CDC/IDSA Clinician Call

Jan. 21, 2023

Welcome & Introductions

Dana Wollins, DrPH, MGC
Vice President
Clinical Affairs & Practice Guidelines
Infectious Diseases Society of America

- 96th in a series of calls, initiated in 2020 as a forum for information sharing among frontline clinicians caring for patients with COVID-19.
- The views and opinions expressed here are those of the presenters and do not necessarily reflect the official policy or position of the CDC or IDSA. Involvement of CDC and IDSA should not be viewed as endorsement of any entity or individual involved.
- This webinar is being recorded and can be found online at www.idsociety.org/cliniciancalls.

CDC/IDSA Clinician Call: COVID-19 Variants, Testing & Treatment: The Latest

1. COVID-19 Epidemiology Update

Pragna Patel, MD, MPH
Acting Chief Medical Officer
Coronavirus and Other Respiratory Viruses Division (proposed)
National Center for Immunization and Respiratory Diseases, U.S. Centers for Disease Control & Prevention

2. The Current Variants Landscape; Plus Diagnostic Algorithm Update

Natalie J. Thornburg, PhD
Acting Chief Laboratory Branch
COVID and Other Respiratory Viruses Division (proposed)
National Center for Immunization and Respiratory Diseases
U.S. Centers for Disease Control & Prevention

3. Update on COVID-19 Therapeutics & Clinical Decision Making

Rajesh T. Gandhi, MD, FIDSA
Director, HIV Clinical Services and Education
Massachusetts General Hospital
Co-Director, Harvard Center for AIDS Research

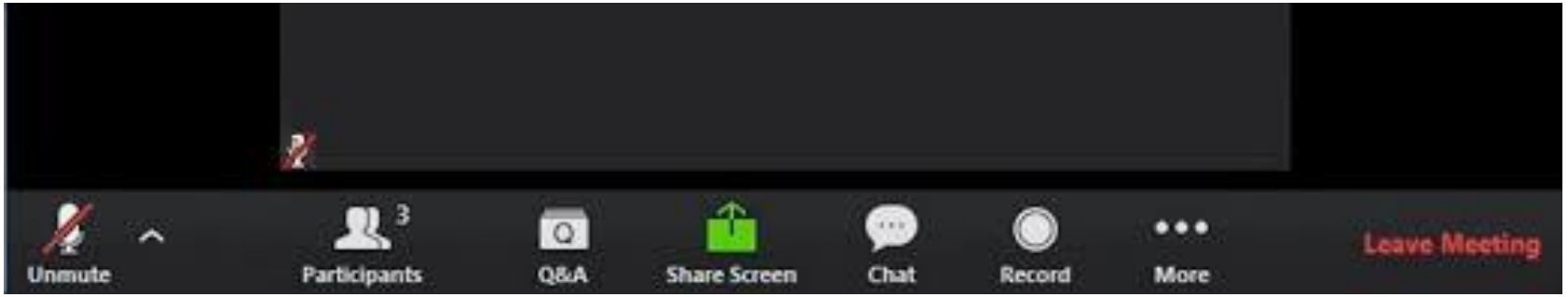
Adarsh Bhimraj, MD, FIDSA
Director, Infectious Disease Education & Fellowship
Houston Methodist Hospital

4. Understanding Viral Rebound: What We Know

Pragna Patel, MD, MPH
Acting Chief Medical Officer
Coronavirus and Other Respiratory Viruses Division (proposed)
National Center for Immunization and Respiratory Diseases, U.S. Centers for Disease Control & Prevention

Question?
Use the “Q&A” Button

Comment?
Use the “Chat” Button



COVID-19
Epidemiology Update

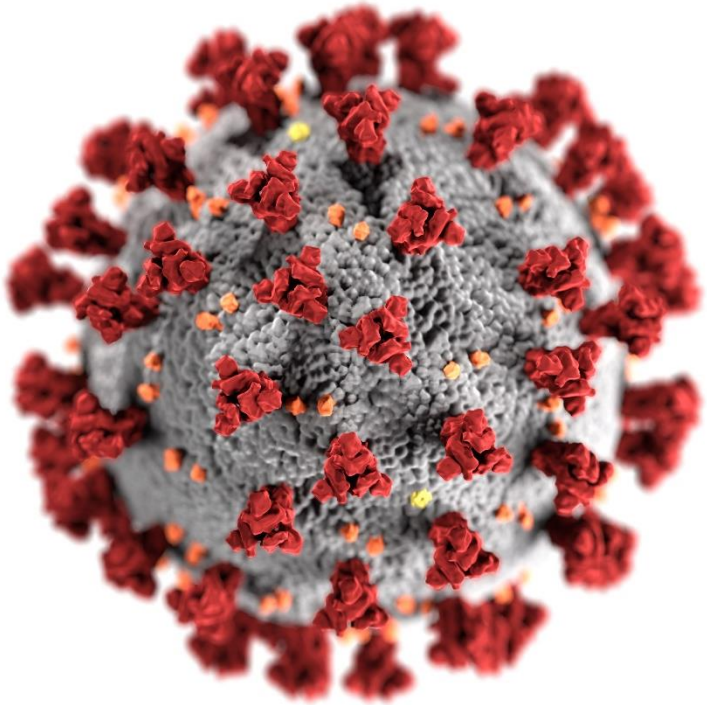
Pragna Patel, MD, MPH

Update on COVID-19 Epidemiology

Pragna Patel, MD MPH
Chief Medical Officer (acting)
Coronavirus and Other Respiratory Viruses Division (proposed), NCIRD, CDC

IDSA/CDC Clinician Call

January 21, 2023



cdc.gov/coronavirus

Daily Trends in COVID-19 Cases in the United States

Weekly Change in COVID-19 Cases, United States

January 22, 2020 - January 18, 2023

101,873,730
Total Cases Reported*

332,212
New Weekly Cases*
Jan 12, 2023 - Jan 18, 2023

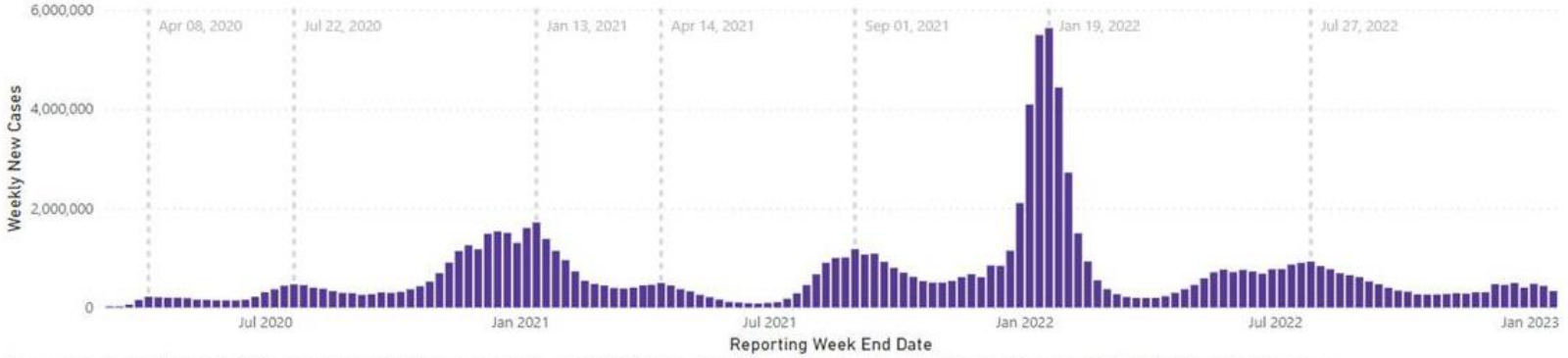
47,458.86
Current 7-Day Average**
Jan 12, 2023 - Jan 18, 2023

62,396.57
Prior 7-Day Average**
Jan 05, 2023 - Jan 11, 2023

-23.9%
Change in 7-Day Average

Peaks in Weekly Total and Weekly Average of Daily Cases**

Peak	Reporting Week End	Weekly Total - New Cases	7-Day Daily Average	% Change From Current Average
2020 - Spring	Apr 08, 2020	219,473	31,353	51.4%
2020 - Summer	Jul 22, 2020	466,693	66,670	-28.8%
2020 - Winter	Jan 13, 2021	1,714,377	244,911	-80.6%
2021 - Spring	Apr 14, 2021	496,751	70,964	-33.1%
2021 - Summer	Sep 01, 2021	1,175,796	167,971	-71.7%
2021 - Winter	Jan 19, 2022	5,629,914	804,273	-94.1%
2022 - Summer	Jul 27, 2022	926,393	132,342	-64.1%



* The graph displays data for Mar 05, 2020, to date. The totals include cases reported since Jan 22, 2020. The grey bar indicates the latest 6-week period used in calculating the current and prior 7-day daily case averages.

** The histogram, total of new cases in the last week, and weekly averages do not include historical cases reported retroactively that are not yet attributed to the correct date of report.
Of 21,397 historical cases reported retroactively, none were reported in the current week and none in the prior week.

Last Updated: Jan 19, 2023, 10:45

Data Source: CDC Case Surveillance, state-level aggregated COVID-19 Cases, HHS Protect; Visualization: CDC CPR DEO Situational Awareness Public Health Science Team

Daily SARS-CoV-2 NAAT Percent Test Positivity and Test Volume, United States

March 01, 2020 – January 16, 2023

1,007,362,591
Total Test Volume

306,307
Current 7-Day Avg. Daily Test Volume
Jan 06, 2023 – Jan 12, 2023

346,677
Prior 7-Day Avg. Daily Test Volume
Dec 30, 2022 – Jan 05, 2023

-11.6%
Percent Change in 7-Day Avg.

12.3%
Current 7-Day Avg. % Positivity
Jan 10, 2023 – Jan 16, 2023

13.6%
Prior 7-Day Avg. % Positivity
Jan 03, 2023 – Jan 09, 2023

-9.3%
Percent Change in 7-Day Avg.

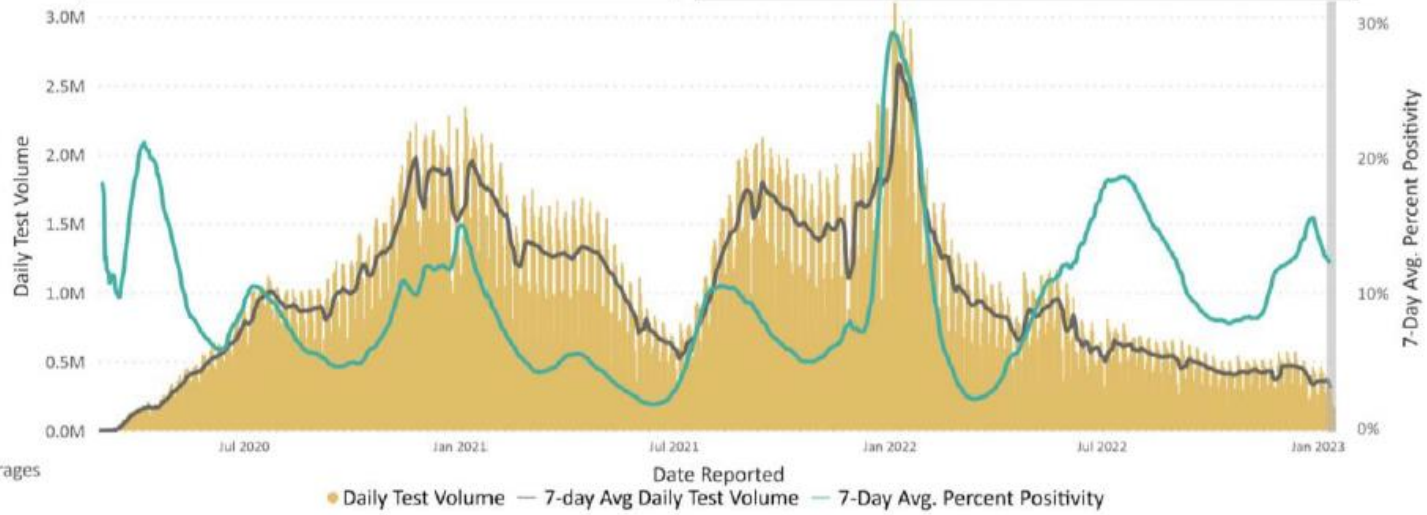
-1.27
Percentage Point Difference in 7-Day Averages

Peaks in Single Day and 7-Day Average Percent Positivity

Peak	Single Day % Positivity	Single Day Date	7-Day Average % Positivity	7-Day Average Date	% Change vs. Current 7-Day Average
1st Peak	11.3%	Jul-05-20	10.5%	Jul-08-20	17.3%
2nd Peak	16.0%	Jan-03-21	15.0%	Jan-03-21	-17.8%
3rd Peak	7.8%	Apr-04-21	5.5%	Apr-12-21	124.7%
Latest	30.8%	Jan-02-22	29.3%	Jan-07-22	-57.9%

Peaks in Single Day and 7-Day Average Test Volume

Peak	Single Day Test Vol	Single Day Date	7-Day Average Test Vol	7-Day Average Date	% Change vs. Current 7-Day Average
1st Peak	1,117,906	Jul-22-20	978,708	Jul-24-20	-68.7%
2nd Peak	2,342,393	Jan-06-21	1,912,164	Nov-25-20	-84.0%
3rd Peak	1,688,819	Apr-14-21	1,288,068	Apr-14-21	-76.2%
Latest	3,144,317	Jan-05-22	2,572,480	Jan-09-22	-88.1%



Data (shaded) for the most recent four days may be incomplete. 7-Day average test volume line ends before the gray shaded area to reduce the influence of incomplete data in the most recent four days. A nucleic acid amplification test (NAAT) remains the "gold standard" for clinical diagnostic detection of SARS-COV-2 and includes viral testing such as real-time reverse transcription polymerase chain reaction (RT-PCR). IA's data were excluded Feb 17, 2022 onward due to incomplete negative test result data, impacting testing volumes and percent positivity. Testing Data update for Sep 15, 2022: NV sent updated testing data dating back to March 2020 after addressing data cleaning issues resulting in an overall drop in test volume.

Last Updated: Jan 19, 2023, 09:06

HHS Protect Unified Laboratory Testing Dataset; Data, Analytics, & Visualization Task Force, Visualization: CDC CPR DEO Situational Awareness Public Health Science Team

New Admissions of Patients with COVID-19 in the United States

New Admissions of Patients with Confirmed COVID-19, United States

August 01, 2020 – January 17, 2023

5,839,044
Total New Admissions
Aug 01, 2020 – Jan 17, 2023

4,614
New Admissions
Jan 17, 2023

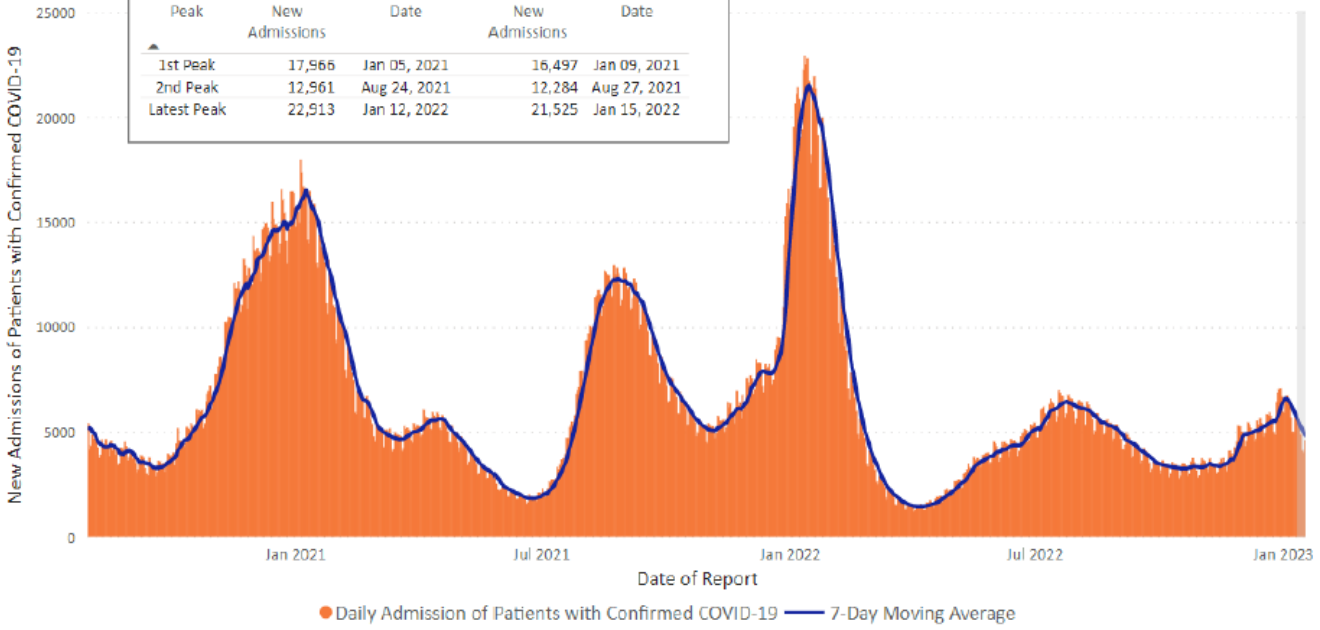
4,834
Current 7-Day Average
Jan 11, 2023 – Jan 17, 2023

5,861
Prior 7-Day Average
Jan 04, 2023 – Jan 10, 2023

-17.5%
Change in 7-Day Average

Peak in New Admissions and Highest 7-Day Moving Average*

Peak	Single Day: New Admissions	Single Day: Date	7-Day Average: New Admissions	7-Day Average: Date
1st Peak	17,966	Jan 05, 2021	16,497	Jan 09, 2021
2nd Peak	12,961	Aug 24, 2021	12,284	Aug 27, 2021
Latest Peak	22,913	Jan 12, 2022	21,525	Jan 15, 2022



Based on reporting from all hospitals (N=5,317). Due to potential reporting delays, data reported in the most recent 7 days (as represented by the shaded bar) should be interpreted with caution. Data reported prior to Aug 01, 2020 are unavailable.

*Small shifts in historic data may occur due to changes in the CMS Provider of Services file, which is used to identify the cohort of included hospitals.

Daily Trends in COVID-19 Deaths in the United States

Weekly Change in COVID-19 Deaths, United States

January 22, 2020 - January 18, 2023

1,099,866
Total Deaths Reported*

3,953
New Weekly Deaths*
Jan 12, 2023 - Jan 18, 2023

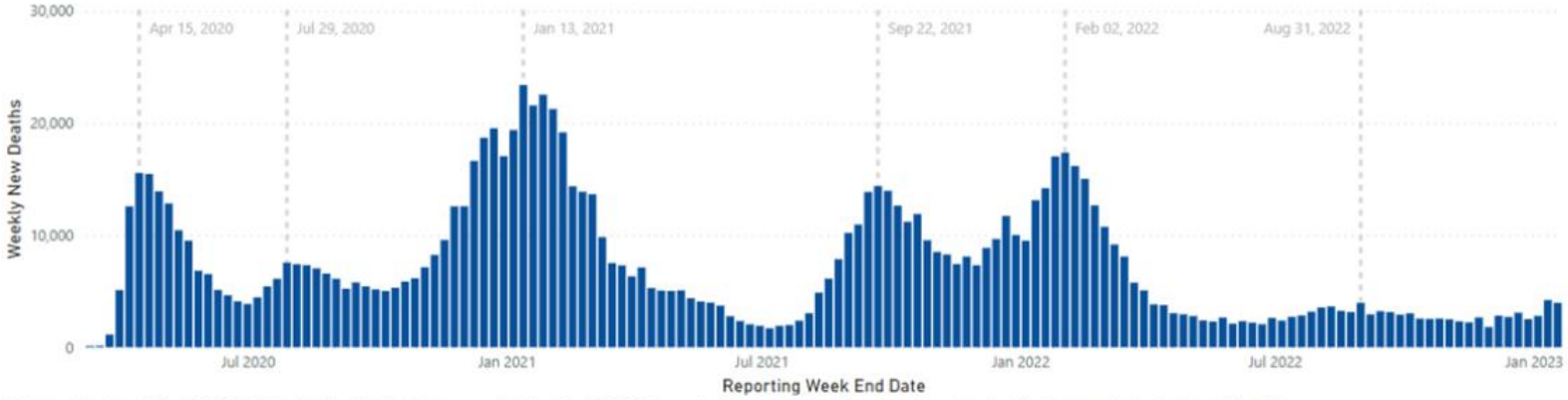
564.71
Current 7-Day Average**
Jan 12, 2023 - Jan 18, 2023

601.29
Prior 7-Day Average**
Jan 05, 2023 - Jan 11, 2023

-6.1%
Change in 7-Day Average

Peaks in Weekly Total and 7-Day Average of Daily Deaths**

Peak	Reporting Week End	Weekly Total - New Deaths	7-Day Daily Average	% Change From Current Average
2020 - Spring	Apr 15, 2020	15,539	2,220	-74.6%
2020 - Summer	Jul 29, 2020	7,546	1,078	-47.6%
2020 - Winter	Jan 13, 2021	23,387	3,341	-83.1%
2021 - Summer	Sep 22, 2021	14,372	2,053	-72.5%
2021 - Winter	Feb 02, 2022	17,351	2,479	-77.2%
2022 - Summer	Aug 31, 2022	3,947	564	0.2%



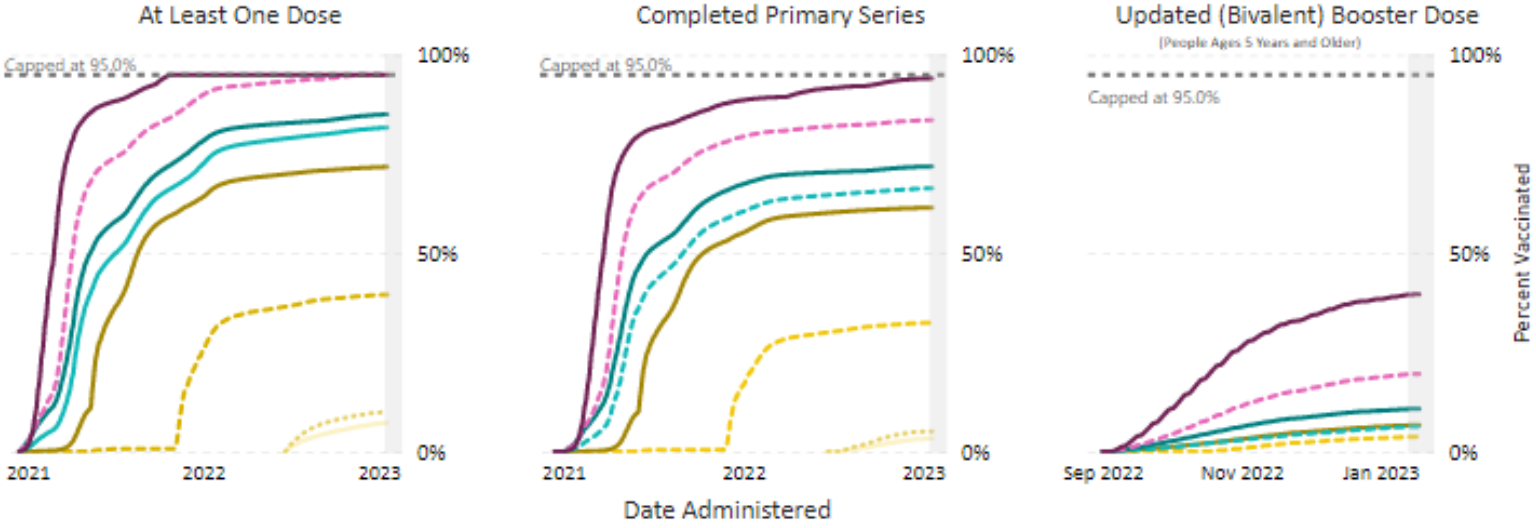
* The graph displays data for Mar 05, 2020, to date. The totals include cases reported since Jan 22, 2020. The grey bar indicates the latest 6-week period used in calculating the current and prior 7-day daily death averages.

