COVID-19 | Test to Treat Equity ECHO

Thursday, December 14, 2022

FAMILY HEALTH CENTERS OF SAN DIEGO

HEALTH SCIENCES

Project ECHO

CDPH

Learning Session Logistics

- Zoom Q&A: questions and comments regarding the presentation
  - Zoom Chat: questions regarding technical or logistical issues
- This session is being recorded. Your attendance is consent to be recorded.
  - Please keep sessions apolitical and non-commercial. Thank you!

Data Use

Project ECHO collects registration, participation, questions/answers, chat comments, and poll responses for this program, and shares this data with FHCSD and the CDPH. Your individual data will be kept confidential and de-identified. These data may be used for reports, maps, communications, surveys, quality assurance, evaluation, research, and to inform new initiatives.

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Today's Agenda

1. Announcements and Introductions [5 min]
2. Introduction to Test & Treat and SARS-CoV-2 Basics [40 min]
   - Christian Ramers, MD, MPH, FIDSA, AAHIVS (Family Health Centers of San Diego)
3. Q&A and Discussion [15 min]
4. Closing

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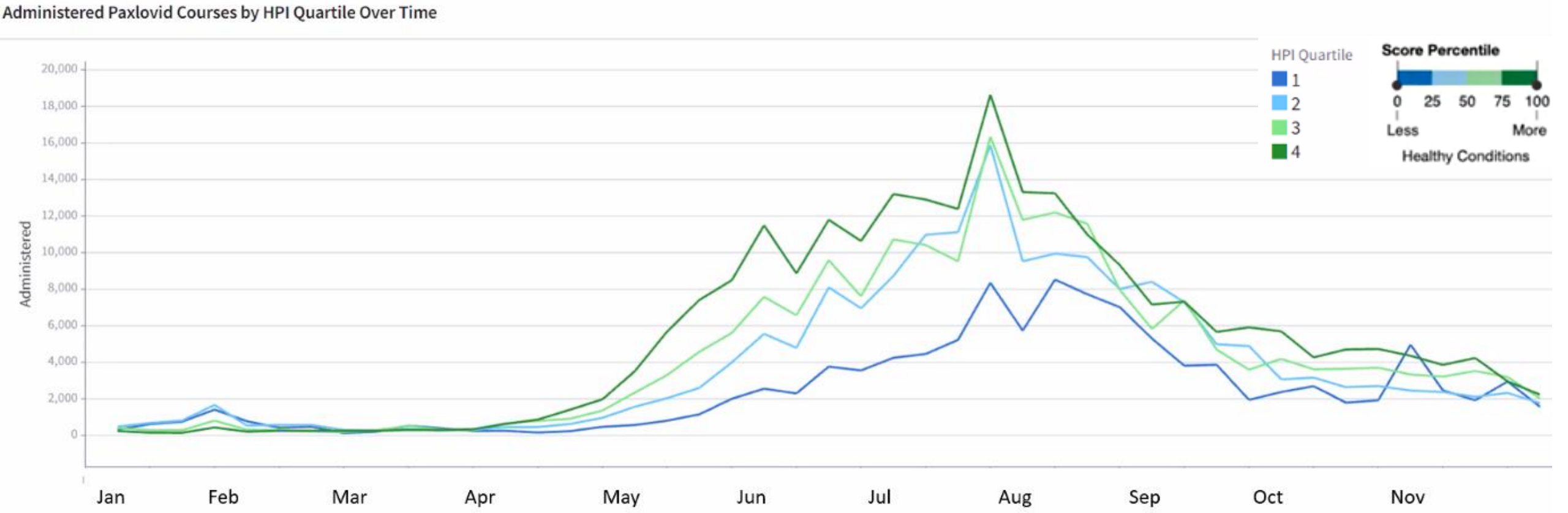
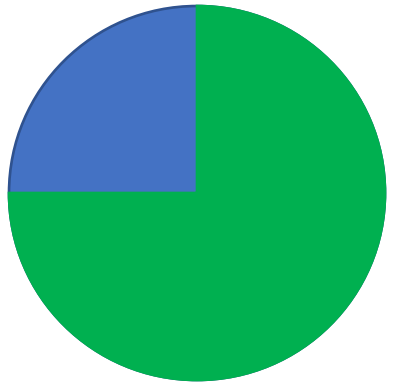
CDPH COVID-19 Test to Treat Equity ECHO

- Why now?
- Key issues facing providers: burnout, staffing challenges, patient mistrust, COVID-19 misinformation, barriers to obtaining/dispensing Paxlovid, hesitant prescribers, COVID fatigue, poor understanding of COVID-19 disease process, **health disparities**

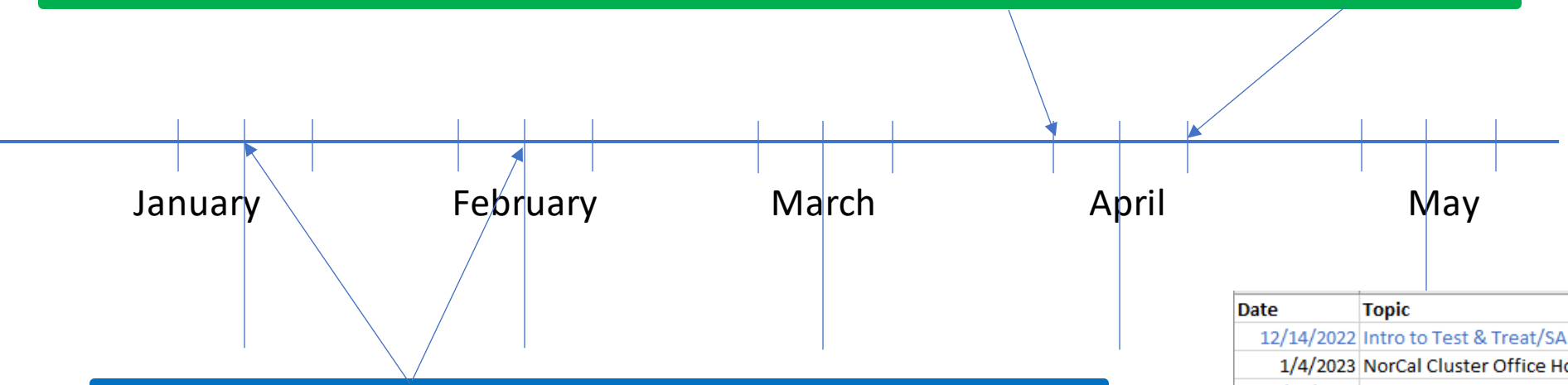


CDPH – data on file

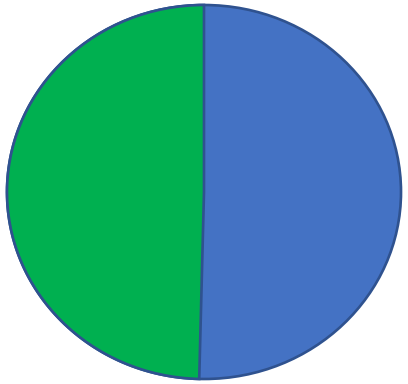
Test & Treat Equity ECHO – Program Vision



Office Hours/Q&A ECHO sessions (1st Wed NorCal, 3rd Wed SoCal)



Interactive Webinars (2nd Wed, open for all)



Date	Topic	Speaker
12/14/2022	Intro to Test & Treat/SARS-CoV-2 Basics	Christian Ramers
1/4/2023	NorCal Cluster Office Hours/Q&A/ ECHO	
1/11/2023	Outpatient Therapeutics for COVID-19	Daniel Griffin?
1/18/2023	SoCal Cluster Office Hours/Q&A/ECHO	
2/1/2023	NorCal Cluster Office Hours/Q&A/ ECHO	
2/8/2023	SARS-CoV-2 Testing	John Lynch?
2/15/2023	SoCal Cluster Office Hours/Q&A/ECHO	
3/1/2023	NorCal Cluster Office Hours/Q&A/ ECHO	
3/8/2023	Natural History and Pathophysiology of COVID-19	Jason Maley?
3/15/2023	SoCal Cluster Office Hours/Q&A/ECHO	
3/22/2023	possible make-up/rescheduled session	
3/29/2023	possible make-up/rescheduled session	
4/5/2023	NorCal Cluster Office Hours/Q&A/ ECHO	
4/12/2023	Practical Aspects & Operational Details	Monica Vidaurrazaga
4/19/2023	SoCal Cluster Office Hours/Q&A/ECHO	
5/3/2023	NorCal Cluster Office Hours/Q&A/ ECHO	
5/10/2023	Overview of Post-COVID Conditions	Ben Abramoff?
5/17/2023	SoCal Cluster Office Hours/Q&A/ECHO	

Upcoming Sessions

- January 11 – Outpatient Therapeutics for COVID-19
- February 8 – SARS-CoV-2 Testing
- March 8 – Natural History and Pathophysiology of COVID-19
- April 12 – Practical Aspects & Operational Details
- May 10 – Overview of Post-COVID Conditions

Regional Office Hours/Q&A ECHOs

- Northern California focused – 1st Wednesday of each month
- Southern California focused – 2nd Wednesday of each month

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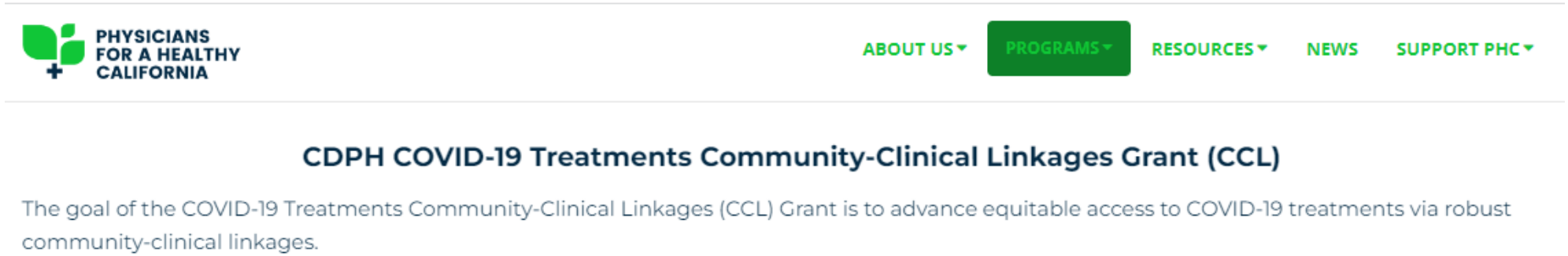
Support and Additional Resources

COVID-19 Test to Treat Clinical Resources

CLINICAL RESOURCES OVERVIEW | COVID-19 DIAGNOSIS | PRESCRIBING MEDICATION | DISPENSING MEDICATION

- **CCI 'high touch technical assistance' 'light touch technical assistance'**
- **Community Clinical Linkages-CBO grant**
  - Up to $100,000 for CBOs to improve community education/linkage
  - Applications due 12/19/22, accepted on rolling basis



- **Submit cases, questions: TestToTreat@fhcsd.org**

- https://www.careinnovations.org/programs/covid-19-test-to-treat/
- https://www.phcdocs.org/covid-equity

COVID-19 Test to Treat Resources https://www.careinnovations.org/programs/covid-19-test-to-treat/

COVID-19 Test to Treat Resource Hub

Welcome, providers! Explore the latest on therapeutic information, workflows, and operational tools to launch and expand Test to Treat pathways.

Clinical Information

Download workflows and adaptable operational tools to help you implement a Test to Treat program.

Therapeutic Information

Compare available treatment options, identify the right medication for your patients, and get the latest on these therapeutics.

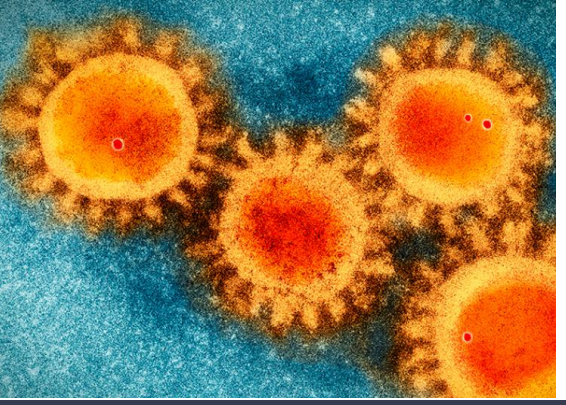
Clinical Information - https://www.careinnovations.org/test-2-treat-overview/clinical-resources-overview/
Therapeutic Information - https://www.careinnovations.org/covid-19-therapeutic-information/

Introductions

- **Caroline Kennedy, MD**
  - Medical Director, Monterey County Health Department

- **Kelvin Vu, DO, FAAFP**
  - Senior VP, Clinical Services Open Door Community Health Centers

- **Monica Vidaurrazaga, MD**
  - Infectious Disease Specialist, co-director FHCSD COVID-19 treatment program



COVID-19 Test & Treat: an introduction

Christian B. Ramers, MD, MPH, FIDSA, AAHIVS

christianr@fhcsd.org - @cramersmd

Chief, Population Health

Medical Director, Laura Rodriguez Research Institute

Director, Graduate Medical Education

Family Health Centers of San Diego

Clinical Associate Professor – **UC San Diego School of Medicine**

Adjunct Associate Professor – **San Diego State Graduate School of Global Public Health**

Senior Clinical Advisor – **CHAI Global Hepatitis Program**

12/14/22

Learning Objective

- **At the conclusion of this lecture you should be able to:**
  - **Utilize** resources to track global & local COVID-19 epidemiology
  - **Find** up-to-date US and San Diego variant proportions
  - Appropriately **evaluate** COVID-19 patients for oral antiviral therapy
  - **Manage** drug-drug interactions with nirmatrelvir/ritonavir
  - **Determine** recommended first-line therapy
  - **Refer** appropriate patients for IV remdesivir infusion

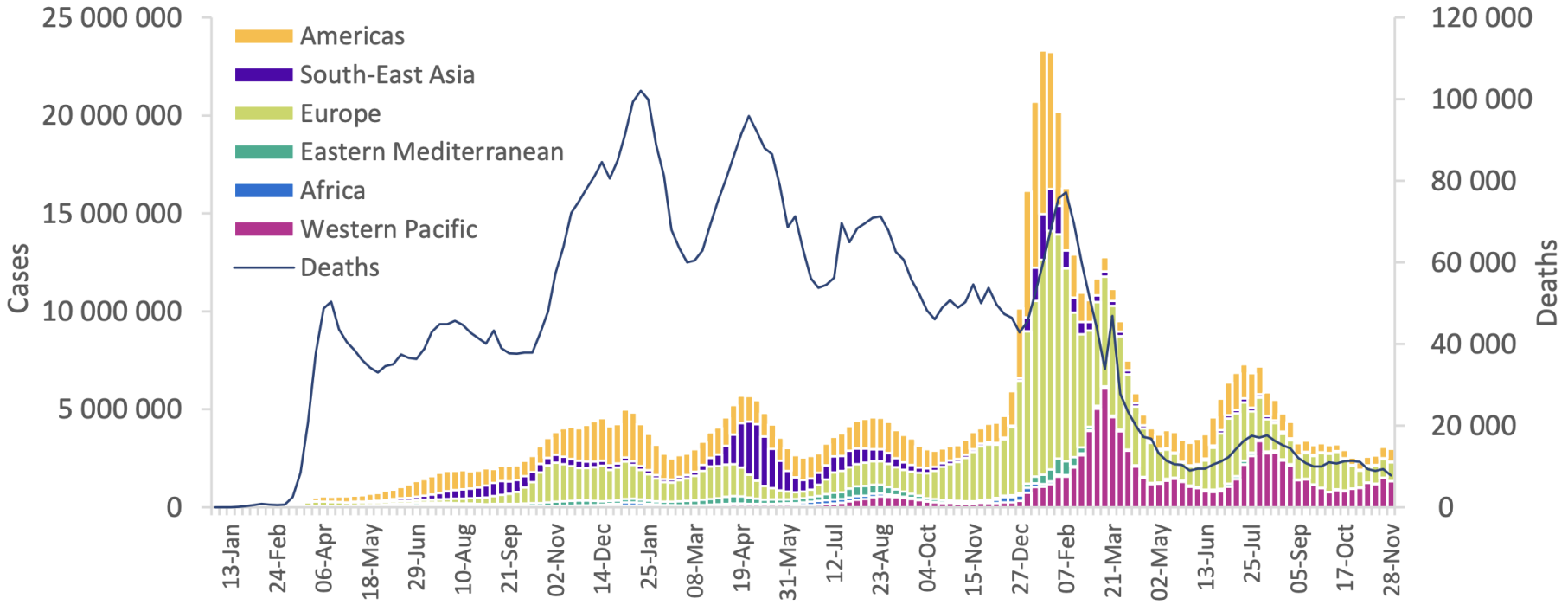
Outline

- **COVID-19 – Where are We?**
  - Global and local Epidemiology
  - Variants
  - Pathophysiology and clinical risk factors

- **Test & Treat Algorithm:** Utilizing COVID-19 therapeutics
  - **Nirmatrelvir/ritonavir** (Paxlovid)
  - **Remdesivir** (Veklury)
  - **Molnupiravir** (Lagevrio)
  - What NOT to use

- **Influenza basics**

Figure 1. COVID-19 cases reported weekly by WHO Region, and global deaths, as of 4 December 2022**



New Cases

- 2.9 million new cases (-3%)

New Deaths

- 7,833 deaths (-17%)

Case numbers driven by:

- **Japan** (749,895; **+7% increase**)
- **France** (385,716; **+38% increase**)
- **Korea** (370,574; -2% decrease)
- **USA** (296,333; -1% decrease)
- **Brazil** (188,043; **+25% increase**)

Deaths driven by:

- **USA** (1,744; -33% decrease)
- **Japan** (1,063; **+6% increase**)
- **Brazil** (632; **+18% increase**)
- **Italy** (462; -22% decrease)
- **France** (424; **+2% increase**)

- New cases stable (-3%; 2.9 million); deaths declined (-17%, 7,833)
- Overall >641 million cases; >6.6 million deaths
- Cases declined or stable in 5/6 WHO regions; AFRO (-78%), SEARO (-27%), EURO (stable), WPRO (-10%), EMRO (-4%), Americas (+14%); Deaths declined or stable in all 6 regions
- Omicron VOC composed 99.2% of sequences to GISAID (BA.5 73.2%, BQ.1 16.2%, BA.4 3.5%, BA.2 6.3%); XBB now making up 2%

Total Cases:

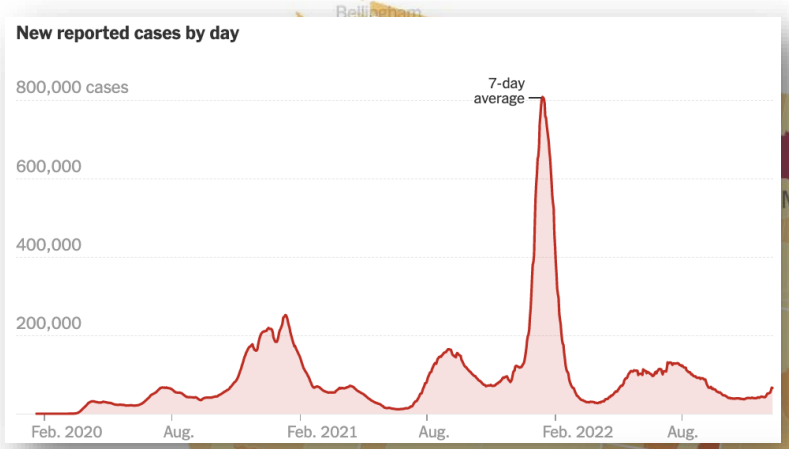
- 641,487094 recorded
- Europe (41%); Americas (28%); W Pacific (16%); SE Asia (9%)

Total Deaths:

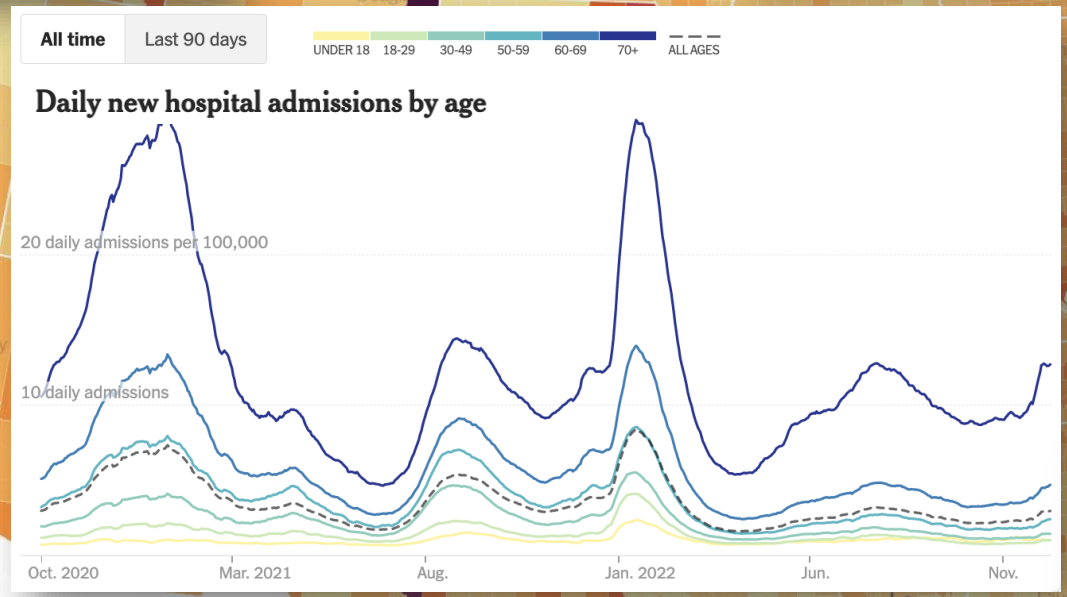
- **6,621,419** recorded
- Americas (43%); Europe (32%); SE Asia (12%)

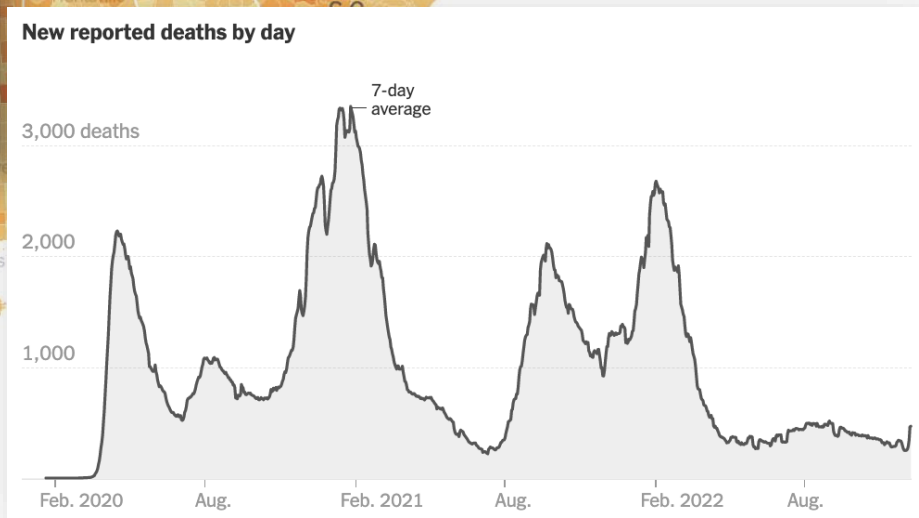
https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---7-december-2022 - accessed 12/10/22

US COVID-19 cases and Deaths



	DAILY AVG. ON DEC. 9	PER 100,000	14-DAY CHANGE
Cases	65,591	20	+53%
Test positivity	12%	—	+32%
Hospitalized	37,921	11	+32%
In I.C.U.s	4,289	1	+23%
Deaths	466	<1	+38%



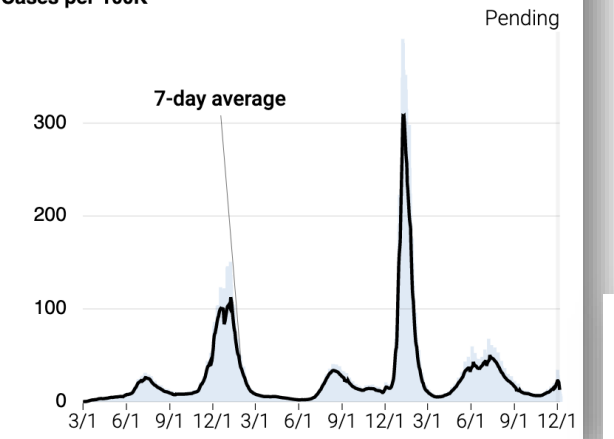


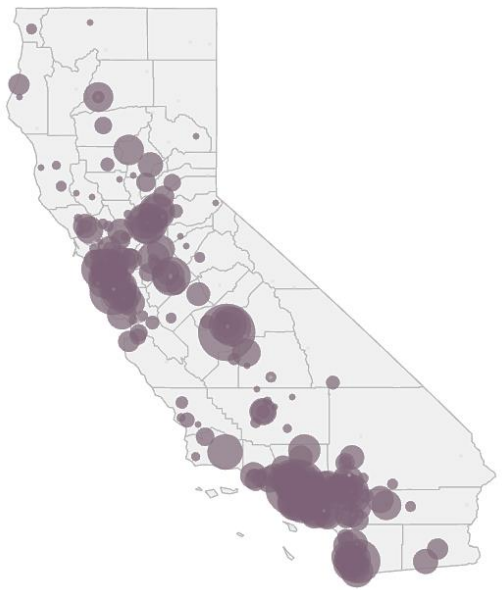
https://www.nytimes.com/interactive/2020/us/coronavirus-us-cases.html - accessed 11/21/22

CA COVID-19 cases, hospitalizations and deaths

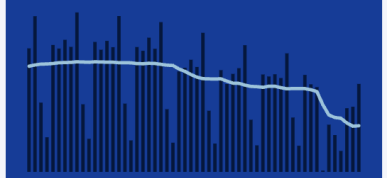
10,726,070 total confirmed cases
7,805 average cases per day
19.4 cases per 100K (7-day average)

Cases per 100K



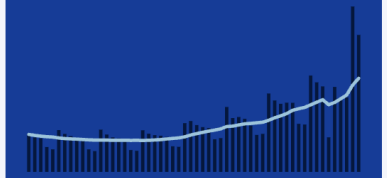


VACCINES ADMINISTERED
86,031,799 total
50,839 daily avg.
72.4% of population vaccinated (with primary series)



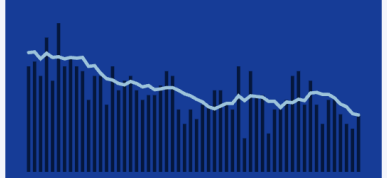
October 6 – November 30

CASES
10,726,070 total
7,805 daily avg.
19.4 new cases (per 100K)



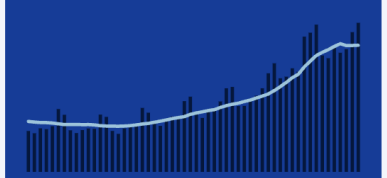
October 5 – November 29

DEATHS
96,995 total
13 daily avg.
0.03 new deaths (per 100K)



September 20 – November 14

TESTS
11.7% test positivity



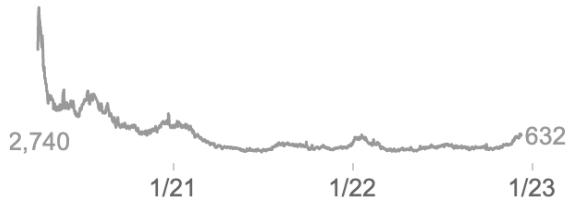
October 10 – December 4

Positive Patients

4,290 | 1 Day Δ -81 -1.9% | 14 Day Rolling Avg. 3,927

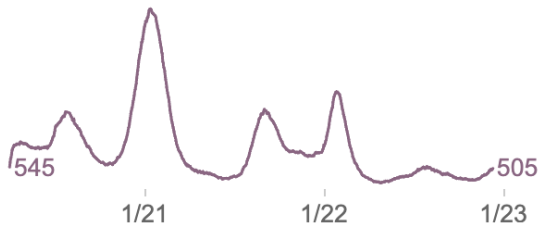
Suspected Patients

632 | 1 Day Δ -40 -6.0% | 14 Day Rolling Avg. 604



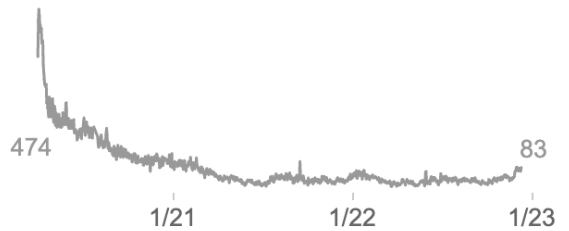
ICU Positive Patients

505 | 1 Day Δ -1 -0.2% | 14 Day Rolling Avg. 442



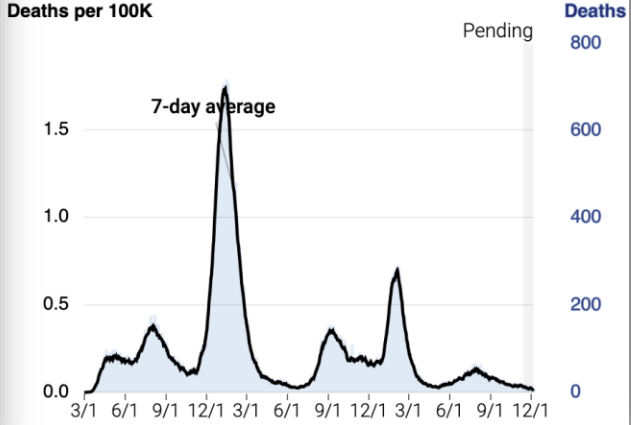
ICU Suspected Patients

83 | 1 Day Δ +10 +13.7% | 14 Day Rolling Avg. 75



96,995 total confirmed deaths
13 average deaths per day
0.03 deaths per 100K (7-day average)

