COVID-19: Treatment

Paul E. Sax, M.D.
Clinical Director, Division of Infectious Diseases
Brigham and Women's Hospital
Professor of Medicine, Harvard Medical School
psax@bwh.harvard.edu
@PaulSaxMD

BRIGHAM HEALTH
BRIGHAM AND WOMEN'S
Department of Medicine

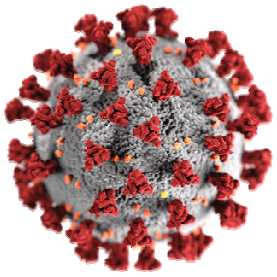
HARVARD MEDICAL SCHOOL
TEACHING AFFILIATE

Disclosures

- None

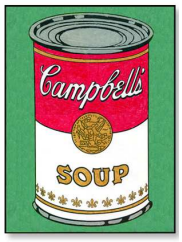
Treatment of COVID-19: Outline

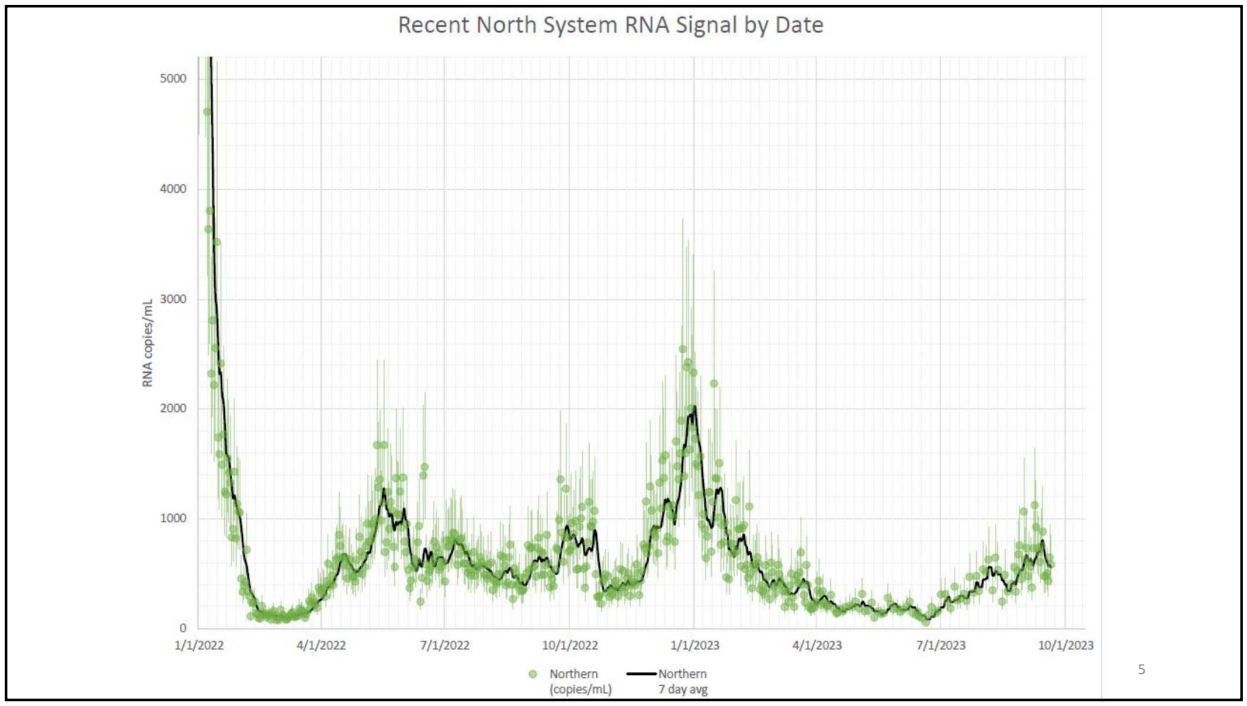
- **What happened in the past year?**
- Clinical presentation and diagnosis
- Treatments available now
- Possible treatments available in the future
- Long Covid