** The histogram, total of new deaths in the last week, and 7-day averages do not include historical deaths reported retroactively that are not yet attributed to the correct date of report.

Of 3,838 historical deaths reported retroactively, none were reported in the current week and 86 in the prior week.

U.S. Vaccination Program – Coverage by Age

	<2 yrs	2-4 yrs	5-11 yrs	12-17 yrs	18-24 yrs	25-49 yrs	50-64 yrs	+65 yrs
At Least One Dose	7.3%	10.0%	39.6%	71.8%	81.7%	85.0%	95.0%	95.0%
Completed Primary Series	3.3%	5.1%	32.5%	61.5%	66.4%	71.9%	83.6%	94.1%
Updated (Bivalent) Booster Dose			3.7%	6.7%	6.3%	10.8%	19.6%	39.6%



https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends

COVID-NET : Rates of laboratory-confirmed COVID-19 hospitalizations by vaccination status

In November 2022, compared to adults ages 18 years and older who received an updated COVID-19 bivalent booster dose, monthly rates of COVID-19-associated hospitalizations were **16.0x Higher in Unvaccinated** and **2.7x Higher in Vaccinated Adults without an updated booster.***

29.9x Higher
in Unvaccinated Adults Ages 18-49 Years

3.2x Higher
in Adults Ages 18-49 Years Vaccinated but Without an Updated booster

13.6x Higher
in Unvaccinated Adults Ages 50-64 Years

2.9x Higher
in Adults Ages 50-64 Years Vaccinated but Without an Updated booster

13.5x Higher
in Unvaccinated Adults Ages 65 Years and Older

2.5x Higher
in Adults Ages 65 Years and Older Vaccinated but Without an Updated booster

These data were posted on December 28, 2022, and reflect hospitalizations through November 2022.

*Notes: Data for October 2022 are not available for all age groups. Data are presented for the first complete month when 14 days passed since at least 5% of the age group-specific population of the COVID-NET surveillance catchment area have received an updated (bivalent) COVID-19 booster dose. For October 2022, that standard (14 days passed since at least 5% of the population received an updated booster dose) was only met for adults ages 65 years and older. Data for adults ages 18–64 years met the standard beginning in November 2022. Data for children and adolescents ages 5–17 years will be added once it meets this standard. Refer to Footnotes for additional details.

For more information about COVID-NET, please see https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.htmlDownload Report

Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years — IVY Network, 18 States, September 8–November 30, 2022

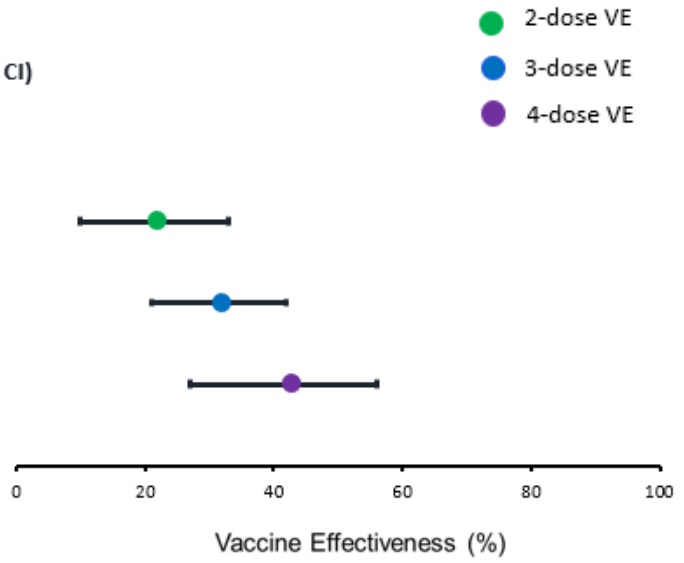
Characteristic	Received BV vaccine dose, by case status, n/N (%)		Median interval† from last vaccine dose to illness onset (IQR), days	Adjusted VE, % (95% CI)§
	Case-patients	Control patients		
Absolute VE (BV booster dose versus no vaccine)				
Unvaccinated (Ref)	—	—	NA	—
BV booster dose¶ ≥7 days before illness onset	20/101 (20)	59/121 (49)	29 (15–45)	84 (64–93)
Relative VE (BV booster dose versus MV-only, by interval since last dose)				
≥2 MV-only mRNA doses, last dose ≥2 mos before illness onset (Ref)	—	—	305 (168–377)	—
BV booster dose ≥7 days before illness onset	20/300 (7)	59/355 (17)	29 (15–45)	73 (52–85)
≥2 MV-only mRNA doses, last dose 2–5 mos before illness onset (Ref)	—	—	137 (111–155)	—
BV booster dose ≥7 days before illness onset	20/82 (24)	59/155 (38)	29 (15–45)	—**
≥2 MV-only mRNA doses, last dose 6–11 mos before illness onset (Ref)	—	—	304 (258–333)	—
BV booster dose ≥7 days before illness onset	20/155 (13)	59/176 (34)	29 (15–45)	78 (57–89)
≥2 MV-only mRNA doses, last dose ≥12 mos before illness onset (Ref)	—	—	528 (386–575)	—
BV booster dose ≥7 days before illness onset	20/103 (19)	59/142 (42)	29 (15–45)	83 (63–92)

Abbreviations: BV = bivalent; MV = monovalent; NA = not applicable; Ref = referent group; VE = vaccine effectiveness.

Surie D, DeCuir J, Zhu Y, et al. Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years — IVY Network, 18 States, September 8–November 30, 2022. MMWR Morb Mortal Wkly Rep 2022;71:1625–1630.

VISION: mRNA COVID-19 VE for hospitalizations among immunocompromised adults for 2, 3, and 4 doses during Omicron BA.2/BA.2.12.1/BA.4/BA.5 sub-lineage predominance*, mid-March 2022–August 2022

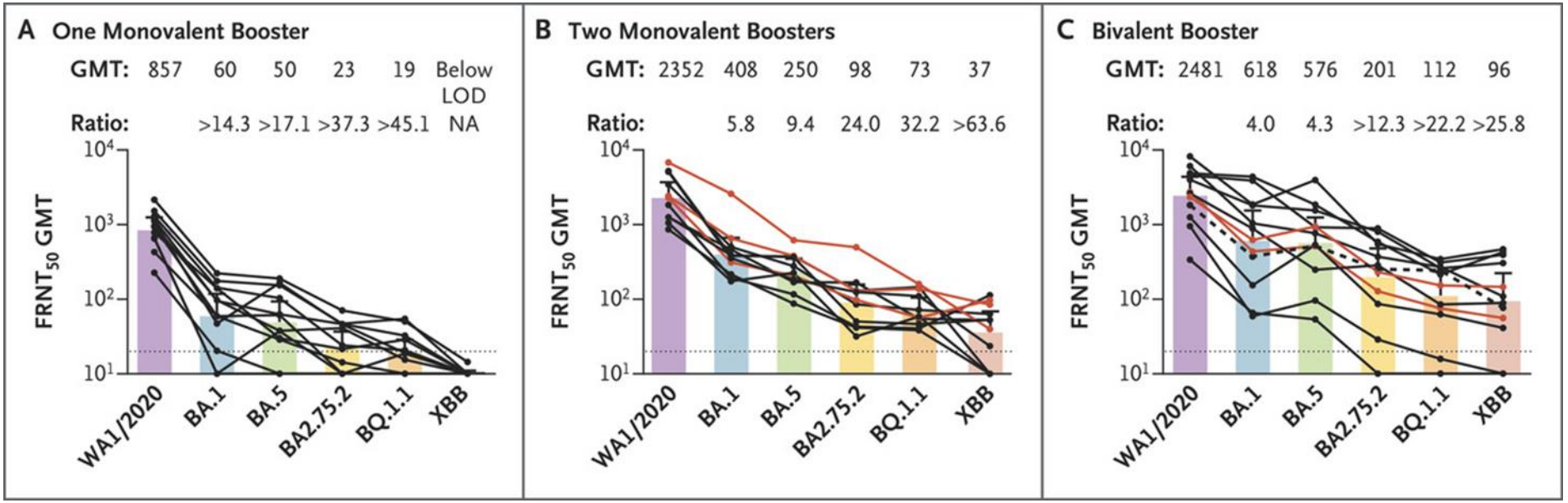
Vaccination status	Total	SARS-CoV-2 positive test result, no. (%)	Median interval since last dose, days (IQR)	VE % (95% CI)
2 doses (≥14 days earlier)	4,312	379 (8.8)	386 (305–441)	22 (10-33)
3 doses (≥90 days earlier)	7,585	710 (9.4)	196 (156–238)	32 (21-42)
4 doses (≥7 days earlier)	2,393	251 (10.5)	61 (34–91)	43 (27-56)



*VE estimates presented here were restricted to a combined period beginning in mid-March 2022 including BA.2/BA.2.12.1 and BA.4/BA.5 periods because of limited 4-dose coverage among 4th-dose eligible persons before mid-March 2022.

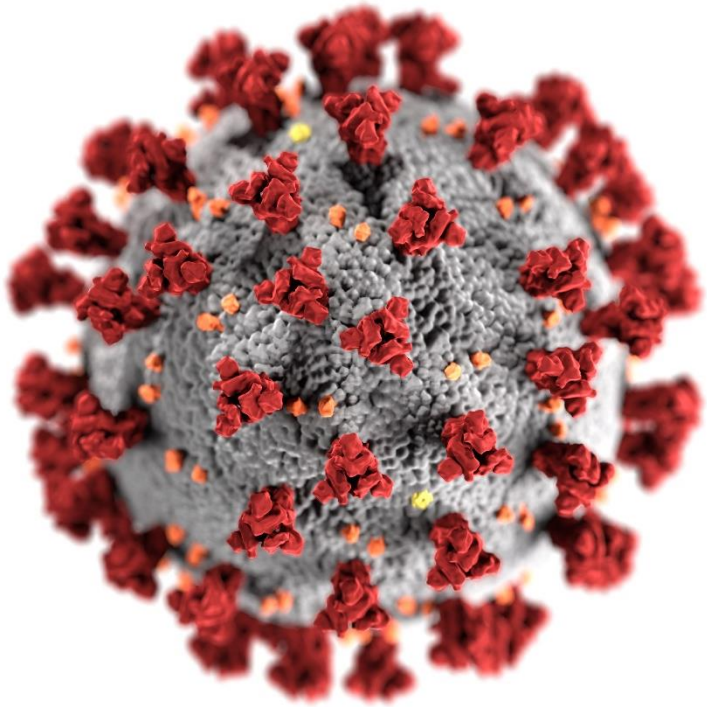
Britton A, Embi PJ, Levy ME, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalizations Among Immunocompromised Adults During SARS-CoV-2 Omicron Predominance — VISION Network, 10 States, December 2021—August 2022. MMWR Morb Mortal Wkly Rep 2022;71:1335–1342.

Neutralization against BA.2.75.2, BQ.1.1, and XBB from mRNA Bivalent Booster



Neutralizing Responses against the WA1/2020 Strain and Omicron Subvariants. Shown is the neutralization activity against the WA1/2020 strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the omicron subvariants BA.1, BA.5, BA.2.75.2, BQ.1.1, and XBB in 12 participants who received one monovalent booster (Panel A), in 11 participants who received two monovalent boosters (Panel B), and in 12 participants who received the updated bivalent booster (Panel C).

Davis-Gardner et al. N Engl J Med 2023; 388:183-185 DOI: 10.1056/NEJMc2214293



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

The Current Variants Landscape; Plus Diagnostic Algorithm Update

Natalie Thornburg, PhD

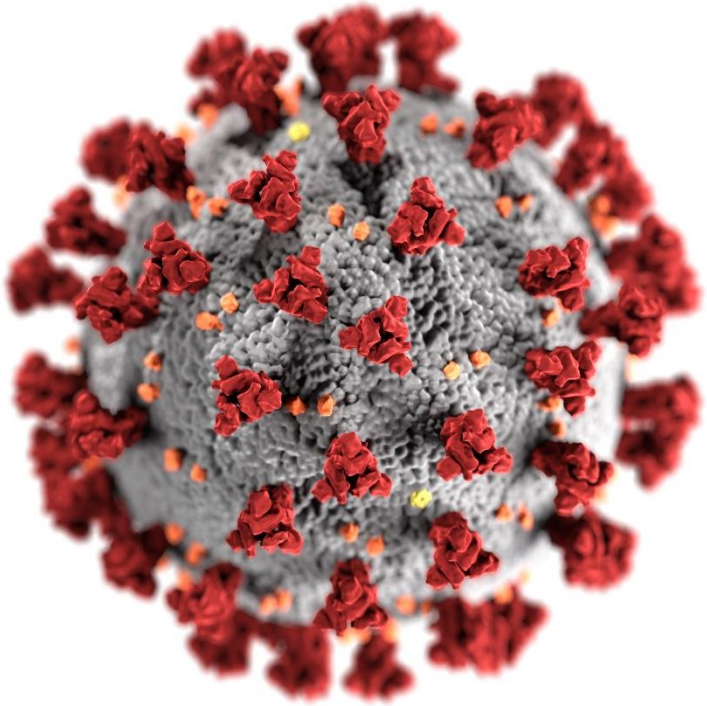
Current Variant Landscape and Diagnostic Testing Algorithm

Natalie Thornburg, PhD

Acting Chief, Laboratory Branch

COVID and Other Respiratory Viruses Division (proposed)

NCIRD, CDC



cdc.gov/coronavirus

Overview

- Current variant landscape

- Diagnostics
  - When to test
  - Types of tests
  - How to interpret tests
  - Performance of current tests with currently circulating viruses

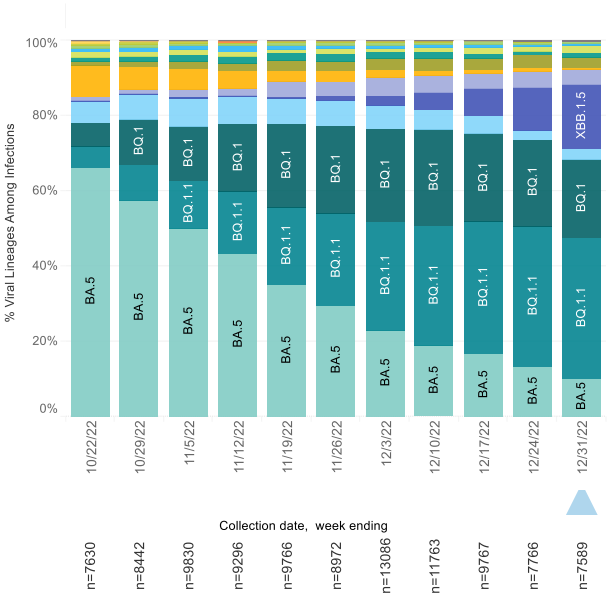
National Weighted Estimates of SARS-CoV-2 Lineages

United States: 12/25/2022 – 12/31/2022

USA

WHO Label	Lineage		US Class	%Total	95%CI
Omicron	BQ.1.1		VOC	37.3%	33.0-41.7%
	BQ.1		VOC	20.9%	17.4-24.6%
	XBB.1.5		VOC	17.1%	9.8-26.7%
	BA.5		VOC	10.0%	8.5-11.7%
	XBB		VOC	4.0%	3.3-4.9%
	BN.1		VOC	2.9%	2.3-3.7%
	BF.7		VOC	2.9%	2.4-3.6%
	BA.2.75		VOC	1.8%	1.4-2.2%
	BA.5.2.6		VOC	1.1%	0.8-1.6%
	BA.2		VOC	0.7%	0.4-1.0%
	BF.11		VOC	0.5%	0.3-0.9%
	BA.4.6		VOC	0.3%	0.1-0.5%
	BA.2.75.2	†	VOC	0.2%	0.1-0.5%
	BA.4	†	VOC	0.0%	0.0-0.1%
	B.1.1.529	†	VOC	0.0%	0.0-0.1%
	BA.1.1	†	VOC	0.0%	NA
	BA.2.12.1	†	VOC	0.0%	NA
Delta	B.1.617.2	†	VBM	0.0%	NA
Other	Other*			0.2%	0.1-0.4%

United States: 10/16/2022 – 12/31/2022



* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

† Estimates are less reliable based on one or more violations of NCHS data presentation standards for proportions: https://www.cdc.gov/nchs/data/series/sr_02/sr02_175.pdf

\# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except XBB.1.5, sublineages of XBB are aggregated to XBB. For all the lineages listed in the above table, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.5 was aggregated to XBB. Lineages BA.2.75.2, XBB, XBB.1.5, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

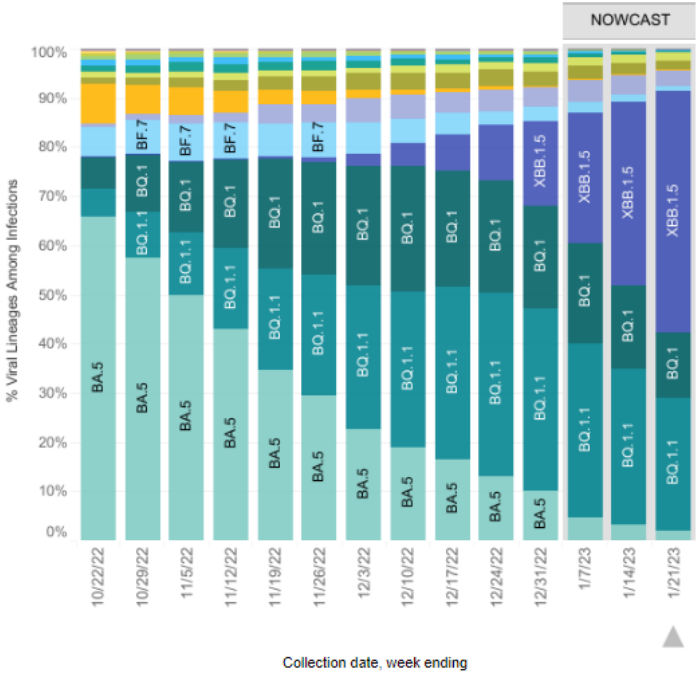
National Nowcast Estimates of SARS-CoV-2 lineages

United States: 1/15/2023 – 1/21/2023 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	49.1%	37.5-60.8%
	BQ.1.1	VOC	26.9%	20.9-33.9%
	BQ.1	VOC	13.3%	10.1-17.4%
	XBB	VOC	3.3%	2.7-4.1%
	BA.5	VOC	2.0%	1.5-2.8%
	BN.1	VOC	1.8%	1.4-2.5%
	BA.2.75	VOC	1.6%	1.2-2.2%
	BF.7	VOC	1.0%	0.8-1.4%
	BA.5.2.6	VOC	0.4%	0.3-0.5%
	BA.2	VOC	0.2%	0.1-0.3%
	BF.11	VOC	0.2%	0.1-0.2%
	BA.4.6	VOC	0.1%	0.0-0.1%
	BA.2.75.2	VOC	0.0%	0.0-0.1%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

United States: 10/16/2022 – 1/21/2023

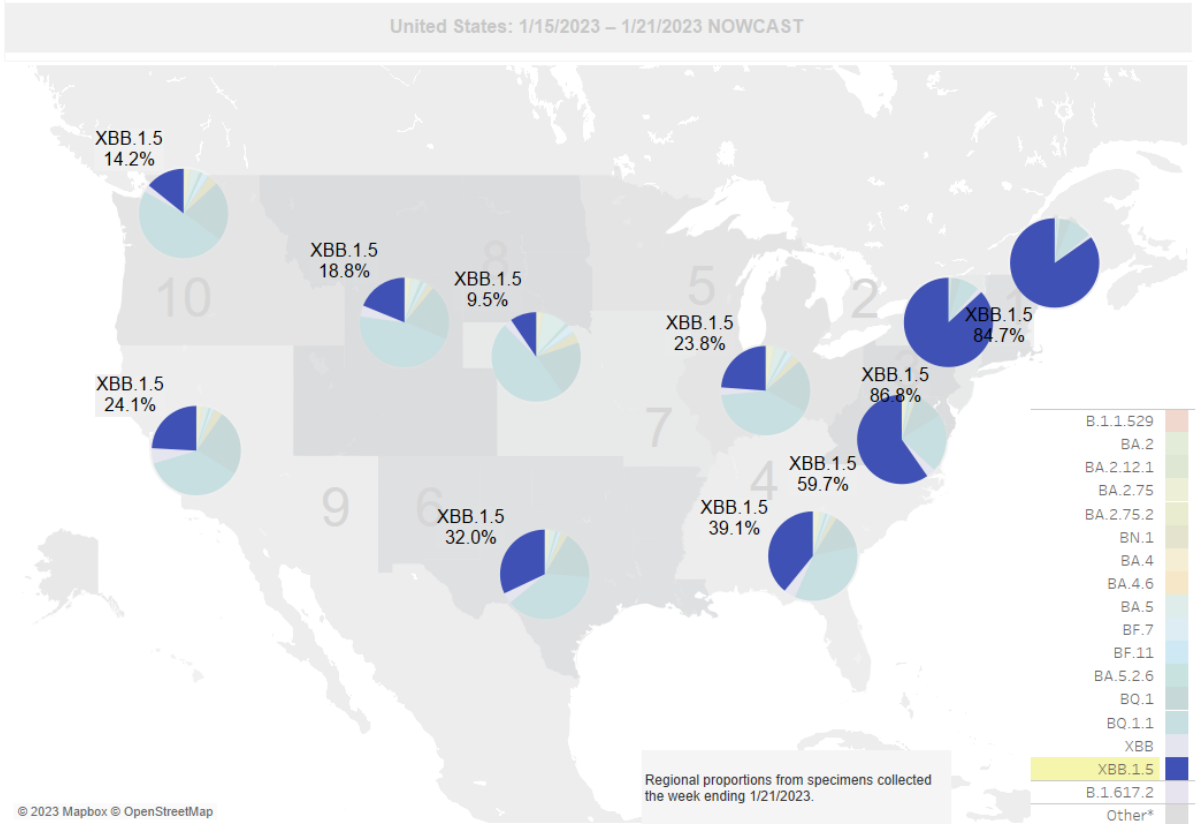


* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

\# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except XBB.1.5, sublineages of XBB are aggregated to XBB. For all the lineages listed in the above table, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.5 was aggregated to XBB. Lineages BA.2.75.2, XBB, XBB.1.5, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

XBB.1.5 predominates in the Northeast



XBB.1.5 is the primary lineage that is increasing in proportion

- XBB.1.5 is the fastest growing lineage nationally
  - Proportional doubling time nationally is **19.8 days** for XBB.1.5. Last weeks predicted doubling time was 16 days
  - XBB.1.5 is still predicted to be growing in every HHS Region

- In this model, all other lineages have very slow or decreasing growth rates nationally

- BQ lineage viruses are decreasing in proportion

- **CH.1.1** has been receiving some media attention this week.
  - It is a **BA.2.75** sub-lineage and is aggregated with BA.2.75 on the data tracker
  - It may have a more dramatic loss of neutralization than XBB.1.5.
  - Its weighted estimate is around 1% for the week ending 12/31
  - Nationally, it is not increasing.
  - It is showing some minor increases in some regions.

