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OU Health

COVID-19: Prevention and Treatment

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Disclosures

Dale W. Bratzler, DO, MPH

- Our team is the recipient of an unrestricted educational grant from Pfizer to provide education on evidence-based treatment of COVID-19.

Objectives:

What do I want you to get from this talk?

- Understand COVID-19 – where are we at now?
- The natural history of infection with SARS-CoV-2
  - Early disease is characterized by viral replication!
- Who is at risk for complications of the disease?
- What do we do if someone tests positive?
  - Early treatment is key to improved outcomes
- What does the future hold for COVID and PASC syndrome?

Myth – this is just a bad flu….

When is the last time you heard of hospitals using refrigerated trucks for bodies, or ICUs overflowing with limited numbers of ventilators….. from the flu?

Case History

- A 75-year-old male patient presented to the office of his primary care physician with cough, low grade fever, and shortness of breath.
  - He had a long history of Type 2 diabetes
  - He also had been diagnosed with chronic obstructive pulmonary disease

- A rapid antigen test done in the office was positive for COVID-19.

- His initial pulse oximetry showed 96% saturation on room air.

What is the appropriate treatment for this non-hospitalized patient with COVID-19?

Case History

- The patient wa[illegible]scribed a methylprednisolone dose pack and a five-day course of azi[illegible]

Most patients with bad COVID start off with mild symptoms!

- Approximately 7-days later the patient [illegible]emergency department in acute respiratory failure wi[illegible]ral ground glass infiltrates on the chest x-ray requiring in[illegible]ion.

- The family withdrew treatment when transfer for ECM[illegible]s recommended.

Case History

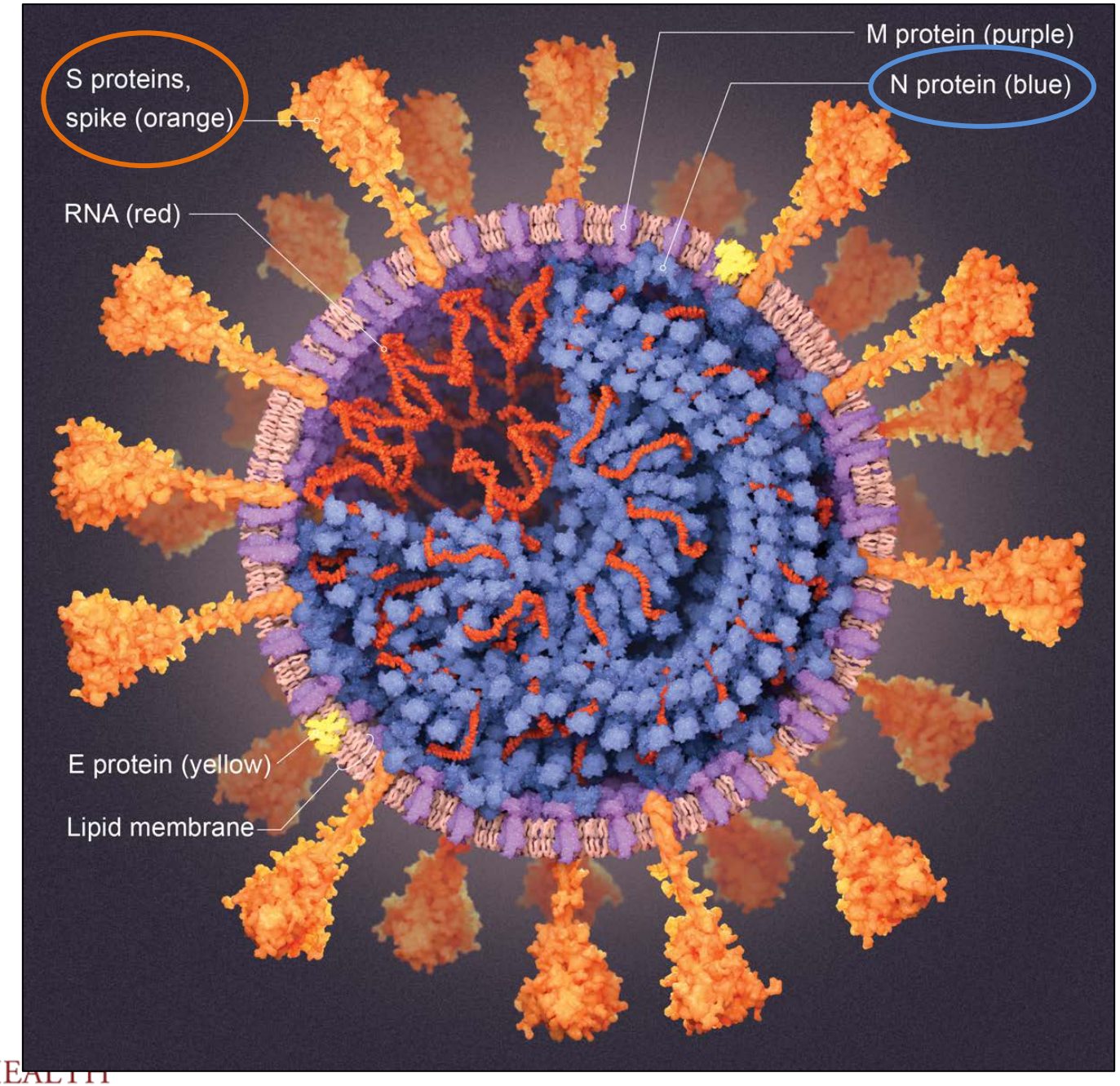
- Lessons from this case –
  - Antibiotics including azithromycin, doxycycline and others have not been shown (in randomized clinical trials) to improve outcomes in non-hospitalized patients with COVID-19 (it's a virus!)
  - Corticosteroids are contraindicated in non-hospitalized patients with COVID-19 unless the patient need corticosteroids for some other condition. Studies have shown that outpatients with COVID-19 who are treated with corticosteroids have a worse prognosis.

Spike protein (S)

Attaches to receptors in your nose and airways when you breath the virus in.

Vaccines make your body produce antibodies against the spike protein.

PCR tests are very sensitive and detect fragments of the RNA in the virus.

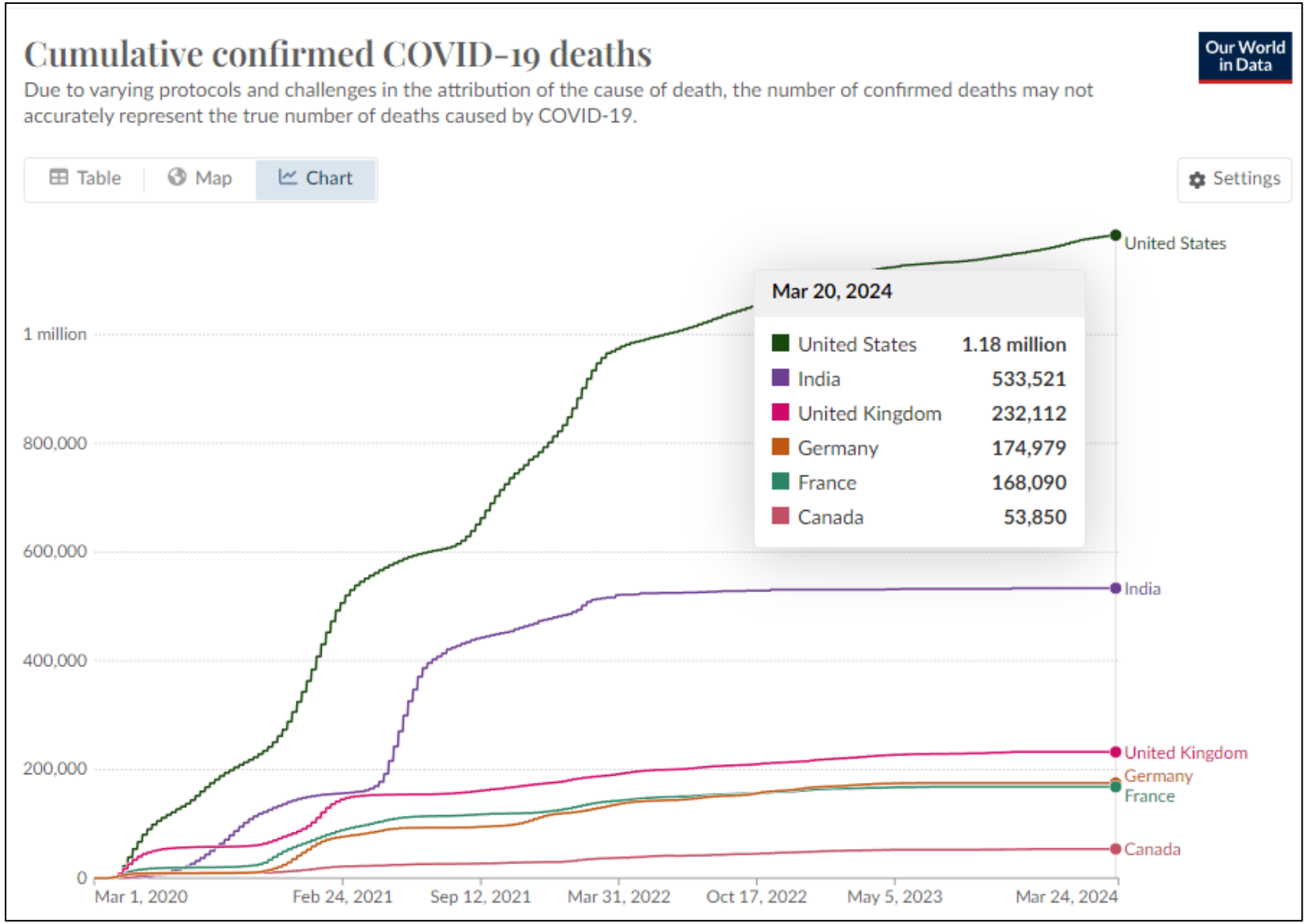


Nucleocapsid protein (N)

Many rapid antigen tests detect this protein

You get anti-N antibodies when you get infected.

https://www.scientificamerican.com/article/a-visual-guide-to-the-sars-cov-2-coronavirus/



United States:

- **6,909,932 hospitalizations**
- **1,187,509 Deaths**
- **676,728,782 Vaccine doses***

Oklahoma:

- **116,999 hospitalizations**
- **20,354 deaths**

US and OK data as of March 30, 2024, from the CDC.
https://covid.cdc.gov/covid-data-tracker

***Doses as of May 11, 2023.**

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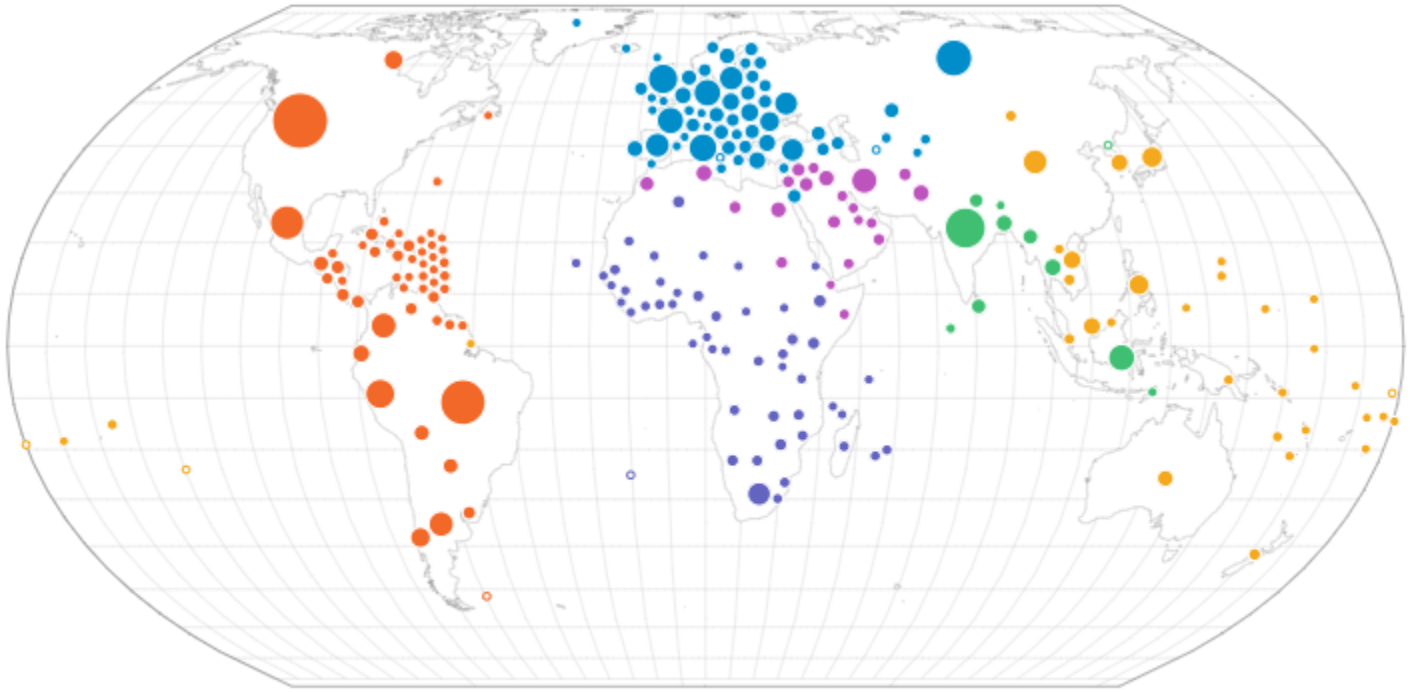
Number of COVID-19 deaths reported to WHO (cumulative total)

World



7,042,222

Reported COVID-19 deaths

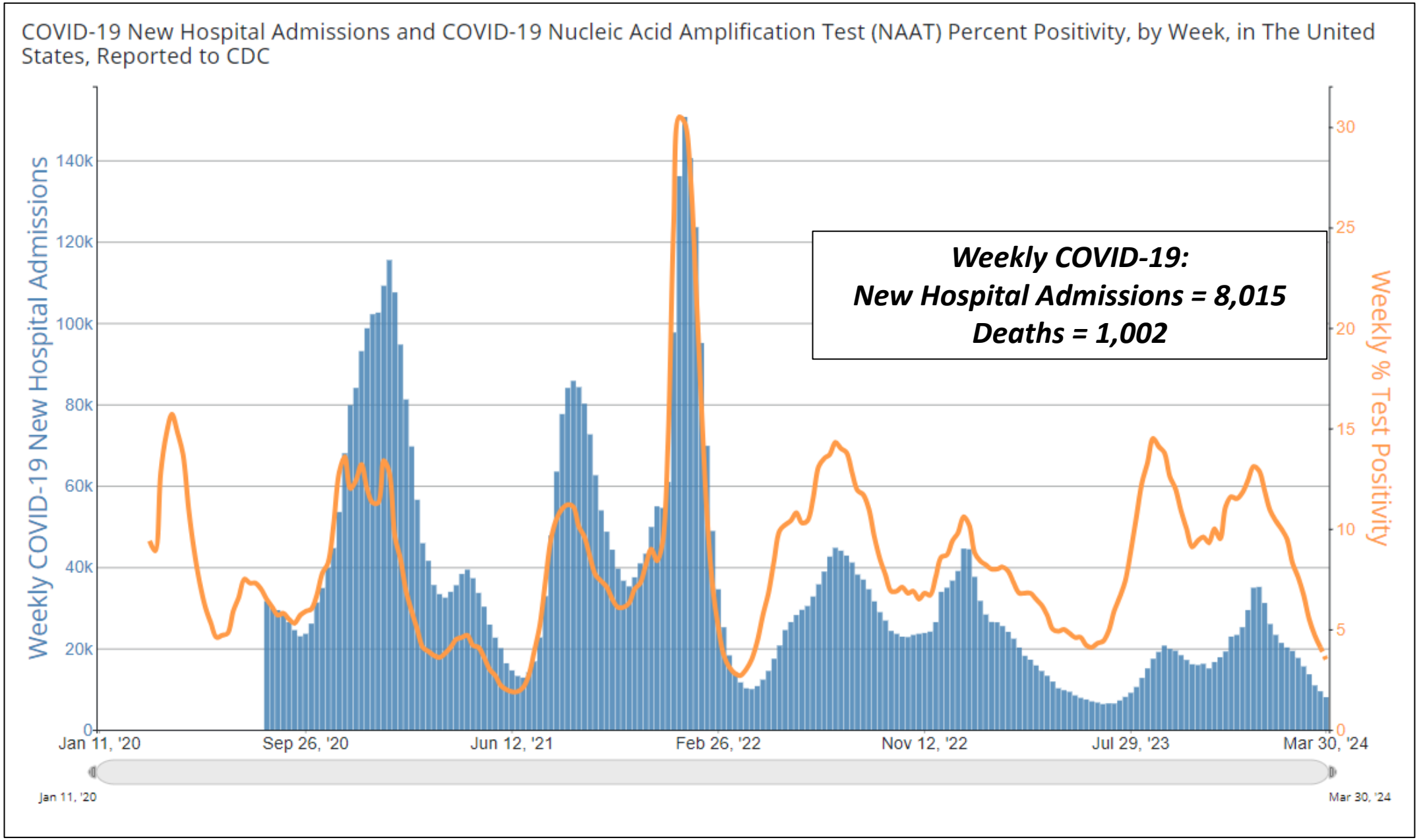
24 March 2024

Number of COVID-19 deaths reported to WHO (cumulative total)

World

Country	Deaths
United States of America	1.2m
Brazil	702.1k
India	533.5k
Show 228 more	
Saint Helena	0

https://data.who.int/dashboards/covid19/deaths?n=c



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https://covid.cdc.gov/covid-data-tracker/#trends_weeklyhospitaladmissions_testpositivity_00

OKLAHOMA
State Department of Health

COVID-19 in Oklahoma

This graph shows a timeline of COVID-19 hospitalizations and sentinel laboratory percent positivity in Oklahoma since September 2021. Use the slide bar in the bottom left to view a timeframe of interest. Hover over a point in time to see the number of hospitalizations or statewide percent positivity for that week.