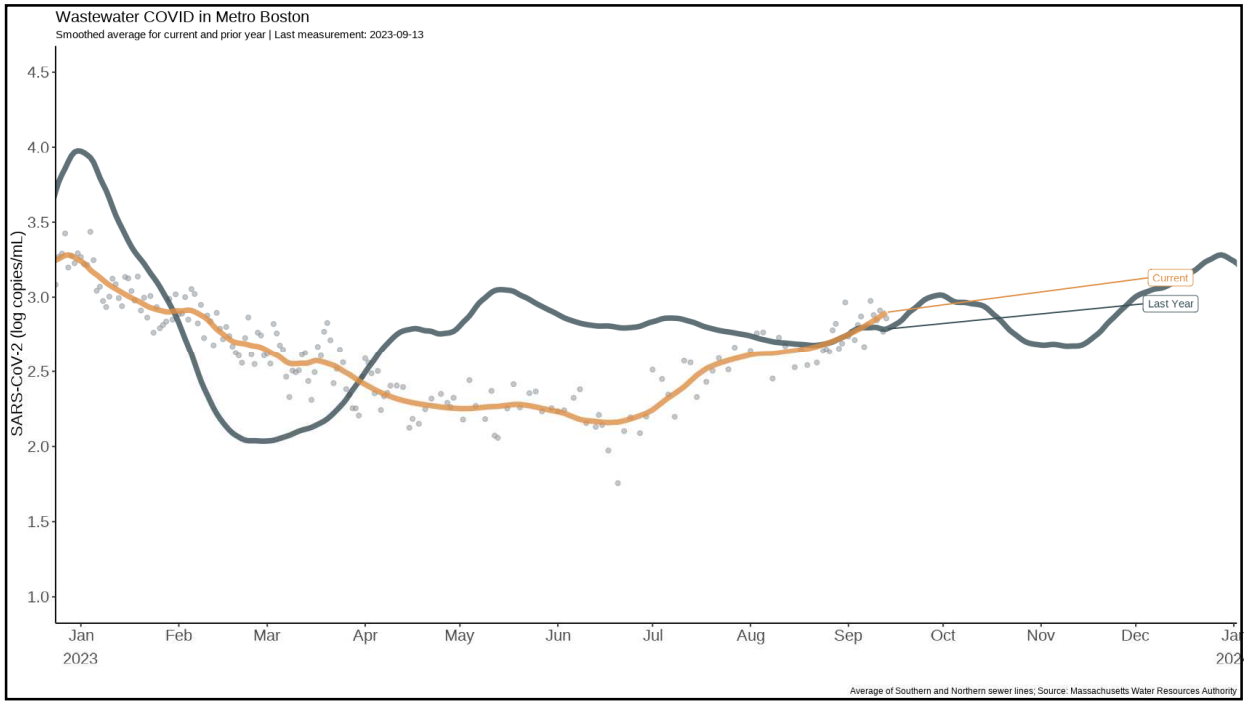


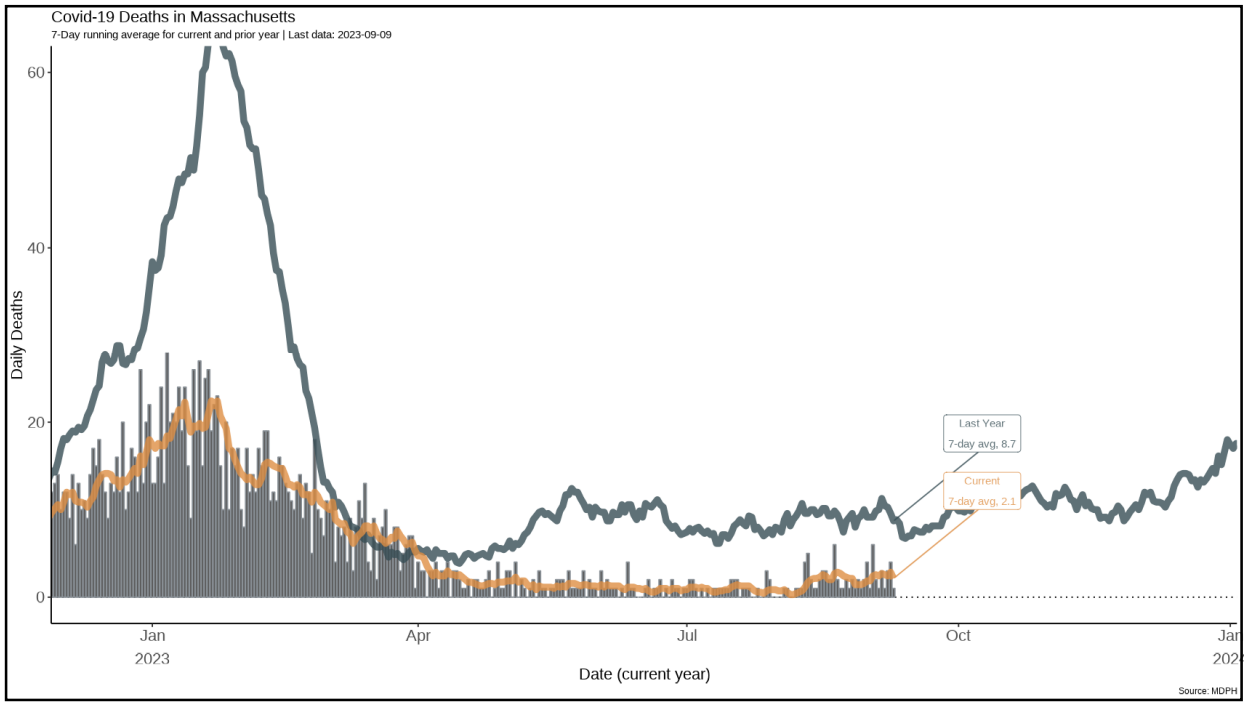
What happened since October 2022?

- Continued dominance Omicron variants, evolving to variant "soup"
- Rise in cases during respiratory virus season – now accompanied by a return of RSV and influenza – as well as late summer
- Decreased per-case severity at the community and hospital level, mostly due to pre-existing immunity from vaccines and/or prior infection
- No available monoclonal antibodies for treatment or prevention
- Ongoing use of outpatient antiviral therapy, in particular nirmatrelvir/ritonavir (Paxlovid)




Recent North System RNA Signal by Date
RNA copies/mL
5000
4000
3000
2000
1000
0
1/1/2022
4/1/2022
7/1/2022
10/1/2022
1/1/2023
4/1/2023
7/1/2023
10/1/2023
Northern (copies/mL)
Northern 7 day avg
5


Wastewater COVID in Metro Boston
Smoothed average for current and prior year | Last measurement: 2023-09-13
SARS-CoV-2 (log copies/mL)
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
Jan 2023
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Current
Last Year
Average of Southern and Northern sewer lines; Source: Massachusetts Water Resources Authority



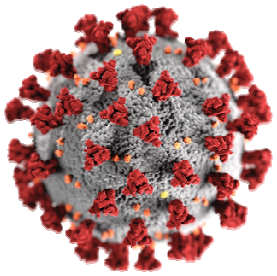
Changes in population-level immunity

RESULTS % of population [95%CI]	Dec 1, 2021	Mar 3, 2022	Nov 9, 2022
Ever infected	59 [47-76]	81 [68-96]	94 [79-99]
Ever exposed	90 [85-95]	97 [94-99]	99 [97-100]
Protected against infection	22 [21-23]	57 [47-69]	63 [51-75]
Protected against severe disease	61 [59-64]	84 [79-90]	89 [83-92]

Klaassen F, et al. Clin Infect Dis 2023.

Treatment of COVID-19: Outline

- What happened in the past year?
- **Clinical presentation and diagnosis**
- Treatments available now
- Possible treatments available in the future
- Long Covid



Case presentation: Late summer 2021, Delta wave

- 55-year-old woman with cough, shortness of breath, and fever
- Chose not to be vaccinated – "I have my reasons"
- Onset of malaise, headache, sore throat, and chills 7 days prior to admission
- Last 24 hours before admission – escalating cough and shortness of breath
- PMHx: obesity (BMI 41), diabetes, hypertension, chronic renal disease
- Daughter insisted she go to the hospital when she couldn't complete sentences over the phone
- Exam: T 101.4, HR 110, BP 170/110, RR 20, RA O2 sat 91%

Case presentation: Today

- 64-year-old man admitted with shortness of breath
- Two prior admissions for congestive heart failure with preserved ejection fraction – this presentation feels the same
- Mild URI symptoms – home COVID-19 antigen test negative x 1
- PMHx: obesity (BMI 41), diabetes, hypertension, chronic renal disease; received initial COVID-19 vaccine series plus 1 booster in February 2022
- Exam: T 99.4, HR 110, BP 170/110, RR 20, RA O2 sat 94%
- CXR: consistent with volume overload
- Admission SARS-CoV-2 PCR: ***positive***

Question

- What is the most likely reason his home COVID-19 antigen test was negative?