Variant Summary

- XBB.1.5 is the primary lineage of Omicron that is increasing in proportion
  - Overall case counts are decreasing as is % PCR positivity
  - Hospitalizations and deaths are also decreasing

- There are no data indicating infection with XBB.1.5 lead to an increase in disease severity

- Upcoming MMWRs

Overview

- Current variant landscape

- Diagnostics
  - When to test
  - Types of tests
  - How to interpret tests
  - Performance of current tests with currently circulating viruses

Diagnostic tests are for symptomatic and exposed persons

- Diagnostic tests are used when someone is:
  - Symptomatic
  - Known exposure to someone with SARS-CoV-2

- Screening tests are performed in specific environments on asymptomatic people
  - High risk settings (such as nursing homes or in health care settings)
  - Before events or travel

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 you that long to test positive

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

Diagnostic tests are based on nucleic acid or protein

- Nucleic acid amplification tests (NAAT)
  - PCRs, LAMP, CRISPR
  - Often lab-based
  - Highly sensitive and specific
  - Patients often test positive for extended period of time, well beyond infectiousness period

- Rapid antigen tests
  - Detect viral protein
  - May be POC (point-of-care) or at home
  - Less sensitive than NAATs
  - Virus must have replicated enough for protein to be detected
  - Delayed positivity

I have not had COVID-19 or I have not had a positive test within the past 90 days.

You may choose NAAT or antigen tests.
If you use an antigen test and your result is negative, multiple tests may be necessary.

I tested positive for COVID-19 in the last 90 days.

My first positive test result was within:

30 days or less

I have symptoms
Use antigen tests. If negative, multiple tests may be necessary.

I do not have symptoms
Testing is not recommended to detect a new infection.

My first positive test result was within:

31-90 days

I have symptoms
Use antigen tests. If negative, multiple tests may be necessary.

I do not have symptoms
Use antigen tests. If negative, multiple tests may be necessary

[COVID-19 Testing: What You Need to Know | CDC]

Interpreting tests

If Your COVID-19 Test is

Positive

Any positive COVID-19 test means the virus was detected and **you have an infection**.

- Isolate and take precautions including wearing a high-quality mask to protect others from getting infected.
- Tell people you had recent contact with that they may have been exposed.
- Monitor your symptoms. If you have any emergency warning signs, seek emergency care immediately.
- Consider contacting a healthcare provider, community health center , or pharmacy to learn about treatment options that may be available to you. Treatment must be started within several days after you first develop symptoms to be effective.
  - You are more likely to get very sick if you are an older adult or have an underlying medical condition. Possible treatment may be available for you.

COVID-19 Testing: What You Need to Know | CDC

Interpreting tests

If Your COVID-19 Test is

Negative

A negative COVID-19 test means the test did not detect the virus, but this **doesn't rule out that you could have an infection**. If you used an antigen test, see FDA instructions on repeat testing.

- If you have symptoms:
  - You may have COVID-19, but tested before the virus was detectable, or you may have another illness.
  - Take general public health precautions to prevent spreading an illness to others.
  - Contact a healthcare provider if you have any questions about your test result or if your symptoms worsen.
- If you do not have symptoms, but were exposed to the virus that causes COVID-19, you should continue to take recommended steps after exposure.
- If you do not have symptoms and you have not been exposed to the virus that causes COVID-19, you may return to normal activities.
  - Continue to take steps to protect yourself and others, including monitoring for symptoms. Get tested again if symptoms appear.

COVID-19 Testing: What You Need to Know | CDC

If a patient is tests negative by RAT

- 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

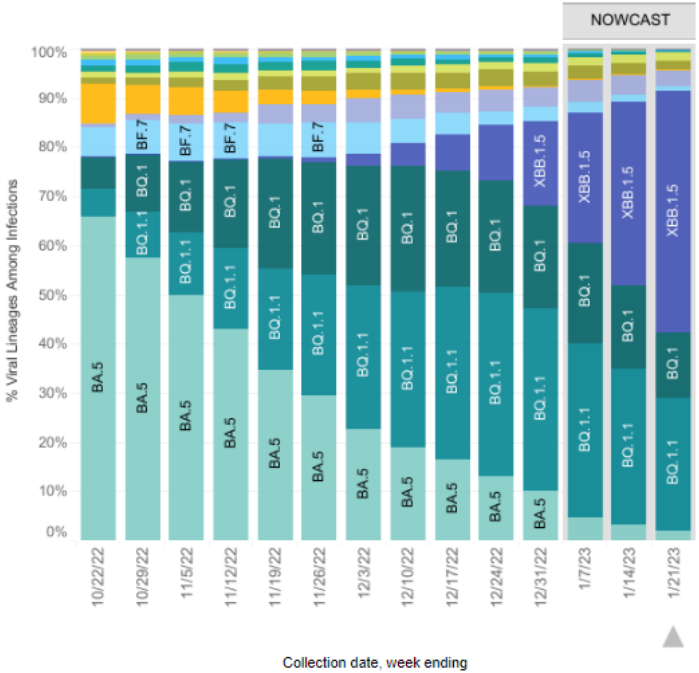
National Nowcast Estimates of SARS-CoV-2 lineages

United States: 1/15/2023 – 1/21/2023 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	49.1%	37.5-60.8%
	BQ.1.1	VOC	26.9%	20.9-33.9%
	BQ.1	VOC	13.3%	10.1-17.4%
	XBB	VOC	3.3%	2.7-4.1%
	BA.5	VOC	2.0%	1.5-2.8%
	BN.1	VOC	1.8%	1.4-2.5%
	BA.2.75	VOC	1.6%	1.2-2.2%
	BF.7	VOC	1.0%	0.8-1.4%
	BA.5.2.6	VOC	0.4%	0.3-0.5%
	BA.2	VOC	0.2%	0.1-0.3%
	BF.11	VOC	0.2%	0.1-0.2%
	BA.4.6	VOC	0.1%	0.0-0.1%
	BA.2.75.2	VOC	0.0%	0.0-0.1%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

United States: 10/16/2022 – 1/21/2023



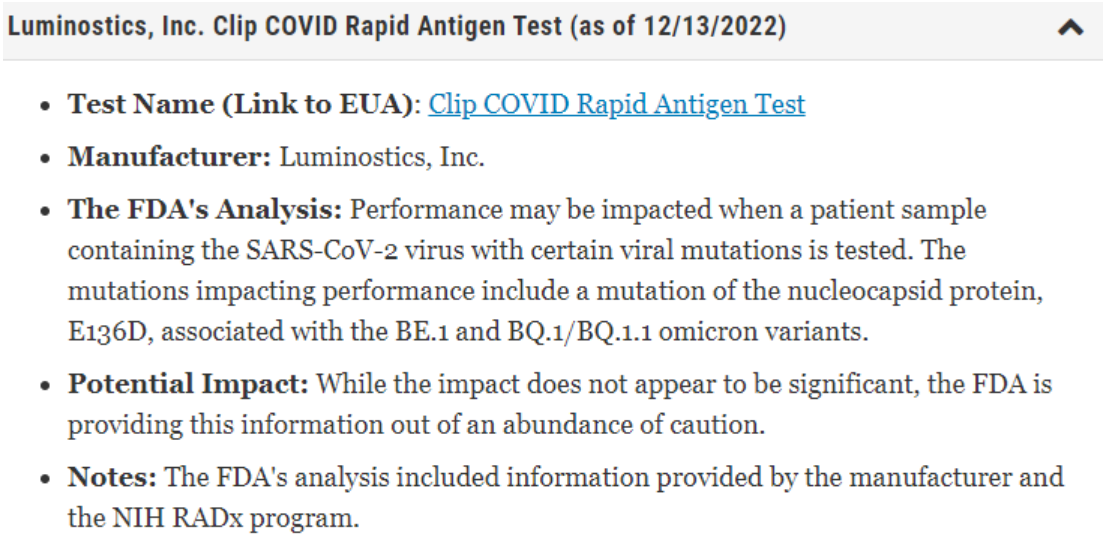
* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

\# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except XBB.1.5, sublineages of XBB are aggregated to XBB. For all the lineages listed in the above table, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.5 was aggregated to XBB. Lineages BA.2.75.2, XBB, XBB.1.5, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 and BQ.1.1 contain the spike substitution R346T.

FDA monitors diagnostic tests

- FDA monitors diagnostic tests for performance with newly emerging lineages
- When FDA identifies specific tests with problems, they are updated here:
  - SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests | FDA



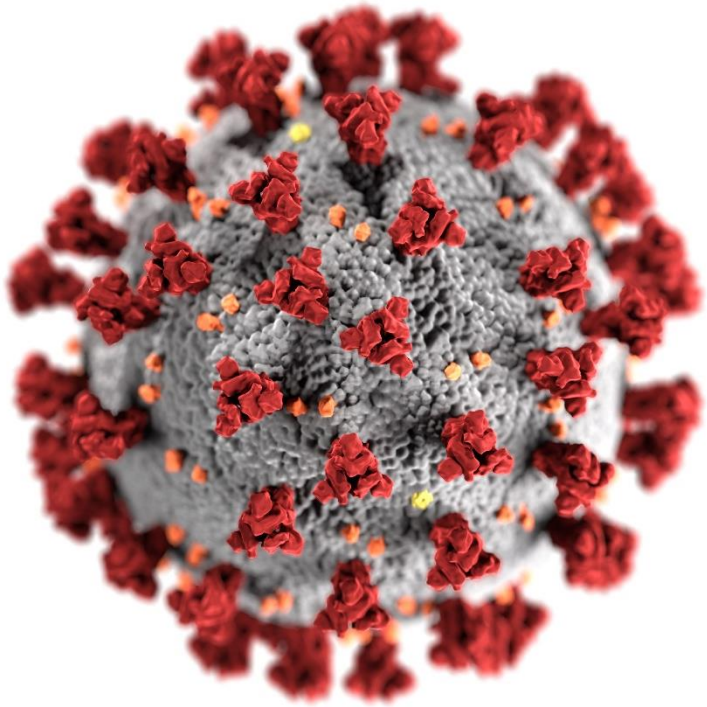
Luminostics, Inc. Clip COVID Rapid Antigen Test (as of 12/13/2022)

- **Test Name (Link to EUA)**: Clip COVID Rapid Antigen Test
- **Manufacturer:** Luminostics, Inc.
- **The FDA's Analysis:** Performance may be impacted when a patient sample containing the SARS-CoV-2 virus with certain viral mutations is tested. The mutations impacting performance include a mutation of the nucleocapsid protein, E136D, associated with the BE.1 and BQ.1/BQ.1.1 omicron variants.
- **Potential Impact:** While the impact does not appear to be significant, the FDA is providing this information out of an abundance of caution.
- **Notes:** The FDA's analysis included information provided by the manufacturer and the NIH RADx program.

Summary

- For Symptomatic patients who haven't had a recent infection, should test using either RAT or NAAT as soon as possible
  - If positive, they should isolate and consider treatment
  - If negative by RAT, they should retest one-to-two more times per FDA guidance, or seek testing with a NAAT
  - If symptomatic patient tests negative at least 3 times by RAT or once by NAAT, alternative diagnoses should be considered

- If a patient has had a recent infection and has new symptoms, use RATs, though multiple negative tests may be needed.



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Update on COVID-19 Therapeutics & Clinical Decision Making

Rajesh Gandhi, MD, FIDSA
Adarsh Bhimraj, MD, FIDSA

COVID-19 Outpatient Treatment Updates
January 20, 2023

Rajesh T. Gandhi, MD

Director, HIV Clinical Services and Education, Massachusetts General Hospital

Co-Director, Harvard University Center for AIDS Research

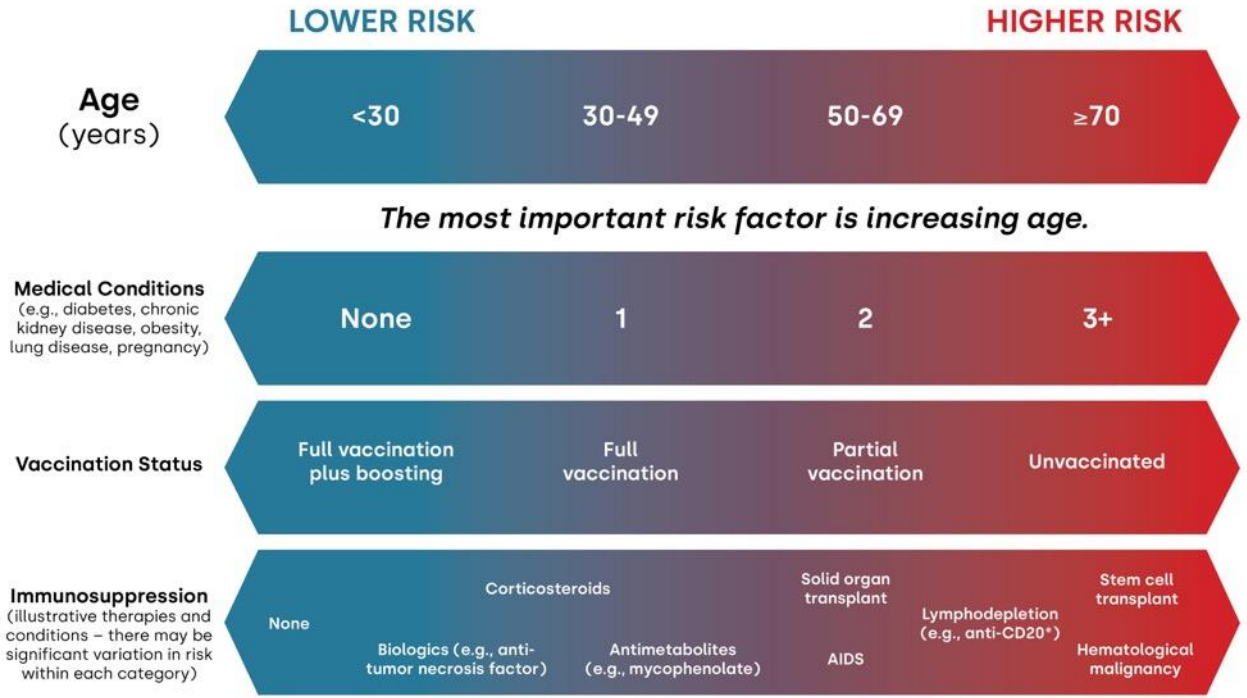
Disclosures (past 2 years):
Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels; Recommendations in this talk are my own and not necessarily those of the Panels

Acknowledgments: Arthur Kim, Jon Li, Courtney Tern

Case

- 62 yo woman presenting with 2 days of fever, cough, myalgias. SARS CoV-2 rapid antigen test positive
- Oxygen saturation >95%
- History of HIV (CD4 cell count 350; HIV RNA undetectable), pulmonary hypertension
- Medications: bictegravir/FTC/TAF; tadalafil 40 mg daily
- Received 2 doses of mRNA COVID-19 vaccine in 2021; has not received any booster doses
- Would you treat? If so, with what?

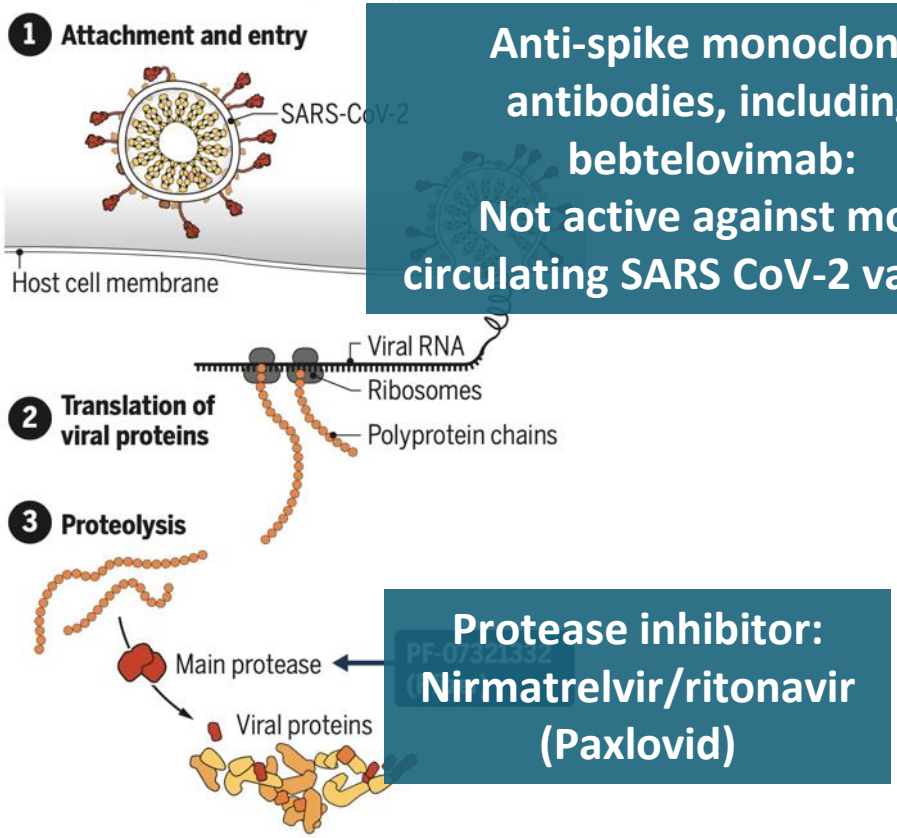
COVID-19 Risk Continuum



This resource was funded in part by a cooperative agreement with the Centers for Disease Control and Prevention (grant number NU50CK000574). The Centers for Disease Control and Prevention is an agency within the Department of Health and Human Services (HHS). The contents of this resource do not necessarily represent the policy of CDC or HHS, and should not be considered an endorsement by the Federal Government.