DATA AS OF WEEK ENDING 03/30/2024

Activity Level

Positivity

Hospitalizations

Variants

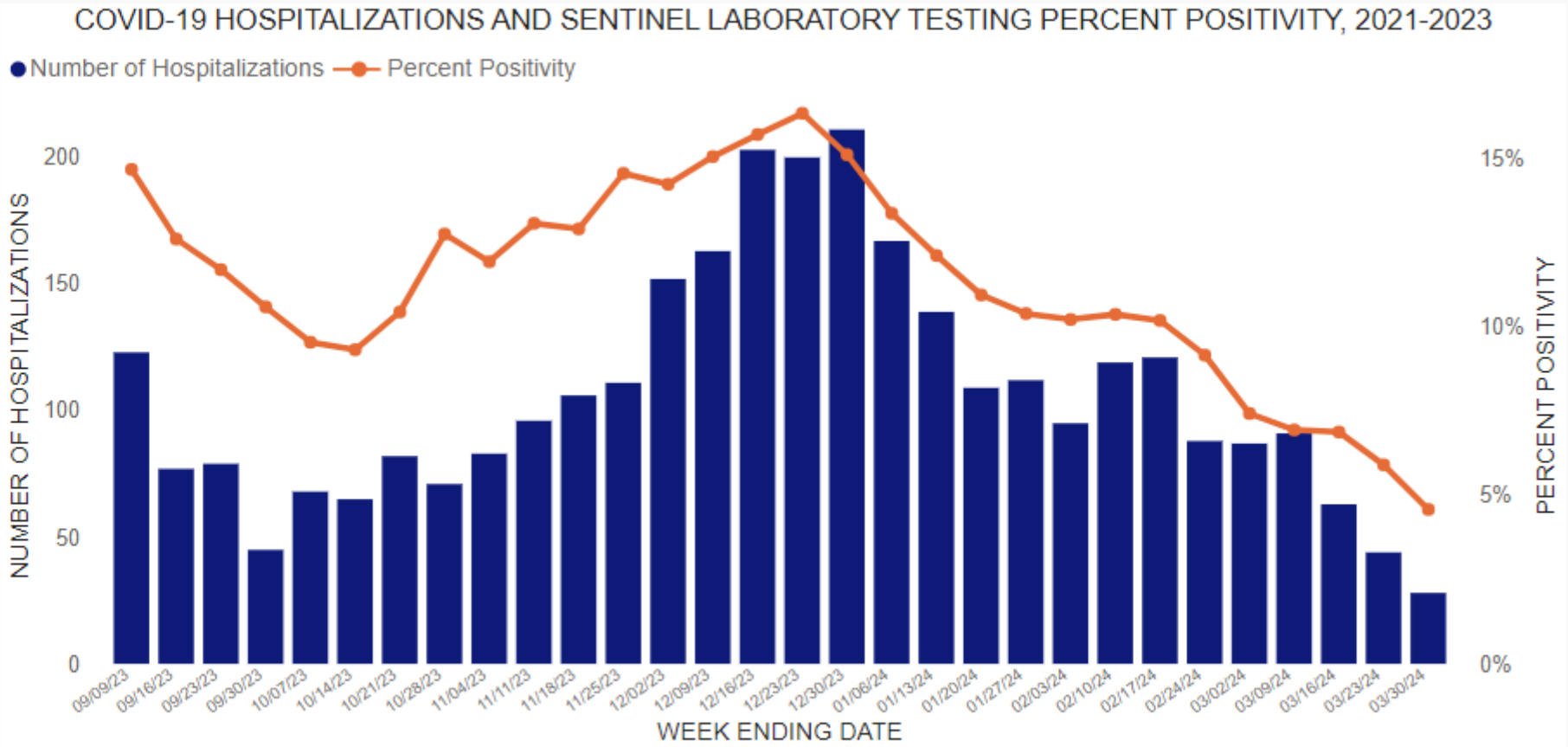
Wastewater

Week Ending Date

9/3/2023

3/30/2024

Please note that when selecting a date, data is reported out by week ending date only.



Hospitalizations and Percent Positivity

Hospitalizations by HHS Region

Hospitalization Rate Per 100,000 by Age Group

Hospitalization Rate Per 100,000 by HHS Region

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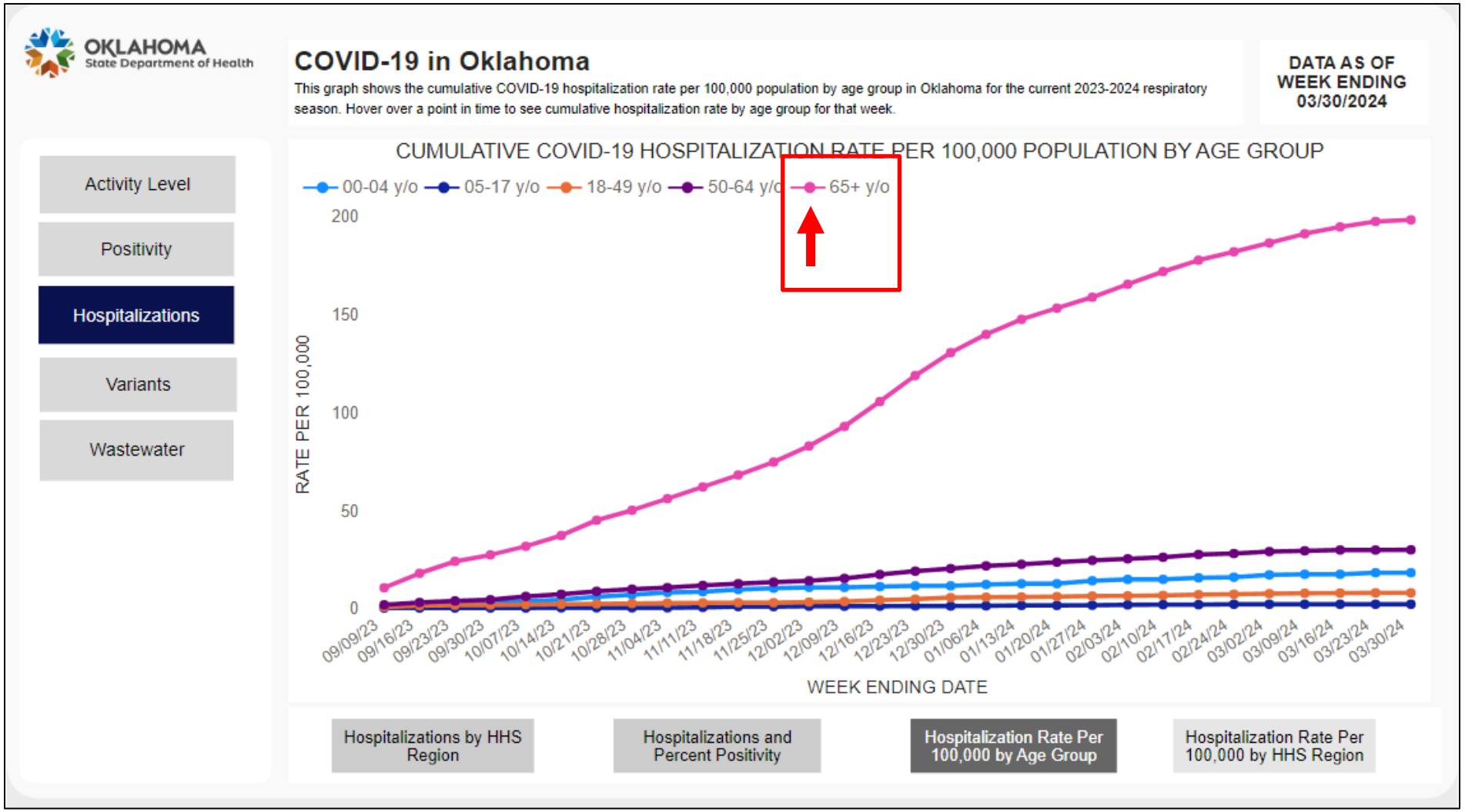
https://oklahoma.gov/health/health-education/acute-disease-service/viral-view/covid-19.html

COVID-19 Hospitalizations of the Elderly



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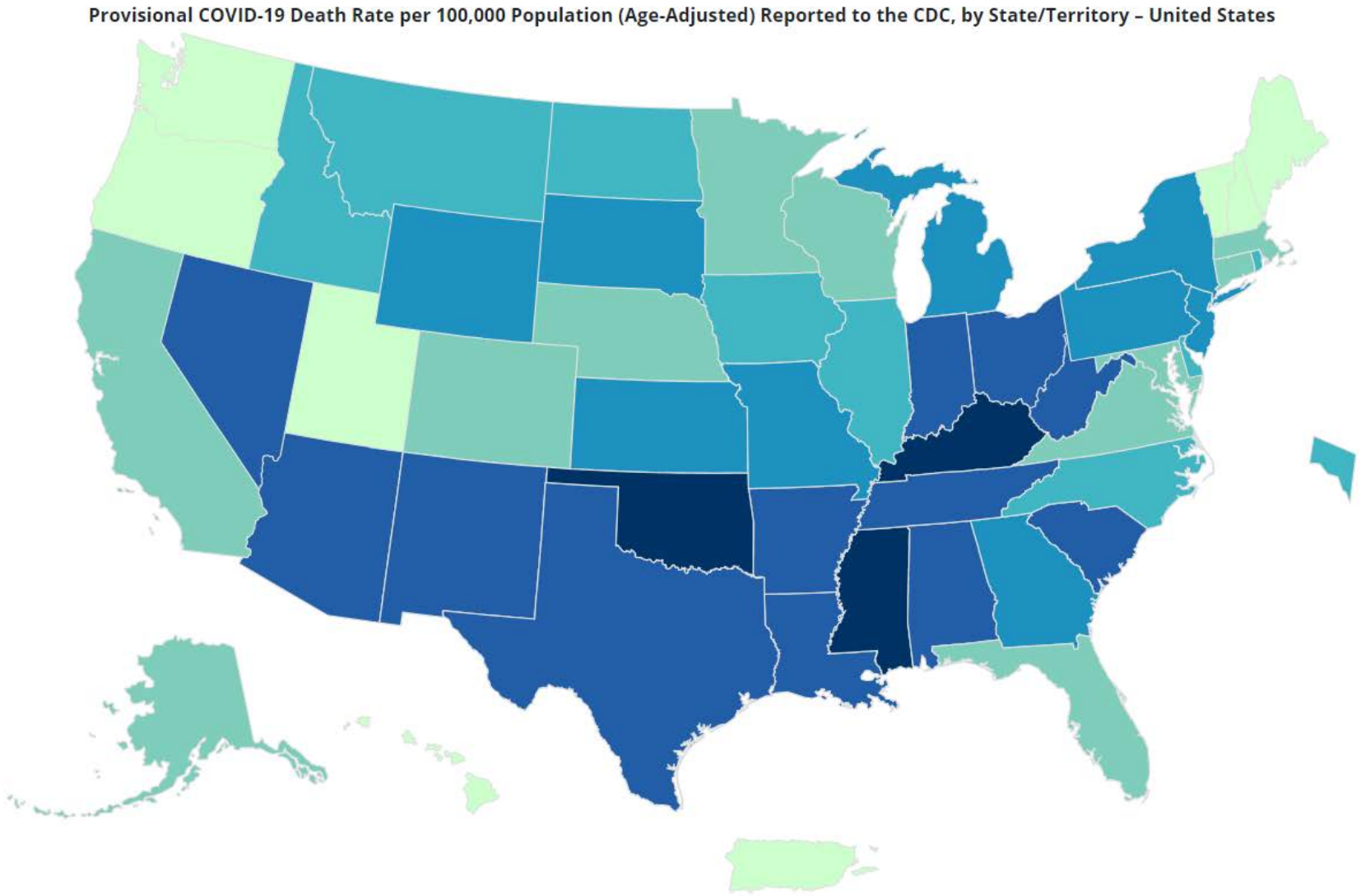
https://oklahoma.gov/content/dam/ok/en/health/health2/aem-documents/prevention-and-preparedness/acute-disease-service/disease-information/flu-view/viral-view/COVID%20Report.pdf



Oklahoma had the second highest death rate in the nation due to COVID-19!

Deaths per 100,000 population:

- **Mississippi – 447**
- **Oklahoma – 444.1**
- **West Virginia – 394**

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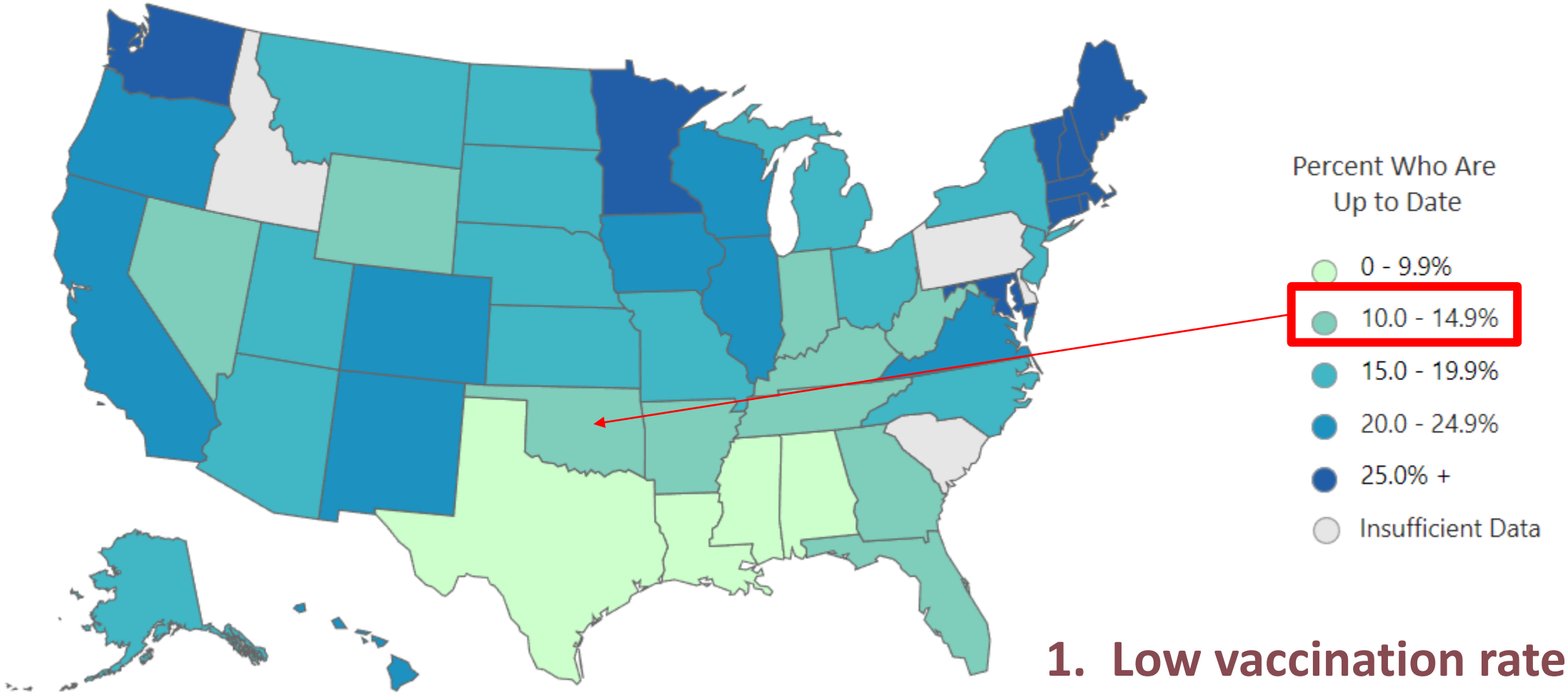
https://covid.cdc.gov/covid-data-tracker/#maps_deaths-rate-total

Why is our death rate high?