A. Insufficient viral replication to trigger positive result
B. Non-specific inhibitory factors causing false-negative results
C. Poor performance of antigen tests with Omicron variant
D. Patient error in performing the test

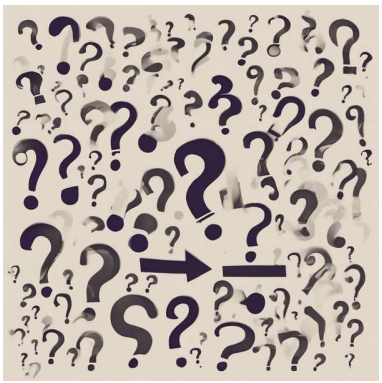
Question

- What is the most likely reason his home COVID-19 antigen test was negative?

A. Insufficient viral replication to trigger positive result
B. Non-specific inhibitory factors causing false-negative results
C. Poor performance of antigen tests with Omicron variant
D. Patient error in performing the test

Questions to consider

- Is this an admission “with” or “for” Covid?
- Why was his home antigen test negative?
- What treatment should he receive, if any?
- What treatments will be available in the future?
- What is his risk of getting Long Covid?



Types of tests for SARS-CoV-2

- **PCR:** detects the presence of viral RNA, indicating infection; gold standard for diagnosis; more broadly called “nucleic acid amplification test” (NAAT)
- **Antigen assays:** immunoassays that detect the presence of viral antigens, indicating infection
- **Antibody assays:** detect IgM and IgG antibodies against the virus, indicating past infection and immune response; useful for COVID-19 surveillance and epidemiology

Overview of Testing for SARS-CoV-2 (COVID-19). Updated Aug 8 2023.
cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html
fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-first-covid-19-diagnostic-test-using-breath-samples

Common COVID-19 diagnostic methods: NAAT vs antigen testing

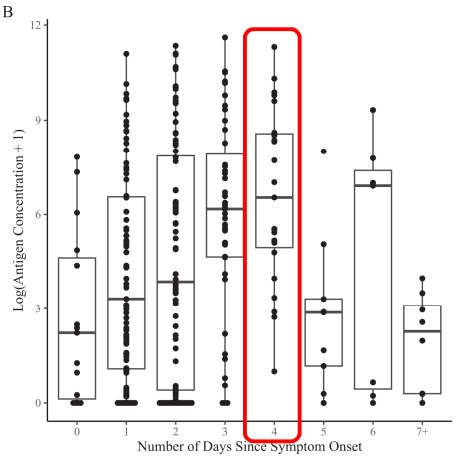
Characteristic	Nucleic Acid Amplification Test (NAAT)	Antigen Test
Intended use	▪ Detect current infection	▪ Detect current infection
Analyte detected	▪ Viral RNA	▪ Viral antigens
Specimen types	▪ Nasal, nasopharyngeal, sputum, saliva	▪ Nasal, nasopharyngeal
Sensitivity	▪ Generally high (68% to 100%)	▪ Moderate (63.7%-79%)
Specificity	▪ High (92% to 100%)	▪ High (98.5%-99.8%)
Test complexity	▪ Varies by test	▪ Relatively easy to use
Authorized for PoC	▪ Most are not, some are	▪ Most are, some are not
Turnaround time	▪ 15 min to >2 days	▪ 15 min
Cost	▪ Moderate (~ $100/test)	▪ Low (~$5 to $50/test)
Considerations	▪ Primary method for COVID-19 diagnosis with multiple RT-PCR kits available ▪ SARS-CoV-2 RNA undetectable by ~Day 14 after onset of illness in some cases/samples	▪ Reduced sensitivity vs PCR may result in false negatives ▪ At-home tests authorized by FDA

Udugama. ACS Nano. 2020;14:3822. Lee. Front Immunol. 2020;11:879.
CDC. Guidance for antigen testing for SARS-CoV-2. Last updated April 4, 2022.

Viral kinetics of SARS-CoV-2 in immune individuals

- Newly-diagnosed patients (n=348) serially assessed with PCR and rapid antigen testing
- Viral loads peaked on day 4 of symptoms
- Rapid antigen tests were 30% positive on day 1, 93% positive on day 4

Immunity = "New Normal"



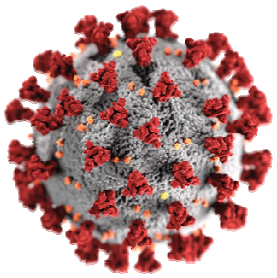
Frediana JK, et al. Clin Infect Dis 2023.

Diagnostic accuracy of PCR and antigen: Key points

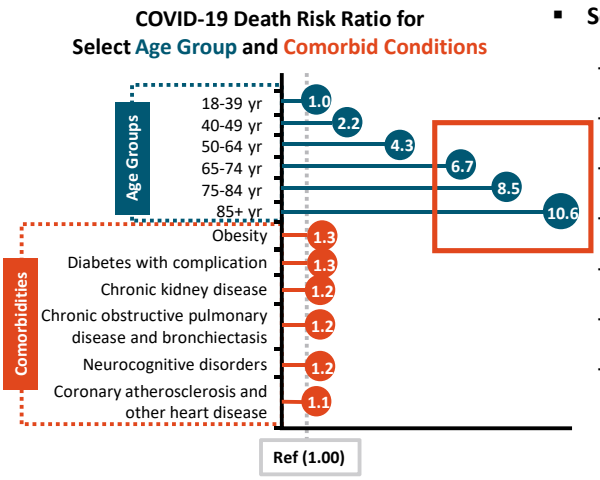
- Most accurate if performed on patients with symptoms consistent with COVID-19
- If antigen is positive in a patient with symptoms, no further testing required for diagnosis
- For all disease status, window from time of symptom onset until first positive test is longer now than at the start of the pandemic, and for antigen test than for PCR – *repeat testing may be necessary*
- After COVID-19 – PCR may stay positive for weeks, *do not use as a test of disease resolution*
- PCR "cycle threshold" sometimes useful (<25, 25-35, >35 as an approximation of high, moderate, and low viral replication)

Treatment of COVID-19: Outline

- What happened in the past year?
- Clinical presentation and diagnosis
- **Treatments available now**
- Possible treatments available in the future
- Long Covid



Prioritize treatment of high-risk patients – especially the old and very old



- **Selected other high-risk criteria**
  - Chronic pulmonary disease
  - Overweight or obese
  - Chronic kidney disease
  - Cardiovascular disease
  - Neurologic disease
  - HIV
  - Pregnancy
  - Tobacco smoker
  - Immunosuppression
  - Sickle cell disease
  - Diabetes
  - Active cancer

cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

COVID-19: NIH Treatment Guidelines

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy	
	Clinical Scenario	**Recommendation**
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other systemic corticosteroids (AIII)** for the treatment of COVID-19.[b]
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir[c] (BIII)**

National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov. Last updated Aug 2022.

