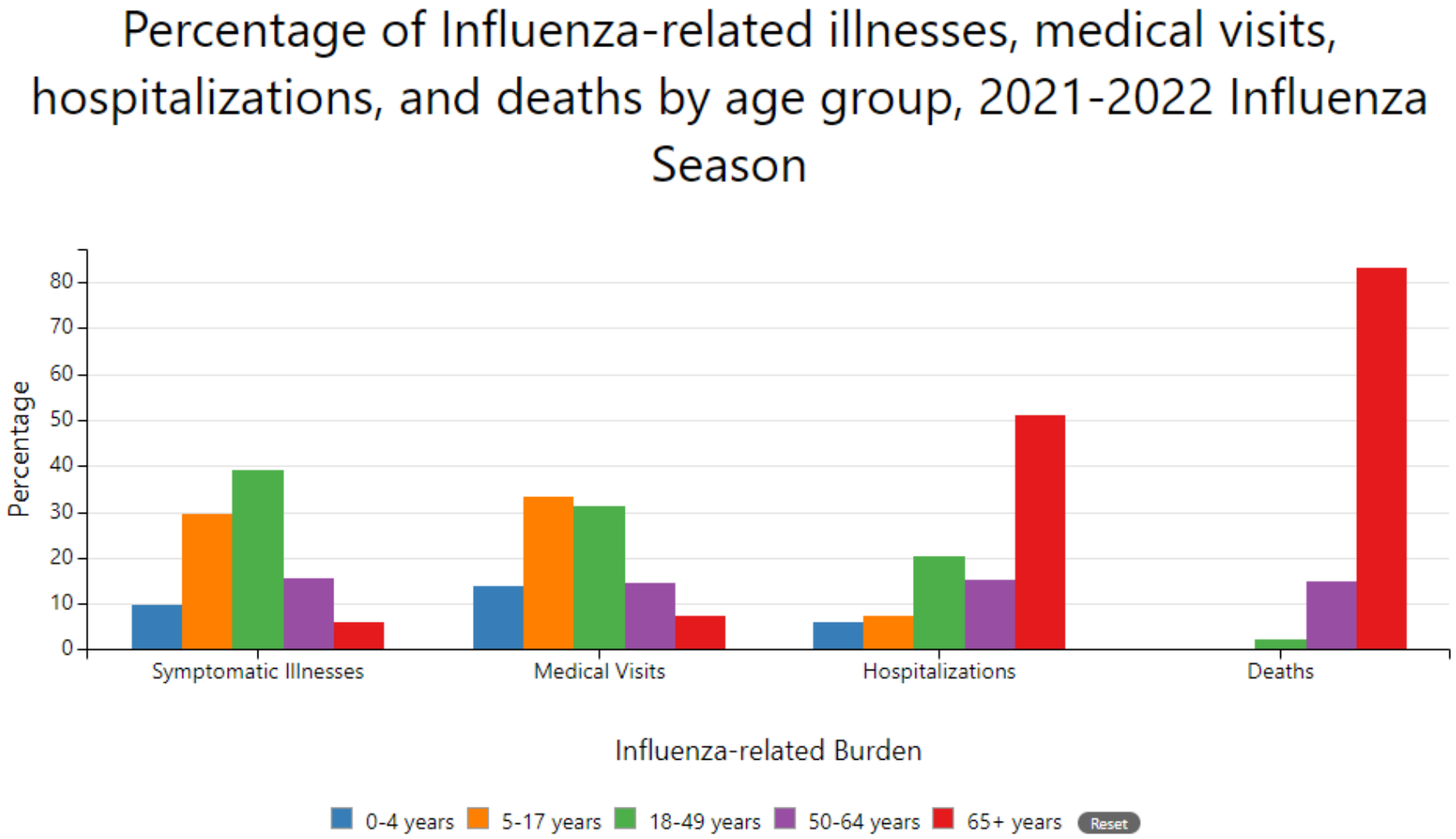
- **Seasonal influenza epidemics vary in severity**

2021-2022 (preliminary estimates):

* 9 million illnesses
* 4 million medical visits
* 100,000 hospitalizations
* 5,000 deaths

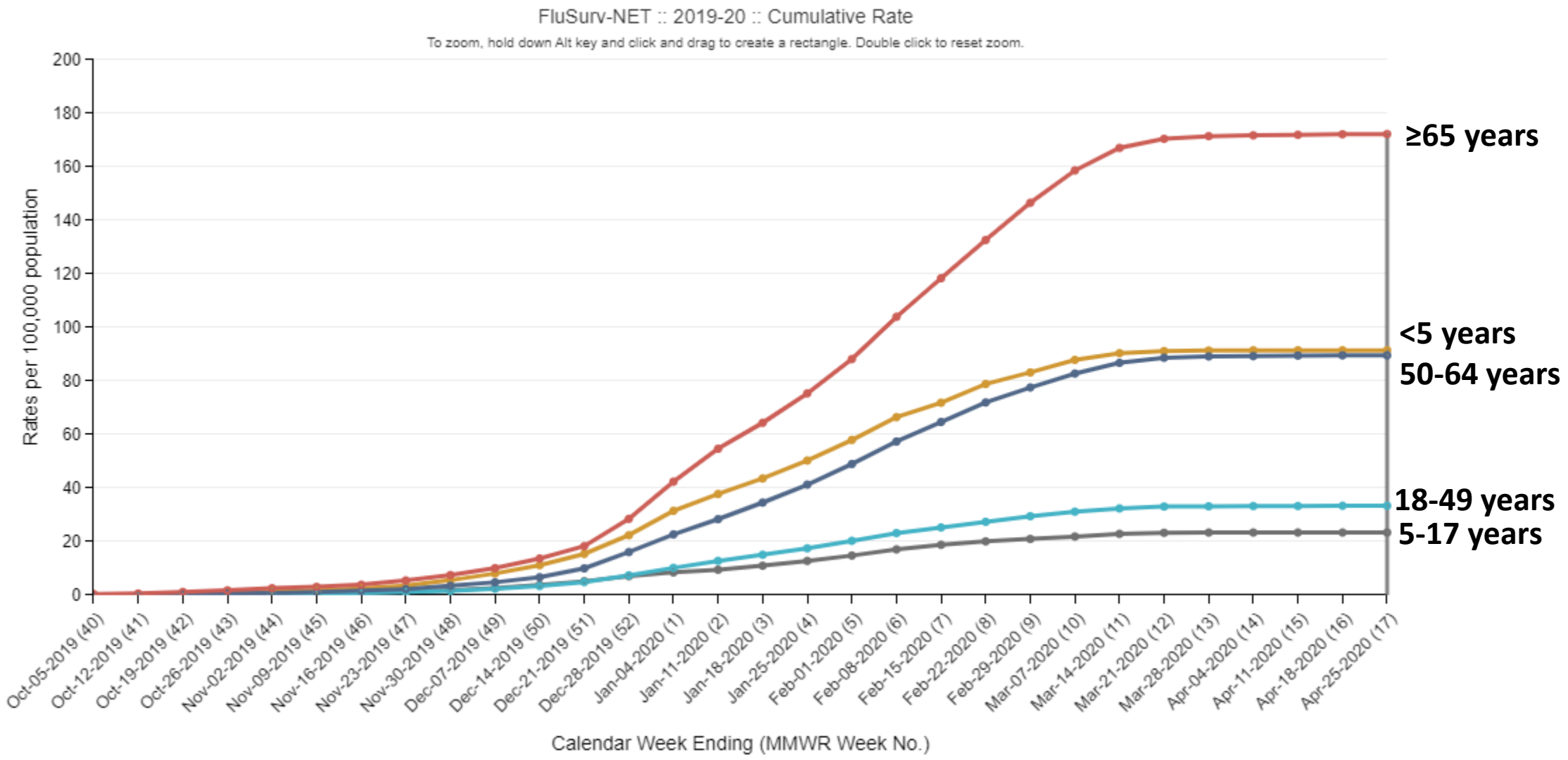
https://www.cdc.gov/flu/about/burden/index.html

Estimated Influenza Disease Burden, U.S. 2021-2022



https://www.cdc.gov/flu/about/burden/2021-2022.htm#:~:text=During%20the%202021%2D2022%20influenza,10%2C000%20hospitalizations%2C%20and%205%2C000%20deaths.

