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OU Health

Variants, Antibodies, and Antivirals – Where are we at with COVID-19

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September 13, 2023

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.

What do I want you to get from this talk?

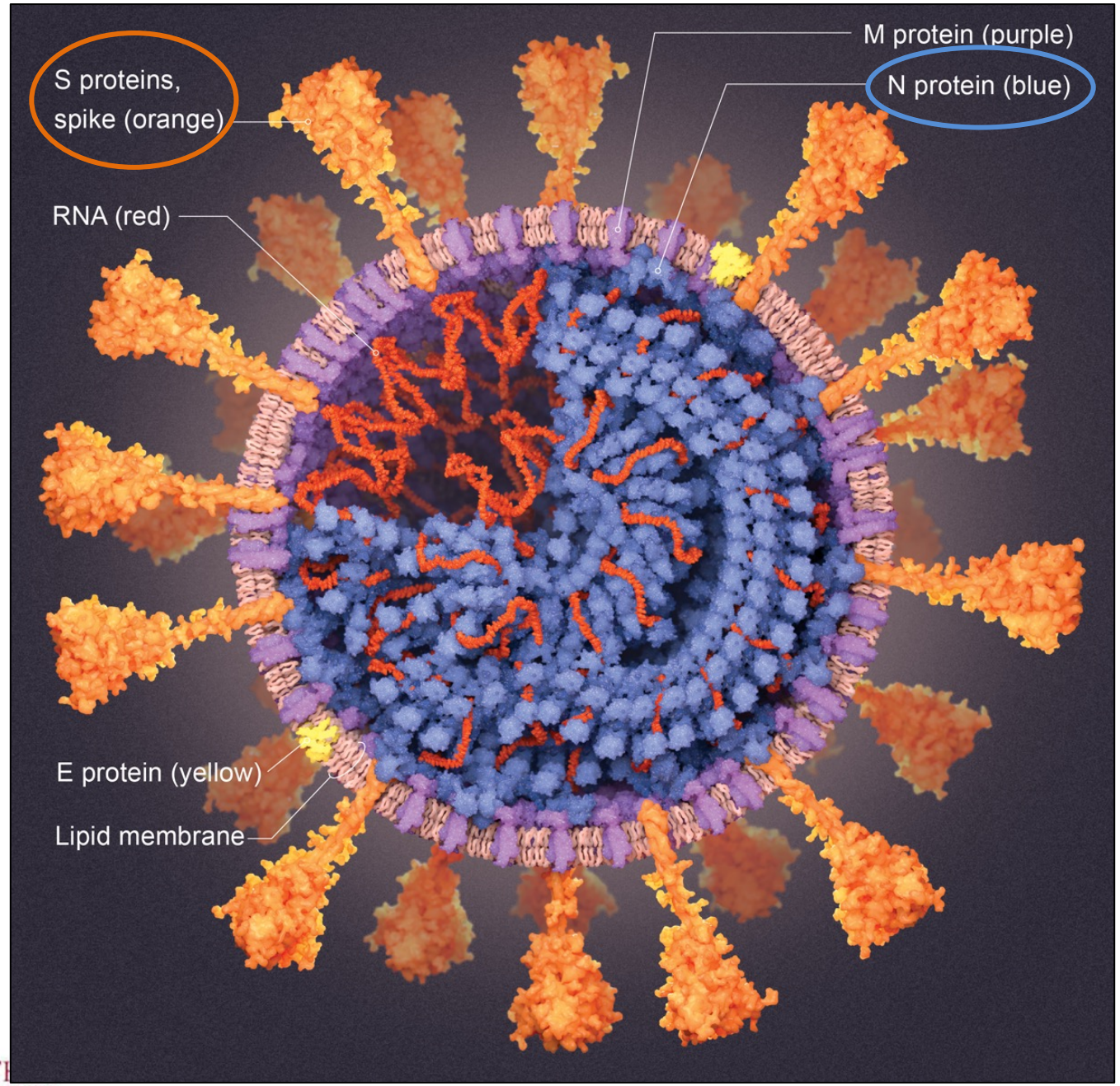
- Understand COVID-19 – where are we at now?
- The natural history of infection with SARS-CoV-2
  - Early disease is characterized by viral replication!
- Who is at risk for complications of the disease?
- What do we do if someone tests positive?
  - Early treatment is key to improved outcomes
- What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

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.

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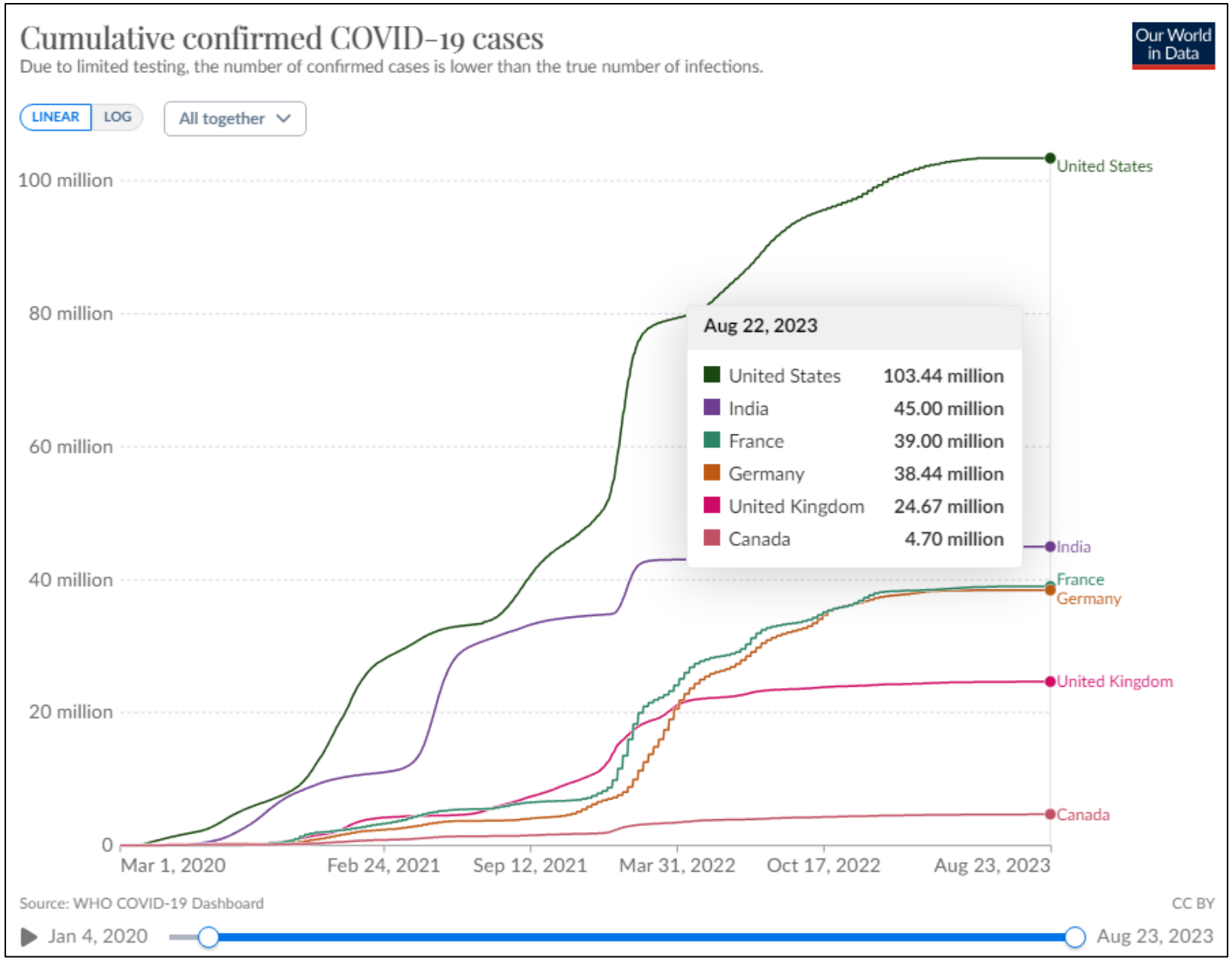
https://www.scientificamerican.com/article/a-visual-guide-to-the-sars-cov-2-coronavirus/



WHO estimates almost 7 million deaths worldwide!