Available treatments for COVID-19

Outpatients

- Remdesivir
- Nirmatrelvir
- Molnupiravir

Inpatients

- Remdesivir
- Nirmatrelvir
- Dexamethasone
- Tocilizumab
- Baracitinib

NIH Guidelines: Management of non-hospitalized patients with COVID-19

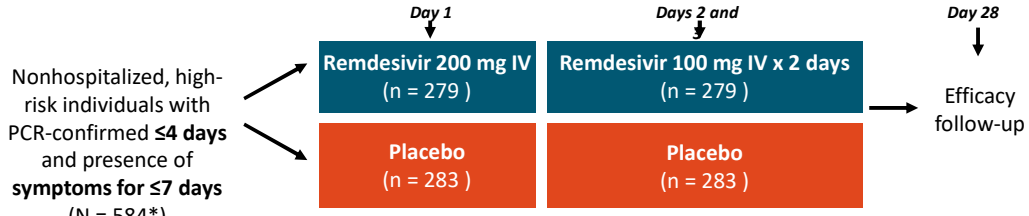
Patient Population	NIH Guidance	Treatment
▪ At **high risk** of progressing to severe COVID-19 and **not** requiring supplemental oxygen or hospitalization	Recommends	▪ In order of preference: ▪ **Nirmatrelvir + ritonavir** within 5 days of symptom onset ▪ **Remdesivir** within 7 days of symptom onset ▪ Alternative agent: ▪ **Molnupiravir** (within 5 days of symptom onset)

The panel recommends *against* the use of dexamethasone or other systemic corticosteroids
For inpatients, *only give if requiring oxygen*

NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated July 21, 2023.

PINETREE: Remdesivir in high-risk outpatients

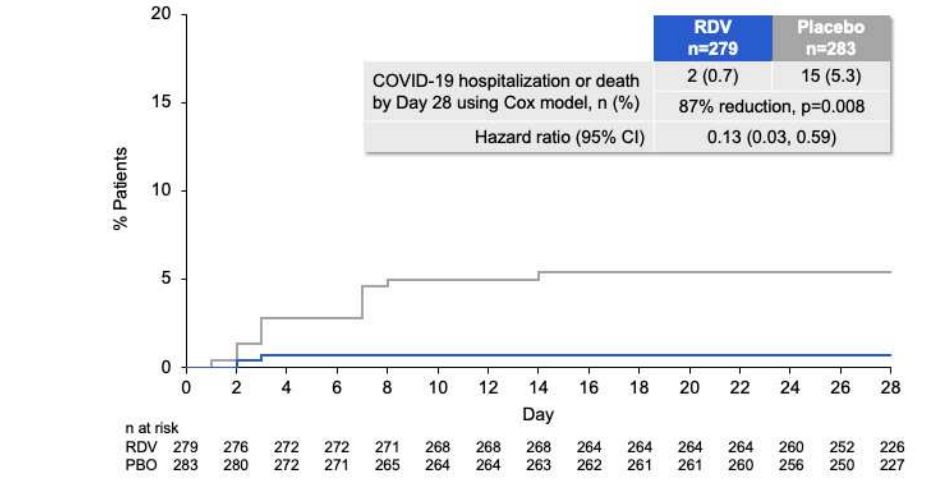
- Randomized, double-blind, placebo-controlled phase III trial at 64 sites in US, Spain, Denmark, and UK



*Study enrollment was terminated early for administrative reasons (slowing enrollment); 562 patients received ≥1 dose of study drug.

- Primary efficacy endpoint: composite COVID-19 hospitalization or all-cause mortality by Day 28
- Primary safety endpoint: proportion with treatment-emergent adverse events

Gottlieb NEJM 2021.



- No death occurred in either group by Day 28

Hazard ratio, 2-sided 95% CI, and p-value estimated using Cox regression with baseline stratification factors as covariates.

Gottlieb NEJM 2021.

Remdesivir

- Outpatient remdesivir effective in reducing risk of hospitalization in high-risk patients
- *Time since symptom onset* is the leading predictor of remdesivir activity
- Implications for inpatient remdesivir
  - Fully FDA approved
  - Useful for early/mild COVID-19 in vulnerable populations – do not delay administration
  - 3 vs 5-day course
  - Pregnant women – labor and delivery units
  - Skilled nursing facilities
  - ***New*: No dose reduction required in renal disease**

Harold Lloyd, *Safety Last!*, 1923

Case outcome

- 64-year-old man admitted with shortness of breath, CHF exacerbation
- Admission SARS-CoV-2 PCR: ***positive***
- Treated with diuresis, IV remdesivir x 3 days – rapid improvement
- Advised to receive updated COVID-19 booster 3 months after recovery

Case presentation

- A 74-year-old man with headache, nasal congestion, chills, and muscle aches
- Symptom onset approximately 3 days ago
- Home antigen test positive
- No shortness of breath
- PMHx: HTN, obesity, atrial fibrillation; received primary 2-dose mRNA COVID vaccine series and two boosters, last fall 2022
- Current medications: lisinopril, chlorthalidone, atorvastatin, apixaban

Question

- What do you recommend?

A. Bebtelovimab
B. Molnupiravir
C. Nirmatrelvir with ritonavir
D. Remdesivir
E. Supportive care only, no antiviral therapy

Question

- What do you recommend?

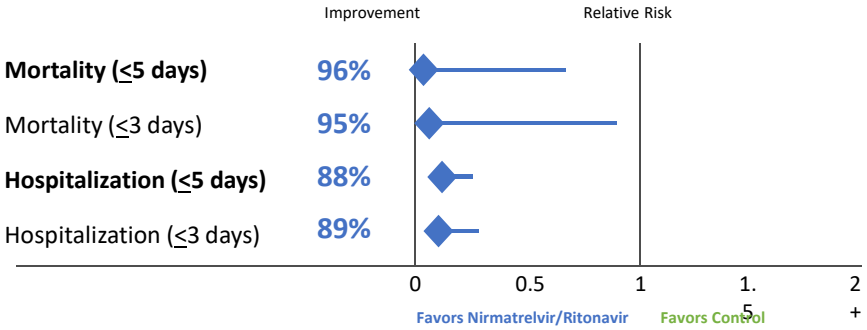
A. Bebtelovimab
B. Molnupiravir
C. Nirmatrelvir with ritonavir
D. Remdesivir
E. Supportive care only, no antiviral therapy

Nirmatrelvir-ritonavir (Paxlovid)

- Oral SARS-CoV-2 protease inhibitor given with pharmacokinetic "booster" (ritonavir) to increase blood levels
- Dosing: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all 3 tablets taken together twice daily for 5 days
  - Dose reduce to 150 mg/100 mg twice daily for eGFR 30-60 mL/min
  - Avoid if eGFR < 30 mL/min
- Proven to improve outcomes in unvaccinated high-risk outpatients with mild-moderate disease
- Government-purchased supply limited how it can be prescribed

EPIC-HR: Oral nirmatrelvir-ritonavir for unvaccinated, high-risk, non-hospitalized adults with COVID-19

Nirmatrelvir/ritonavir vs placebo (N = 2,246) early treatment RCT:
96% lower mortality (*P* = .0005) and **88% lower hospitalization (*P* < .0001)**



Hammond J, et al. *N Engl J Med*. 2022;386:1397-1408.