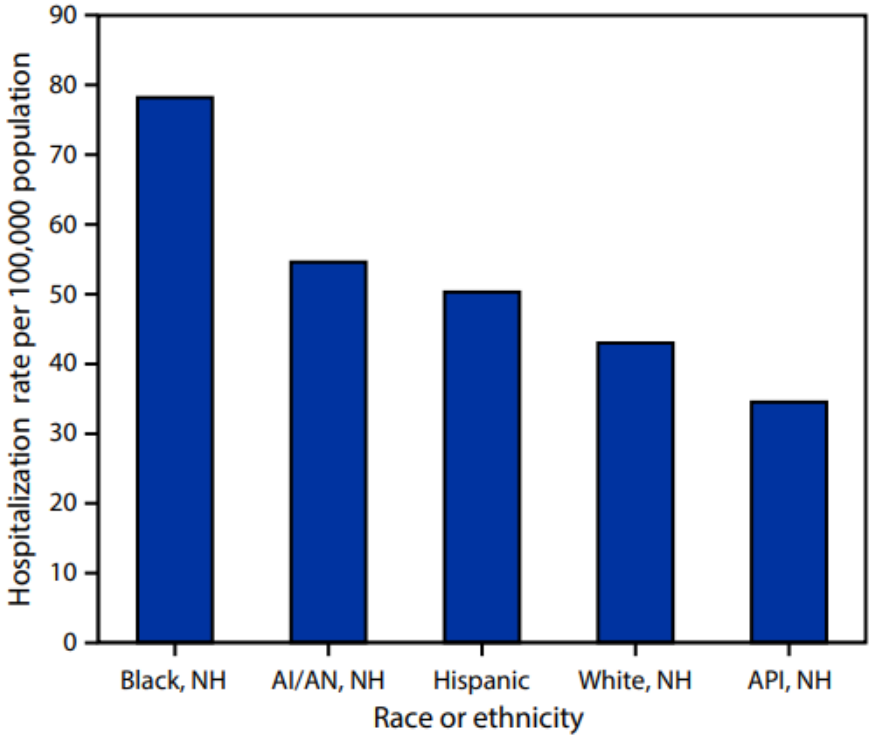
Lab-confirmed Influenza Hospitalization Rates by Age Group, 2019-2020



https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html

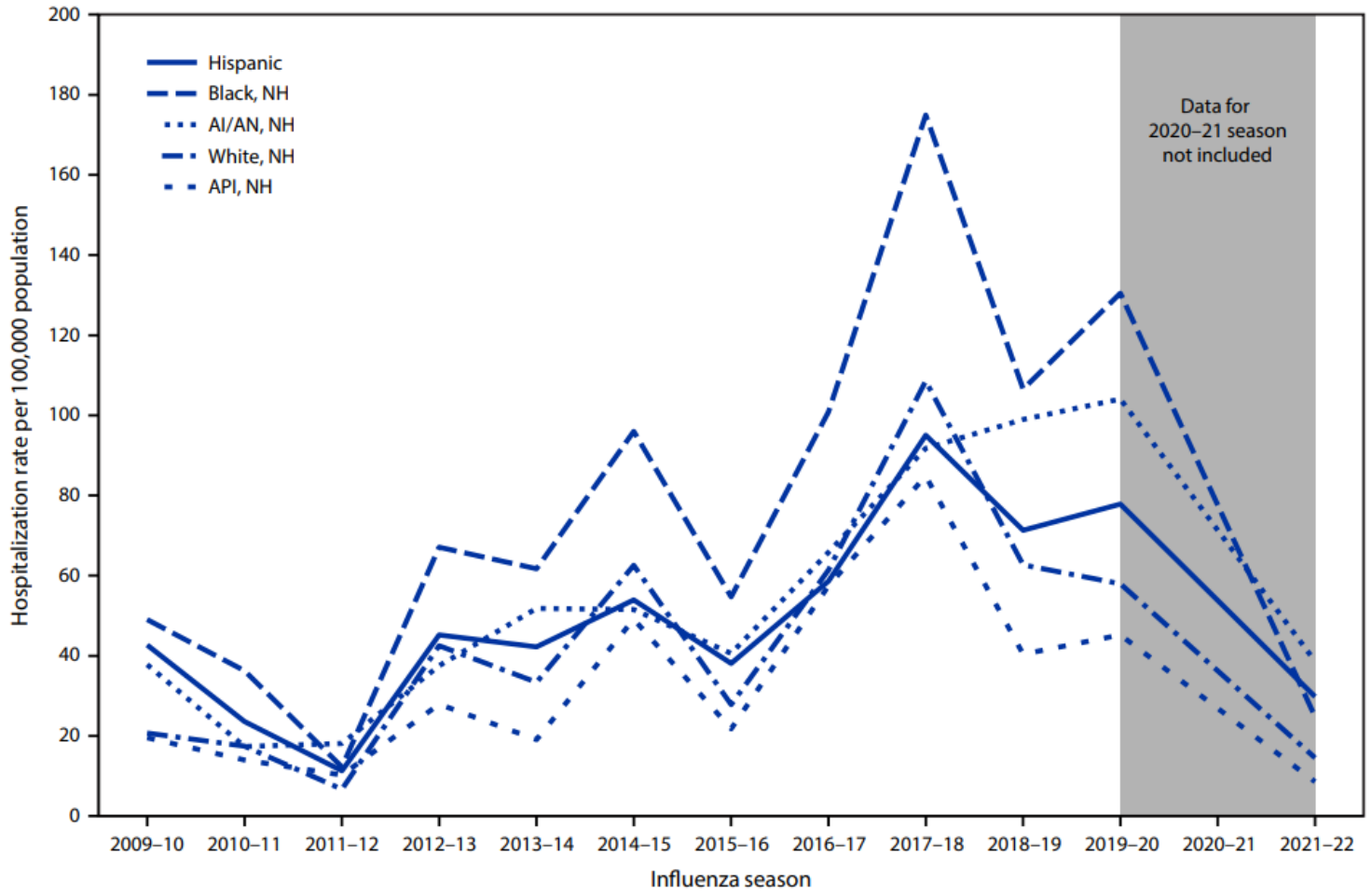
Racial and Ethnic Disparities in Adult Influenza Hospitalizations, U.S.

FIGURE 1. Age-adjusted Influenza-associated hospitalization rates* among adults aged ≥18 years, by race and ethnicity — Influenza-Associated Hospitalization Surveillance Network, United States, 2009–10 through 2021–22†



Abbreviations: AI/AN = American Indian or Alaska Native; API = Asian or Pacific Islander; NH = non-Hispanic.
* Hospitalizations per 100,000 population.
† Excluding 2020–21 season.

FIGURE 2. Age-adjusted Influenza-associated hospitalization rates among adults, by race and ethnicity and influenza season — Influenza-Associated Hospitalization Surveillance Network, United States, 2009–10 through 2019–20 and 2021–22*



Abbreviations: AI/AN = American Indian or Alaska Native; API = Asian or Pacific Islander; NH = non-Hispanic.
* Data for 2020–21 season are not included.

Black CL et al., MMWR October 28, 2022

Preliminary In-Season Burden Estimates, 2022-2023

CDC estimates* that, from **October 1, 2022** through **November 5, 2022**, there have been:

2,800,000 – 6,600,000
flu **illnesses**

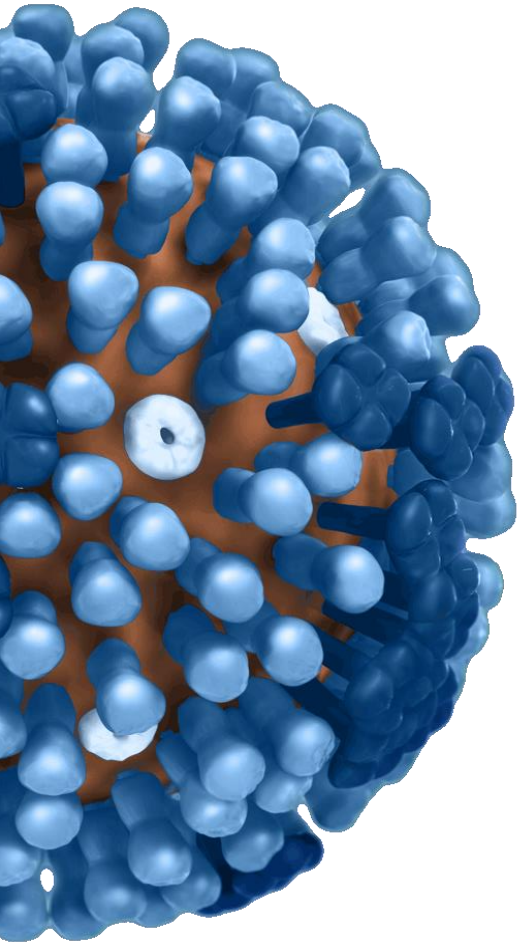
1,400,000 – 3,300,000
flu **medical visits**

23,000 – 48,000
flu **hospitalizations**

1,300 – 3,600
flu **deaths**

*Because influenza surveillance does not capture all cases of flu that occur in the U.S., CDC provides these estimated ranges to better reflect the larger burden of influenza. These estimates are calculated based on data collected through CDC's Influenza Hospitalization Surveillance Network (FluSurv-NET) and are **preliminary**.

