Diagnostic Testing and Treatment Guidelines for COVID-19 and Influenza

Clinician Outreach and Communication Activity (COCA) Call

Thursday, February 1, 2024

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Objectives

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

1. List available tests and when to test for SARS-CoV-2 and influenza viruses, including indications for repeat testing.
2. Describe recommended antivirals for treating influenza and COVID-19 and clinical benefits.
3. Cite factors for deciding who to treat for COVID-19 and influenza.
4. Review indications for empiric treatment of influenza and COVID-19.

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 Presenters

- **Pragna Patel, MD, MPH**
  Chief Medical Officer
  Coronaviruses and Other Respiratory Viruses Division
  National Center for Immunization and Respiratory Diseases
  Centers for Disease Control and Prevention

- **Tim Uyeki, MD, MPH, MPP**
  Chief Medical Officer
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COVID-19 Diagnosis and Treatment

Pragna Patel, MD, MPH
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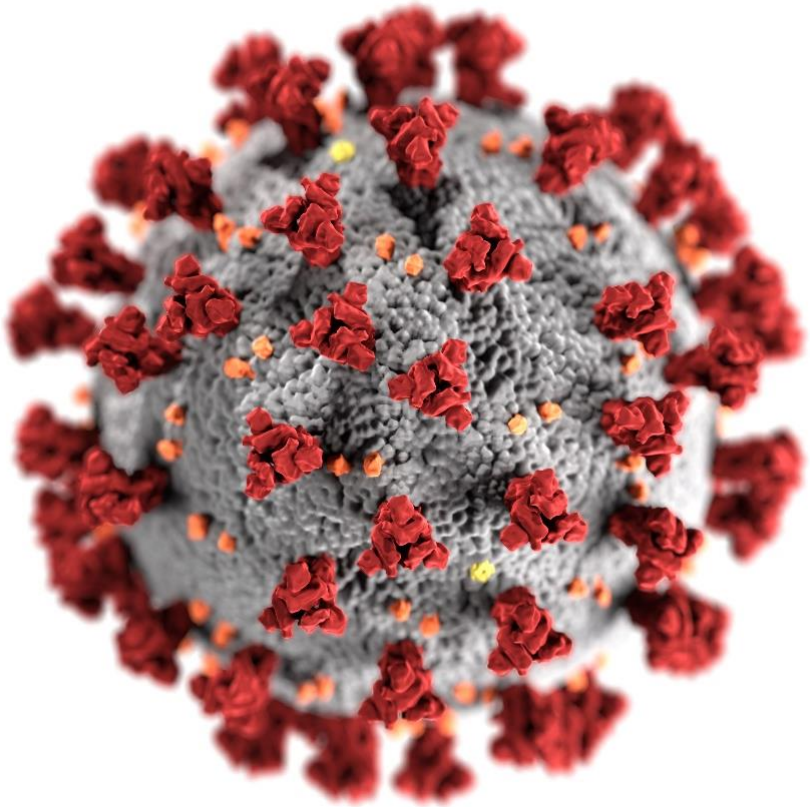
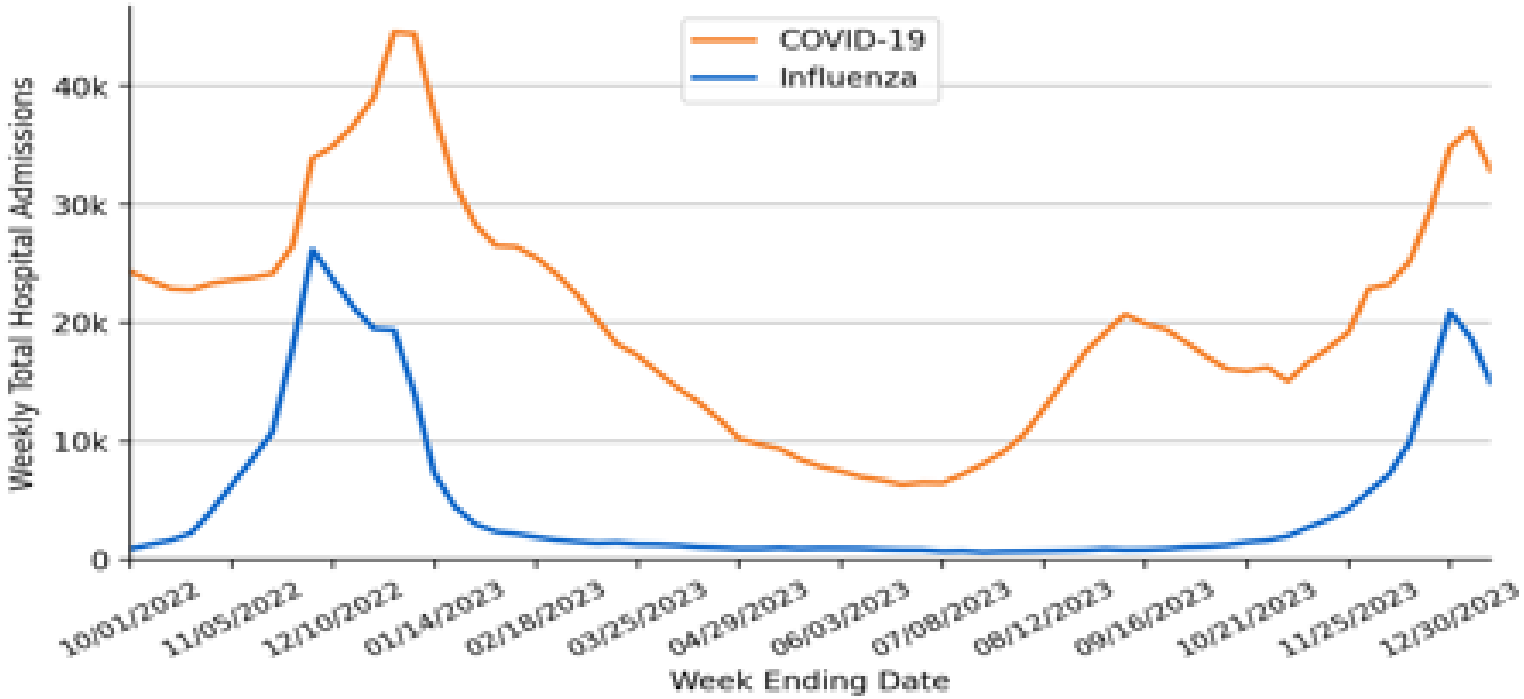


cdc.gov/coronavirus

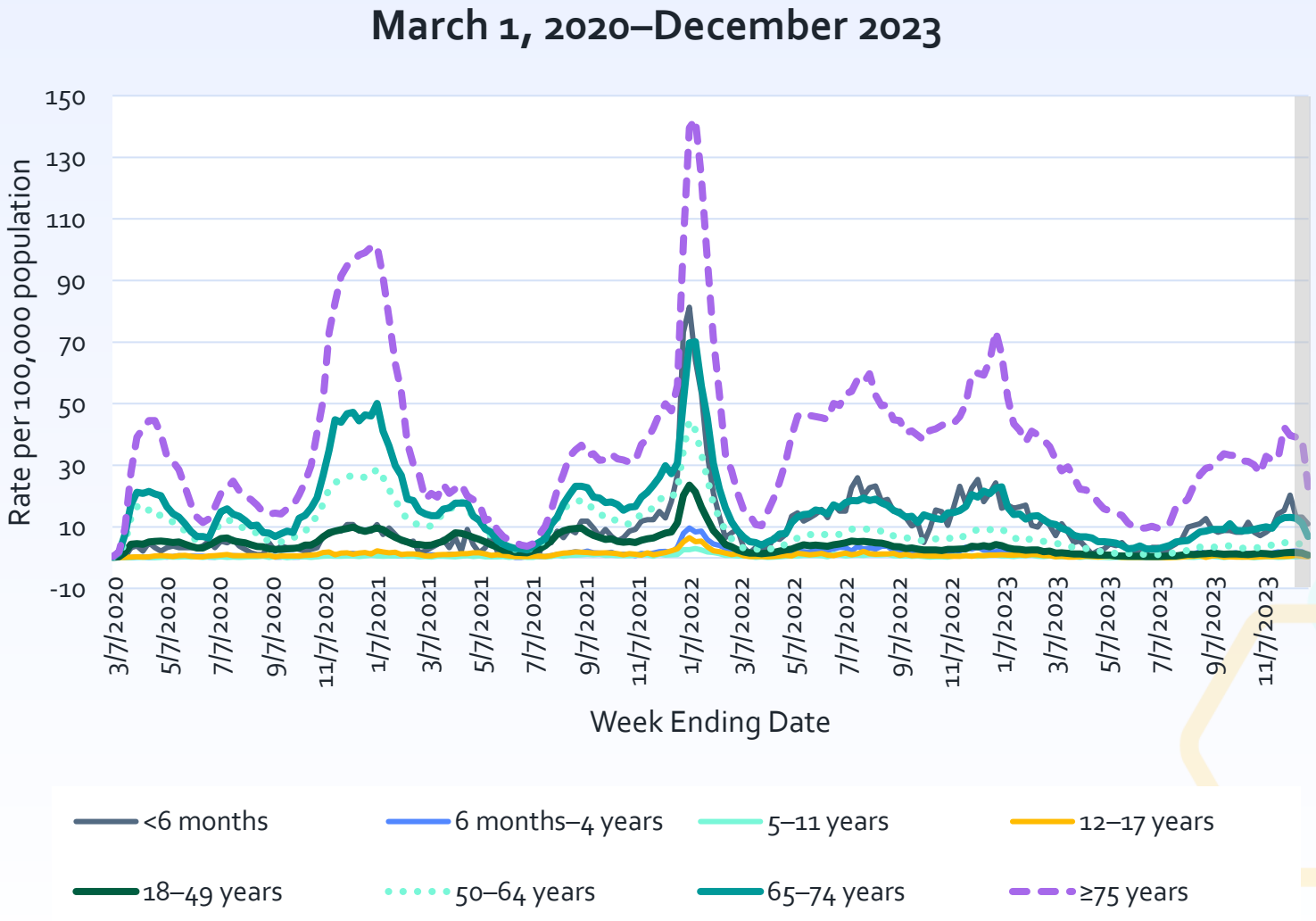
Hospital Admissions Due to COVID-19 and Influenza