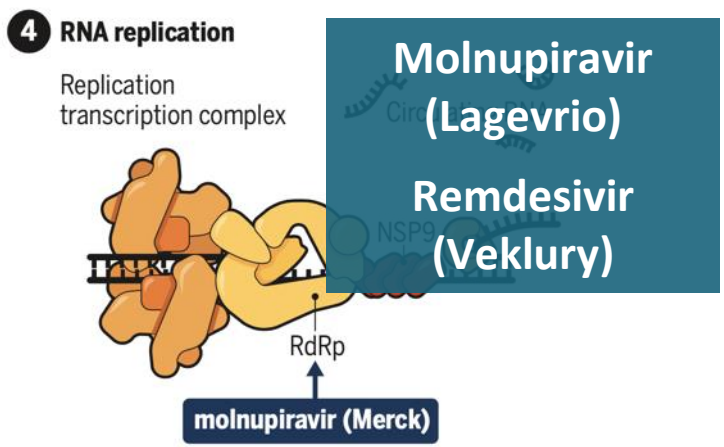
Original illustration by Dr. William Werbel. Adapted for the COVID-19 Real-Time Learning Network. Brought to you by CDC and IDSA

SARS CoV-2 Antivirals



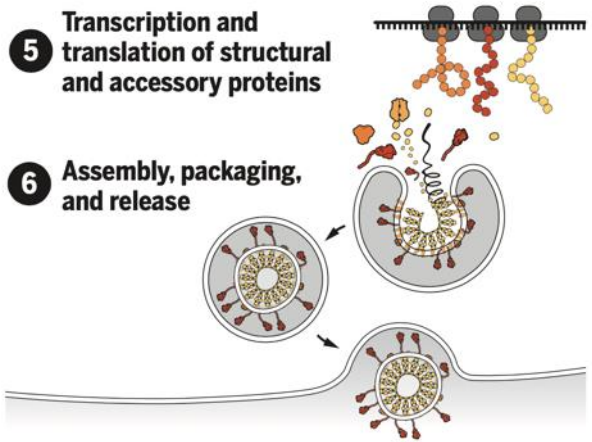
Anti-spike monoclonal antibodies, including bebtelovimab: Not active against most circulating SARS CoV-2 variants

Protease inhibitor: Nirmatrelvir/ritonavir (Paxlovid)



Molnupiravir (Lagevrio)

Remdesivir (Veklury)



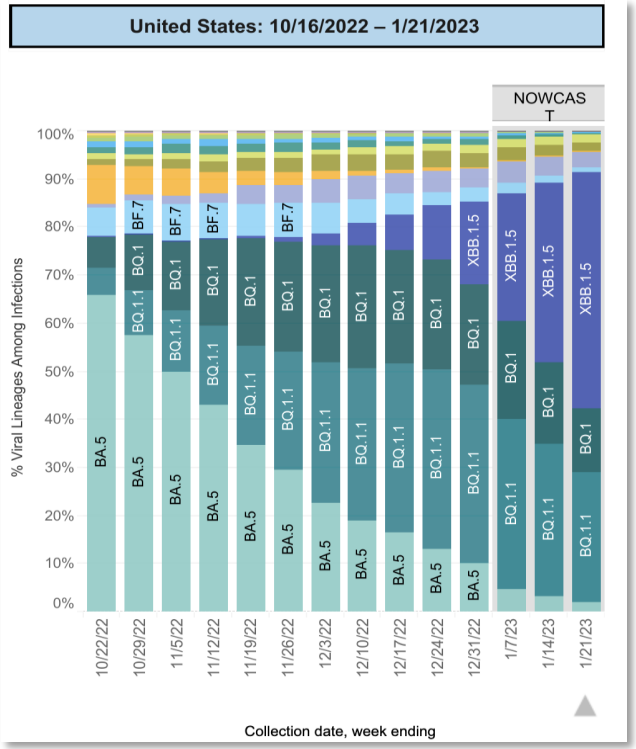
Modified from https://www.science.org/doi/epdf/10.1126/science.acx9605

Omicron variants resistant to Bebtelovimab (Beb)

Jan 21, 2023: XBB.1.5, BQ.1.1, BQ.1, XBB: vast majority of US isolates

Most prevalent variants

- XBB.1.5: 49.1%
- BQ.1.1: 26.9%
- BQ.1: 13.3%
- XBB: 3.3%



Omicron	Beb
BQ.1, 1.1	✗
XBB, XBB.1.5	✗

Modified from slide by Dr Jon Li

Nov 30, 2022:

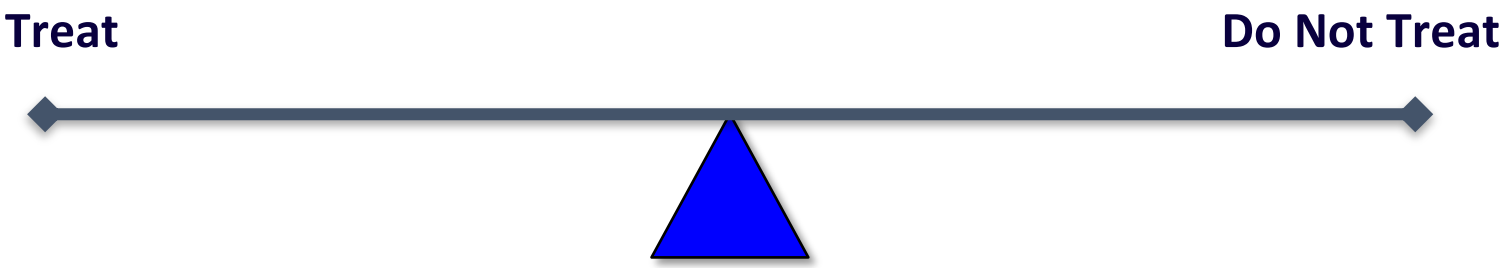
FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region

Small molecule antivirals anticipated to be active against new variants

	1) Nirmatrelvir/r	2) Remdesivir	3) Molnupiravir
Efficacy (hospitalization/death in unvaccinated, high risk)	• **Relative risk reduction: 88% (EPIC-HR)** • Absolute risk: 6.3%→0.8% • NNT: 18	• **Relative risk reduction: 87% (PINETREE)** • Absolute risk: 5.3%→0.7% • NNT: 22	• **Relative risk reduction: 30% (MOVe-OUT)** • Absolute risk: 9.7%→6.8% • NNT: 35
Pros	• 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
Cons	• Drug drug interactions	• Requires IV infusion on 3 consecutive days	• Lower efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

Modified from Table in Gandhi RT, Malani P, del Rio C, JAMA, Jan 14, 2022

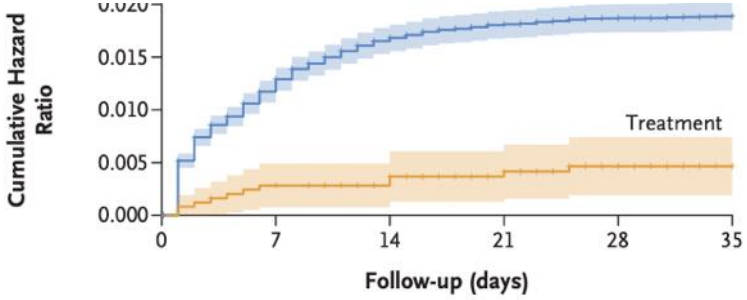
Should Vaccinated People be Treated?



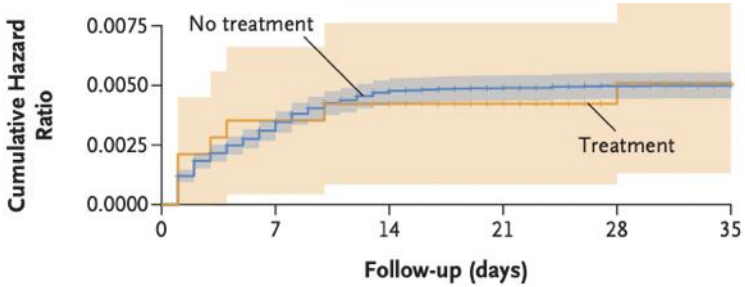
Nirmatrelvir/r in People with Previous Immunity

- Retrospective cohort study in Israel
- N/r (n=3902); No N/r (n=105,352)
- ~80% had previous immunity (vaccination, prior infection, both)
- ≥65 y: hospitalization less likely in treated group (hazard ratio, 0.27). Benefit regardless of previous immunity status.
- Patients aged 40–64, hospitalizations similar in treated and untreated groups

Age ≥ 65 y



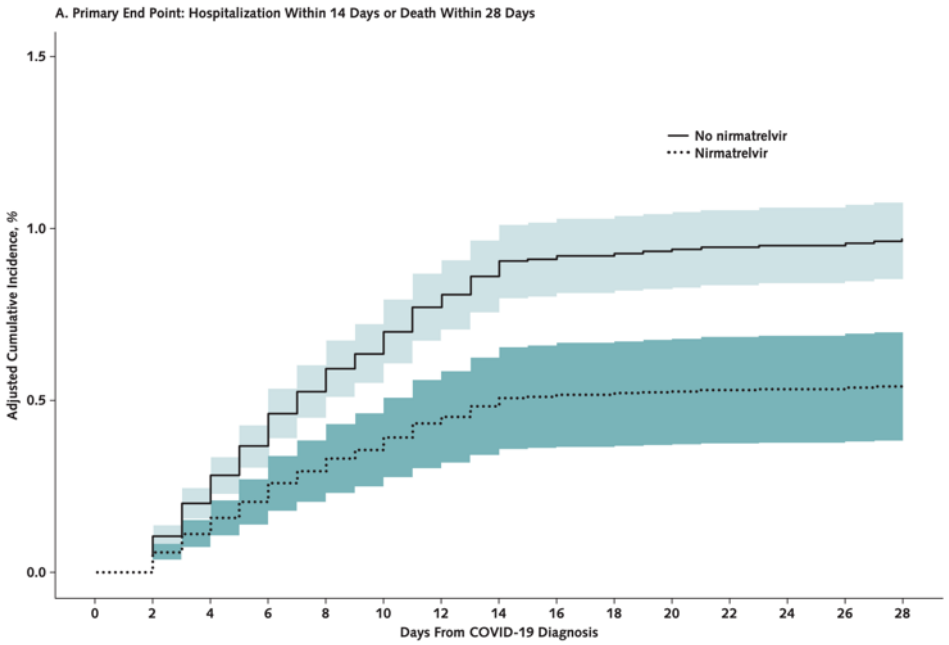
Age 40-64 y



Arbel R, NEJM, 2022

Nirmatrelvir/r for Early COVID-19 in Large US Health System

- 44,551 outpatients aged 50 years or older with COVID-19
- 90% with ≥3 vaccine doses
- Hospitalization/death: 0.55% (NMV/r) vs. 0.97% (no NMV/r)
- NMV/r recipients: lower risk for hospitalization (adjusted RR=0.60) and death (adjusted RR=0.29)



Dryden-Peterson S, Ann Intern Med, 2022

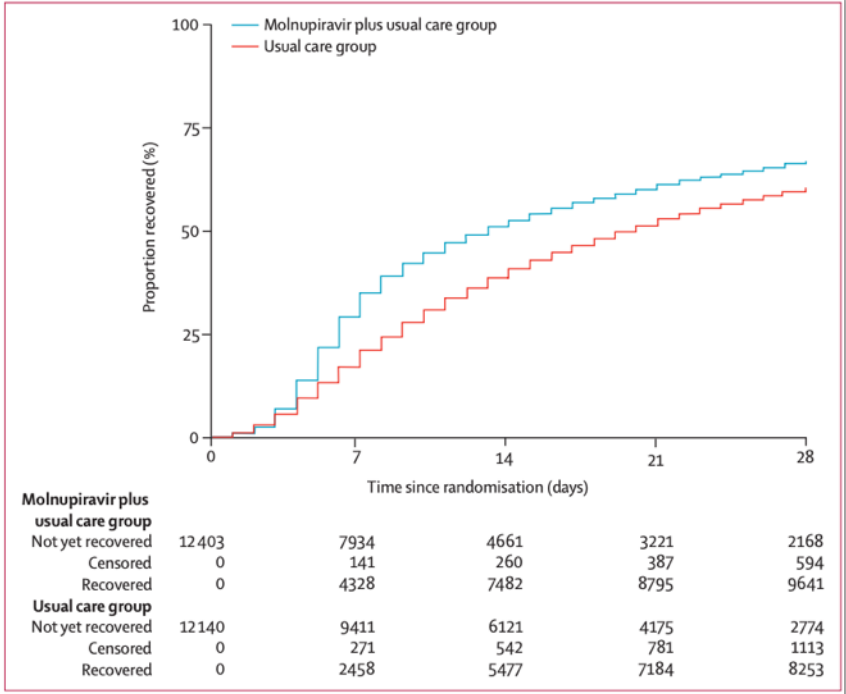
Nirmatrelvir/ritonavir: Drug Drug Interactions

- Ritonavir inhibits CYP3A during treatment (5 days) and for additional 2-3 days after treatment completed
  - Some medicines should not be coadministered, eg rivaroxaban, amiodarone, rifampin, tadalafil (for pulmonary hypertension)
  - Others may need to be held or markedly dose reduced, eg calcineurin inhibitors
  - Other medications may be temporarily stopped: eg, atorvastatin, rosuvastatin
- Useful resources:
  - NIH COVID-19 Treatment Guidelines
  - IDSA Management of Drug Interactions: Resource for Clinicians
  - Univ. of Liverpool COVID-19 Drug Interaction Checker

https://www.covid19treatmentguidelines.nih.gov/
https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/management-of-drug-interactions-with-nirmatrelvirritonavir-paxlovid/
https://www.covid19-druginteractions.org/

Molnupiravir (MOV) in Vaccinated Adults: PANORAMIC

- Open-label, randomized controlled trial in UK, Dec 2021 to April 2022
- ≈25,000 non-hospitalized adults with COVID and symptoms for ≤5 days
- MOV + usual care vs. usual care
- Aged ≥50 y or ≥18 y with high-risk comorbidity
- 94% received ≥3 COVID vaccine doses
- Hospitalization/death: 1% in both groups
- Time to self-reported recovery: 9 days (MOV) vs. 15 days (usual care)



Molnupiravir plus usual care group					
Not yet recovered	12403	7934	4661	3221	2168
Censored	0	141	260	387	594
Recovered	0	4328	7482	8795	9641
Usual care group					
Not yet recovered	12140	9411	6121	4175	2774
Censored	0	271	542	781	1113
Recovered	0	2458	5477	7184	8253

Figure 3: **Time from randomisation to first reported recovery from COVID-19**

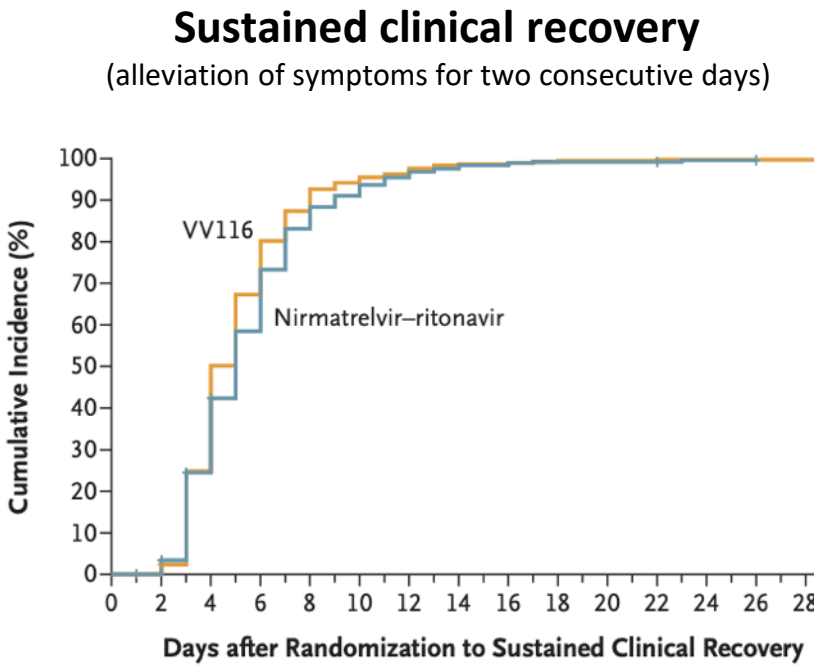
Butler CC, Lancet, 2022

Should Vaccinated People Be Treated? My Take

- Gradient of benefit: higher risk patients likely to derive more benefit
- Recommend treatment for older people, regardless of vaccination status
- For younger people who are vaccinated/boosted, recommend treatment if they have conditions that confer substantial risk, including obesity, heart or lung disease, immunosuppression, other high-risk conditions
- Not yet known whether early treatment ameliorates post-acute sequelae of SARS CoV-2 (PASC) – important research and knowledge gap

VV116 vs Nirmatrelvir-Ritonavir (NMV/r)

- VV116: oral remdesivir analogue
- Phase 3, observer-blinded, randomized trial during Omicron outbreak in China
- 771 adults with mild to moderate COVID-19 and high risk of progression to severe disease
- About 75% fully vaccinated or boosted
- Randomized: VV116 or NMV/r for 5 days
- Time to sustained clinical recovery: VV116 non-inferior to NMV/r; median time to symptom resolution was 7 days in both groups
- No deaths or progression to severe disease

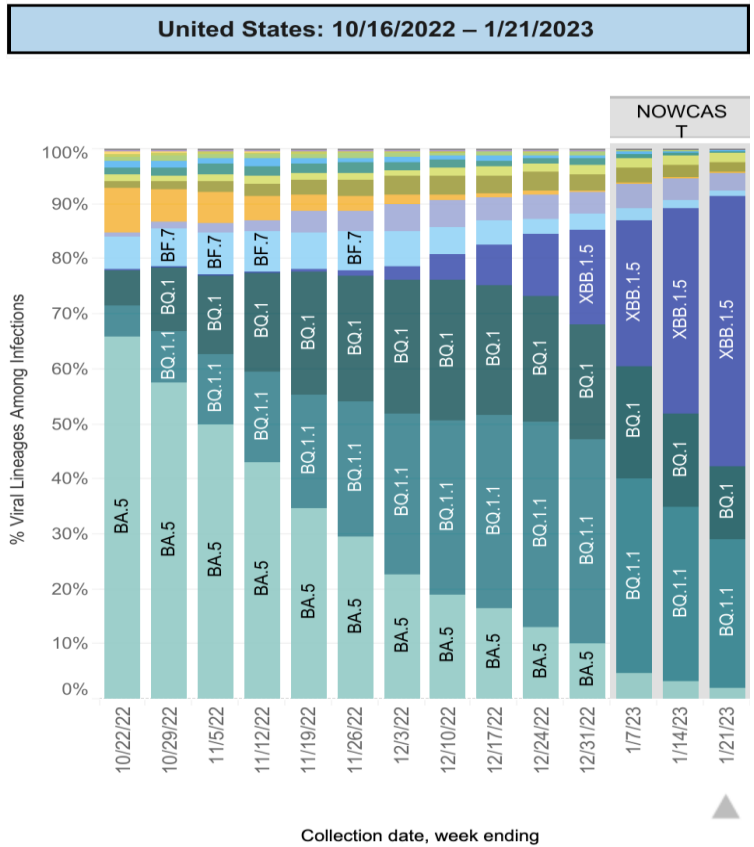


Cao Z, NEJM, 2022

Back to the Case

- 62 yo woman presenting with 2 days of fever, cough, myalgias. SARS CoV-2 rapid antigen test positive.
- Oxygen saturation >95%
- HIV (CD4 cell count 350; HIV RNA undetectable), pulmonary hypertension. Medications: bictegravir/FTC/TAF; tadalafil 40 mg daily
- 2 doses of mRNA COVID-19 vaccine in 2021; has not been boosted
- Treatment recommended. Because NMV/r cannot be given with her pulmonary hypertension medicine (tadalafil), she received iv remdesivir with rapid clinical improvement

New Omicron variants resistant to tixagevimab/cilgavimab



Jan 21, 2023: about 94% of US variants anticipated to be resistant to tixagevimab/cilgavimab

Omicron	Tixa/cil
XBB, XBB.1.5	✗
BQ.1, 1.1	✗
BF.7	✗

Modified from slide by Dr Jon Li

NIH | COVID-19 Treatment Guidelines

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-evusheld/

The COVID-19 Treatment Guidelines Panel's Statement on Tixagevimab Plus Cilgavimab (Evusheld) as Pre-Exposure Prophylaxis of COVID-19

Last Updated: January 10, 2023

- Tixagevimab/cilgavimab unlikely to be effective in preventing COVID-19 for vast majority because of high prevalence of resistant Omicron subvariants
- Given lack of other PrEP options, clinicians could still administer tixagevimab/cilgavimab after considering individual's risks and regional prevalence of resistant subvariants
- Immunocompromised individuals who receive tixagivimab/cilgavimab should be counseled to continue measures to avoid infection (including keeping up to date with vaccination) and to seek testing and treatment if symptoms of COVID-19 develop

Update: Treatment of Severe & critical COVID-19

Adarsh Bhimraj, MD

Director, Infectious Disease Education and Fellowship

Houston Methodist Hospital

Disclosures (past 2 years):
Chair, Infectious Diseases Society of America COVID-19 Treatment Guidelines Panel;
Recommendations in this talk are my own and not necessarily those of the Panel

Acknowledgments: Dr. Raj Gandhi

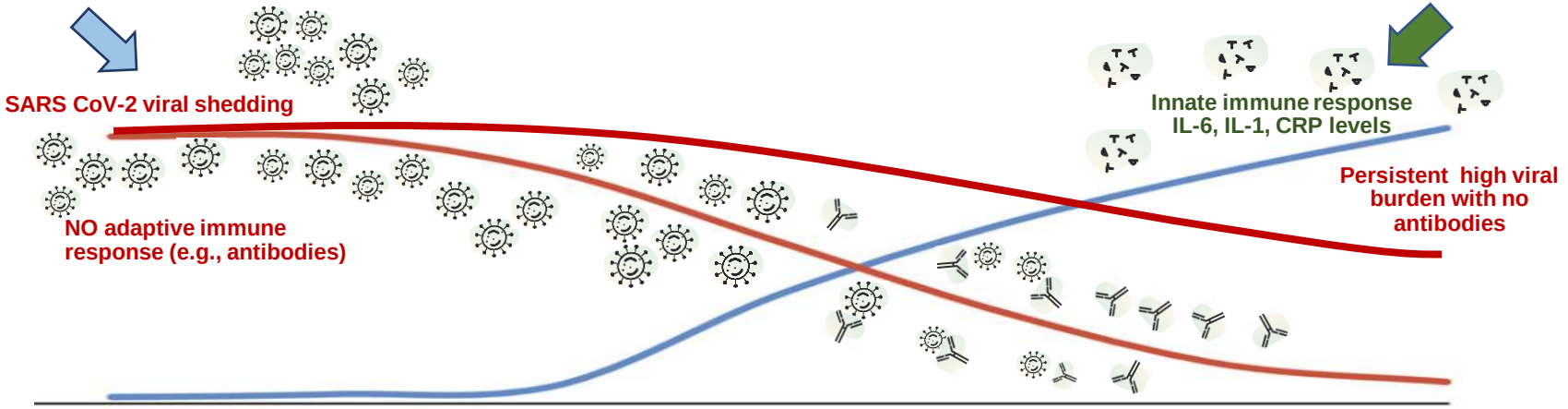
Treatment across the COVID-19 spectrum

Drugs targeting the virus (Evaluated in RCTs)

- Nirmratrelavir/ritonavir
- Remdesivir
- Molnupiravir
- Anti-spike monoclonal ABs
- Convalescent plasma

Immunomodulatory drugs (Evaluated in RCTs)

- Corticosteroids
- IL6 inhibitors
- JAK inhibitors
- IL1 inhibitors
- TNF α inhibitors
- T Cell stimulation modulators (abatacept)



Asymptomatic	Mild	Moderate	Severe & not critical	Critical HiFlow/ NIV	Critical IMV/ECMO
+SARS Co-V2 with no Sx	Mild Sx -URI	Lung involvement with normal SpO2 (>94%)	Lung involvement with hypoxemia (SpO2 <=94%)- needing only suppl.O2 by NC	Lung involvement needing HiFlow O2 or NIV	Lung involvement needing IMV or ECMO

What do the guidelines say?
convalescent plasma for Rx of COVID-19

Subpopulation with COVID-19	AABB	NIH	IDSA	FDA EUA
Hospitalized immunocompetent	Recommend against in unselected groups Suggest use if –ve SARS Cov-2 antibodies	Recommend against	Recommend against	Not authorized
Ambulatory immunocompetent with high risk for progression	Suggest use	Insufficient evidence. Neither for or against	Suggest use if no other options	Not authorized
Immunocompromised	Suggest use	Insufficient evidence. Neither for or against	No recommendation	Authorized high-titer units only

Jason V. B Et al. Ann Intern Med.2022;175:1332-1334.

AABB: Association for advancement of Blood and Biotherapies
NIH: National Institute of Health
IDSA: Infectious Diseases Society of America
FDA: Federal Drug Administration
EUA: Emergency Use Authorization

Suggest use
Recommend against/ not authorized
Suggest against
Neither for or against

Evidence for CCP use in hospitalized patients

Hospitalized immunocompetent: Mortality

№ of patients		Effect		Certainty	Importance
convalescent plasma	no convalescent plasma	Relative (95% CI)	Absolute (95% CI)		
2163/9082 (23.8%)	2007/8150 (24.6%)	**RR 0.98** (0.93 to 1.03)	**5 fewer per 1,000** (from 17 fewer to 7 more)	⨁⨁⨁◯ MODERATE	CRITICAL

Bhimraj A, et al IDSA guidelines on Rx COVID-19. **2022**; Version 10.1.1.