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



Influenza Vaccination

Influenza Vaccines, U.S. 2022-2023 Season

Trade name (manufacturer)	Presentations	Age indication	μg HA (IIV4s and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal, if present), μg/0.5 mL
Inactivated (IIV4) (standard-dose, egg-based vaccines†)					
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**	IM¶	—
	5.0-mL MDV§	**≥6 mos§ (needle/syringe) 18 through 64 yrs (jet injector)**	**15 μg/0.5 mL**	IM¶	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¶	—
Fluzone Quadrivalent (Sanofi Pasteur)	0.5-mL PFS**	**≥6 mos**	**15 μg/0.5 mL**	IM¶	—
	0.5-mL SDV**	**≥6 mos**	**15 μg/0.5 mL**	IM¶	—
	5.0-mL MDV**	**≥6 mos**	**15 μg/0.5 mL 7.5 μg/0.25 mL**	IM¶	25
Cell-culture (ccIIV4) (standard-dose, cell culture–based vaccine)					
Flucelvax Quadrivalent (Seqirus)	0.5-mL PFS	**≥6 mos**	**15 μg/0.5 mL**	IM¶	—
	5.0-mL MDV	**≥6 mos**	**15 μg/0.5 mL**	IM¶	25
HD-IIV4 (high-dose, egg-based vaccine†)					
Fluzone High-Dose Quadrivalent (Sanofi Pasteur)	0.7-mL PFS	**≥65 yrs**	**60 μg/0.7 mL**	IM¶	—
Adjuvanted (aIIV4) (standard-dose, egg-based† vaccine with MF59 adjuvant)					
Fluad Quadrivalent (Seqirus)	0.5-mL PFS	**≥65 yrs**	**15 μg/0.5 mL**	IM¶	—
Recombinant (RIV4) (recombinant HA vaccine)					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	**≥18 yrs**	**45 μg/0.5 mL**	IM¶	—
Live Attenuated (LAIV4) (egg-based vaccine†)					
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	—

Grohskopf LA et al., MMWR 2022

Influenza Vaccine Recommendations 2022-2023

- Annual influenza vaccination is recommended for all persons aged 6 months and older who do not have contraindications
- All influenza vaccines for 2022-2023 are quadrivalent (4 antigens)
  - Influenza A(H3N2), Influenza A(H1N1)pdm09, Influenza B/Victoria lineage, and Influenza B/Yamagata lineage viruses
- On June 22, 2022, the Advisory Committee on Immunization Practices **(ACIP) recommended influenza vaccination of persons aged ≥65 years with "higher dose and adjuvanted" vaccines:**
  - **High-dose (4x antigen concentration), Adjuvanted, or Recombinant (3x antigen concentration) influenza Vaccine**
  - If not available, then standard-dose vaccine is recommended

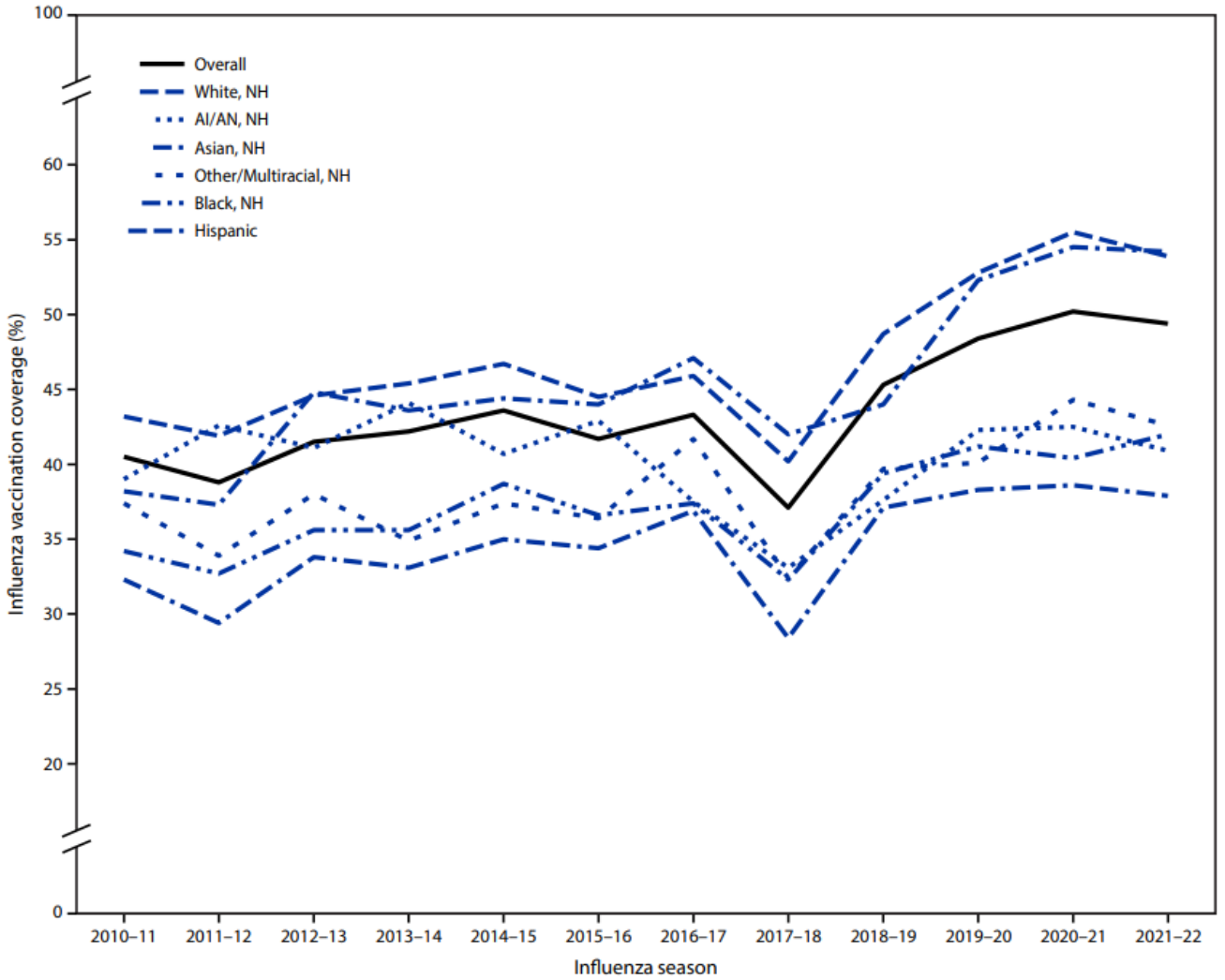
Influenza Vaccine Effectiveness (VE)

- Influenza vaccine effectiveness varies by virus antigen and match to circulating virus strains
  - VE against medically attended influenza illness has ranged from low to moderate (10-60%) since 2009
  - Of influenza A(H3N2) viruses that have been analyzed in the United States since May 2022, most A(H3N2) viruses are genetically and antigenically closely related to the updated A(H3N2) vaccine component.
  - ➢ These data suggest influenza vaccination this season should offer protection against the predominant A(H3N2) viruses to date
- **Influenza vaccination can prevent severe influenza**
  - VE **(51%)** against hospitalization for influenza A(H1N1)pdm09 in adults [VE was @0% for influenza A(H3N2) (2018-19)]
  - VE **(65%)** against ICU admission for influenza in children (2019-2020)
  - VE **(65%)** against influenza-related death in children (2010-2014)

Ferdinands JM et al., JID 2021; Olson SJ et al., CID 2022; Flannery B et al., Pediatrics 2017

Racial and Ethnic Disparities in Adult Influenza Vaccination Coverage, U.S.

FIGURE 3. Influenza vaccination coverage among adults aged ≥18 years, by race and ethnicity and influenza season — Behavioral Risk Factor Surveillance System, United States, 2010–11 through 2021–22



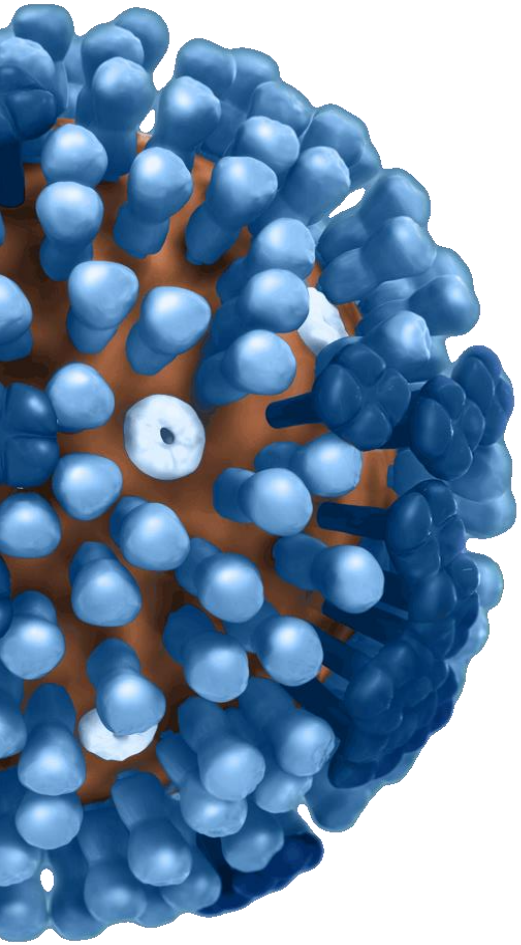
Abbreviations: AI/AN = American Indian or Alaska Native; NH = non-Hispanic.