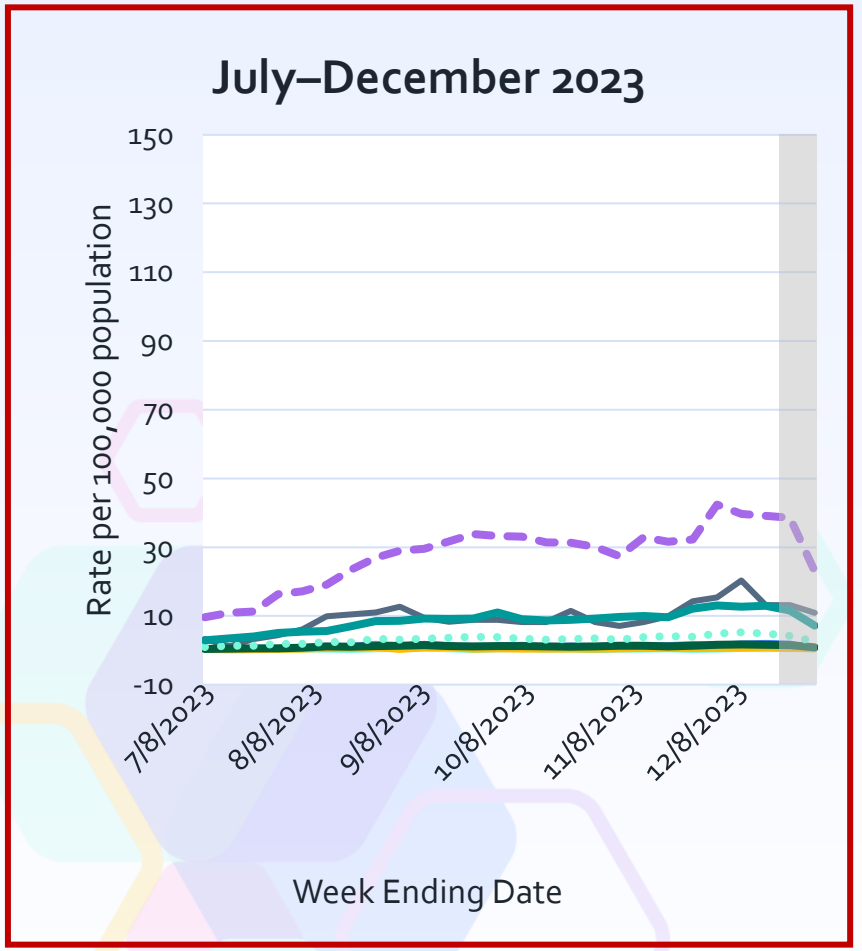
Trends in Hospital Admissions Attributed to
COVID-19 and Influenza through 1/13/2024



Total number of new hospital admissions of patients with laboratory-confirmed COVID-19 and influenza in the previous week (including both adult and pediatric patients), reported to CDC's National Healthcare Safety Network (NHSN); data as of 1/26/24, data through 1/13/24. *See Data Sources and Methods for details*.

Rates of COVID-19-Associated Hospitalizations by Age, March 2020–December 2023





Rates highest in ≥75 years, followed by infants <6 months and adults 65–74 years

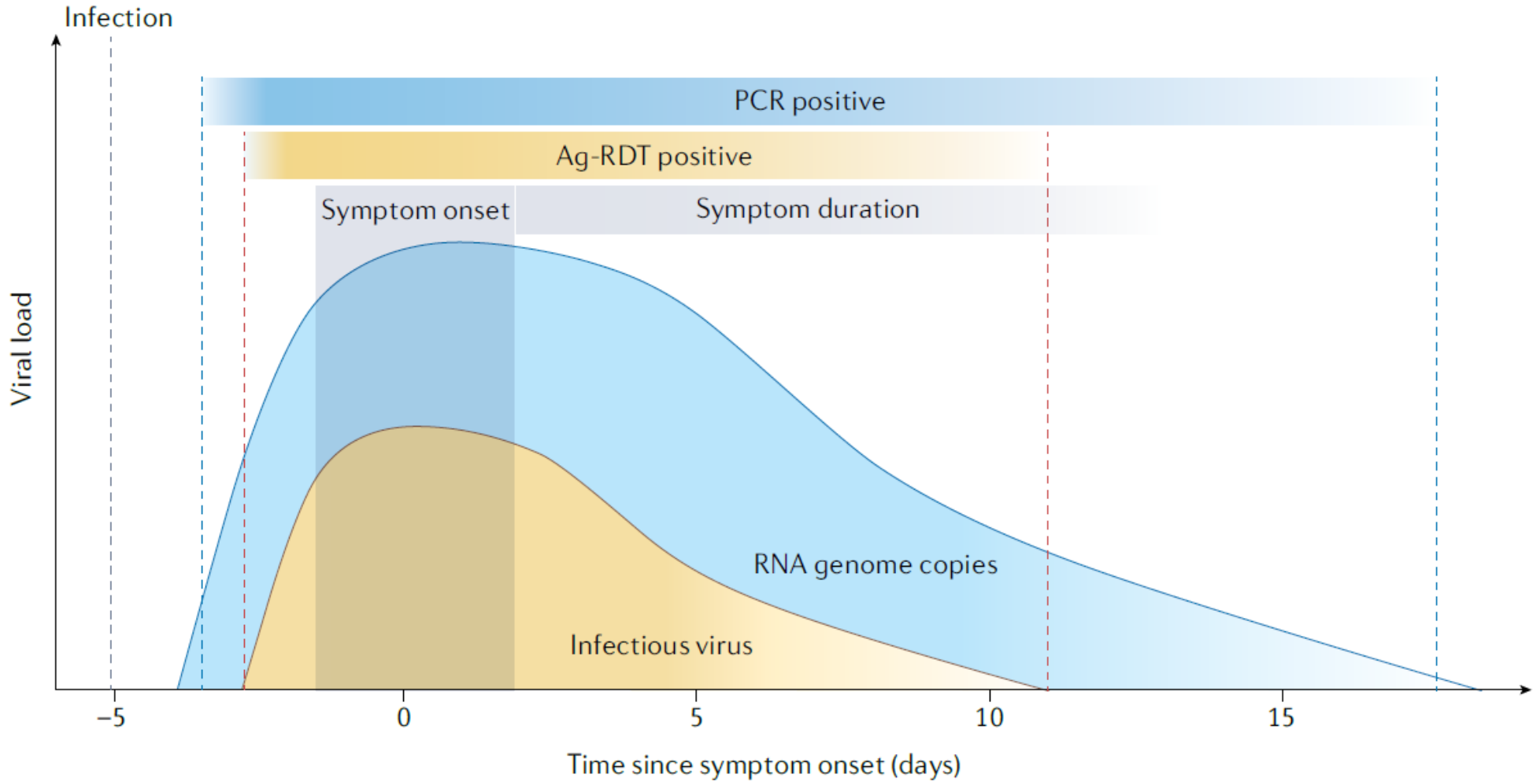
Gray shading on chart indicate potential reporting delays. Interpretation of trends should be excluded from these weeks.

Risk Factors for Severe Disease

- Risk factors for severe COVID-19 include:
  - Age over 50 years, with risk increasing substantially at age ≥ 65 years
  - Being unvaccinated or not being up to date on COVID-19 vaccinations
  - Specific medical conditions, including immunocompromising conditions, chronic lung disease, cardiovascular disease, diabetes, obesity
- Some groups are disproportionately affected by COVID-19 because of many factors, including limited access to vaccines and healthcare.

Testing

Viral Kinetics of SARS-CoV-2 Infection Relative to Symptom Onset



Puhach et al. SARS CoV 2 viral load and shedding kinetics. Nature Reviews.2023

Diagnostic test timing

- If symptomatic, patients should test immediately
  - Limit exposure to others
  - Starting treatment as early as possible for high risk

- If asymptomatic and known exposure, test at least 5 days after exposure
  - Wear a high-quality mask when around others inside the home or in public for 10 days after exposure
  - The incubation period of SARS-CoV-2 is about 3-5 days, and it may take that long to test positive

https://www.cdc.gov/coronavirus/2019-ncov/your-health/if-you-were-exposed.html

If a patient tests negative by Rapid Antigen Test

- FDA recommends
  - If symptomatic, test at least twice 48 hours apart. A third test might be needed if the patient is concerned they have COVID-19.
  - If asymptomatic, but believe they have been exposed, test with RAT at least 3 times, each 48 hours apart to be considered truly negative

- Consider reflex testing to NAAT
  - If NAAT is negative, consider alternative diagnoses such as flu, RSV, or strep throat

Treatment

COVID-19 Treatment Guidelines

Does Not Require Hospitalization or Supplemental Oxygen

All patients should be offered symptomatic management **(AIII)**.

For patients who are at high risk of progressing to severe COVID-19,[a] use 1 of the following treatment options:

Preferred Therapies

Listed in order of preference:

- **Ritonavir-boosted nirmatrelvir (Paxlovid)[b,c] (AIIa)**
- **Remdesivir[c,d] (BIIa)**

Alternative Therapies

For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:

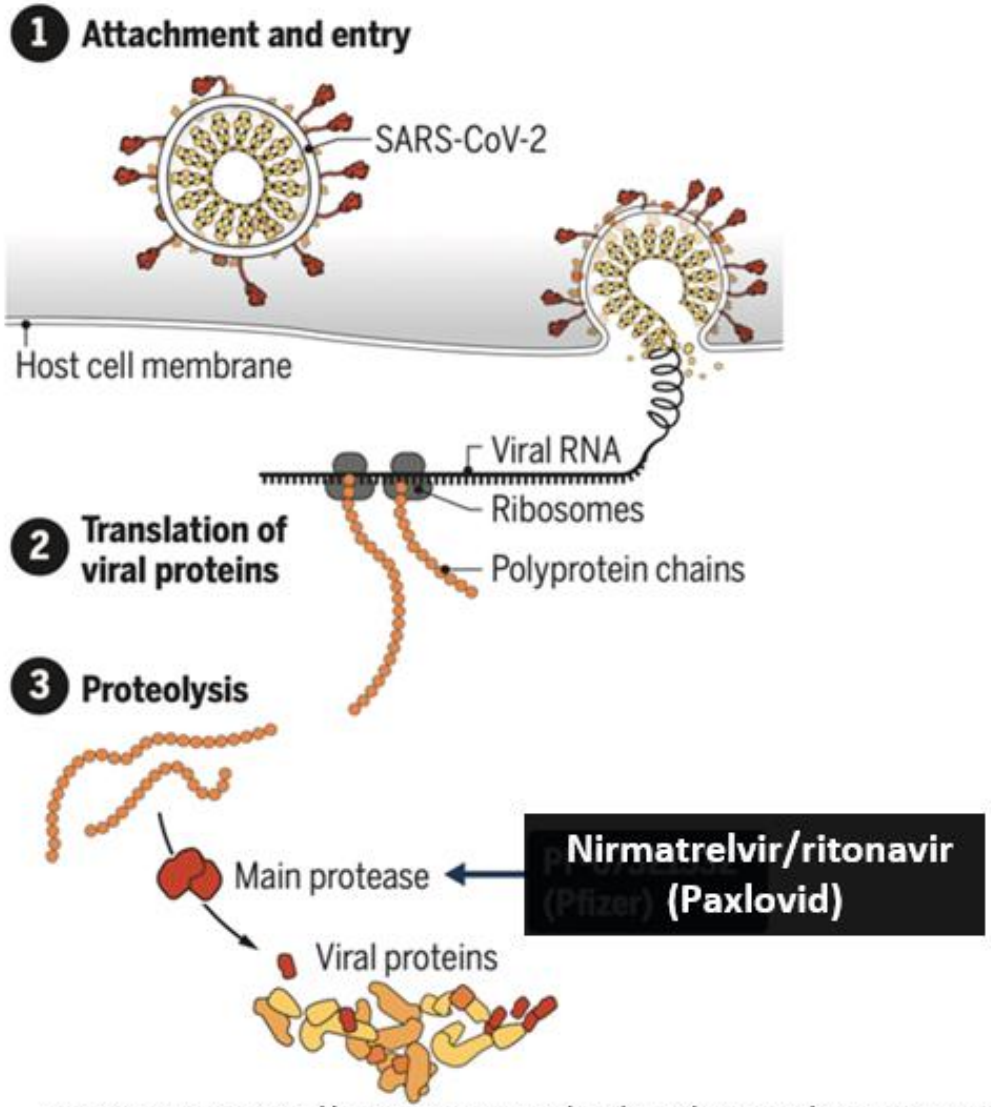
- **Molnupiravir[c,f] (CIIa)**

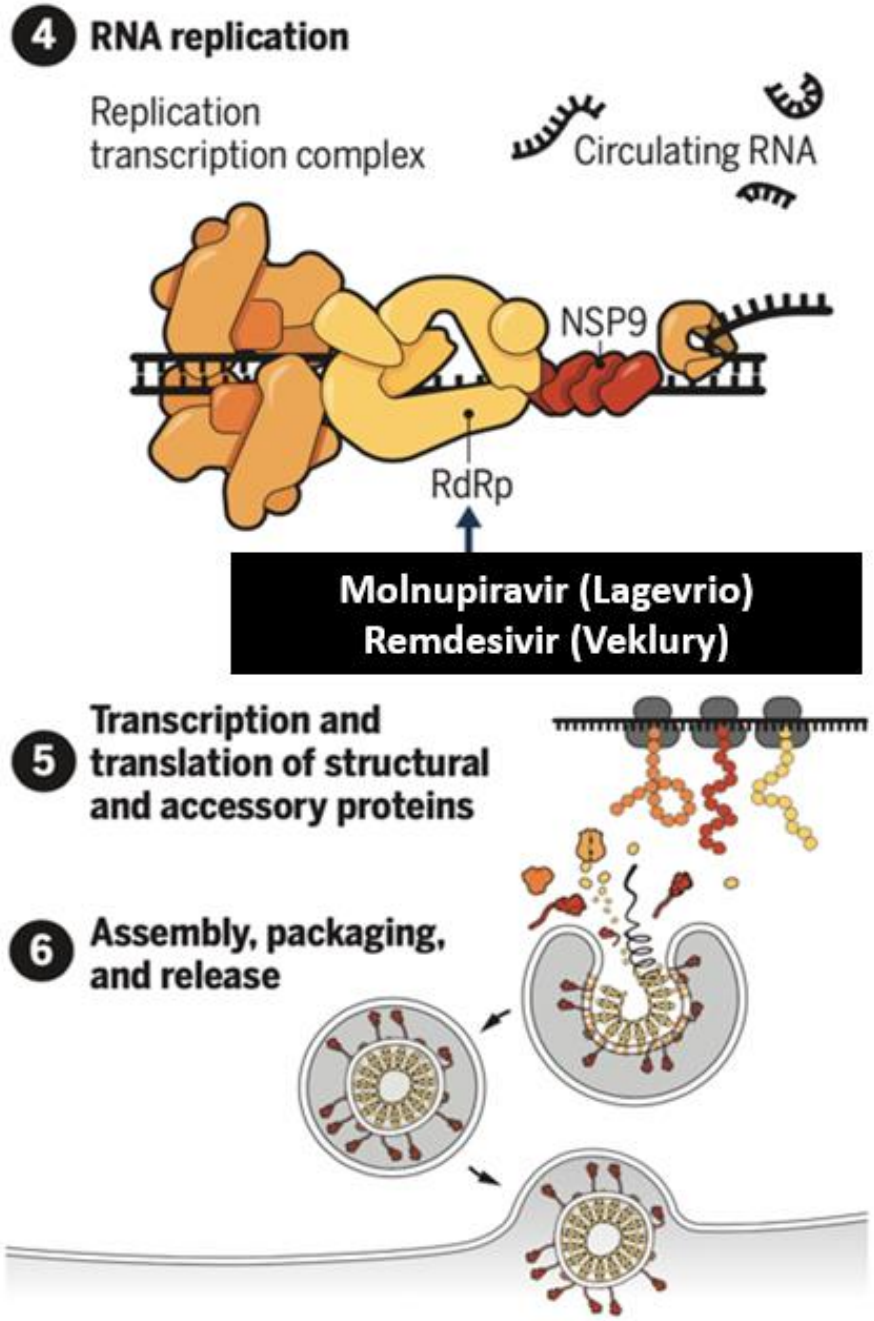
The Panel **recommends against** the use of **dexamethasone[g]** or **other systemic corticosteroids** in the absence of another indication **(AIII)**.

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management/clinical-management-summary/

[a] CDC webpage for criteria of high risk; [b] Caution about drug-drug interactions; [c] If hospitalized, treatment course can be completed; [d] Remdesivir is 3 consecutive day infusion; [f] Molnupiravir has lower efficacy than preferred options; [g] There is currently a lack of safety and efficacy data using glucocorticoids in non-hospitalized patients

SARS CoV-2 Antivirals





Modified from https://www.science.org/doi/epdf/10.1126/science.acx9605

Antivirals – Advantages and Disadvantages

	Nirmatrelvir + Ritonavir	Remdesivir	Molnupiravir
Eligible population (non-hospitalized, unvaccinated)	>18 years + one risk factor	>12 years + one risk factor OR > 60 years	> 18 years + one risk factor
Relative risk reduction	**88% (EPIC-HR)**	**87% (PINETREE)**	**30% (MOVe-OUT)**
Absolute risk reduction	6.3%→0.8%	5.3%→0.7%	9.7%→6.8%
Number needed to treat (NNT)	`18	22	35
Advantages	• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy	• Highly efficacious • Studied in pregnancy • Few/no drug interactions	• Oral regimen • Not anticipated to have drug interactions
Disadvantages	• Drug-drug interactions	Limited accessibility given need for an IV infusion	• Lower efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

Dosing Details

	Dosing	Duration	Time from Illness Onset	Specific Issues
Nirmatrelvir (N) + Ritonavir (R)	• *eGFR ≥60mL/min*: N 300 mg + R 100 gm po bid • *eGFR ≥30 to <60 mL/min*: N 150 mg + R 100 mg po bid	5 days	≤5 days	• Renal dosing in some cases • Do not use if GFR <30 mL/min • Not recommended with severe liver disease • Drug-drug interactions
Remdesivir	Day 1: 200 mg IV Day 2-3: 100 mg IV	3 days	≤7 days	• Infusion over 30-120 min • Infusions over 3 consecutive days
Molnupiravir	800 mg po bid	5 days	≤5 days	• Persons of reproductive age should use birth control

Efficacy and safety of nirmatrelvir/ritonavir (Paxlovid) for COVID-19: A rapid review and meta-analysis

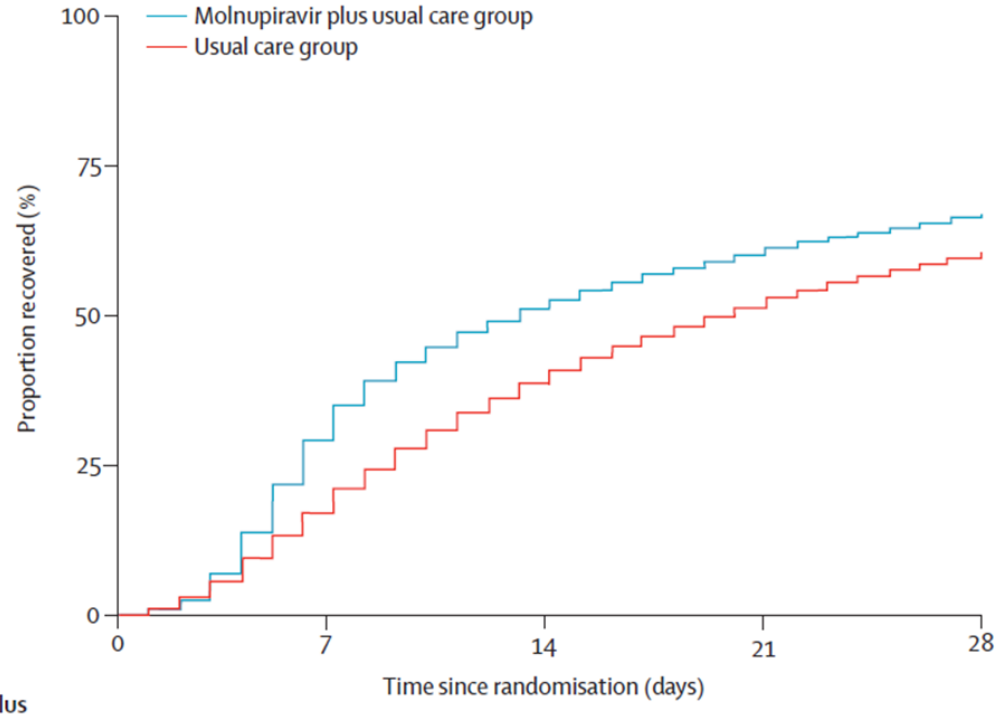
- Preferred Reporting Items for Systematic reviews and Meta- Analysis-Rapid Review guideline
- Twenty-three studies involving 314 353 patients were included in the analysis

Outcome	Odds Ratio (OR)	95% Confidence Interval (CI)
Mortality Rate	0.25	0.14–0.45
Hospitalization Rate	0.40	0.24-0.69
Mortality or Hospitalization Rate	0.17	0.06-0.46

Amani B, Amani B. Efficacy and safety of nirmatrelvir/ritonavir (Paxlovid) for COVID-19: a rapid review and meta-analysis. *J Med Virol*. 2023;95:e28441.doi:10.1002/jmv.28441

Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

- Multicenter, open-label, multigroup, prospective, platform adaptive randomized controlled trial between Dec 8, 2021, and April 27, 2022
- Mean age of the population = 56.6 years (SD 12.6); 94% had had at least three doses of COVID-19 vaccine
- Molnupiravir did not reduce the frequency of COVID-19-associated hospitalizations or death (1% in each group)
- Participants in the molnupiravir plus usual group more often reported early sustained recovery



Molnupiravir plus usual care group					
Not yet recovered	12 403	7934	4661	3221	2168
Censored	0	141	260	387	594
Recovered	0	4328	7482	8795	9641
Usual care group					
Not yet recovered	12 140	9411	6121	4175	2774
Censored	0	271	542	781	1113
Recovered	0	2458	5477	7184	8253

Butler et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial *Lancet* 2023; 401: 281–93