Percent of the Total Population Who Are Up to Date with COVID-19 Vaccines

Administrations through September 12, 2023

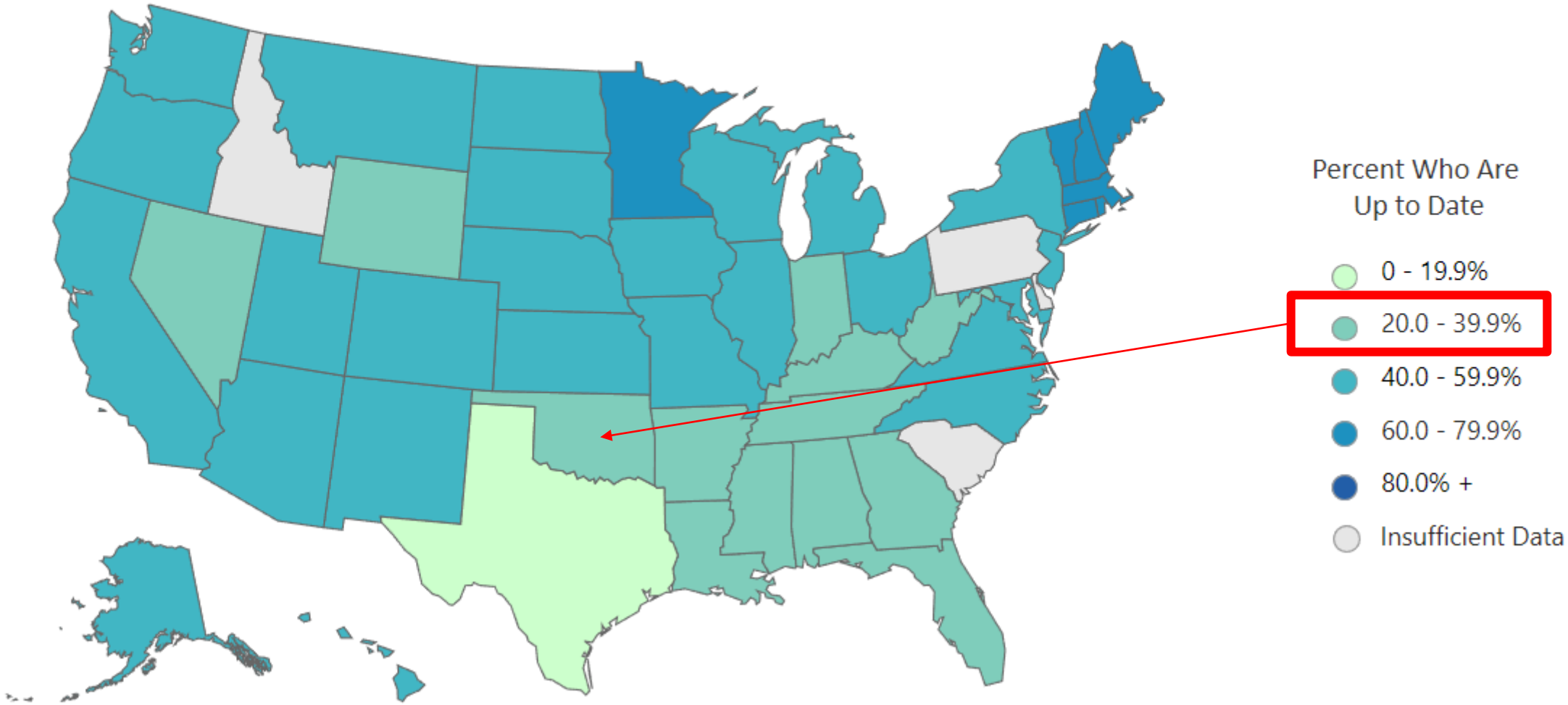


1. Low vaccination rates.

https://covid.cdc.gov/covid-data-tracker/#vaccination-states-jurisdictions

Percent of Adults 65 Years and Older Who Are Up to Date with COVID-19 Vaccines

Administrations through September 12, 2023



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https://covid.cdc.gov/covid-data-tracker/#vaccination-states-jurisdictions

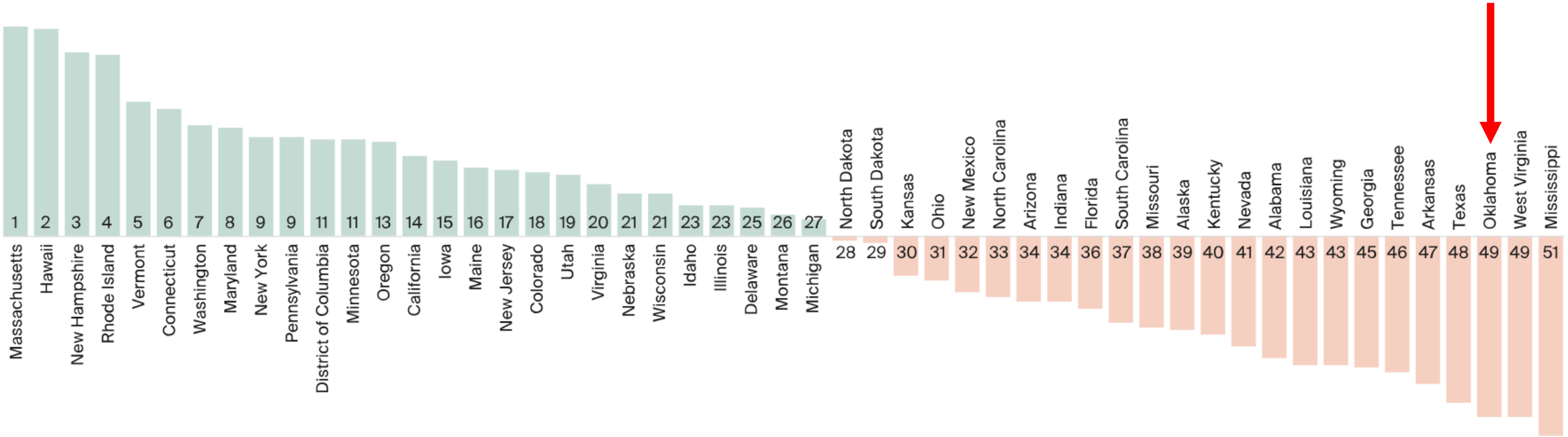
Commonwealth 2023 Report on Health Outcomes

"The lowest-performing states were Oklahoma, West Virginia, and Mississippi."

Massachusetts, Hawaii, and New Hampshire top the overall rankings on health system performance for 2023.

2. We have a poor health population.

Overall Rankings for 2023 Scorecard on State Health System Performance



https://www.commonwealthfund.org/publications/scorecard/2023/jun/2023-scorecard-state-health-system-performance

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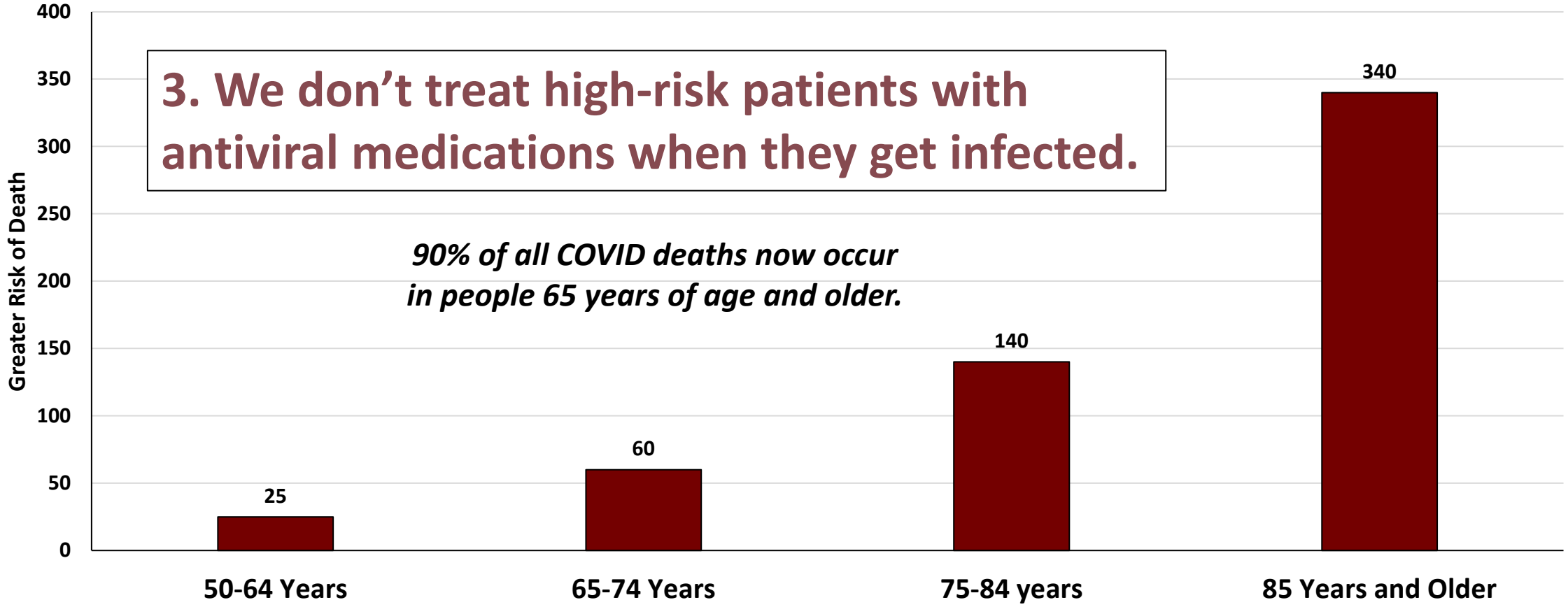
Risk of Death From COVID-19

As compared to people ages 18-29 years….

People 85 and older are 340 times more likely to die if they get COVID compared to the 18–29-year-old person!



3. We don't treat high-risk patients with antiviral medications when they get infected.

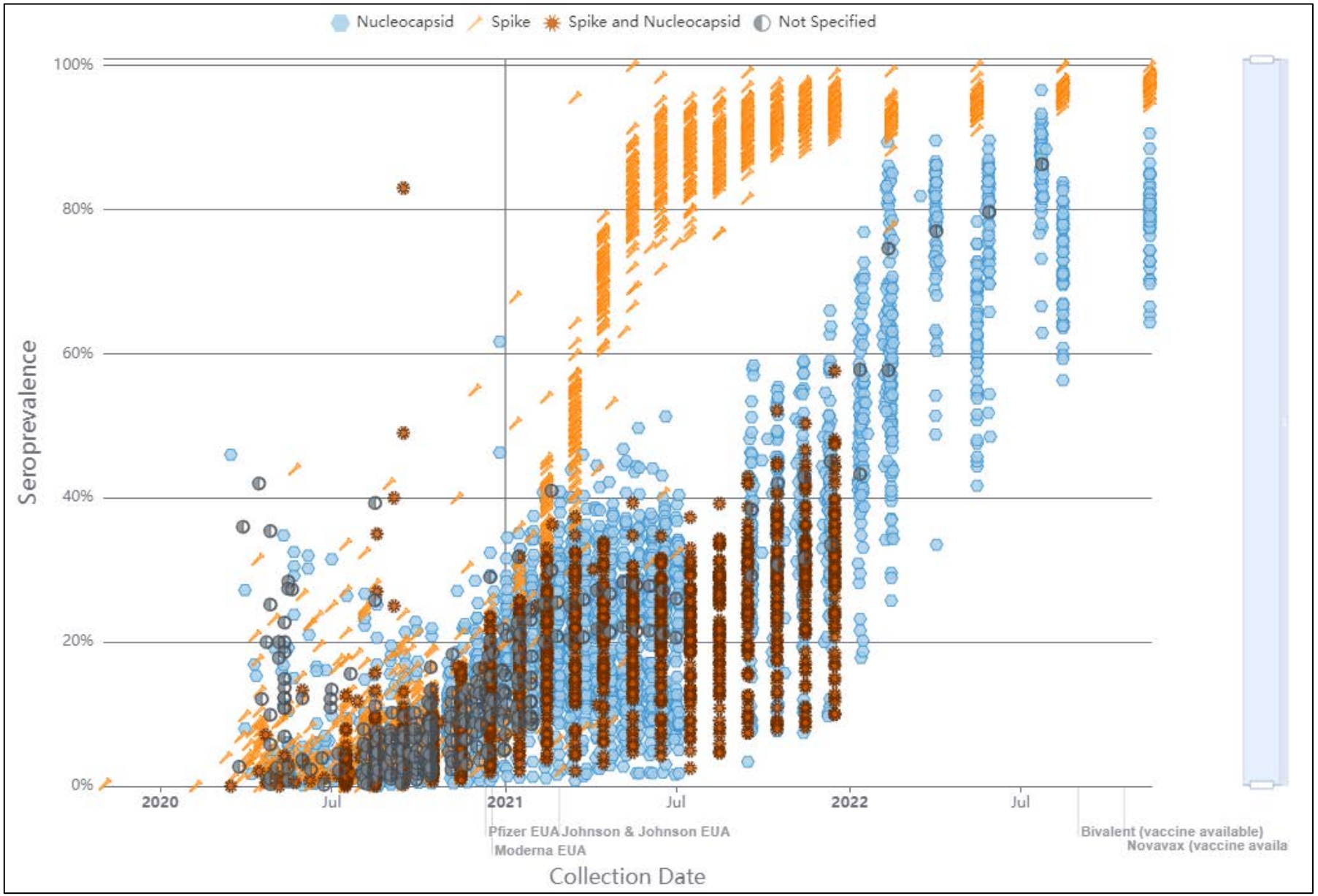
90% of all COVID deaths now occur in people 65 years of age and older.

That’s where we’ve been – what’s different now??

Why are cases and deaths down so much now?

- Almost every American has either had COVID* or has been vaccinated.

*Whether they know it or not!

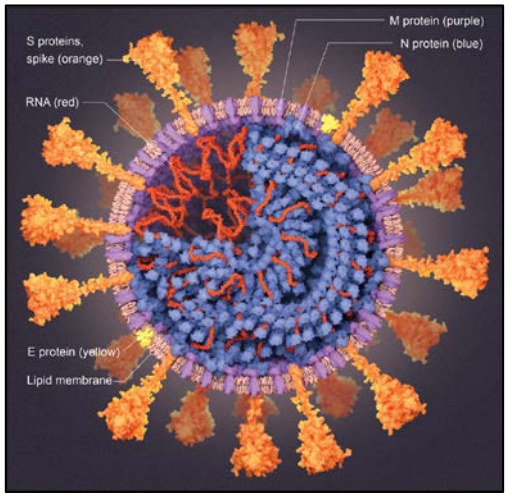


Antibodies to:

Spike glycoprotein

Nucleocapsid proteins

To both….