Hospitalized immunocompromised: Mortality

	Illustrative comparative risks (95% CI)[b]				
All cause mortality	Assumed risk, controls (standard of care)	Corresponding risk, intervention (convalescent plasma)	Relative effect, RR (95% CI)	No. of participants	Quality of the evidence (GRADE)[c]
All studies (RCTs and non-RCTs)	265 per 1000	172 per 1000 (from 132 to 207)	0.63 (0.50 to 0.78)	1774 Patients (8 trials, 3 RCTs and 5 non-RCTs)	2 of 4; Low (downgraded for serious ROB)
RCTs only	284 per 1000	165 per 1000 (from 97 to 278)	0.58 (0.34/0.98)	214 Participants (3 RCTs)	3 of 4; Moderate (downgraded for ROB)
Cohort studies only	264 per 1000	169 per 1000 (from 132 to 216)	0.64 (0.50/0.82)	1560 Participants (5 trials)	2 of 4; Low (downgraded for serious risk of bias)

Senfeld JW et al. JAMA Netw Open. 2023;6(1):e2250647. doi:10.1001/jamanetworkopen.2022.50647

Case 2

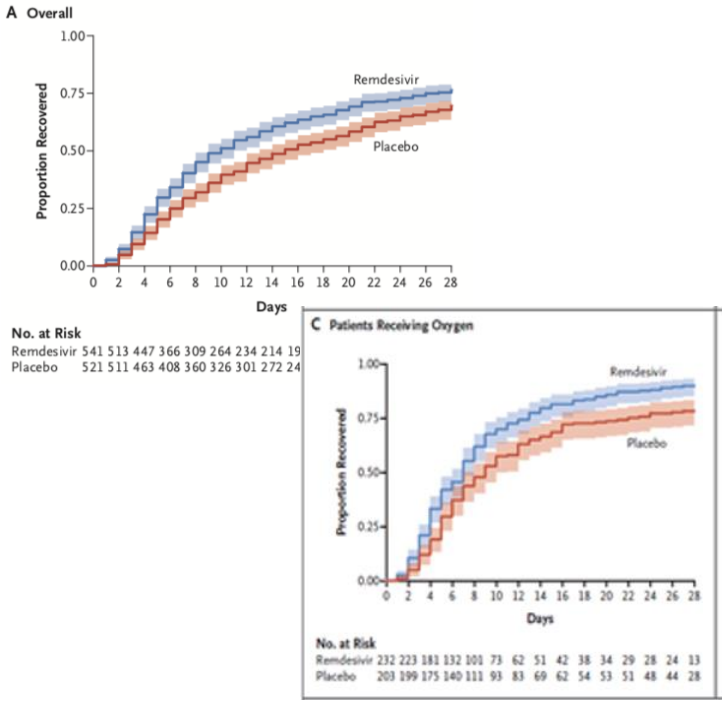
- 65-year-old female
- BMI (Body Mass Index) of 30
- Hypertension & Coronary diseases
- 6 days of fever, cough, dyspnea and diarrhea
- SARS CoV-2 PCR +
- In the emergency room for worsening dyspnea
- SpO2 (pulse oximetry): 90% on Room air >SpO2: 95% on 3 liters O2 by Nasal canula
- CRP 10 mg/dL, WBC 18,000/µL
- AST 60 U/L, ALT 65 U/L

What would you do?

Remdesivir (RDV) in Hospitalized Patients

- Nucleotide prodrug: inhibits viral RNA polymerase
- ACTT-1: Hospitalized pts, lower respiratory tract infection randomized to RDV or placebo
  - Recovery (time to hospital discharge) more rapid with RDV than placebo (10 vs 15 d)
  - Benefit of RDV clearest in those on supplemental oxygen but not intubated or on high-flow O2
  - Mortality:
    - 11.4% RDV, 15.2% placebo
    - Hazard ratio 0.73, 95% CI, 0.52-1.03

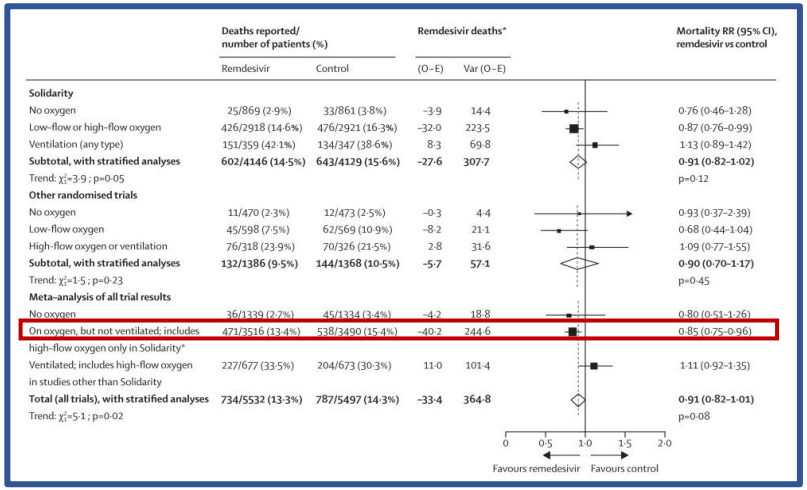
ACTT-1: Time to Recovery



Beigel JH, et al. N Engl J Med 2020; 383(19): 1813-26.

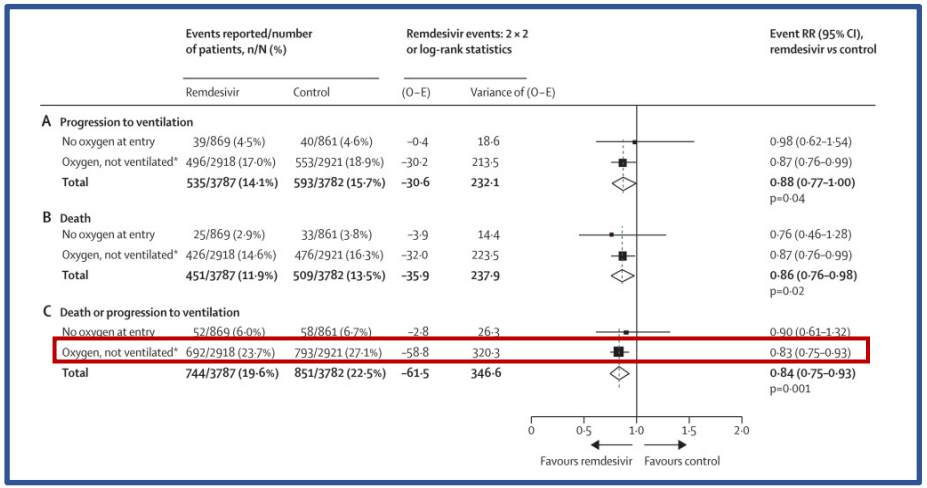
Remdesivir: WHO solidarity meta-analysis

Mortality



	Deaths reported/ number of patients (%)		Remdesivir deaths*		Mortality RR (95% CI), remdesivir vs control
	Remdesivir	Control	(O−E)	Var (O−E)	
Solidarity					
No oxygen	25/869 (2·9%)	33/861 (3·8%)	−3·9	14·4	0·76 (0·46–1·28)
Low-flow or high-flow oxygen	426/2918 (14·6%)	476/2921 (16·3%)	−32·0	223·5	0·87 (0·76–0·99)
Ventilation (any type)	151/359 (42·1%)	134/347 (38·6%)	8·3	69·8	1·13 (0·89–1·42)
Subtotal, with stratified analyses	**602/4146 (14·5%)**	**643/4129 (15·6%)**	**−27·6**	**307·7**	**0·91 (0·82–1·02)**
Trend: χ^2_1=3·9 ; p=0·05					p=0·12
Other randomised trials					
No oxygen	11/470 (2·3%)	12/473 (2·5%)	−0·3	4·4	0·93 (0·37–2·39)
Low-flow oxygen	45/598 (7·5%)	62/569 (10·9%)	−8·2	21·1	0·68 (0·44–1·04)
High-flow oxygen or ventilation	76/318 (23·9%)	70/326 (21·5%)	2·8	31·6	1·09 (0·77–1·55)
Subtotal, with stratified analyses	**132/1386 (9·5%)**	**144/1368 (10·5%)**	**−5·7**	**57·1**	**0·90 (0·70–1·17)**
Trend: χ^2_1=1·5 ; p=0·23					p=0·45
Meta-analysis of all trial results					
No oxygen	36/1339 (2·7%)	45/1334 (3·4%)	−4·2	18·8	0·80 (0·51–1·26)
On oxygen, but not ventilated; includes high-flow oxygen only in Solidarity*	471/3516 (13·4%)	538/3490 (15·4%)	−40·2	244·6	0·85 (0·75–0·96)
Ventilated; includes high-flow oxygen in studies other than Solidarity	227/677 (33·5%)	204/673 (30·3%)	11·0	101·4	1·11 (0·92–1·35)
Total (all trials), with stratified analyses	**734/5532 (13·3%)**	**787/5497 (14·3%)**	**−33·4**	**364·8**	**0·91 (0·82–1·01)**
Trend: χ^2_1=5·1 ; p=0·02					p=0·08

Progression to mechanical ventilation



	Events reported/number of patients, n/N (%)		Remdesivir events: 2 × 2 or log-rank statistics		Event RR (95% CI), remdesivir vs control
	Remdesivir	Control	(O−E)	Variance of (O−E)	
A **Progression to ventilation**					
No oxygen at entry	39/869 (4·5%)	40/861 (4·6%)	−0·4	18·6	0·98 (0·62–1·54)
Oxygen, not ventilated*	496/2918 (17·0%)	553/2921 (18·9%)	−30·2	213·5	0·87 (0·76–0·99)
Total	**535/3787 (14·1%)**	**593/3782 (15·7%)**	**−30·6**	**232·1**	**0·88 (0·77–1·00)**
					p=0·04
B **Death**					
No oxygen at entry	25/869 (2·9%)	33/861 (3·8%)	−3·9	14·4	0·76 (0·46–1·28)
Oxygen, not ventilated*	426/2918 (14·6%)	476/2921 (16·3%)	−32·0	223·5	0·87 (0·76–0·99)
Total	**451/3787 (11·9%)**	**509/3782 (13·5%)**	**−35·9**	**237·9**	**0·86 (0·76–0·98)**
					p=0·02
C **Death or progression to ventilation**					
No oxygen at entry	52/869 (6·0%)	58/861 (6·7%)	−2·8	26·3	0·90 (0·61–1·32)
Oxygen, not ventilated*	692/2918 (23·7%)	793/2921 (27·1%)	−58·8	320·3	0·83 (0·75–0·93)
Total	**744/3787 (19·6%)**	**851/3782 (22·5%)**	**−61·5**	**346·6**	**0·84 (0·75–0·93)**
					p=0·001

Small effect against death or progression to ventilation (or both)

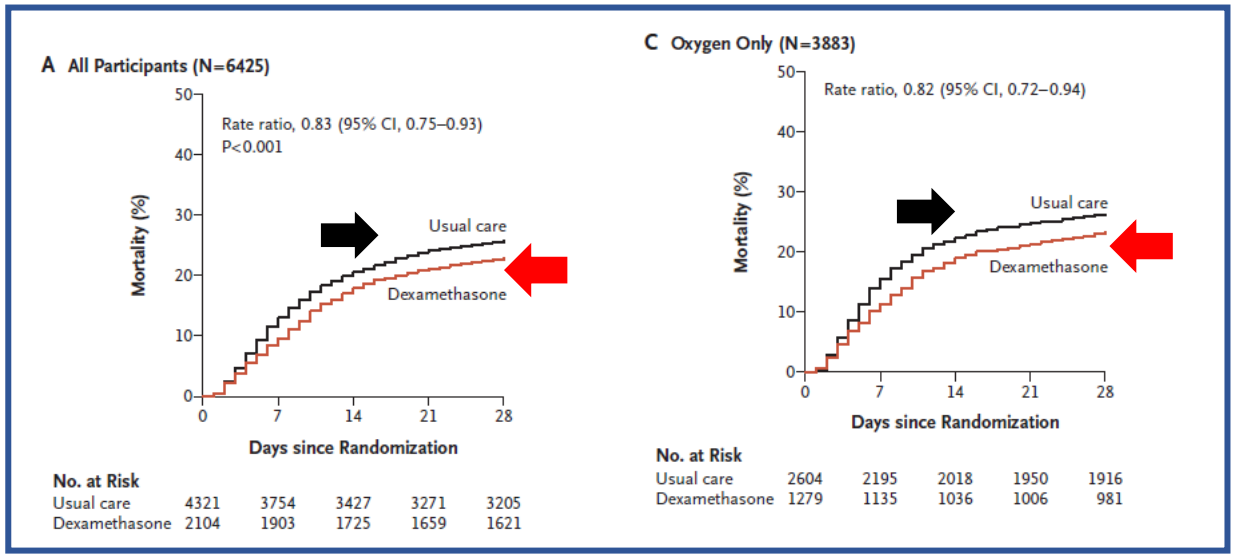
WHO Solidarity collaborative group The Lancet 2022 3991941-1953DOI: (10.1016/S0140-6736(22)00519-0)

Corticosteroids in severe noncritical COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

Dexamethasone in RECOVERY trial : 28-day Mortality



28-day Mortality: In patients on O2 low flow 23.3% vs. Usual care 26.2%;Rate Ratio, 0.82 (95% CI, 0.72 to 0.94)

Horby,PW,et,al. N Engl J Med 2021; 384:693-704

CASE 2 continued…

65-year-old female, BMI 30, hypertension & coronary diseases admitted with COVID-19 pneumonia needing 2-3 L of O2 by nasal canula

- Started on remdesivir and dexamethasone 6 mg daily
- 48 hours later she is more dyspneic needing 5-6 L O2 by nasal cannula.
- CRP increased from 10 on admission to 20 mg/dl

What would you do?

Severe noncritical COVID-19 not improving or worsening on dexamethasone 6mg/d and remdesivir?

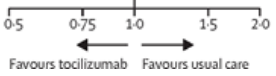
- Is there a role for higher dose dexamethasone in sub-populations with severe non-critical diseases?
  - COVID STEROID 2 Trial- 28-day mortality was 27.1% with 12-mg/d vs 32.3% for 6-mg/d
    JAMA. 2021;326(18):1807-1817. doi:10.1001/jama.2021.18295
  - COVIDICUS trial 60-day mortality was 25.9% with 20mg/d x 5d+10mg/d x 5d vs 26.8% 6mg/d
    JAMA Intern Med. 2022;182(9):906–916. doi:10.1001/jamainternmed.2022.2168
  - RECOVERY (no O2 or simple O2)- 28-day mortality was 18% with 20mg/d x 5d+10mg/d x 5d vs 12% 6mg/d
    - https://www.medrxiv.org/content/10.1101/2022.12.16.22283578v1

- Are there sub-populations who will benefit from “augmented” immunomodulatory therapy in severe, but non-critical diseases?
  - IL6 inhibitors -Tocilizumab
  - JAK inhibitors- Baricitinib
  - Other immunomodulatory agents

Tocilizumab in non-ventilated patients

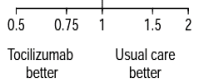
28-day mortality in those not on ventilatory support

	Tocilizumab group	Usual care group	Risk ratio (95% CI)
Age, years (χ^2_1=0·0; p=0·88)			
<70	273/1331 (21%)	309/1355 (23%)	0·88 (0·74–1·03)
70–79	212/478 (44%)	245/480 (51%)	0·82 (0·68–0·99)
≥80	136/213 (64%)	175/259 (68%)	0·92 (0·73–1·15)
Sex (χ^2_1=2·4; p=0·12)			
Men	417/1337 (31%)	529/1437 (37%)	0·80 (0·71–0·91)
Women	204/685 (30%)	200/657 (30%)	0·97 (0·80–1·18)
Ethnicity (χ^2_1=0·0; p=0·98)			
White	476/1530 (31%)	573/1597 (36%)	0·83 (0·73–0·94)
Black, Asian, or minority ethnic	99/354 (28%)	123/378 (33%)	0·83 (0·64–1·09)
Unknown	46/138 (33%)	33/119 (28%)	1·20 (0·77–1·88)
Days since symptom onset (χ^2_1=1·1; p=0·30)			
≤7	214/668 (32%)	256/660 (39%)	0·78 (0·65–0·94)
>7	407/1354 (30%)	473/1433 (33%)	0·88 (0·77–1·01)
Respiratory support at randomisation (χ^2_1=0·8; p=0·38)			
No ventilator support*	180/935 (19%)	214/933 (23%)	0·81 (0·67–0·99)
Non-invasive ventilation†	310/819 (38%)	366/867 (42%)	0·86 (0·74–1·00)
Invasive mechanical ventilation‡	131/268 (49%)	149/294 (51%)	0·93 (0·74–1·18)
Use of corticosteroids§ (χ^2_1=7·7; p=0·01)			
Yes	482/1664 (29%)	600/1721 (35%)	0·79 (0·70–0·89)
No	139/357 (39%)	127/367 (35%)	1·16 (0·91–1·48)
Unknown	0/1 (0%)	2/6 (33%)	–
All participants	**621/2022 (31%)**	**729/2094 (35%)**	**0·85 (0·76–0·94)**
			p=0·0028



Composite of death or IMV in those not on ventilatory support

	Tocilizumab	Usual care	RR (95% CI)
Age, years (χ^2_1=2.0; p=0.15)			
<70	292/1121 (26%)	347/1116 (31%)	0.84 (0.73–0.96)
≥70 <80	192/424 (45%)	236/430 (55%)	0.83 (0.72–0.94)
≥80	135/209 (65%)	171/254 (67%)	0.96 (0.84–1.09)
Sex (χ^2_1=5.9; p=0.01)			
Men	408/1153 (35%)	551/1227 (45%)	0.79 (0.71–0.87)
Women	211/601 (35%)	203/573 (35%)	0.99 (0.85–1.16)
Ethnicity (χ^2_1=0.0; p=0.84)			
White	488/1370 (36%)	604/1418 (43%)	0.84 (0.76–0.92)
Black, Asian, or Minority Ethnic	99/285 (35%)	118/291 (41%)	0.86 (0.69–1.06)
Unknown	32/99 (32%)	32/91 (35%)	0.92 (0.62–1.37)
Days since symptom onset (χ^2_1=0.3; p=0.59)			
≤7	236/628 (38%)	287/624 (46%)	0.82 (0.72–0.93)
>7	383/1126 (34%)	467/1175 (40%)	0.86 (0.77–0.95)
Respiratory support at randomization (χ^2_1=0.8; p=0.38)			
No ventilator support*	217/935 (23%)	268/933 (29%)	0.81 (0.69–0.94)
Non-invasive ventilation†	402/819 (49%)	486/867 (56%)	0.88 (0.80–0.96)
Use of corticosteroids‡ (χ^2_1=3.5; p=0.06)			
Yes	495/1480 (33%)	617/1500 (41%)	0.81 (0.74–0.89)
No	124/273 (45%)	136/295 (46%)	0.99 (0.82–1.18)
Unknown	0/1 (0%)	1/5 (20%)	
All participants	**619/1754 (35%)**	**754/1800 (42%)**	**0.84 (0.77–0.92)**
			p<0.0001



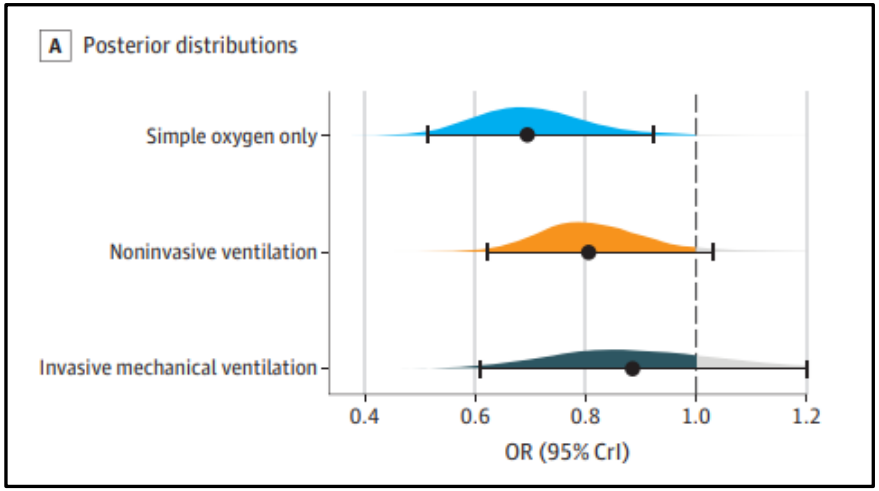
RECOVEY collaborative group The Lancet 2021 3971637-1645DOI: (10.1016/S0140-6736(21)00676-0)

Mortality by COVID-19 severity with tocilizumab+ steroids

Bayesian reanalysis of a meta-analysis of 15 studies from WHO REACT working group metanalysis

Subgroup by resp support	No. of pts	Odds of survival
Simple O2	2117	**0.70 (95% CrI 0.50-0.91)**
Noninvasive ventilation	2505	**0.81 (95% CrI, 0.63-1.03)**
Mechanical ventilation	717	**0.89 (95% CrI, 0.61-1.22)**

Posterior distributions and probability of a mortality benefit



Albuquerque et al JAMA Netw Open. 2022;5(2):e220548.