United States:

- **107,107,491 Cases**
- **6,272,227 hospitalizations**
- **1,138,602 Deaths**
- **676,728,782 Vaccine doses**

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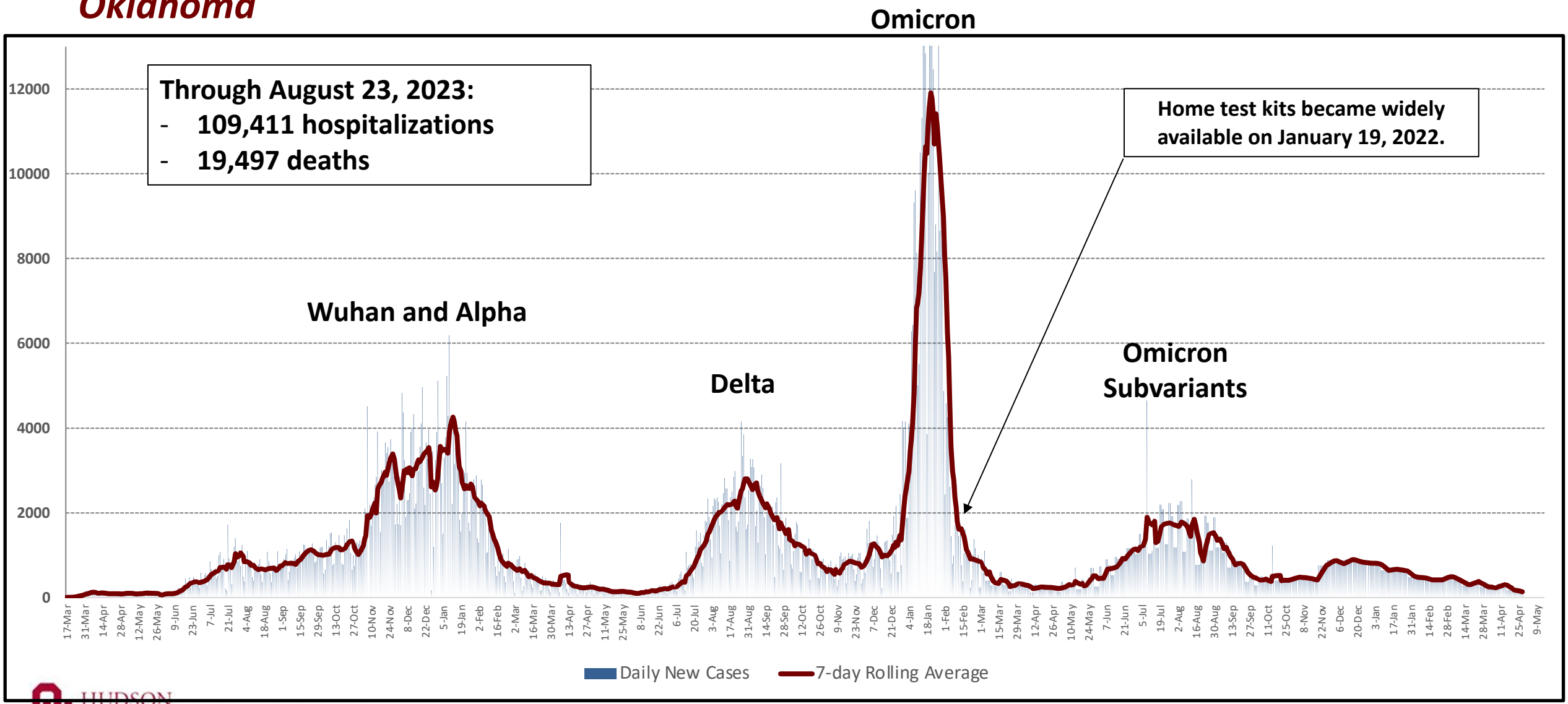
US data as of August 29, 2023, from the CDC.
https://covid.cdc.gov/covid-data-tracker

Daily New Cases with 7-day Rolling Average

Oklahoma



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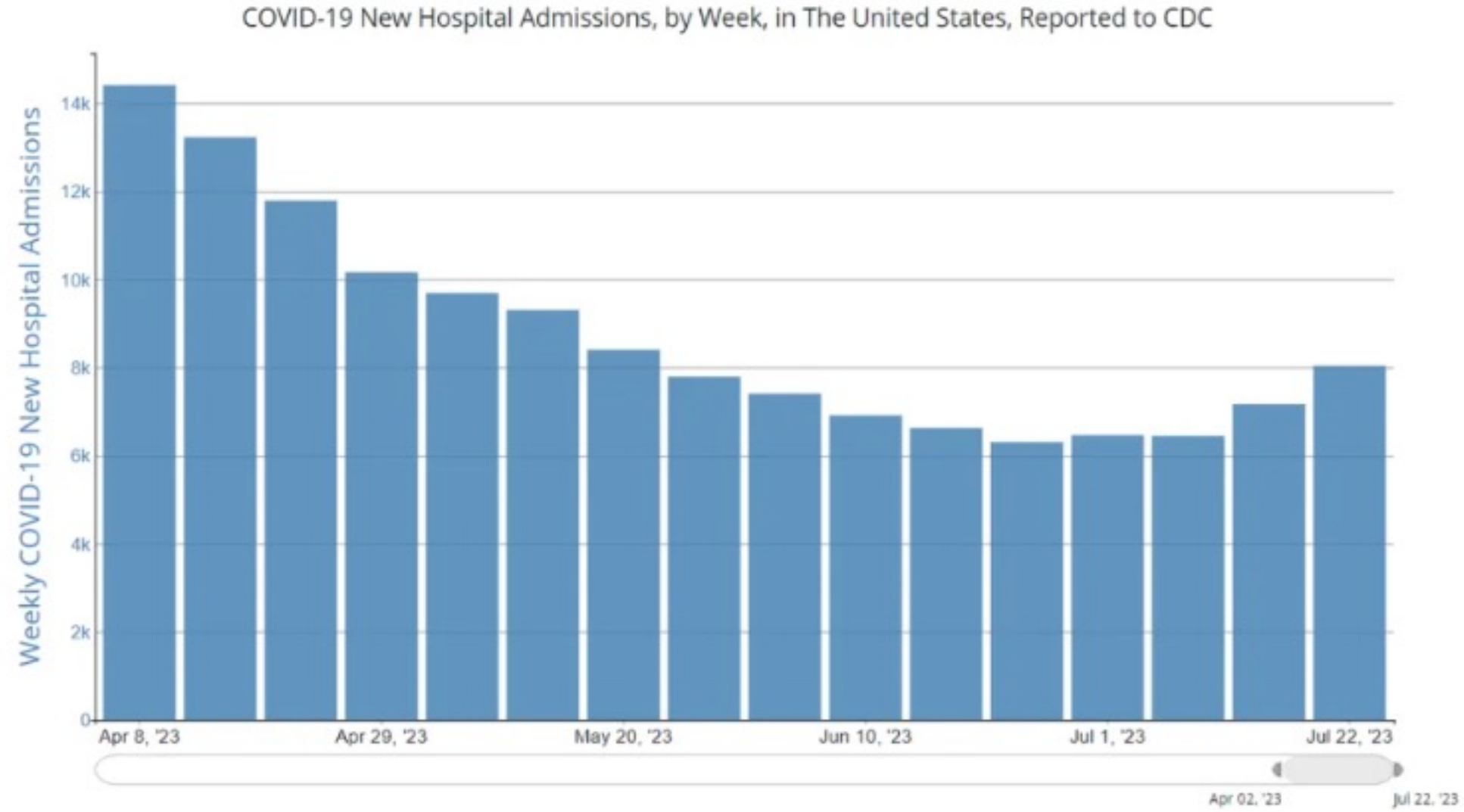
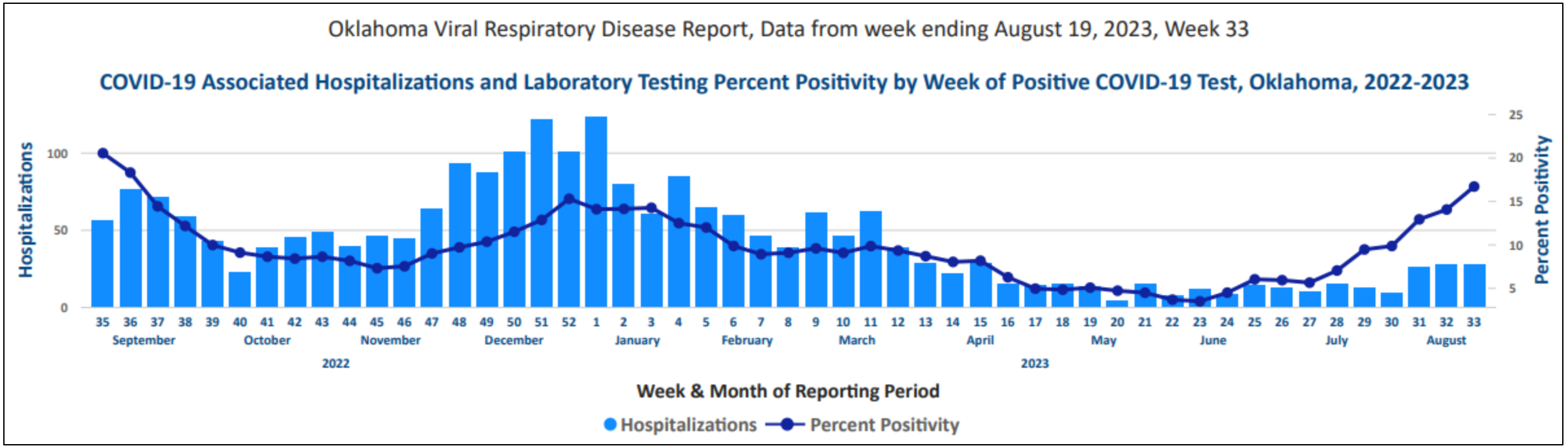
https://covid.cdc.gov/covid-data-tracker/#maps_new-admissions-rate-state