Deaths per 100K | **Deaths**

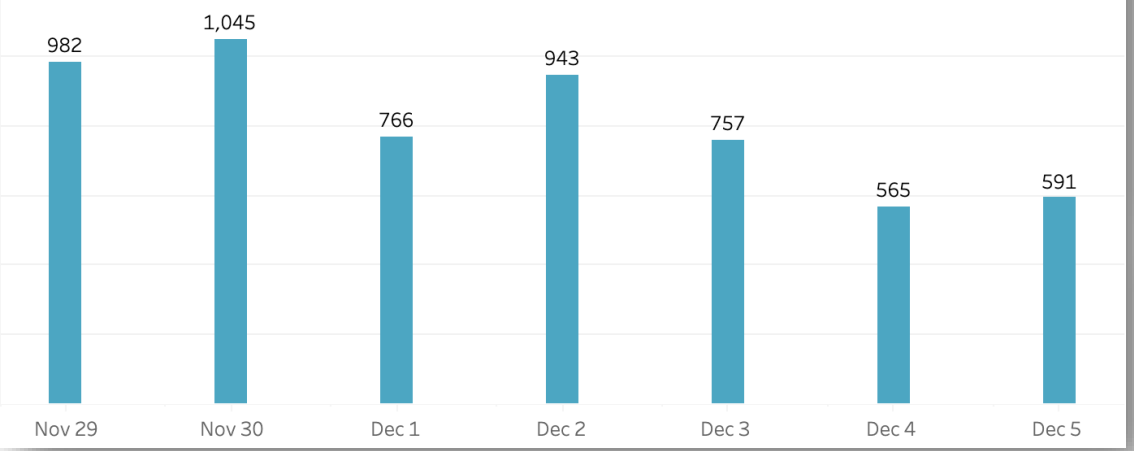


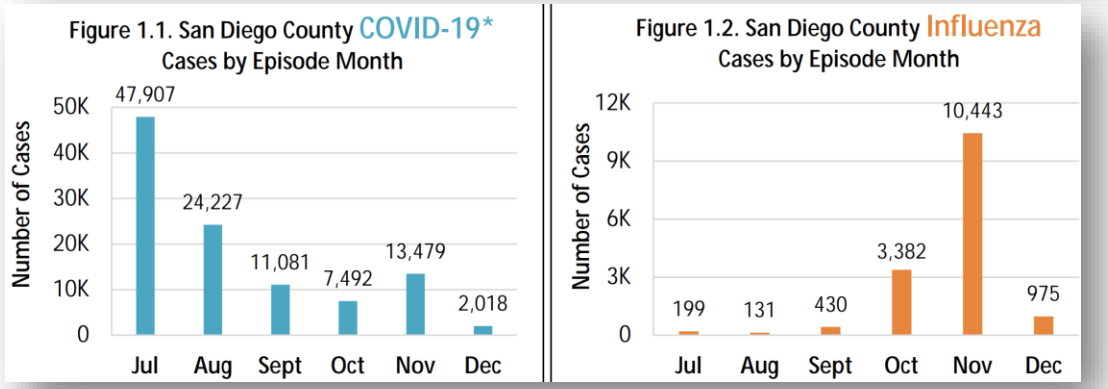
https://covid19.ca.gov/state-dashboard/ ; https://public.tableau.com/views/COVID-19HospitalsDashboard/Hospitals?:embed=y&:showVizHome=no - Accessed 12/11/22

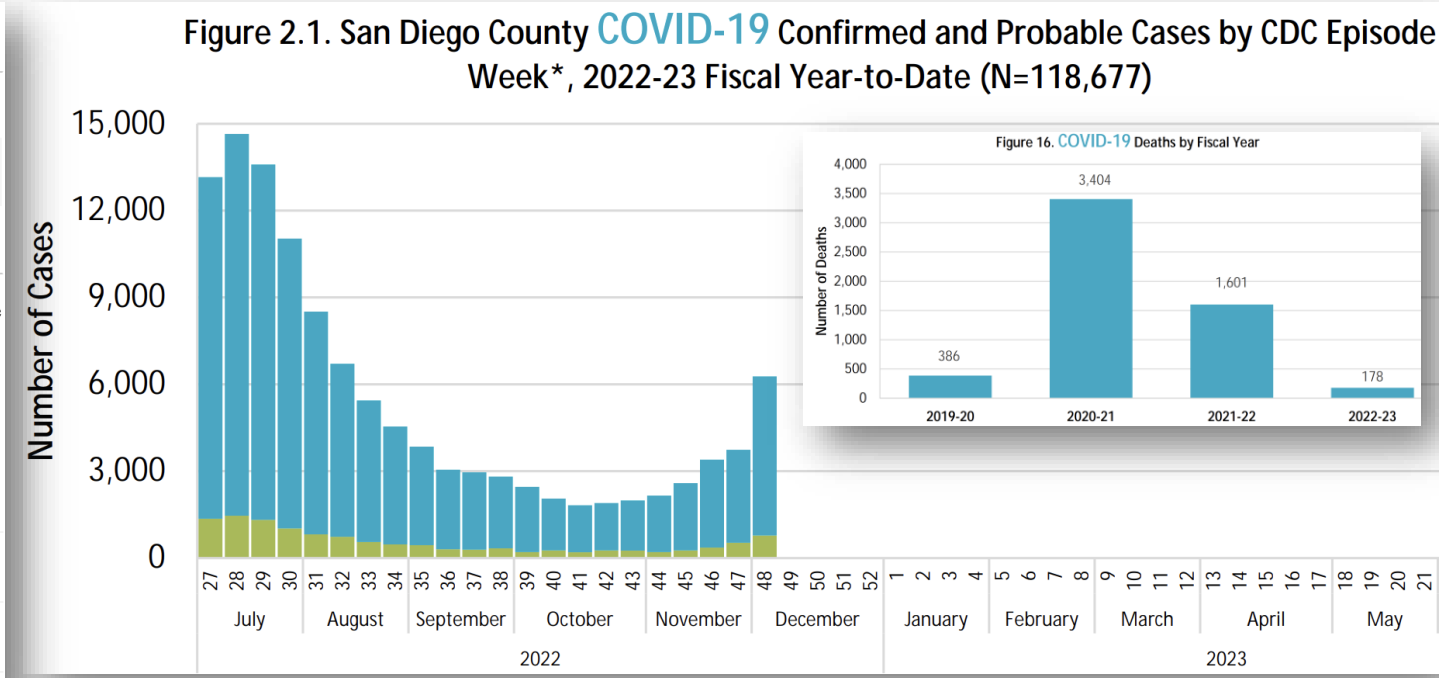
	Cumulative Count	Change from Previous Report	Percentage	Cumulative Rate per 100,000
Total Confirmed Cases	947,909	5,649	100.0%	28,281
Hospitalizations	36,309	180	3.8%	
Deaths	5,584	15	0.6%	

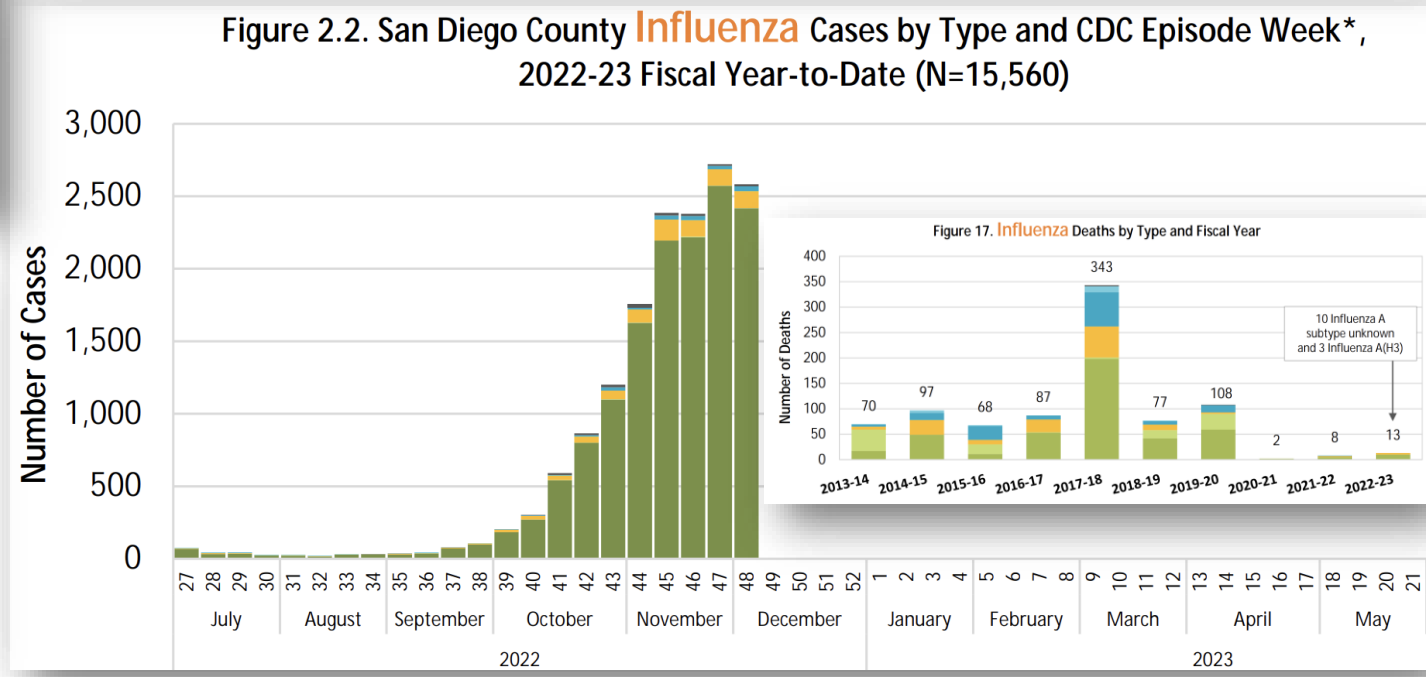
*Known hospitalizations; information is incomplete for many cases under investigation. Periodically, larger numbers of hospitalizations may be added on one day as a result of batched reports and quality assurance processes.
Cases, hospitalizations, and deaths are added to this table as information becomes available; this may not be indicative of when the event occurred.

COVID-19 Case Counts for Previous 7 Days by Date Reported, San Diego County



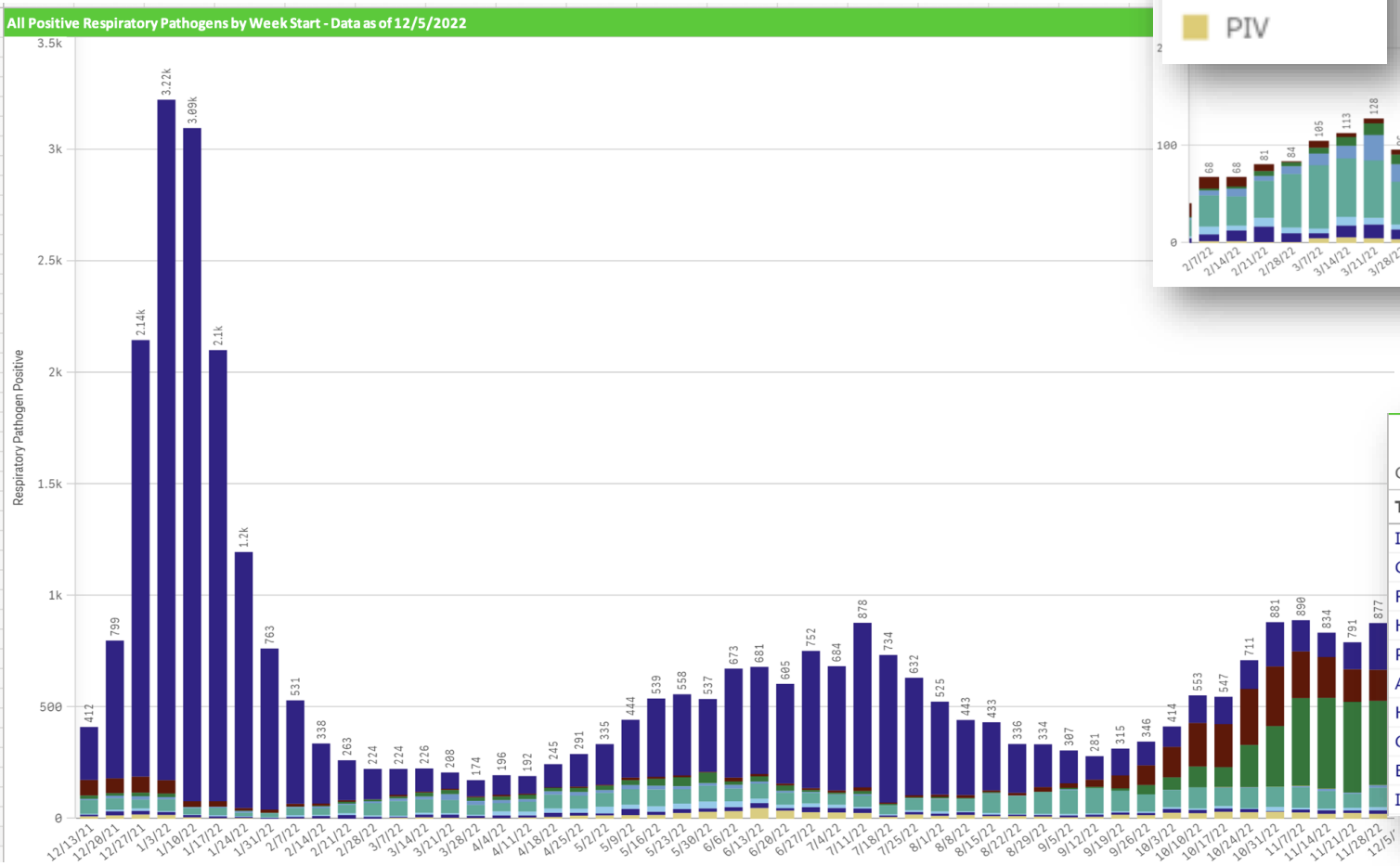


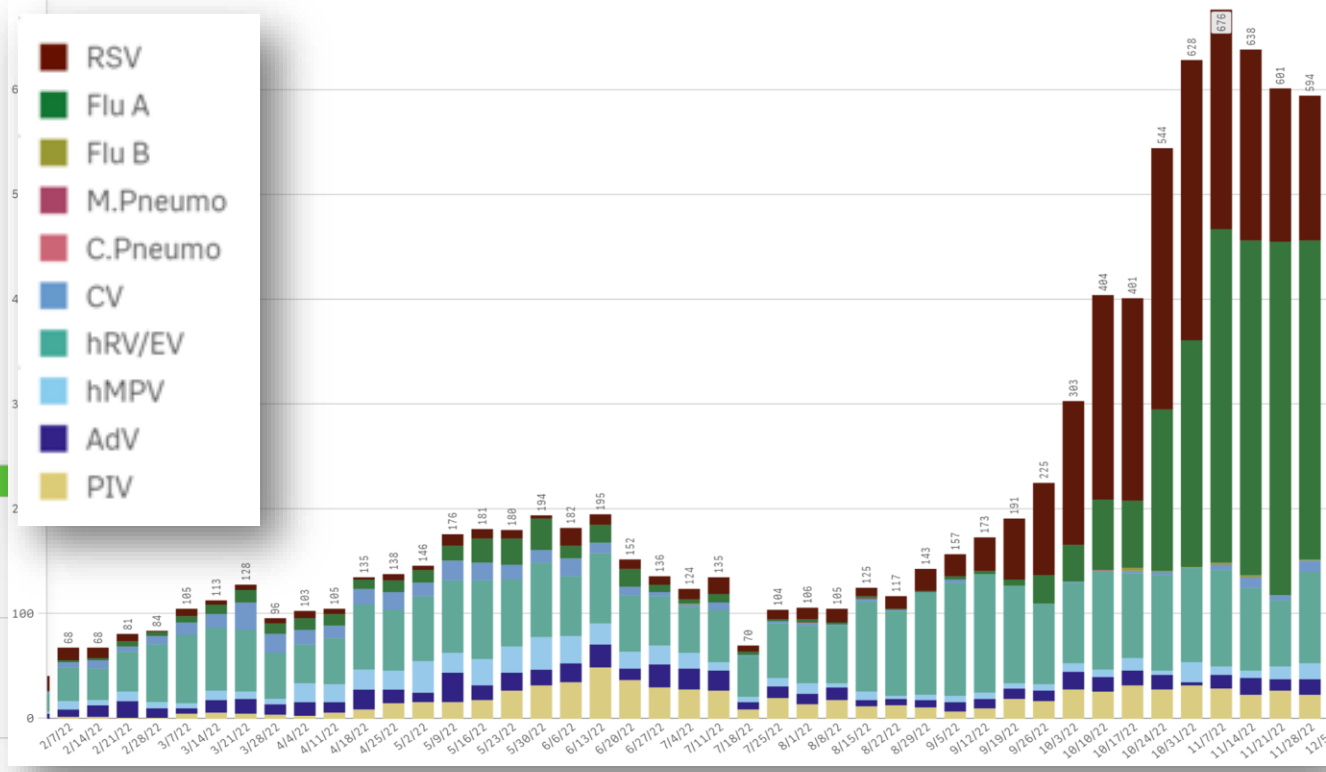




https://www.sandiegocounty.gov/content/dam/sdc/hhsa/programs/phs/Epidemiology/SDC_Respiratory_Virus_Surveillance_Report.pdf - accessed 12/10/22

Rady Children's Virology Report





Component Group	Pathogen Positive Previous Week 11/28/2022 - 12/4/2022	Pathogen Tests Previous Week 11/28/2022 - 12/4/2022	Previous Week Positive Rate
Totals	**785**	**4,829**	**16.3%**
Influenza A	304	1,048	29.0%
COVID-19(SARS-CoV-2,PCR)	212	3,152	6.7%
RSV	138	1,048	13.2%
Human Rhinovirus/Enterovirus	87	370	23.5%
Parainfluenza	23	370	6.2%
Adenovirus	15	370	4.1%
Human Metapneumovirus	15	370	4.1%
Coronavirus(other than COVID-19)	11	370	3.0%
B.Pertussis/Parapertussis	2	48	4.2%
Influenza B	1	1,048	0.1%

Rady Children's Hospital Respiratory Pathogens Report - accessed 12/5/22

Figure 3.1. Cumulative COVID-19 Confirmed and Probable Cases by CDC Episode Week* and Fiscal Year

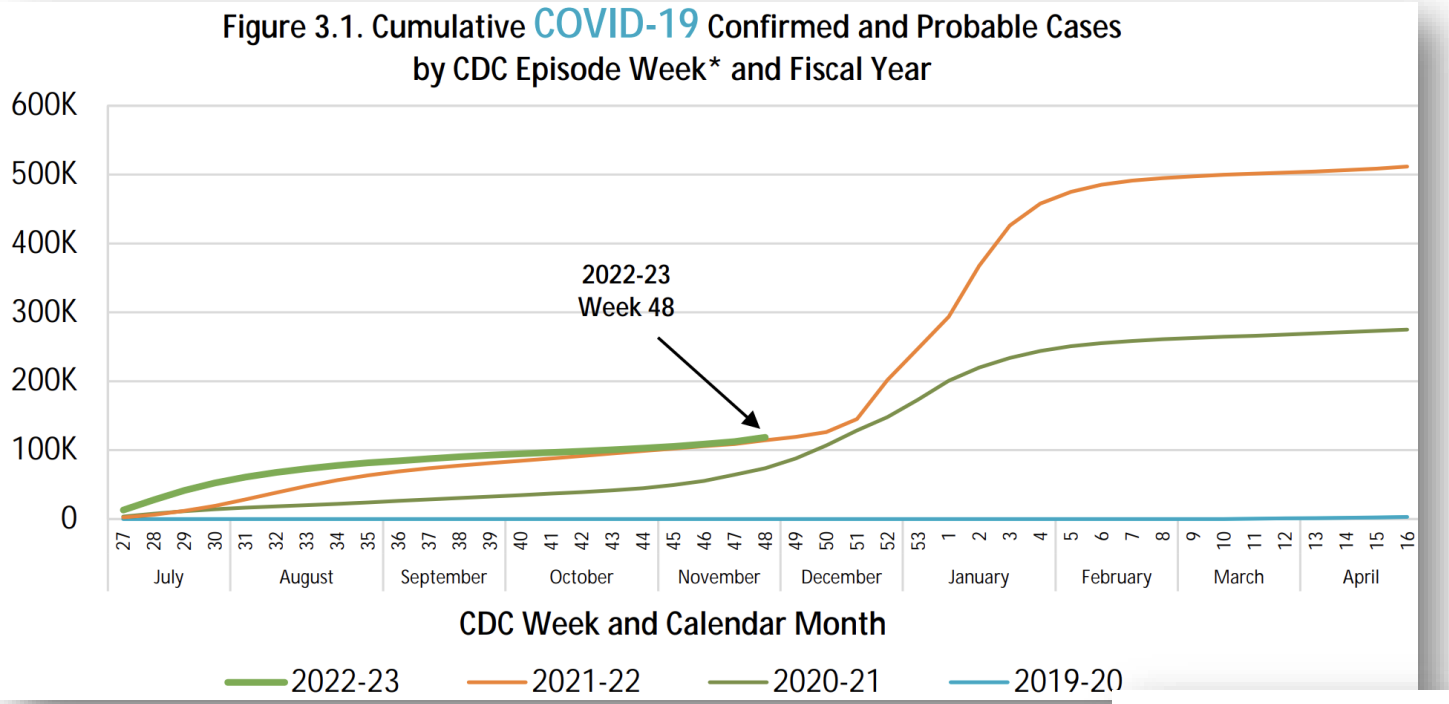
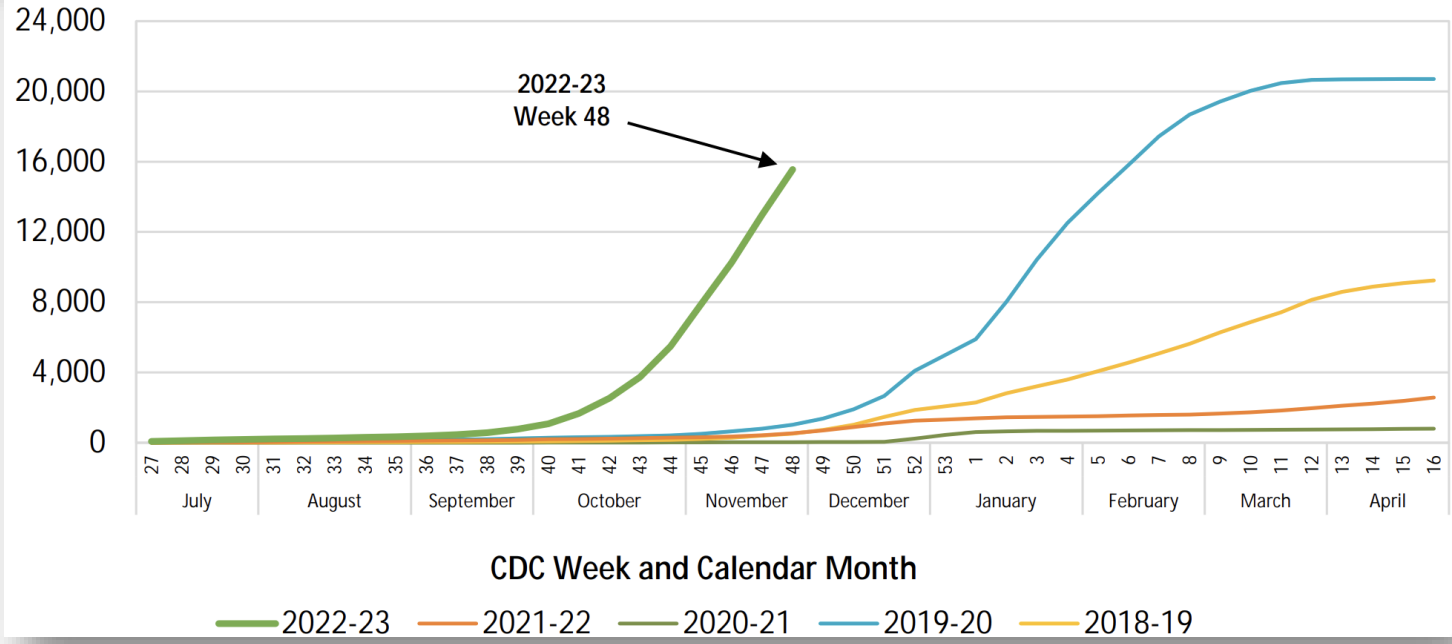
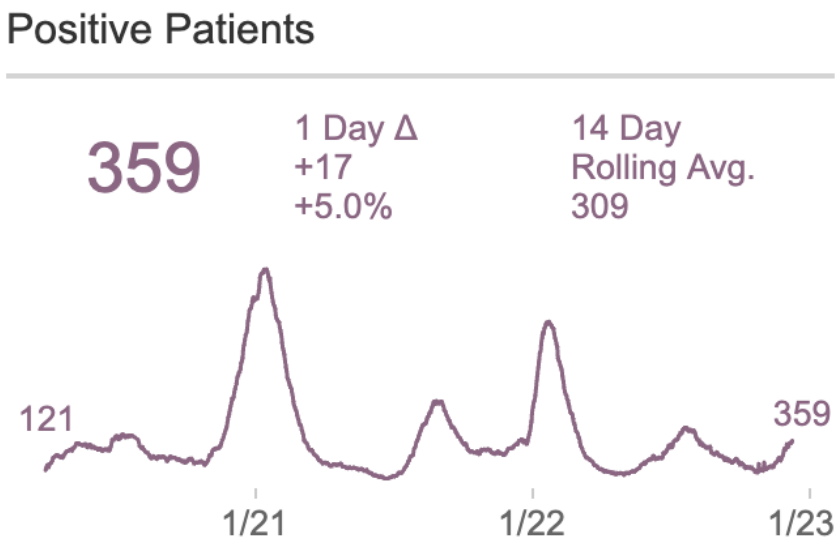


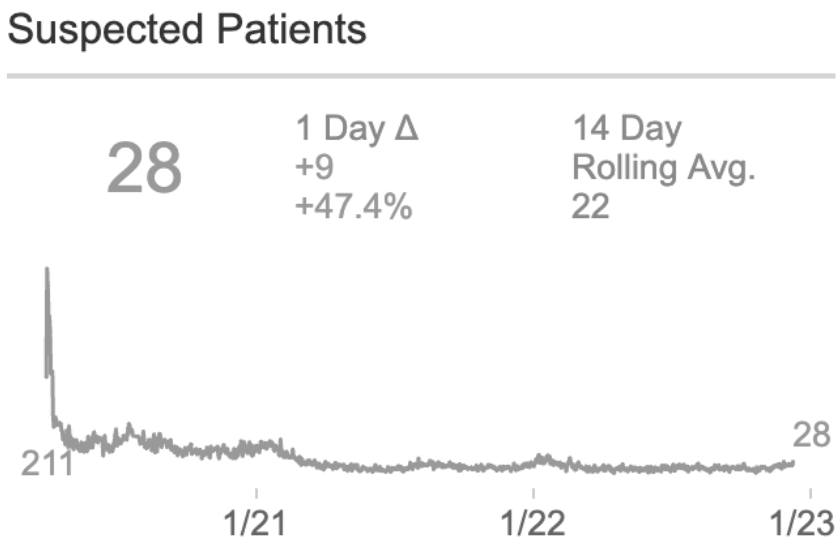
Figure 3.2. Cumulative Influenza Cases by CDC Episode Week* and Fiscal Year

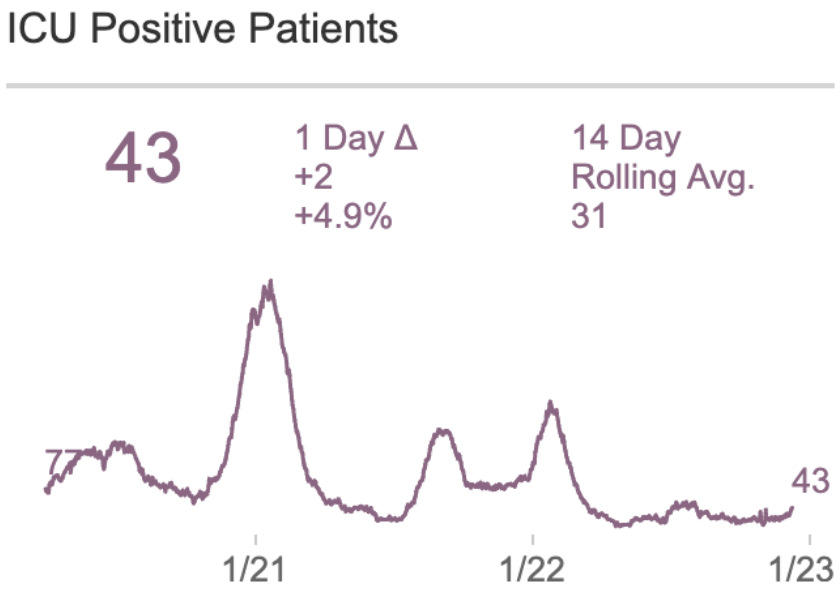


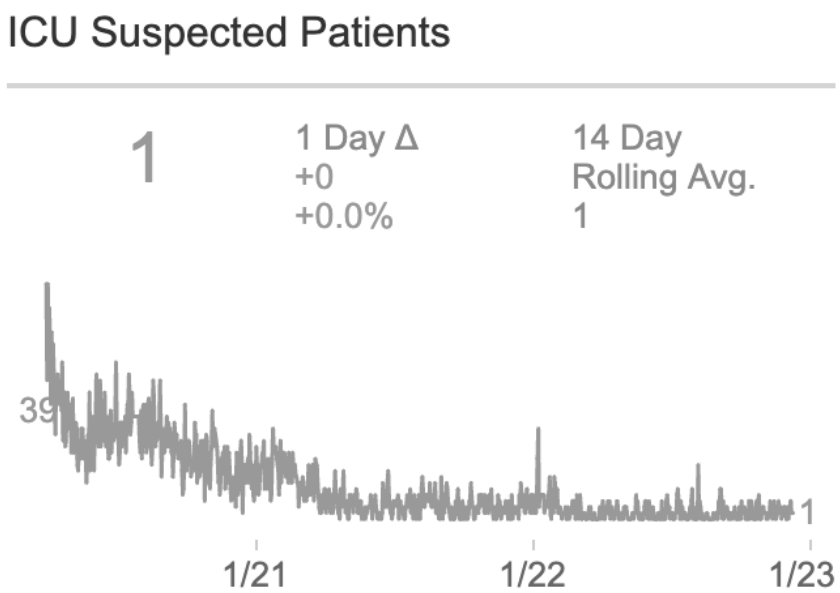
https://www.sandiegocounty.gov/content/dam/sdc/hhsa/programs/phs/Epidemiology/SDC_Respiratory_Virus_Surveillance_Report.pdf - accessed 12/10/22