Tocilizumab RCTs: WHO REACT meta-analysis

28-day Mortality in Tocilizumab RCTs

Anti-IL-6 agent and trial name	No. of events/total patients: Usual care or placebo	Anti-IL-6	Odds ratio (95% CI)	Weight, %
Tocilizumab				
ARCHITECTS	2/11	0/10	0.18 (0.01-4.27)	0.09
BACC-Bay	4/82	9/161	1.15 (0.34-3.87)	0.63
CORIMUNO-TOCI-1	8/67	7/63	0.92 (0.31-2.71)	0.79
CORIMUNO-TOCI-ICU	10/43	8/49	0.64 (0.23-1.82)	0.85
COV-AID[a]	7/72	9/81	1.16 (0.41-3.29)	0.84
COVACTA	28/144	58/294	1.02 (0.62-1.68)	3.62
COVIDOSE2-SS-A	2/8	0/19	0.07 (<0.01-1.58)	0.09
COVIDSTORM	0/13	0/26	NA[b]	
COVINTOC	15/88	11/91	0.67 (0.29-1.55)	1.30
COVITOZ	0/9	0/17	NA[b]	
EMPACTA	11/128	26/249	1.24 (0.59-2.60)	1.67
HMO-020-0224	8/17	11/37	0.48 (0.15-1.56)	0.65
ImmCoVA	2/27	2/22	1.25 (0.16-9.67)	0.22
PreToVid[c]	34/180	21/174	0.59 (0.33-1.06)	2.63
RECOVERY	729/2094	621/2022	0.83 (0.73-0.95)	53.76
REMAP-CAP[d]	116/358	85/353	0.66 (0.48-0.92)	8.43
REMDACTA	41/210	78/430	0.91 (0.60-1.39)	5.18
TOCIBRAS	6/64	14/65	2.65 (0.95-7.42)	0.87
TOCOVID	0/134	0/136	NA[b]	
Subgroup I^2 = 3.3%	1023/3749	960/4299	0.83 (0.74-0.92)	81.61

Favors anti-IL-6 | Favors usual care or placebo

- 27 RCTs, 10,930 pts
- Odds Ratio death for tocilizumab
  - 0.83 (95% CI, 0.74-0.92; *P* < .001)
- Odds Ratio death for sarilumab
  - 1.08 (95% CI, 0.86-1.36; *P* = .52)
- Subgroup that received corticosteroids benefitted

Mortality with steroid use in Tocilizumab RCTs

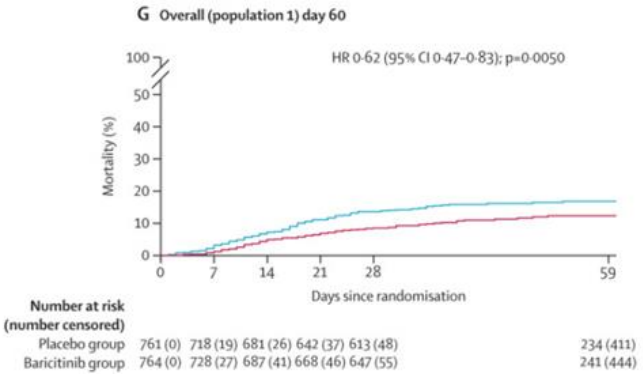
Outcome and treatment	I^2, %	No. of events/total patients: Control	Anti-IL-6	Odds ratio (95% CI)	Ratio of odds ratios (95% CI)
28-d mortality					
Tocilizumab					
No corticosteroid use	0	211/898	254/1192	1.06 (0.85-1.33)	0.69 (0.52-0.91)
Corticosteroid use	0	793/2585	693/2815	0.77 (0.68-0.87)	

Favors anti-IL-6 | Favors control

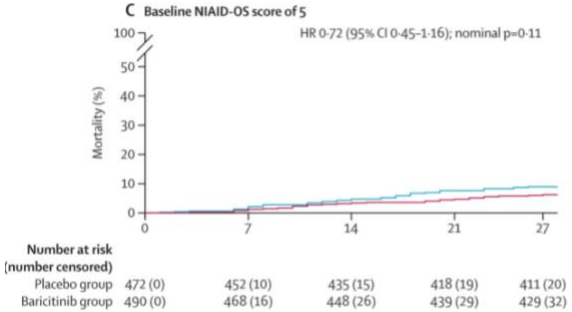
WHO REACT working group JAMA. 2021;326(6):499-518. doi:10.1001/jama.2021.11330

Baricitinib for severe noncritical COVID-19
COV-BARRIER STUDY

Overall population



On supplemental low flow oxygen



60-day all-cause mortality overall

- Baricitinib 10% (n=79) vs placebo 15% (n=116) HR 0·62 [95% CI 0·47–0·83]; p=0·0050

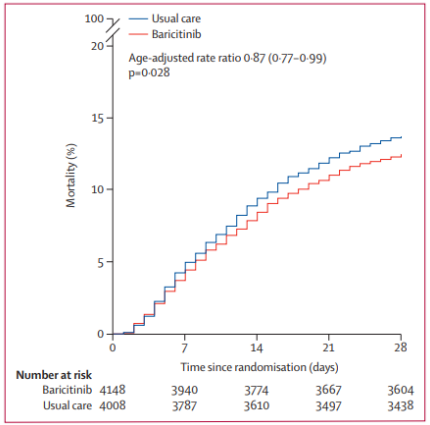
60-day mortality OS 5 subgroup

- Baricitinib 34/490 [7%] vs Placebo 49/472 [10%]
- HR 0·70 [95% CI 0·45–1·09], p=0·071

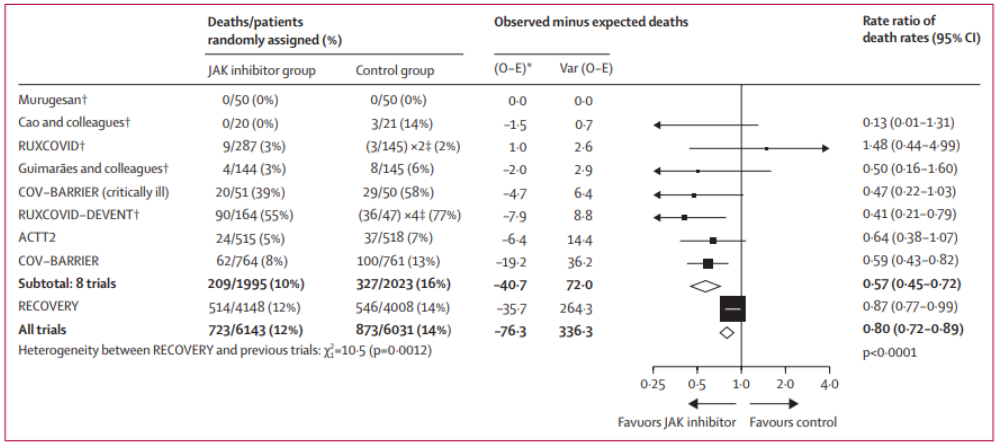
Marconi V Et al. The Lancet Respiratory Medicine DOI: (10.1016/S2213-2600(21)00331-3

Baricitinib-RECOVERY trial

28-day mortality in RECOVERY



28-day mortality metanalysis of RCT's



	Deaths/patients randomly assigned (%)		Observed minus expected deaths		Rate ratio of death rates (95% CI)
	JAK inhibitor group	Control group	(O–E)*	Var (O–E)	
Murugesan†	0/50 (0%)	0/50 (0%)	0·0	0·0	
Cao and colleagues†	0/20 (0%)	3/21 (14%)	−1·5	0·7	0·13 (0·01–1·31)
RUXCOVID†	9/287 (3%)	(3/145) ×2‡ (2%)	1·0	2·6	1·48 (0·44–4·99)
Guimarães and colleagues†	4/144 (3%)	8/145 (6%)	−2·0	2·9	0·50 (0·16–1·60)
COV-BARRIER (critically ill)	20/51 (39%)	29/50 (58%)	−4·7	6·4	0·47 (0·22–1·03)
RUXCOVID-DEVENT†	90/164 (55%)	(36/47) ×4‡ (77%)	−7·9	8·8	0·41 (0·21–0·79)
ACTT2	24/515 (5%)	37/518 (7%)	−6·4	14·4	0·64 (0·38–1·07)
COV-BARRIER	62/764 (8%)	100/761 (13%)	−19·2	36·2	0·59 (0·43–0·82)
Subtotal: 8 trials	**209/1995 (10%)**	**327/2023 (16%)**	**−40·7**	**72·0**	**0·57 (0·45–0·72)**
RECOVERY	514/4148 (12%)	546/4008 (14%)	−35·7	264·3	0·87 (0·77–0·99)
All trials	**723/6143 (12%)**	**873/6031 (14%)**	**−76·3**	**336·3**	**0·80 (0·72–0·89)**

Heterogeneity between RECOVERY and previous trials: χ^2_1=10·5 (p=0·0012)

p<0·0001

0·25 0·5 1·0 2·0 4·0

Favuors JAK inhibitor Favours control

	Baricitinib	Usual care	RR (95% CI)
Respiratory support at randomisation (χ^2_1= 0.9; p=0.33)			
None	15/228 (7%)	19/237 (8%)	0.78 (0.39–1.53)
Simple oxygen	256/2770 (9%)	253/2743 (9%)	0.94 (0.79–1.12)
Non invasive ventilation	204/1016 (20%)	230/911 (25%)	0.75 (0.62–0.90)
Invasive mechanical ventilation	38/134 (28%)	44/117 (38%)	0.90 (0.58–1.39)

RECOVERY collaborative group Lancet. 2022; **400**: 359-368

CASE 2 continued…

- Patient was transferred to the ICU and rapidly progressed to needing high-flow oxygen on remdesivir and dexamethasone 6mg/d.

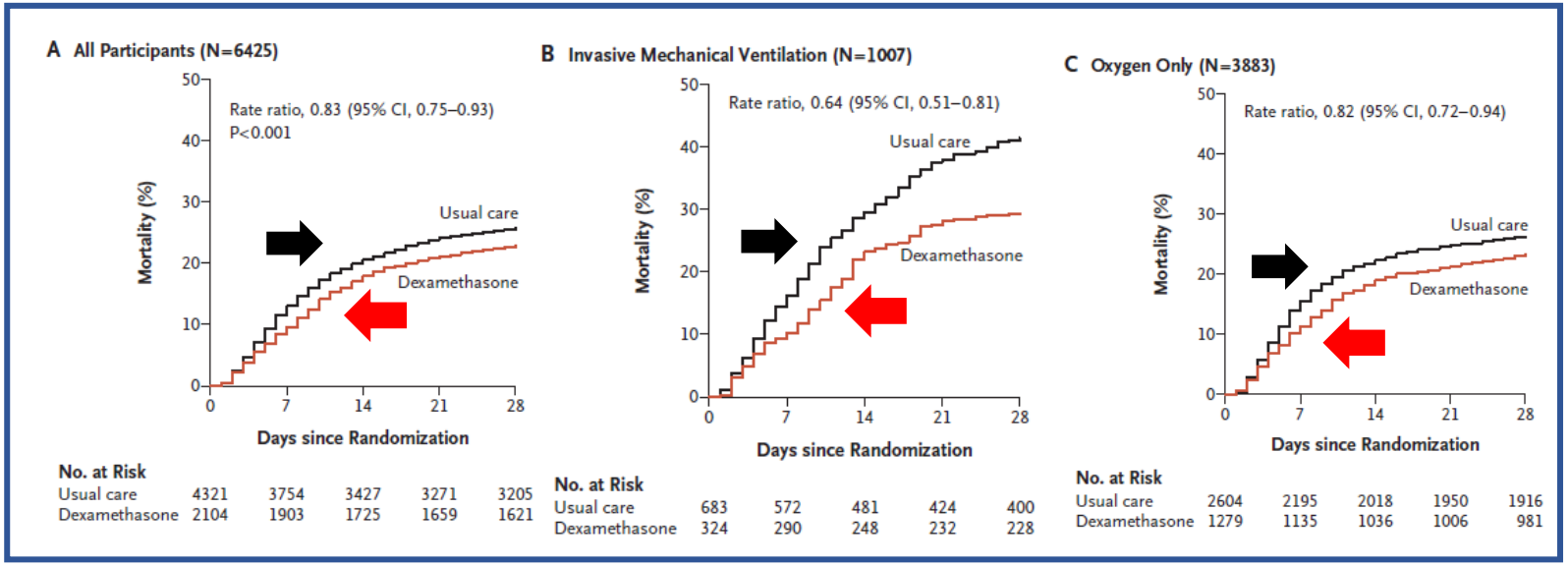
What would you do?

Corticosteroids in critical COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

Dexamethasone RECOVERY trial 28-day Mortality



28-day Mortality:

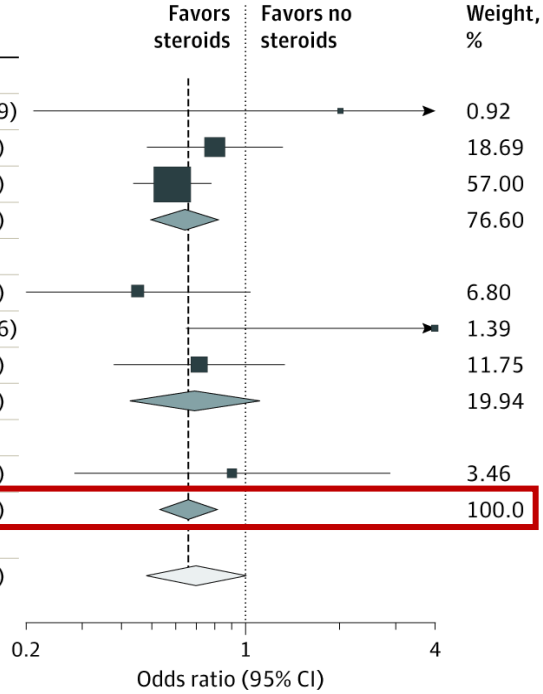
- In patients on mechanical ventilation
  - Dex 29.3% vs. usual care 41.4%; rate ratio, 0.64 (95% CI, 0.51 to 0.81)

Horby,PW,et,al. N Engl J Med 2021; 384:693-704

Corticosteroids in critical COVID-19

Systemic Corticosteroids and Mortality in Critically Ill Patients With COVID-19: A Meta-analysis

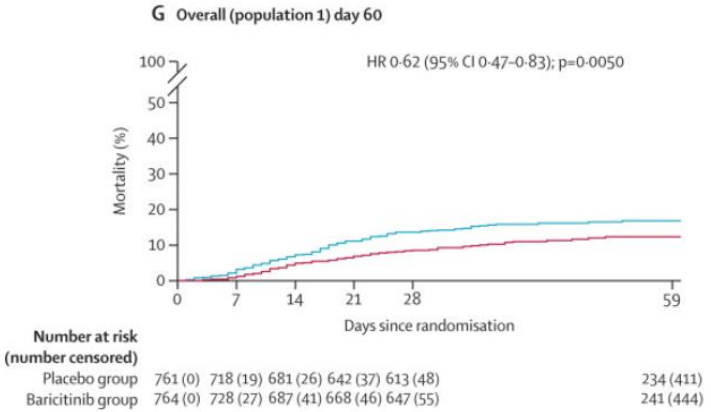
Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect)			222/678	425/1025	0.66 (0.53-0.82)	100.0
$P = .31$ for heterogeneity; $I^2 = 15.6\%$						
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	



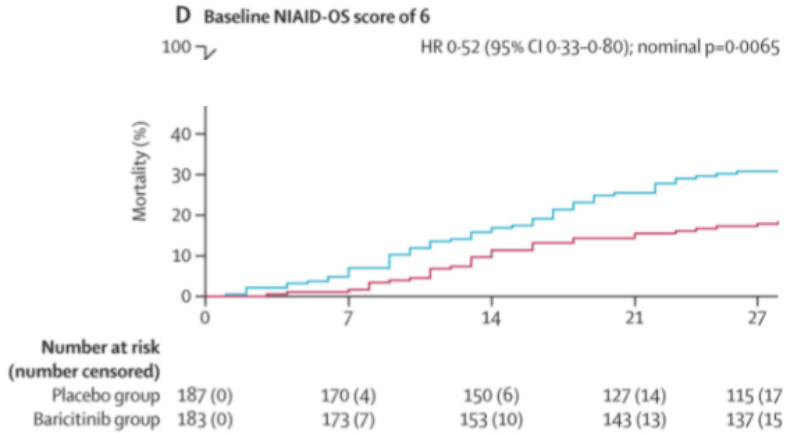
JAMA. 2020;324(13):1330-1341. doi:10.1001/jama.2020.17023

Baricitinib in critical COVID-19: non-invasive ventilation
COV-Barrier study

Overall population



On Hi-flow o2 or non-invasive ventilation



60-day all-cause mortality overall

- Baricitinib 10% (n=79) vs placebo 15% (n=116)
- HR 0·62 [95% CI 0·47–0·83]; p=0·0050

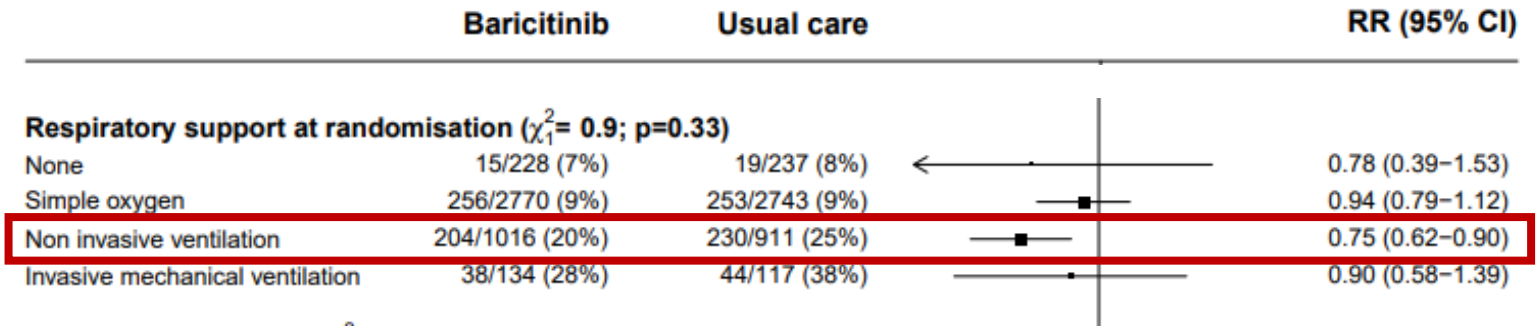
60-day all-cause mortality High-flow o2

- Baricitinib 42/183 [23%] *vs* placebo 63/187 [34%]
- HR 0·58 [0·39–0·86], p=0·014

Marconi V et al The Lancet Respiratory Medicine DOI: (10.1016/S2213-2600(21)00331-3

Baricitinib-RECOVERY trial

28-day mortality

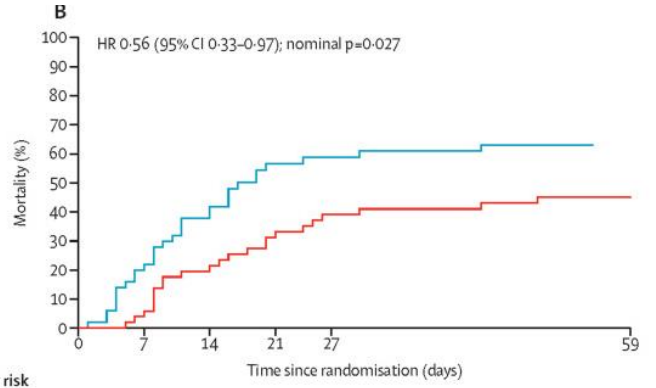


	Baricitinib	Usual care	RR (95% CI)
Respiratory support at randomisation (χ^2_1= 0.9; p=0.33)			
None	15/228 (7%)	19/237 (8%)	0.78 (0.39–1.53)
Simple oxygen	256/2770 (9%)	253/2743 (9%)	0.94 (0.79–1.12)
Non invasive ventilation	204/1016 (20%)	230/911 (25%)	0.75 (0.62–0.90)
Invasive mechanical ventilation	38/134 (28%)	44/117 (38%)	0.90 (0.58–1.39)

Baricitinib in COVID-19 patients on IMV or ECMO

Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial

E Wesley Ely, Athimalaipet V Ramanan, Cynthia E Kartman, Stephanie de Bono, Ran Liao, Maria Lucia B Piruzeli, Jason D Goldman, José Francisco Kerr Saraiva, Sujatro Chakladar, Vincent C Marconi, on behalf of the COV-BARRIER Study Group*



Ely Ew et al. Lancet Respir Med 2022; 10, 4, 327-36

№ of patients		Effect		Certainty	Importance
baricitinib	no baricitinib	Relative (95% CI)	Absolute (95% CI)		
Mortality-Pooled data from RECOVERY +COV BARRIER 2					
61/185 (33.0%)	75/167 (44.9%)	**RR 0.74** (0.57 to 0.97)	**117 fewer per 1,000** (from 193 fewer to 13 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL
Invasive mechanical ventilation free days					
51	50	-	MD **2.36 vent free days more** (6.1 more to 1.4 fewer) [c]	⨁⨁◯◯ LOW	IMPORTANT

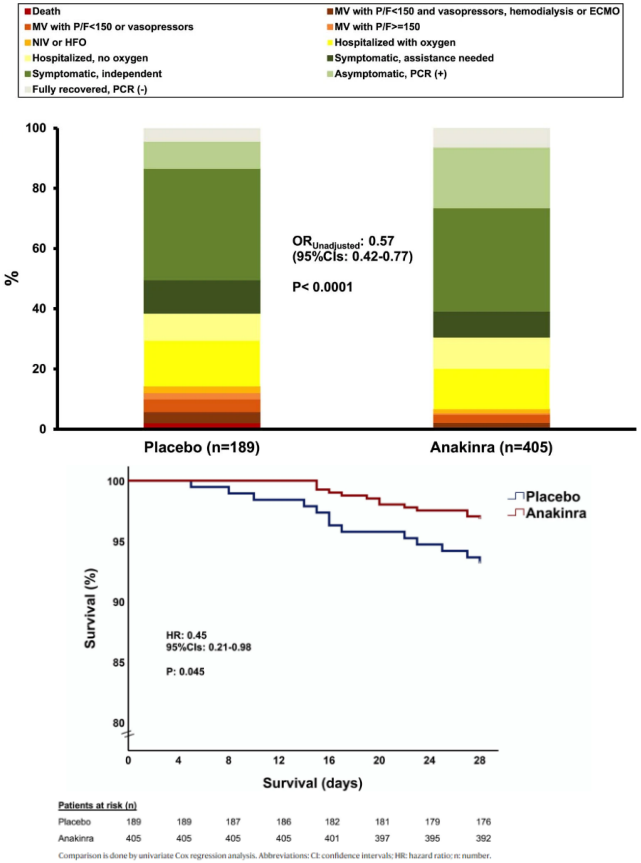
Bhimraj A et al. IDSA guidelines on Rx COVID-19. **2022**; Version 10.1.1**.**

Anakinra (IL-1 inhibitor) for hospitalized patients with COVID-19

SAVE-MORE trial

- Double blind RCT
- Anakinra 100 mg SC/d x 10 days
- Anakinra (n=405) vs placebo (189)
- COVID-19 pt. with suPAR* ≥ 6ng/ml
- 91% severe COVID-19
- 85.9% received dexamethasone
- Day-28 aOR of worse WHO CPS score
  - **Ankinra vs placebo-0.37, 95% CI 0.26–0.50.**
- 28-day mortality
  - **Anakinra 3.2% vs 6 (HR 0.48, CI 0.22-1.04)**