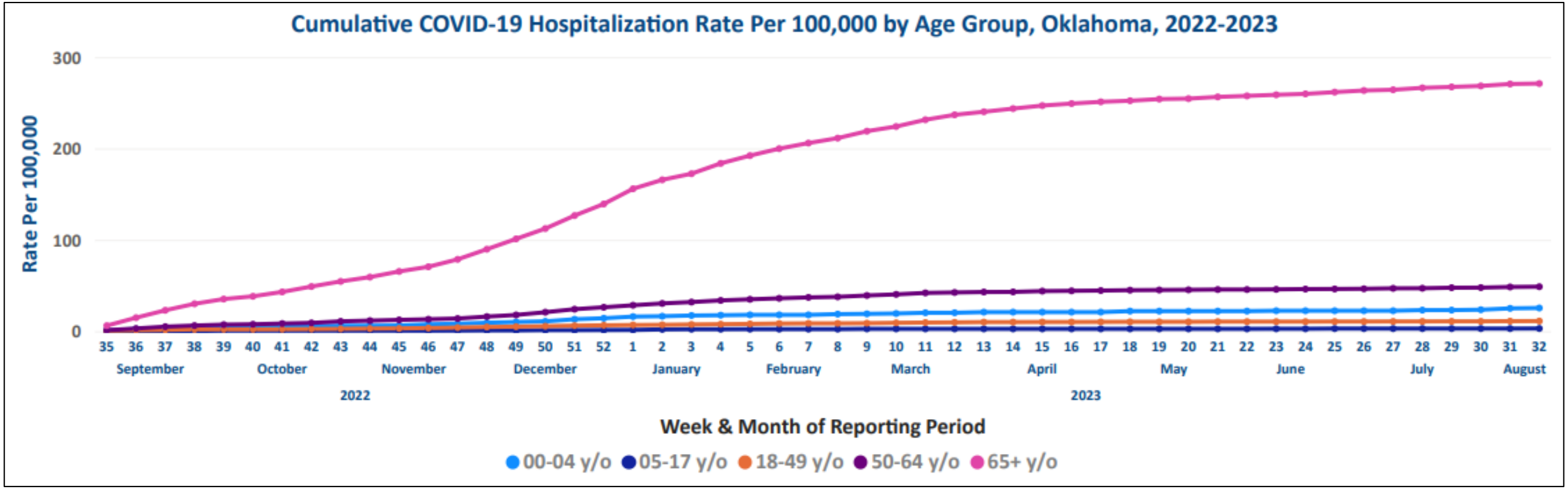
Cases and hospitalizations are rising again!



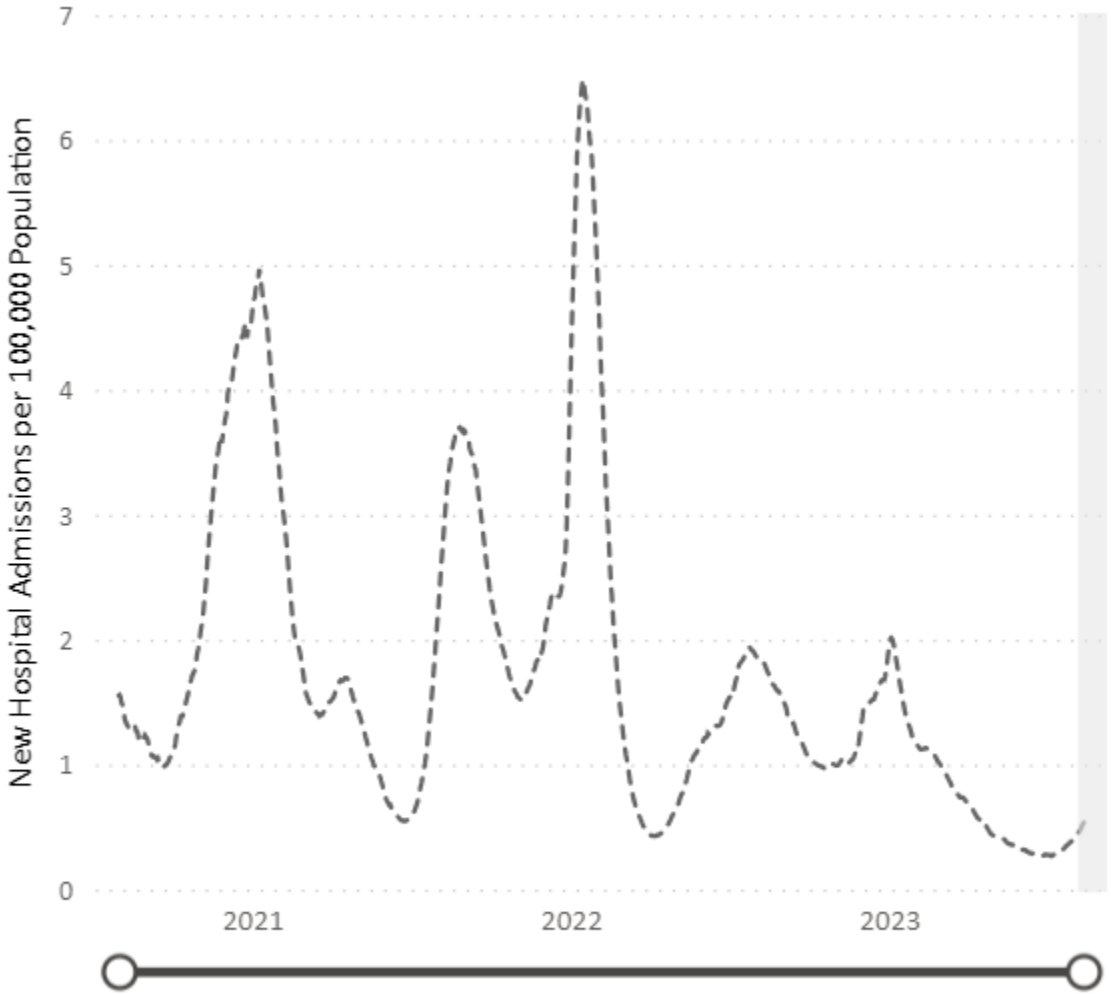
Oklahoma Data – test positivity is way up!