Nirmatrelvir-ritonavir taste disturbance (dysgeusia)

"I imagine this is what grapefruit juice mixed with soap would taste like."

Gutman R. https://www.theatlantic.com/health/archive/2022/05/pfizer-paxlovid-covid-pill-side-effects/629772.

Drug interactions with nirmatrelvir-ritonavir are common

- Ritonavir inhibits cytochrome p450 3A4 enzyme → increases levels of many drugs
- Induces other enzymes → reduces exposures
- Always check on-line resources!
  - Liverpool COVID-19 drug interactions
  - IDSA Guidelines
  - NIH Guidelines
  - Micromedex
  - UpToDate

www.covid19-druginteractions.org/checker/

- Drug can only be given for 5 days under EUA
- Duration of drug interactions – *8 days*
- Some common drugs can be held (statins)
- Some dose-reduced (apixaban)
- Some contraindicated (rivaroxaban, salmeterol, amiodarone, others)

Among the top 100 prescribed drugs, **only two have interactions so severe that nirmatrelvir/ritonavir should be avoided altogether: rivaroxaban and salmeterol.**

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Rivaroxaban	↑	Increased bleeding	Avoid nirmatrelvir/ritonavir
Salmeterol	↑	Increased cardiac effects	Avoid nirmatrelvir/ritonavir

The following table contains information on management of commonly prescribed medications that are known to interact with nirmatrelvir/ritonavir. This list was derived from ClinCalc's Top 200 Prescribed Medications in the United States in 2019. Please note:

- Inclusion on this list is not a contraindication to prescribe nirmatrelvir/ritonavir. Rather, additional management considerations may be necessary as shown below.
- If a drug is not on this list, it should still be checked for interactions, as it may be a less commonly prescribed medication that has interactions or is contraindicated.
- Routine lab testing for transaminases or creatinine is not needed, and clinical judgement should be used.

Concomitant Medication	Nirmatrelvir/ Ritonavir Effect on Drug Level	Possible Effect	Recommendation During Nirmatrelvir/Ritonavir Treatment
Alprazolam	↑	Excess sedation	Consider dose reduction, but do not stop if chronic use
Apixaban	↑	Increased bleeding	Dose dependent: • Apixaban 2.5 mg: Avoid nirmatrelvir/ ritonavir • Apixaban 5mg or 10 mg: Reduce dose by 50% until 3 days after nirmatrelvir/ritonavir

Case continues

- The patient is prescribed nirmatrelvir with ritonavir (Paxlovid), and told to reduce his apixaban dose by 50% for the 5 days he is on treatment, plus an additional 3 days (8 days total)
- He tolerates the treatment well except for mild taste disturbance
- Home rapid antigen test turns negative on day 4 of treatment
- 4 days after stopping, he notes nasal congestion and mild sore throat
- A repeat rapid home antigen test is again positive

Question

- What is the most likely explanation?

A. Re-infection from another person with COVID-19 who has a different variant
B. Symptomatic rebound after stopping treatment, with infectious virus that can be transmitted to others
C. Symptomatic rebound after stopping treatment, with non-infectious virus no longer contagious to others

Question

- What is the most likely explanation?

A. Re-infection from another person with COVID-19 who has a different variant

B. Symptomatic rebound after stopping treatment, with infectious virus that can be transmitted to others

C. Symptomatic rebound after stopping treatment, with non-infectious virus no longer contagious to others

Nirmatrelvir rebound syndrome

- Occurs in 15-30% of treated patients
- Onset 3-8 days after stopping
- Symptoms usually similar to or milder than initial episode
- Virus that rebounds is infectious
- Unknowns
  - Mechanism
  - Risk factors
  - Prevention
  - Optimal management
  - Does it prolong period of infectivity?

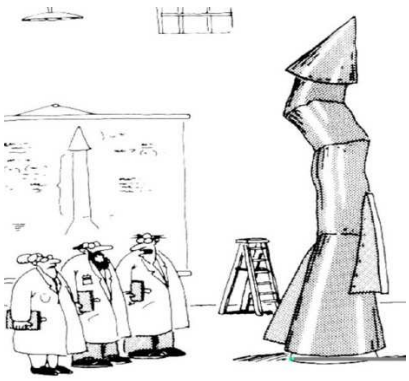
Fauci says he believes Paxlovid kept him out of the hospital, even though he tested positive again.

Dr. Anthony Fauci, President Biden's top pandemic adviser, sought to discourage doubts about the antiviral drug Paxlovid following what appeared to be a "rebound" of Covid-19 after taking the pills.

Charness ME, et al. New Engl J Med 2022. Edelstein GE medRxiv 2023; :2023.06.23.23288598.

Nirmatrelvir rebound syndrome

- Occurs in 15-30% of treated patients
- Onset 3-8 days after stopping
- Symptoms usually similar to or milder than initial episode
- Virus that rebounds is infectious
- Unknowns
  - Mechanism
  - Risk factors
  - Prevention
  - Optimal management
  - Does it prolong period of infectivity?



"It's time to face reality, my friends... We're not exactly rocket scientists."

Charness ME, et al. New Engl J Med 2022. Edelstein GE medRxiv 2023; :2023.06.23.23288598.