**soluble urokinase plasminogen activator receptor*



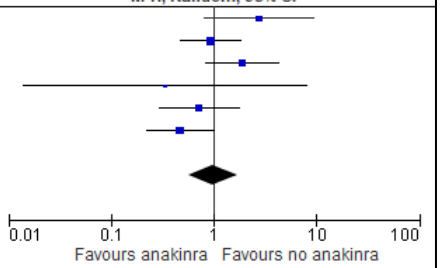
- https://www.fda.gov/media/163075/download- FDA EUA accessed 1-16-23
- Nat Med **27**, 1752–1760 (2021). https://doi.org/10.1038/s41591-021-01499-z

Anakinra (IL-1 inhibitor) for hospitalized COVID patients

Mortality

Study or Subgroup	Anakinra Events	Anakinra Total	No anakinra Events	No anakinra Total	Weight	Risk Ratio M-H, Random, 95% CI
Audemard-Verger 2022	9	37	3	34	13.1%	2.76 [0.81, 9.35]
CORIMUNO-19 2021	13	59	13	55	23.6%	0.93 [0.47, 1.83]
Declercq 2021	10	44	9	74	20.2%	1.87 [0.82, 4.24]
Elmekaty 2022	0	40	1	40	2.8%	0.33 [0.01, 7.95]
Kharazmi 2021	5	15	7	15	18.5%	0.71 [0.29, 1.75]
Kyriazopoulou 2021	13	405	13	189	21.8%	0.47 [0.22, 0.99]
Total (95% CI)		**600**		**407**	**100.0%**	**0.98 [0.57, 1.70]**
Total events	50		46			

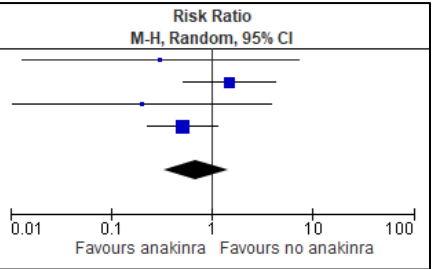
Heterogeneity: Tau² = 0.21; Chi² = 9.82, df = 5 (P = 0.08); I² = 49%
Test for overall effect: Z = 0.06 (P = 0.95)



Need for mechanical ventilation

Study or Subgroup	Anakinra Events	Anakinra Total	No anakinra Events	No anakinra Total	Weight	Risk Ratio M-H, Random, 95% CI
Audemard-Verger 2022	0	35	1	32	5.1%	0.31 [0.01, 7.24]
CORIMUNO-19 2021	8	59	5	55	36.0%	1.49 [0.52, 4.28]
Kharazmi 2021	0	15	2	15	5.9%	0.20 [0.01, 3.85]
Kyriazopoulou 2021	12	405	11	189	52.9%	0.51 [0.23, 1.13]
Total (95% CI)		**514**		**291**	**100.0%**	**0.69 [0.33, 1.44]**
Total events	20		19			

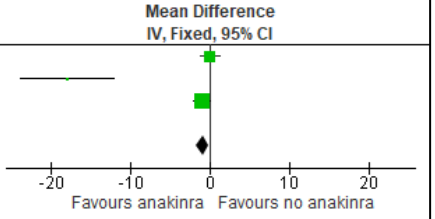
Heterogeneity: Tau² = 0.10; Chi² = 3.54, df = 3 (P = 0.32); I² = 15%
Test for overall effect: Z = 0.99 (P = 0.32)



Hospitalization duration

Study or Subgroup	Anakinra Mean	Anakinra SD	Anakinra Total	No anakinra Mean	No anakinra SD	No anakinra Total	Weight	Mean Difference IV, Fixed, 95% CI
Elmekaty 2022	10	2.96	40	10	2.96	40	39.3%	0.00 [-1.30, 1.30]
Kharazmi 2021	10	3.7	15	28	11.1	15	1.9%	-18.00 [-23.92, -12.08]
Kyriazopoulou 2021	11	5.78	405	12	6.3	189	58.8%	-1.00 [-2.06, 0.06]
Total (95% CI)			**460**			**244**	**100.0%**	**-0.93 [-1.74, -0.11]**

Heterogeneity: Chi² = 33.92, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 2.24 (P = 0.03)



Forest plots courtesy Rebecca Morgan & Yngve Falck-Ytter –GRADE Methodologists

Infliximab in Hospitalized Adults with Moderate or Severe COVID-19 (ACTIV-1 IM)

- Randomized, double-blind, placebo-controlled trial of infliximab (single dose iv infusion) vs SOC (n=1033)
  - 94% received remdesivir, 92% received steroids
- Primary endpoint of time to recovery: no significant difference
- Infliximab: improved 28-day mortality and 14-day clinical status
- No difference in serious adverse events, including infections

	28-day mortality	Comment
Infliximab	10.1%	41% reduction in odds of dying
Placebo	14.5%	

O'Halloran J et al, medRxiv 2022.09.22.22280245; doi: https://doi.org/10.1101/2022.09.22.22280245 and ID Week, LB

Slide from Dr. Raj Gandhi

Abatacept in Hospitalized adults with Moderate or Severe COVID-19 (ACTIV-1 IM)

- Randomized, placebo-controlled trial of abatacept (T cell costimulation modulator; single dose infusion) vs. SOC (n=1019)
- Primary outcome of time to recovery: no significant difference
- Abatecept improved 28-day mortality
  - Strongest effect in those with CRP>75
- No difference in serious adverse events, including infections

	28-day mortality	Comment
Abatecept	11%	38% reduction in odds of dying
Placebo	15.1%	

Ko E et al, medRxiv 2022.09.22.22280247; doi: https://doi.org/10.1101/2022.09.22.22280247 and ID Week, LB

Slide from Dr. Raj Gandhi

What Do The Guidelines Say?

Recommend use

Suggest use

Recommend against

Suggest against

https://www.covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-hospitalized-adults/

https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

https://www.who.int/publications/i/item/WHO-2019-nCoV-therapeutics-2022.5

Severity	NIH	IDSA	WHO
No supp. oxygen	Remdesivir (BIII)	Remdesivir	Remdesivir
	Dexamethasone	Dexamethasone	Dexamethasone
Conventional oxygen	Remdesivir (BIIa)	Remdesivir	Remdesivir
	Dexamethasone + remdesivir (BIIa) - May add baricitinib or tocilizumab (BIIa)[1]	Dexamethasone + Baricitinib (or tofacitinib)[2] Tocilizumab (or sarilumab)[3]	Dexamethasone Baricitinib Tocilizumab (or sarilumab)
HFNC oxygen, NIV, MV, ECMO	Dexamethasone (AI)[4] For most patients, add: - Baricitinib (AI) or - Tocilizumab (BIIa)	Dexamethasone	Dexamethasone Baricitinib Tocilizumab (or sarilumab)
		Baricitinib (or tofacitinib)[2] Tocilizumab (or sarilumab)[2]	

[1]Receiving dexamethasone and rapidly increasing O2 needs/systemic inflammation; if baricitinib not available, may use tofacitinib; if tocilizumab not available, may use sarilumab.

[2]If elevated inflammatory markers; [3]If progressive disease with elevated inflammatory markers

[4]Some would add remdesivir in patients (including immunocompromised) on HFNC/NIV or recently placed on MV

Slide from Dr. Raj Gandhi

Unanswered key questions in treating COVID-19

- Do benefits seen in treating immune naïve individuals infected with earlier SARS CoV-2 variants apply to individuals with immunity (from vaccination and prior infections) infected with current circulating SARS CoV-2 variants

- Are immunomodulatory therapies shown to work in immunocompetent individuals with COVID-19 efficacious and safe in immunocompromised individuals?

- Could specific immunologic biomarkers help target patients who will benefit from specific immunomodulators in early severe diseases?

- Could quantitative viral load assessment identify hospitalized patients with severe or critical diseases who will benefit from antiviral therapies (e.g., immunocompromised patients)?

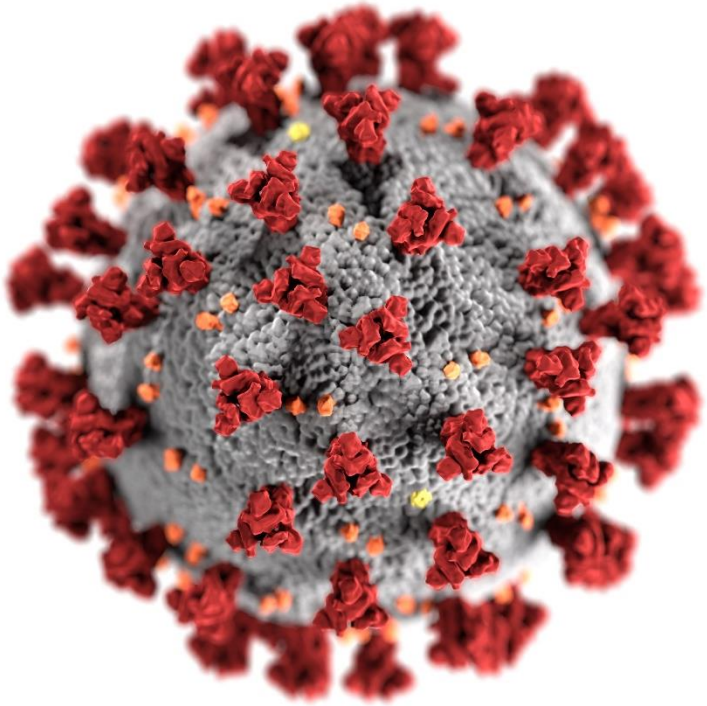
- Is there a role for combination antiviral or immunomodulatory therapies?

Understanding Viral Rebound: What We Know

Pragna Patel, MD, MPH

COVID-19 Viral Rebound

Pragna Patel, MD MPH
Chief Medical Officer (acting)
Coronavirus and Other Respiratory Viruses Division (proposed)
National Center for Immunization and Respiratory Diseases
Centers for Disease Control and Prevention



IDSA/CDC Clinician Call
January 21, 2023

cdc.gov/coronavirus

COVID-19 Rebound After Paxlovid Treatment

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network, May 24, 2022, 9:00 AM ET (CDCHAN-00467)

- Case reports of recurrent illness and/or positive test after testing negative a few days after (ritonavir-boosted nirmatrelvir) Paxlovid™ treatment
- Manufacturer noted in the clinical trial that a small number of participants had ≥1 positive SARS-CoV-2 RT-PCR test results after testing negative, or an increase in the amount of SARS-CoV-2 detected by PCR (NP swabs) after completing their assigned treatment course in the study.
- This finding was observed *both* in persons randomized to Paxlovid™ and to placebo in clinical trial
- There was *no* increased occurrence of hospitalization or death.
- There was no evidence that the rebound in detectable viral RNA was the result of SARS-CoV-2 resistance to Paxlovid™

COVID-19 Rebound After Paxlovid Treatment

Distributed via the CDC Health Alert Network, May 24, 2022, 9:00 AM ET (CDCHAN-00467)

- There is currently no evidence that additional treatment for COVID-19 is needed.
- CDC **recommends re-isolating** during the rebound
  - CDC Health Advisory: https://emergency.cdc.gov/han/2022/han00467.asp
    - Isolate again and restart the recommended 5-day isolation period at the time of recurrence of symptoms or a new positive COVID-19 test result.
    - End re-isolation after 5 days if you are fever-free for 24 hours without the use of fever-reducing medication and your symptoms are improving.
    - Wear a mask for 10 days after day 1 of the start of rebound symptoms.

Viral Rebound and Symptom Recurrence

Observational studies and results from the EPIC-HR trial have described SARS-CoV-2 viral rebound and the recurrence of COVID-19 symptoms in some patients who have completed treatment with ritonavir-boosted nirmatrelvir.[15-18] The frequency, mechanism, and clinical implications of these events are unclear. Viral rebound and the recurrence of COVID-19 symptoms can also occur in the absence of treatment with ritonavir-boosted nirmatrelvir.[19,20]

The EPIC-HR trial demonstrated a clinical benefit of ritonavir-boosted nirmatrelvir in patients who were not vaccinated and who were at high risk of progressing to severe COVID-19. To date, the recurrence of COVID-19 symptoms following the use of ritonavir-boosted nirmatrelvir has not been associated with progression to severe COVID-19. Therefore, concerns about the recurrence of symptoms should not be a reason to avoid using ritonavir-boosted nirmatrelvir.[19,21,22]

Longer treatment courses of ritonavir-boosted nirmatrelvir are not authorized by the current EUA, and there are insufficient data on the efficacy of administering a second course.

- Viral rebound can occur in the absence of treatment
- The recurrence of symptoms should not be a reason to avoid using ritonavir-boosted nirmatrelvir
- Longer courses of treatment are not authorized
- No data on efficacy of second course but currently

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/

In the NEWS: COVID Rebound Not Limited to Those Who Took Paxlovid

As more people report Covid rebounds after Paxlovid, experts insist cases are rare

Should you take Paxlovid if you are mildly ill?

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

COVID rebound is surprisingly common — even without Paxlovid

Viral levels resurge in more than 10% of untreated people with COVID-19, but early data hint that the rebound is even more pronounced after antiviral treatment.

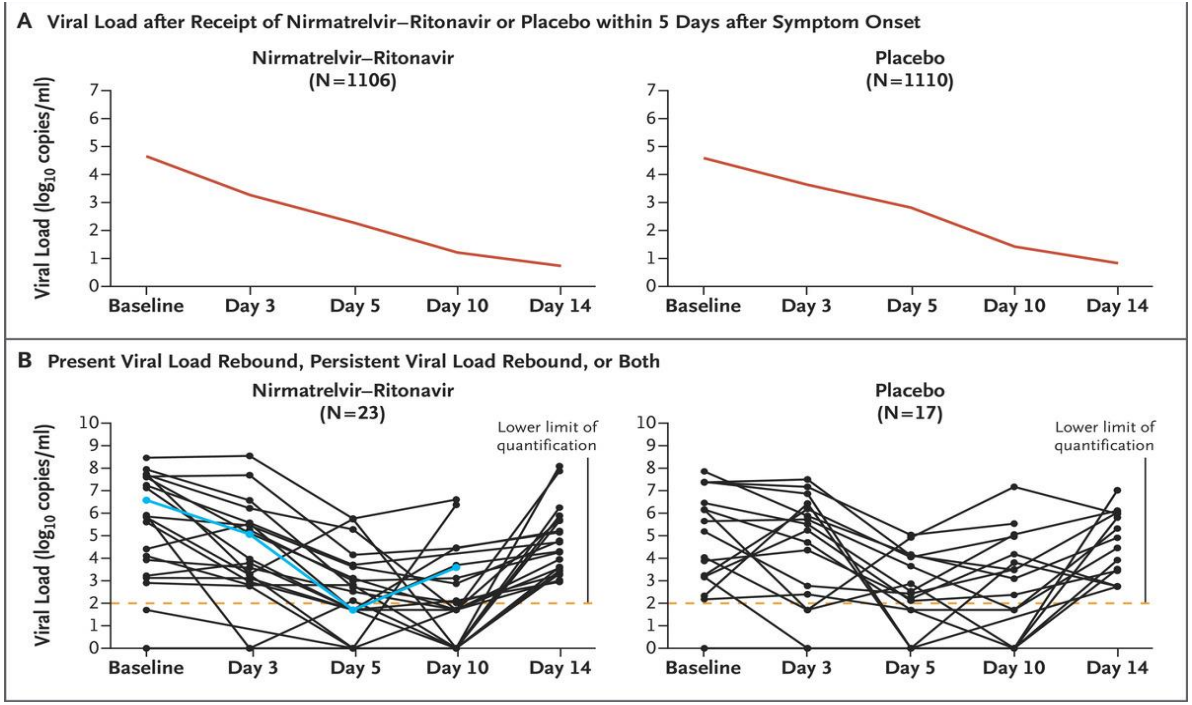
Officials with COVID who take Paxlovid keep getting rebound positives. It's now happened with Biden, Fauci, and the head of the CDC

What Is Paxlovid Rebound, and How Common Is It?

President Biden is part of a minority of people who have experienced Paxlovid rebound, but experts say the drug should still be prescribed for those who need it

Covid Rebound with Pfizer's Paxlovid Less Than Expected

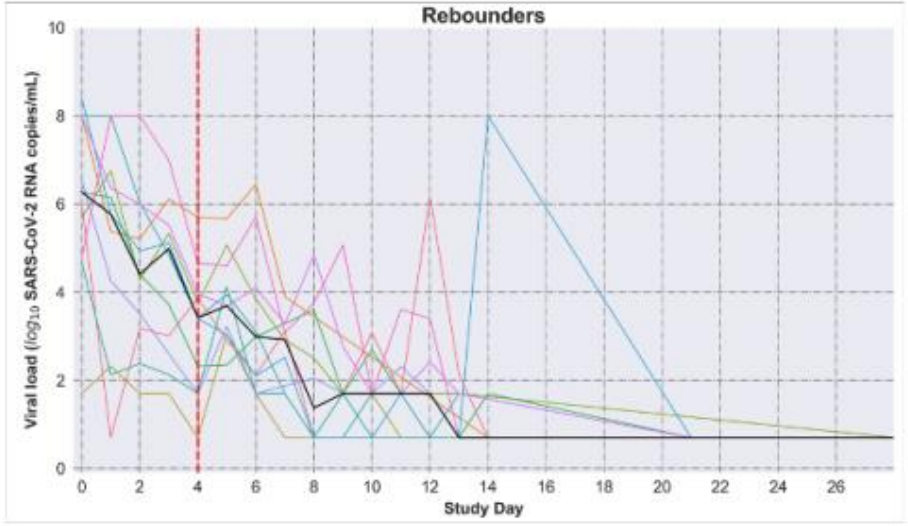
Nirmatrelvir–Ritonavir and Viral Load Rebound in Covid-19

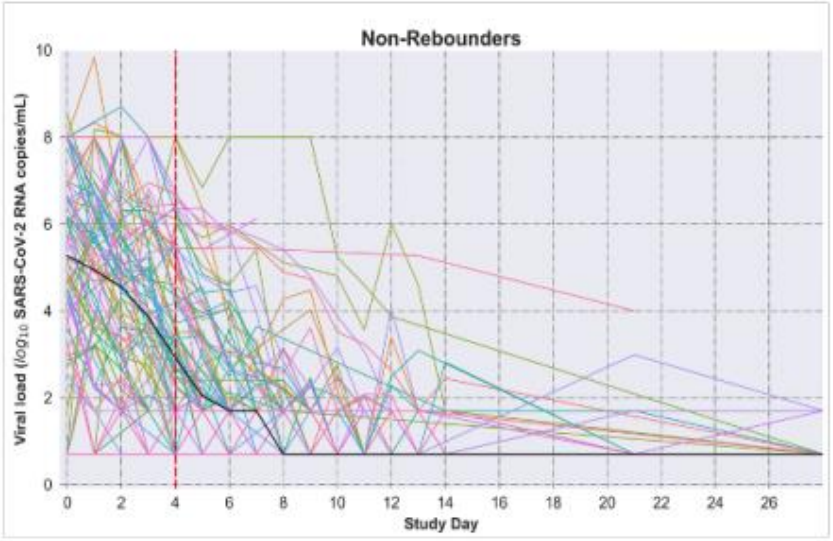


Anderson et al. Nirmatrelvir–Ritonavir and Viral Load Rebound in Covid-19. N Engl J Med 2022;387:1047-1049.

Viral and Symptom Rebound in Untreated COVID-19 Illness

- Viral rebounders had similar baseline viral RNA levels and duration of detectable SARS-CoV-2 RNA.
- Viral RNA rebounders were found to be older than non-rebounders (median 54 vs 47 years, P=0.04).
- Viral rebound or symptom relapse in the absence of antiviral treatment is common.

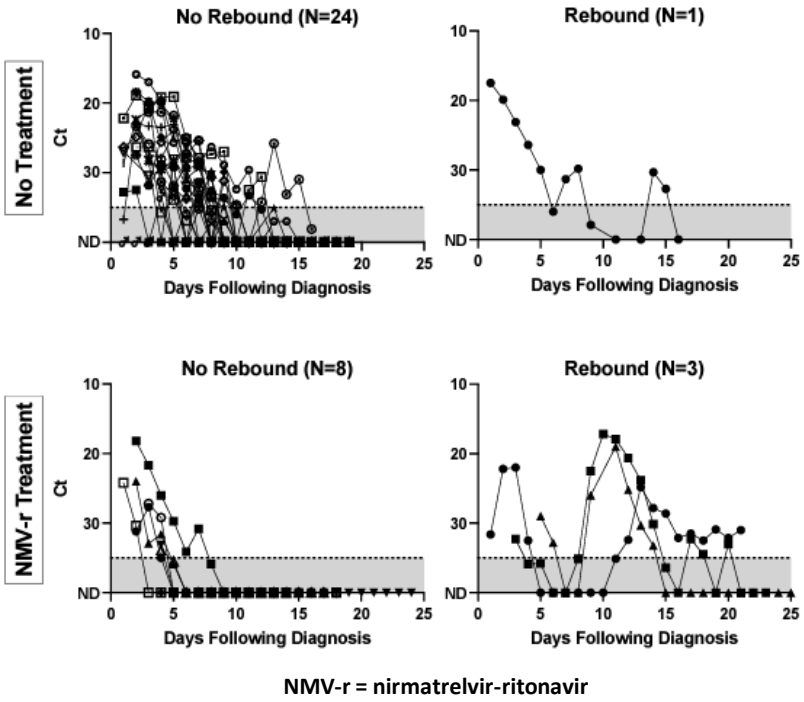




Deo et al. Viral and Symptom Rebound in Untreated COVID-19 Infection. medRxiv.2022

Viral Kinetics among mRNA Vaccinated Persons

- Higher rebound in treated group (3/11 vs. 1/25)
- Participants in the treated group were more likely than in the untreated group to:
  - be older (44y (25-48) vs. 16y (5-66),
  - have comorbidities,
  - to have ever smoked/vaped, and
  - to be overweight/obese
- Viral kinetics similar in treatment and no treatment groups: median time to rebound from first negative test was 5 days
- Limitation: small sample size



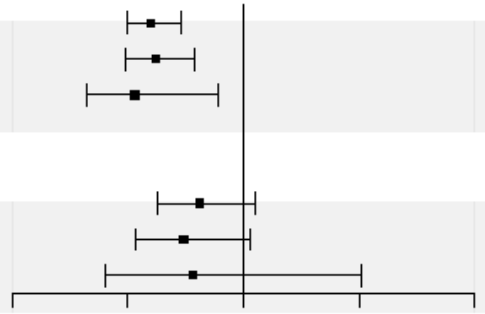
NMV-r = nirmatrelvir-ritonavir

Dai et al. Viral Kinetics of SARS-CoV-2 Omicron Infection in mRNA-Vaccinated Individuals Treated and Not Treated with Nirmatrelvir-Ritonavir.medRxiv. 2022

Rebound after nirmatrelvir-ritonavir and molnupiravir

Risks for COVID-19 rebound in patients treated with nirmatrelvir-ritonavir did not differ from those treated with molnupiravir.