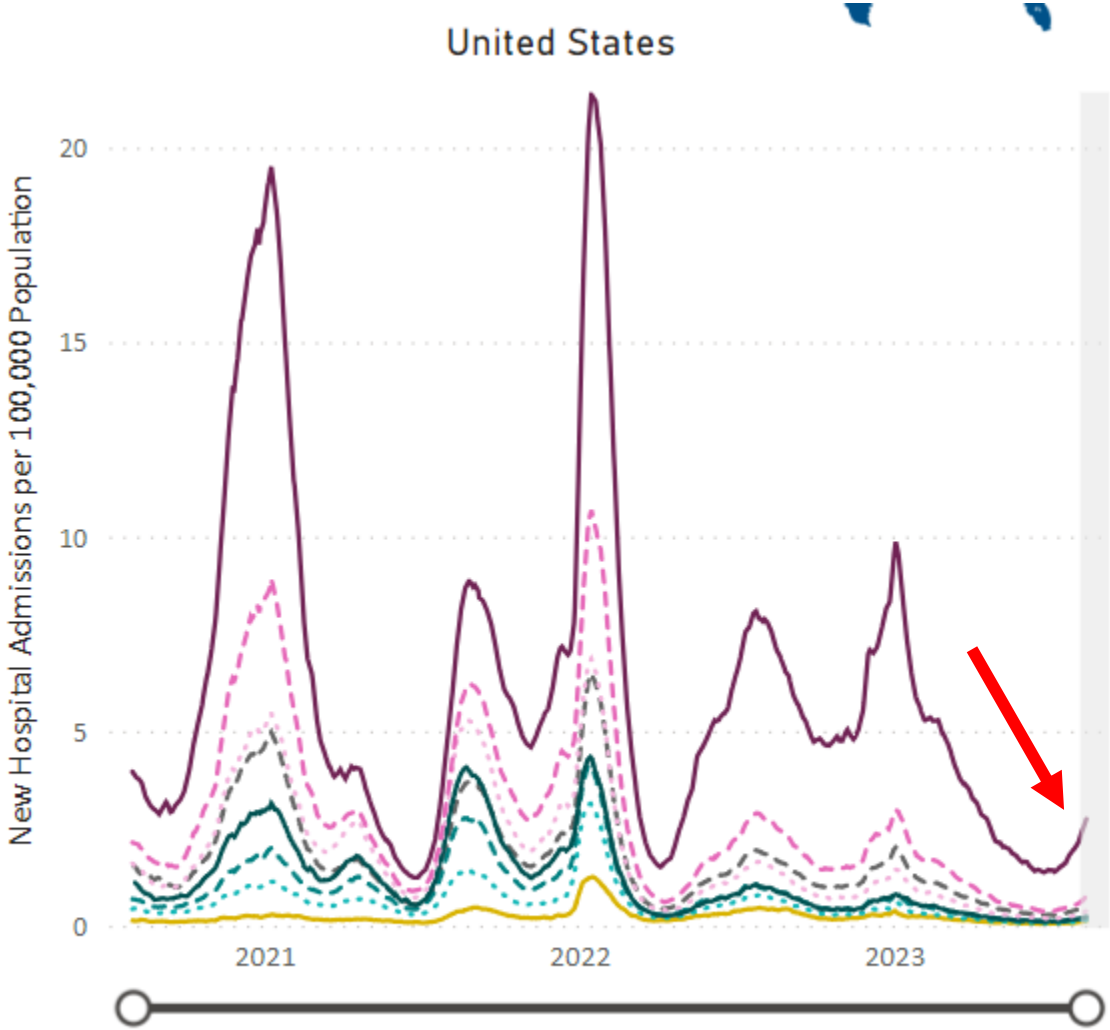


COVID-19 Has Become a Disease of the Elderly



Increased Hospitalizations – particularly in those 70 years of age and older

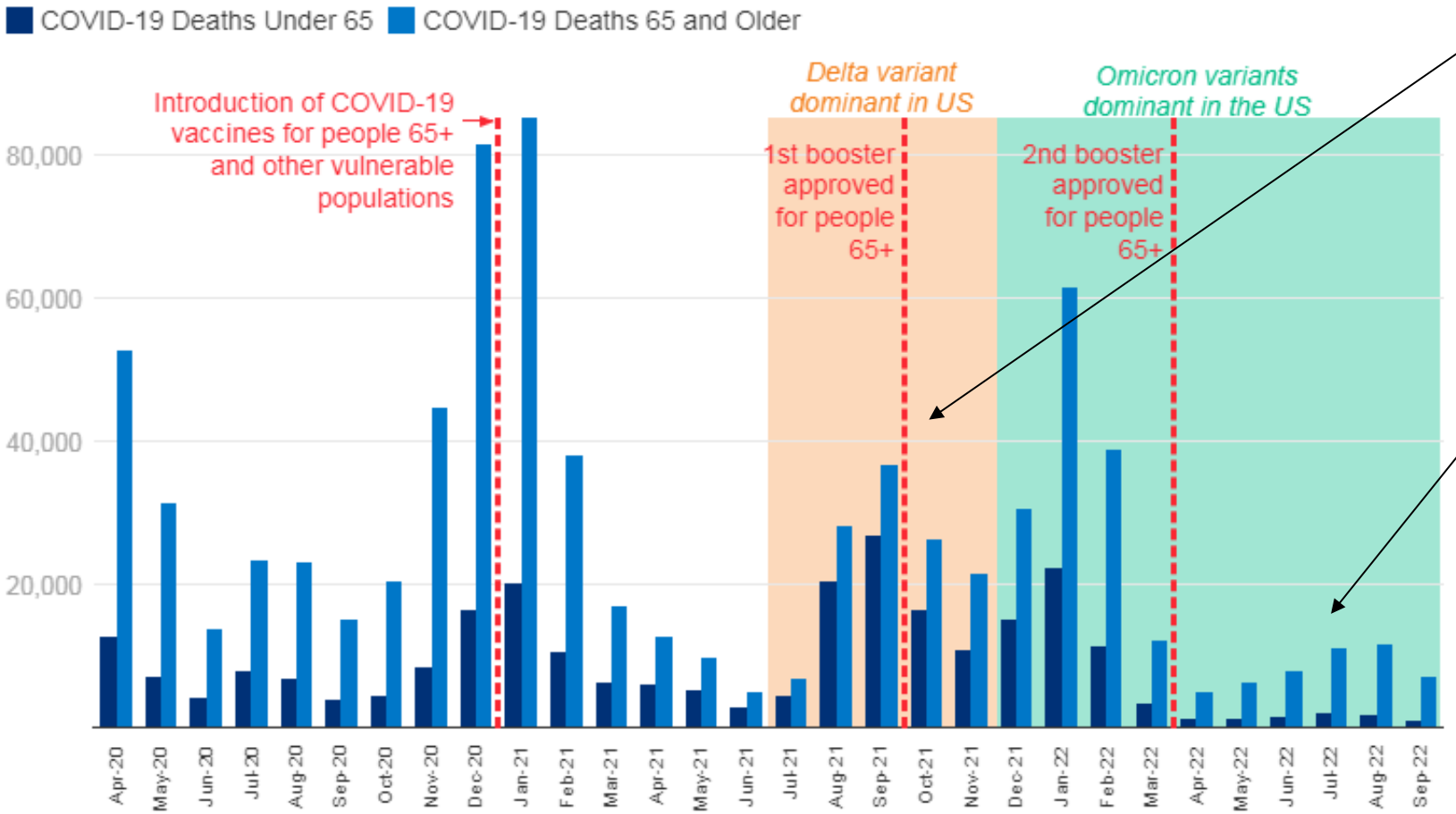




Age Group — 0 - 17 Years ····· 18 - 29 Years - - - 30 - 39 Years — 40 - 49 Years ····· 50 - 59 Years - - - 60 - 69 Years — 70+ Years - - - All Ages

Figure 1

Deaths Due to COVID-19 Rose Faster for Older than Younger Adults in the Summer of 2022



SOURCE: KFF analysis of CDC Provisional COVID-19 Death Counts by Sex and Age, as of the week ending October 1, 2022. • PNG

KFF

Delta killed the young and old!