Black CL et al., MMWR October 28, 2022

Influenza Vaccination Coverage 2022-2023

- Influenza activity continues to increase while vaccine uptake is lagging according to CDC's FluVaxView.
  - So far this season, influenza vaccination coverage in adults and pregnant people is significantly lower compared to this time last season.
  - While influenza vaccination among children is similar to this time last season, coverage among children is down 6 percentage points from two years ago.
- The number of doses of influenza vaccine given in pharmacies and retail locations is similar to last season, but doses given in doctor's offices are down steeply.

Weekly Flu Vaccination Dashboard | FluVaxView | Seasonal Influenza (Flu) | CDC



Influenza Testing

Why Test for Influenza?

- **Signs and symptoms of influenza overlap with those caused by other co-circulating respiratory viruses (e.g. SARS-CoV-2, RSV)**
- **Accurate and prompt influenza diagnosis is important for clinical decision-making** (ambulatory & inpatient settings)
  - **Guide antiviral treatment** *(if testing will change clinical management, versus prescribing empiric antiviral treatment)*
  - **Facilitate implementation of Infection prevention & control measures**
    - Prevention and control of nosocomial transmission in hospitals
    - Control of other institutional outbreaks
  - **Guide other clinical decisions**
    - Reduce inappropriate antibiotic use, reduce use of other diagnostic tests, reduce time in clinical care (e.g. Emergency Department)

Egilmezer E et al., Rev Med Virol 2018; Brendish NJ et al., Lancet Resp Med 2017

Influenza Tests in Clinical Settings

- **Variety of diagnostic tests available to clinicians to detect influenza viruses in respiratory specimens**
  - Differ by time to produce results, information provided, approved respiratory specimens, approved clinical settings, and **accuracy**
    - Point-of-care assays (CLIA-waived)
    - Moderately complex (requires clinical laboratory)
    - Highly complex (large clinical laboratories, public health labs)

Influenza Tests Available for Clinicians: Antigen Detection

- **Antigen detection**
  - Detect influenza A and influenza B viral antigens in respiratory specimens (FDA-cleared for upper respiratory tract specimens)
  - **Rapid immunoassays** (rapid tests) (10-15 minutes)
    - With or without analyzer device
  - Direct fluorescent antibody staining (2-4 hours)
    - Requires florescent microscope
  - ***Low to moderately high sensitivities, high specificity to detect influenza viral antigens compared to nucleic acid detection assays***

Influenza Tests Available for Clinicians: Nucleic Acid Detection

- **Nucleic acid detection (molecular assays)**
  - Detect influenza A and B virus nucleic acids in respiratory specimens
    - Most are FDA-approved for upper respiratory tract specimens, some approved for lower respiratory tract specimens
  - **Rapid molecular assays** (15-30 minutes to results)
  - **Other molecular assays** (60-80 minutes to 4-8 hours to results)
    - Single-plex PCR: Detect influenza A and B viruses
    - Multiplex PCR: Detect influenza viruses and other respiratory pathogens
    - ➢ FDA Emergency Use Authorization (EUA) issued for assays that detect influenza viruses and SARS-CoV-2
  - ➢ ***High sensitivity and high specificity***

https://www.cdc.gov/flu/professionals/diagnosis/table-nucleic-acid-detection.html; https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-molecular; https://www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html

Rapid Influenza Molecular Assays Have High Sensitivity

Pooled Sensitivity to detect influenza A and B viruses versus RT-PCR (N=162 studies) (Pooled Specificity >98%)

- Rapid antigen tests: **53-54%**
- Rapid antigen tests with analyzer device: **77-80%** (digital immunoassays)
- Molecular assays: **92-95%**


Annals of Internal Medicine REVIEW

Diagnostic Accuracy of Novel and Traditional Rapid Tests for Influenza Infection Compared With Reverse Transcriptase Polymerase Chain Reaction

A Systematic Review and Meta-analysis

Joanna Merckx, MD, MSc; Rehab Wali, BSc, MBBS; Ian Schiller, MSc; Chelsea Caya, MScPH; Genevieve C. Gore, MLIS; Caroline Chartrand, MD, MSc; Nandini Dendukuri, PhD; and Jesse Papenburg, MD, MSc

- **Meta-analysis of Rapid Influenza Molecular Assays (N=29 studies)**
  - Pooled Sensitivity: **87.9%**
  - Pooled Specificity: **97.4%**


Clinical Infectious Diseases

REVIEW ARTICLE

IDSA Infectious Diseases Society of America hivma hiv medicine association

Rapid Molecular Tests for Influenza, Respiratory Syncytial Virus, and Other Respiratory Viruses: A Systematic Review of Diagnostic Accuracy and Clinical Impact Studies

Laura M. Vos,[1] Andrea H. L. Bruning,[2] Johannes B. Reitsma,[3] Rob Schuurman,[4] Annelies Riezebos-Brilman,[4] Andy I. M. Hoepelman,[1] and Jan Jelrik Oosterheert[1]

Merckx J et al., Annals of Int Med 2017; Vos LM et al., Clin Infect Diseases 2019

Influenza Diagnostic Tests*

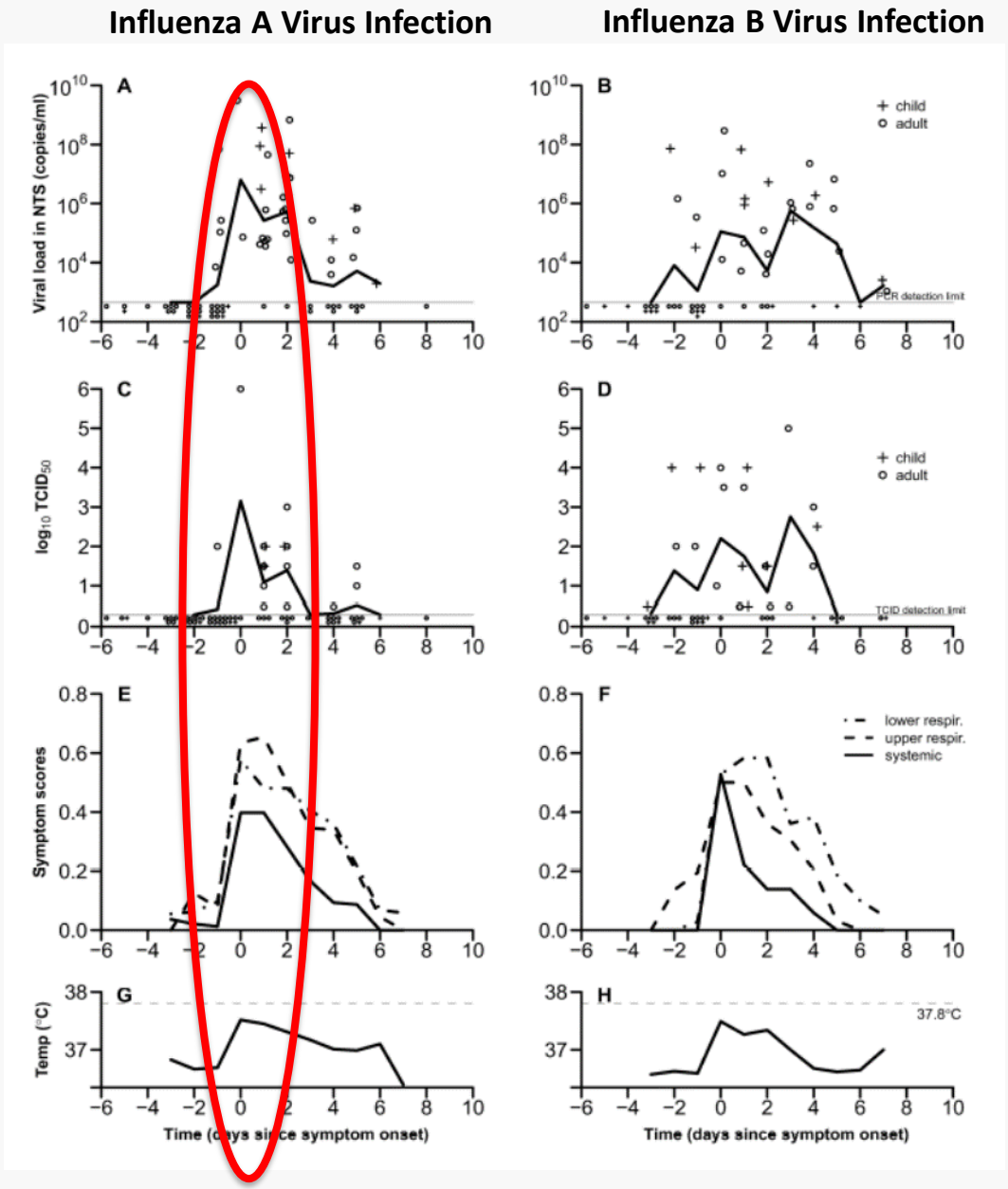
Test	Method	Time to Results	Performance	Notes†
Rapid diagnostic test	Antigen detection	10 min	Low to moderate sensitivity; high specificity	Negative results may not rule out influenza; most assays are approved for point-of-care use; multiplex assays can identify and distinguish among influenza A, influenza 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
Tissue cell virus culture	Virus isolation	3–10 d	Generally high sensitivity (can vary by virus); high specificity	Negative results may not rule out influenza

** Respiratory tract specimens should be collected as close to illness onset as possible for testing. Serologic testing requires paired acute and convalescent sera and is not recommended except for public health investigations and research. Updated information and guidance on the use of influenza diagnostic tests and interpretation of results are available at www.cdc.gov/flu/professionals/diagnosis/index.htm.*

† These tests are FDA-cleared or are available through FDA EUAs for high- or moderate-complexity clinical laboratories or point-of-care use, including by Clinical Laboratory Improvement Amendments waiver.