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NIH NATIONAL CANCER INSTITUTE | NIH National Institute of Allergy and Infectious Diseases | CDC Centers for Disease Control and Prevention

COVID-19 SeroHub

https://covid19serohub.nih.gov/

If we want to stop this cycle of hospitalizations and death……

Vaccination is, by far, the most important thing we can do!

- Vaccination:
  - Prevents COVID-19 infection. (~around 50% effectiveness)
  - Dramatically reduces the risk of severe complications, hospitalization, and death from COVID-19.
  - Reduces viral burden and likely reduces spread of the disease.
  - Reduces the likelihood of long-COVID (PASC syndrome).

Antibody levels wane – particularly in the elderly and in those with immunosuppression – need to revaccinate!

Long-term effectiveness of COVID-19 vaccines against infections, hospitalisations, and mortality in adults: findings from a rapid living systematic evidence synthesis and meta-analysis up to December, 2022

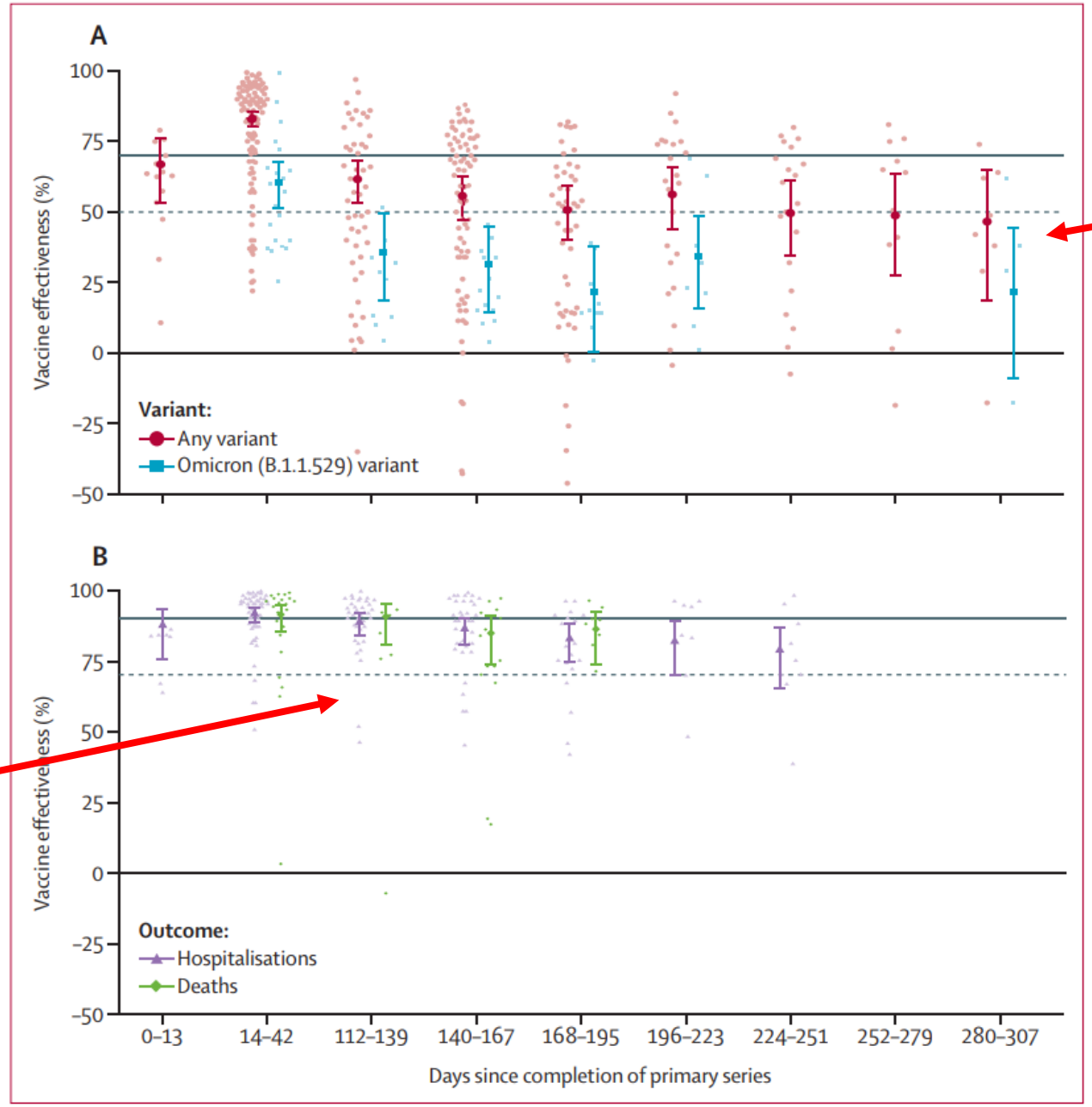
Nana Wu, Keven Joyal-Desmarais, Paula A B Ribeiro, Ariany Marques Vieira, Jovana Stojanovic, Comfort Sanuade, Doro Yip, Simon L Bacon

Lancet Respir Med 2023; 11: 439–52

Summary

Background Synthesising evidence on the long-term vaccine effectiveness of COVID-19 vaccines (BNT162b2 [Pfizer–BioNTech], mRNA-1273 [Moderna], ChAdOx1 nCoV-19 [AZD1222; Oxford–AstraZeneca], and Ad26.COV2.S [Janssen])

Lancet Respir Med 2023; 11: 439–52.



While vaccine effectiveness against subsequent COVID infection waned over time……

…….protection against hospitalization and death remained strong!

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Lancet Respir Med 2023; 11: 439–52.

Global COVID vaccination saved 2.4 million lives in first 8 months, study estimates

Mary Van Beusekom, MS, *October 31, 2023*

Topics: COVID-19

SHARE

The COVID-19 vaccination campaign in 141 countries averted 2.4 million excess deaths by August 2021 and would have saved another 670,000 more lives had vaccines been distributed equitably, estimates a **working paper** from University of Southern California (USC) and Brown University researchers.

The National Bureau of Economic Research circulated the non–peer-reviewed working paper for discussion and comment this week. The researchers estimated the real-world effectiveness of the global COVID-19 vaccine rollout on all-cause death rates, including both the direct and indirect effects of the pandemic.

"Within eight months, over 2 billion people were vaccinated globally, making it the largest public health campaign in history," the study authors wrote.

"To the best of our knowledge, this is the first study that estimates the effect of COVID-19 vaccines on the global all-cause mortality

USAID / Flickr cc

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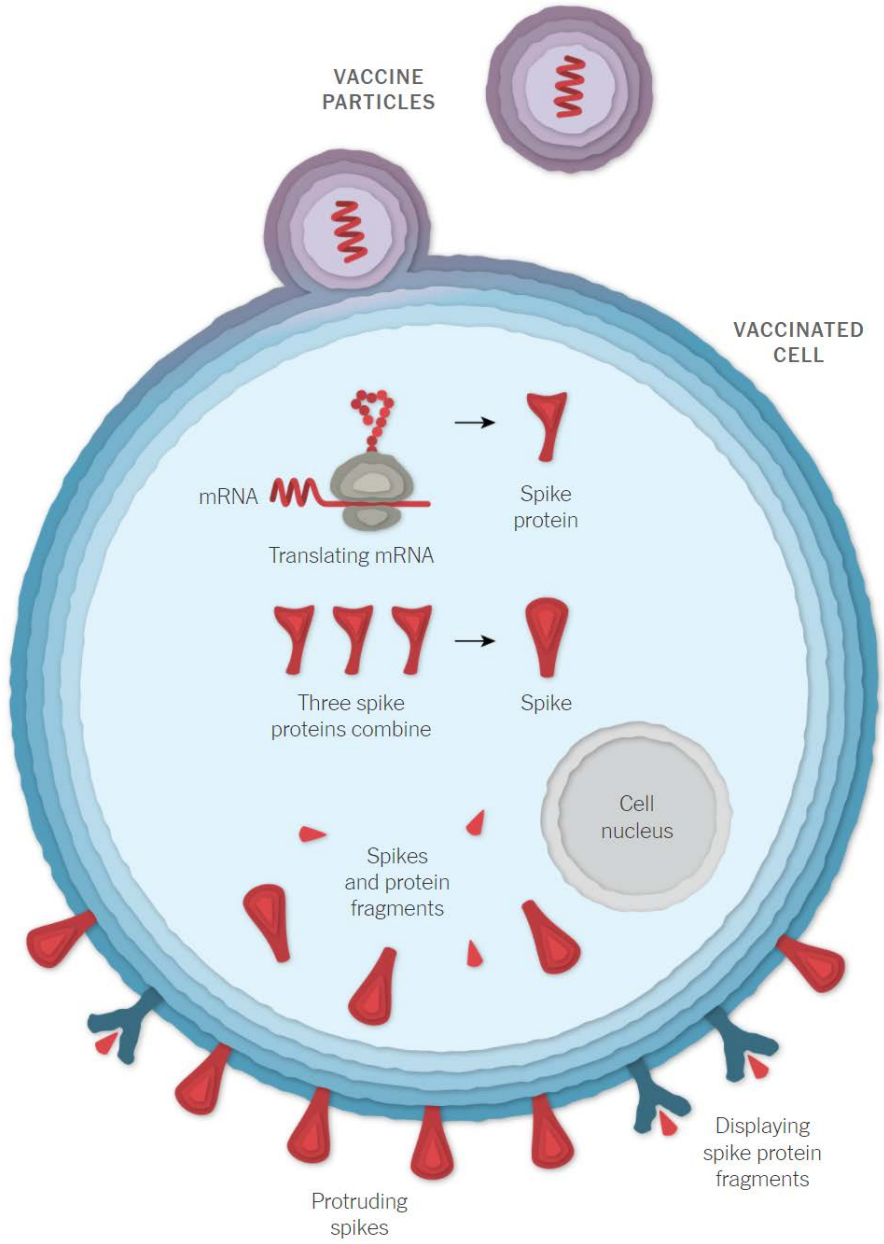
https://www.cidrap.umn.edu/covid-19/global-covid-vaccination-saved-24-million-lives-first-8-months-study-estimates

mRNA Vaccines (Pfizer and Moderna)

- The vaccine that is injected contains mRNA that will encode for the spike protein. That mRNA is surrounded with a lipid nanoparticle that prevents immediate breakdown of the mRNA on injection.
- The mRNA from the vaccine is taken up by the cells to enter the ribosome complex to produce spike protein.



https://www.nytimes.com/interactive/2021/health/how-covid-19-vaccines-work.html

Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers

Table 2. Multivariable Logistic Regression Analysis of the Association of Long COVID (N = 229) With Patient Characteristics[a]

	OR (95% CI)	*P* value
Male sex	0.65 (0.44-0.98)	.04
Age[b]	1.23 (1.01-1.49)	.04
BMI[b]	1.10 (0.92-1.31)	.30
Allergies	1.50 (1.06-2.11)	.02
No. of comorbidities[c]	1.32 (1.04-1.68)	.03
COVID-19 wave		
2	0.72 (0.48-1.08)	.11
3	1.34 (0.26-7.01)	.73
Vaccine dose[d]		
1	0.86 (0.21-3.49)	.83
2	0.25 (0.07-0.87)	.03
3	0.16 (0.03-0.84)	.03

In this longitudinal observational study conducted among health care workers with SARS-CoV-2 infections not requiring hospitalization, 2 or 3 doses of vaccine, compared with no vaccination, were associated with lower long COVID prevalence.

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JAMA August 16, 2022 Volume 328, Number 7

Antimicrobial Stewardship & Healthcare Epidemiology (2023), **3**, e168, 1–16
doi:10.1017/ash.2023.447

SHEA

Original Article

The effectiveness of COVID-19 vaccine in the prevention of post-COVID conditions: a systematic literature review and meta-analysis of the latest research

Alexandre R. Marra MD, MS[1,2,3], Takaaki Kobayashi MD[1], Gustavo Yano Callado[2], Isabele Pardo[2], Maria Celidonio Gutfreund[2], Mariana Kim Hsieh[2], Vivian Lin MD[2], Mohammed Alsuhaibani MBBS[4], Shinya Hasegawa MD[1], Joseph Tholany MD[1], Eli N. Perencevich MD, MS[1,3], Jorge L. Salinas MD[5], Michael B. Edmond MD, MPH, MPA[6] and Luiz Vicente Rizzo MD[2]

[1]Department of Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA, [2]Faculdade Israelita de Ciências da Saúde Albert Einstein, Hospital Israelita Albert Einstein, São Paulo, SP, Brazil, [3]Center for Access & Delivery Research & Evaluation (CADRE), Iowa City Veterans Affairs Health Care System, Iowa City, IA, USA, [4]Department of Pediatrics, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [5]Stanford University, Stanford, CA, USA and [6]West Virginia University School of Medicine, Morgantown, WV, USA

"Thirty-two studies with 775,931 individuals evaluated the effect of vaccination on post-COVID conditions, of which, twenty-four studies were included in the meta-analysis…. …. Vaccine effectiveness was 36.9% (23.1%–48.2%) among those who received two doses of COVID-19 vaccine before COVID-19 infection and 68.7% (64.7%–72.2%) among those who received three doses before COVID-19 infection."

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals

K. Faksova [a,*], D. Walsh [b,c], Y. Jiang [b,c], J. Griffin [c], A. Phillips [d], A. Gentile [e], J.C. Kwong [f,g,h], K. Macartney [d,i], M. Naus [j,n], Z. Grange [k], S. Escolano [l], G. Sepulveda [m], A. Shetty [m], A. Pillsbury [d], C. Sullivan [k], Z. Naveed [j,n], N.Z. Janjua [j,n], N. Giglio [e], J. Perälä [o], S. Nasreen [f,p,x], H. Gidding [d,i], P. Hovi [q], T. Vo [r], F. Cui [s], L. Deng [d], L. Cullen [k], M. Artama [r], H. Lu [b,c], H.J. Clothier [c,m], K. Batty [t], J. Paynter [u], H. Petousis-Harris [c,u], J. Buttery [c,m,v], S. Black [c,u], A. Hviid [a,w]

"As of November 2023, at least 70.5 % of the world's population had received at least one dose of a COVID-19 vaccine. This unparalleled scenario underscores the pressing need for comprehensive vaccine safety monitoring as very rare adverse events associated with COVID-19 vaccines may only come to light after administration to millions of individuals."

13.5 billion doses of COVID-19 vaccines have been administered worldwide.

Table 4

Aggregated OE Ratios by last dose, haematologic conditions, period 0–42 days.

		THR		ITP		PEM		CVST		SVT	
Dose	Vaccine	OE Ratio	95%CI	OE Ratio	95%CI	OE Ratio	95%CI	OE Ratio	95%CI	OE Ratio	95%CI
1	ChAdOx1	1.07	(1.03,1.12)	1.40	(1.24,1.58)	1.20	(1.16,1.24)	3.23	(2.51,4.09)	1.02	(0.89,1.16)
	BNT162b2	1.11	(1.08,1.14)	1.08	(1.01,1.16)	1.29	(1.26,1.32)	1.49	(1.26,1.75)	1.25	(1.17,1.34)
	mRNA-1273	1.33	(1.25,1.42)	1.13	(0.93,1.37)	1.33	(1.26,1.40)	1.48	(0.92,2.23)	1.23	(1.03,1.47)
2	ChAdOx1	0.96	(0.91,1.01)	1.02	(0.88,1.18)	0.96	(0.92,1.00)	1.15	(0.70,1.77)	0.95	(0.82,1.10)
	BNT162b2	0.92	(0.89,0.94)	0.93	(0.86,1.00)	0.99	(0.97,1.01)	1.25	(1.06,1.46)	1.03	(0.96,1.10)
	mRNA-1273	0.98	(0.92,1.04)	0.80	(0.65,0.97)	1.05	(0.99,1.10)	1.43	(0.95,2.06)	1.17	(1.01,1.36)
3	ChAdOx1	1.95	(1.29,2.84)	3.65	(0.75,10.67)	1.88	(1.32,2.58)	0		3.59	(0.43,12.96)
	BNT162b2	0.78	(0.75,0.81)	0.85	(0.77,0.93)	0.96	(0.93,0.98)	1.14	(0.89,1.44)	0.90	(0.82,0.99)
	mRNA-1273	0.73	(0.67,0.79)	0.72	(0.57,0.91)	0.97	(0.92,1.02)	0.94	(0.49,1.65)	0.94	(0.77,1.13)
4	BNT162b2	1.04	(0.95,1.13)	1.18	(0.99,1.41)	0.99	(0.94,1.04)	0.99	(0.47,1.81)	1.30	(1.06,1.59)
	mRNA-1273	1.08	(0.93,1.24)	0.96	(0.59,1.47)	1.03	(0.93,1.13)	0		1.53	(1.05,2.16)

AESI: THR= Thrombocytopenia, ITP= Idiopathic thrombocytopenia, PEM= Pulmonary embolism, CVST=Cerebral venous sinus thrombosis, SVT= Splanchnic vein thrombosis

ChAdOx1 – Oxford/AstraZeneca adenovirus vaccine (removed from US market in May 2023).
BNT162b2 – Pfizer mRNA vaccine.
mRNA-1273 – Moderna mRNA vaccine.