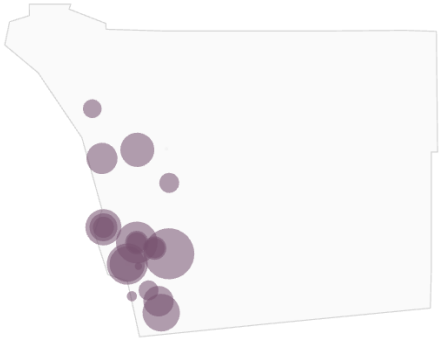
COVID-19 Hospitalizations, ICU admissions – San Diego – 12/9/22









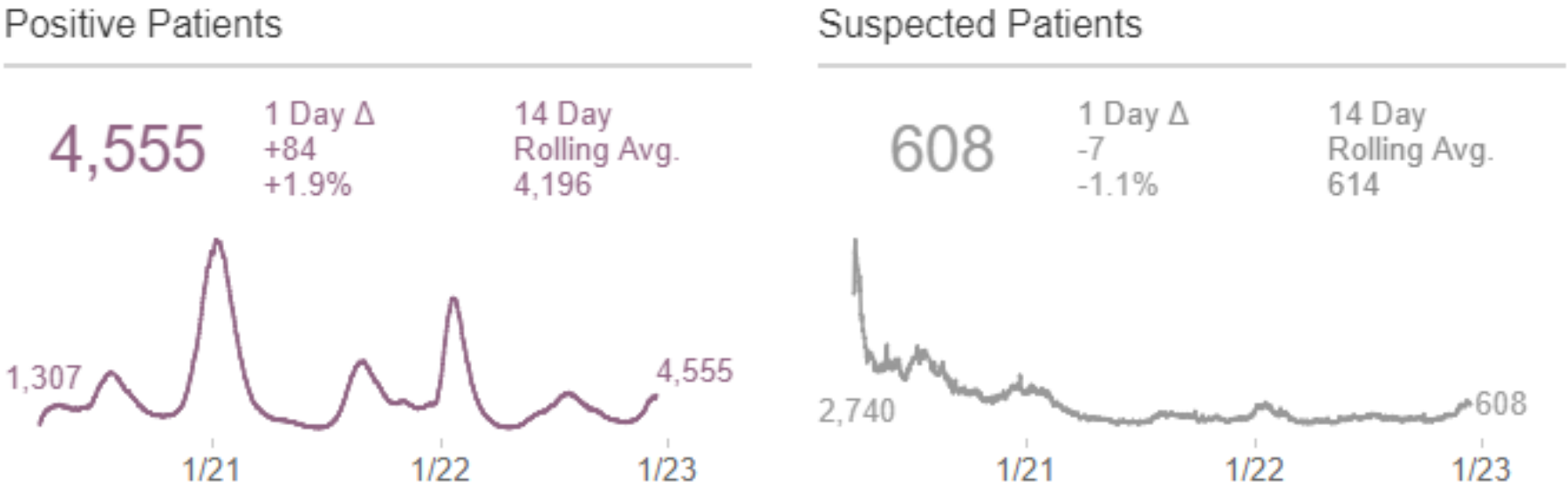


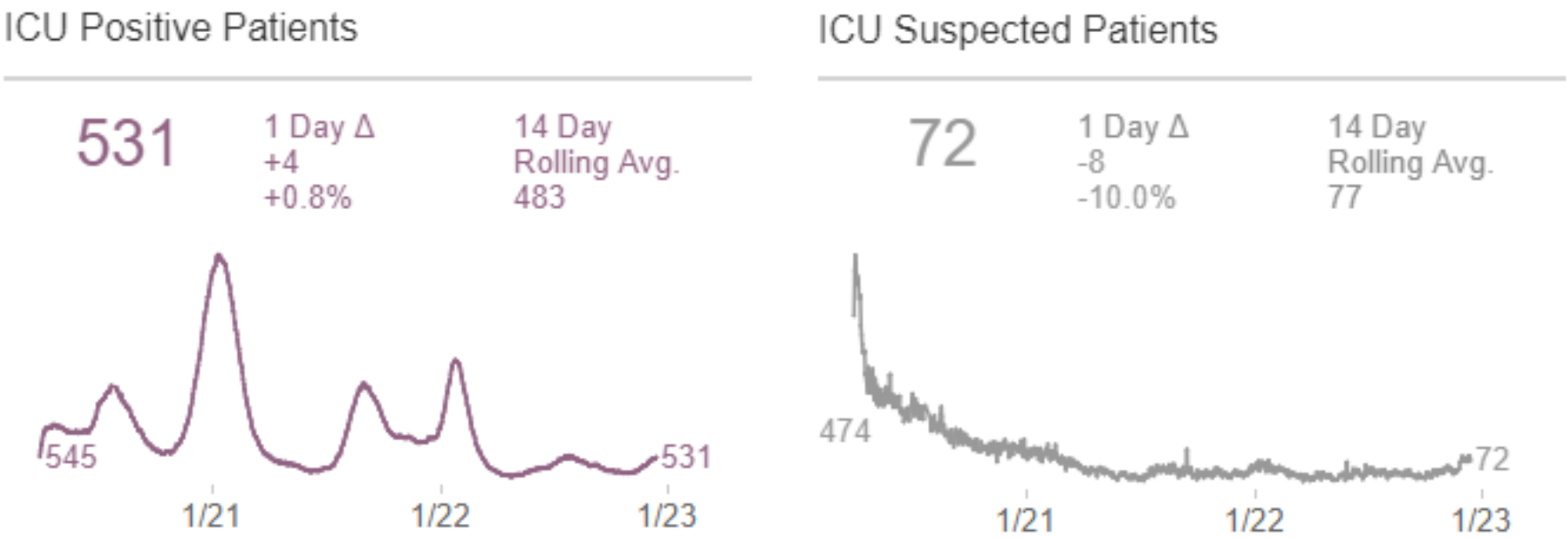
Peak Hospitalizations (1/14/21): **1,728**

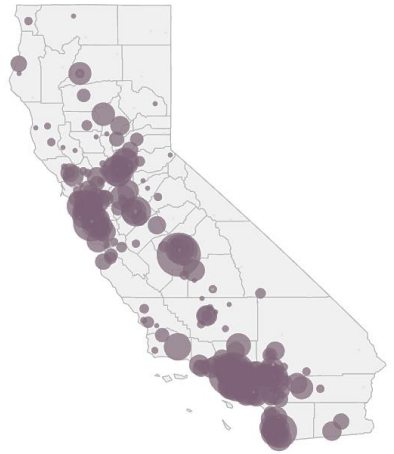
Peak ICU Admissions (1/20/21): **447**

https://public.tableau.com/views/COVID-19HospitalsDashboard/Hospitals?:embed=y&:showVizHome=no – Accessed 12/9/22

COVID-19 Hospitalizations, ICU admissions – CA – 12/14/22





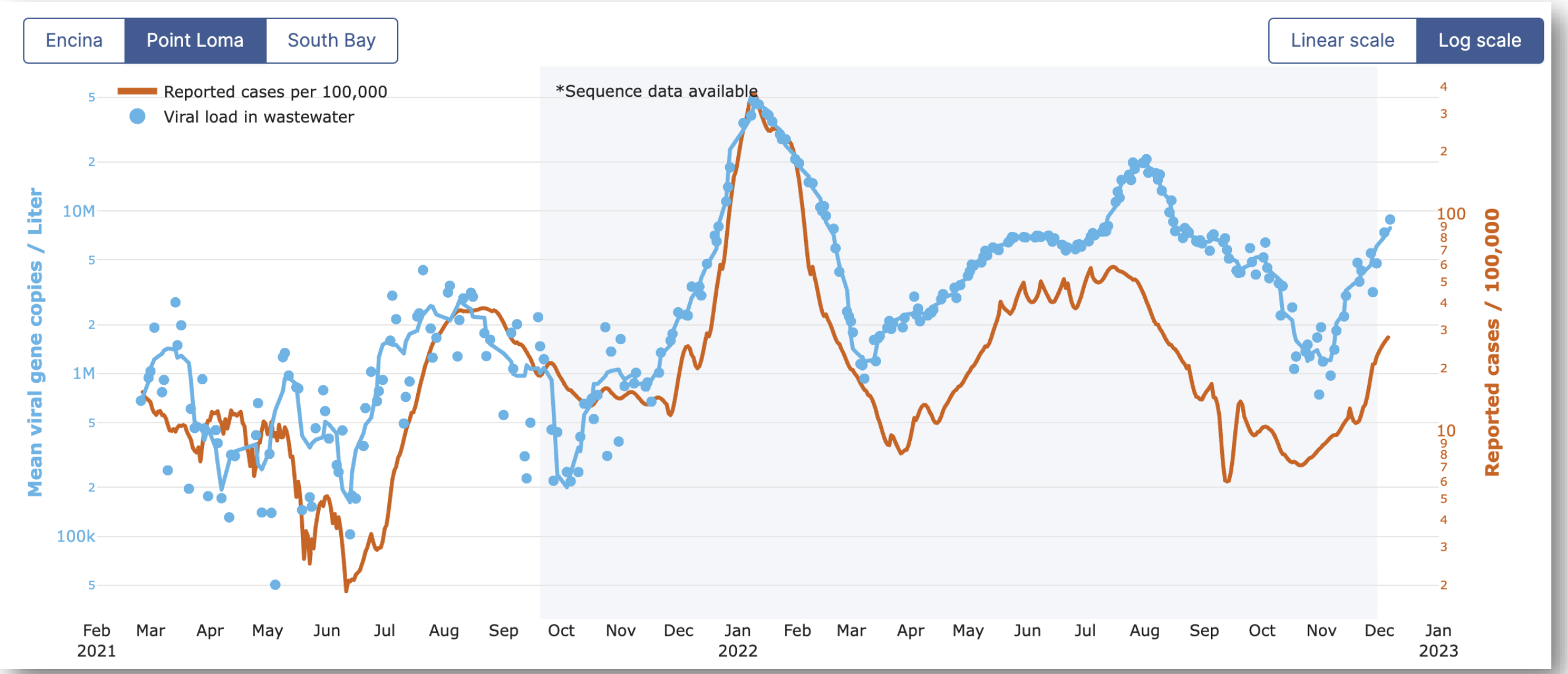


Peak Hospitalizations
(1/6/21): **21,938**

Peak ICU Admissions
(1/10/21): **4,868**

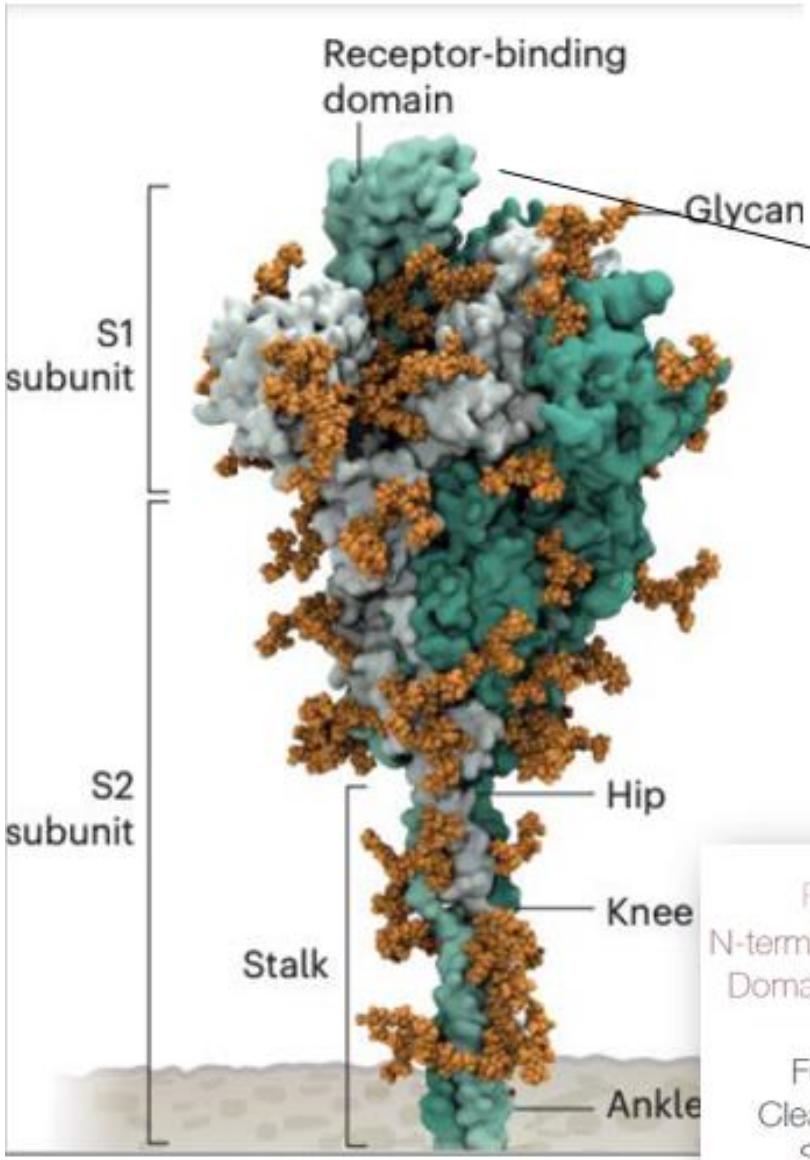
https://public.tableau.com/views/COVID-19HospitalsDashboard/Hospitals?:embed=y&:showVizHome=no – Accessed 12/14/22

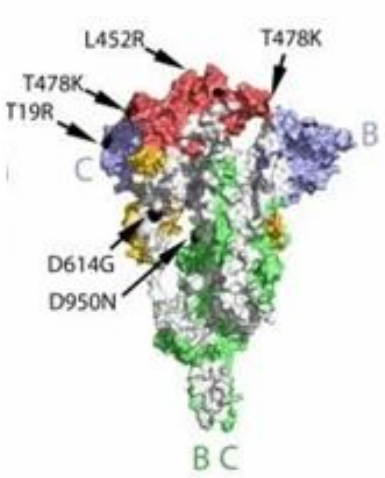
San Diego SARS-CoV-2 Wastewater surveillance – 12/11/22

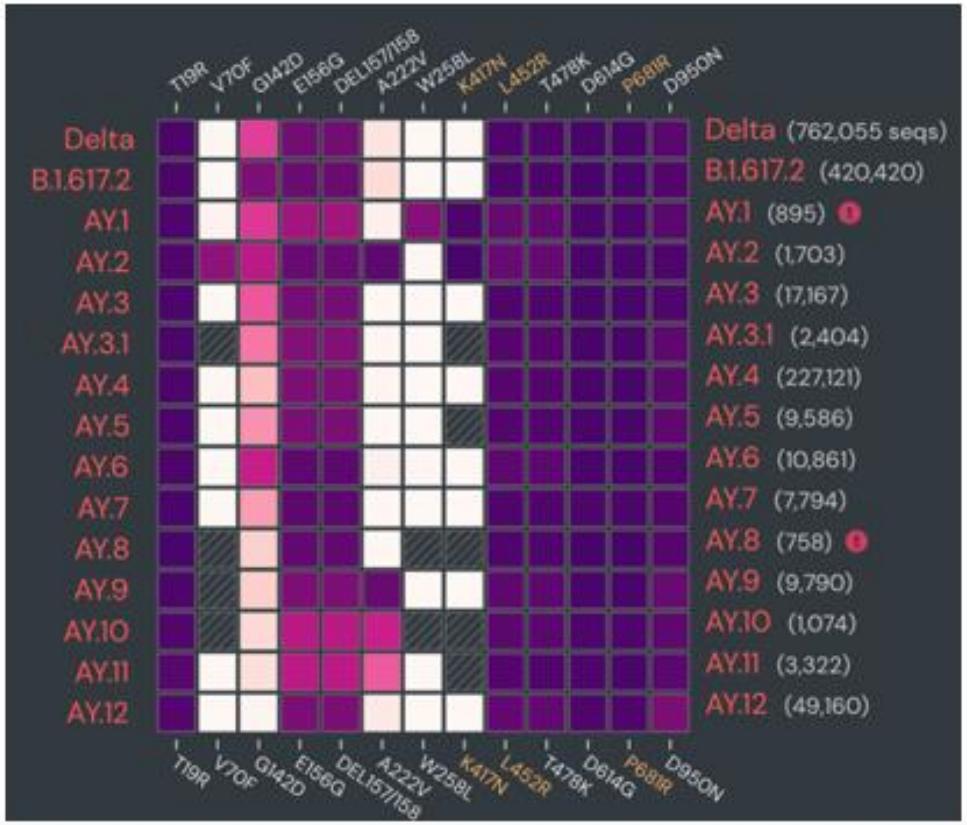


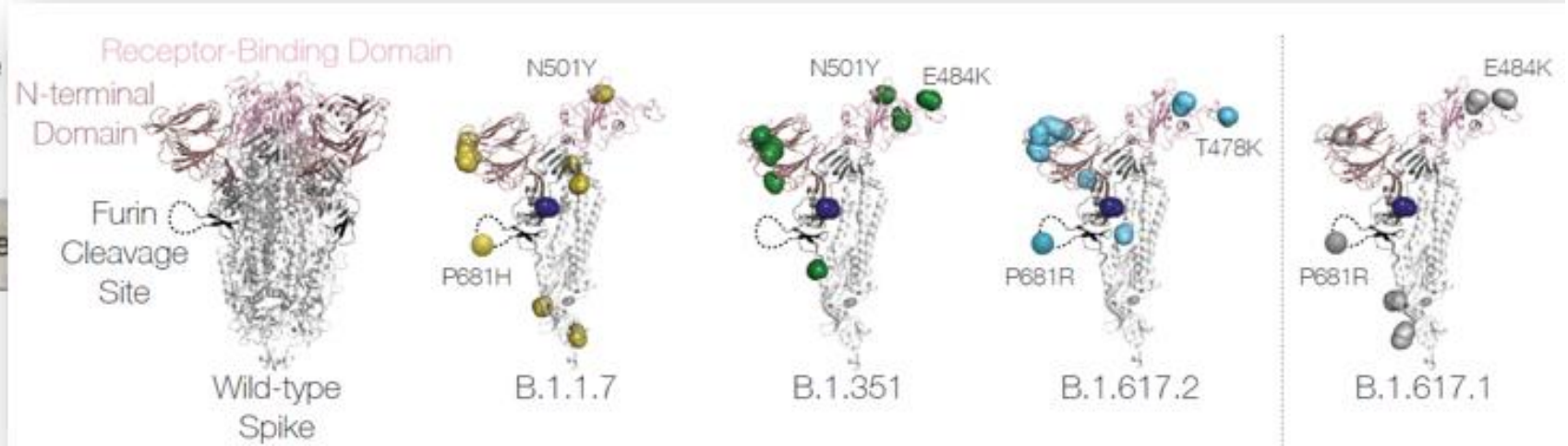
San Diego Wastewater Surveillance - SEARCH (searchcovid.info) – accessed 12/11/22

SARS-CoV-2 Variants



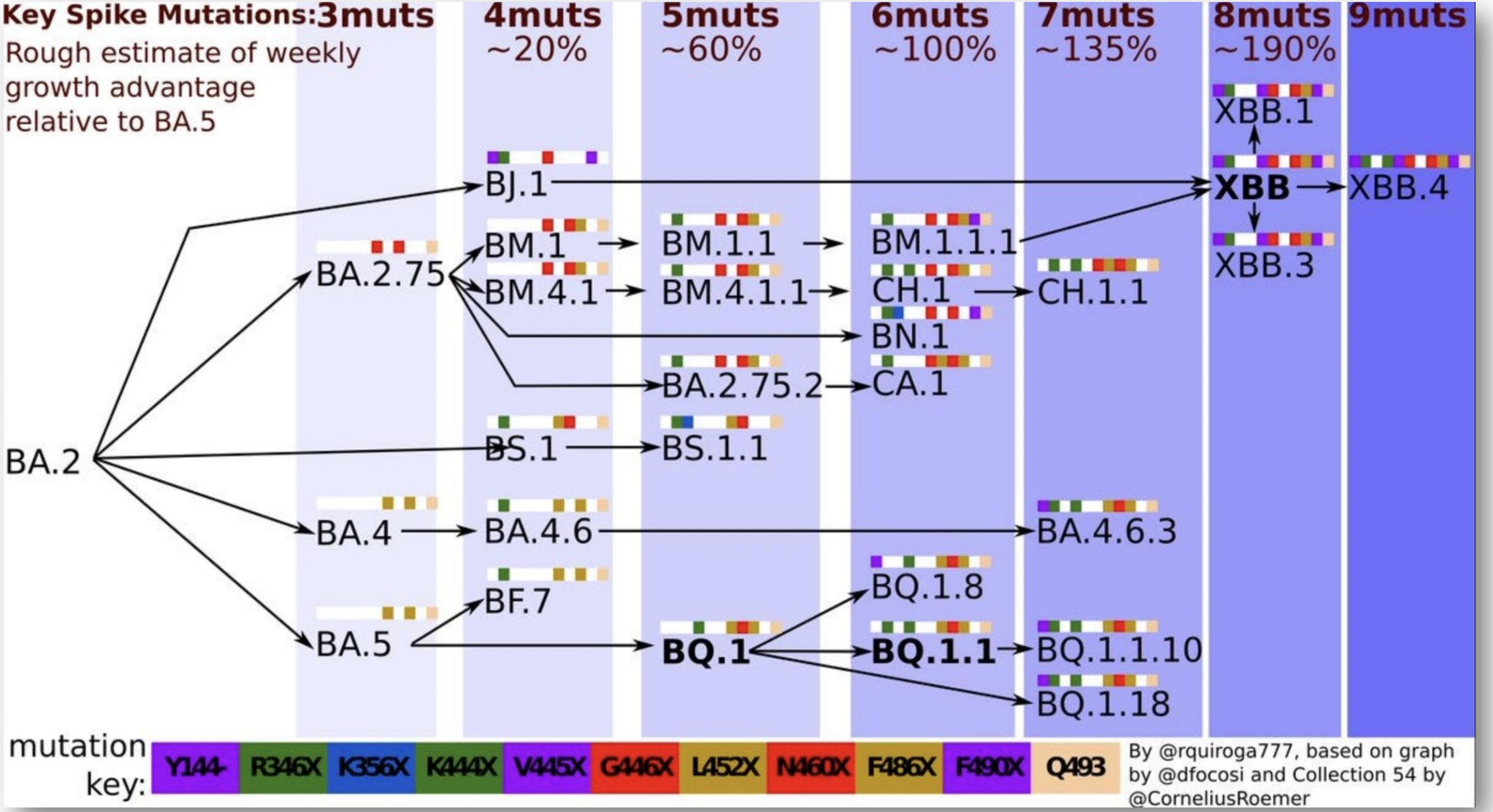






outbreak.info

SARS-CoV-2 Omicron Variants



https://twitter.com/rquiroga777/status/1593292309273214977

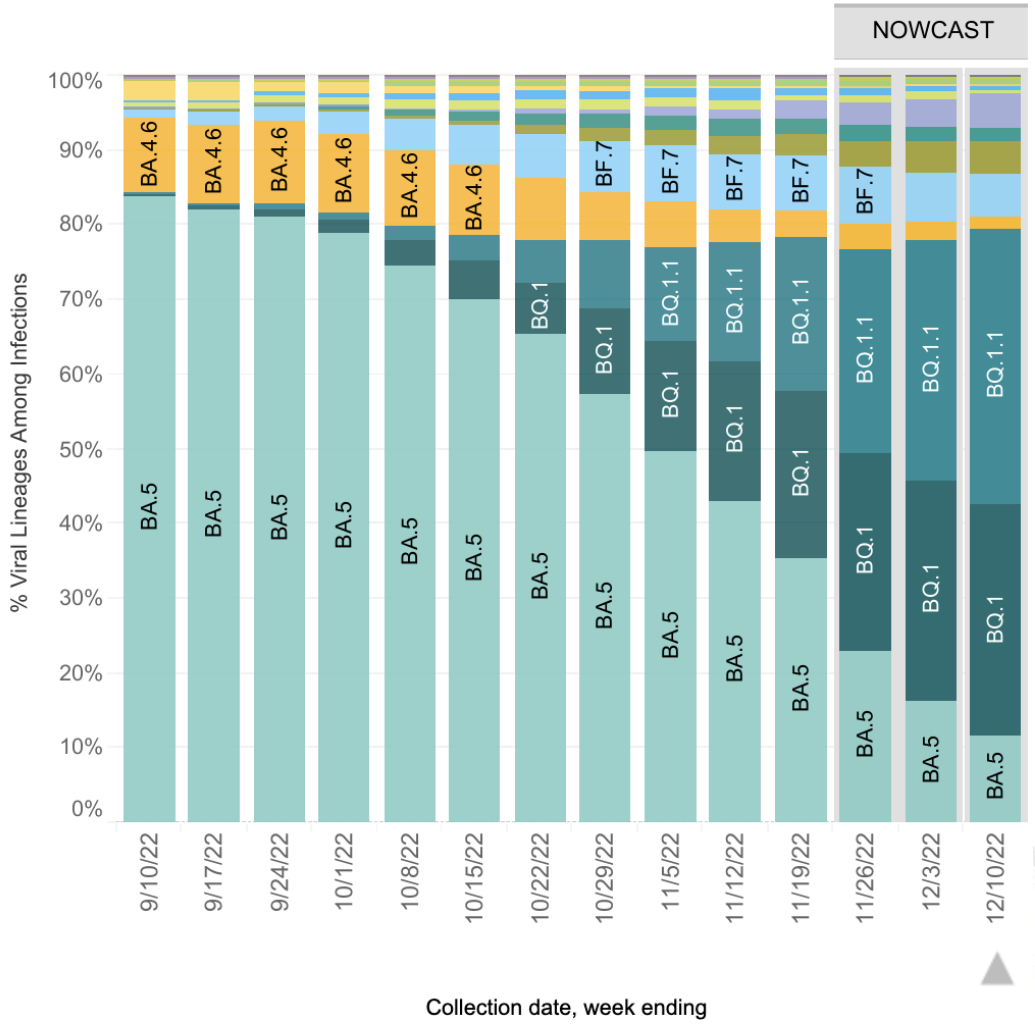
SARS-CoV-2 Variants – US CDC data (9/4/22-12/10/22)

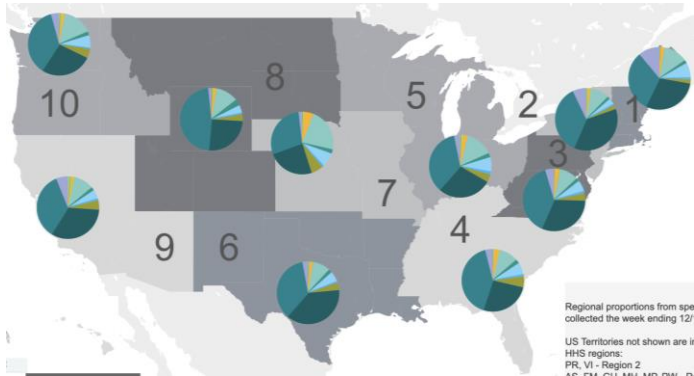
United States: 12/4/2022 – 12/10/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BQ.1.1	VOC	36.8%	34.1-39.6%
	BQ.1	VOC	31.1%	29.0-33.4%
	BA.5	VOC	11.5%	10.3-12.7%
	BF.7	VOC	5.7%	5.0-6.5%
	XBB	VOC	4.7%	2.6-8.1%
	BN.1	VOC	4.3%	3.8-4.9%
	BA.5.2.6	VOC	1.7%	1.4-2.0%
	BA.4.6	VOC	1.6%	1.4-1.9%
	BF.11	VOC	0.8%	0.6-1.0%
	BA.2	VOC	0.7%	0.5-1.1%
	BA.2.75	VOC	0.6%	0.5-0.7%
	BA.2.75.2	VOC	0.4%	0.3-0.5%
	BA.4	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	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%	0.0-0.1%