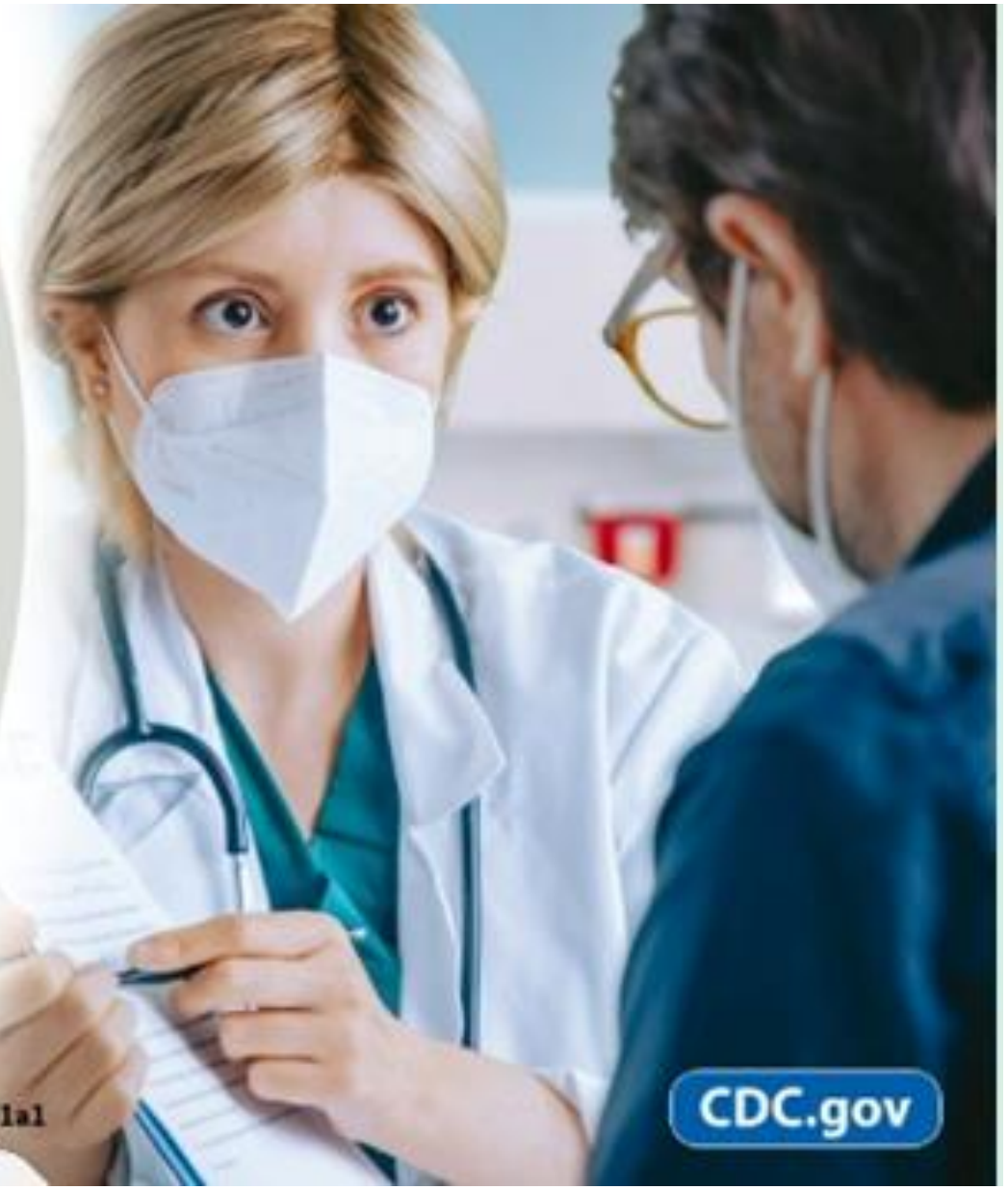
Treatment Considerations

Antiviral treatment for COVID-19 is lifesaving

Current evidence suggests:

- Patients with COVID-19 rebound
  - experience return of mild symptoms 3-7 days after initial illness or positive test
  - might or might not have taken antiviral treatment
- No hospitalizations or deaths due to rebound were reported in the reviewed studies

Antivirals should be prescribed to all eligible COVID-19 patients



MMWR

bit.ly/mm7251a1

DECEMBER 22, 2023

CDC.gov

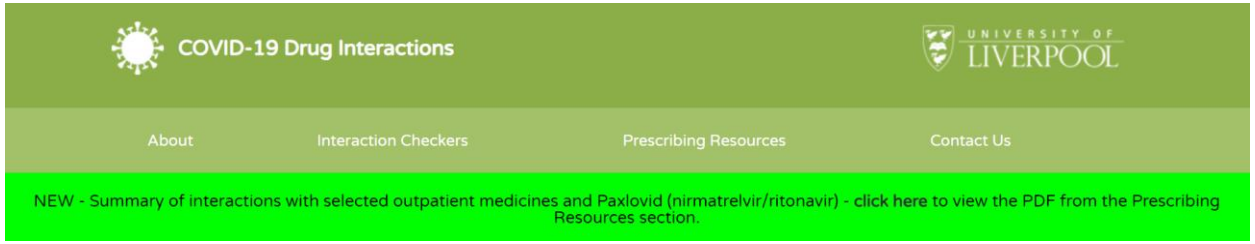
SARS-CoV-2 Rebound With and Without Use of COVID-19 Oral Antivirals. *MMWR*.2023

Ritonavir-boosted Nirmatrelvir: Drug-Drug Interactions

NIH Guidelines
Drug-Drug Interactions Chapter

https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

Liverpool COVID-19
Drug Interactions Database



https://covid19-druginteractions.org/checker

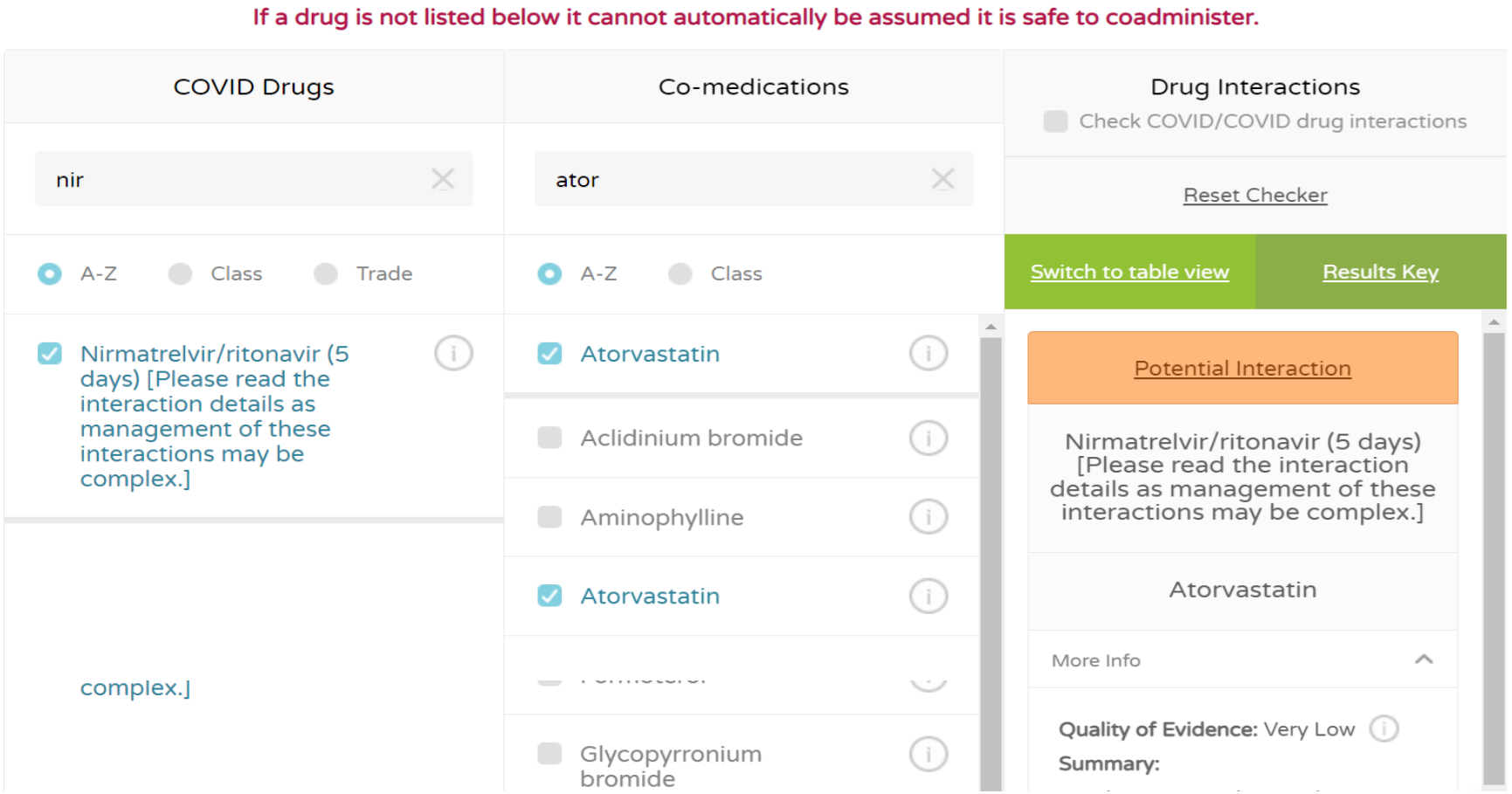
FDA Website Resources

- Fact Sheet for Health Care Providers: https://www.fda.gov/media/155050/download
- PAXLOVID Patient Eligibility Screening Checklist Tool for Prescribers: https://www.fda.gov/media/158165/download

Ritonavir-boosted Nirmatrelvir: Drug-Drug Interactions

Liverpool COVID-19 Drug Interactions Database

https://covid19-druginteractions.org/checker



Paxlovid: Drug-drug interactions

Prescribe Alternative COVID-19 Therapy

Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-Infectives

- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Immunosuppressants

- Voclosporin

Cardiovascular

- Amiodarone
- Clopidogrel[a,b]
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine
- Propafenone
- Quinidine

Neuropsychiatric

- Clozapine
- Lurasidone
- Midazolam (oral)
- Pimozide

Pulmonary Hypertension[c]

- Sildenafil
- Tadalafil
- Vardenafil

Miscellaneous

- Bosentan
- Certain chemotherapeutic agents[d]
- Ergot derivatives
- Lumacaftor/ivacaftor
- St. John's wort
- Tolvaptan

Temporarily Withhold Concomitant Medication, if Clinically Appropriate

Anticoagulants

- Rivaroxaban[e]

Anti-Infectives

- Erythromycin

BPH

- Alfuzosin
- Silodosin

Cardiovascular

- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[f]

- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifiers

- Atorvastatin[g]
- Lomitapide
- Lovastatin[g]
- Rosuvastatin[g]
- Simvastatin[g]

Migraine

- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric

- Suvorexant
- Triazolam[h]

Erectile Dysfunction

- Avanafil

Respiratory

- Salmeterol

Miscellaneous

- Certain chemotherapeutic agents[d]
- Colchicine[i]
- Finerenone
- Flibanserin
- Naloxegol

Paxlovid Drug-Drug Interactions | COVID-19 Treatment Guidelines (nih.gov)

Pharmacist Decision Making Support for Paxlovid (nirmatrelvir/ritonavir)

Does patient meet ALL of the following eligibility criteria?