Table 5
Aggregated OE Ratios by last dose, cardiovascular conditions, period 0–42 days.

		MYO		PER	
Dose	Vaccine	OE Ratio	95%CI	OE Ratio	95%CI
1	ChAdOx1	1.36	(1.08,1.68)	1.29	(1.15,1.44)
	BNT162b2	2.78	(2.61,2.95)	1.54	(1.47,1.62)
	mRNA-1273	3.48	(3.00,4.01)	1.74	(1.54,1.97)
2	ChAdOx1	1.31	(1.01,1.68)	1.27	(1.12,1.43)
	BNT162b2	2.86	(2.70,3.03)	1.38	(1.32,1.45)
	mRNA-1273	6.10	(5.52,6.72)	1.67	(1.50,1.85)
3	ChAdOx1	0		6.91	(3.45,12.36)
	BNT162b2	2.09	(1.88,2.32)	1.19	(1.10,1.28)
	mRNA-1273	2.01	(1.60,2.49)	1.39	(1.20,1.59)
4	BNT162b2	2.06	(1.47,2.80)	1.55	(1.30,1.83)
	mRNA-1273	2.91	(1.45,5.21)	2.64	(2.05,3.35)

AESI: MYO= Myocarditis, PER= Pericarditis

ChAdOx1 – Oxford/AstraZeneca adenovirus vaccine (removed from US market in May 2023).
BNT162b2 – Pfizer mRNA vaccine.
mRNA-1273 – Moderna mRNA vaccine.

Global Vaccine Safety Project –

One more thing to remember about this study

- This study compared adverse events that happened after the vaccines were rolled out to the rate of these events before the vaccines were in use.
  - It did not compare the rates of these events to the rate of events that occurred after the COVID-19 pandemic started.
    - e .g. estimated extra myocarditis events to be between one and 10 per million persons in the month following vaccination, which was substantially lower than the 40 extra events per million persons observed following SARS-CoV-2 infection period.

Circulation Research

COMPENDIUM ON COVID-19 AND CARDIOVASCULAR DISEASE

COVID-19, Myocarditis and Pericarditis

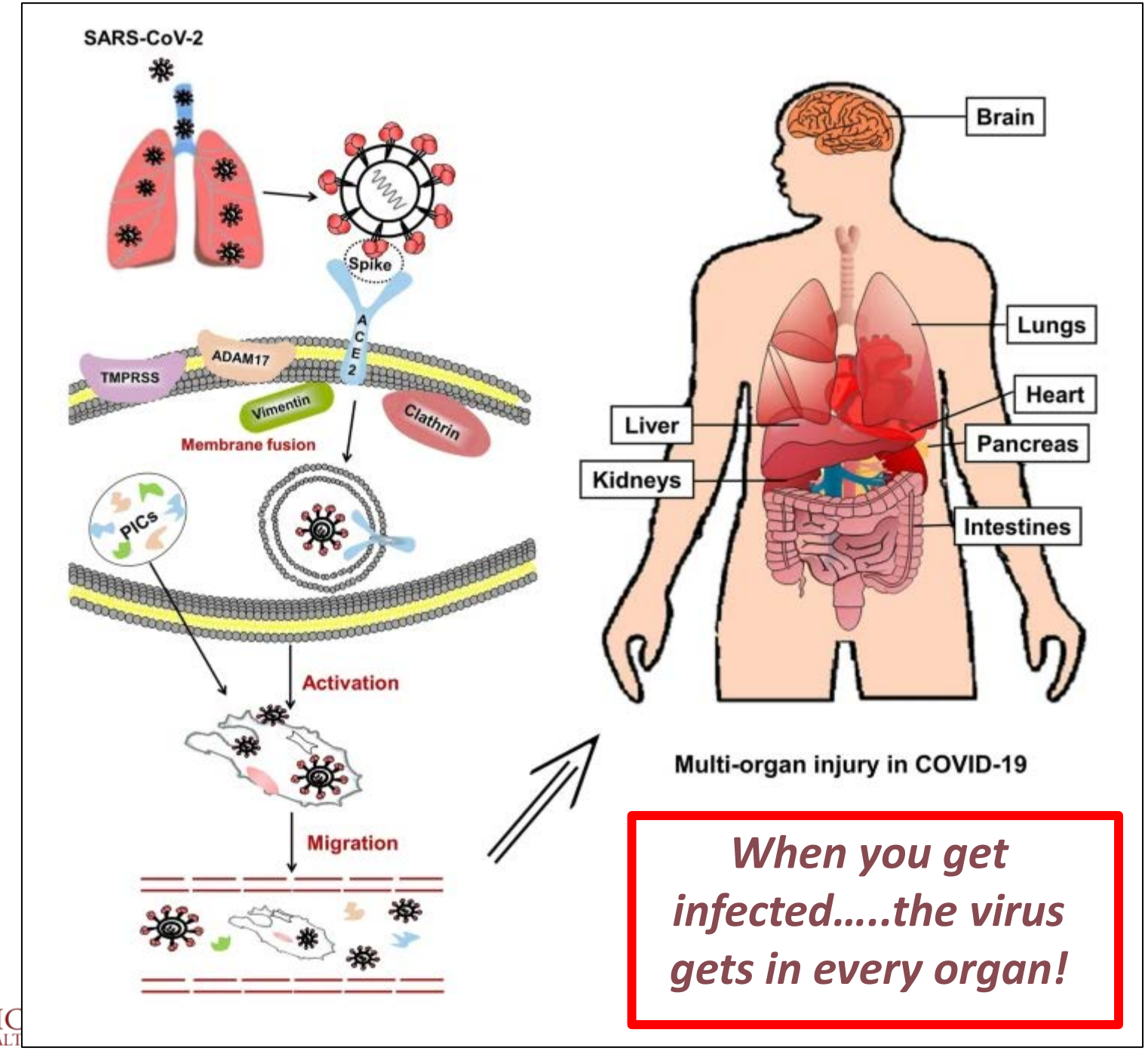
DeLisa Fairweather, Danielle J. Beetler, Damian N. Di Florio, Nicolas Musigk, Bettina Heidecker, Leslie T. Cooper Jr

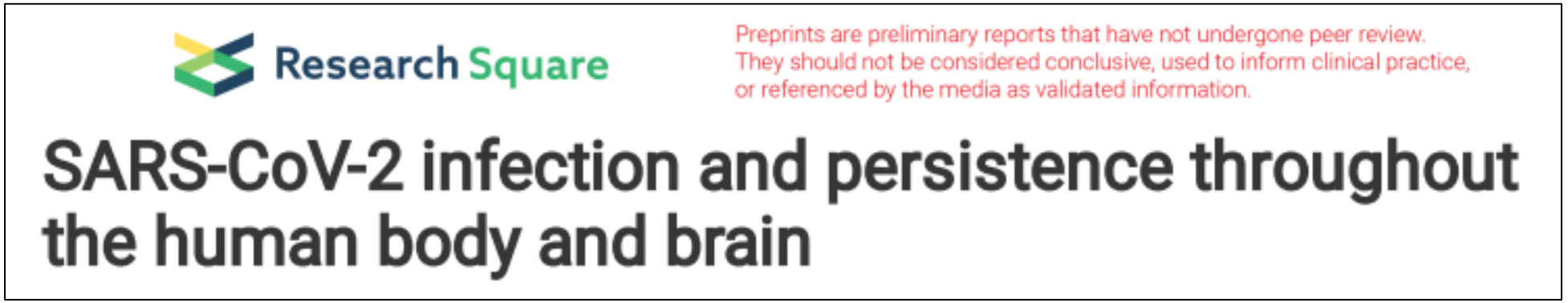
"The incidence of myocarditis pre-COVID was reported at 1 to 10 cases/100,000 individuals and with COVID ranging from 150 to 4000 cases/100,000 individuals."

Study funded by the NIH, American Heart Association, and the Mayo Clinic

Despite of all of the progress, some of our patients will still get infected with SARS-CoV-2

What is the natural history of COVID infection?


SARS-CoV-2
Spike
ACE2
TMPRSS
ADAM17
Vimentin
Clathrin
Membrane fusion
PICs
Activation
Migration
Brain
Lungs
Heart
Liver
Pancreas
Kidneys
Intestines
Multi-organ injury in COVID-19
When you get infected…..the virus gets in every organ!



- ***Autopsy study of 44 people who died after recovery from COVID-19***

- ***Extensive tissue sampling from throughout the bodies looking for long-term persistent SARS-CoV-2 virus***

https://assets.researchsquare.com/files/rs-1139035/v1_covered.pdf?c=1640020576

Study Findings – are there viral reservoirs?

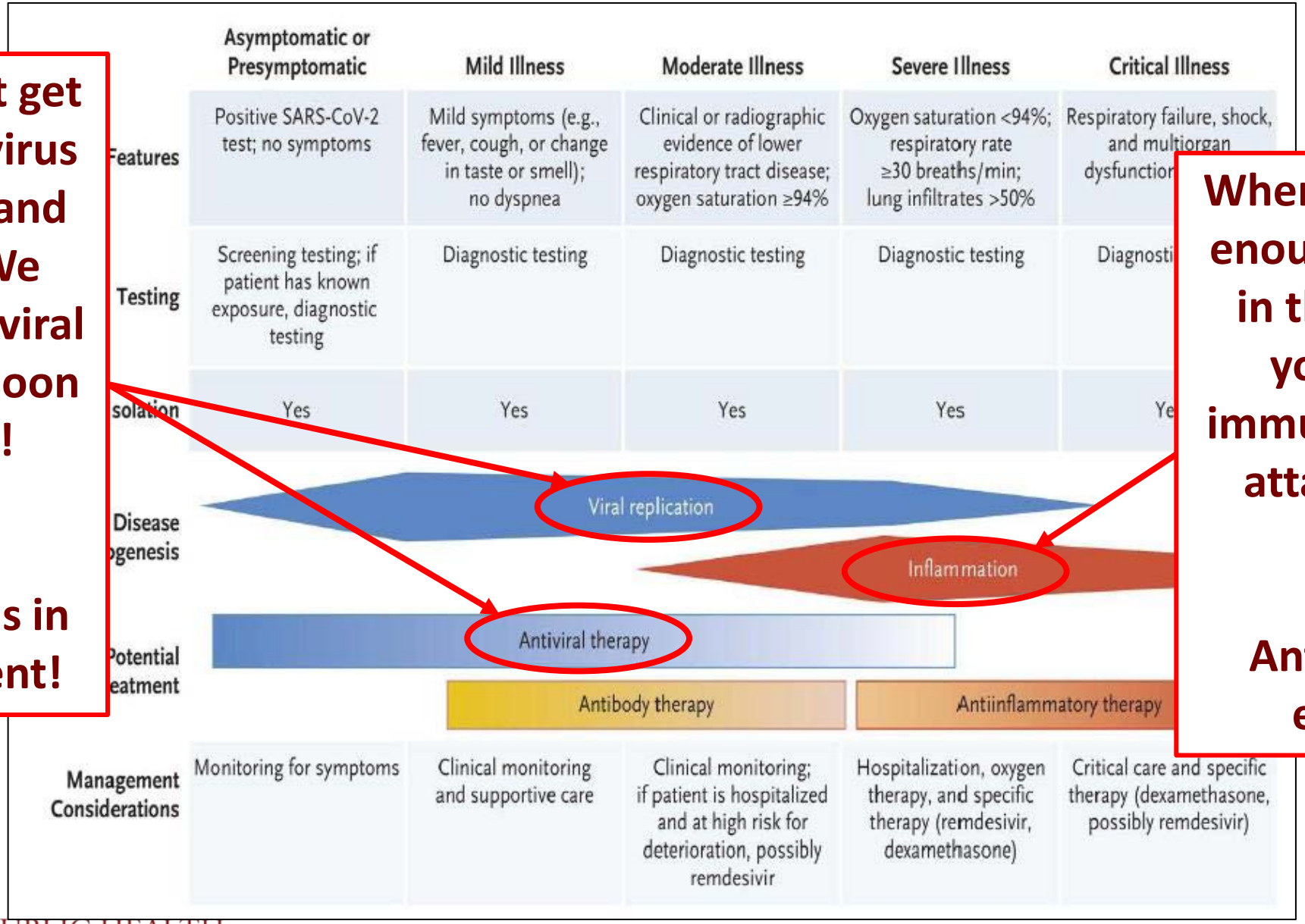
"We show that SARS-CoV-2 is widely distributed, even among patients who died with asymptomatic to 76 mild COVID-19, and that virus replication is present in multiple pulmonary and extrapulmonary tissues early in infection. Further, we detected persistent SARS-CoV-2 RNA in multiple anatomic sites, including regions throughout the brain, for up to 230 days following symptom onset."

https://assets.researchsquare.com/files/rs-1139035/v1_covered.pdf?c=1640020576

COVID Disease Progression

When you first get infected, the virus is replicating and spreading. We treat with antiviral medicines as soon as possible!

Don't take corticosteroids in early treatment!



When you are sick enough to end up in the hospital, your body's immune system is attacking your organs!

Antivirals less effective!

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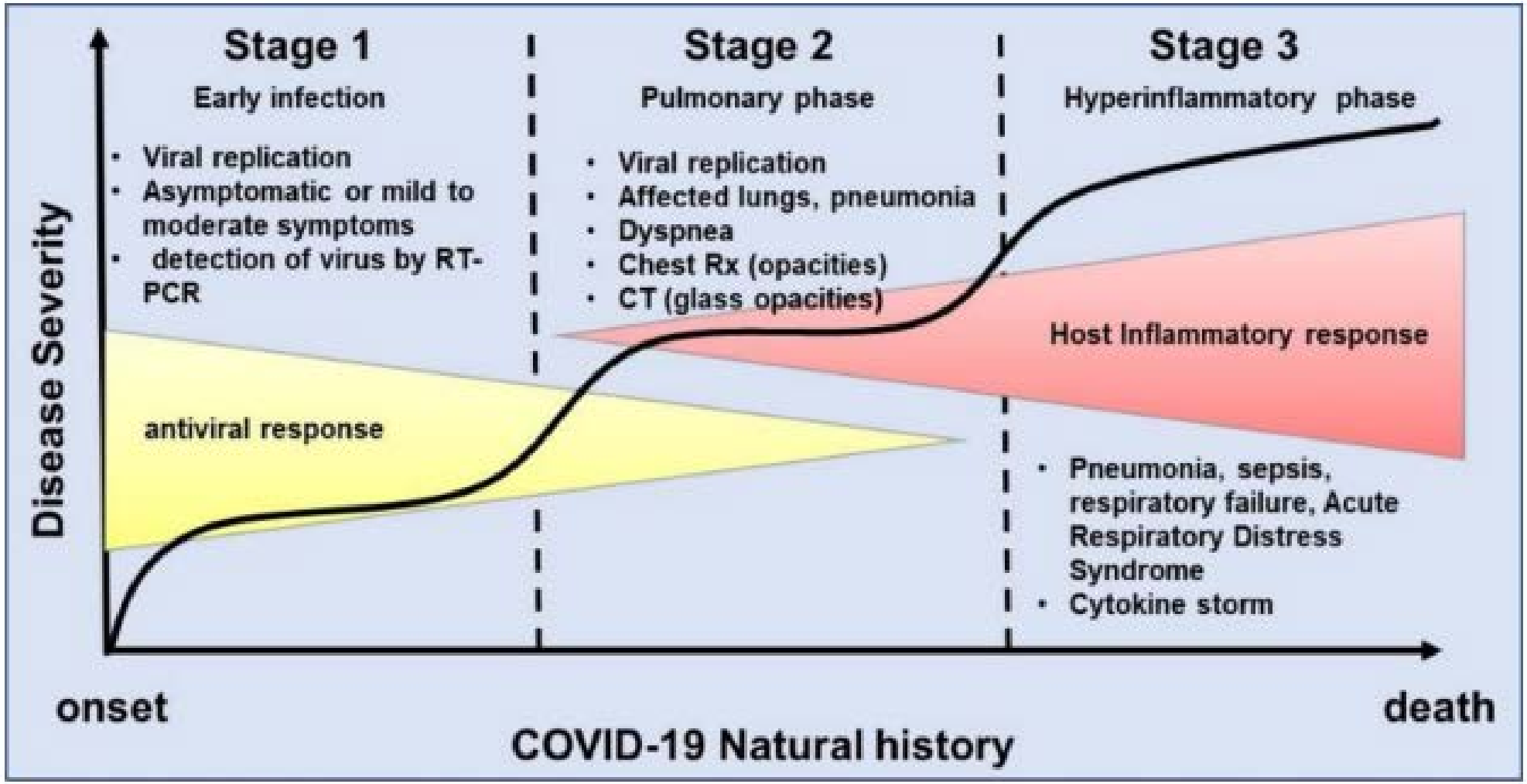
N Engl J Med. 2020 Oct 29;383.