Deaths now occur primarily in the elderly.

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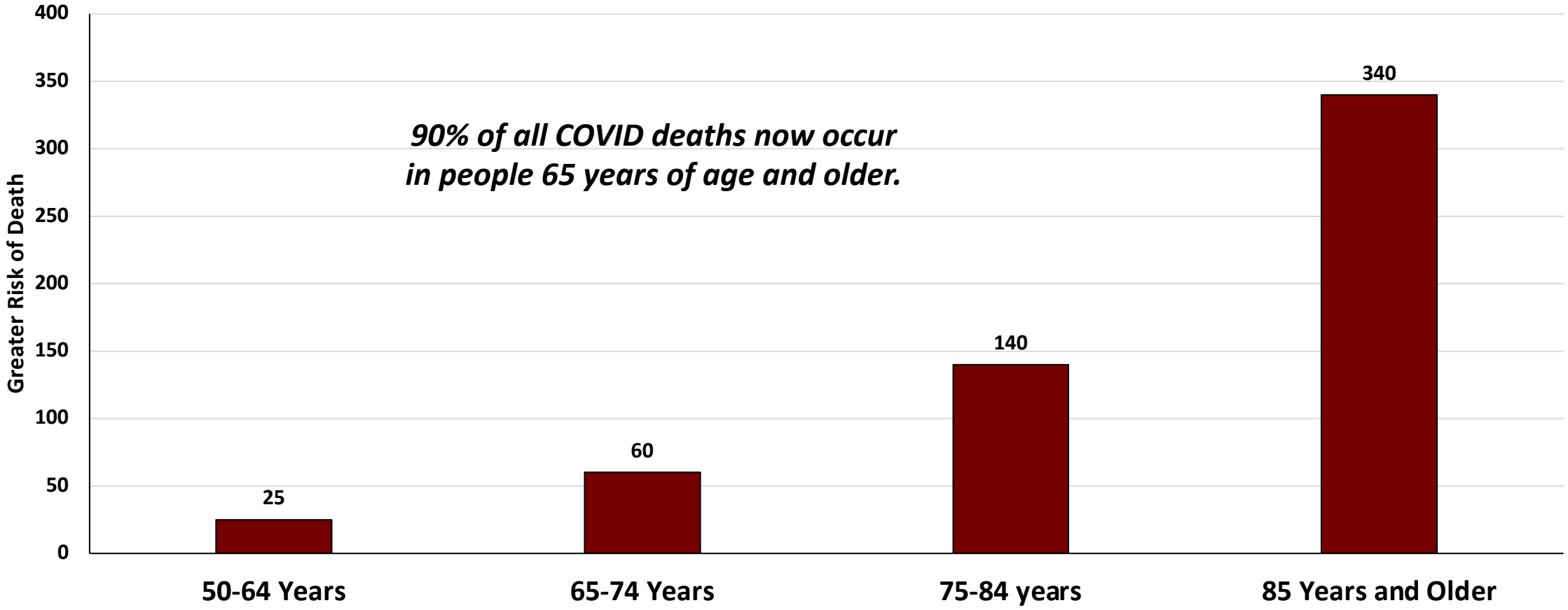
https://www.kff.org/coronavirus-covid-19/issue-brief/deaths-among-older-adults-due-to-covid-19-jumped-during-the-summer-of-2022-before-falling-somewhat-in-september/

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!



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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.
  - 81.3 % of US population has had at least one COVID vaccine dose
  - Up to 95% + of the US population has antibodies against COVID.

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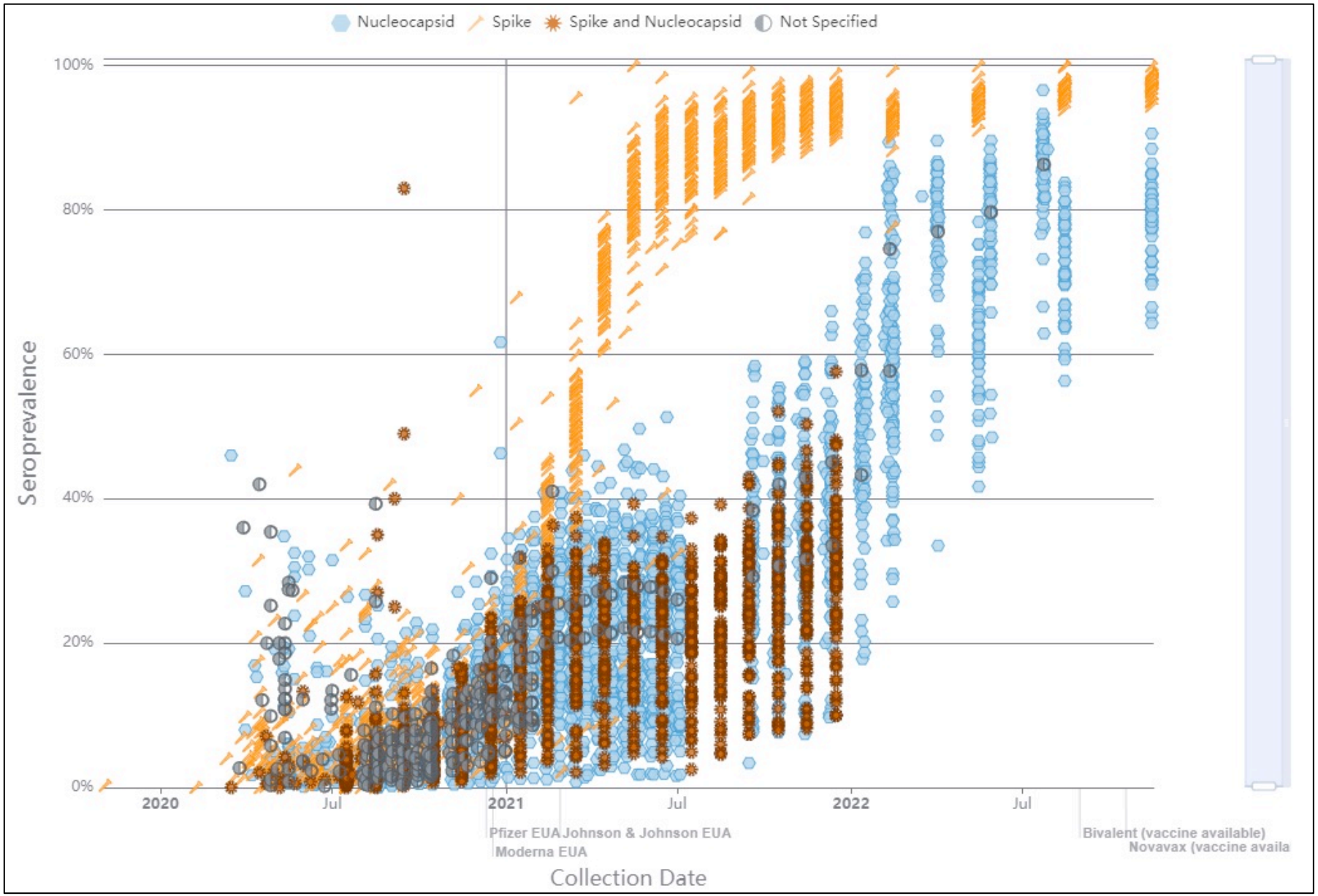
*Whether they know it or not!