- ❑ **Patient reports positive FDA-authorized COVID-19 viral test**
  A COVID-19 test may be administered by the pharmacy to determine if the patient is positive for COVID-19 disease. Patients who report a positive home test result from a rapid antigen diagnostic test or a PCR test meet this requirement.
- ❑ **Patient reports the onset of one or more mild to moderate symptom(s) of COVID-19 disease within the last 5 days**
- ❑ **Patient is NOT experiencing one or more symptom(s) of severe COVID-19 disease**
  Symptoms of sever COVID-19 disease include:
  - SpO2 ≤ 94% on room air
  - Respiratory frequency of >30 bpm
- ❑ **Patient reports at least one or more of the following mild to moderate symptoms of COVID-19 disease**
  - Oxygen saturation ≥94% on room air
  - Fever
  - Cough
  - Sore throat
  - Malaise
  - Headache
  - Muscle pain
  - Nausea/vomiting
  - Diarrhea
  - Loss of taste/smell

  Reference NIH's overview of the Clinical Spectrum of SARS-CoV-2 Infection for more information about how mild to moderate disease is defined.
- ❑ **Patient is ≥12 years of age and weighs ≥40 kg**
- ❑ **Presence of at least one or more of the following risk factors for progression to severe COVID-19 disease**
  - Older Age (≥65 years old)
  - Respiratory Disease
  - Cardiovascular Disease
  - Diabetes
  - Obesity (BMI ≥ 30kg/m2)
  - Overweight (BMI > 25)
  - Chronic Kidney Disease
  - Sickle Cell Disease
  - Immunocompromised

If YES: Proceed to next question.

If NO: The patient is not eligible to receive nirmatrelvir/ritonavir. Counsel patient on the availability of other treatment options and to seek medical attention if their symptoms worsen.

Self-knowledge Check:

Based on current evidence, what is the most effective public health intervention to prevent long COVID?

A. Convalescent therapy
B. COVID-19 vaccination
C. Early antiviral therapy
D. Hand washing
E. Masking

Answer:

Based on current evidence, what is the most effective public health intervention to prevent long COVID?

A. Convalescent therapy
B. **COVID-19 vaccination**
C. Early antiviral therapy
D. Antibiotics
E. Masking

Rationale: Current evidence shows that persons who received two doses of the COVID-19 vaccine had 36-40% lower odds of developing long COVID.

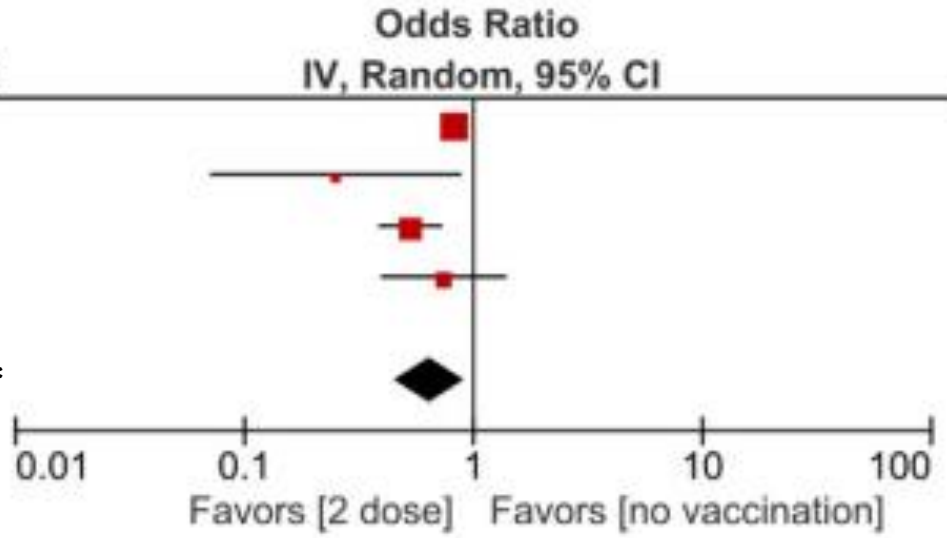
Protective effect of COVID-19 vaccination against long COVID syndrome: A systematic review and meta-analysis

- Vaccination before SARS-CoV-2 infection was associated with a lower risk of long COVID
- Vaccination after SARS-CoV-2 infection was not associated with symptomatic changes of long COVID

Table. Two-dose vaccination versus one-dose vaccination

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Al-Aly [16]	-0.1936	0.0134	42.0%	0.82 [0.80, 0.85]
Azzolini [17]	-1.3863	0.6363	7.0%	0.25 [0.07, 0.87]
Emecen [23]	-0.6349	0.1563	32.2%	0.53 [0.39, 0.72]
Meza-Torres [22]	-0.3011	0.3142	18.8%	0.74 [0.40, 1.37]
Total (95% CI)			**100.0%**	**0.64 [0.45, 0.92]***

Heterogeneity: Tau² = 0.08; Chi² = 11.52, df = 3 (P = 0.009); I² = 74%
Test for overall effect: Z = 2.39 (P = 0.02)



*Similar findings comparing two-dose vaccination to one-dose vaccination: OR=0.60 [0.43-0.83]

Wantanabe et al., Protective effect of COVID-19 vaccination against long COVID syndrome: A systematic review and meta-analysis. *Vaccine*.2023

Vaccination is the most effective way to protect patients against COVID-19

- 1 updated COVID-19 dose for everyone 6 months and older[1]
- No additional dose for adults 65+ recommended at this time
- Children 6 months through 4 years and immunocompromised patients may need additional doses

[1]Unvaccinated people 12 years and over who choose to get Novavax should get 2 doses of updated Novavax vaccine

Use of COVID-19 Vaccines in the United States: Interim Clinical Considerations

Programs Provide Free or Low-cost Options for COVID-19 Outpatient Antiviral Therapeutics

PAXLOVID (nirmatrelvir packaged with ritonavir)

- Patients, caregivers, provider or pharmacists can enroll patients for these programs for free or low cost Paxlovid via Pfizer's Paxcess website. No one needs to pay full price for Paxlovid. Everyone on Medicare, Medicaid and uninsured have access for free, either directly at the counter or via enrollment in the PAP.
- Publicly insured and uninsured patients receive **free Paxlovid through December 31, 2024**, with the U.S. government (USG) **Patient Assistance Program (PAP)** operated by Pfizer. This program uses USG-procured Paxlovid inventory and includes any patient who is:
  - Publicly insured, including through Medicaid or Medicare (with or without Part D, Part B, or Part C and inclusive of Medicare Advantage)
  - Uninsured
- Patients with private (commercial) insurance can use the Pfizer co-pay savings program for Paxlovid at little or no cost

LAGEVRIO (molnupiravir)

- The MerckHelps Patient Assistance Program provides Lagevrio free of charge to patients who meet eligibility criteria and who, without assistance, could not otherwise afford the product. Learn more at MerckHelps.com/Lagevrio

In addition, federal entities, including HRSA-supported health centers, Indian Health Service health centers, and others, have continued access to free, USG-procured Paxlovid and Lagevrio supply for their patients.

VEKLURY (remdesivir) for outpatient use

- Gilead has an Advancing Access® program to help eligible patients. Learn more here: Advancing Access® program

Influenza Testing and Antiviral Treatment

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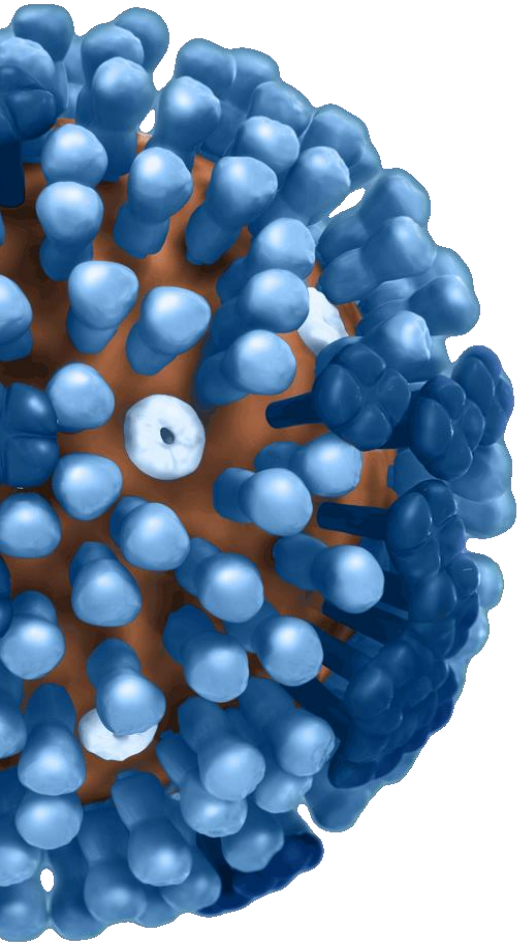
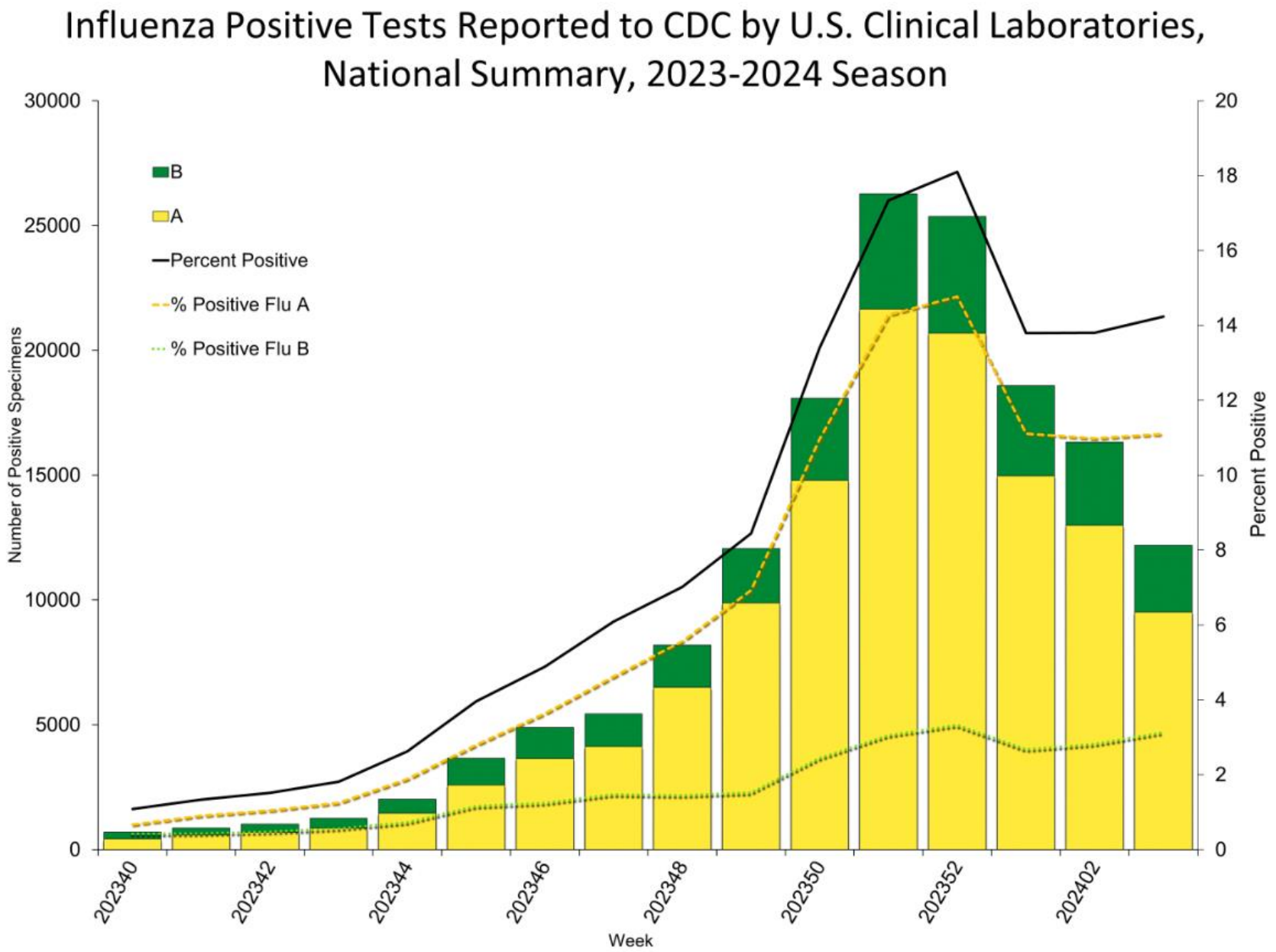
Chief Medical Officer
Influenza Division, NCIRD, CDC