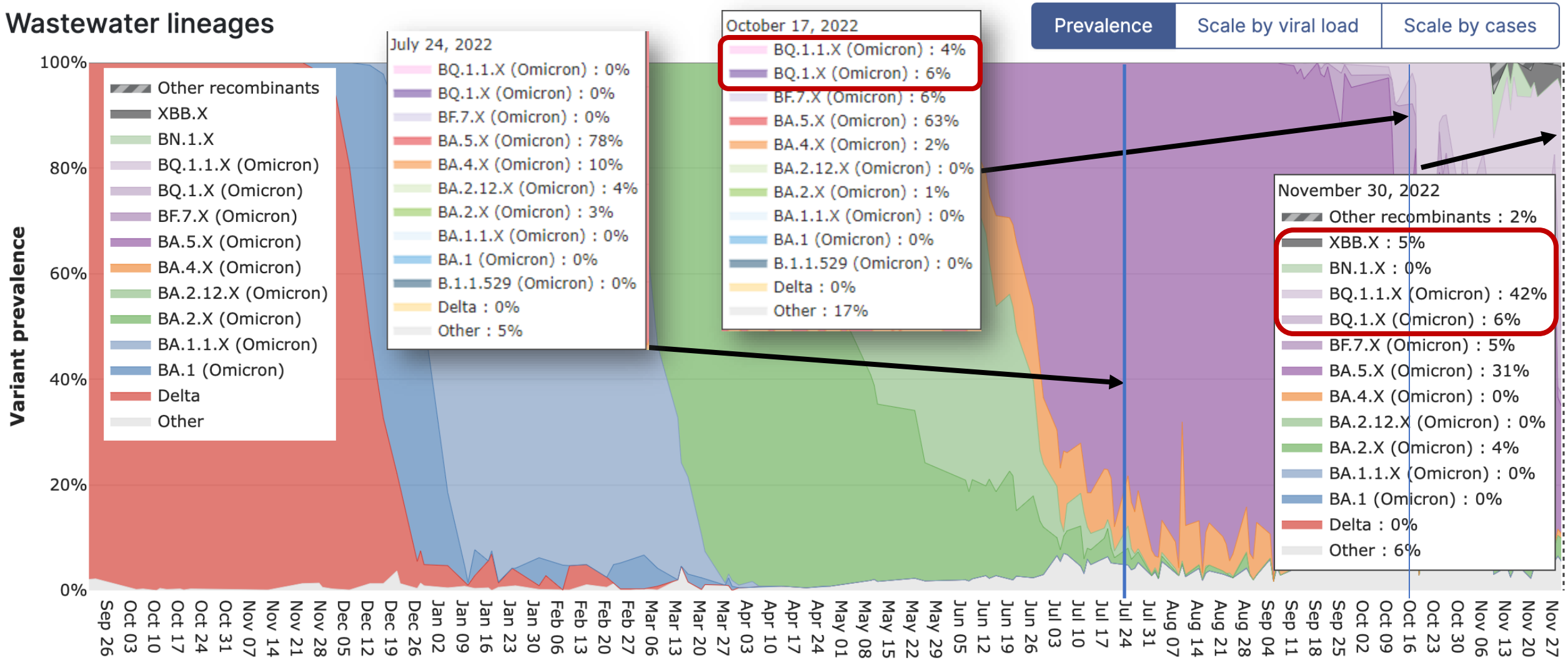
United States: 9/4/2022 – 12/10/2022





https://covid.cdc.gov/covid-data-tracker/#variant-proportions – accessed 12/11/22

SARS-CoV-2 Variants – SD Wastewater surveillance



San Diego Wastewater Surveillance - SEARCH (searchcovid.info) – accessed 12/11/22

Updated EUA for Bebtelovimab

Table 2: Bebtelovimab Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Spike Protein Variants

Lineage with Spike Protein Substitution	Country First Identified	WHO Nomenclature	Key Substitutions Tested[a]	Fold Reduction in Susceptibility
BA.1.1	South Africa	Omicron [+R346K]	BA.1 + R346K	No change[b]
BA.2	South Africa	Omicron [BA.2]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N + N440K + S477N + T478K + E484A + Q493R + Q498R + N501Y + Y505H	No change[b]
BA.2.12.1	USA	Omicron [BA.2+L452Q]	BA.2 + L452Q	No change[b]
BA.2.75	India	Omicron [BA.2+D339H, G446S, N460K, R493Q (reversion)]	BA.2 + D339H + G446S + N460K + R493Q (reversion)	No change[b]
BA.2.75.2	India	Omicron [BA.2.75+R346T+F486S]	BA.2.75 + R346T + F486S	No change[b]
BA.4/BA.5	South Africa	Omicron [BA.4/BA.5]	G339D + S371F + S373P + S375F + T376A + D405N + R408S + K417N +	No change[b]
BA.4.6/BF.7	USA/Belgium	Omicron [BA.4+R346T]	BA.4 + R346T	No change[b]
BQ.1	Nigeria	Omicron [BA.5+K444T+N460K]	BA.5 + K444T + N460K	>672[d]
BQ.1.1	Multiple	Omicron [BA.5+R346T+K444T+N460K]	BA.5 + R346T + K444T + N460K	>672[d]

https://www.fda.gov/media/156152/download
https://www.fda.gov/drugs/drug-safety-and-availability/fda-announces-bebtelovimab-not-currently-authorized-any-us-region
https://www.covid19treatmentguidelines.nih.gov/therapies/update-on-bebtelovimab/?utm_source=site&utm_medium=home&utm_campaign=highlights

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / Drug Safety and Availability / FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region

FDA Announces Bebtelovimab is Not Currently Authorized in Any US Region

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NIH COVID-19 Treatment Guidelines MENU

Home / Therapies / Update on Bebtelovimab

The COVID-19 Treatment Guidelines Panel's Update on Bebtelovimab

Last Updated: December 6, 2022

The prevalence of SARS-CoV-2 Omicron subvariants that are anticipated to be resistant to bebtelovimab (i.e., BQ.1, BQ.1.1, XBB) has been rapidly increasing in the United States. As of December 2, 2022, the combined prevalence of these subvariants is estimated to be over 68%.[1]

Due to the increasing prevalence of these resistant strains, the Food and Drug Administration revised the Emergency Use Authorization for bebtelovimab on November 30, 2022. Bebtelovimab is not currently authorized for the treatment of COVID-19 in any region of the United States.[2]

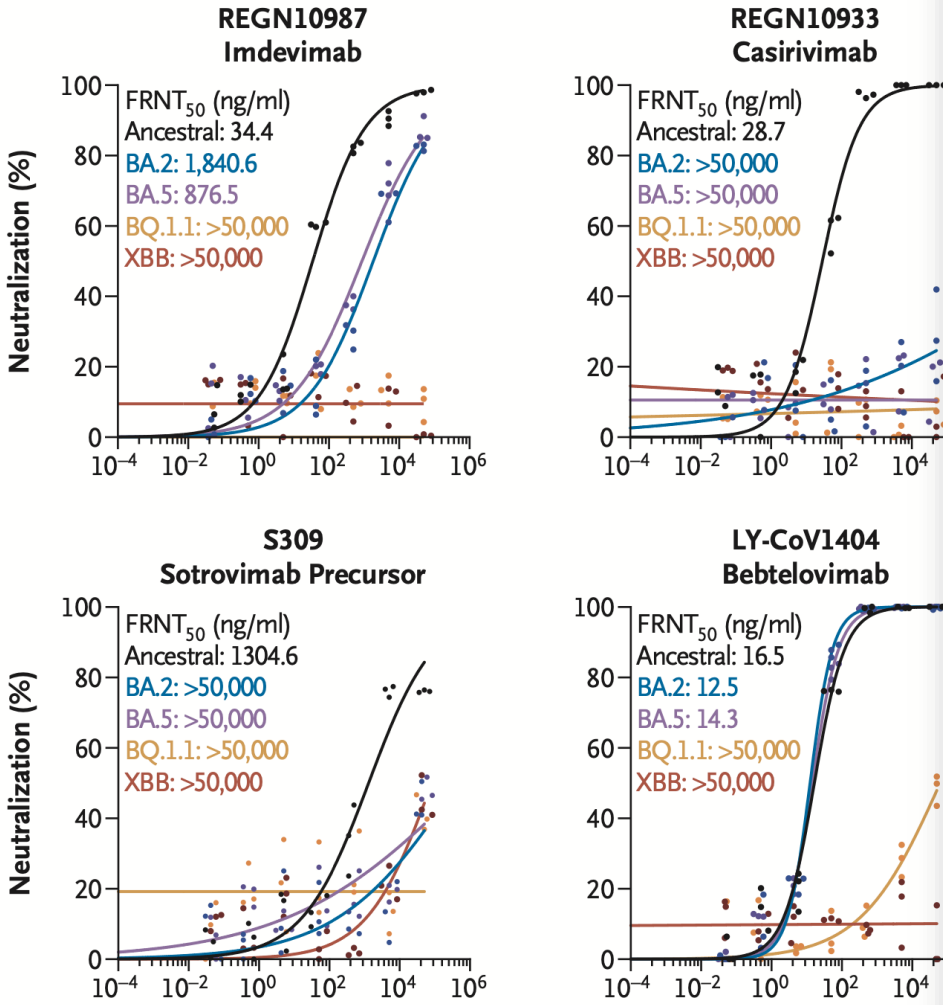
The COVID-19 Treatment Guidelines Panel (the Panel) now **recommends against** the use of **bebtelovimab** for the treatment of nonhospitalized patients with COVID-19 who are at high risk of progressing to severe COVID-19 (**AIII**).

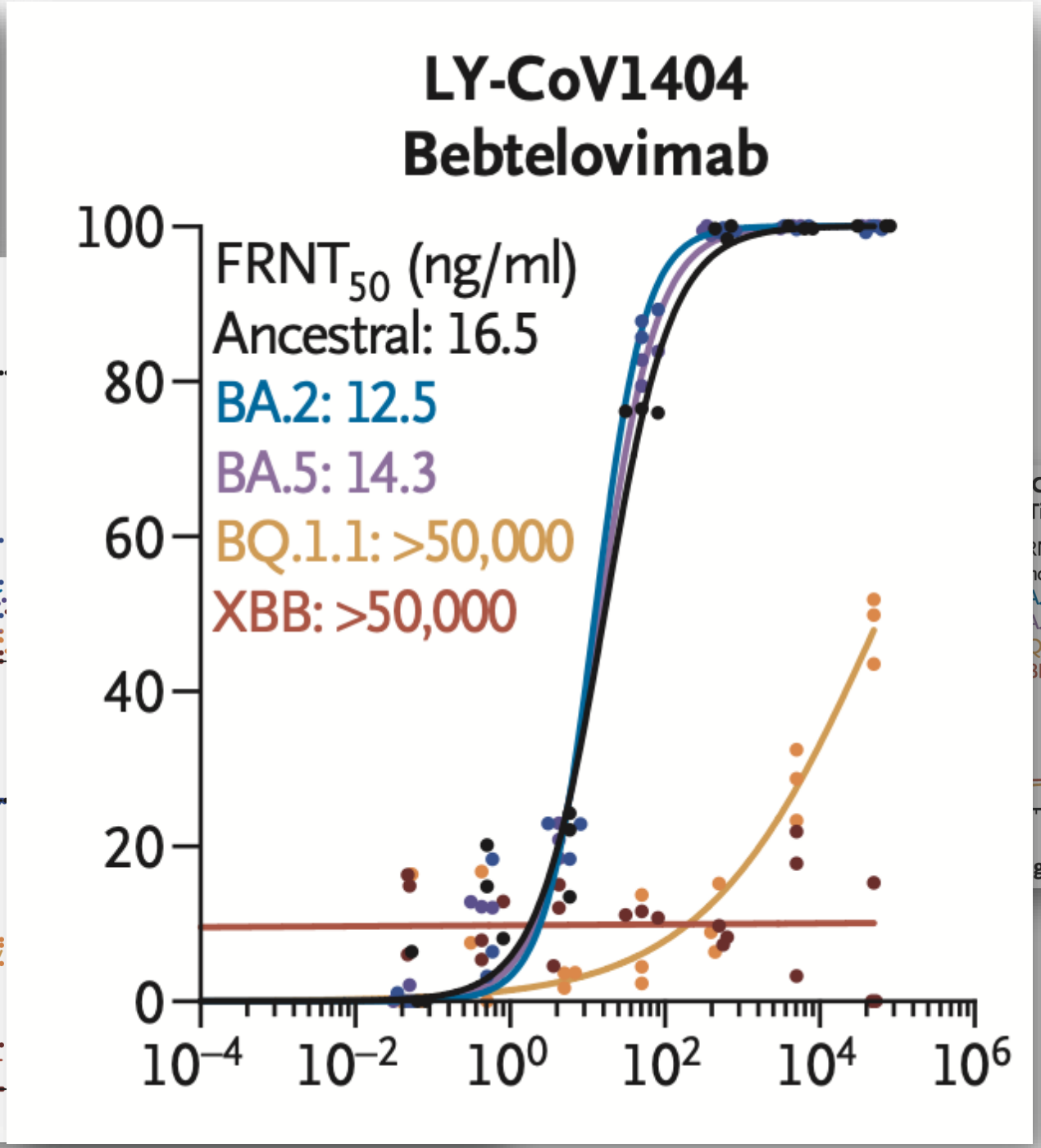
The NEW ENGLAND JOURNAL of MEDICINE

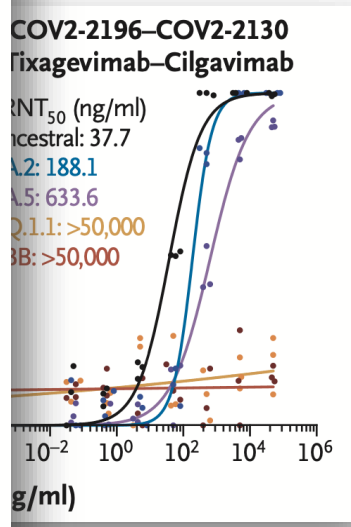
CORRESPONDENCE

Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB

A Neutralizing Activity of Monoclonal Antibodies





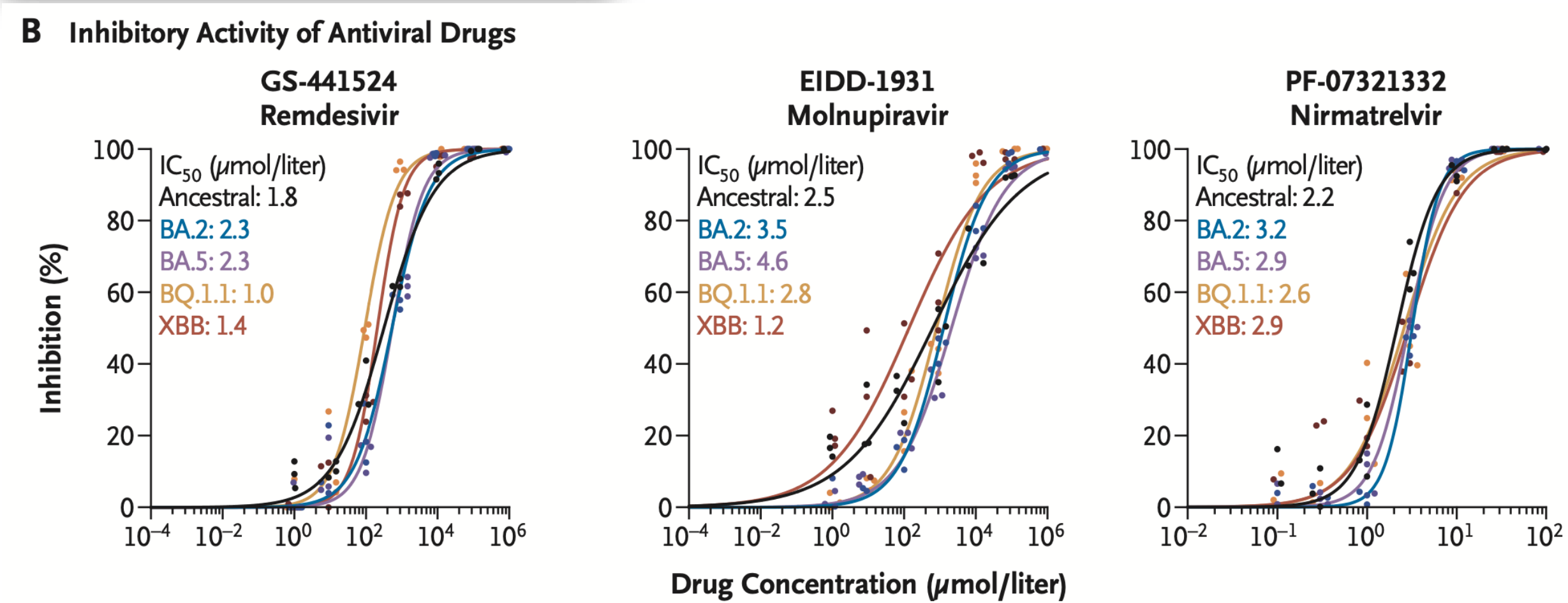


https://www.nejm.org/doi/full/10.1056/NEJMc2214302 - accessed 12/11/22

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Efficacy of Antiviral Agents against Omicron Subvariants BQ.1.1 and XBB

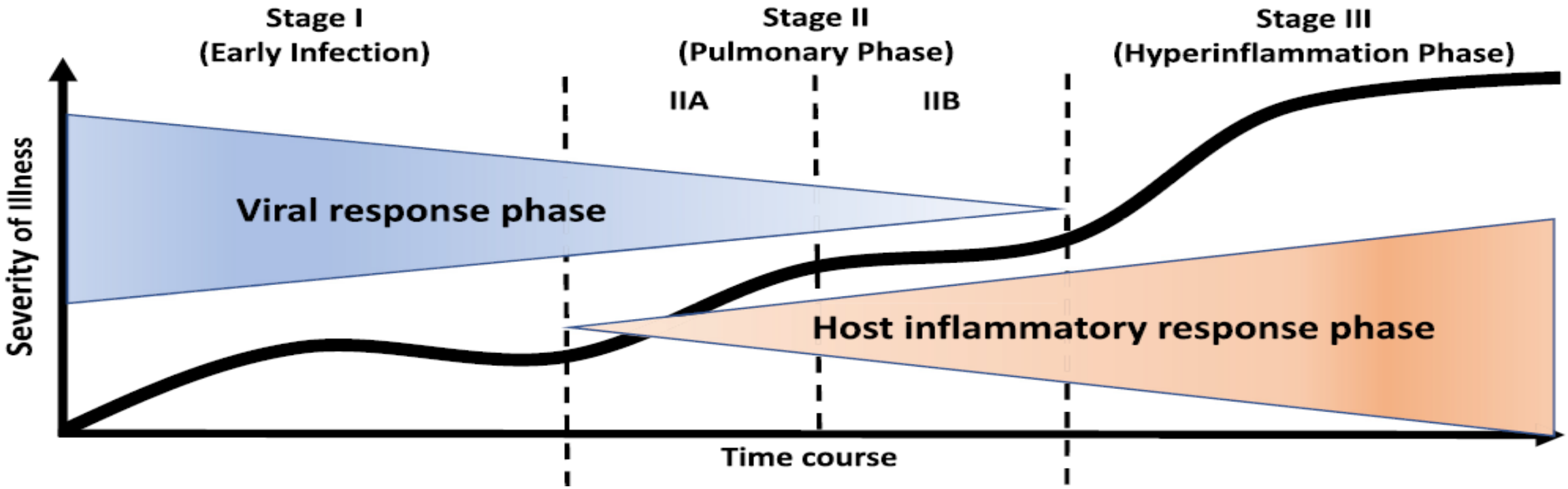


https://www.nejm.org/doi/full/10.1056/NEJMc2214302 - accessed 12/11/22

Summary: Epidemiology and Variants

- SARS-CoV-2 epidemiology remains unpredictable with some seasonal variation
- With wide availability of rapid home antigen tests, officially reported case numbers are less reliable, however wastewater surveillance and genomic sequencing remain valuable tools to describe contours of pandemic
- New variants—defined by additive mutations in the spike protein gene--continue to evolve and cause outbreaks due to evasion of vaccine-mediated and natural immunity
- Current increase in cases, hospitalizations, and deaths driven by **XBB**, **BQ.1**, and **BQ.1.1** variants which are no longer susceptible to monoclonal antibodies.
- Oral and IV antivirals **nirmatrelvir/ritonavir**, **molnupiravir** and **remdesivir** maintain activity against all known variants.

Biphasic nature of COVID-19: viral → inflammatory stage



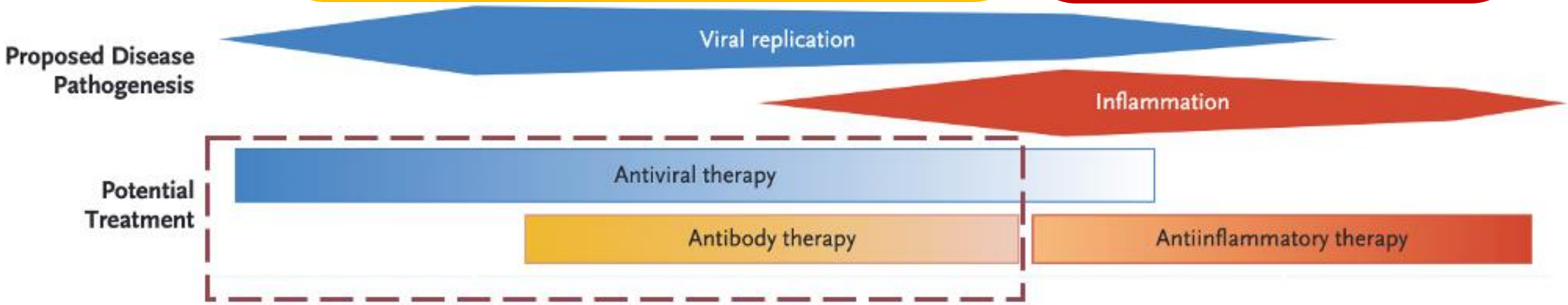
Important to consider **TIMING** of infection (2-3 weeks clinical course),
BIPHASIC NATURE of COVID-19 (Viral and Inflammatory Phase),
and **WIDE SPECTRUM** of severity and clinical manifestations

Asymptomatic/mild disease – loss of smell/taste – Long COVID – pneumonia/resp failure – MIS-C/MIS-A – thromboembolic - Death

- **Because of bi-phasic nature, therapies must be appropriately tailored to disease phase:**
  - **Anti-viral agents** are most effective when used **EARLY**
  - **Anti-inflammatory agents** are most effective when used **LATER**

Viral and inflammatory phases have different clinical characteristics

	Asymptomatic or Pre-symptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g fever, cough, sore throat)	Clinical evidence of lower respiratory tract diseases; oxygen saturation >93%	Oxygen saturation ≤ 93%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Isolation	Yes	Yes	Yes	Yes	Yes

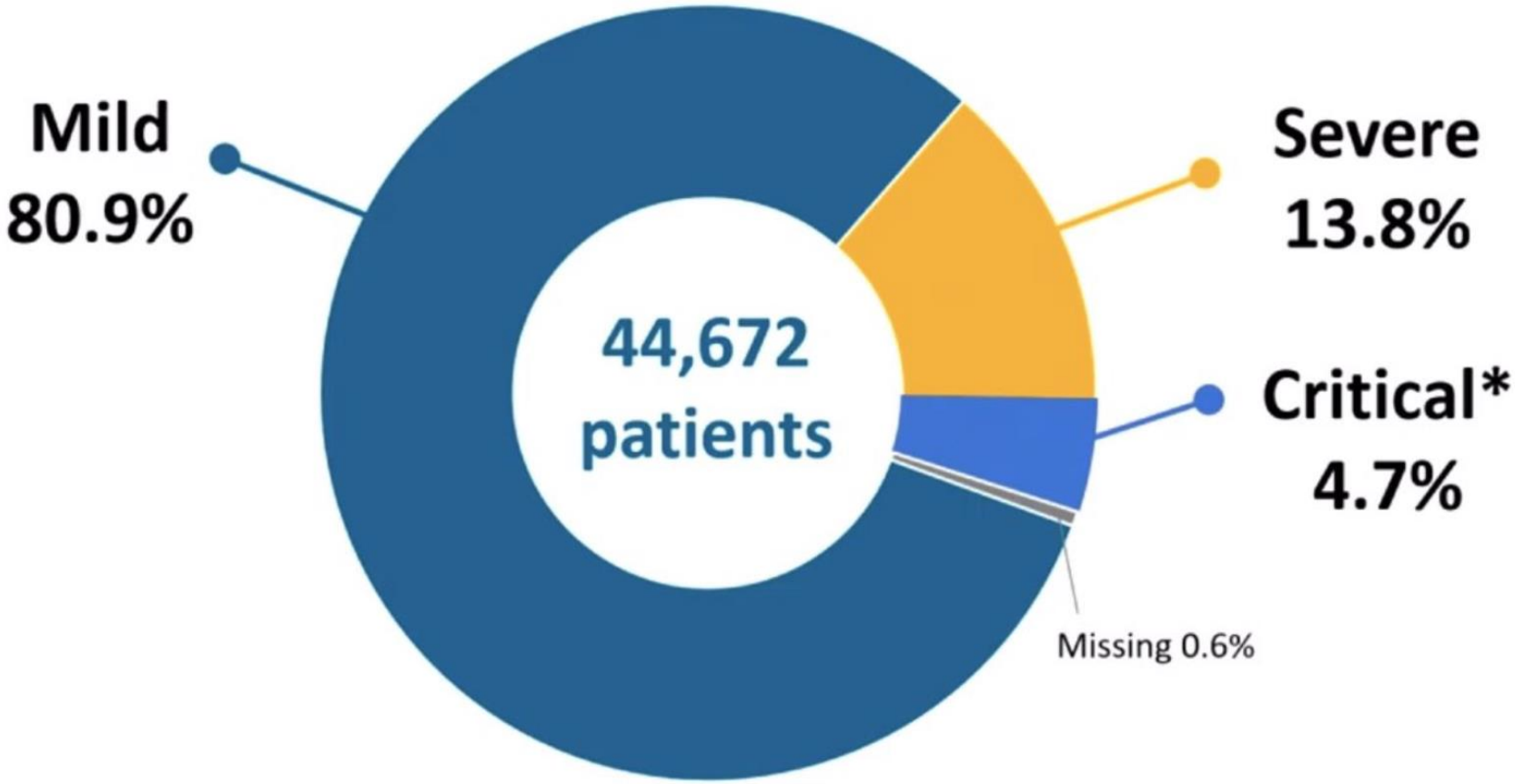


- **Anti-viral agents must be used during time of viral replication (mild to moderate illness) and are ineffective once disease has progressed into inflammatory phase**

Gandhi RT, et al. N Engl J Med. 2020;383:1757-1766

Only 20% of COVID-19 patients will have Severe/Critical outcome

COVID-19: Severity of Illness through 2/11/20 (N = 44,672)[1]



adapted from Zhang 2020, China CDC Weekly Report; 2(8):113-122.