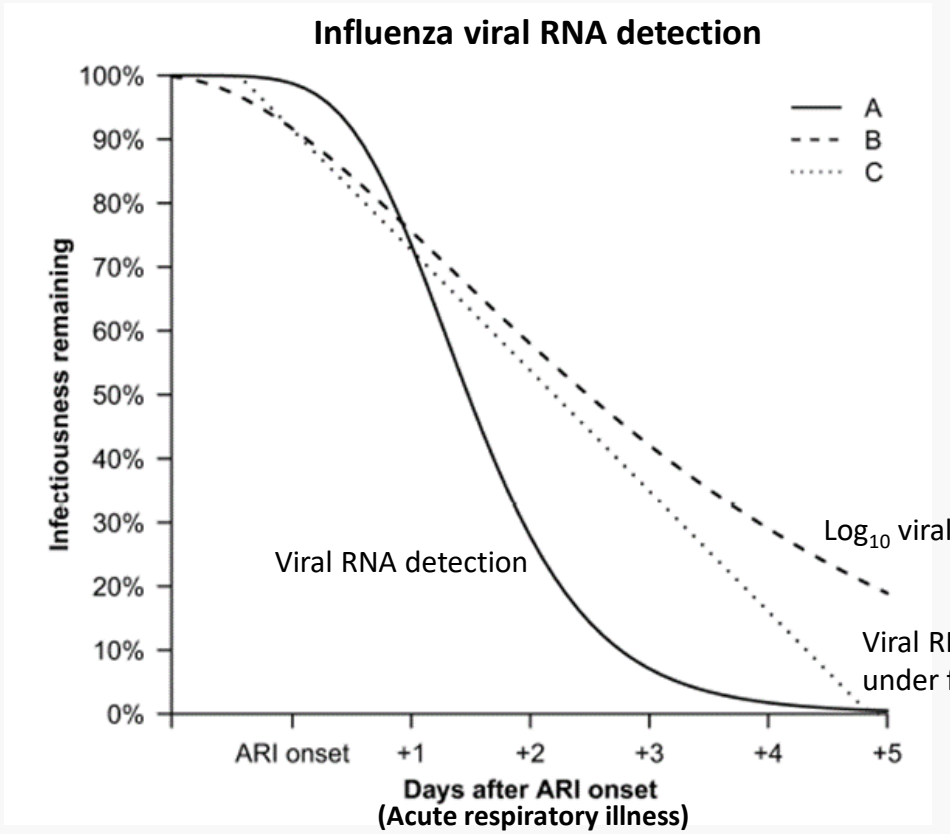
Uyeki TM Annals of Int Med 2021

Influenza Viral Shedding Typically Peaks Within 24 Hours of Illness Onset



Influenza virus infection

- **Virus can be detected the day before illness onset, virus levels peak within 24 hours after onset**
  - **Highest infectious period is within 3 days after symptom onset**
- Young children can be infectious for longer periods
- Critically ill patients might have longer influenza viral replication in the lower respiratory tract
- Severely immunocompromised persons can be infectious for weeks to months



Lau LL et al., J Infect Dis 2010

Influenza A(H1N1)pdm09 Viral Shedding Varies by Disease Severity

Viral Shedding is Longer with Severe Disease

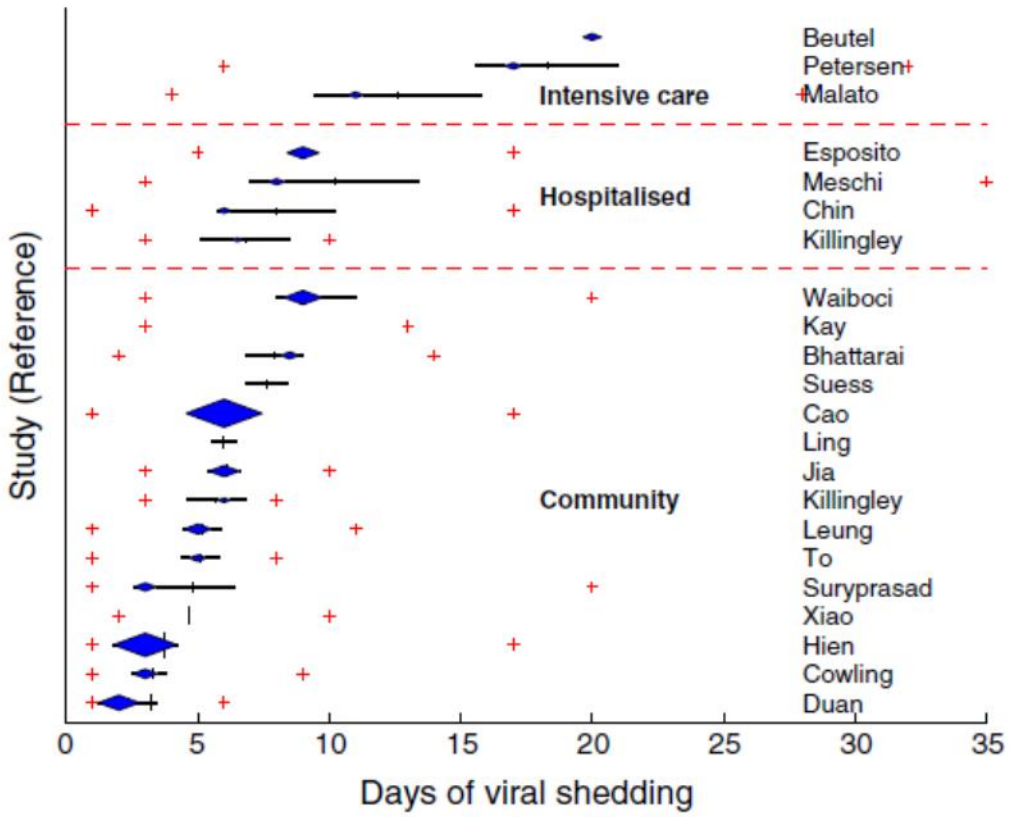


Figure 1. Shedding duration of influenza A(H1N1)pdm09 by study and patient setting. (Legend: cross = minimum and maximum; middle of diamond = median; area of diamond = study size; vertical line = mean; horizontal line = 95% confidence interval)