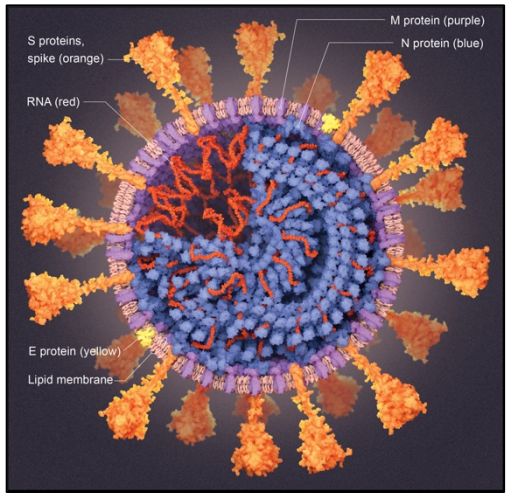


Antibodies to:

Spike glycoprotein

Nucleocapsid proteins

To both….



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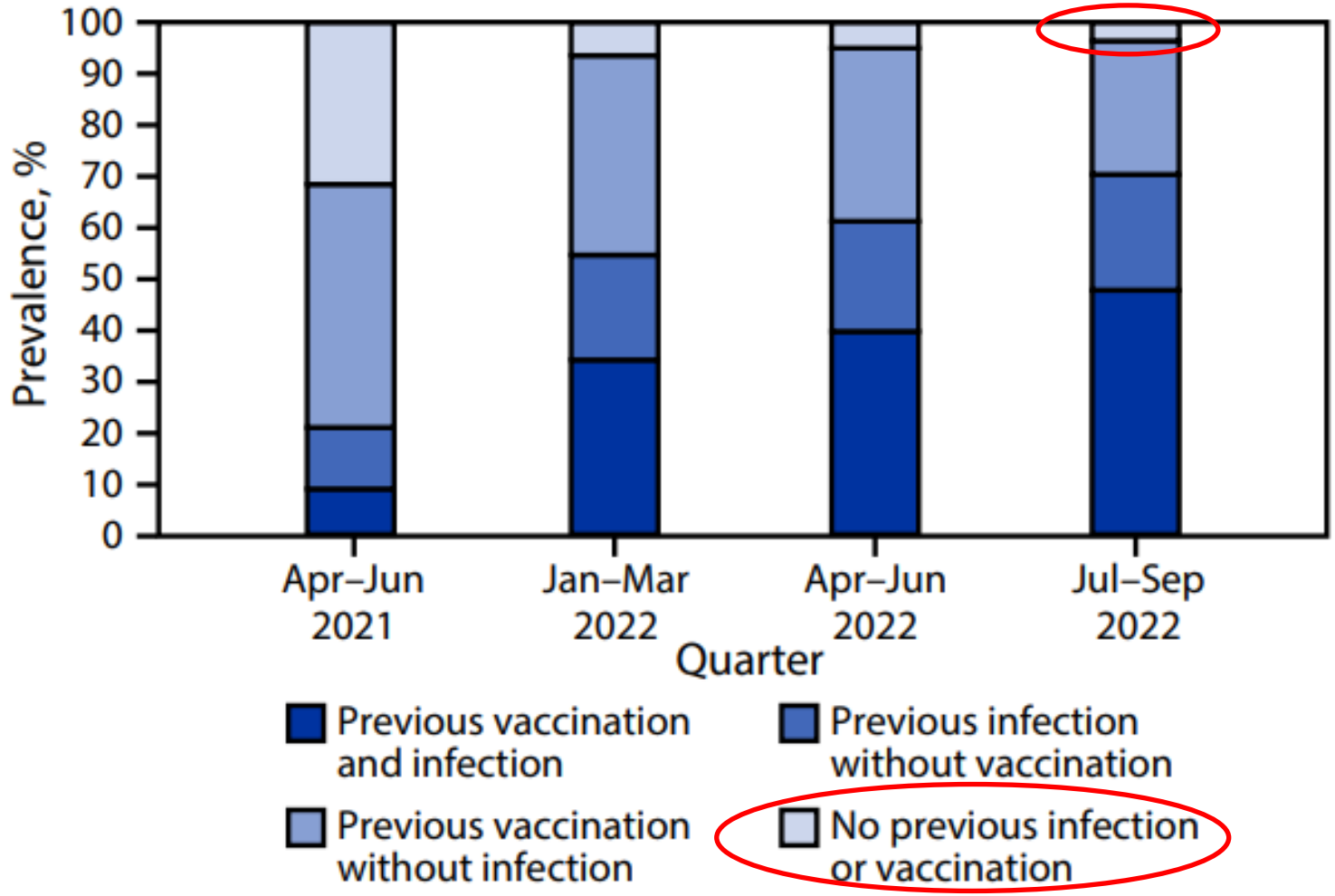
NIH NATIONAL CANCER INSTITUTE | NIH National Institute of Allergy and Infectious Diseases | CDC Centers for Disease Control and Prevention

COVID-19 SeroHub

https://covid19serohub.nih.gov/

FIGURE 1. Prevalences of vaccine-induced, infection-induced, and hybrid* immunity† against SARS-CoV-2 among blood donors aged ≥16 years — United States, April 2021–September 2022



Vaccination is, by far, the most important thing we can do to reduce the complications of COVID!

- Vaccination:
  - Prevents COVID-19 infection.
  - 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).

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

A-Z Index
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Morbidity and Mortality Weekly Report (*MMWR*)

CDC

Risk Factors for Severe COVID-19 Outcomes Among Persons Aged ≥18 Years Who Completed a Primary COVID-19 Vaccination Series — 465 Health Care Facilities, United States, December 2020–October 2021

Weekly / January 7, 2022 / 71(1);19–25

Christina Yek, MD[1,2,*]; Sarah Warner, MPH[1,*]; Jennifer L. Wiltz, MD[3]; Junfeng Sun, PhD[1]; Stacey Adjei, MPH[3]; Alex Mancera, MS[1]; Benjamin J. Silk, PhD[3]; Adi V. Gundlapalli, MD, PhD[3]; Aaron M. Harris, MD[3]; Tegan K. Boehmer, PhD[3]; Sameer S. Kadri, MD[1] (View author affiliations)

Very large study of 1.2 million people who had completed the primary COVID vaccinations between December 2020 and October 2021.

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https://www.cdc.gov/mmwr/volumes/71/wr/mm7101a4.htm

Bottom Line Findings

- **Fully vaccinated** persons were protected from most complications:
  - Risk of severe COVID-19-associated outcomes – 0.015%
  - Risk of death – 0.0033%

- All persons with severe outcomes had at least one (out of eight) underlying risk factor for poor outcomes

Of those who died, 78% had four or more risk factors.

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Severe COVID-19 outcomes were defined as hospitalization with a diagnosis of acute respiratory failure, need for noninvasive ventilation (NIV), admission to an intensive care unit (ICU) including all persons requiring invasive mechanical ventilation, or death (including discharge to hospice)

https://www.cdc.gov/mmwr/volumes/71/wr/mm7101a4.htm

Eight Risk Factors for Severe Disease in the Fully Vaccinated

These risk factors are common in Oklahoma!