February 1, 2024



Influenza Activity and Disease Burden



Public health laboratory testing

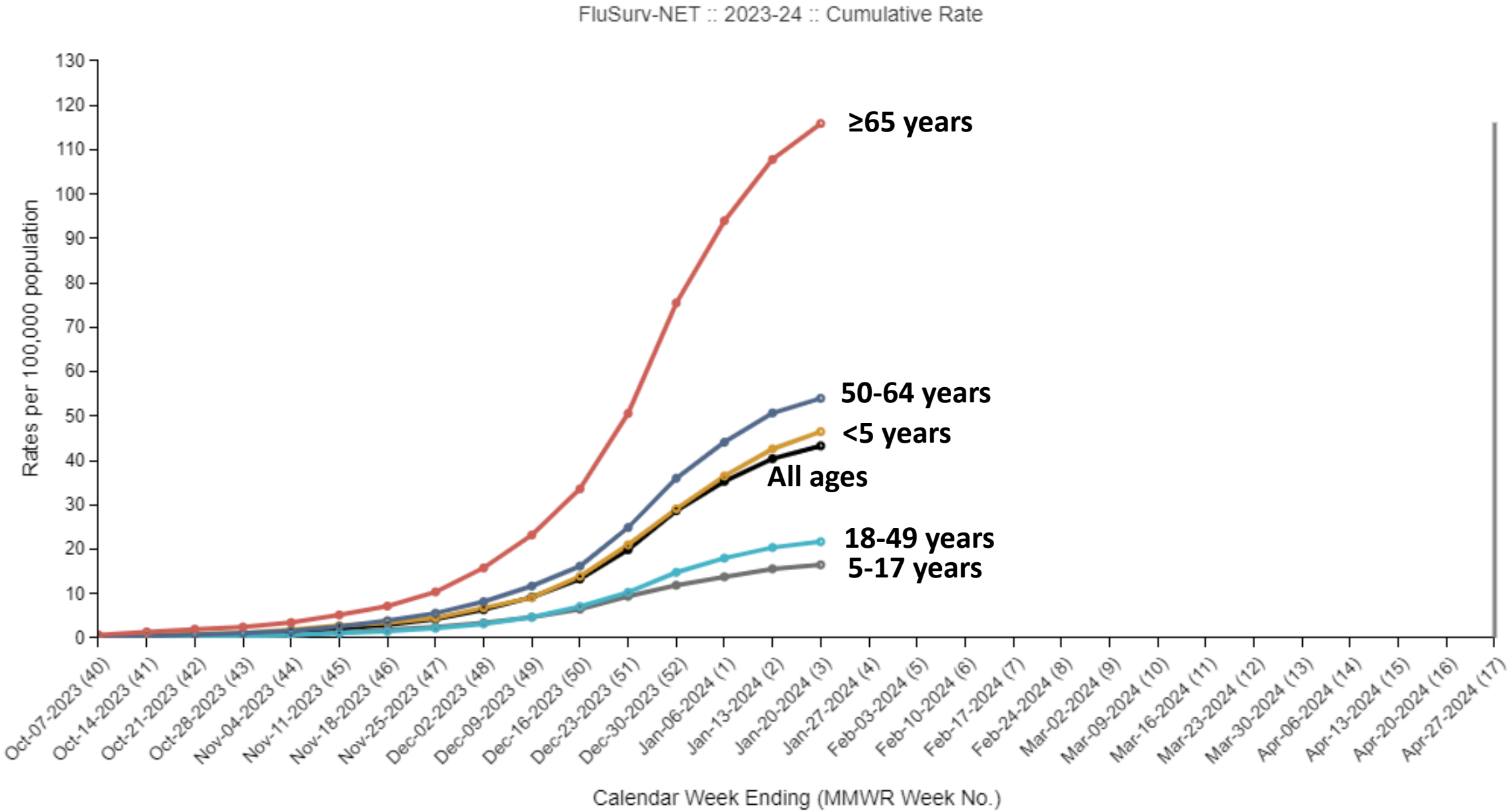
Influenza A: 82.6%

- **A(H1N1)pdm09: 80.1%**
- A(H3N2): 19.9%

Influenza B: 17.4%

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

Lab-confirmed Influenza Hospitalization Rates by Age Group, 2023-2024



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

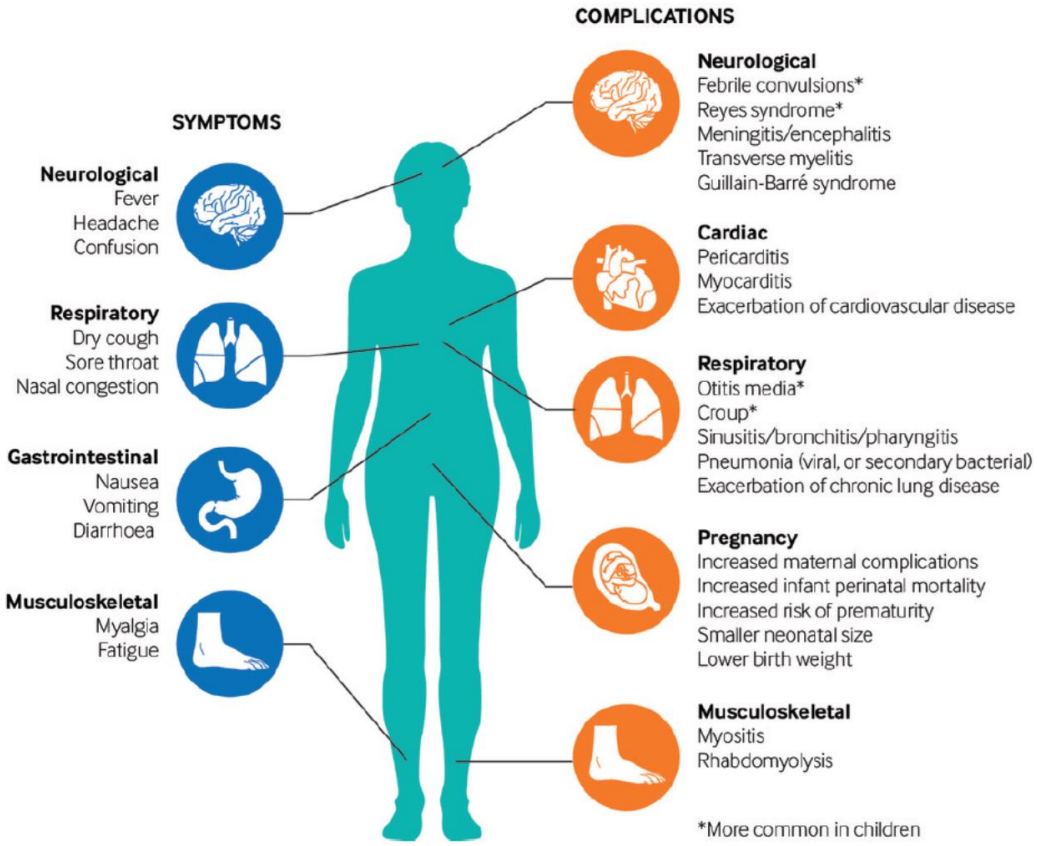
Spectrum of Influenza Virus Infection

- Disease severity and clinical manifestations vary by age, host factors, immunity, influenza virus type/subtype
  - **Asymptomatic infection**
  - **Uncomplicated illness** [incubation period: 1-2 days (range 1-3)]
    - Upper respiratory tract illness (with or without fever)
    - Fever may not be present (such as in elderly, immunosuppressed)
    - Typical: abrupt onset of fever, cough, chills, myalgia, fatigue, headache, sore throat, runny nose
    - Gastrointestinal symptoms (more common in young children)
    - Infants can have fever alone, irritability, may not have respiratory symptoms
  - **Complicated illness**

Uyeki Clin Infect Dis 2019; Uyeki Lancet 2022

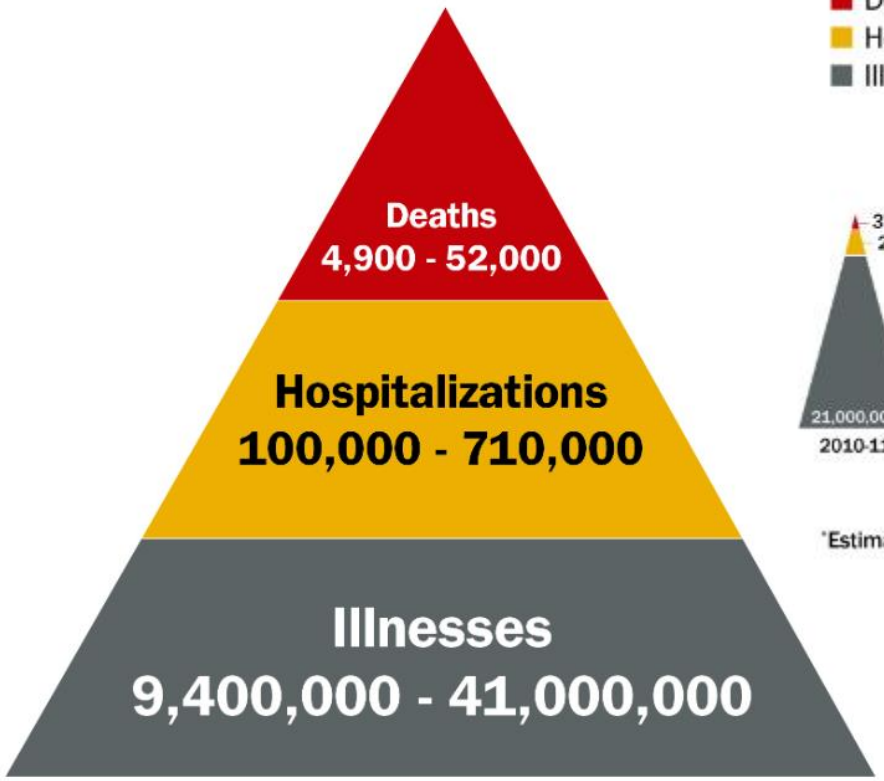
Influenza Complications

- **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 Streptococcus
  - **Musculoskeletal:** myositis, rhabdomyolysis
  - **Multi-organ failure** (respiratory, renal failure, septic shock)
  - **Healthcare-associated infections** (e.g. bacterial or fungal ventilator-associated pneumonia)