Viral Shedding Duration is Similar in Children and Adults

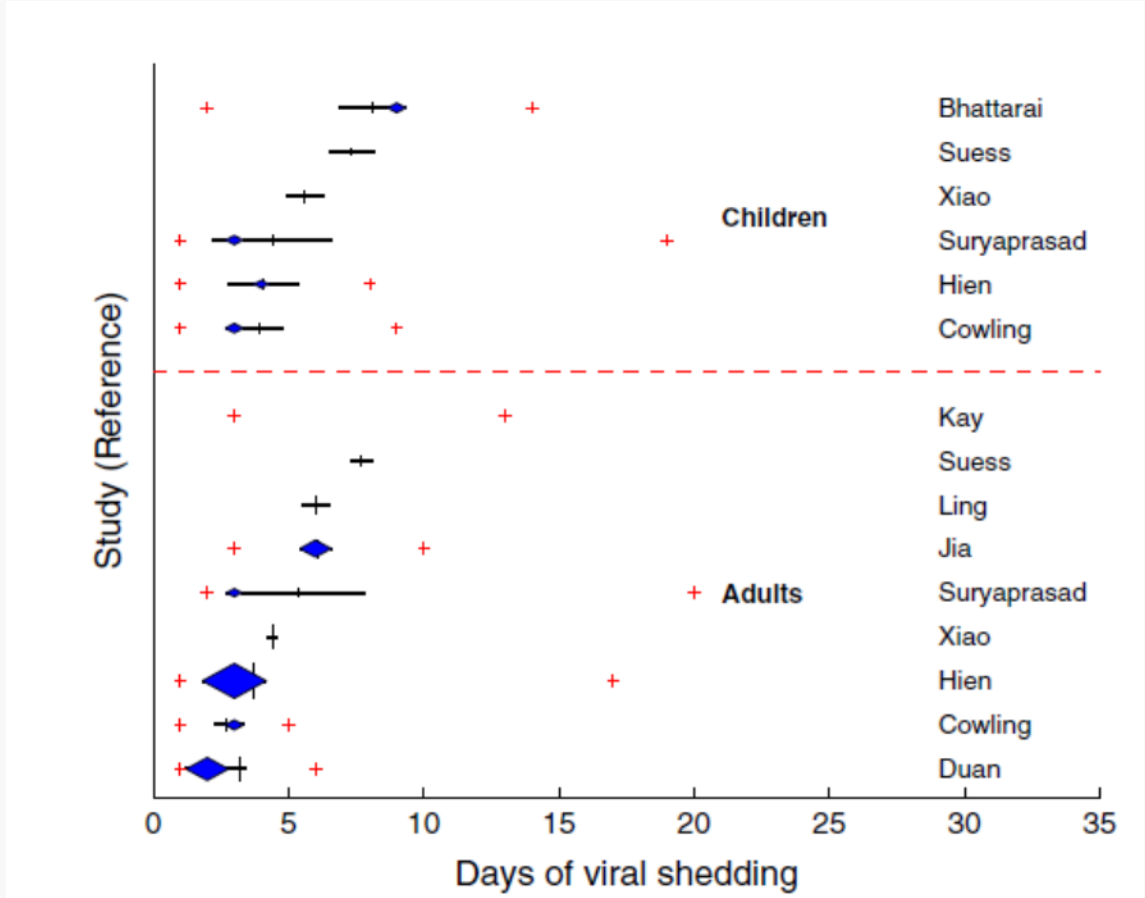


Figure 2. Shedding duration of influenza A(H1N1)pdm09 in studies of community-based cases, by study and age group.

Fielding JE et al., Influenza and Other Respiratory Viruses 2014

Influenza Testing and Specimen Source

- **Upper respiratory tract**
  - **Influenza viruses are generally detectable for 3-4 days by antigen detection; and 5-6 days by nucleic acid detection in uncomplicated disease, longer in infants and immunosuppressed**
    - ***Highest yield: Nasopharyngeal (NP) swabs (ideally collected within 3-4 days of illness onset)***
      - Other acceptable specimens: nasal swabs, NP aspirates, nasal aspirates, combined nasal and throat swabs
  - **Slower clearance of influenza viruses in severe disease**
  - **Influenza viral replication and RNA detection may be prolonged with corticosteroids, immunosuppression**
- **Lower respiratory tract**
  - **Higher, prolonged viral replication in severe lower respiratory tract (LRT) disease**
    - **Influenza viruses may be detectable in LRT specimens when cleared from the upper respiratory tract**
      - **RT-PCR was negative in 10-19% of patients in upper respiratory tract specimens versus lower respiratory tract (BAL specimens) for influenza A(H1N1)pdm09 viral RNA**

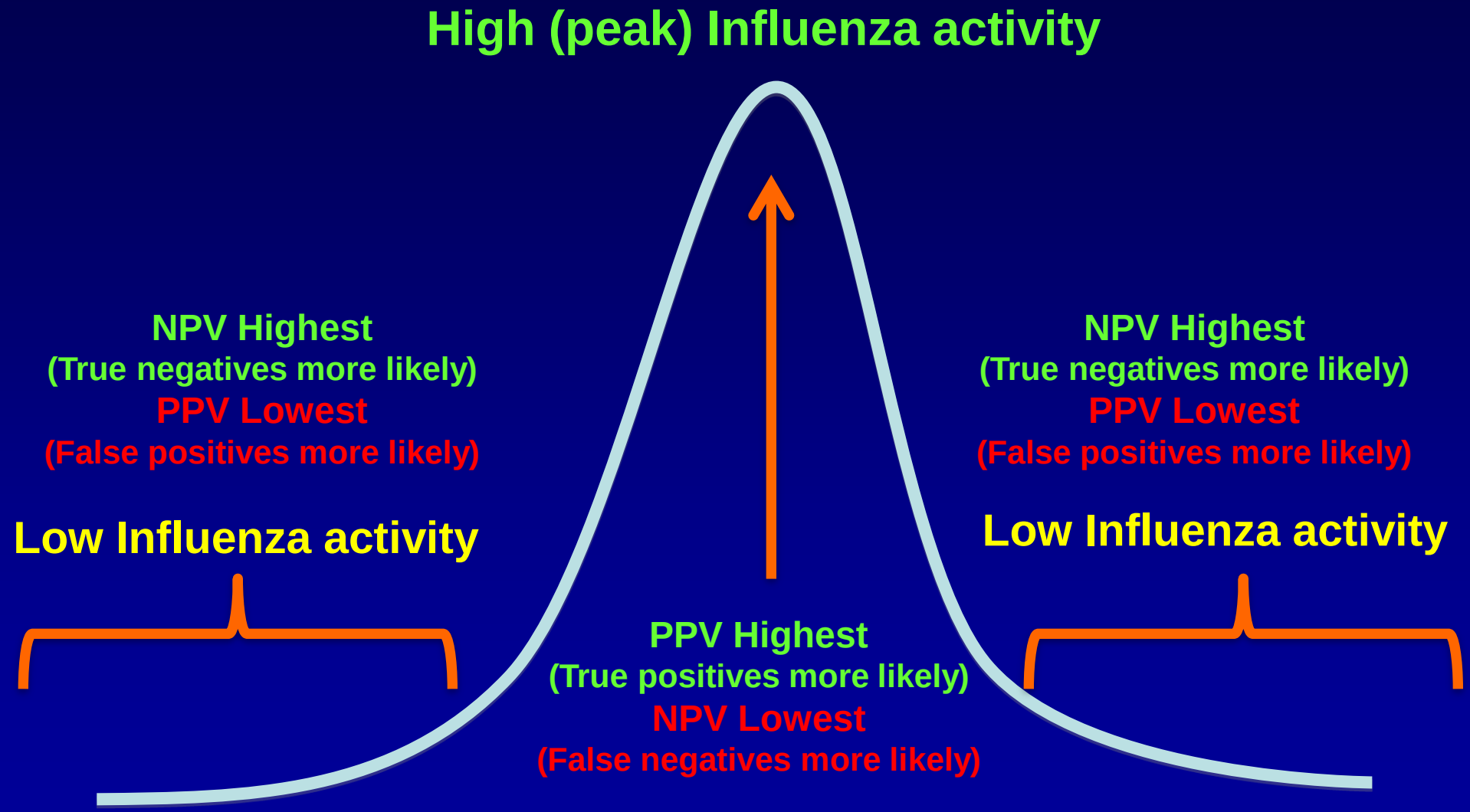
Rello J et al., Crit Care 2009; Fleury H et al., Eurosurveillance 2009; Blyth CB et al., NEJM 2009

Importance of Influenza Prevalence

- **Influenza activity (prevalence) impacts:**
  - Influenza testing decisions (when to test?)
  - **How to interpret results** (e.g. negative results)?
  - Treatment decisions (when to prescribe empiric antiviral treatment?)

- **Clinicians should be aware of local influenza activity**
  - State and local influenza surveillance data, local hospital laboratory data
  - National influenza surveillance data (e.g. U.S. CDC)

Prevalence (Influenza Activity) and Predictive Values of Influenza Tests



Uyeki Chapter 177; Feigin and Cherry's Pediatric Infect Dis 2013

Influenza Testing Recommendations: Outpatients*

- **Which outpatients should be tested for influenza during influenza season?**
  (Test if the results will influence clinical management)
  - **High-risk persons with influenza-like illness, pneumonia, non-specific acute respiratory illness**
  - **Patients with acute onset of respiratory symptoms and exacerbation of chronic medical conditions** (e.g. asthma, COPD, heart failure) or known influenza complications
  - **Consider testing for:**
    - **Persons not at high-risk for complications of influenza who present with acute respiratory illness** *(ILI, pneumonia, ARI without fever) if the results might change clinical management (support antiviral treatment, reduce unnecessary antibiotic use, reduce more diagnostic testing or time in the emergency department)*

*History of influenza vaccination does not exclude influenza

Uyeki TM et al., IDSA 2018 Influenza Clinical Practice Guidelines Clinical Infect Dis 2019

Influenza Testing Recommendations: Hospitalized Patients*

- **Which patients being hospitalized should be tested for influenza during influenza season?**
  - **All patients requiring admission with acute respiratory illness**, including pneumonia, with or without fever
  - **All patients with acute worsening of chronic cardiopulmonary disease** (e.g. COPD, asthma, coronary artery disease, heart failure)
  - **All immunocompromised and high-risk patients with acute onset of respiratory symptoms with or without fever**
  - **All patients during hospitalization who develop acute onset of respiratory symptoms with or without fever, or respiratory distress, without a clear diagnosis**

*History of influenza vaccination does not exclude influenza

Uyeki TM et al., IDSA 2018 Influenza Clinical Practice Guidelines Clinical Infect Dis 2019

What Respiratory Specimens Should Be Collected?