Biomedicine & Pharmacotherapy, Volume 129, September 2020
https://doi.org/10.1016/j.biopha.2020.110493

What do we do when someone tests positive?

Well, this is what I do…..

- Assess the risk for severe disease….are they:
  - Elderly,
  - Immunocompro
  - Have underlying chro

Most patients with bad COVID start off with mild symptoms!

- If I answer "yes" to any of the a symptoms, I start treatment with antiviral medication POSSIBLE. I do not wait for someone to get sick befo

NIH Guidelines for Treatment of Non-hospitalized Adults

Patients Who Are at High Risk of Progressing to Severe COVID-19[b,c,d]
CLOSE −
Preferred therapies. Listed in order of preference: • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[e] **(AIIa)**. Start as soon as possible and within 5 days of symptom onset. See footnote on drug-drug interactions.[f] • **Remdesivir**[e,g] **(BIIa)**. Start as soon as possible and within 7 days of symptom onset. *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:*[h] • **Molnupiravir**[e,i] **(CIIa)**. Start as soon as possible and within 5 days of symptom onset. There is insufficient evidence for the Panel to recommend either for or against initiating these antiviral agents after the timeframes listed above.

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/

What if someone in the hospital for other reasons tests positive for COVID-19?

Hospitalized for Reasons Other Than COVID-19		
CLOSE –		
Clinical Scenario	**Antiviral or Immunomodulator Therapy Recommendation**	**Anticoagulant Therapy Recommendation**
Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.[b]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients

Example:

Patient with decompensated cirrhosis in the hospital who developed URI symptoms and subsequently tested positive on day 9 of their hospital stay.

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

NIH Guidelines for Treatment of Non-hospitalized Adults

- Symptom management should be initiated for all patients **(AIII)**.
- The Panel **recommends against** the use of **dexamethasone**[a] or other systemic corticosteroids in the absence of another indication **(AIIb)**.

[a] There is currently a lack of safety and efficacy data on the use of dexamethasone in outpatients with COVID-19. Using systemic glucocorticoids in outpatients with COVID-19 may cause harm.

https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/

What did the randomized trials of COVID antivirals show?

- **Ritonavir-boosted Nirmatrelvir** (multiple drug-drug interactions, can't use if eGFR < 30 ml/min)
  - 89% effective at preventing hospitalization and death[1]

- **Remdesivir (an IV infusion)**
  - 86% effective at preventing hospitalization and death[2]

- **Molnupiravir** (cannot be used in < 18-year-olds and in pregnancy)
  - 31% effective at preventing hospitalization and death[3]

1. Hammond J, et al. *N Engl J Med*. 2022:386.
2. https://www.nejm.org/doi/full/10.1056/NEJMoa2116846
3. *N Engl J Med* 2022;386:509-20.

The Journal of Infectious Diseases

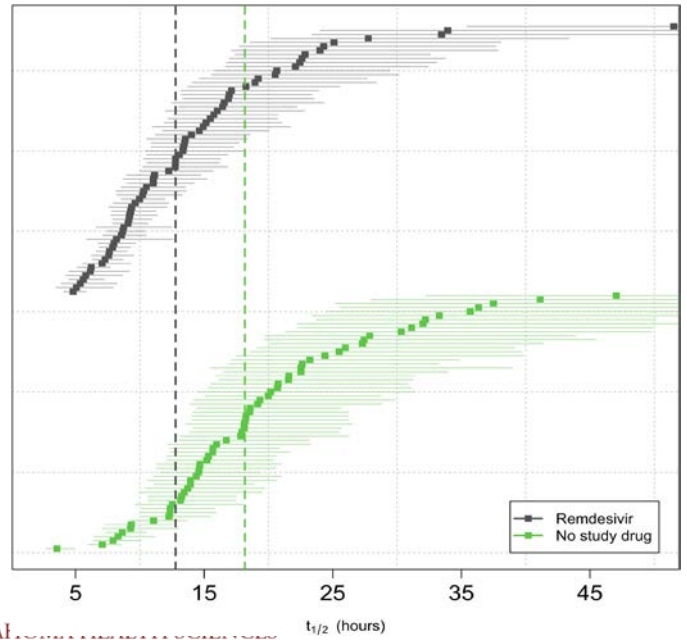
MAJOR ARTICLE

Clinical Antiviral Efficacy of Remdesivir in Coronavirus Disease 2019: An Open-Label, Randomized Controlled Adaptive Platform Trial (PLATCOV)

Podjanee Jittamala,[1,2,a] William H. K. Schilling,[1,3,a,©] James A. Watson,[1,3,©] Viravarn Luvira,[4] Tanaya Siripoon,[4] Thundon Ngamprasertchai,[4] Pedro J. Almeida,[5] Maneerat Ekkapongpisit,[1] Cintia Cruz,[1,3] James J. Callery,[1,3] Simon Boyd,[1,3] Orawan Anunsittichai,[1] Maliwan Hongsuwan,[1] Yutatirat Singhaboot,[4] Watcharee Pagornrat,[1] Runch Tuntipaiboontana,[1] Varaporn Kruabkontho,[1] Thatsanun Ngernseng,[1] Jaruwan Tubprasert,[1] Mohammad Yazid Abdad,[1,3] Srisuda Keayarsa,[4] Wanassanan Madmanee,[1] Renato S. Aguiar,[6] Franciele M. Santos,[6] Elizabeth M. Batty,[1,3] Pongtorn Hanboonkunupakarn,[7] Borimas Hanboonkunupakarn,[1,4] Sakol Sookprome,[7] Kittiyod Poovorawan,[1,4] Mallika Imwong,[1,8] Walter R. J. Taylor,[1,3] Vasin Chotivanich,[9] Chunlanee Sangketchon,[10] Wiroj Ruksakul,[9] Kesinee Chotivanich,[1,4] Sasithon Pukrittayakamee,[1,4] Arjen M. Dondorp,[1,3,©] Nicholas P. J. Day,[1,3] Mauro M. Teixeira,[5] Watcharapong Piyaphanee,[4,©] Weerapong Phumratanaprapin;[4] and Nicholas J. White;[1,3] for the PLATCOV Collaborative Group

"It is now appreciated that anti-viral medications are more effective early in COVID-19 infections when viral burdens are highest, and they provide less benefit later in the course of illness in hospitalized patients where anti-inflammatory interventions show life-saving benefit."

Viral clearance half-lives



Conclusion: *"Parenteral remdesivir accelerates viral clearance in early symptomatic COVID-19."*

The Journal of Infectious Diseases, jiad275, https://doi.org/10.1093/infdis/jiad275
Published: 20 July 2023

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Case History – 2

- An 83-year-old female developed fever, cough, myalgias and headache. She went to urgent care where her rapid COVID test was positive. They gave the patient an injection of methylprednisolone and sent her home. The family called concerned that she seemed quite ill and likely needed treatment. They had previously lost a family member to the disease.
  - Though the patient lived independently, she had numerous medical problems including chronic atrial fibrillation (on apixaban), congestive heart failure, hypertension, hyperlipidemia (on atorvastatin), and chronic renal disease. Her recently tested eGFR was 36 (mL/min).

Is this patient at risk of complications of COVID-19? What is the appropriate treatment for this non-hospitalized patient with COVID-19?

Case History – 3

- She is at incredibly high risk for complications of COVID-19 including hospitalization and death.

- Despite her extensive medical history and renal insufficiency, she is a candidate for any one of the three approved antiviral medications
  - Ritonavir-boosted nirmatrelvir
  - Remdesivir (IV daily for three days)
  - Molnupiravir

Patient Eligibility Screening Checklist Tool for Prescribers

This checklist is intended as an aid to support clinical decision making for prescribers. However, use of this checklist is not required to prescribe under the EUA.

Medical History

- ❑ Has mild to moderate COVID-19[1]
- ❑ Age ≥ 18 years OR ≥ 12 years of age and weighing at least 40 kg
- ❑ Has one or more risk factors for progression to severe COVID-19[2]
- ❑ Symptom onset within 5 days (Prescriber is encouraged to include a note to the pharmacist in the prescription stating: Please fill prescription by [insert date]. This prescription date is within 5 days from symptom onset and complies with the patient eligibility the EUA.)
- ❑ Not requiring hospitalization due to severe or critical COVI
- ❑ No known or suspected severe renal impairment (eC
  - Note that a dose reduction is required for mpairment (eGFR ≥30-<60 mL/min); see the Fact
  - To assess renal function:
    - Physicians, advan and physician assistants who are licensed or authorize drugs may rely on patient history and access to the pati an assessment regarding the likelihood of renal im der ordering a serum creatinine or calculating the on rate (eGFR) for certain patients after assessment on a ed on history or exam.
    - harmacists must have sufficient information available, such as through ealth records less than 12 months old or consultation with a health care er in an established provider-patient relationship with the individual patient; see he Fact Sheet for Healthcare Providers.
- ❑ No k or suspected severe hepatic impairment (Child-Pugh Class C)
  - To assess hepatic impairment:
    - Physicians, advanced practice registered nurses, and physician assistants who are licensed or authorized under state law to prescribe drugs may rely on patient history and access to the patient's health records to make an assessment regarding the likelihood of hepatic impairment.
    - State-licensed pharmacists must have sufficient information available, such as through access to health records less than 12 months old or consultation with a health care provider in an established provider-patient relationship with the individual patient; see the Fact Sheet for Healthcare Providers.

Risk assessment

[1] https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/#:~:text=Patients%20with%20mild%20illness%20may,on%20exertion%2C%20or%20abnormal%20imaging

[2] Determining whether a patient is at high risk for progression to severe COVID-19, including hospitalization or death, is based on the provider's assessment of the individual patient being considered for treatment of COVID-19 and that patient's medical history. For information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the Centers for Disease Control and Prevention (CDC) website: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

https://www.fda.gov/media/158165/download

Patient Eligibility Screening Checklist Tool for Prescribers

Other Drugs with Established and Other Potentially Significant Drug Interactions with (listed alphabetically by generic name)

Interaction Codes:

XXX — Coadministration of this drug with PAXLOVID is CONTRAINDICATED. For further information, refer to the Fact Sheet for Healthcare Providers and the individual Prescribing Information for the drug.

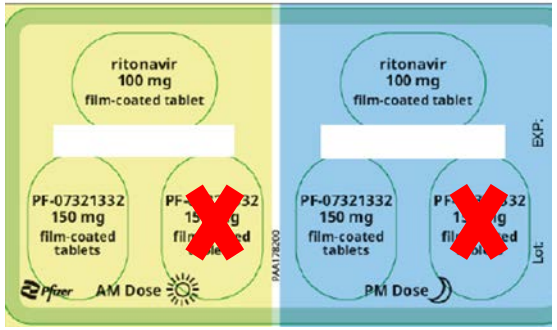
Coadministration of this drug with PAXLOVID should be avoided d/or holding of this drug, dose adjustment of this drug, or special ing is necessary. Consultation with the prescriber of the teracting drug is recommended. For further information, Care Provider Fact Sheet and the individual for the drug.

Drug-drug Interactions

The table below provides a list drug interactions, including contraindicated drugs, in addition to mitant Medications above (HMG-CoA reductase inhibitors [statins], ontaining ethinyl estradiol, and medications for HIV-1 treatment, ***are a guide and are not considered a comprehensive list of all poss ct with PAXLOVID. The healthcare provider should consult othe ch as the prescribing information for the interacting drug for compreh ng or monitoring with concomitant use of a strong CYP3A inhibitor su***

Drug	Drug Class	Co n
abemaciclib	Anticancer drug	***
alfuzosin	Alpha 1-adrenoreceptor antagonist	XXX
aliskiren	Cardiovascular agent	***
amiodarone	Antiarrhythmic	XXX
amlodipine	Calcium channel blocker	***
apalutamide	Anticancer drug	XXX
apixaban	Anticoagulant	***
aripiprazole	Neuropsychiatric agent	***
avanafil	PDE5 inhibitor	***
bedaquiline	Antimycobacterial	***
betamethasone	Systemic corticosteroid	***
brexpiprazole	Neuropsychiatric agent	***
bosentan	Endothelin receptor antagonist	***
budesonide	Systemic corticosteroid	***
bupropion	Antidepressant	***

Case History – 3



- Elected to treat the patient with ritonavir-boosted nirmatrelvir but that required:
  - Stopping atorvastatin during treatment
  - Reducing the patient's apixaban from 2.5 mg twice daily to 2.5 mg once a day
  - Because her eGFR was only 36 mL/min, we worked with the pharmacist on dispensing the nirmatrelvir.
    - Dose modified to 100 mg ritonavir + one 150 mg nirmatrelvir tablet twice a day for 5 days*

- Remdesivir (200 mg IV on day one, then 100 mg IV on days 2 and 3) was an option but arranging the infusion on the weekend was going to be a challenge and difficult for the patient to do.

*The usual dose of ritonavir-boosted nirmatrelvir is one 100 mg ritonavir pill + two 150 mg nirmatrelvir pills twice a day for 5 days (three pills twice a day) in patients with normal renal function.