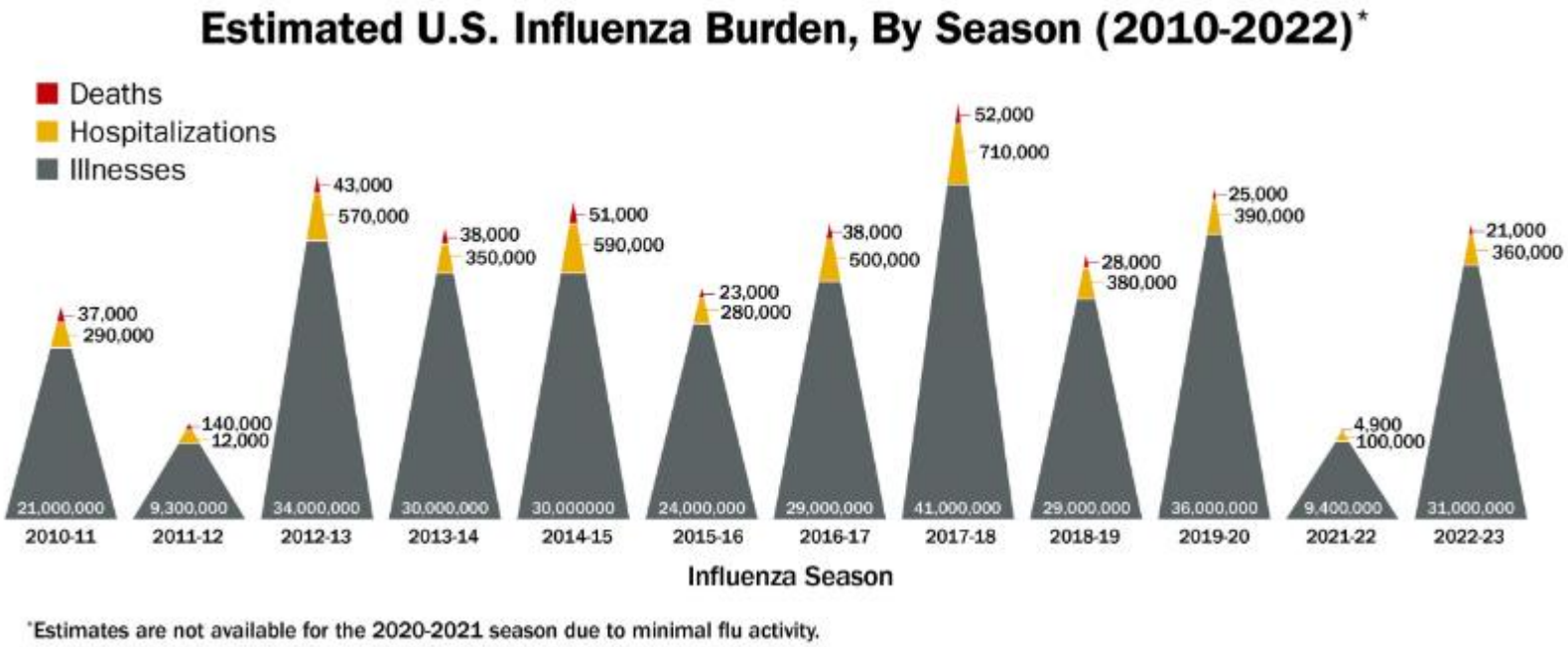


Ghebrehewet BMJ 2016

Estimated Influenza Disease Burden



Estimated Influenza Disease Burden 2010 - 2022



- **Seasonal influenza epidemics vary in severity**

2023-2024 (preliminary estimates as of January 20, 2024):

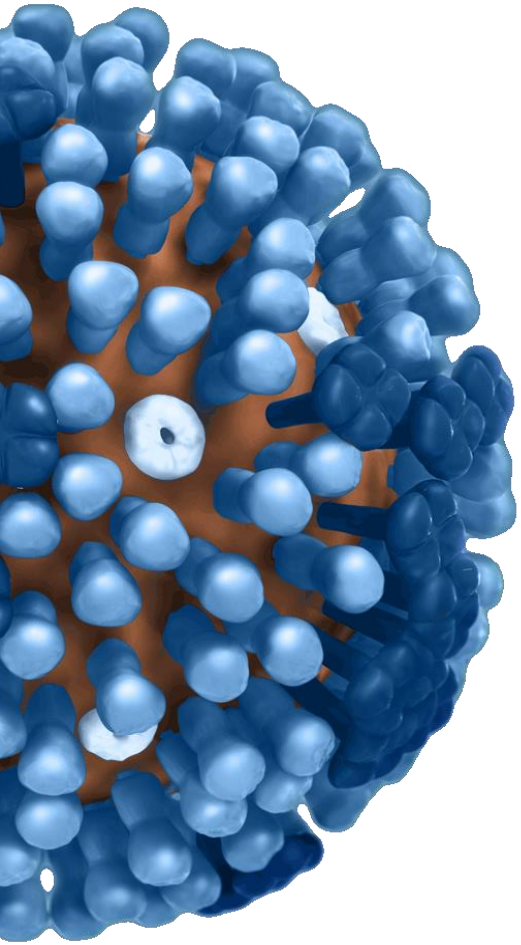
* 18-35 million illnesses
* 8.4-16 million medical visits
* 210,000 to 440,000 hospitalizations
* 13,000 to 38,000 deaths

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

Groups at Increased Risk for Influenza Complications and Severe Illness

- **Children <2 years and adults ≥65 years**
- **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's 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**

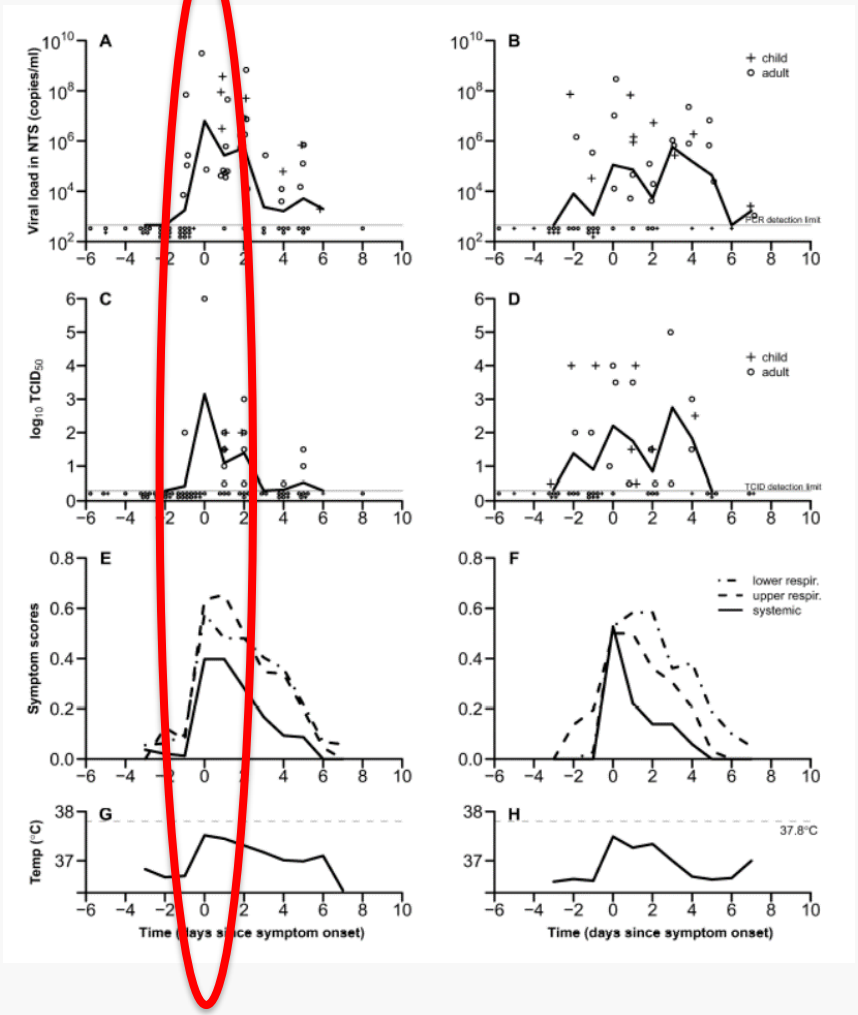
https://www.cdc.gov/flu/highrisk/index.htm



Influenza Testing

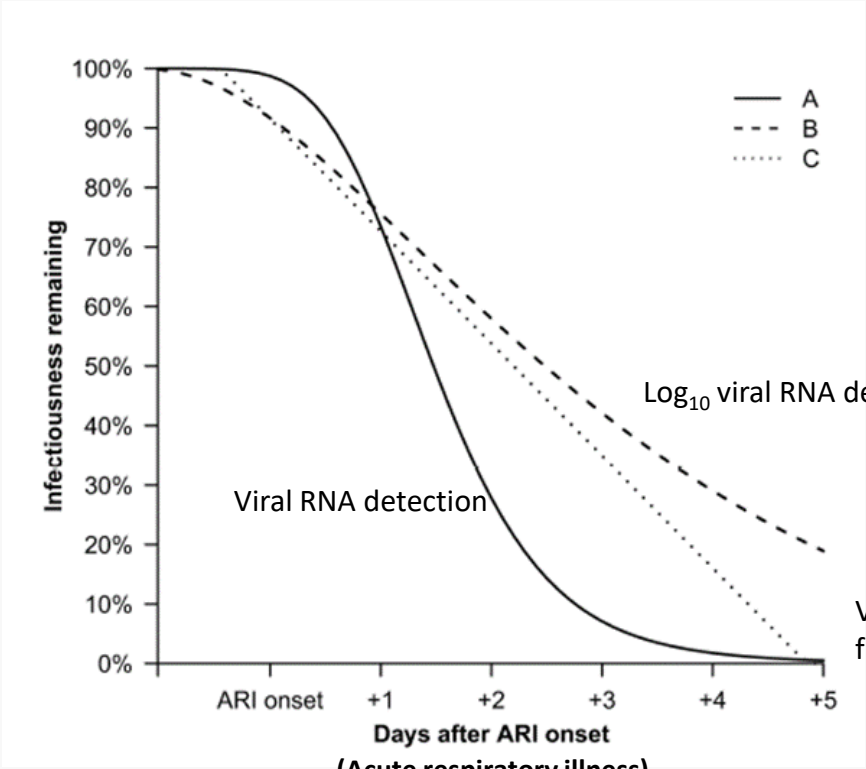
Influenza Viral Shedding Typically Peaks Within 24 Hours of Illness Onset