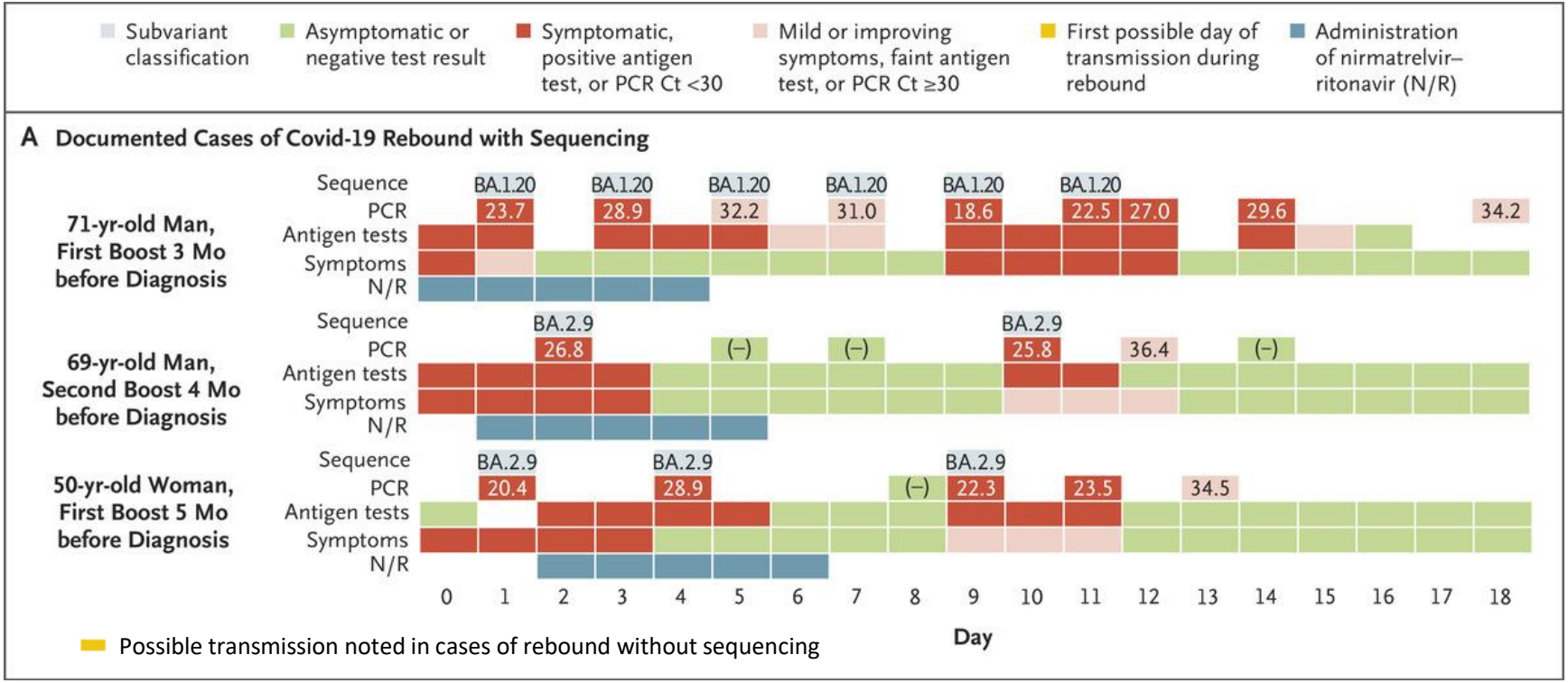
Rebound outcome	Paxlovid	Molnupiravir	HR (95% CI)
Before matching			
COVID infections	3.53%(398/11270)	5.86%(139/2374)	0.60 (0.50–0.73)
COVID symptoms	2.31%(260/11270)	3.75%(89/2374)	0.62 (0.49–0.79)
Hospitalizations	0.44%(50/11270)	0.84%(20/2374)	0.53 (0.32–0.89)
After matching			
COVID infections	4.54%(101/2226)	5.95%(132/2226)	0.81 (0.63–1.05)
COVID symptoms	2.61%(58/2226)	3.77%(84/2226)	0.74 (0.53–1.03)
Hospitalizations	0.67%(15/2226)	0.90%(20/2226)	0.78 (0.40–1.51)



Propensity-score matching for demographics, 194 adverse socioeconomic determinants of health, comorbidities, immunosuppressant usage, organ transplantation, and EHR-documented COVID-19 vaccination status.

Wang et al. COVID-19 rebound after Paxlovid and Molnupiravir during January-June 2022.medRxiv.2022

Time Course of Cases of COVID-19 Rebound



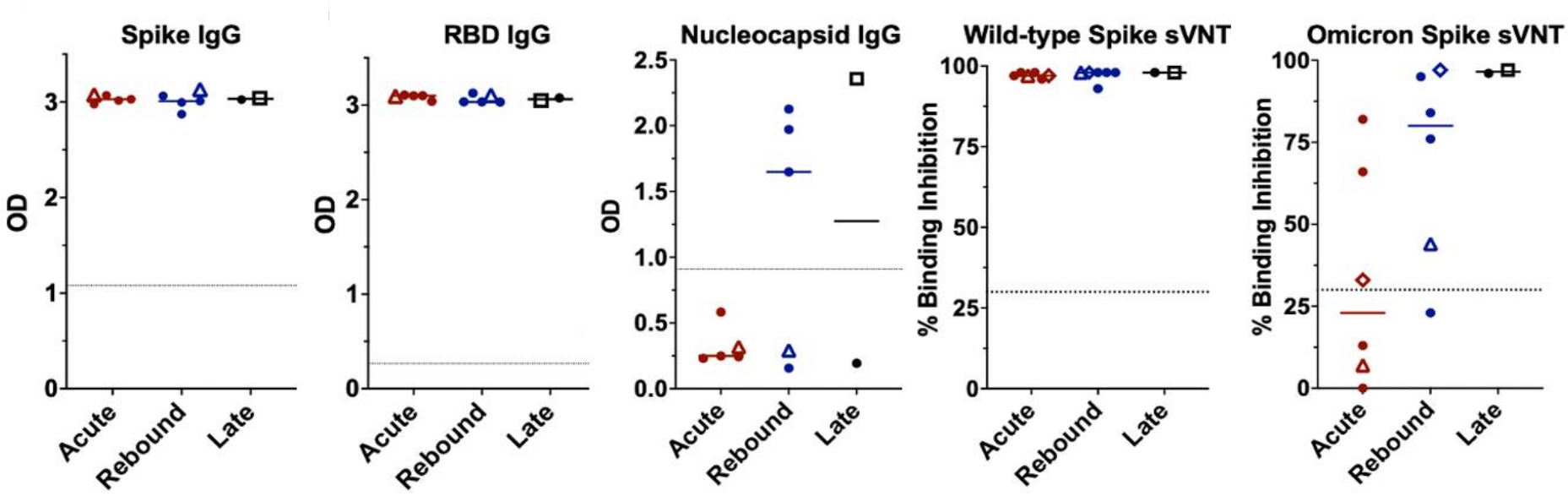
Charness et al. Rebound of SARS-CoV-2 Infection after Nirmatrelvir–Ritonavir Treatment.NEJM.2022

Observational Studies of COVID-19 Rebound

- Most persons who experience COVID-19 rebound have had mild illness. The rebound illness improved or resolved in a few days.
- Occurs 2 to 8 days after resolution of acute illness.
- COVID-19 rebound did not represent reinfection with the virus or resistance to treatment.
- COVID-19 rebound is a relatively infrequent event and has been seen with several Omicron sub-lineages such as BA.2 and BA.5.
- A few cases have had culturable virus which supports CDC's recommendation to re-isolate when rebound occurs.
- COVID-19 rebound has been seen with patients treated with nirmatrelvir-ritonavir as well as molnupiravir and in untreated patients, suggesting that rebound can be part of the natural history of infection.

Carlin et al. Virologic and Immunologic Characterization of Coronavirus Disease 2019 Recrudescence After Nirmatrelvir/Ritonavir Treatment .CID.2022; Charness et al. Rebound of SARS-CoV-2 Infection after Nirmatrelvir–Ritonavir Treatment.NEJM.2022; Raganath et al. Rebound Phenomenon after Nirmatrelvir/Ritonavir Treatment of Coronavirus Disease-2019 in High-Risk Persons.CID.2022; Wong et al. Incidence of Viral Rebound After Treatment With Nirmatrelvir-Ritonavir and Molnupiravir.JAMA Net Open. 2022; Soares et al. Viral Load Rebound in Placebo and Nirmatrelvir-Ritonavir Treated COVID-19 Patients Is Not Associated with Recurrence of Severe Disease or Mutations. Res Sq.2022; Wang et al. COVID-19 rebound after Paxlovid treatment during Omicron BA.5 vs BA.2.12.1 subvariant predominance period. medRxiv.2022

Adaptive immune response during rebound



Lines represent median and points represent individual results. The 2 longitudinal patients are identified by an open triangle and open diamond, respectively. The open square represents the coronavirus disease 2019 (COVID-19) rebound patients who did not receive nirmatrelvir-ritonavir. Antibody levels by enzyme-linked immunosorbent assay (ELISA) against the spike protein, spike - receptor binding domain (RBD), and the nucleocapsid protein presented as optical density (OD). ELISA data not available for longitudinal patient-1 (diamond). Surrogate viral neutralization test (sVNT) to detect neutralizing antibodies against the wild-type (I) and Omicron (J) spike protein presented as percent binding inhibition.

BP Epling, et al. Clinical rebound of COVID-19 following nirmatrelvir/ritonavir is not associated with delayed immune response or severe disease. *Clini Infect Dis 2022.*

Viral load during the course of SARS CoV-2 infection

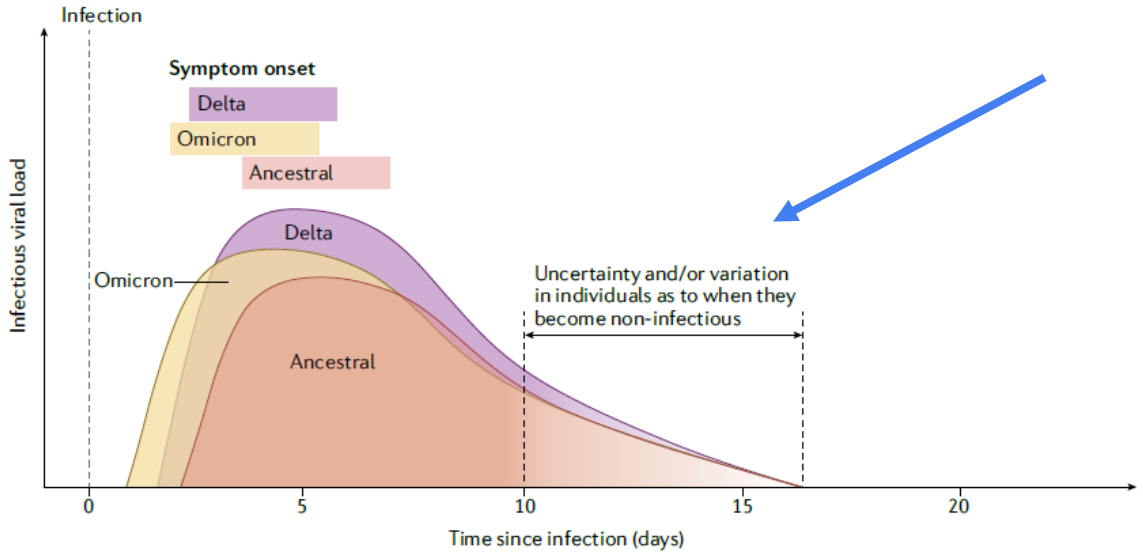


Fig. 3 | Infectious viral load and symptom onset in SARS-CoV-2 Delta and Omicron BA.1 variants of concern. Overall patterns of shedding dynamics are conserved between SARS-CoV-2 variants. In comparison to ancestral SARS-CoV-2, Delta and Omicron BA.1 have shorter incubation periods, estimated as approximately 3.7–4 days for Delta and approximately 3–3.4 days for Omicron BA.1. Higher infectious viral loads were detected in patients infected with Delta than in patients infected with Omicron BA.1 or ancestral SARS-CoV-2. Only a limited number of studies have determined when virus shedding for Delta and Omicron BA.1 ends, so this time point is not well defined. Owing to the low number of studies comparing the end of the infectious period between different SARS-CoV-2 variants of concern, the end point of infectivity is not well defined (shown as a colour gradient). Details of the underlying studies used to generate Fig. 3 can be found in Supplementary Table 2.

Puhach eta al. SARS-CoV-2 viral load and shedding kinetics.Nature Reviews Micro2022

Key Considerations

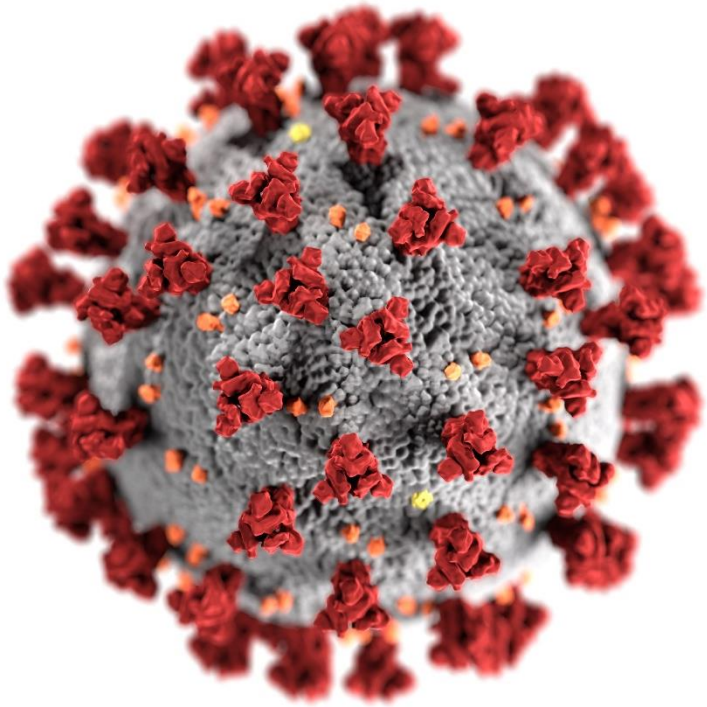
- Need to standardize definition of viral rebound – probably best to use re-emergence of virus as symptoms are subjective

- Studies including genomic comparisons of viral strains involved in both episodes, determination of infectivity by viral culture, assessment of innate and adaptive immunity, and monitoring inflammatory targets, would contribute to understanding the underlying pathophysiology of these COVID-19 recurrences

- Challenging to conduct a clinical trial because it would be unethical to withhold treatment in patients at risk for severe disease and self selection in observational studies (i.e., people who decline or refuse treatment) creates bias

Summary

- COVID-19 rebound is likely a natural disease process and occurs regardless of vaccination and treatment status and corresponds with robust immune response
- Persons on treatment may be at higher risk for rebound given the drug pressure that suppresses viral RNA replication. When it is removed, the virus could reactivate.
  - This has been seen with other viruses such as HIV
- Ascertainment bias is possible given that persons on treatment are closely followed
- It is possible that viral rebound occurs in persons on treatment because they are at high risk for severe disease and may have host factors that contribute. Risk factors for rebound seem to be similar but more studies are needed.



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Q&A/ Discussion

Selected Resources

Dr. Patel

- https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends
- https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.htmlDownload Report
- https://www.nejm.org/doi/full/10.1056/NEJMc2214293?query=featured_home

Dr. Thornburg

- https://www.cdc.gov/coronavirus/2019-ncov/your-health/if-you-were-exposed.html
- https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/testing.html#when-to-get-tested
- https://www.fda.gov/medical-devices/safety-communications/home-covid-19-antigen-tests-take-steps-reduce-your-risk-false-negative-results-fda-safety
- SARS-CoV-2 Viral Mutations: Impact on COVID-19 Tests | FDA

Dr. Gandhi and Dr. Bhimraj

- https://www.science.org/doi/epdf/10.1126/science.acx9605
- https://www.fda.gov/media/163075/download- FDA EUA accessed 1-16-23

Selected Resources

Dr. Patel

- https://emergency.cdc.gov/han/2022/han00467.asp

https://www.covid19treatmentguidelines.nih.gov/therapies/antivirals-including-antibody-products/ritonavir-boosted-nirmatrelvir--paxlovid-/

- https://www.nejm.org/doi/full/10.1056/NEJMc2205944
- https://www.medrxiv.org/content/10.1101/2022.08.01.22278278v1
- https://www.medrxiv.org/content/10.1101/2022.08.04.22278378v1
- https://www.medrxiv.org/content/10.1101/2022.06.21.22276724v1
- https://www.nejm.org/doi/full/10.1056/NEJMc2206449
- https://www.nejm.org/doi/full/10.1056/NEJMc2206449
- https://pubmed.ncbi.nlm.nih.gov/35698452/.CID.2022
- https://pubmed.ncbi.nlm.nih.gov/36472873/
- https://www.researchsquare.com/article/rs-1720472/v2
- https://www.researchsquare.com/article/rs-1720472/v2
- https://www.medrxiv.org/content/10.1101/2022.08.04.22278450v1
- https://www.nature.com/articles/s41579-022-00822-w

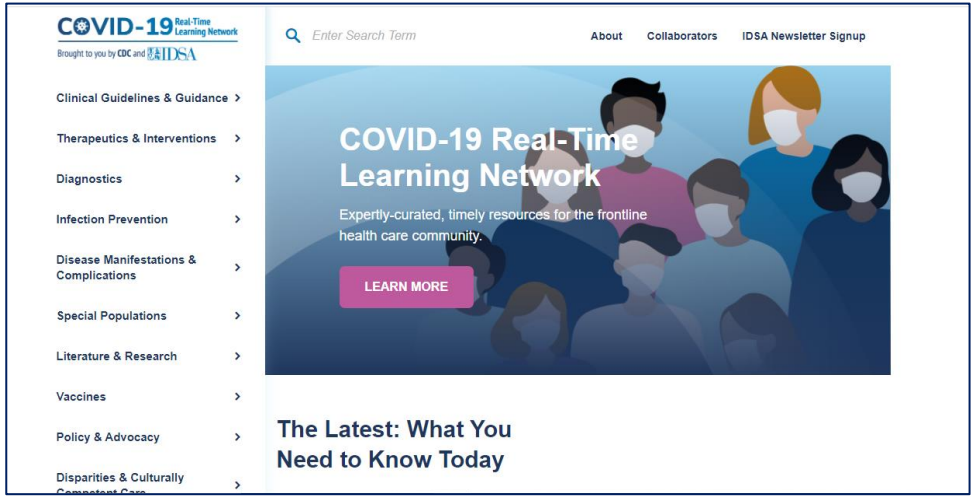
Program Links:

- This webinar is being recorded and can be found with the slides online at https://www.idsociety.org/cliniciancalls
- COVID-19 Real-Time Learning Network: https://www.idsociety.org/covid-19-real-time-learning-network/
- Vaccine FAQ: https://www.idsociety.org/covid-19-real-time-learning-network/vaccines/vaccines-information--faq/

COVID-19 Real-Time Learning Network

Brought to you by CDC and IDSA

An online community bringing together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.



Specialty Society Collaborators

American Academy of Family Physicians
American Academy of Pediatrics
American College of Emergency Physicians
American College of Obstetricians & Gynecologists
American College of Physicians
American Geriatrics Society
American Thoracic Society
Pediatric Infectious Diseases Society
Society for Critical Care Medicine
Society for Healthcare Epidemiology of America
Society of Hospital Medicine
Society of Infectious Diseases Pharmacists

www.COVID19LearningNetwork.org
@RealTimeCOVID19
#RealTimeCOVID19

CDC-IDSA Partnership: Clinical Management Call Support

FOR WHOM?

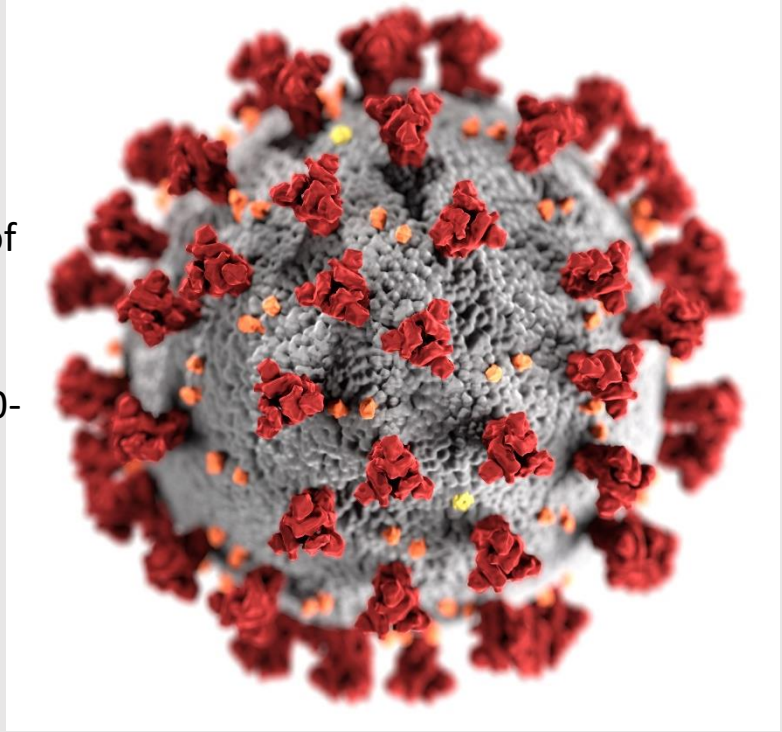
- Clinicians who have questions about the clinical management of COVID-19

WHAT?

- Calls from clinicians will be triaged by CDC to a group of IDSA volunteer clinicians for peer-to-peer support

HOW?

- Clinicians may call the main CDC information line at 800-CDC-INFO (800-232-4636)
- To submit your question in writing, go to www.cdc.gov/cdc-info and click on Contact Form



IDSA
Infectious Diseases Society of America

cdc.gov/coronavirus

THANK YOU

We want to hear from you!

Please complete the post-call survey.

A recording of this call, slides and the answered Q&A will be posted at
www.idsociety.org/cliniciancalls

-- library of all past calls available --

Contact Us:

Dana Wollins (dwollins@idsociety.org)
Deirdre Lewis (dlewis@idsociety.org)