Risk Factor	Increased Risk of Severe Disease or Death*
≥ 65 years	3.2-fold higher risk
Immunosuppressed	1.9-fold higher risk
Diabetes	1.5-fold higher risk
Chronic kidney disease	1.6-fold higher risk
Chronic neurologic disease	1.5-fold higher risk
Chronic cardiac disease	1.4-fold higher risk
Chronic pulmonary disease	1.7-fold higher risk
Chronic liver disease	1.7-fold higher risk

*In fully vaccinated individuals.

https://www.cdc.gov/mmwr/volumes/71/wr/mm7101a4.htm

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CORONAVIRUS

Prior SARS-CoV-2 infection enhances and reshapes spike protein–specific memory induced by vaccination

Véronique Barateau[1†], Loïc Peyrot[1†], Carla Saade[1†], Bruno Pozzetto[1,2†], Karen Brengel-Pesce[3†], Mad-Hélénie Elsensohn[4,5], Omran Allatif[1], Nicolas Guibert[6], Christelle Compagnon[3], Natacha Mariano[7], Julie Chaix[7], Sophia Djebali[1], Jean-Baptiste Fassier[6], Bruno Lina[1,8], Katia Lefsihane[1], Maxime Espi[1], Olivier Thaunat[1], Jacqueline Marvel[1], Manuel Rosa-Calatrava[1], Andres Pizzorno[1], Delphine Maucort-Boulch[4,5], Laetitia Henaff[1,9], Mitra Saadatian-Elahi[1,9], Philippe Vanhems[1,9], Stéphane Paul[1,2*‡], Thierry Walzer[1*‡], Sophie Trouillet-Assant[1,3*‡], Thierry Defrance[1*‡]

".....our data suggest that prior SARS-CoV-2 infection increases the titers of SARS-CoV-2 spike protein–specific antibody responses elicited by subsequent vaccination and induces modifications in the composition of the spike protein–specific memory B cell pool that are compatible with enhanced functional protection at mucosal sites."

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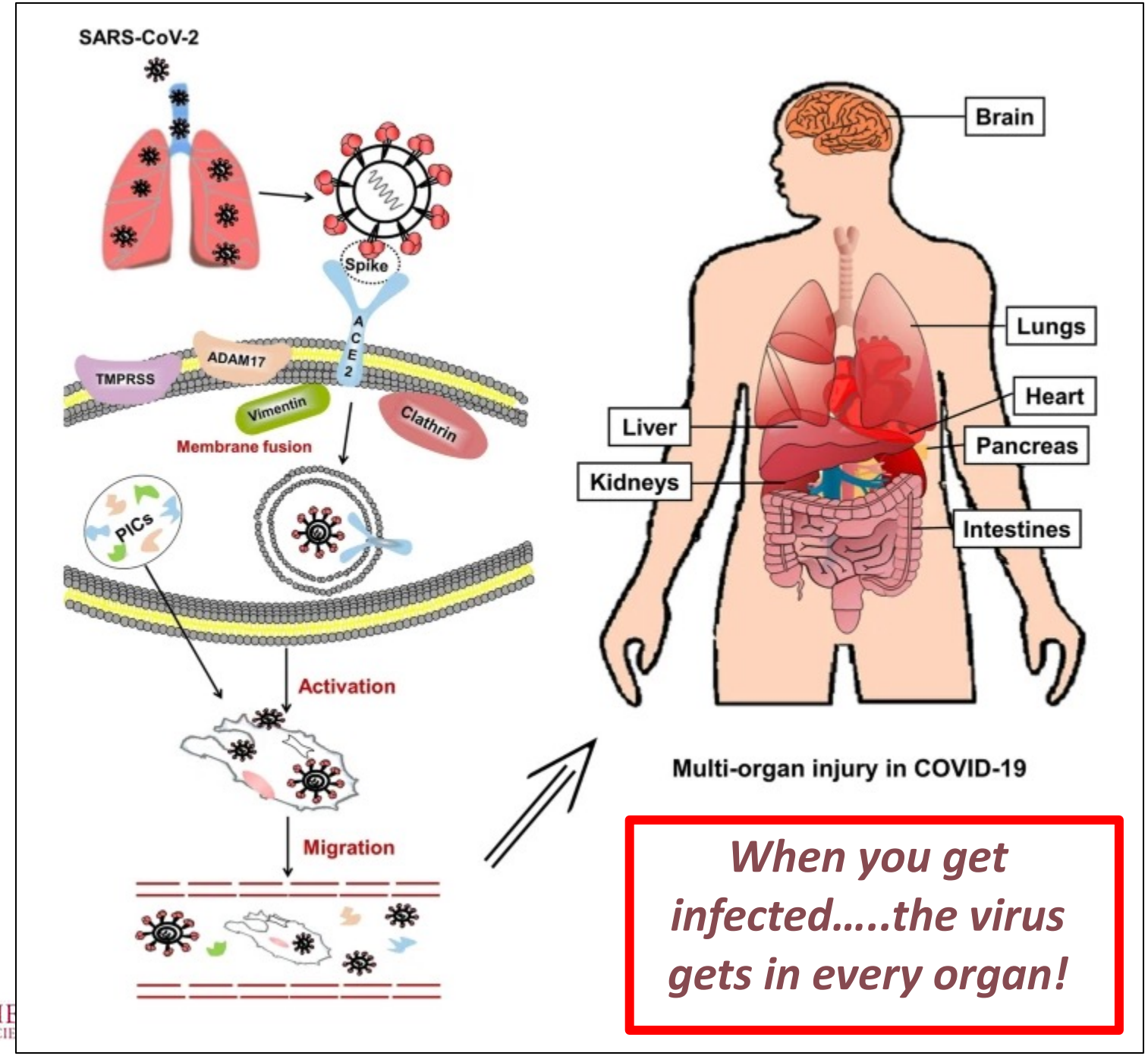
Despite of all of the progress, some of our patients will still get infected with SARS-CoV-2

What is the natural history of COVID infection?