Research

JAMA Internal Medicine | Original Investigation

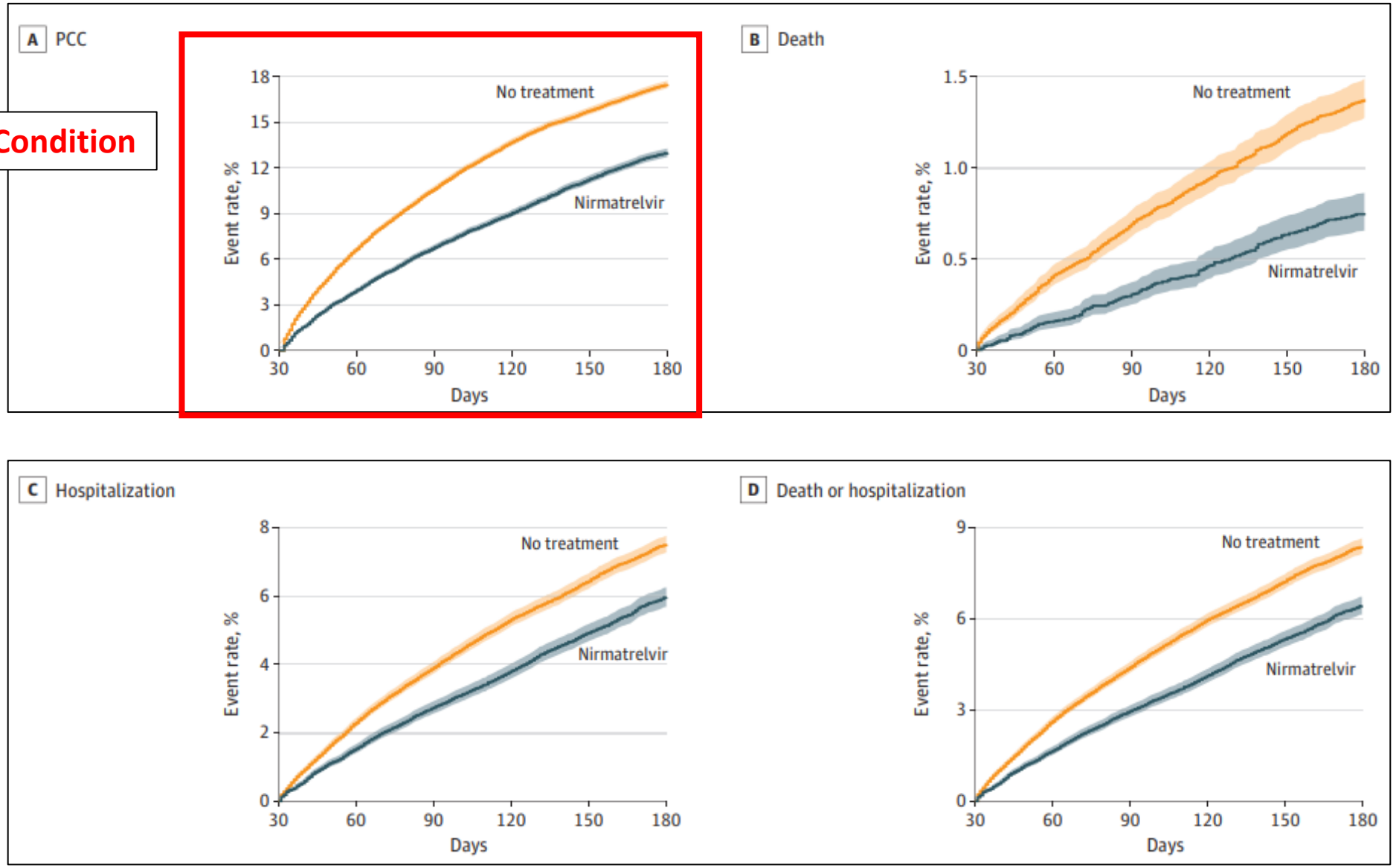
Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition

Yan Xie, PhD; Taeyoung Choi, MPH; Ziyad Al-Aly, MD

Nirmatrelvir was associated with reduced risk of PCC in people who were unvaccinated, vaccinated, and boosted, and in people with primary SARS-CoV-2 infection and reinfection.

JAMA Intern Med. 2023;183(6):554-564. doi:10.1001/jamainternmed.2023.0743
Published online March 23, 2023.

Post COVID Condition



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PCC = Post COVID Condition

JAMA Intern Med. 2023;183(6):554-564. doi:10.1001/jamainternmed.2023.0743
Published online March 23, 2023.

Letters

RESEARCH LETTER

Nirmatrelvir and Molnupiravir and Post–COVID-19 Condition in Older Patients

While the COVID-19 pandemic appears to be winding down, its effects are still felt by the millions of people worldwide experiencing post–COVID-19 condition (PCC, or long COVID).[1] The antiviral drug nirmatrelvir (marketed as Paxlovid [Pfizer], in combination with ritonavir) and molnupiravir (Lagevrio [Merch]) are recommended as first- and second-line treatments for acute illness in patients with specific risk factors (eg, diabetes).[2] However, there are still no US Food and Drug Administration–approved drugs for the treatment or prevention of PCC. Recent studies among US veterans (mostly male) suggest that nirmatrelvir and molnupiravir reduce the risk of some sequelae of COVID-19.[3,4] We performed a cohort study of the 2 drugs in PCC in older patients who were Medicare enrollees.

Supplemental content

"…..among 3,975,690 outpatients with COVID-19, 57% remained in our study after exclusion. Among them, 19.5% received nirmatrelvir and 2.6% received molnupiravir. PCC incidence among patients receiving nirmatrelvir was 11.8%, 13.7% for molnupiravir, and 14.5% for neither, absolute risk reduction was 2.7% for nirmatrelvir, 0.8% for molnupiravir, with hazard ratios (HRs) of 0.87 (95% CI, 0.86-0.88; P < .001) for nirmatrelvir and 0.92 (95% CI, 0.90-0.94; P < .001) for molnupiravir, compared with no treatment…"

JAMA Internal Medicine Published online October 23, 2023

JAMA Health Forum™

Original Investigation

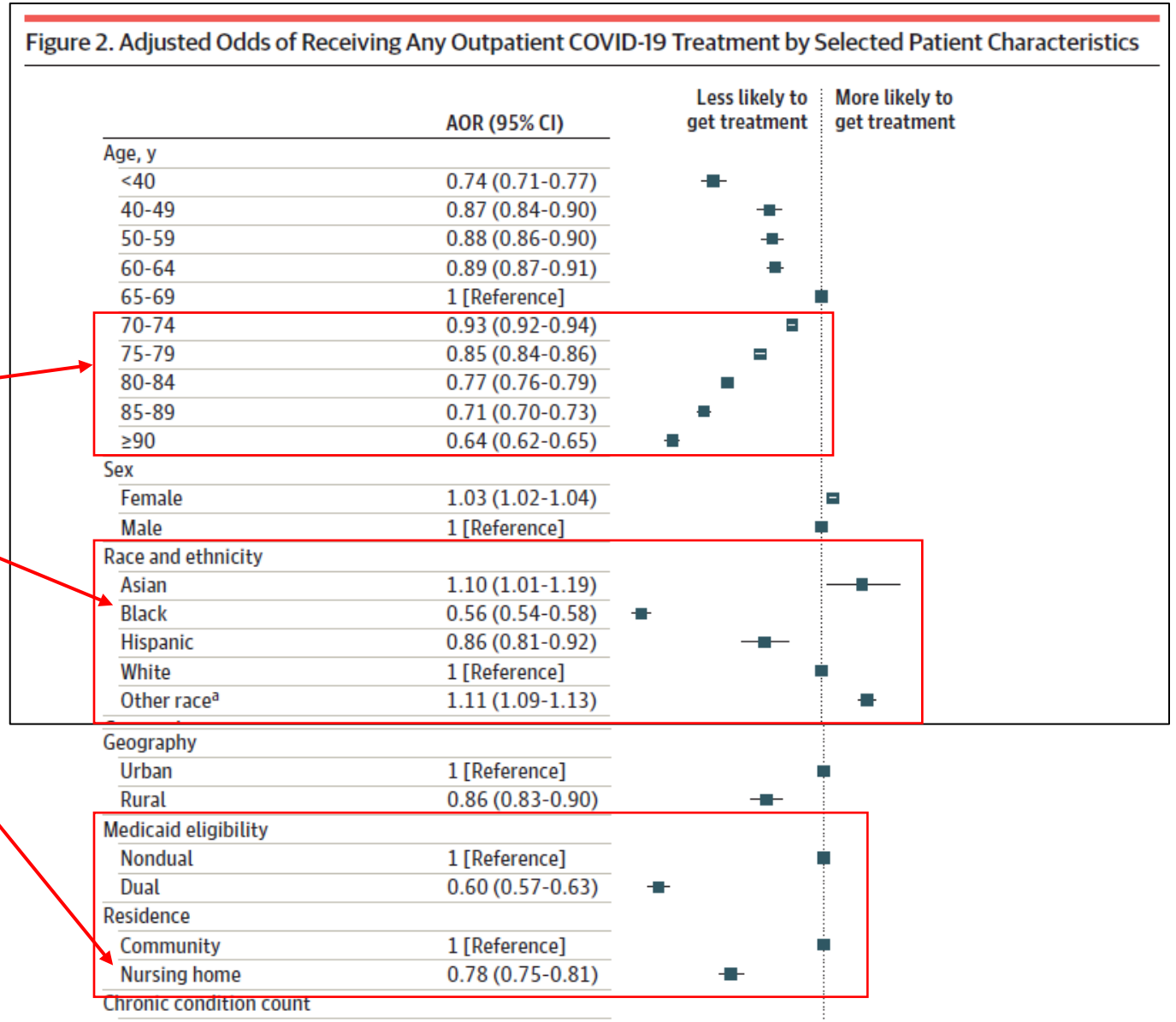
Clinical Risk and Outpatient Therapy Utilization for COVID-19 in the Medicare Population

Andrew D. Wilcock, PhD; Stephen Kissler, PhD; Ateev Mehrotra, MD; Brian E. McGarry, PT, PhD; Benjamin D. Sommers, MD, PhD; David C. Grabowski, PhD; Yonatan H. Grad, MD; Michael L. Barnett, MD

What are we doing???

"In this cross-sectional study of patients enrolled in Medicare in 2022, those at the highest risk for severe COVID-19 infection received COVID-19 therapy less often than those with the least risk. Disparities in therapy access were found by patient age, race and ethnicity, Medicaid eligibility, and nursing home residence."

Figure 2. Adjusted Odds of Receiving Any Outpatient COVID-19 Treatment by Selected Patient Characteristics



	AOR (95% CI)
Age, y	
<40	0.74 (0.71-0.77)
40-49	0.87 (0.84-0.90)
50-59	0.88 (0.86-0.90)
60-64	0.89 (0.87-0.91)
65-69	1 [Reference]
70-74	0.93 (0.92-0.94)
75-79	0.85 (0.84-0.86)
80-84	0.77 (0.76-0.79)
85-89	0.71 (0.70-0.73)
≥90	0.64 (0.62-0.65)
Sex	
Female	1.03 (1.02-1.04)
Male	1 [Reference]
Race and ethnicity	
Asian	1.10 (1.01-1.19)
Black	0.56 (0.54-0.58)
Hispanic	0.86 (0.81-0.92)
White	1 [Reference]
Other race[a]	1.11 (1.09-1.13)
Geography	
Urban	1 [Reference]
Rural	0.86 (0.83-0.90)
Medicaid eligibility	
Nondual	1 [Reference]
Dual	0.60 (0.57-0.63)
Residence	
Community	1 [Reference]
Nursing home	0.78 (0.75-0.81)
Chronic condition count	

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JAMA Health Forum. 2024;5(1):e235044. doi:10.1001/jamahealthforum.2023.5044

Antiviral therapy included nirmatrelvir, molnupiravir, or remdesivir.

Infectious Disease > COVID-19

Why Aren't More Doctors Prescribing Paxlovid to High-Risk Patients?

— It's not all about drug-drug interactions, experts say

by Katherine Kahn, Staff Writer, MedPage Today ; Cheryl Clark, Contributing Writer, MedPage Today January 29, 2024

"…..people on Medicare who were at highest risk for severe COVID-19 were actually less likely to receive outpatient antiviral treatments, such as nirmatrelvir/ritonavir, than Medicare beneficiaries at lower risk…..

…..Moreover, when researchers performed a simulation analysis of data, they found that reallocation of nirmatrelvir/ritonavir according to patient risk could have prevented about 10,300 hospitalizations and 16,500 deaths in 2022 alone…"

"Review of 110 immunosuppressed patients with non-severe COVID-19 at risk for progression who did not receive an antiviral drug found that 80% were not offered such treatment. For nearly one half of these, the only reason given for not offering antiviral treatment was mild symptoms."

How do we explain long-COVID symptoms?

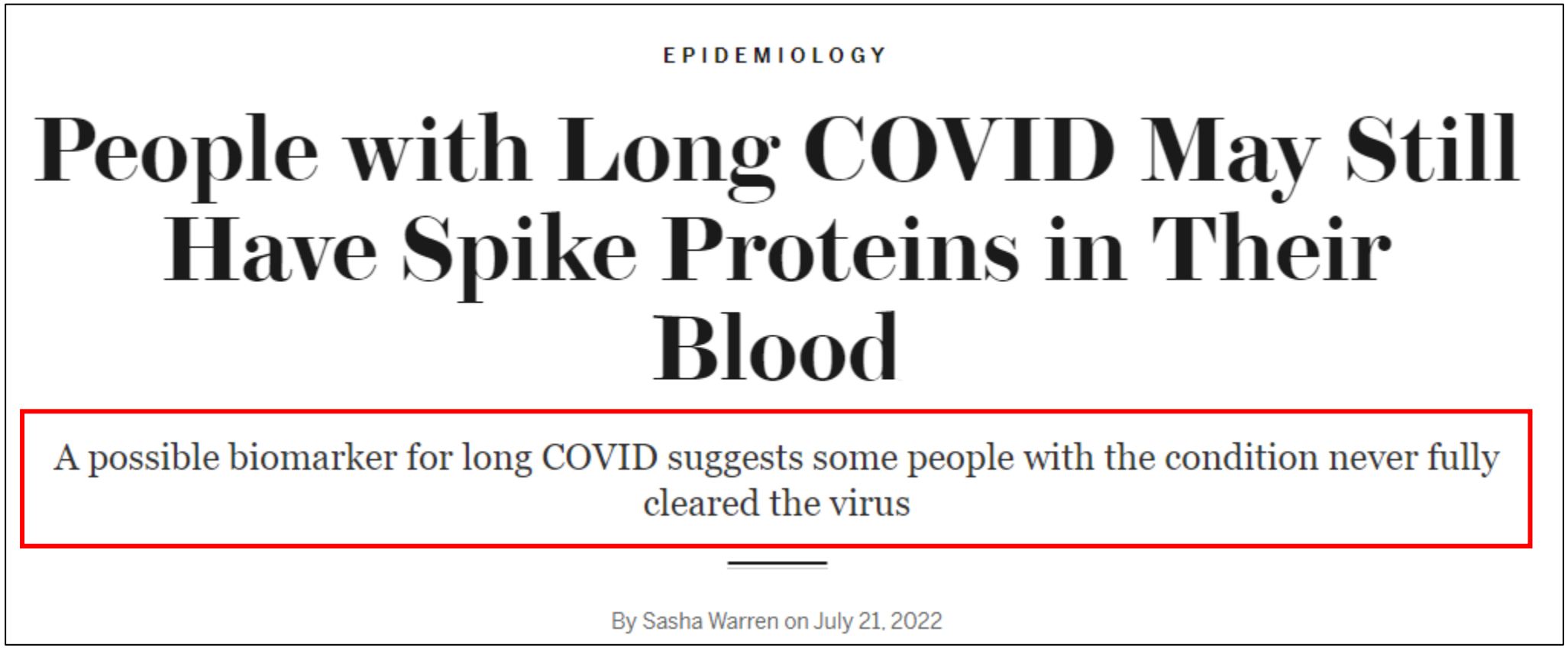
Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

Patients more likely to develop long-COVID symptoms:

- ***Unvaccinated***
- ***Chronically ill patients***
- ***Patients who have more severe disease***

JAMA. doi:10.1001/jama.2023.8823
Published online May 25, 2023.



EPIDEMIOLOGY

People with Long COVID May Still Have Spike Proteins in Their Blood

A possible biomarker for long COVID suggests some people with the condition never fully cleared the virus

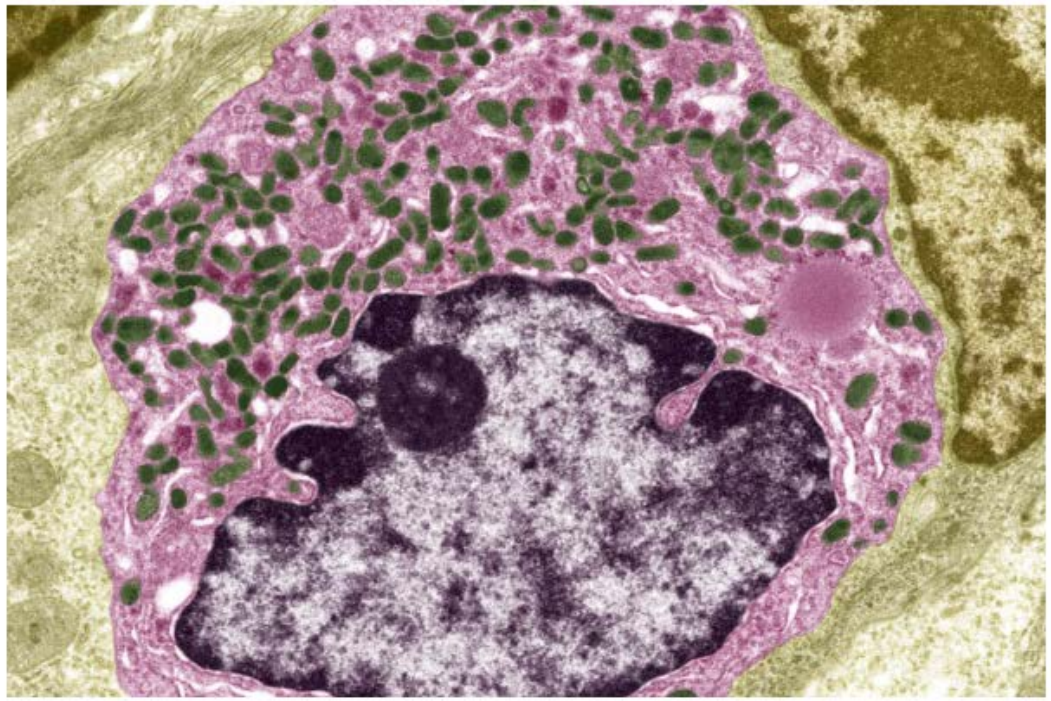
By Sasha Warren on July 21, 2022

".....researchers reported detecting a fragment of SARS-CoV-2 in blood samples from long COVID sufferers up to a year after their original infection."

https://www.scientificamerican.com/article/people-with-long-covid-may-still-have-spike-proteins-in-their-blood1/#:~:text=The%20presence%20and%20intensity%20of,to%20blame%20for%20long%20COVID.