- **Outpatients: Collect upper respiratory tract specimens as soon after illness onset as possible, preferably with 4 days of symptom onset**
  - **Nasopharyngeal (NP) specimens**
  - If NP specimens are not available, collect combined nasal and throat specimens
  - Mid-turbinate nasal swab specimens should be collected over throat swabs
  - Flocked swabs should be used over non-flocked swabs
- **Hospitalized patients:**
  - **Patients without severe lower respiratory tract disease:**
    - ***Collect NP specimens, mid-turbinate nasal, or combined nasal-throat swab specimens***
  - **Patients with respiratory failure receiving invasive mechanical ventilation:**
    - ***Collect endotracheal aspirate (or bronchoalveolar lavage (BAL) fluid specimens - if performed for other diagnostic purposes)***

Uyeki TM et al., IDSA 2018 Influenza Clinical Practice Guidelines Clinical Infect Dis 2019

What Influenza Tests Are Recommended?

- **Outpatients:**
  - **Rapid influenza molecular assays are recommended over rapid influenza antigen detection tests**
- **Hospitalized patients:**
  - **RT-PCR or other 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**

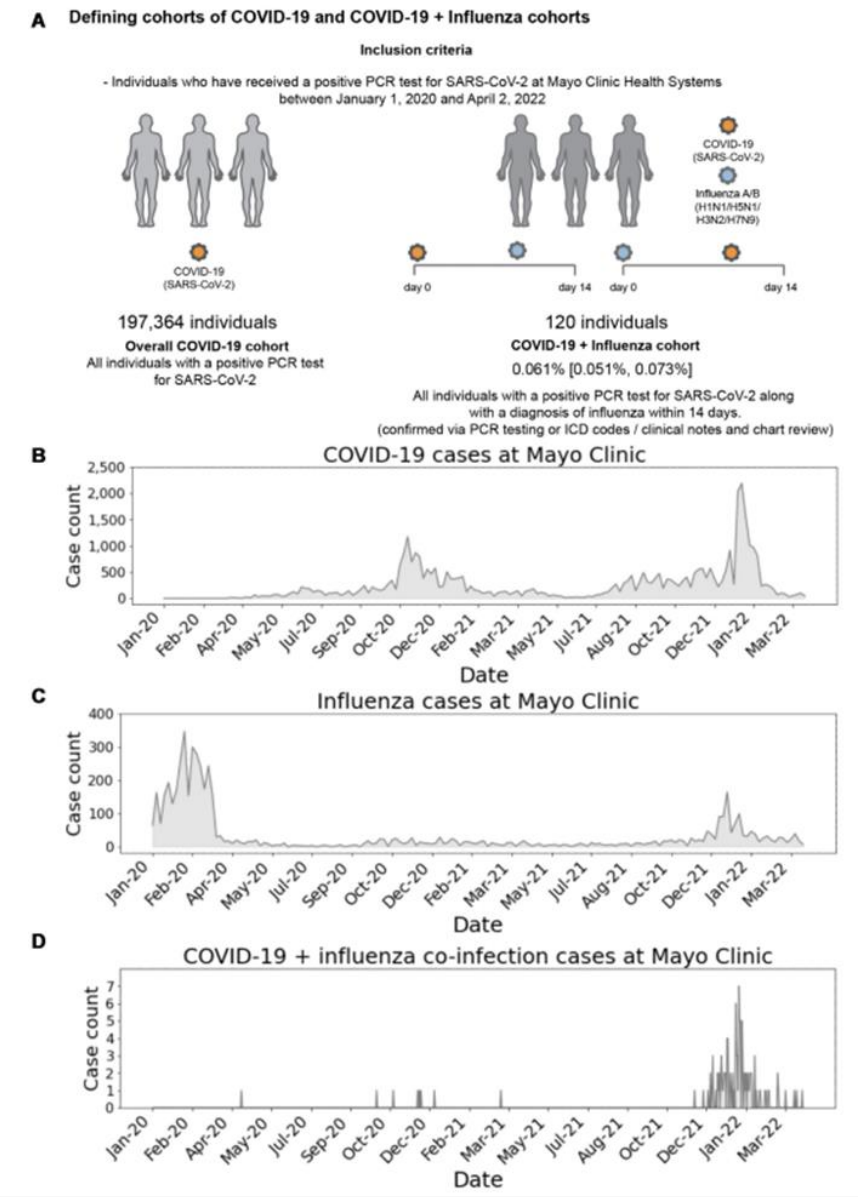
- ***Do not order viral culture for initial or primary diagnosis of influenza***
- ***Do not order serology for influenza***
  - **Results from a single serum specimen cannot be reliably interpreted, and collection of paired acute and convalescent sera 2-3 weeks apart are needed**

Uyeki TM et al., IDSA 2018 Influenza Clinical Practice Guidelines Clinical Infect Dis 2019

Co-circulation of Influenza Viruses and SARS-CoV-2

- **Co-infection with influenza A or B viruses and SARS-CoV-2 occurs**
  - Documented in case reports, case series
  - Frequency, severity, and risk factors unknown but frequency appears to be uncommon (may result in more severe disease)
- **Overlapping signs, symptoms, some differences**
  - Incubation period is usually shorter for influenza (1-3 days) than COVID-19 (2-5 days)
  - Viral shedding, period of viral RNA detection is generally shorter for influenza
  - Ageusia/dysgeusia, anosmia are more common with COVID-19 than influenza
  - Diarrhea can occur in young children with influenza; at any age with COVID-19
  - Onset of complications/severe disease is earlier with influenza
- **High-risk groups for influenza and COVID-19 are similar**
  - ➢ In addition, young children are at increased risk for influenza complications

➢ **Testing for influenza A/B and SARS-CoV-2 can help guide antiviral treatment in persons at high risk for complications and identify co-infections**



Beltran-Corellini A et al., Eur J Neurology 2020; Zayet S et al., Microbes and Infect 2020; Stowe J et al., Int J Epidemiology 2021; Pawlowski C et al., PNAS Nexus 2022

Multiplex Assays for Influenza Viruses and SARS-CoV-2

- **Multiplex Antigen Detection Assays**
  - **Two assays that can detect Influenza A and B viruses and SARS-CoV-2 simultaneously in respiratory specimens have received FDA Emergency Use Authorization (EUA)**
    - **Results in 15 minutes**
    - **High complexity, moderate complexity, CLIA-waived**
- **Multiplex Nucleic Acid Detection Assays**
  - **Several assays that can detect Influenza A and B viruses and SARS-CoV-2 simultaneously in respiratory specimens have received FDA EUA or De Novo 510(k) clearance or premarket approval (PMA)**
    - **Variable turnaround time to results (20 minutes to 8 hours)**
    - **High complexity, moderate complexity, CLIA-waived**

https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-molecular; https://www.cdc.gov/flu/professionals/diagnosis/table-flu-covid19-detection.html

SARS-CoV-2 and Influenza Virus Co-infection

Co-infection can result in severe disease

- U.K. study from January 20-April 25, 2020 (N = 19,256)
  - **Influenza virus infection was associated with a lower risk of SARS-CoV-2 infection** (n = 4443) (adjusted odds ratio [OR],0.42;95%CI,0.31-0.56)
  - ➢ **SARS-CoV-2 and influenza virus co-infection** (n = 58) **was associated with a higher risk of intensive care unit admission** (adjusted OR, 2.08;95%CI, 1.17-3.70) **or death** (adjusted OR, 2.27; 95% CI, 1.23-4.19) **compared with SARS-CoV-2 infection alone**
- U.K. study of hospitalized COVID-19 patients (Feb. 2020-Dec. 2021)
  - N=212,446 adults; n=6,965 had other respiratory virus testing results
    - 8.4% had respiratory viral co-infections; Influenza virus: 227; RSV: 220; Adenoviruses: 136
  - ➢ **SARS-CoV-2 and influenza virus co-infection was significantly associated with 4.14 times the odds of invasive mechanical ventilation** (weighted OR: 4.14,2.00-8.49; p<0.0001) **versus SARS-CoV-2 infection alone** (RSV, Adenoviruses: not significant)
  - ➢ **SARS-CoV-2 and influenza virus co-infection was significantly associated with 2.35 times the odds of in-hospital mortality** (weighted OR: 2.35, 1.07-5.12; p<0.031) **versus SARS-CoV-2 infection alone**

Stowe J et al., Int J Epidemiology 2021; Swets MC et al., Lancet 2022

Self Knowledge Check

The following is **true** regarding recommended influenza tests:

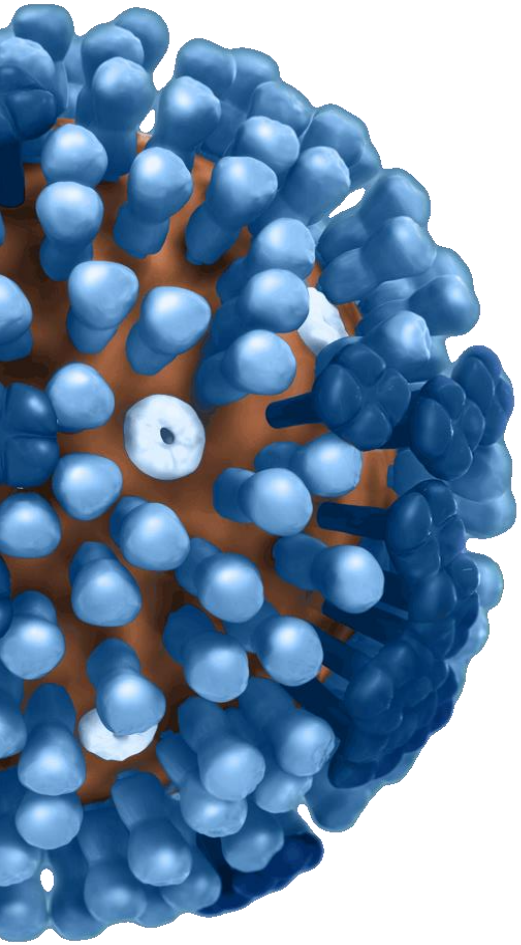
A. Rapid influenza molecular assays are recommended over rapid antigen tests for outpatients
B. Molecular assays and serology are recommended for hospitalized patients
C. Viral culture is recommended for hospitalized patients
D. All of the above

Self-knowledge Check

The correct answer is A

Rapid influenza molecular assays have high sensitivity and high specificity and are therefore recommended over rapid influenza antigen tests for detection of influenza viruses in upper respiratory specimens in outpatients.

For hospitalized patients with suspected influenza, molecular assays are recommended, but antigen detection tests (rapid antigen and immunofluorescence), viral culture, and serology are not recommended.



Antiviral Treatment

Recommended Antivirals for Treatment of Influenza, U.S. 2022-2023

Four FDA-approved antivirals are 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 in the U.S.]
  - **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) ≥12 years (high-risk)

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

CDC Antiviral Treatment Recommendations

- **Focused on prompt treatment of persons with severe disease and those at increased risk of influenza complications**
- **Antiviral treatment is *recommended as soon as possible*** for **any patient with confirmed or suspected influenza who is:**
  - **Hospitalized** (without waiting for testing results)
  - **Outpatients with complicated or progressive illness of any duration**
  - **Outpatients who are at high risk for influenza complications**
- 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)

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

Recommended Antiviral Treatment for Outpatients

- **For outpatients with complications or progressive disease and suspected or confirmed influenza (e.g., pneumonia, or exacerbation of underlying chronic medical conditions), antiviral treatment with oral oseltamivir is recommended as soon as possible.**
- **For outpatients with suspected or confirmed uncomplicated influenza, oral oseltamivir, inhaled zanamivir, intravenous peramivir, or oral baloxavir may be used for early treatment, depending upon approved age groups and contraindications.**
  - In one randomized controlled trial, baloxavir had greater efficacy than oseltamivir in high-risk adolescents and adults with influenza B virus infection
- *Clinicians can consider starting early (≤48 hours after illness onset) empiric antiviral treatment of non-high-risk outpatients with suspected influenza [e.g., influenza-like illness (fever with either cough or sore throat)], based upon clinical judgement, including without an office visit.* ***SARS-CoV-2 and other etiologies of influenza-like illness should also be considered.***

Ison MG et al., Lancet Infect Dis 2020

Oseltamivir Efficacy in Uncomplicated Influenza

Randomized controlled 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)
  - **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)
  - **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 RE et al., Clinical Infect Dis 2018; Dobson J et al., Lancet 2015

Baloxavir Efficacy in Uncomplicated Influenza

RCTs have shown that baloxavir treatment has similar clinical benefit to oseltamivir and significant clinical benefit versus placebo when started within 48 hours after illness onset

- RCT in non-high-risk children (aged 1 to <12 yrs)
  - **Treatment started ≤48 hours of onset (oseltamivir vs. baloxavir):**
    - **Single-dose baloxavir** (n=115) **had similar median time to alleviation of influenza signs and symptoms** (138 hours) **versus 5 days of oseltamivir** (150 hours) (n=58)

- RCTs in adults (aged ≥12 yrs)
  - **Treatment started ≤48 hours of onset (baloxavir vs. placebo vs. oseltamivir):**
    - **Single-dose baloxavir** (n=456) **significantly reduced illness duration by a median of 26.5 hours vs. placebo** (n=231) **in *non-high-risk persons*** (95% CI, 72.6 to 87.1 hours; p<0.001)
      - **Median time to alleviation of symptoms was similar for baloxavir and oseltamivir** (n=377)
    - **Single-dose baloxavir** (n=388) **significantly reduced illness duration by a median of 29 hours vs. placebo** (n=386) **in *persons with ≥1 high-risk condition*** (95% CI 14·6 to 42·8; p<0.0001)
      - **Median time to improvement of symptoms was similar for baloxavir and oseltamivir**
        - **Baloxavir significantly reduced median time to improvement of influenza B symptoms by 27 hours versus oseltamivir** (95% CI: 6.9 to 42.3 hours; p=0.025)

Baker J et al., Ped Infect Dis J 2020; Hayden FG et al., NEJM 2018; Ison MG et al., Lancet Infect Dis 2020

Special Populations

CDC Recommendations

- **Pregnant women**
  - **For treatment of pregnant people and up to 2 weeks postpartum, oral oseltamivir is preferred**
    - **Baloxavir is *not recommended*** for treatment of pregnant people or breastfeeding mothers
      - No efficacy or safety data for baloxavir in pregnant or lactating people
      - Substantial evidence of oseltamivir safety for pregnancy and birth outcomes
- **Immunocompromised persons**
  - **Prolonged influenza viral replication is a possibility, with emergence of antiviral resistant viruses during/after treatment**
    - Monitoring for antiviral resistance is advised
    - Infection prevention and control precautions are recommended to reduce nosocomial transmission risk
  - **Neuraminidase inhibitor treatment is recommended**
  - **Baloxavir is *not recommended* (risk of resistance emergence)**

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

Oseltamivir Recommended for Hospitalized Patients

- **Oseltamivir treatment (oral or enterically-administered) is recommended as soon as possible for hospitalized patients with confirmed or suspected influenza** (without waiting for testing results)
  - Recommendation is based on observational studies
    - Starting oseltamivir at admission is associated with reduced hospital length of stay in adults; early initiation of treatment is associated with shorter hospital duration in children and adults, and may reduce mortality risk in adults
  - Inhaled zanamivir and oral baloxavir are ***not recommended*** because of the lack of data in hospitalized influenza patients
  - Insufficient data for peramivir treatment of hospitalized influenza patients
    - For patients who cannot tolerate or absorb oral or enterically-administered oseltamivir (e.g. gastric stasis, malabsorption, or gastrointestinal bleeding), intravenous peramivir is an option
  - Optimal duration of oseltamivir treatment for critically ill patients is unclear

Uyeki TM et al., Lancet 2022

Additional CDC Resources

- CDC Influenza homepage: https://www.cdc.gov/flu/
- Influenza surveillance: https://www.cdc.gov/flu/weekly/fluactivitysurv.htm
- Influenza vaccination coverage: https://www.cdc.gov/flu/fluvaxview/index.htm
- For Healthcare Professionals: https://www.cdc.gov/flu/professionals/index.htm
  - Influenza Vaccination homepage: https://www.cdc.gov/flu/professionals/vaccination/index.htm
  - 2022-23 ACIP Influenza Recommendations: https://www.cdc.gov/mmwr/volumes/71/rr/pdfs/rr7101a1-H.pdf
  - Influenza Testing homepage: https://www.cdc.gov/flu/professionals/diagnosis/index.htm
  - Influenza Antivirals homepage: https://www.cdc.gov/flu/professionals/antivirals/index.htm

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- Using the Zoom Webinar System
  - Click on the “Q&A” button
  - Type your question in the “Q&A” box
  - Submit your question

- If you are a patient, please refer your question to your healthcare provider.

- If you are a member of the media, please direct your questions to CDC Media Relations at 404-639-3286 or email media@cdc.gov

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- All continuing education for COCA Calls is issued online through the CDC Training & Continuing Education Online system at https://tceols.cdc.gov/.

- Those who participate in today's COCA Call and wish to receive continuing education please complete the online evaluation by **Monday, December 19, 2022,** with the course code **WC4520-111522**. The access code is **COCA111522.**

- Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between **December 20, 2022,** and **December 20, 2024,** and use course code **WD4520-111522.** The access code is **COCA111522.**

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- **When:** A few hours after the live call ends*
- **What:** Video recording
- **Where:** On the COCA Call webpage https://emergency.cdc.gov/coca/calls/2022/callinfo_111522.asp

**A transcript and closed-captioned video will be available shortly after the original video recording posts on the COCA Call webpage.*

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- Join us for our next COCA Call tomorrow, Thursday, November 17 at 2 PM ET.
  - Topic: New 2022 CDC Clinical Practice Guideline for Prescribing Opioids for Pain

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