Immunomodulators targeting moderate-severe disease – decreased use with lower disease severity

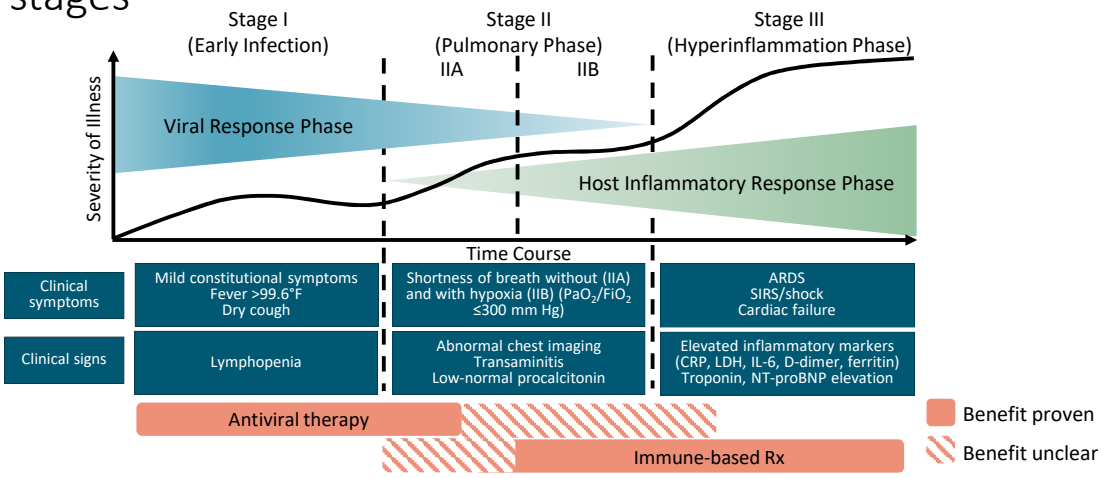
Outpatients

- Remdesivir
- Nirmatrelvir
- Molnupiravir

Inpatients

- Remdesivir
- Nirmatrelvir
- Dexamethasone
- Tocilizumab
- Baracitinib

COVID-19 therapies provide benefit at different stages



ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; LDH, lactate dehydrogenase; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; SIRS, systemic inflammatory response syndrome; PaO_2/FiO_2, arterial oxygen partial pressure/fractional inspired oxygen.

Siddiqi HK, Mehra MR. *J Heart Lung Transplant*. 2020;39:405.

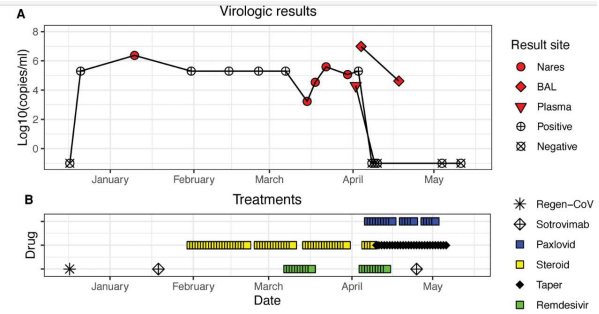
Treatment of moderate-severe COVID-19 in the hospital

Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir[e] (BIIa)**
	Most patients	Use **dexamethasone plus remdesivir[e] (BIIa)**. If remdesivir cannot be obtained, use **dexamethasone (BI)**.
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib[f]** or **IV tocilizumab[f]** to 1 of the options above **(BIIa)**.

National Institutes of Health. https://www.covid19treatmentguidelines.nih.gov.. Last updated Aug 2022.

Prolonged COVID-19 in immunocompromised patients

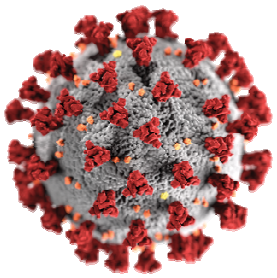
- Reported especially in patients with impaired humoral immunity, such as recipients of anti-CD20 based drugs (e.g., rituximab)
- Viral replication may last *months,* with waxing/waning symptoms
- True across diseases (arthritis, MS, cancer) – especially severe in lymphoma and hematologic malignancies
- Optimal treatment not known – case reports of promising results with prolonged combination therapies
  - Nirmatrelvir
  - Remdesivir
  - Convalescent plasma



Ford ES, et al. Clin Infect Dis 2023;76:926-9.

Treatment of COVID-19: Outline

- What happened in the past year?
- Clinical presentation and diagnosis
- Treatments available now
- **Possible treatments available in the future**
- Long Covid



Investigational treatments with promising data

- Other SARS-CoV-2 protease inhibitors
  - Ensitrelvir
  - EDP-235
- Oral analogues of remdesivir
  - Obeldesivir
  - VV116
- Peginterferon lambda
- Still more monoclonal antibodies?

SCIENCEINSIDER | HEALTH

Interferon therapy shows striking results against COVID-19

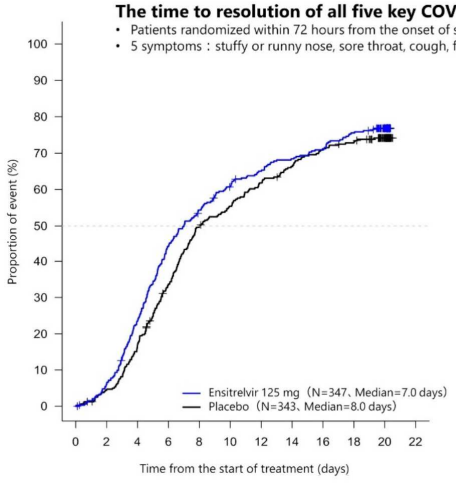
Given early, one shot sliced hospitalization risk by half in large trial

5 MAY 2022 · 4:00 PM · BY MEREDITH WADMAN

Ensitrelvir in low-risk outpatients

The time to resolution of all five key COVID-19 symptoms

- Patients randomized within 72 hours from the onset of symptoms
- 5 symptoms：stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness



Time from onset to randomization：<72 hours

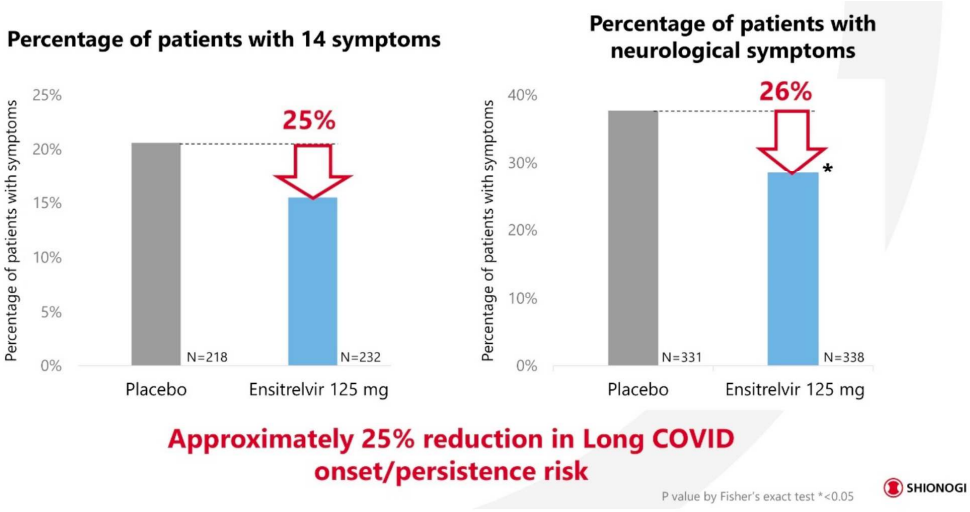
		125 mg N = 347	Placebo N = 343
Median [95% CI]		167.9 [145.0, 197.6]	192.2 [174.5, 238.3]
Difference in median vs. placebo [95% CI]		-24.3 [-78.7, 11.7]	---
Stratified Peto-Prentice's generalized Wilcoxon test vs. placebo [a]	P value	0.0407	---