Scientists Offer a New Explanation for Long Covid

In some patients, remnants of the coronavirus in the gut may stifle production of serotonin, an important neurotransmitter, researchers suggest.



A colored transmission electron micrograph showing an intestinal endocrine cell, with granules containing serotonin in green. Steve Gschmeissner/Science Source

By Pam Belluck

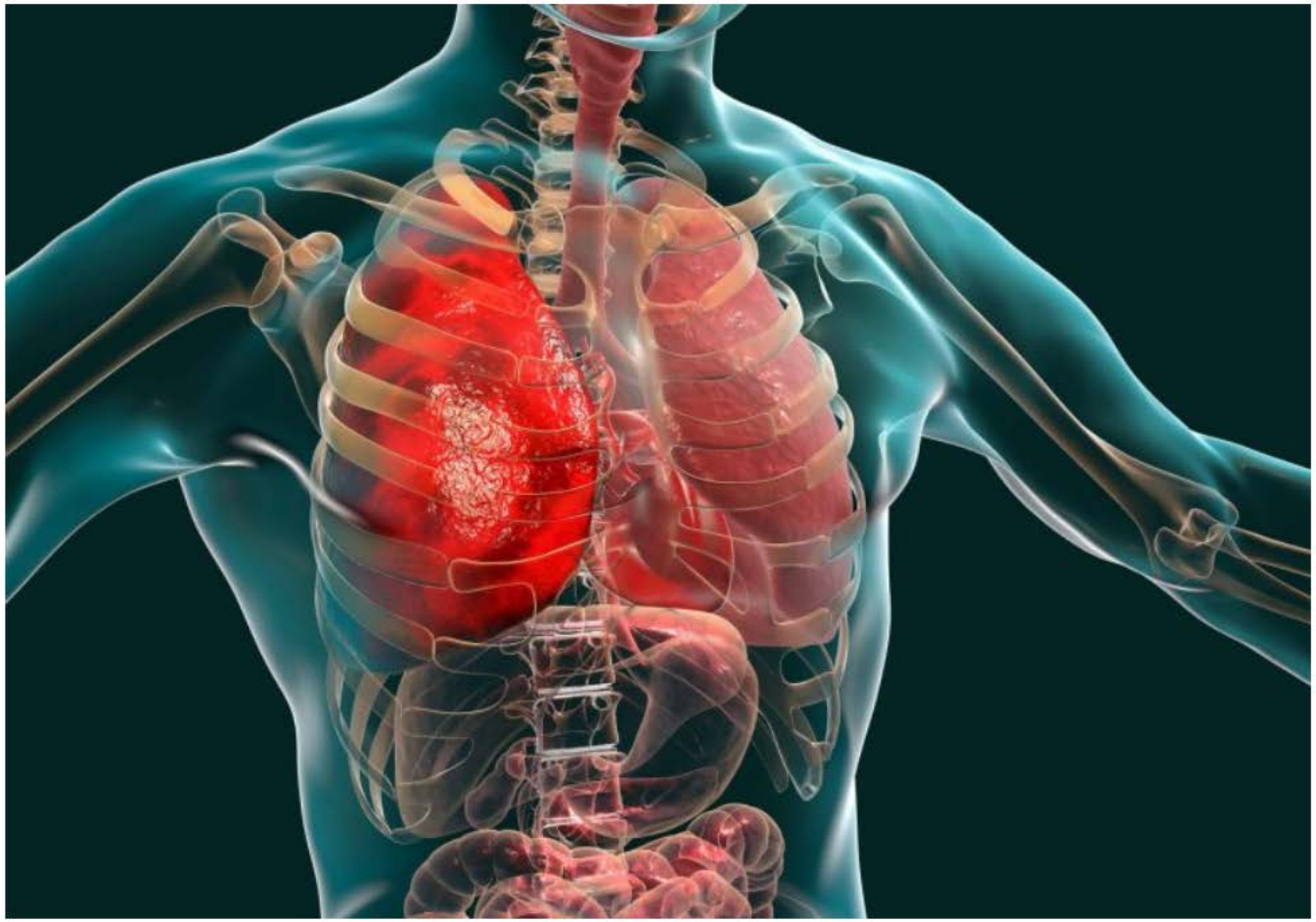
Oct. 16, 2023 Updated 12:15 p.m. ET

Immune mediated

COVID-19 Can Trigger Self-Attacking Antibodies – Even in People That Had No Symptoms of Infection

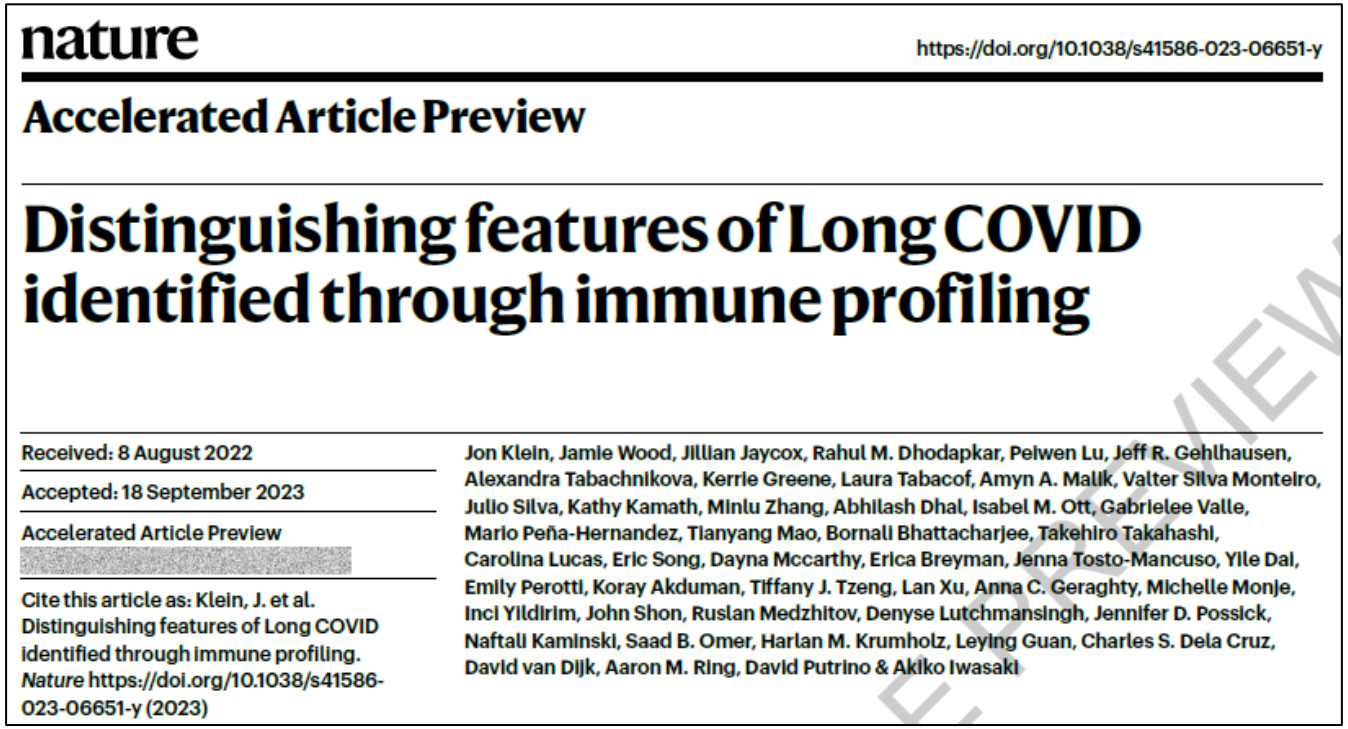
TOPICS: Antibodies Cedars-Sinai Medical Center COVID-19 Immunology Infectious Diseases Popular

By CEDARS-SINAI MEDICAL CENTER JANUARY 6, 2022



Cedars-Sinai Investigators Found Evidence of an Overactive Immune Response.

https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-021-03184-8



nature

https://doi.org/10.1038/s41586-023-06651-y

Accelerated Article Preview

Distinguishing features of Long COVID identified through immune profiling

Received: 8 August 2022

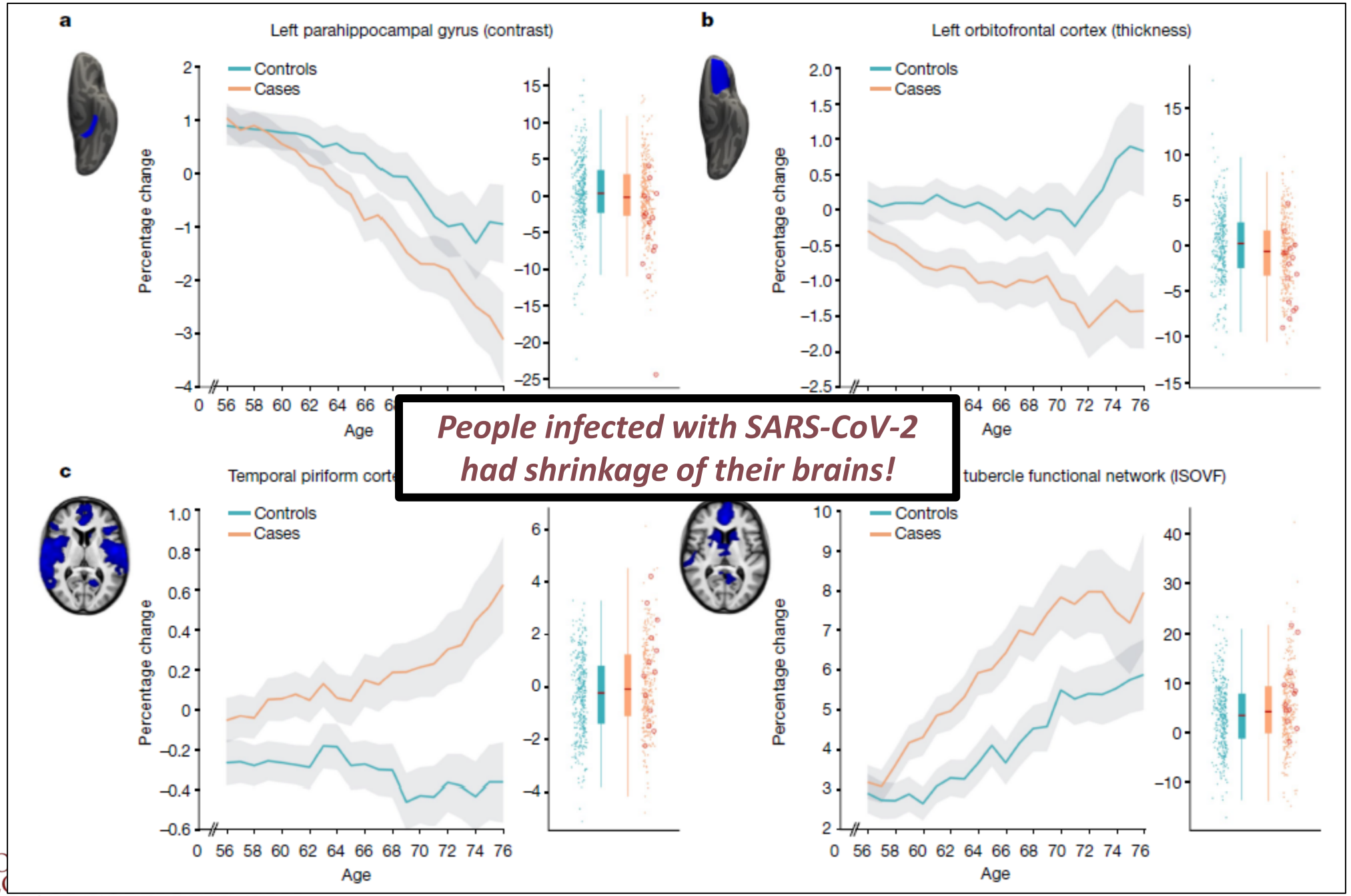
Accepted: 18 September 2023

Accelerated Article Preview

Cite this article as: Klein, J. et al. Distinguishing features of Long COVID identified through immune profiling. *Nature* https://doi.org/10.1038/s41586-023-06651-y (2023)

Jon Klein, Jamie Wood, Jillian Jaycox, Rahul M. Dhodapkar, Peiwen Lu, Jeff R. Gehlhausen, Alexandra Tabachnikova, Kerrie Greene, Laura Tabacof, Amyn A. Malik, Valter Silva Monteiro, Julio Silva, Kathy Kamath, Minlu Zhang, Abhilash Dhal, Isabel M. Ott, Gabrielee Valle, Mario Peña-Hernandez, Tianyang Mao, Bornali Bhattacharjee, Takehiro Takahashi, Carolina Lucas, Eric Song, Dayna Mccarthy, Erica Breyman, Jenna Tosto-Mancuso, Yile Dai, Emily Perotti, Koray Akduman, Tiffany J. Tzeng, Lan Xu, Anna C. Geraghty, Michelle Monje, Inci Yildirim, John Shon, Ruslan Medzhitov, Denyse Lutchmansingh, Jennifer D. Possick, Naftali Kaminski, Saad B. Omer, Harlan M. Krumholz, Leying Guan, Charles S. Dela Cruz, David van Dijk, Aaron M. Ring, David Putrino & Akiko Iwasaki

Here, 273 individuals with or without LC were enrolled in a cross-sectional study that included multi-dimensional immune phenotyping and unbiased machine learning methods to identify biological features associated with LC. Marked differences were noted in circulating myeloid and lymphocyte populations relative to matched controls, as well as evidence of exaggerated humoral responses directed against SARS-CoV-2 among participants with LC.


a
Left parahippocampal gyrus (contrast)
Controls
Cases
Percentage change
Age
b
Left orbitofrontal cortex (thickness)
Controls
Cases
Percentage change
Age
People infected with SARS-CoV-2 had shrinkage of their brains!
c
Temporal piriform corte
Controls
Cases
Percentage change
Age
tubercle functional network (ISOVF)
Controls
Cases
Percentage change
Age

Final thoughts…..

- The nature of infection with SARS-CoV-2 has changed – the elderly and immunosuppressed are at greatest risk of complications and death!
- Vaccination remains the best option to prevent disease complications – antibody titers wane over time (particularly in the elderly)
  - High-risk individuals who test positive for COVID-19 need to receive early antiviral treatment!
- Long COVID symptoms are common – the etiology is being studied but may include persistent viral reservoirs and immune response and inflammation

We can and should do better!

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Geriatrics > General Geriatrics

Do We Simply Not Care About Old People?

— The pandemic was a wake-up call on how we care for older adults

by Judith Graham, KFF Health News February 18, 2024

"The death toll was shocking, as were reports of chaos in nursing homes and seniors suffering from isolation, depression, untreated illness, and neglect. Around 900,000 older adults have died of COVID to date, accounting for three of every four Americans who have perished in the pandemic."

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