* 1,023 (49%) deaths among 2,087 critically ill patients

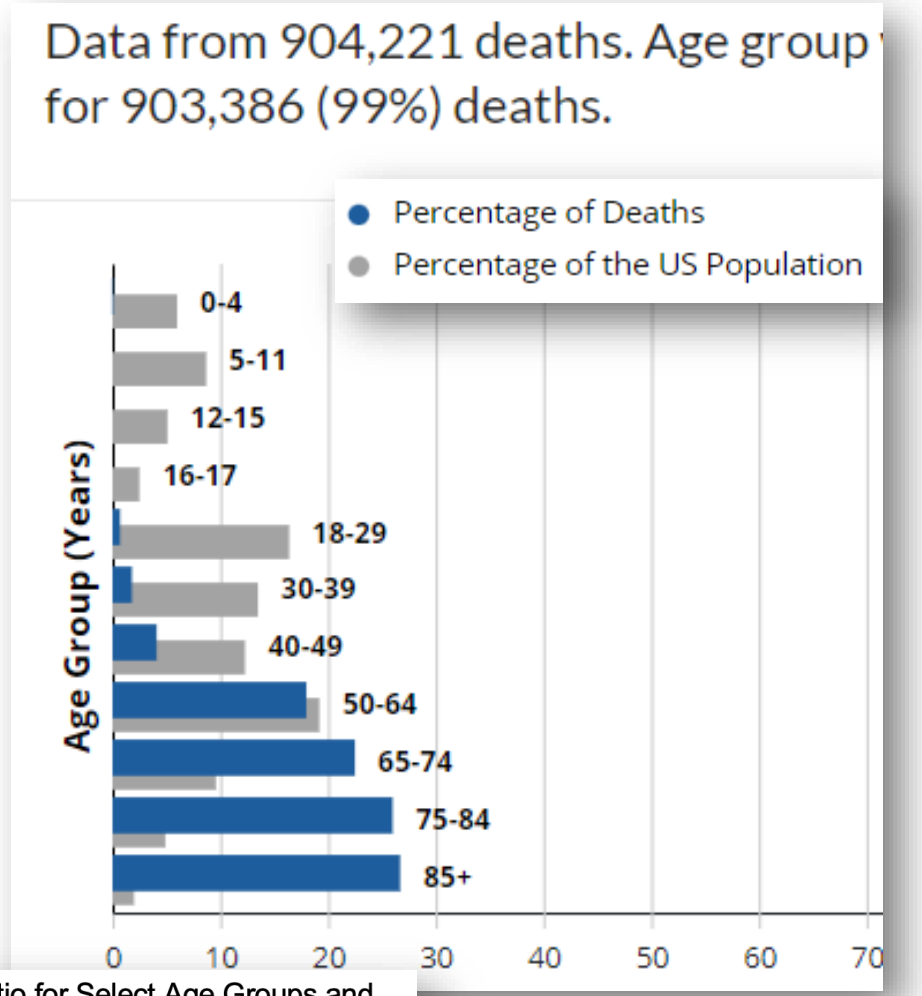
* These numbers are 'pre-vaccination', and vaccines are likely to reduce the percentage of severe/critical disease

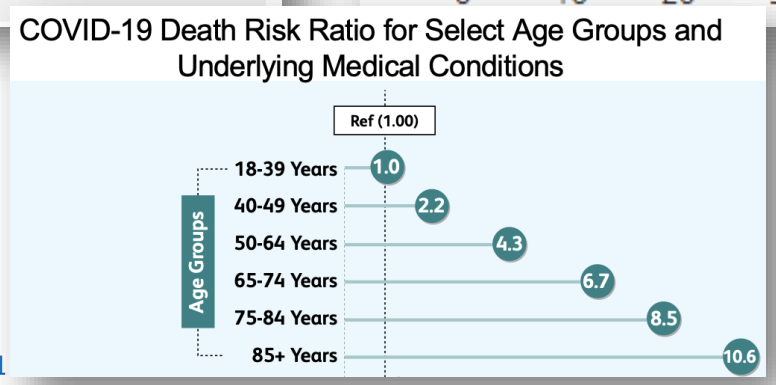
1) https://special.croi.capitalreach.com – Dr. John Brooks – US CDC

Age is the most important risk factor for severe disease

- In the United States, 81% of deaths occurred in those ≥ age 65
- Risk of hospitalization/death starts to increase ≥ age 50
  - (18% of deaths in 50-64 yr old group)
- Case Fatality rate by age:
  - ≥85 years 10-27%
  - 65-84 years 3-11%
  - 55-64 years 1-3%
  - <55 years <1%

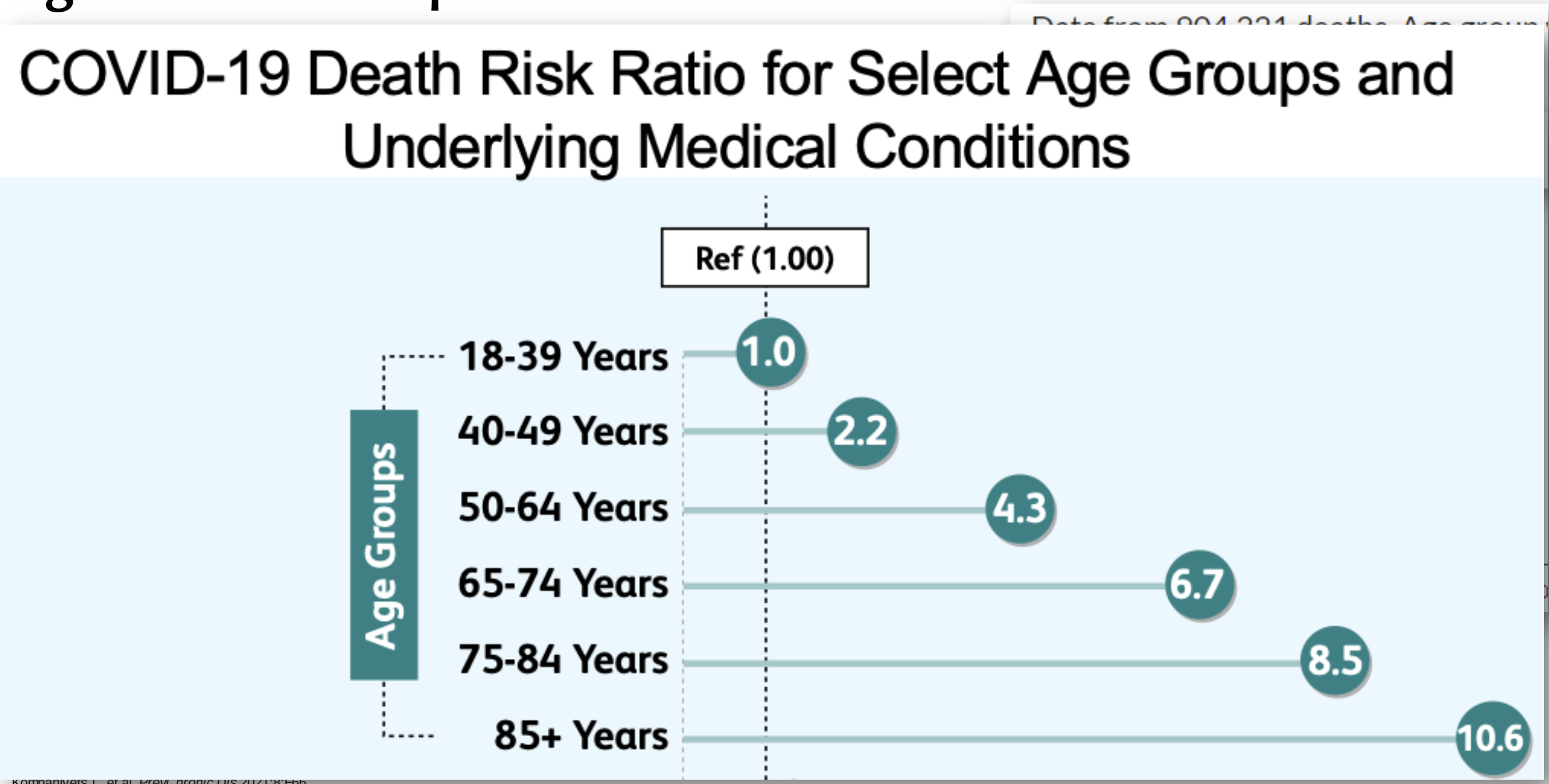
Rate compared to 18-29 years old[1]	0-4 years old	5-17 years old	18-29 years old	30-39 years old	40-49 years old	50-64 years old	65-74 years old	75-84 years old	85+ years old
Cases[2]	1x	1x	Reference group	1x	1x	1x	1x	1x	1x
Hospitalization[3]	1x	<1x	Reference group	2x	2x	3x	5x	8x	15x
Death[4]	<1x	<1x	Reference group	4x	10x	25x	60x	140x	340x





Kompaniyets L, et al. *PrevChronic Dis* 2021;8:E66
https://covid.cdc.gov/covid-data-tracker/#demographics
https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html

Age is the most important risk factor for severe disease



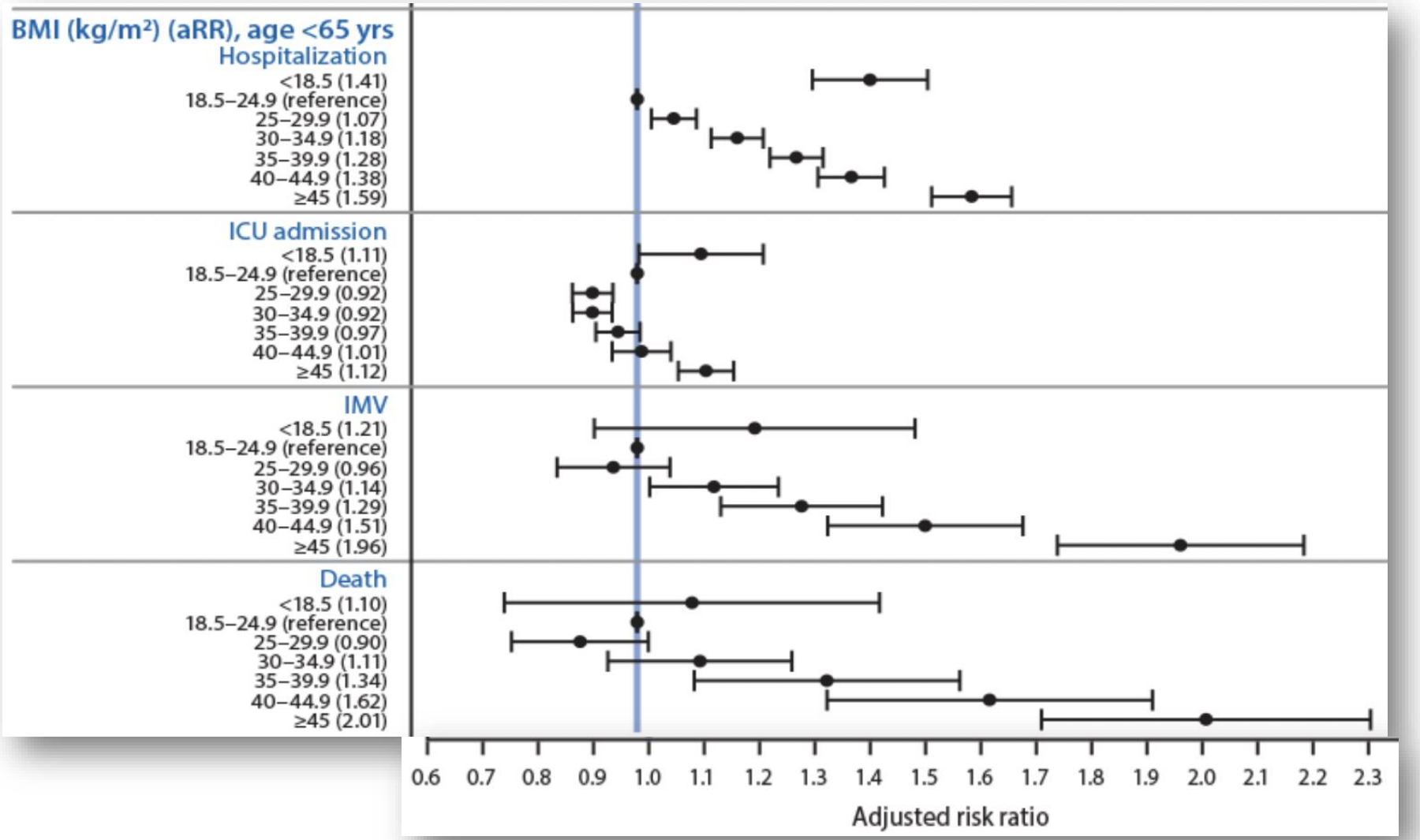
Kompaniyets L, et al. *PrevChronic Dis* 2021;8:E66

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

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-age.html

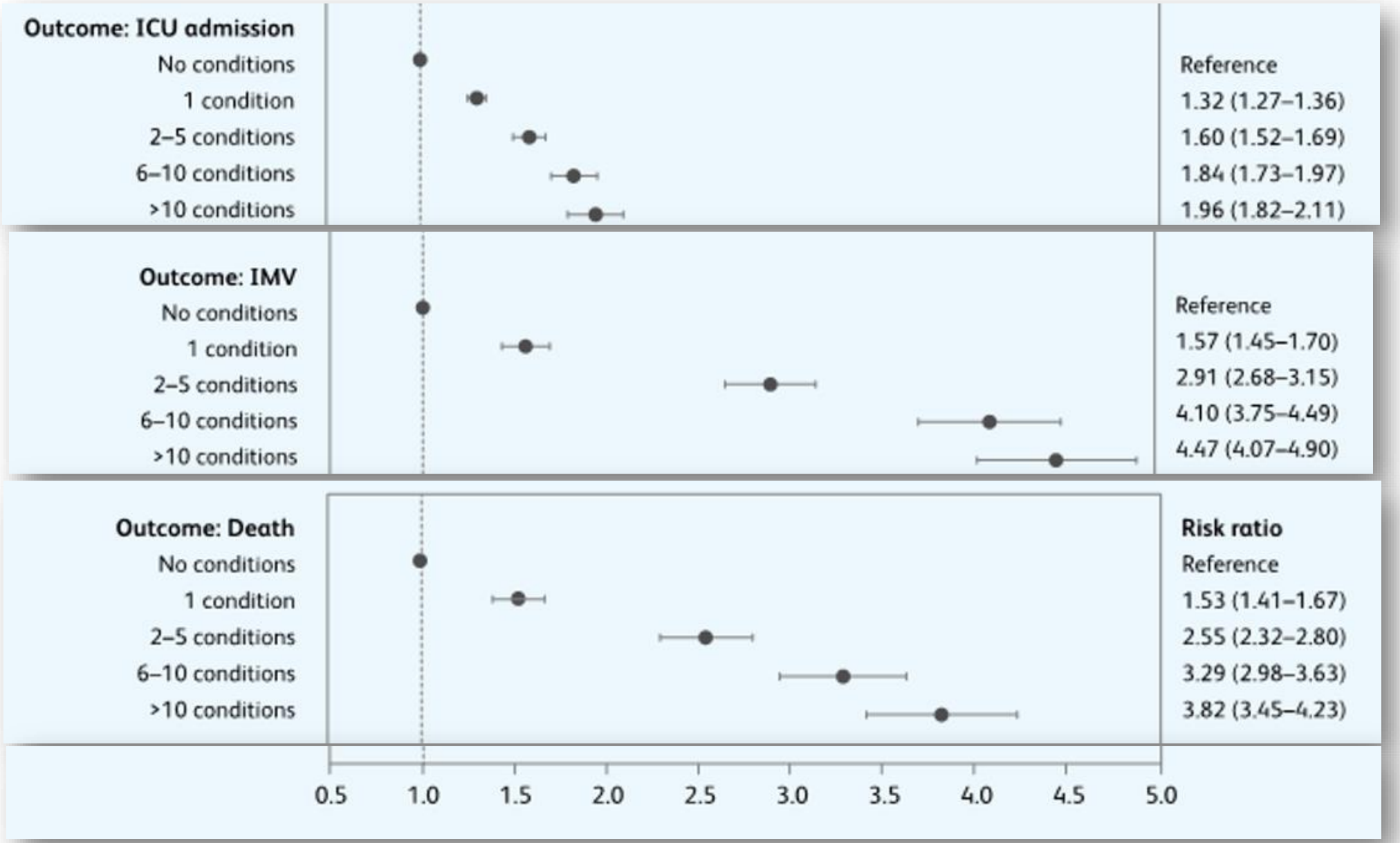
Obesity and high BMI are associated with severe outcomes

FIGURE 1. Association between body mass index (BMI) and severe COVID-19–associated illness* among adults aged ≥18 years, by age group — Premier Healthcare Special COVID-19 Release (PHD-SR),† United States, March–December 2020§



MMWR Morb Mortal Wkly Rep 2020 Mar 27;69(12):343-346; https://www.cdc.gov/mmwr/volumes/70/wr/mm7010e4.htm#F1_down ; Bierle M, et al. *J Prim Care Community Health.* 2021

Higher number of comorbidities associated with poor outcomes



.Kompaniyets L, et al. *PrevChronic Dis* 2021;8:E66.

Large list of comorbidities associated with poor outcomes

Higher Risk | *Meta-Analysis or Systematic Review Demonstrated Good or Strong Evidence*

- Asthma
- Cancer
- Cerebrovascular Disease
- Chronic Kidney Disease*
- Chronic lung diseases limited to:
  - Interstitial lung disease, pulmonary embolism, pulmonary hypertension, bronchiectasis, COPD (chronic obstructive pulmonary disease)
- Chronic liver diseases limited to:
  - Cirrhosis, non-alcoholic fatty liver disease, alcoholic liver disease, autoimmune hepatitis
- Cystic Fibrosis
- Diabetes mellitus, type 1 and type 2*‡
- Disabilities‡:
  - Attention-Deficit/Hyperactivity Disorder (ADHD), cerebral palsy, congenital malformations (birth defects), limitations with self-care or activities of daily living, intellectual and developmental disabilities, learning disabilities, and spinal cord injuries
- Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
- HIV (human immunodeficiency virus)
- Mental health disorders limited to:
  - Mood disorders (including depression) and schizophrenia spectrum disorders
- Neurologic conditions limited to dementia‡
- Obesity (BMI ≥30 kg/m^2 or ≥95th percentile in children)*‡
- Primary Immunodeficiencies
- Pregnancy and recent pregnancy
- Physical inactivity
- Smoking, current and former
- Solid organ or hematopoietic cell transplantation
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

Suggestive Higher Risk | *Evidence supported by mostly cohort, case-control, or cross-sectional studies (systematic reviews are available for some conditions in children with underlying conditions)*

- Overweight (BMI ≥25 kg/m^2, but <30 kg/m^2)
- Sickle Cell Disease
- Substance use disorders
- Thalassemia

Mixed Evidence | *Meta-analysis or systematic review is inconclusive*

- Alpha 1 antitrypsin deficiency
- Bronchopulmonary Disease
- Hepatitis B
- Hepatitis C
- Hypertension*

https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html. – accessed 12/11/22

COVID-19 therapeutics - Prioritization

- **MASS score**

Category	Points
☐ Age > 65 yo	2
☐ BMI > 35	1
☐ DMII	2
☐ CKD	3
☐ CVD disease + age > 55yo	2
☐ Resp. Disease + age > 55yo	2
☐ HTN + age > 55yo	1
☐ Immunosuppression	3
Total Points = _____	

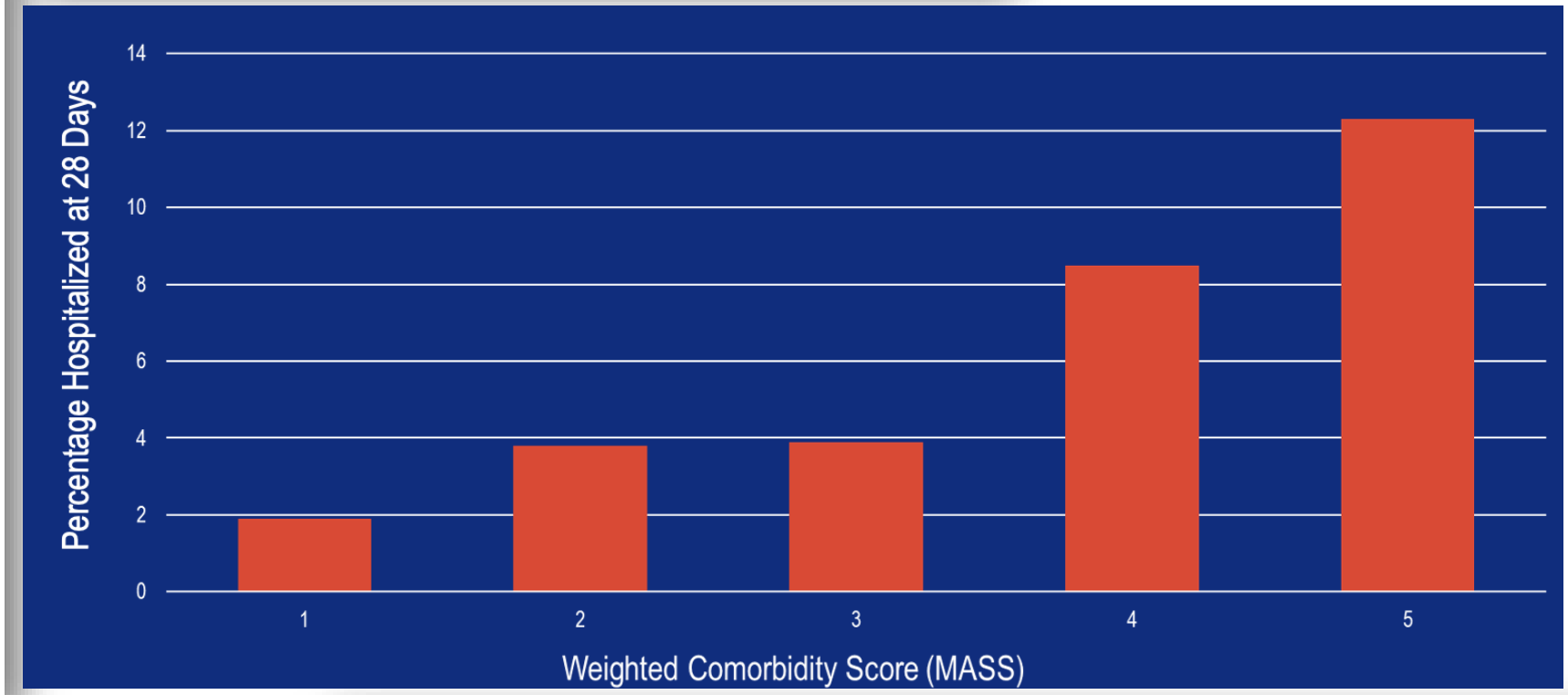
The Journal of Infectious Diseases

MAJOR ARTICLE

Real-World Clinical Outcomes of Bamlanivimab and Casirivimab-Imdevimab Among High-Risk Patients With Mild to Moderate Coronavirus Disease 2019

Ravindra Ganesh,[1,a,©] Lindsey M. Philpot,[1,a] Dennis M. Bierle,[1] Ryan J. Anderson,[1] Lori L. Arndt,[2] Richard F. Arndt,[2] Tracy L. Culbertson,[3] Molly J. Destro Borgen,[1] Sara N. Hanson,[3] Brian D. Kennedy,[4] Brian B. Kottke,[3] Jennifer J. Larsen,[1] Priya Ramar,[1] Jordan K. Rosedahl,[1] Maria Teresa Seville,[5] Leigh L. Speicher,[6] Sidna M. Tulledge-Scheitel,[1] Caroline G. Wilker,[7] and Raymund R. Razonable[1,©]; for the Monoclonal Antibody Treatment Program

[1]Mayo Clinic, Rochester, Minnesota, USA, [2]Mayo Clinic Health System, Eau Claire, Wisconsin, USA, [3]Mayo Clinic Health System, Mankato, Minnesota, USA, [4]Mayo Clinic Health System, Lake City, Minnesota, USA, [5]Mayo Clinic Arizona, Phoenix, Arizona, USA, [6]Mayo Clinic, Jacksonville, Florida, USA, and [7]Mayo Clinic Health System–Franciscan Healthcare, La Crosse, Wisconsin, USA



People with Certain Medical Conditions

https://doi.org/10.1093/infdis/jiab377 ; Bierle M et al J Prim Care Comm Health 2021
https://www.fda.gov/media/155050/download ;
https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

COVID-19 therapeutics - Prioritization

NIH | COVID-19 Treatment Guidelines

Home / Overview / Prioritization of Therapeutics

Prioritization of Anti-SARS-CoV-2 Therapies for the Treatment of COVID-19 in Nonhospitalized Patients When There Are Logistical Constraints

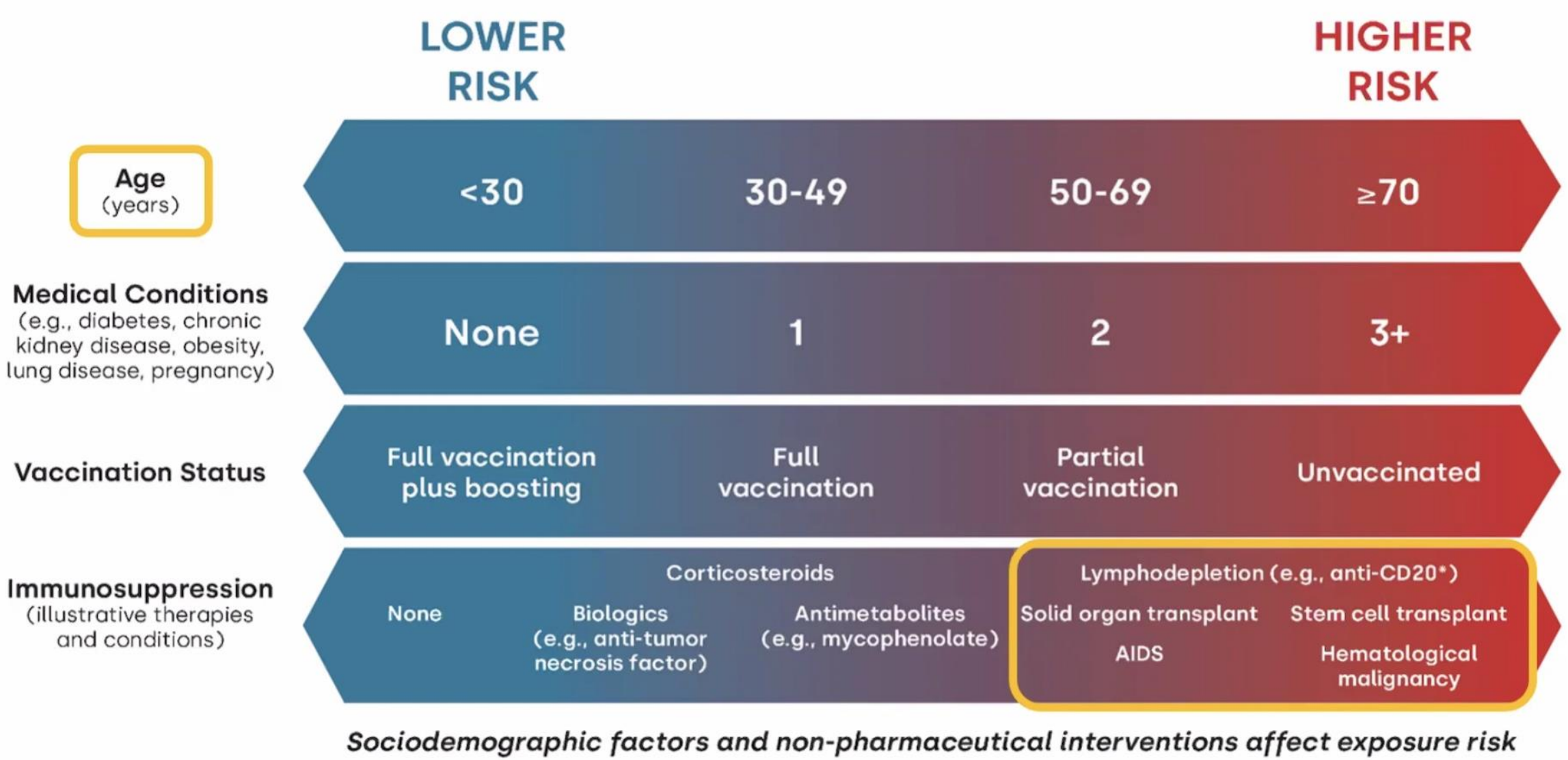
Last Updated: December 1, 2022

The prioritization guidance in this section should be used **only** when logistical constraints limit the availability of therapies. When there are no logistical constraints, the COVID-19 Treatment Guidelines Panel (the Panel) recommends that therapies for treatment of SARS-CoV-2 be prescribed for **any** eligible individual as recommended in these Guidelines.

Tier	Risk Group
1	• Immunocompromised individuals not expected to mount an adequate immune response to COVID-19 vaccination or SARS-CoV-2 infection due to their underlying conditions, regardless of vaccine status (see Immunocompromising Conditions below); *or* • Unvaccinated individuals at the highest risk of severe disease (anyone aged ≥75 years or anyone aged ≥65 years with additional risk factors).
2	• Unvaccinated individuals not included in Tier 1 who are at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors)
3	• Vaccinated individuals at risk of severe disease (anyone aged ≥65 years or anyone aged <65 years with clinical risk factors) **Note:** Vaccinated individuals who are not up to date with their immunizations are likely at higher risk for severe disease; patients within this tier who are in this situation should be prioritized for treatment.

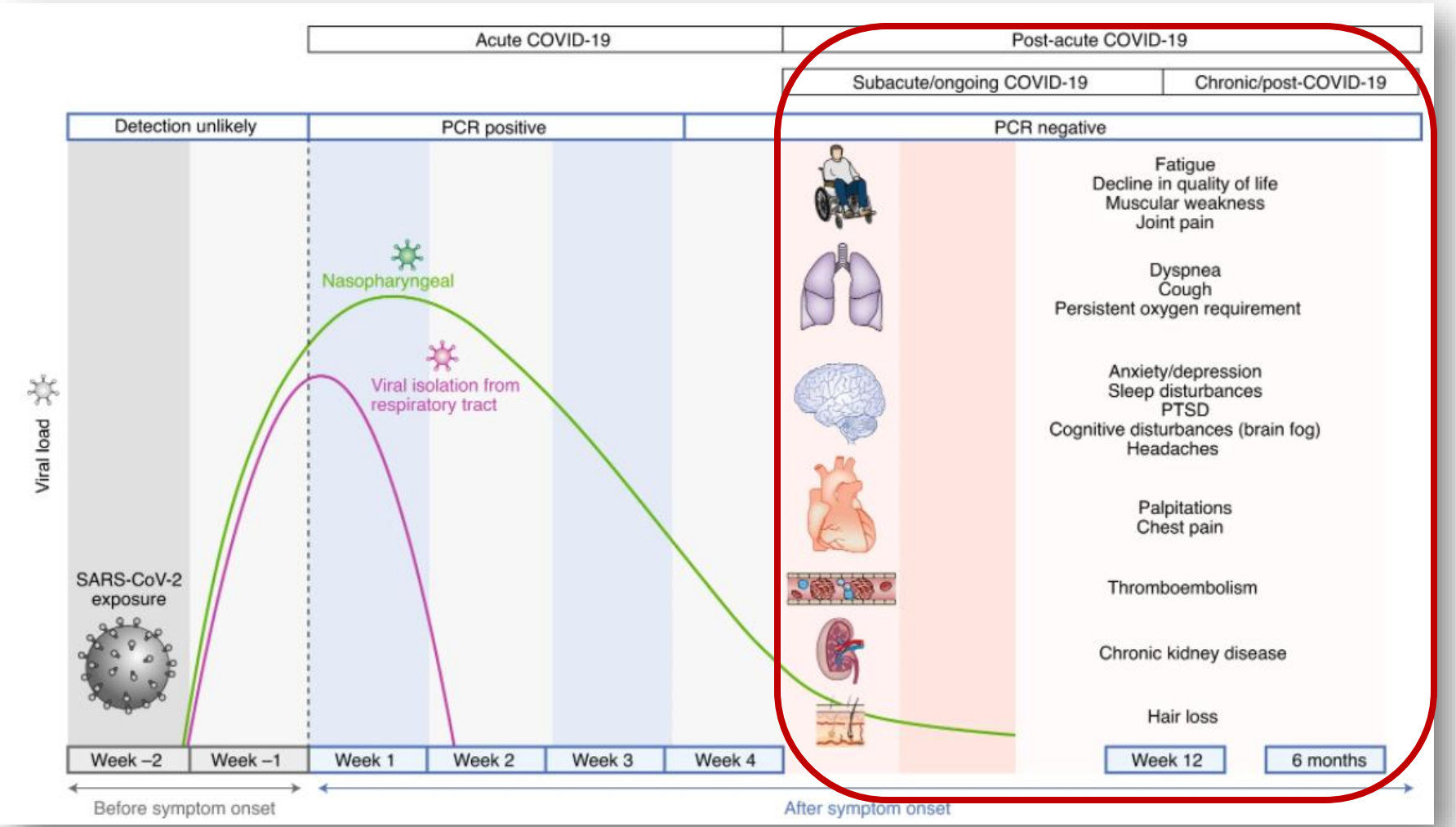
https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/?utm_source=site&utm_medium=home&utm_campaign=highlights

COVID-19 Risk Continuum (age, immune status, co-morbidity, vax)



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

Long-COVID, aka 'Post-Acute Sequelae of COVID-19' (PASC)



Most Common Symptoms:

- Shortness of breath
- Fatigue
- Post-Exertional malaise
- Brain fog
- Chronic cough
- Chest pain
- Headache
- Palpitations
- Muscle/joint aches
- Numbness/tingling
- Diarrhea
- Insomnia
- Fever/Temperature dysregulation
- Pain
- Loss of taste/smell