CI = Confidence Interval
[a] Adjusted by the following stratum (SARS-CoV-2 vaccination history [Yes or No])

Significant reduction in the time to resolution of 5 symptoms of COVID-19 characteristic of Omicron strain compared to placebo (primary endpoint achieved)

SHIONOGI

Symptoms of Long Covid at 3-6 months decreased with treatment



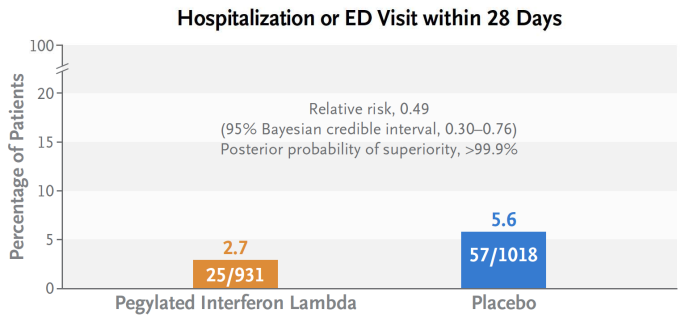
Approximately 25% reduction in Long COVID onset/persistence risk

P value by Fisher's exact test *<0.05

SHIONOGI

Interferon lambda vs placebo

- 1949 adults presenting within 7 days of symptom onset
- At least one risk factor for severe disease
- 84% with at least one dose of a Covid-19 vaccine
- 50% reduction in clinical endpoints



Reiss G, et al. N Engl J Med 2023; 388:518-528.

OPINION

The best treatment for COVID-19 could be the one you can't get

The FDA turned down a request from Eiger BioPharmaceuticals for emergency use authorization of its promising treatment for COVID. It should reconsider its decision.

By **Paul Sax and David Boulware** Updated February 10, 2023, 11:47 a.m.

Advantages of interferon lambda

- Active across variants
- "One and done" subcutaneous shot
- Adverse event rate comparable to placebo arm
- No drug interactions

Boston Globe, February 10, 2023.

Question

- Among "repurposed" drugs for Covid-19, which of the following has the most convincing favorable data from prospective clinical trials?

A. Atorvastatin
B. Fluticasone
C. Colchicine
D. Fluvoxamine
E. Ivermectin
F. Metformin
G. Vitamin D

Question

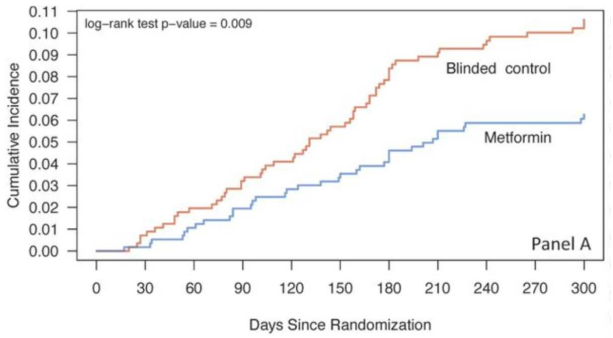
- Among “repurposed” drugs for Covid-19, which of the following has the most convincing favorable data from prospective clinical trials?

A. Atorvastatin
B. Fluticasone
C. Colchicine
D. Fluvoxamine
E. Ivermectin
F. Metformin
G. Vitamin D

Metformin reduces diagnosis of Long Covid

- **Metformin**

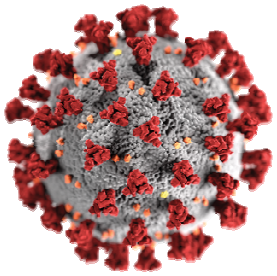
Incidence of Long Covid in TOGETHER trial, metformin vs placebo



Bramante CT, et al. Lancet ID 2023.

Treatment of COVID-19: Outline

- What happened in the past year?
- Clinical presentation and diagnosis
- Treatments available now
- Possible treatments available in the future
- **Long Covid**



Case

- A 26-year-old woman experienced COVID-19 in December 2020, when she developed a 10 days of fever, cough, and headache
- Seen in the emergency department and briefly on oxygen; discharged with supportive treatment only
- Although constitutional symptoms resolved, she continues to complain of fatigue, difficulty concentrating (“brain fog”), chest pain, palpitations, and dyspnea on exertion – all worse when she is tired
- Symptoms have waxed and waned, but have been severe enough to cause her to delay getting her graduate degree

Question

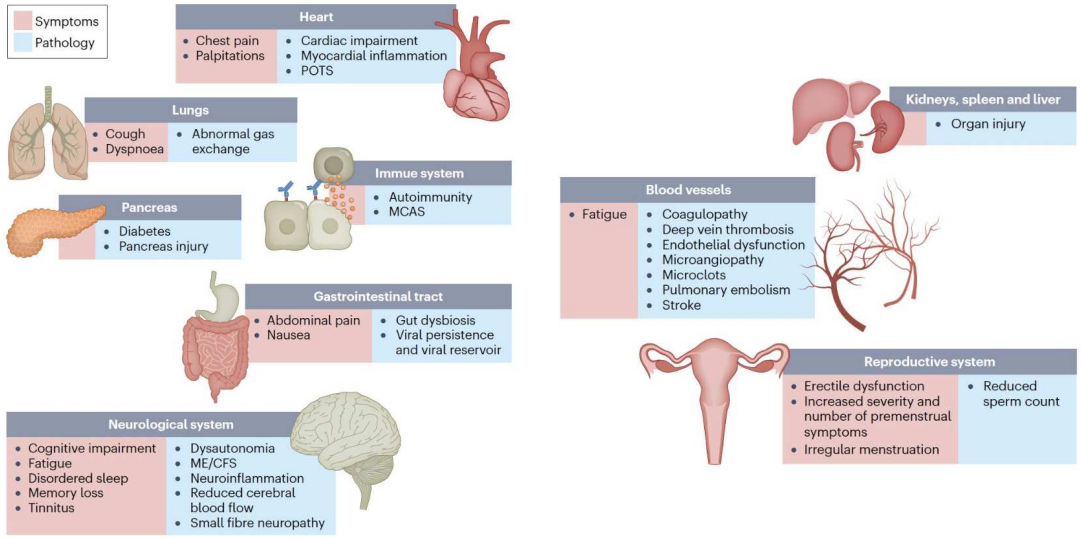
- Which of the following symptoms is commonly reported in Long Covid, or Post-Acute Sequelae of SARS-CoV-2 (PASC)?