Influenza A Virus Infection **Influenza B Virus Infection**



- **Influenza viruses can be detected in the upper respiratory tract one day before illness onset; virus levels peak within 24 hours after onset**
- **Highest infectious period is within 3 days after onset**
  - **Young children can be infectious for longer periods**
  - **Critically ill patients might have longer influenza viral replication in the lower respiratory tract**

Influenza viral RNA detection



Viral RNA >900 copies/ml under fitted curve

Lau J Infect Dis 2010

Respiratory Specimens for Detecting Influenza Viruses

- **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 viral 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 Crit Care 2009; Fleury Eurosurveillance 2009; Blyth NEJM 2009

Influenza Tests Available 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**
    - **Antigen detection** (FDA-cleared single-plex, multiplex)
      - FDA-authorized multiplex assays (e.g., also detect SARS-CoV-2)
    - **Nucleic acid detection** (FDA-cleared single-plex, multiplex)
      - FDA-authorized multiplex assays (e.g., also detect SARS-CoV-2, some detect RSV)
      - One test is FDA-authorized for home use (self-collected anterior nasal swabs (≥14 years) or adult-collected (≥2 years)
    - **Point-of-care assays** (CLIA-waived)
    - **Moderately complex** (requires clinical laboratory)
    - **Highly complex** (large clinical laboratories, public health labs)

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
(e.g., Influenza A/B, SARS-CoV-2, RSV, other viral targets)

***Proper interpretation of test results is very important, especially interpreting negative results**

Self-knowledge Check: The following statements regarding influenza testing are true EXCEPT:

A. A nasopharyngeal swab is the preferred respiratory specimen to detect influenza viruses.
B. Molecular assays have high sensitivity to detect influenza viruses in respiratory specimens.
C. Rapid antigen tests and molecular assays can detect influenza viruses in saliva specimens up to 7 days after symptom onset.
D. Some molecular assays can yield results within 30 minutes.
E. False positive results are uncommon with rapid antigen tests and molecular assays because of their high specificities.

Answer: The following statements regarding influenza testing are true EXCEPT:

A. A nasopharyngeal swab is the preferred respiratory specimen to detect influenza viruses.
B. Molecular assays have high sensitivity to detect influenza viruses in respiratory specimens.
C. **Rapid antigen tests and molecular assays can detect influenza viruses in saliva specimens up to 7 days after symptom onset.**
D. Some molecular assays can yield results within 30 minutes.
E. False positive results are uncommon with rapid antigen tests and molecular assays because of their high specificities.

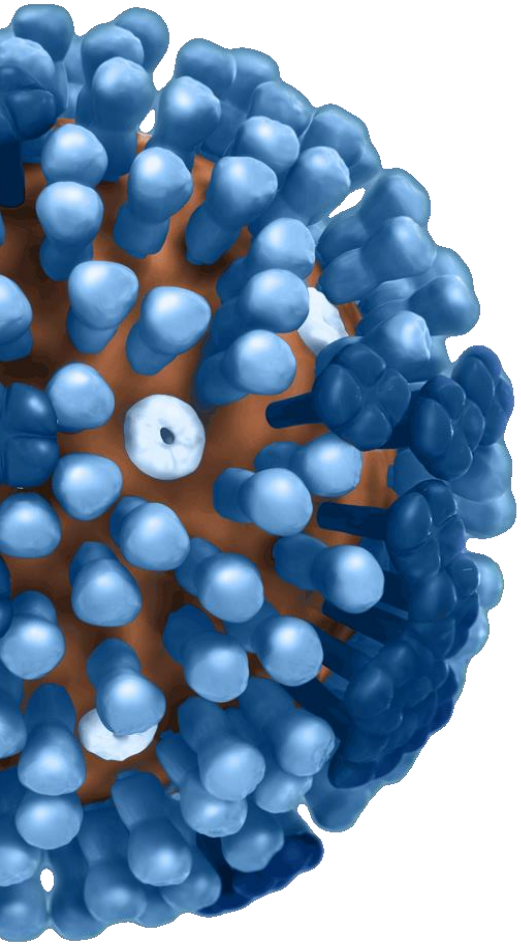
Rationale: saliva specimens are not recommended for detection of influenza viruses

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 IDSA 2018 Influenza Clinical Practice Guidelines Clin Infect Dis 2019



Antiviral Treatment

Antiviral Treatment

Focused 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*

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

Recommended Antivirals for Treatment of Influenza, U.S. 2023-2024

Four FDA-approved antivirals are recommended (no evidence of resistance among circulating seasonal influenza A and B viruses)

- **All have demonstrated efficacy and are FDA-approved for early treatment (<2 days of illness onset) in outpatients with uncomplicated influenza**
- **Neuraminidase inhibitors (NAIs): block release of influenza viruses from infected cells**
  - **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: inhibit influenza viral replication**
  - **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

Meta-analyses of Oseltamivir Efficacy 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; **Increased risk of vomiting** RR 1.63; 95% CI 1.3-2.04)
    - **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)
    - **Increased risk of nausea** (RR 1.60; 95% CI 1.29-1.99) and **vomiting** (RR 2.43; 95% CI: 1.83-3.23)

Malosh Clinical Infect Dis 2018; Dobson Lancet 2015

Baloxavir Efficacy in Uncomplicated Influenza

RCTs: 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 adolescents and 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)
      - **Baloxavir significantly reduced influenza viral RNA levels at 24 hours, and reduced infectious virus detection versus oseltamivir (24 hours vs. 72 hours, p<0.001)**
    - **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 Ped Infect Dis J 2020; Hayden NEJM 2018; Ison Lancet Infect Dis 2020

Special Populations

CDC Recommendations

- **Pregnant People**
  - **Oseltamivir is recommended for treatment of pregnant people and up to 2 weeks postpartum**
    - **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 (e.g., oseltamivir)**
  - **Baloxavir is *not recommended* (greater risk of resistance emergence than oseltamivir)**

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

Reminder: Vaccination is the most effective way to protect patients against Influenza

- One dose of influenza vaccine for everyone ≥6 months
- Children 6 months through 8 years may need 1 additional dose
- High-dose, recombinant, or adjuvanted influenza vaccines are preferred for **adults ≥65 years**

Resources

Influenza Testing

- Information for Clinicians on Influenza Virus Testing: https://www.cdc.gov/flu/professionals/diagnosis/index.htm
- Testing and Treatment of Influenza When SARS-CoV-2 and Influenza Viruses are Co-circulating
  - Clinical guidance for hospitalized and non-hospitalized patients: https://www.cdc.gov/flu/professionals/diagnosis/testing-guidance-for-clinicians.htm
  - Clinical Guidance for Patients with Acute Respiratory Illness Being Hospitalized: https://www.cdc.gov/flu/professionals/diagnosis/testing-guidance-for-clinicians-hospitalized.htm
  - Clinical Guidance for Patients with Acute Respiratory Illness Not Being Hospitalized: https://www.cdc.gov/flu/professionals/diagnosis/testing-guidance-for-outpatient.htm
  - Testing and Management Considerations for Nursing Home Residents with Acute Respiratory Illness: https://www.cdc.gov/flu/professionals/diagnosis/testing-management-considerations-nursinghomes.htm

Antiviral Treatment of Influenza

- Antiviral treatment recommendations: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
- IDSA Influenza Clinical Practice Guidelines: https://academic.oup.com/cid/article/68/6/e1/5251935

Resources Continued

- Interim Clinical Considerations for COVID-19 Treatment in Outpatients
- COVID-19 Treatment blog
- Treatment Options for COVID-19 | HHS/ASPR
- ASPR COVID-19 therapeutics commercialization transition guide
- NIH COVID-19 therapeutics guidelines
- FDA COVID-19 therapeutics
- Test to Treat
- COVID-19 Therapeutics Locator
- Overview of Testing for SARS-CoV-2, the virus that causes COVID-19
- Resources to Prepare for Flu, COVID-19, and RSV | CDC

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.

Joining the Q&A Session

- **Meghan Pennini, Ph.D.**
  Chief Vaccines and Therapeutics Officer
  HHS Coordination Operations and Response Element (H-CORE)
  Administration for Preparedness and Response
  U.S. Department of Health and Human Services

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TRAIN

- **January 1, 2024**: Move from Training and Continuing Education Online (TCEO) to CDC TRAIN (https://www.train.org/cdctrain).

- **Existing Activities**: Continue to use TCEO for existing activities that have CE set to expire in 2024, since these courses will not move to CDC TRAIN. You may also use TCEO for existing activities with CE set to expire in 2025, before the courses transition to CDC TRAIN sometime next year. If you begin one of these courses in TCEO, we will let you know when the course will move to CDC TRAIN.

- **Transcripts & Certificates**: You can access and download CE transcripts and certificates in TCEO through the end of 2025.

- Instructions will be available on both platforms and a learner support team will be available to answer questions.

Continuing Education

- All continuing education for COCA Calls is issued online through CDC TRAIN at CDC TRAIN (https://www.train.org/cdctrain).

- Those who participate in today's COCA Call and wish to receive continuing education please complete the online evaluation by **March 4, 2024,** with the **course code WC4520R-020124.** The **registration code** is **COCA020124.**

- Those who will participate in the on-demand activity and wish to receive continuing education should complete the online evaluation between **March 5, 2024,** and **March 5, 2026,** and use **course code WD4520R-020124.** The **registration code** is **COCA020124.**

Today's COCA Call will be Available to View On-Demand

- **When:** A few hours after the live call ends*
- **What:** Video recording
- **Where:** On the COCA Call webpage
  - https://emergency.cdc.gov/coca/calls/2024/callinfo_020124.asp

A transcript and closed-captioned video will be available shortly after the original video recording posts at the above link.

Upcoming COCA Calls & Additional Resources

- **Date:** Thursday, February 29, 2024
- **Time:** 2:00–3:00 P.M. ET
- **Topic:** Xylazine-adulterated Fentanyl Overdose: Clinical and Public Health Implications

- Continue to visit https://emergency.cdc.gov/coca/ to get more details about upcoming COCA Calls.

- Subscribe to receive notifications about upcoming COCA calls and other COCA products and services at emergency.cdc.gov/coca/subscribe.asp.

Thank you for joining us today!

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TTY: 1-888-232-6348 www.cdc.gov

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