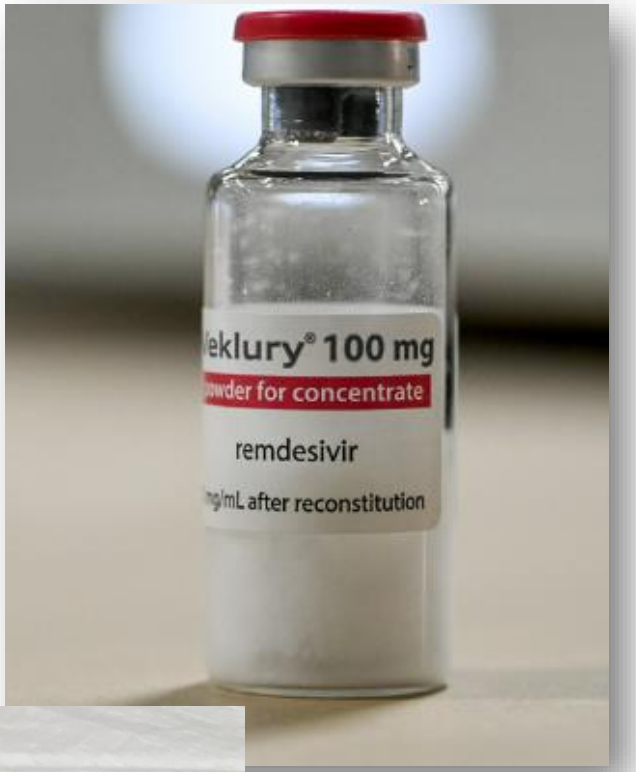
- Defined as persistent symptoms such as fatigue, shortness of breath, chest pain, brain fog, joint or muscle pains or general decline in quality of life beyond 4 weeks from onset of symptoms.
- Studies have shown that 10-30% of COVID-19 survivors meet criteria for PASC diagnosis
- Can occur with any disease severity

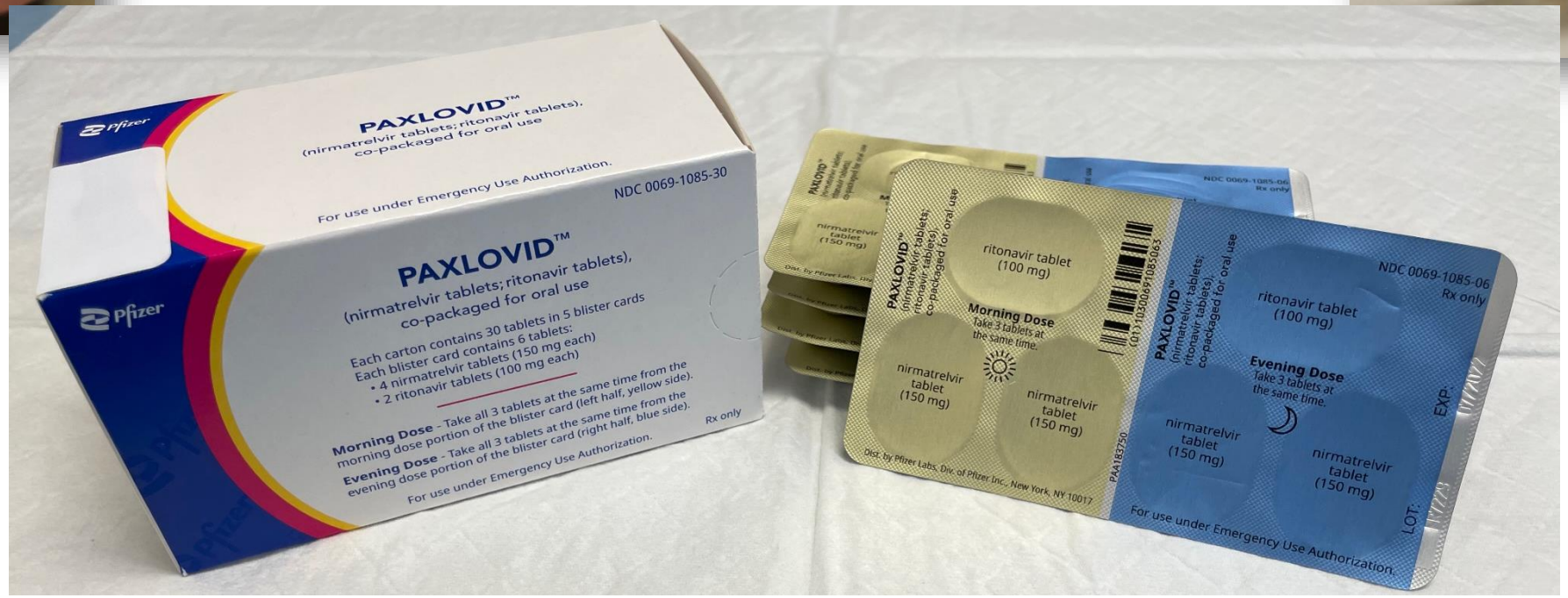
https://www.nature.com/articles/s41591-021-01283-z

Summary: Pathophysiology & Clinical Risk Factors

- The clinical spectrum of COVID-19 is diverse including asymptomatic infections, inflammatory syndromes, and even longer-lasting post-COVID conditions
- COVID-19 is **bi-phasic** with an early viral phase and a late inflammatory phase
  - therapies must be tailored to disease phase: anti-viral agents are most effective when used early; anti-inflammatory agents are most effective when used late.
- Disease severity classification (mild, moderate, severe, critical) is an important clinical skill to provide patients with appropriate levels of care
- Age, immunosuppression, vaccination status, presence of obesity and medical comorbidities can predict which patients are more likely at high risk to progress to severe disease, hospitalization and death
- Anti-viral treatment is indicated for any patient with an elevated risk for severe disease


NDC 0006-5055-06
molnupiravir
capsules
200 mg
For use under Emergency Use Authorization (EUA)
Each capsule contains 200 mg molnupiravir.
Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).
Dispense in original container.
Scan QR code or go to www.molnupiravir.com to access the FDA-authorized Fact Sheet for dosage and administration.
Rx only
40 Capsules


eklury® 100 mg
owder for concentrate
remdesivir
g/mL after reconstitution


Pfizer
PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets),
co-packaged for oral use
For use under Emergency Use Authorization.
NDC 0069-1085-30
PAXLOVID™
(nirmatrelvir tablets; ritonavir tablets),
co-packaged for oral use
Each carton contains 30 tablets in 5 blister cards
Each blister card contains 6 tablets:
• 4 nirmatrelvir tablets (150 mg each)
• 2 ritonavir tablets (100 mg each)
Morning Dose - Take all 3 tablets at the same time from the morning dose portion of the blister card (left half, yellow side).
Evening Dose - Take all 3 tablets at the same time from the evening dose portion of the blister card (right half, blue side).
For use under Emergency Use Authorization.
Rx only
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ritonavir tablet (100 mg)
Morning Dose
Take 3 tablets at the same time.
Evening Dose
Take 3 tablets at the same time.
NDC 0069-1085-06
Rx only
Dist. by Pfizer Labs. Div. of Pfizer Inc., New York, NY 10017
PAA183750
For use under Emergency Use Authorization.
EXP.
LOT:

NIH COVID-19 Treatment Guidelines

Recommended

1. Nirmatrelvir/ritonavir (AIIa)

- ≤ 5 d symptoms, PO x 5d, 88% efficacy, active against all variants
- Renal dosing if eGFR 30-60 mL/min
- Complex DDI's; ***manage*** with Liverpool DDI app

2. Remdesivir (BIIa)

- ≤ 7 symptoms, IV x 3d, 87% efficacy, active against all variants
- Variable commercial insurance coverage

Alternative

~~3. Bebtelovimab (CIII)~~

- ~~≤ 7 symptoms, IV x 3d, 87% efficacy, active against all variants~~
- **Not recommended when BQ.1+BQ.1.1 > 50%**

4. Molnupiravir (CIIa)

- ≤ 5 d symptoms, PO x 5d, 30-50% efficacy, ≥ age 18, teratogenic
- No DDI's, but lower efficacy limits use

For Treatment of Mild to Moderate COVID-19 in Nonhospitalized Adults Who Are at High Risk of Progressing to Severe COVID-19

- The Panel has recommended bebtelovimab as an alternative treatment for COVID-19 when neither of the preferred treatments (ritonavir-boosted nirmatrelvir [Paxlovid] or remdesivir) are available, feasible to use, or clinically appropriate. However, when resistant Omicron subvariants (e.g., BQ.1, BQ.1.1) represent the majority[a] of infections in the region,[b,c] clinicians cannot rely on bebtelovimab to be effective for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir are expected to be active against these resistant subvariants.
- The Panel continues to recommend the following anti-SARS-CoV-2 therapies as preferred treatments for COVID-19. These drugs are listed in order of preference:
  - **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
  - **Remdesivir (BIIa)**
- The following alternative therapies should be used **ONLY** when neither of the preferred therapies are available, feasible to use, or clinically appropriate. These drugs are listed in alphabetical order:
  - ~~**Bebtelovimab**, but **ONLY** when the majority[a] of circulating Omicron subvariants in the region[b,c] are susceptible (CIII)~~
  - **Molnupiravir (CIIa)**

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-omicron-subvariants/?utm_source=site&utm_medium=home&utm_campaign=highlight

Basic Principles of Test to Treat for COVID-19

1. **Confirm** positive SARS-CoV-2 PCR or Antigen test and high risk for progression to severe disease
2. **Classify** severity of disease (mild/moderate vs. severe/critical)
3. **Determine** onset of symptoms (< 5 or < 7 days)
4. **Consider** clinical features (renal function, pregnancy, age, DDI's)
5. **Select** oral or IV anti-viral therapy

- **Nirmatrelvir/ritonavir** (Paxlovid) PO x 5 days
- **Remdesivir** (Veklury) IV x 3 days

Only if above not available:

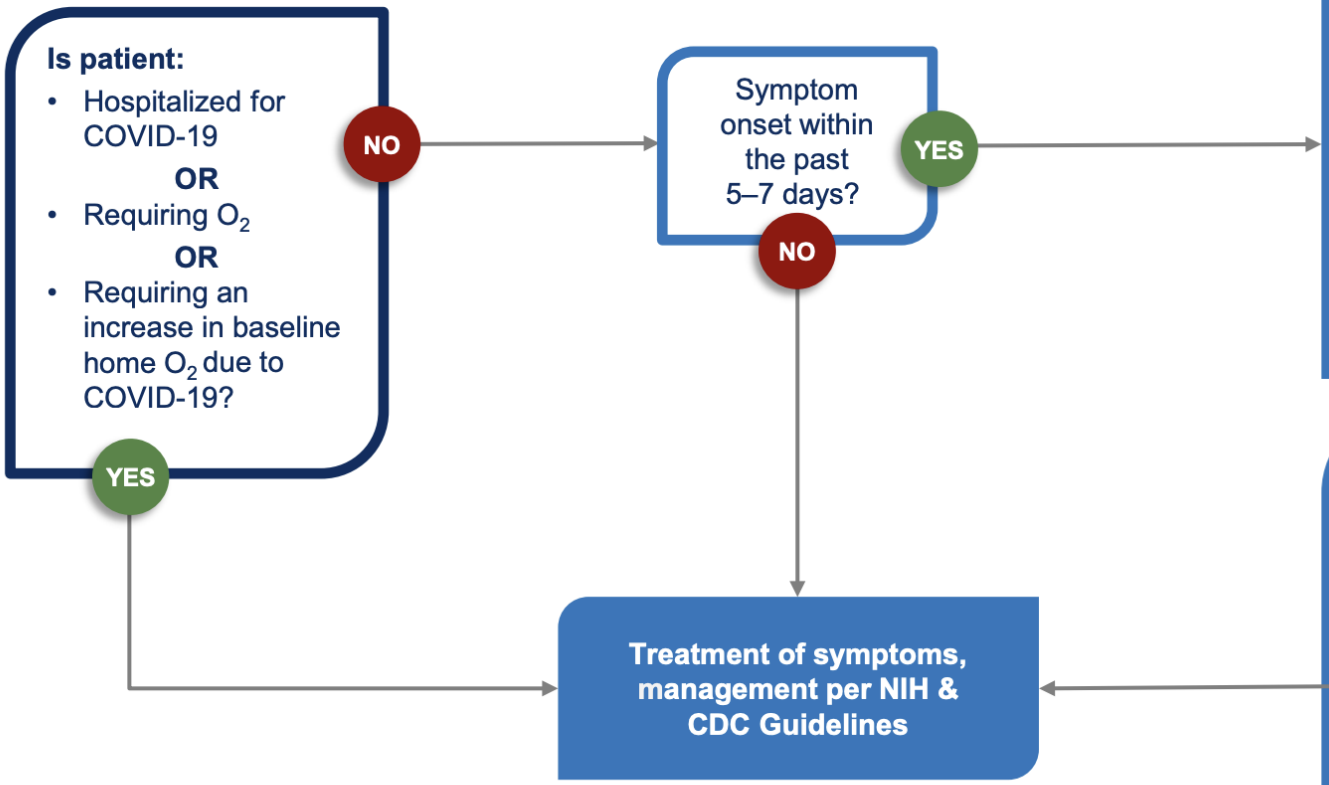
- **Molnupiravir** (Lagevrio) PO x 5 days

SEP2022

COVID-19 Outpatient Therapeutics

Clinical Decision Aid for Ages 12+ years

Adult or pediatric patient (ages 12 and older weighing at least 40 kg) with mild to moderate COVID-19 and at high risk for progression to severe disease



Consider one of the following therapeutics, if available, feasible, and clinically appropriate[1]:

Paxlovid[2] within 5 days of symptom onset If patient does not have severe renal impairment (eGFR <30mL/min) OR severe hepatic impairment (Child-Pugh Class C)

- **eGFR ≥ 60mL/min:** 300 mg nirmatrelvir taken with 100 mg ritonavir twice daily for 5 days
- **eGFR ≥ 30mL/min to < 60 mL/min:** 150 mg nirmatrelvir taken together with 100 mg ritonavir twice daily for 5 days
- Evaluate concomitant use of CYP3A inducers and medications with high dependency on CYP3A for clearance as these may be contraindicated[2,3]

OR

Veklury (remdesivir)[4] 200 mg IV x 1 dose on Day 1, 100 mg IV x 1 on Days 2–3 begun **within 7 days of symptom onset if patient does not have severe renal impairment (eGFR <30mL/min)**

Prescribers must review and comply with the mandatory requirements outlined in **the Paxlovid EUA[2]** or **the Veklury Prescribing Information[4].**

If Paxlovid and Veklury (remdesivir) are not available, feasible or clinically appropriate, consider one of the following therapeutics:

~~**bebtelovimab[5] within 7 days of symptom onset**~~
~~175 mg single IV injection~~

Lagevrio (molnupiravir)[6] if patient age 18 or older AND possibility of pregnancy, if applicable, ruled out:

800 mg by mouth every 12h for 5 days begun **within 5 days of symptom onset**

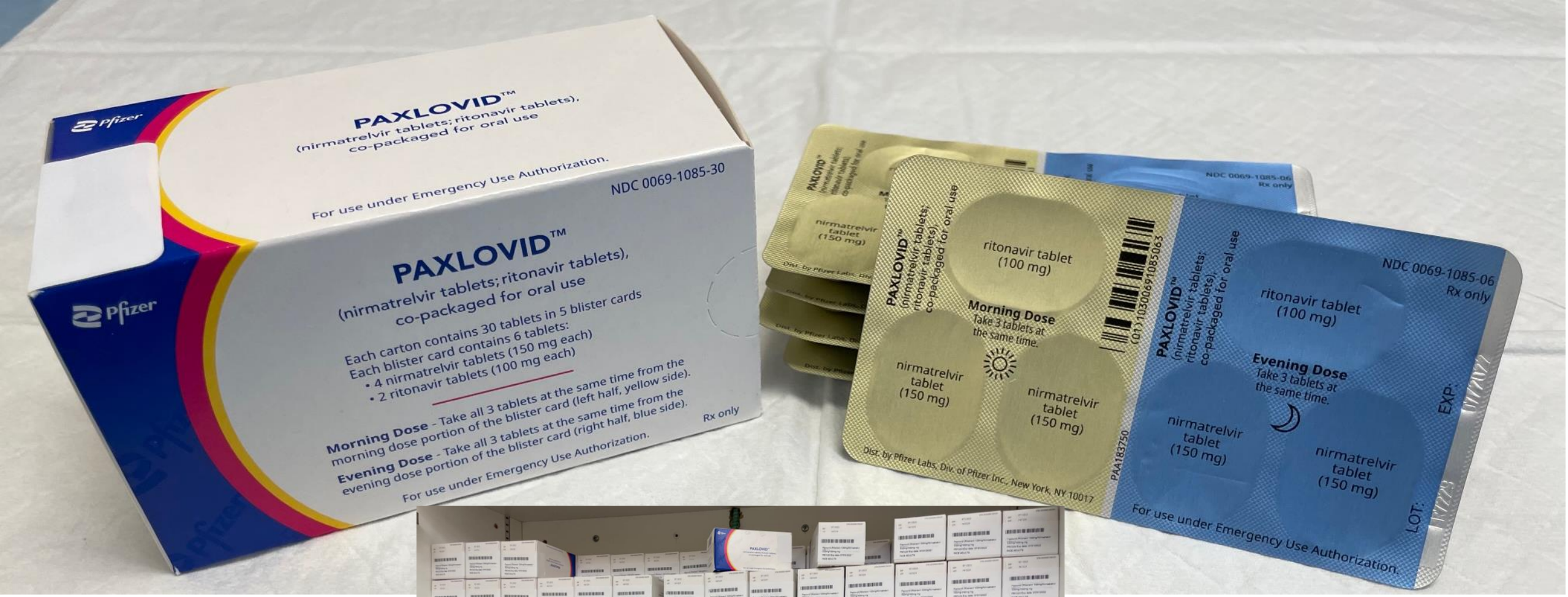
Prescribers must review and comply with the mandatory requirements outlined in **the bebtelovimab[5]** or **Lagevrio (molnupiravir) EUA[6]**

References:

[1] NIH COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
[2] Paxlovid EUA. https://www.fda.gov/media/155050/download
[3] NIH's COVID-19 Treatment Guidelines Panel: Ritonavir-Boosted Nirmatrelvir (Paxlovid). https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/
[4] Veklury (remdesivir) Prescribing Information. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
[5] Bebtelovimab EUA. https://www.fda.gov/media/156152/download

ASPR Administration for Strategic Preparedness and Response

https://aspr.hhs.gov/COVID-19/Therapeutics/Documents/COVID-Therapeutics-Decision-Aid.pdf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Pfizer
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For use under Emergency Use Authorization.
Rx only
nirmatrelvir tablet (150 mg)
ritonavir tablet (100 mg)
Morning Dose
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Dist. by Pfizer Labs, Div. of Pfizer Inc., New York, NY 10017
PAA183750
NDC 0069-1085-06
Rx only
Evening Dose
Take 3 tablets at the same time.
EXP.
LOT:
For use under Emergency Use Authorization.

Pfizer Science Products News About Contact Us

Pfizer Announces Additional Phase 2/3 Study Results Confirming Robust Efficacy of Novel COVID-19 Oral Antiviral Treatment Candidate in Reducing Risk of Hospitalization or Death

Tuesday, December 14, 2021 - 06:45am

Paxlovid (Nirmatrelvir/ritonavir) SARS-CoV-2 3CL Protease Inhibitor

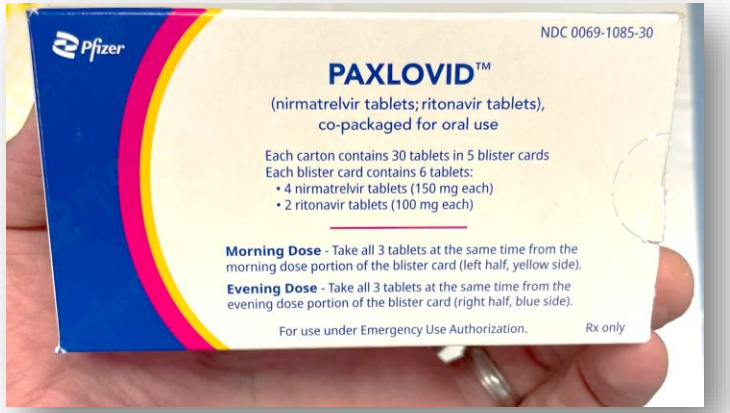
- **Phase 2/3 EPIC-HR trial:** N = **2,246** Non-hospitalized adult patients with mild-to-moderate COVID-19 and at least 1 risk factor for progression to severe COVID-19
- 3 pills given BID x 5 days
  - If within 3 days: Paxlovid reduced risk of hospitalization/death by **89%** from placebo **(6.5%, 44/682 → 0.7%, 5/697)**
  - If within 5 days: Paxlovid reduced risk of hospitalization/death by **88%** from placebo **(6.3%, 66/1046 → 0.8%, 8/1039)**
  - **ZERO** deaths in Paxlovid group; to **TWELVE** (1.2%) in the placebo group.

US Government has procured 20 million courses

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results

COVID-19 therapeutics – Nirmatrelvir/ritonavir (Paxlovid)

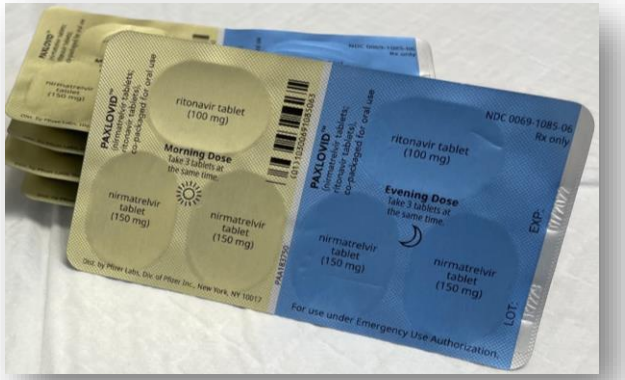
- **Nirmatrelvir 300 mg/ritonavir 150 mg PO BID x 5 days**
- SARS-CoV-2 main protease (Mpro, a.k.a. 3CLpro or Nsp5) inhibitor
- **FDA EUA**: 'For the treatment of mild to moderate COVID-19 in adults and pediatric patients (≥ 12 yrs and ≥ 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death'



88% reduction in hospitalization if started within 5 days of symptom onset

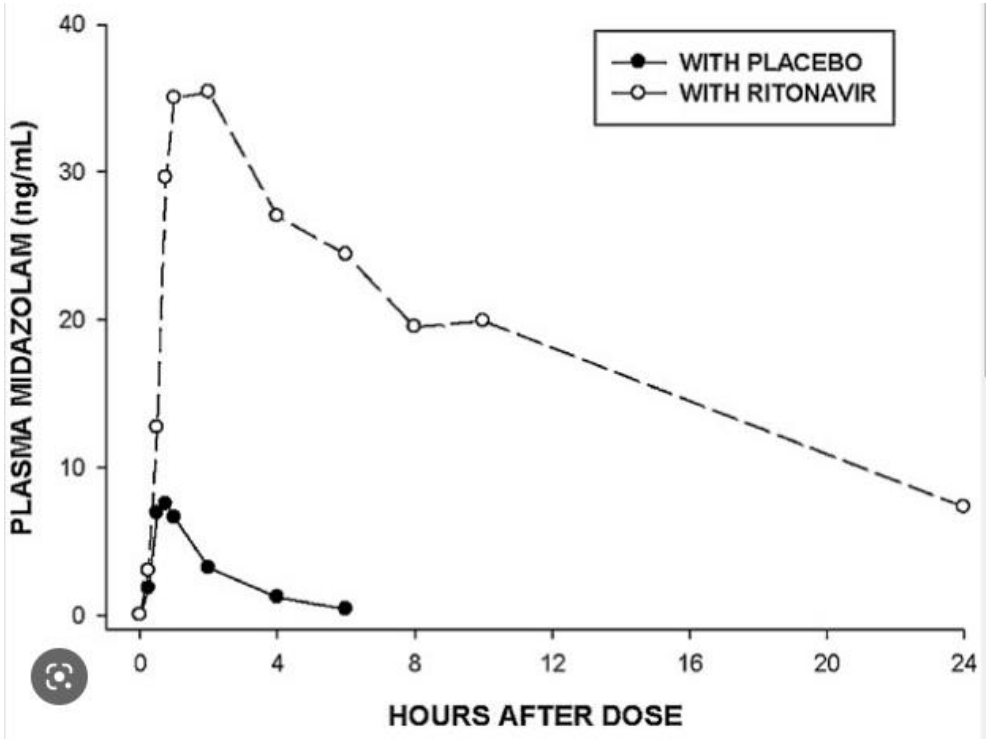
Clinical Considerations

- **Drug-Drug interactions** with CONTRAINDICATIONS (see www.covid19-druginteractions.org) for coadministration with drugs highly dependent on CYP3A for clearance and some potent CYP3A inducers
- Dose reduction for **moderate renal impairment** (eGFR 30-60 mL/min; CKD stage ≥ III)
- Not recommended for **severe renal impairment** (eGFR < 30 mL/min; CKD stage IV or V)
- Indications for Treatment
- Use in Pregnancy
- 'Paxlovid Rebound'



Ritonavir Drug-Drug Interactions

- Ritonavir is an HIV Protease Inhibitor that was also observed to be a strong inhibitor of Cytochrome P450 enzymes (CYP3A4) resulting in dramatically slower metabolism of P450-metabolized drugs



https://www.medrxiv.org/content/10.1101/2020.05.19.20106658v1.full
https://accp1.onlinelibrary.wiley.com/doi/10.1002/jcph.609

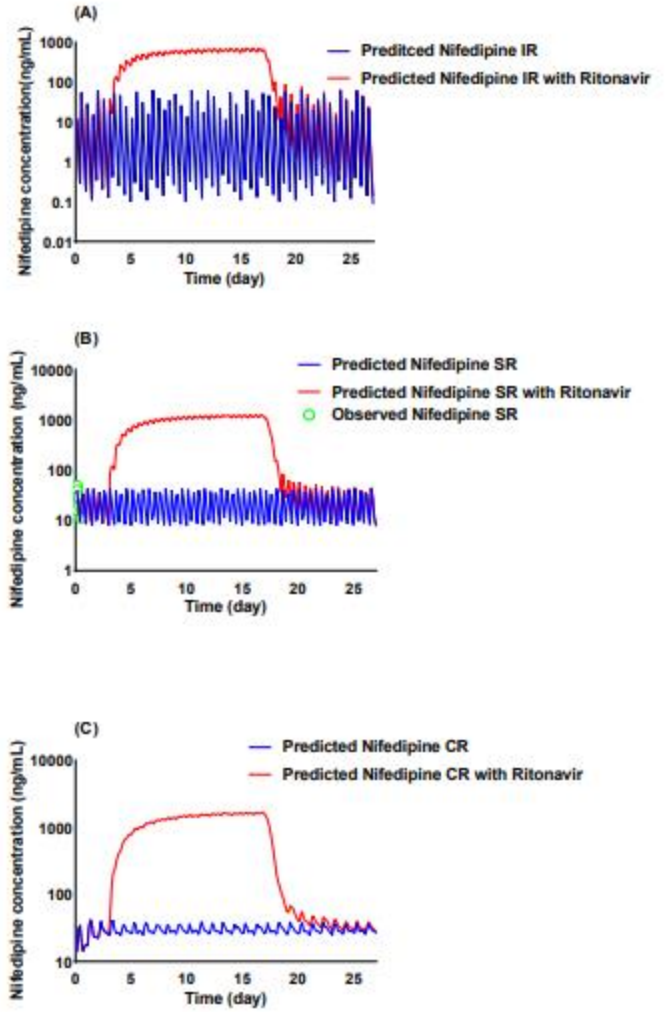
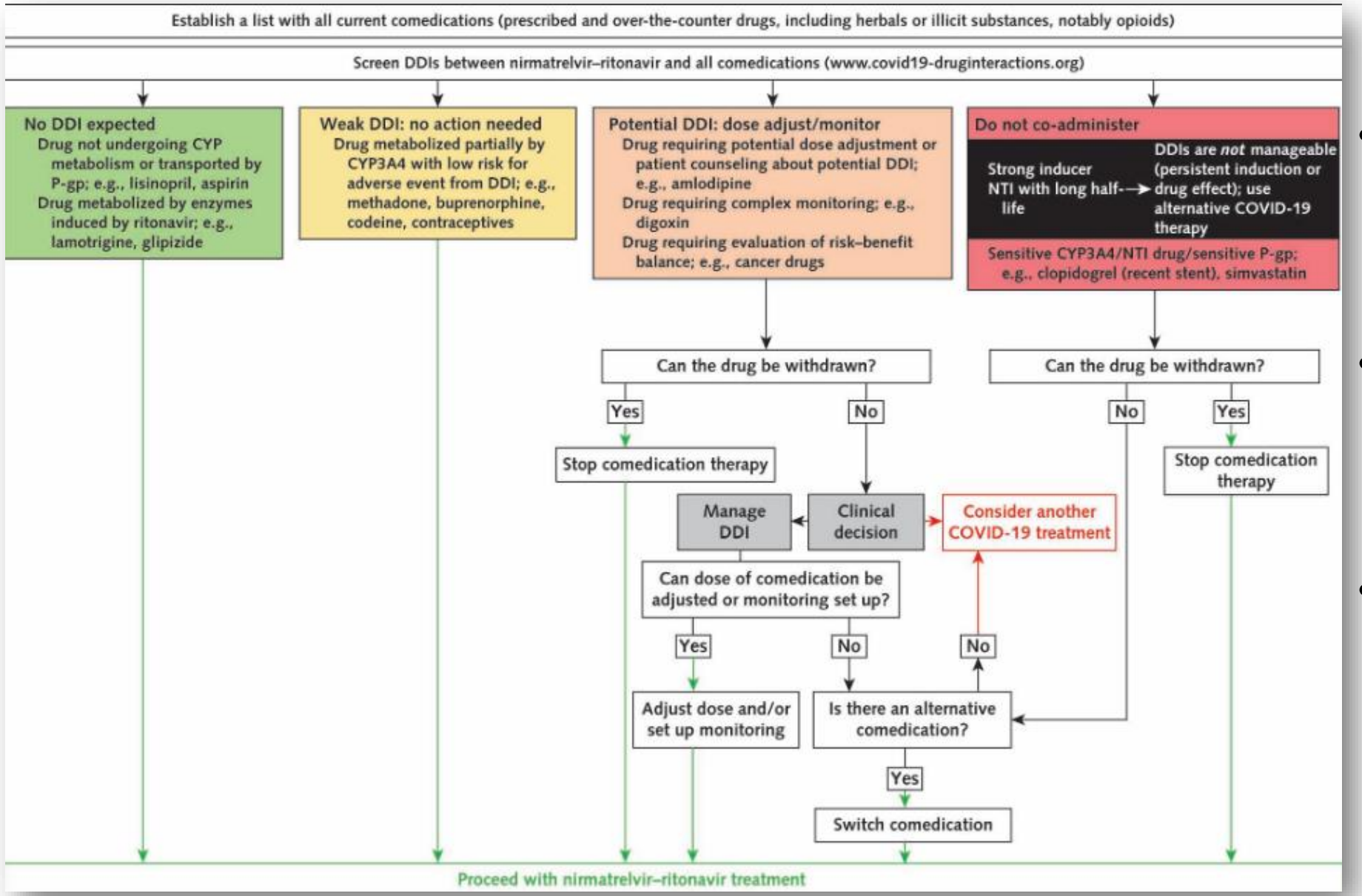


Figure 6 Model prediction of time-based changes in the drug–drug interaction (DDI) magnitude of nifedipine and ritonavir (RTV) over multiple days. (A) IR nifedipine 10 mg every 12 hours (Q12H) × 3 days + (nifedipine 10 mg Q12H + RTV 100 mg Q12H) × 14days+ nifedipine 10 mg Q12H × 10 days. (B) SR nifedipine 30 mg Q12H × 3 days + (30 mg Q12H +RTV 100 mg Q12H) ×14 days+ nifedipine 30 mg Q12H × 10 days. (C) CR nifedipine 60 mg Q24H × 3 days+ (60 mg Q24H + RTV 100 mg Q12H) ×14 days+ nifedipine 60 mg Q24H × 10 days. The red and blue solid lines represent the concentration curves of combined nifedipine with RTV and nifedipine alone, respectively.