A. Fatigue
B. Brain fog
C. Chest pain and palpitations
D. Shortness of breath
E. All of the above

Question

- Which of the following symptoms is commonly reported in Long Covid, or Post-Acute Sequelae of SARS-CoV-2 (PASC)?

A. Fatigue
B. Brain fog
C. Chest pain and palpitations
D. Shortness of breath
E. All of the above



Davis HE, et al. Nature Reviews Microbiology 2023.

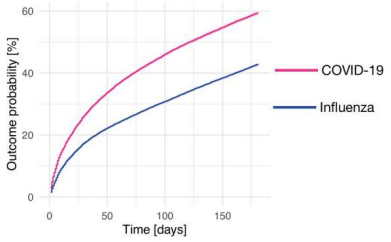
Long Covid: Clinical phenotypes and cause

- Neurocognitive, cardiovascular, pulmonary all reported
- Overlap syndromes *very* common
- Multiple proposed mechanisms
  - Autonomic nervous system dysfunction
  - Vascular injury due to microvascular clotting
  - Autoantibodies
  - Direct tissue injury
- Residual SARS-CoV-2 detected in some patients – viable virus vs antigenic remnants?

Swank Z, et al. medRxiv 2022. https://doi.org/10.1101/2022.06.14.22276401.

How common is Long Covid?

- Answer highly variable depending on definition and study design – 10-50% after symptomatic infection
- Risk factors for higher likelihood of residual symptoms
  - Initial illness severity
  - Female sex
  - Higher BMI
  - Pre-existing conditions
- Vaccination reduces risk of Long Covid, possibly by reducing disease severity

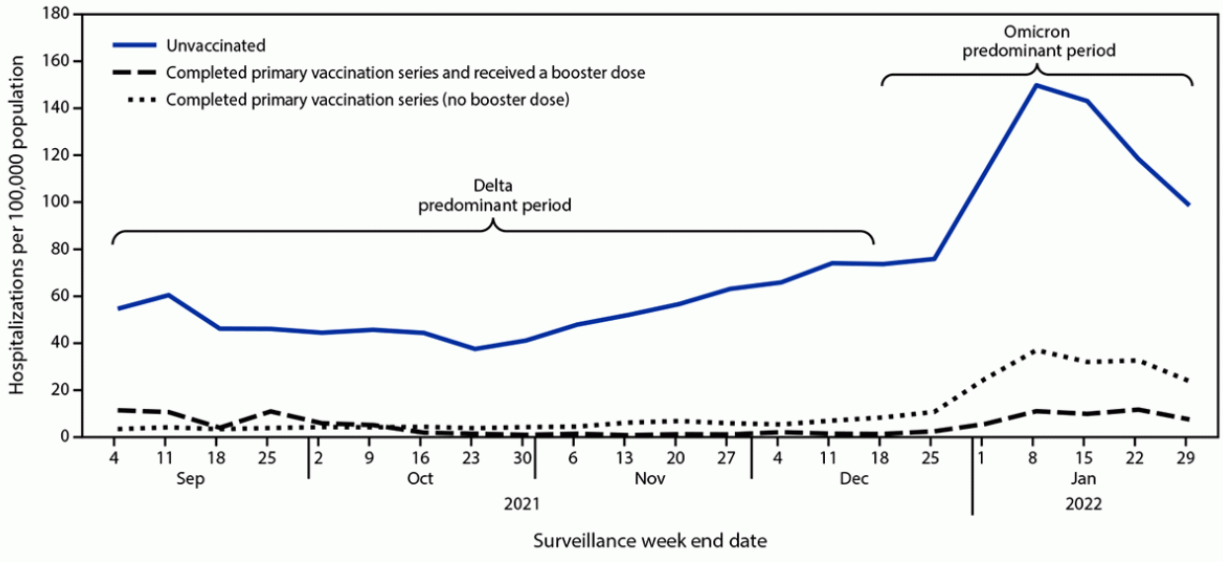


NEWS | 20 June 2022

How common is long COVID? Why studies give different answers

Enormous databases do not necessarily allow scientists to solve long COVID mysteries, such as how well vaccination protects against the condition.

Taquet M, et al. PLOS Medicine 2021; https://doi.org/10.1371/journal.pmed.1003773. Nature 2022.



Taylor CA, et all. MMWR Mar 22 2022.

Proposed treatments for symptoms of Long Covid

Symptom	Treatment
Post-exertional malaise	Physical pacing
POTS and dysautonomia syndromes	β-blockers, pyridostigmine, fludrocortisone, midodrine; increased salt intake; compression stockings; transcutaneous vagal stimulation; stellate ganglion blockade
Cognitive dysfunction	Cognitive pacing, post-concussion protocols
Fatigue, brain fog	Low-dose aripiprazole, naltrexone
Abnormal clotting	Anticoagulants, apheresis
Viral persistence of SARS-CoV-2	Paxlovid
Viral reactivations	Valacyclovir, famciclovir, valganciclovir
GI symptoms	Probiotics

Davis HE, et al. Nature Reviews Microbiology 2023.

Treatment of COVID-19: Six take-home points!

1. COVID-19 remains common, but diseases severity has steadily declined
2. Don't rely on a single antigen test to rule out the diagnosis; PCR still the gold standard for inpatients
3. Focus on *high-risk* individuals for treatment – reduces risk of severe disease, may decrease risk of Long Covid
4. Remdesivir for high-risk hospitalized patients, even with mild disease
   - *Do not delay starting*
5. Nirmatrelvir/ritonavir (Paxlovid) first-line in outpatient setting
   - Reduces risk of hospitalization and death in high-risk unvaccinated
   - Many drug interactions
   - Rebounds
6. Strategies that reduces risk of disease severity reduce risk of Long Covid