Approach to Ritonavir-based drug-drug interactions (DDI's)



- **Q:** Can co-medication be temporarily with drawn/held?
- **Q:** Can dose adjustment be achieved?
- **Q:** Is clinical monitoring safe and appropriate

https://www.acpjournals.org/doi/full/10.7326/M22-0281 ;

Nirmatrelvir/ritonavir (Paxlovid) DDI's

NIH | COVID-19 Treatment Guidelines

Management Strategies for Drug-Drug Interactions

Consider the magnitude and significance of the potential interaction when choosing management strategies for patients who are to receive ritonavir-boosted nirmatrelvir. Potential strategies include:

- Temporarily withholding the concomitant medication,
- Increasing monitoring for potential adverse reactions to the concomitant medication,
- Adjusting the dose of the concomitant medication,
- Using an alternative to the concomitant medication, *or*
- Using alternative COVID-19 therapies (see Therapeutic Management of Nonhospitalized Adults With COVID-19).

Use the chosen strategy for the 5-day duration of ritonavir-boosted nirmatrelvir treatment and for at least 2 to 3 days after treatment completion. The strategy may need to continue for a longer duration if ritonavir-boosted nirmatrelvir is initiated in an elderly patient or if the interacting medication has a long half-life.

Prescribe Alternative COVID-19 Therapy

For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.

Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-infective agents

- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Immunosuppressants

- Voclosporin

Cardiovascular agents

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

Neuropsychiatric agents

- Clozapine
- Lumateperone
- Lurasidone
- Midazolam (oral)
- Pimozide

Pain medications

- Meperidine (pethidine)

Pulmonary hypertension medications

- Sildenafil
- Tadalafil
- Vardenafil

Miscellaneous

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

https://www.acpjournals.org/doi/full/10.7326/M22-0281 ;
https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/ ;

Nirmatrelvir/ritonavir (Paxlovid) DDI's

NIH | COVID-19 Treatment Guidelines

Temporarily Withhold Concomitant Medication, if Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is an adult of advanced age or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Rivaroxaban[d]

Anti-infectives
- Erythromycin

BPH
- Alfuzosin
- Silodosin

Cardiovascular
- Aliskiren
- Ranolazine
- Ticagrelor[b]
- Vorapaxar

Immunosuppressants[e]
- Everolimus
- Sirolimus
- Tacrolimus

Lipid-modifiers
- Atorvastatin[f]
- Lomitapide
- Lovastatin[f]
- Rosuvastatin[f]
- Simvastatin[f]

Migraine
- Eletriptan
- Rimegepant
- Ubrogepant

Neuropsychiatric
- Suvorexant
- Triazolam[g]

Erectile dysfunction
- Avanafil

Respiratory
- Salmeterol

Miscellaneous
- Certain chemotherapeutic agents[c]
- Colchicine[h]
- Finerenone
- Flibanserin
- Naloxegol

Adjust Concomitant Medication Dose and Monitor for Adverse Effects

Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for specific dosing recommendations.[i] If the dose of the concomitant medication cannot be adjusted, withhold the medication (if clinically appropriate) or use an alternative concomitant medication or COVID-19 therapy.

Anticoagulants
- Apixaban
- Dabigatran
- Edoxaban

Anti-infectives
- Clarithromycin
- Itraconazole
- Ketoconazole
- Maraviroc
- Rifabutin

BPH
- Tamsulosin

Cardiovascular
- Cilostazol
- Digoxin
- Mexiletine

Diabetes
- Saxagliptin

Erectile dysfunction
- Sildenafil
- Tadalafil
- Vardenafil

Immunosuppressants
- Cyclosporine[e]
- Dexamethasone[j]
- Fedratinib
- Ruxolitinib
- Tofacitinib
- Upadacitinib

Migraine
- Almotriptan[h]

Neuropsychiatric
- Alprazolam[g]
- Aripiprazole
- Brexpiprazole
- Buspirone
- Cariprazine
- Chlordiazepoxide[g]
- Clobazam[g]
- Clonazepam[g]
- Clorazepate[g]
- Diazepam[g]
- Estazolam[g]
- Flurazepam[g]
- Iloperidone
- Lumateperone
- Pimavanserin
- Quetiapine
- Trazodone

Pain
- Fentanyl
- Hydrocodone
- Oxycodone

Pulmonary hypertension
- Riociguat

Miscellaneous
- Certain chemotherapeutic agents[c]
- Darifenacin
- Elexacaftor/tezacaftor/ivacaftor
- Eluxadoline
- Ivacaftor
- Solifenacin
- Tezacaftor/ivacaftor

Continue Concomitant Medication and Monitor for Adverse Effects

Pre-emptive dose adjustment is not required but may be considered based on an individualized assessment of the patient's risk for adverse reactions. Educate patients about potential adverse effects. Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for monitoring guidance and dose adjustment information as needed.[i]

Anticoagulants
- Warfarin

Anti-infectives
- Brincidofovir[k]
- Cobicistat-or ritonavir-boosted antiretrovirals
- Isavuconazole
- Posaconazole
- Voriconazole

BPH
- Doxazosin
- Terazosin

Diabetes
- Glyburide

Cardiovascular
- Amlodipine
- Diltiazem
- Felodipine
- Nifedipine
- Sacubitril
- Valsartan
- Verapamil

Migraine
- Zolmitriptan

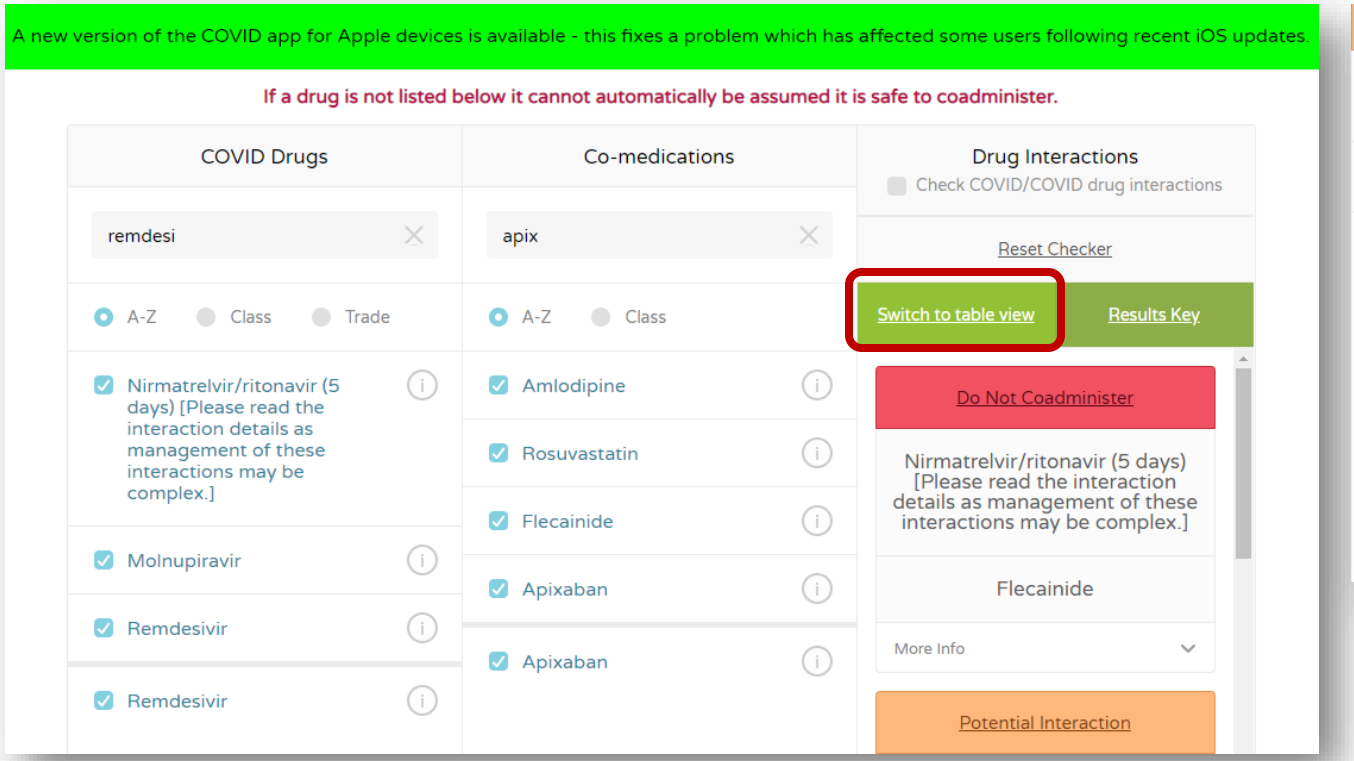
Neuropsychiatric
- Haloperidol
- Hydroxyzine
- Mirtazapine
- Risperidone
- Ziprasidone
- Zolpidem

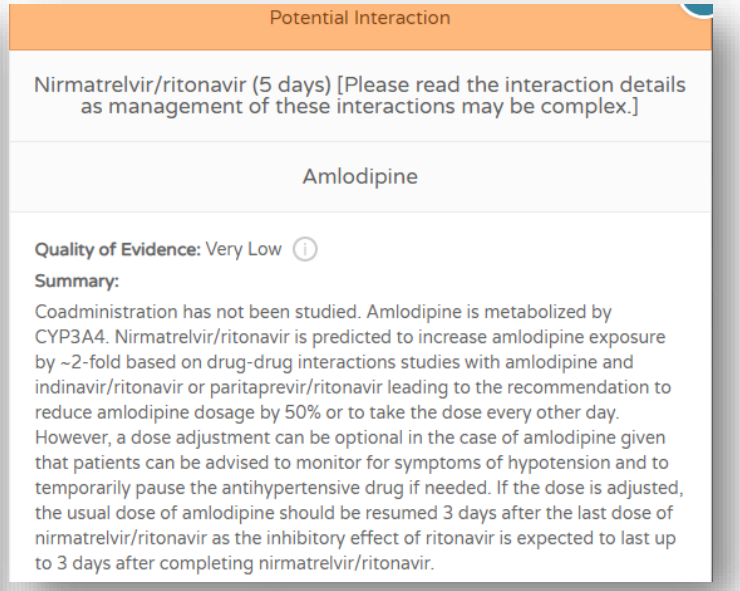
Pain
- Buprenorphine
- Hydromorphone
- Methadone
- Morphine
- Tramadol

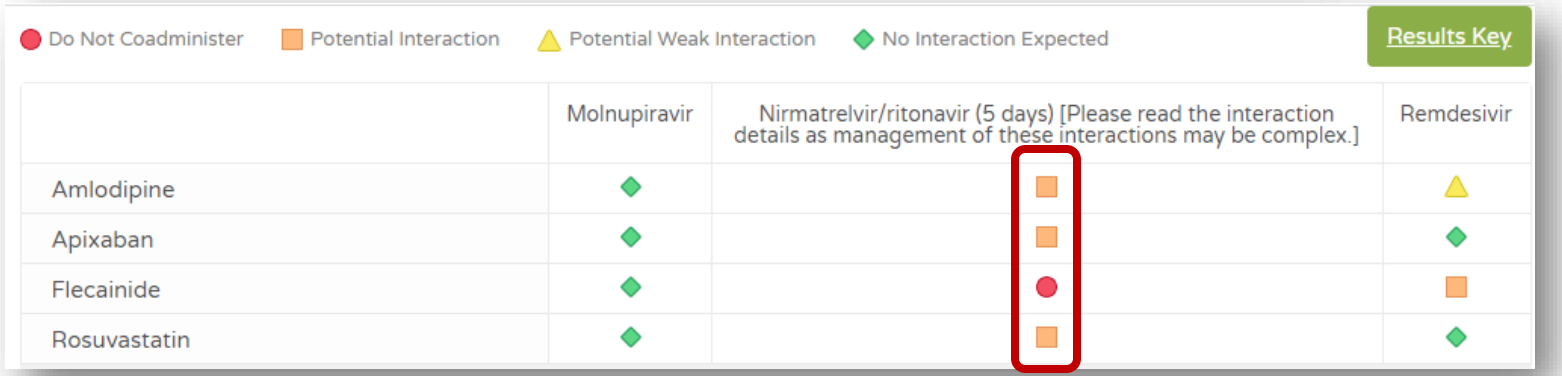
Miscellaneous
- Certain chemotherapeutic agents[c]
- Certain conjugated monoclonal antibodies[l]
- Oxybutynin

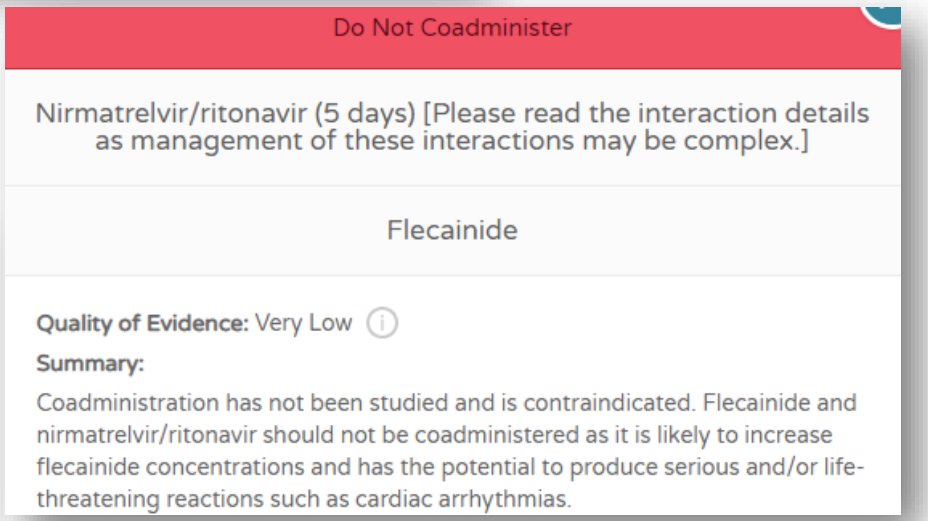
https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/ ;

COVID-19 therapeutics – Nirmatrelvir/ritonavir (Paxlovid) DDI's



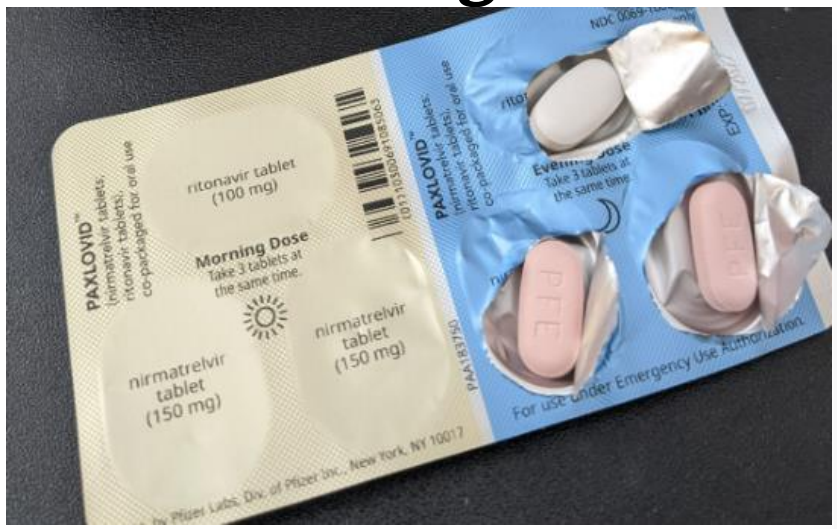


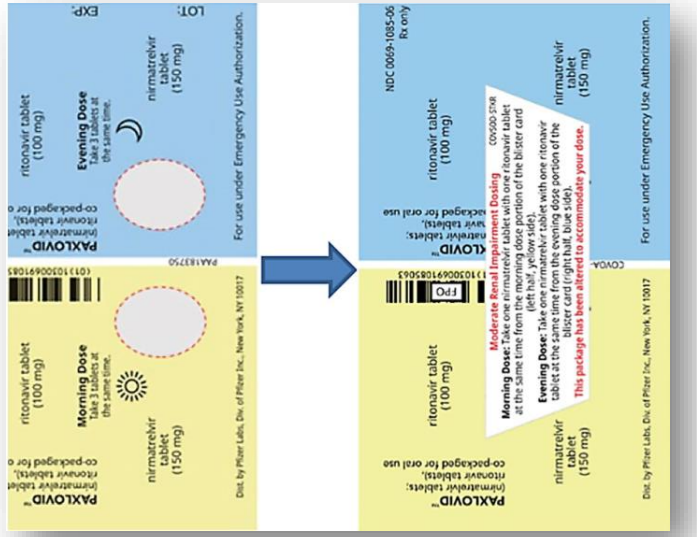


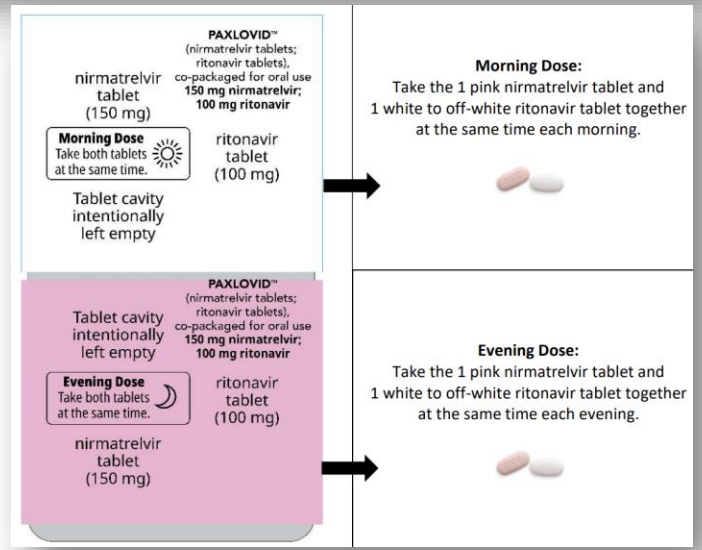


www.covid19-druginteractions.org

Renal Dosing Considerations – Nirmatrelvir/ritonavir (Paxlovid)







- **Dosing for normal renal function (eGFR >60 ml/min):**
  Nirmatrelvir 300 mg (#2 150 mg tabs)/ritonavir 100 mg PO BID x 5d

- **Dosing for impaired renal function (CKD 3: eGFR 30-59 ml/min):**
  Nirmatrelvir **150 mg**/ritonavir 100 mg PO BID x 5d

- **Not recommended in severe renal impairment (CKD 4-5 eGFR < 30 ml/min)**
- **Not recommended in severe hepatic impairment (CPT class C)**

www.covid19-druginteractions.org Paxlovid package insert

Paxlovid in Pregnancy?

ACOG
The American College of Obstetricians and Gynecologists

- ‘Pregnancy is included among the conditions that put individuals at high risk for clinical progression. This makes pregnant patients, including those with pregnancy as their only risk factor, eligible to receive outpatient oral SARS-CoV-2 protease inhibitor therapy, according to the EUA.’
- ‘There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures approximately 10 times higher than exposure at the authorized human dose of PAXLOVID. Published observational studies on ritonavir use in pregnant’ women have not identified an increased risk of birth defects.
- ‘Lactation is not a contraindication for the use of this oral SARS-CoV-2 Protease Inhibitor. Lactating individuals with one or more risk factors for severe COVID-19 illness may receive SARS-CoV-2 protease inhibitor for treatment’

https://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics

Q: Should oral SARS-CoV-2 protease inhibitor therapy be used as a treatment option for pregnant patients? (REVISED)

Last updated January 10, 2022 at 12:44 p.m. EST.

Recently, an oral severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protease inhibitor, PAXLOVID (which includes nirmatrelvir, a SARS-CoV-2 main protease inhibitor, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor) became available only under emergency use authorization (EUA) (EUA, EUA Fact Sheet). It is recommended for the treatment of outpatients with mild to moderate COVID-19 infection with a positive result of a SARS-CoV-2 viral test and who are at high risk of clinical progression as defined by the EUA criteria. Pregnancy is included among the conditions that put individuals at high risk for clinical progression. This makes pregnant patients, including those with pregnancy as their only risk factor, eligible to receive outpatient oral SARS-CoV-2 protease inhibitor therapy, according to the EUA. Obstetric care clinicians may consider the use of the oral SARS-CoV-2 protease inhibitor for the treatment of non-hospitalized COVID-19 positive pregnant individuals with mild to moderate symptoms, particularly if one or more additional risk factors are present (eg body mass index >25, chronic kidney disease, diabetes mellitus, cardiovascular disease). Clinicians should weigh the available data against the individual risks of COVID-19 in pregnancy in each situation.

There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In an embryo-fetal development study with nirmatrelvir, reduced fetal body weights following oral administration of nirmatrelvir to pregnant rabbits were observed at systemic exposures approximately 10 times higher than exposure at the authorized human dose of PAXLOVID. Published observational studies on ritonavir use in pregnant women have not identified an increased risk of birth defects. Ritonavir has been used extensively during pregnancy in people living with HIV, which suggests that it has an acceptable safety profile during pregnancy. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir or ritonavir at systemic exposures greater than or equal to 3 times higher than clinical exposure at the authorized human dose of PAXLOVID (EUA Fact Sheet). The short-term exposure to these medications must be balanced against the maternal and fetal risks associated with untreated COVID-19 in pregnancy.

If utilizing protease inhibitor (PAXLOVID) treatment, this treatment should be initiated orally as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset. PAXLOVID should be administered orally with or without food. The recommended dosage is 300 mg of nirmatrelvir (two 150 mg tablets) with 100 mg of ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days.

Obstetric care clinicians should be aware that the concomitant use of PAXLOVID and certain other drugs (including medications used in obstetric settings such as nifedipine, methylergonovine, fentanyl, midazolam, or betamethasone) may result in potentially significant drug interactions. Prescribing clinicians should consult the full prescribing information prior to and during treatment for potential drug interactions (EUA Fact Sheet).

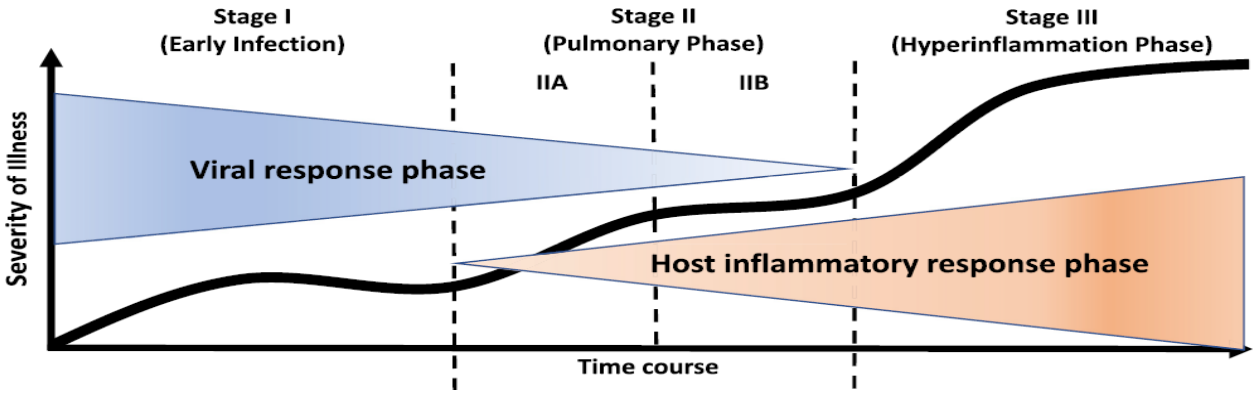
Lactation is not a contraindication for the use of this oral SARS-CoV-2 protease inhibitor (EUA Fact Sheet). Lactating individuals with one or more risk factors for severe COVID-19 illness may receive SARS-CoV-2 protease inhibitor for treatment. There are no available data on the presence of nirmatrelvir in human or animal milk, the effects on the breastfed infant, or the effects on milk production. A transient decrease in body weight was observed in the nursing offspring of rats administered nirmatrelvir. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PAXLOVID and any potential adverse effects on the breastfed infant from PAXLOVID or from the underlying maternal condition (EUA Fact Sheet).

Efforts should be made to ensure that communities most affected by SARS-CoV-2 have equitable access to these treatments.

‘Paxlovid Rebound’ or ‘COVID Rebound’?

- Introduction: *“The uptake of Paxlovid in individuals infected with COVID-19 has been significantly limited by concerns around the Paxlovid rebound phenomenon despite the scarcity of evidence around its epidemiology”*
- Methods: Decentralized, digital prospective, observational cohort
  - Paxlovid (N = 127) vs. control (N = 43) defined by patients’ decision to take Paxlovid
  - Symptom surveys and 12 Ag tests collected via telehealth proctored exams
- Results:

	Paxlovid (n=127)	No Paxlovid (n=43)	p-value
COVID-19 Recovery			
Viral (Testing) Rebound	18 (14.2)	4 (9.3)	0.41
Symptom Rebound	24 (18.9)	3 (7.0)	0.06
Consistently Positive	5 (3.9)	0 (0.0)	0.20
Symptom Start to Test Negative, Days (SD)*	6.4 (3.0)	6.1 (2.9)	0.53



- Conclusions:
  - Rebound after clearance of test positivity is higher than previously reported
  - However, a similar rate of rebound was observed in the Paxlovid and control arms (14.2% vs. 9.3%, P = 0.41)

https://www.nejm.org/doi/full/10.1056/NEJMoa2116846 - accessed 11/21/22

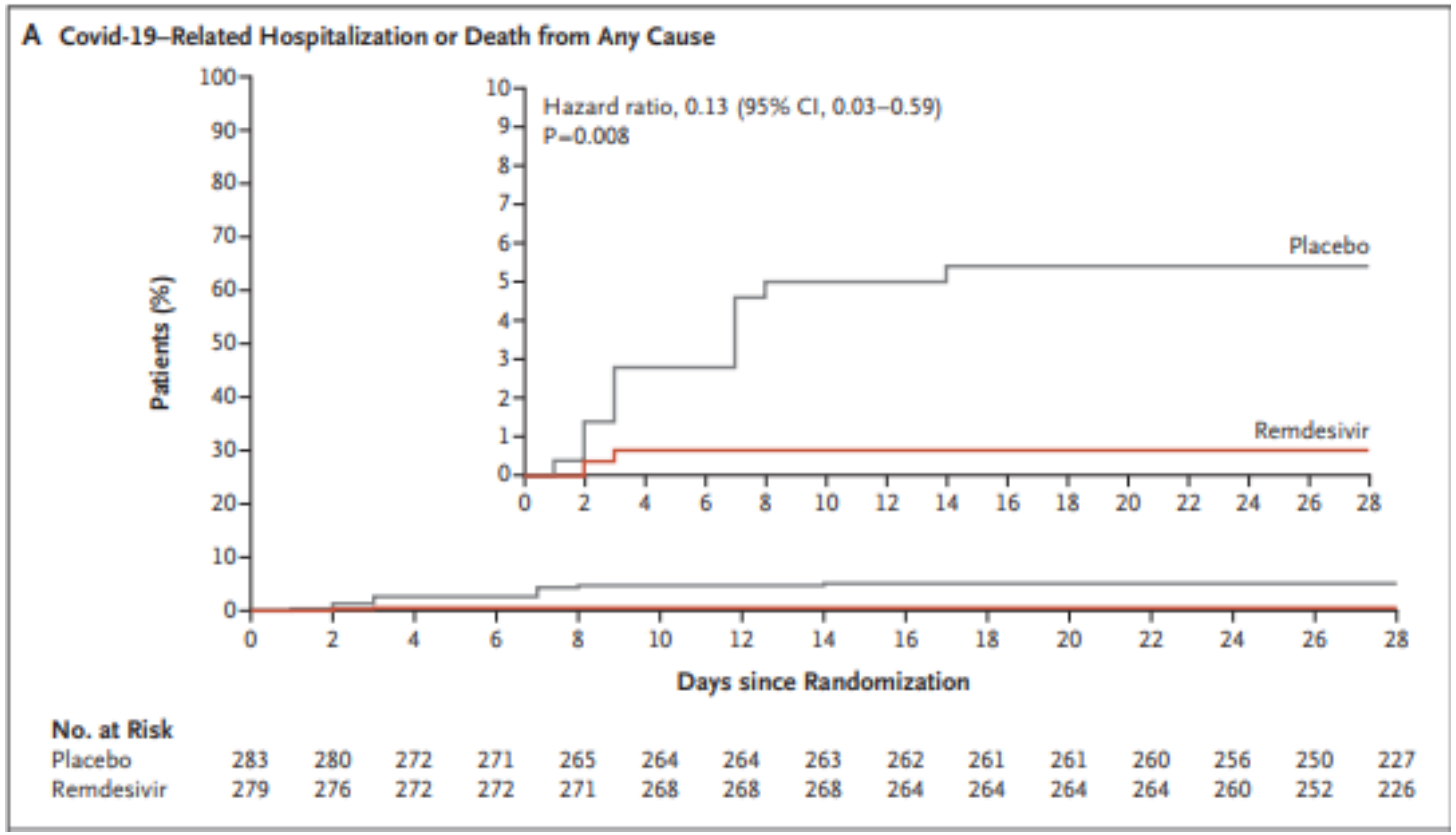
Re-Introducing… Remdesivir

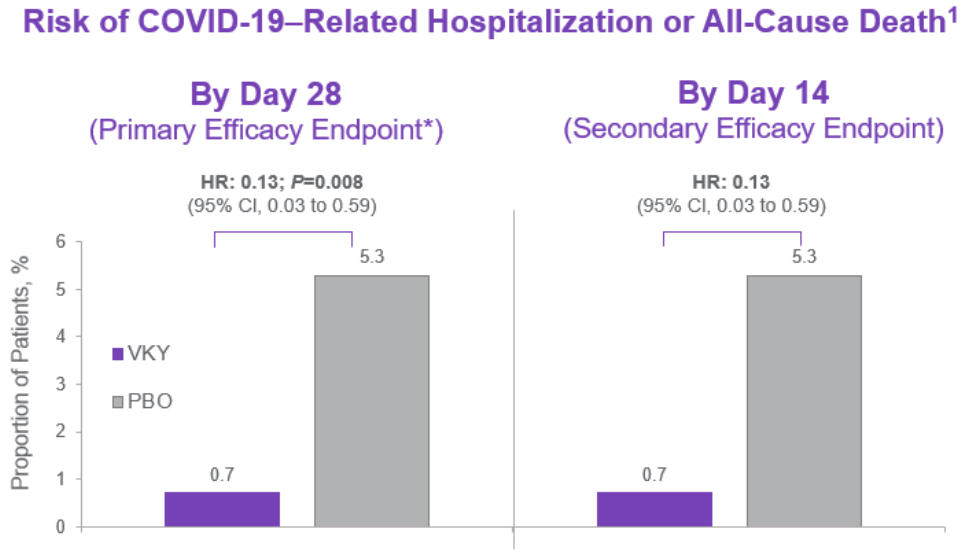
- FDA-approved for use in hospitalized patients with SARS-CoV-2
- PINETREE – Double-blinded Placebo-controlled RCT (N = 562)
  - Outpatients with SARS-CoV-2, symptoms within < 7 days (unvaccinated)
  - At least one risk factor for severe disease (mean age 50, 61.6% DM II, 55% Obesity)
  - Results: **87% reduction in hospitalization or death**

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 27, 2022 VOL. 386 NO. 4

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†





- No deaths occurred at Day 28 in either arm of the study[1,2]

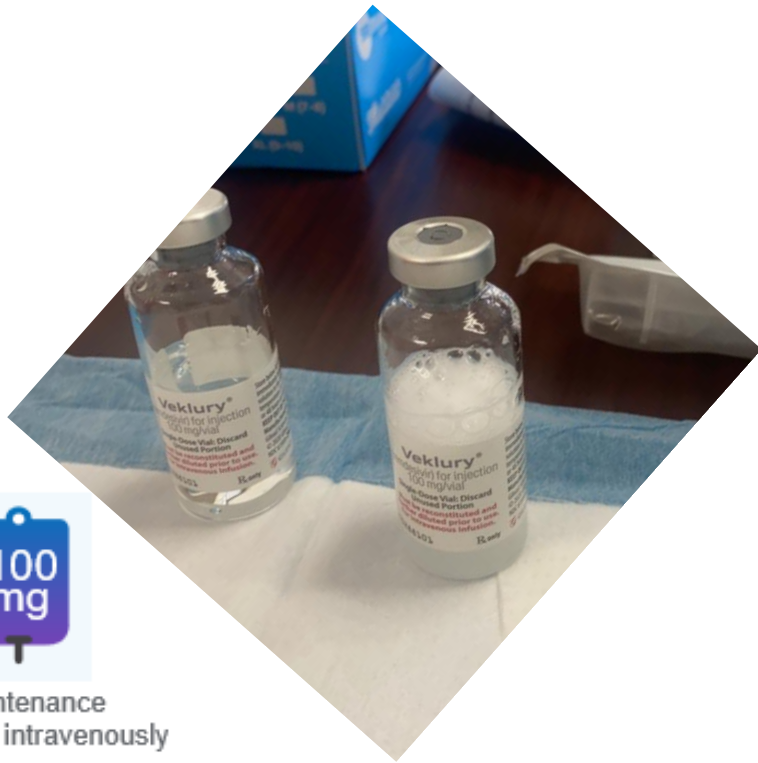
*Of the 8 patients who were adolescents, none had a COVID-19–related hospitalization or death from any cause by Day 28.
HR = hazard ratio; PBO = placebo; VKY = VEKLURY.
1. Gottlieb RL, et al. *N Engl J Med.* 2022;386(4):305-315. 2. VEKLURY. Prescribing Information. Gilead Sciences, Inc.; 2022.

https://www.nejm.org/doi/full/10.1056/NEJMoa2116846 - accessed 11/21/22

Remdesivir – challenging, but possible

Implementation Considerations

- Indicated down to age 28 days/3 kg (FHCSD will give if > 18 yrs)
- eGFR must be > 30 mL/min
- IV administration x 3 consecutive days
  - Must initiate therapy on Tuesday/Wednesday at Hillcrest Annex
  - 30-120 minute infusion
- Must be ≤ 7 days from symptom onset
- Active against all known SARS-CoV-2 variants
- Limited data in pregnancy
- Currently no evidence supporting 'combination therapy'
  - Could consider PO Molnupiravir if it will be several day wait for first IV infusion day
- **Variable Payer Coverage:**
  - Medi-cal: full coverage
  - ACA plans/Private: variable but mostly denials
  - MediCare: covered with 10-20% co-pay (~$500)



https://www.nejm.org/doi/full/10.1056/NEJMoa2116846 - accessed 11/21/22


NDC 0006-5055-06
molnupiravir
capsules
200 mg
For use under Emergency Use Authorization (EUA)
Each capsule contains 200 mg molnupiravir.
Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F).
Dispense in original container.
Scan QR code or go to www.molnupiravir.com to access the FDA-authorized Fact Sheet for dosage and administration.
Rx only
40 Capsules


3,750 × 2,500


molnupiravir
200 mg

COVID-19 therapeutics – Molnupiravir (Lagevrio)

- **Molnupiravir 800 mg (iv 200 mg capsules) PO Q12 hrs x 5 days**
- Nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis
- FDA EUA: 'For the treatment of mild to moderate COVID-19 in **adults** with positive results of direct SARS-CoV-2 viral testing, and who are at risk for progression to severe COVID-19, including hospitalization or death, *and for whom alternate COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate*'

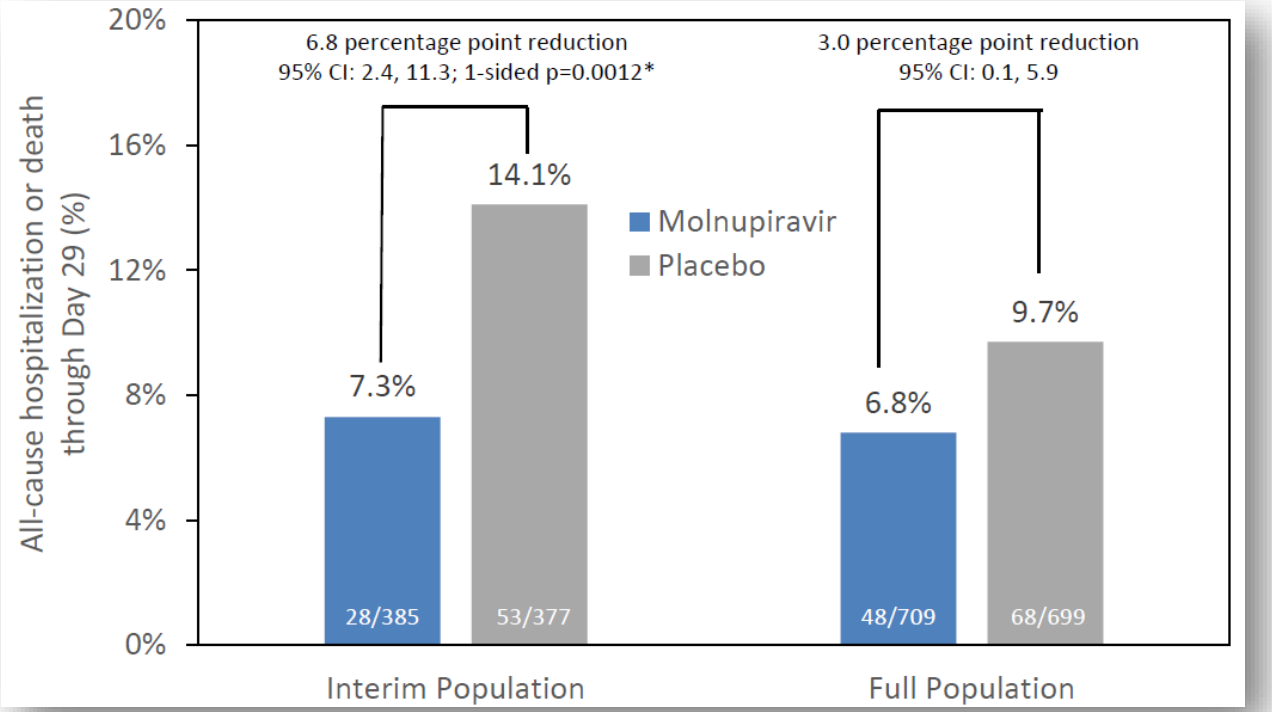
30-50% reduction in hospitalization if started within 5 days of symptom onset

Clinical Considerations

- Not recommended for use during **pregnancy** (embryo-fetal toxicity)
- Advise individuals of **childbearing potential** to use effective contraception correctly and consistently for the duration of treatment and for 4 days after last dose. Pregnancy surveillance program https://pregnancyreporting.msd.com/
- Breastfeeding not recommended during treatment and for 4 days after the last dose
- Non-clinical studies to fully assess potential to affect offspring of treated males not completed (if sexually active with individual of childbearing potential, contraception advised for at least 3 months after last dose)
- Not authorized for use in patients **< 18 yrs** (may affect bone and cartilage growth)

Molnupiravir package insert: https://www.fda.gov/media/155054/download

Molnupiravir: Updated Efficacy Analysis



	Relative Risk Reduction
Interim analysis (N=775)	49%
Full Population (N=1433)	30%

	Relative Risk Reduction
Seropositive	N/A
Seronegative	42%

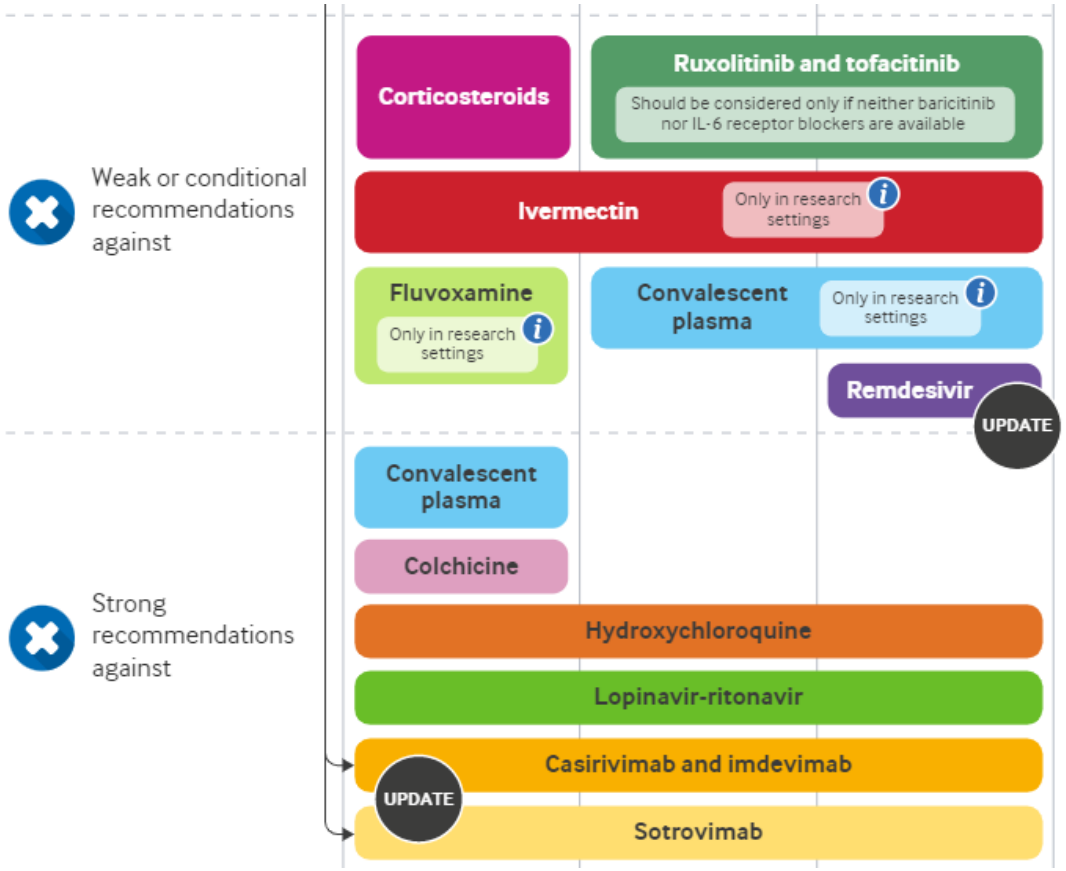
Incidence of Hospitalization or Death Through Day 29 by Baseline Antibody Status in P002, Part, 2 Full Analysis

SARS-CoV-2 Baseline Antibody Status[a]	MOV 800 mg N=709 n/m (%)	Placebo N=699 n/m (%)	Difference (MOV – Placebo) % (95% CI)[b]
Positive	5/136 (3.7)	2/146 (1.4)	2.3 (-1.7, 7.1)
Negative	39/541(7.2)	64/520 (12.3)	-5.1 (-8.8, -1.6)

https://www.fda.gov/media/154418/download ; https://www.fda.gov/media/154473/download

There are treatment options available which WHO recommends against

WHO Recommends Against



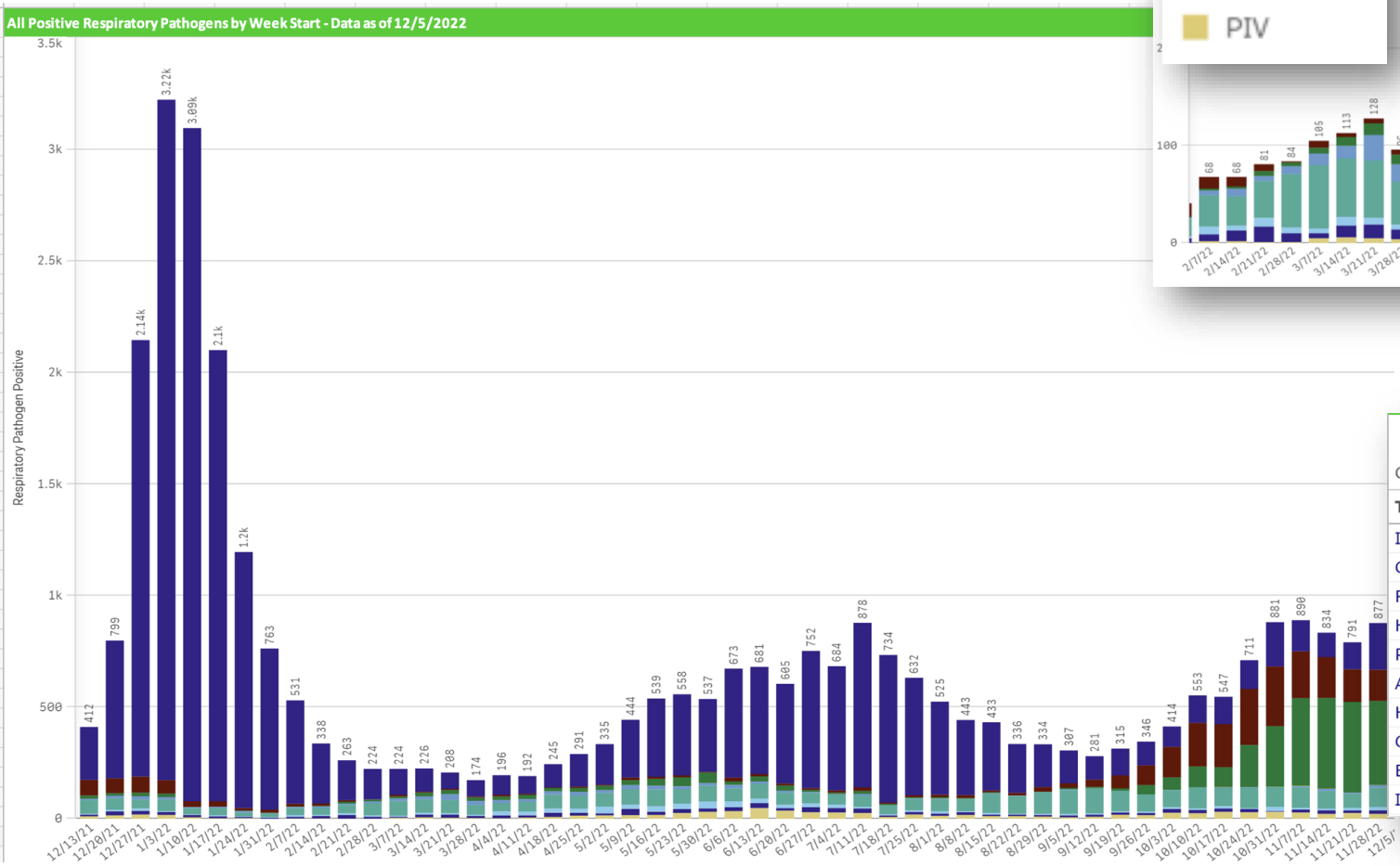
Context

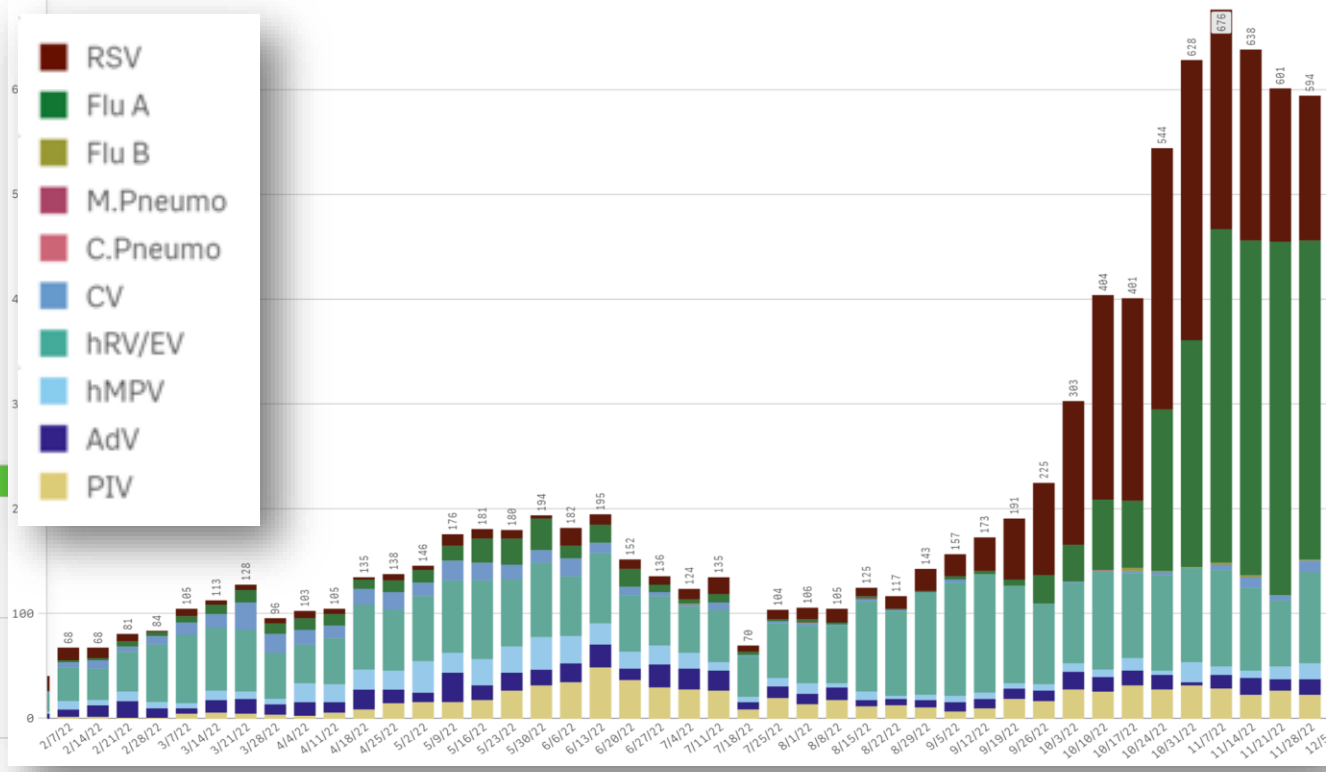
- **Corticosteroids/Dexamethasone:** Evidence of increased mortality when used in mild disease in RECOVERY trial.
- **Ivermectin:** Numerous trials have shown no benefit. Levels needed to exhibit an antiviral effect in vitro are not achievable in vivo.
- **Fluvoxamine:** No benefit observed in adequately powered clinical trials.
- **Antibiotics:** Numerous trials, including RECOVERY, found no benefit to azithromycin. Rates of antimicrobial resistance have been rising as a result of the pandemic.
- **Colchicine:** RECOVERY trial and others found no benefit.
- **Lopinavir/Ritonavir:** Multiple trials have shown no clinical benefit.
- **Hydroxychloroquine:** No benefit and potential harm.
- **Monoclonal Antibodies**: No longer active against majority of circulating strains.

https://www.bmj.com/content/370/bmj.m3379

Q&A

Rady Children's Virology Report



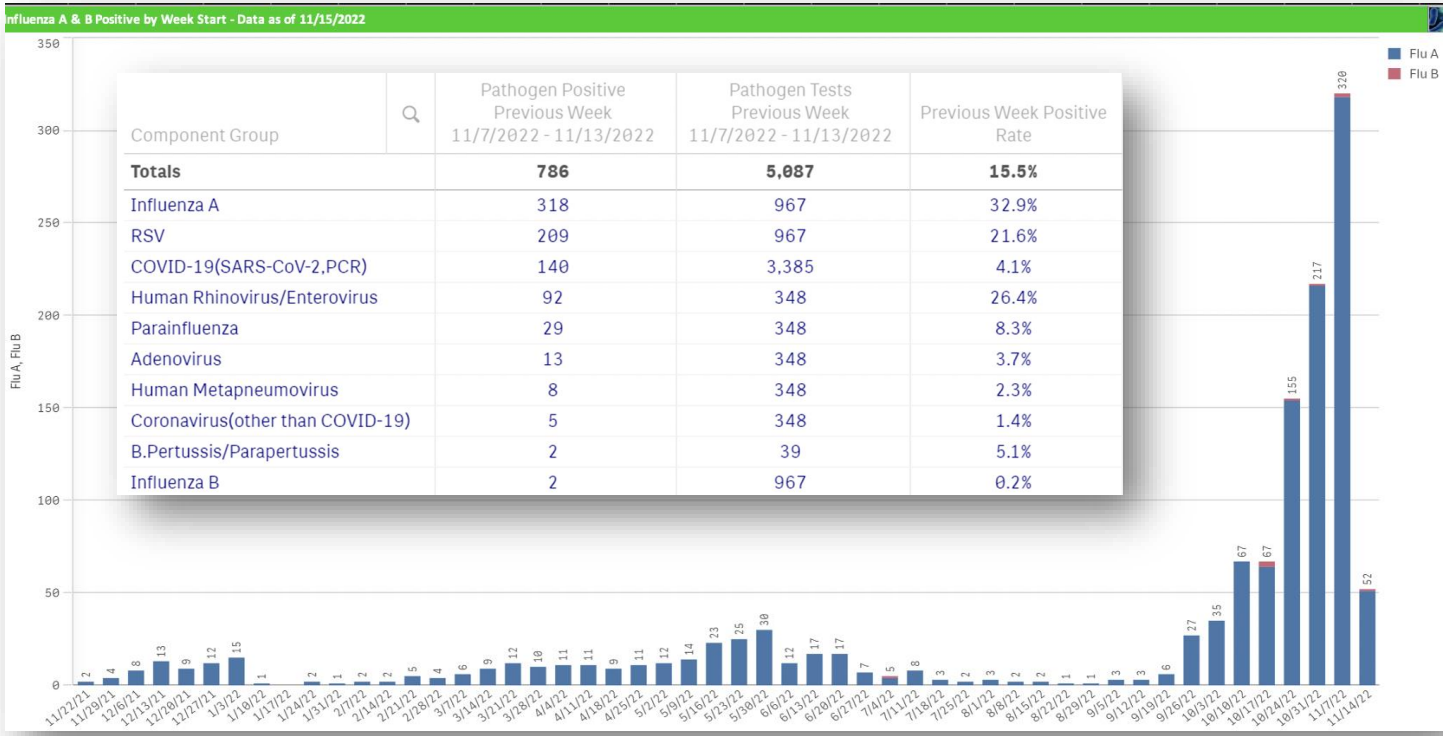


Component Group	Pathogen Positive Previous Week 11/28/2022 - 12/4/2022	Pathogen Tests Previous Week 11/28/2022 - 12/4/2022	Previous Week Positive Rate
Totals	**785**	**4,829**	**16.3%**
Influenza A	304	1,048	29.0%
COVID-19(SARS-CoV-2,PCR)	212	3,152	6.7%
RSV	138	1,048	13.2%
Human Rhinovirus/Enterovirus	87	370	23.5%
Parainfluenza	23	370	6.2%
Adenovirus	15	370	4.1%
Human Metapneumovirus	15	370	4.1%
Coronavirus(other than COVID-19)	11	370	3.0%
B.Pertussis/Parapertussis	2	48	4.2%
Influenza B	1	1,048	0.1%

Rady Children's Hospital Respiratory Pathogens Report - accessed 12/5/22

Influenza on the Rise

- Nearly all Influenza A (99.8%), H3N2 (66.3%); H1N1 (33.8%)
- This year's flu vaccine contains 4 strains: H3N2, H1N1, and two Influenza B strains
- Antigenic testing at CDC indicates that **this year's vaccine is a 92-95% match with the circulating strains**.
- Influenza vaccination is an expectation for healthcare workers. Those who decline vaccine are required to wear masks through the whole season and should not use FHCSD lunchrooms.
- Vaccination is clearly the best prevention, but for some groups chemoprophylaxis can be considered
- BD Veritor Rapid SARS-CoV-2/Influenza swabs available in most FHCSD clinics



Component Group	Pathogen Positive Previous Week 11/7/2022 - 11/13/2022	Pathogen Tests Previous Week 11/7/2022 - 11/13/2022	Previous Week Positive Rate
Totals	**786**	**5,087**	**15.5%**
Influenza A	318	967	32.9%
RSV	209	967	21.6%
COVID-19(SARS-CoV-2,PCR)	140	3,385	4.1%
Human Rhinovirus/Enterovirus	92	348	26.4%
Parainfluenza	29	348	8.3%
Adenovirus	13	348	3.7%
Human Metapneumovirus	8	348	2.3%
Coronavirus(other than COVID-19)	5	348	1.4%
B.Pertussis/Parapertussis	2	39	5.1%
Influenza B	2	967	0.2%

https://www.cdc.gov/flu/weekly/index.htm#VirusCharacterization
https://www.fda.gov/vaccines-blood-biologics/lot-release/influenza-vaccine-2022-2023-season;

Influenza Management

- Oseltamivir is effective at reducing complications, hospitalization, and mortality in some high-risk groups when given **within 48 hrs**.
- Approved down to age 0, for treatment, chemoprophylaxis (basically pre-exposure prophylaxis) or post-exposure prophylaxis

Clinical Infectious Diseases
IDSA GUIDELINE

Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenza[a]

Timothy M. Uyeki,[1] Henry H. Bernstein,[2] John S. Bradley,[3,4] Janet A. Englund,[5] Thomas M. File Jr,[6] Alicia M. Fry,[1] Stefan Gravenstein,[7] Frederick G. Hayden,[8] Scott A. Harper,[9] Jon Mark Hirshon,[10] Michael G. Ison,[11] B. Lynn Johnston,[12] Shandra L. Knight,[13] Allison McGeer,[14] Laura E. Riley,[15] Cameron R. Wolfe,[16] Paul E. Alexander,[17,18] and Andrew T. Pavia[19]

- 12/2018 IDSA practice guidelines **recommend** Oseltamivir for the following groups (irrespective of vaccination history):
  - Patients with influenza requiring **hospitalization**
  - Outpatients of any age with **severe or progressive influenza disease**
  - Outpatients of any age with **high risk for complications** due to chronic medical condition or immunocompromise
  - Children **< 2** years old
  - Adults **≥ 65** years old
- Clinicians can *__consider__* Oseltamivir for the following patients:
  - Outpatients with any risk presenting < 48 hrs from symptom onset
  - Symptomatic household contacts of persons with high risk of complications (to minimize transmission)
  - Symptomatic healthcare workers who care for persons with high risk of complication (to minimize transmission)

https://www.idsociety.org/practice-guideline/influenza/