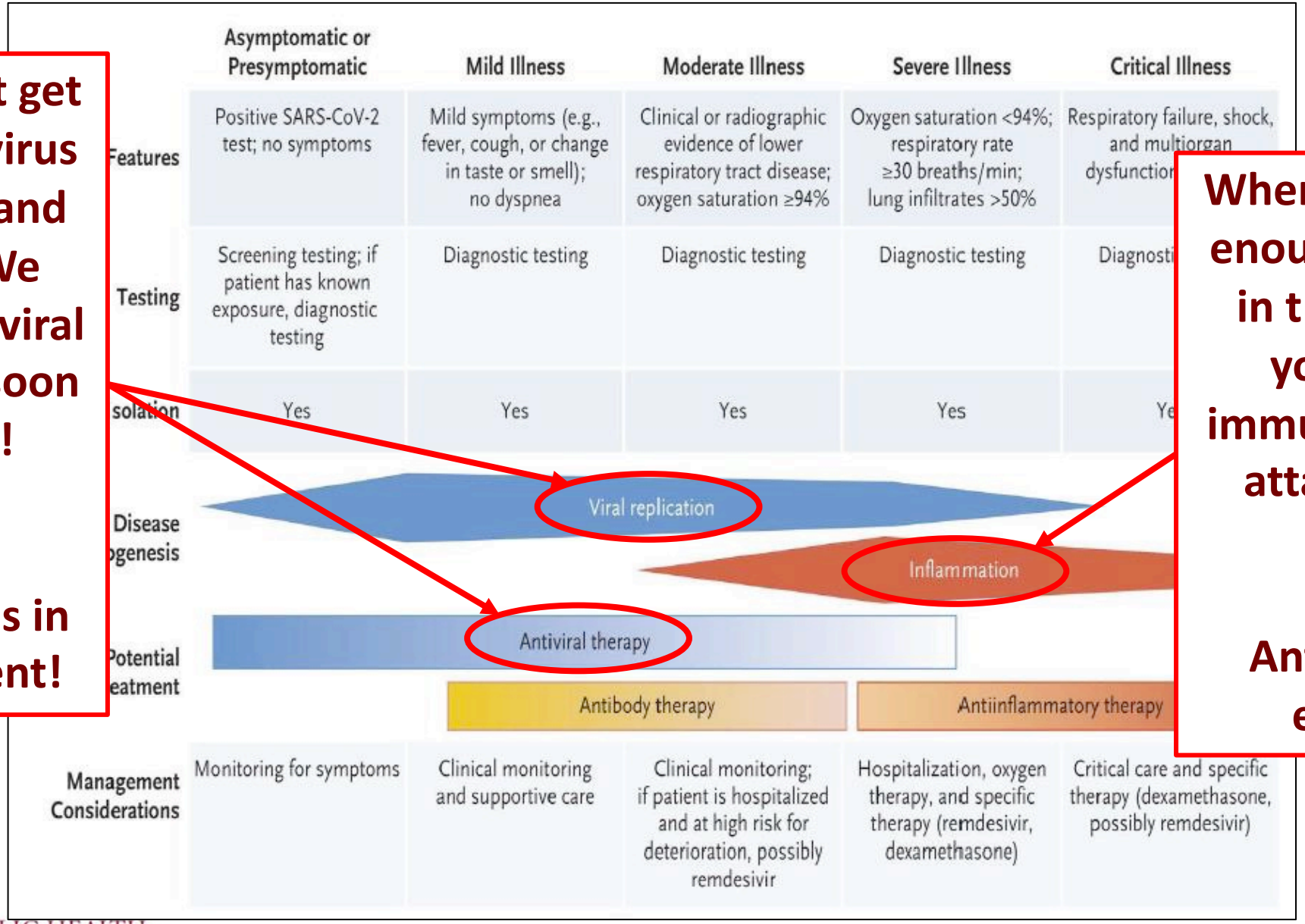


When you get infected…..the virus gets in every organ!

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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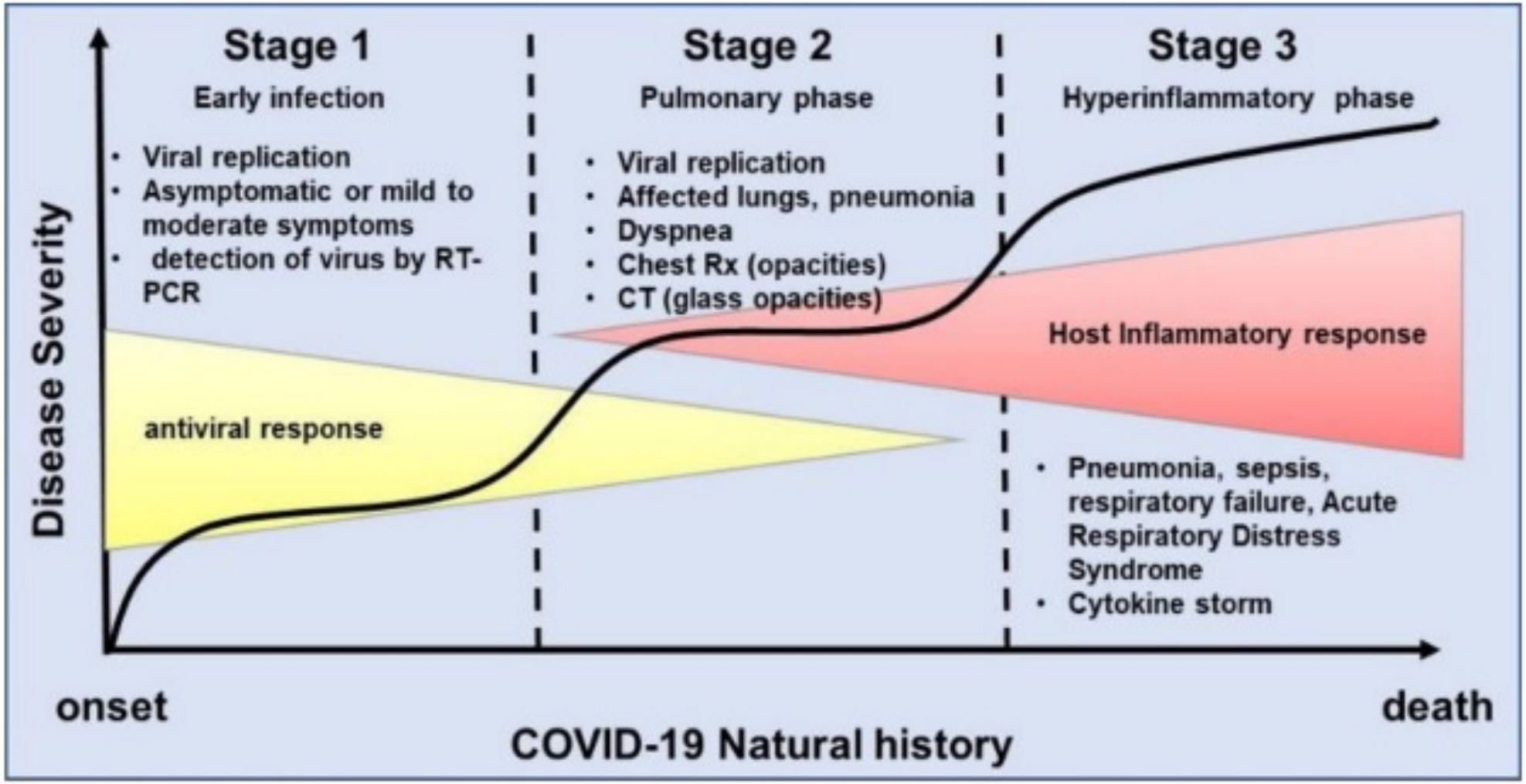
N Engl J Med. 2020 Oct 29;383.



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 person's risk for severe disease….are they:
  - Elderly,
  - Immunocompromised, or
  - Have underlying chronic conditions.

- If I answer "yes" to any of the above, I start treatment with antiviral medications AS SOON AS POSSIBLE. I do not wait for someone to have symptoms or to get sick before I treat.

NIH Guidelines for Treatment of Non-hospitalized Adults

Patients Who Are at High Risk of Progressing to Severe COVID-19[b,c]
CLOSE —
Preferred therapies. Listed in order of preference: • **Ritonavir-boosted nirmatrelvir (Paxlovid)[d] (AIIa)**; see footnote on drug interactions[e] • **Remdesivir[d,f] (BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir[d,g,h] (CIIa)**

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

International Journal of Infectious Diseases 131 (2023) 155–161

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

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

Mortality and risk factors of vaccinated and unvaccinated frail patients with COVID-19 treated with anti-SARS-CoV-2 monoclonal antibodies: A real-world study

Riccardo Nevola[1], Giovanni Feola[2], Rachele Ruocco[1], Antonio Russo[3], Angela Villani[1], Raffaele Fusco[2], Stefania De Pascalis[3], Micol Del Core[1], Giovanna Cirigliano[1], Mariantonietta Pisaturo[3], Giuseppe Loffredo[1], Luca Rinaldi[1], Aldo Marrone[1], Mario Starace[3], Pellegrino De Lucia Sposito[2], Domenico Cozzolino[1], Teresa Salvatore[1], Miriam Lettieri[4], Raffaele Marfella[1], Ferdinando Carlo Sasso[1], Nicola Coppola[2], Luigi Elio Adinolfi[1,*]

"The data from our study show that the use of corticosteroids in the early phase of SARS-CoV-2 infection is associated with a deleterious effect on mortality. To optimize the treatment of frail patients, we suggest that corticosteroids should be avoided in the early phase of mild-moderate infection, when viral replication is at its highest and the immunological response has not yet adequately developed."

What do we give an at-risk person who tests positive for COVID-19?

- **Ritonavir-boosted Nirmatrelvir**
  - 89% effective at preventing hospitalization and death[1]
- **Remdesivir (an IV infusion)**
  - 86% effective at preventing hospitalization and death[2]
- **Molnupiravir**
  - 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.

Case History - 1

- 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

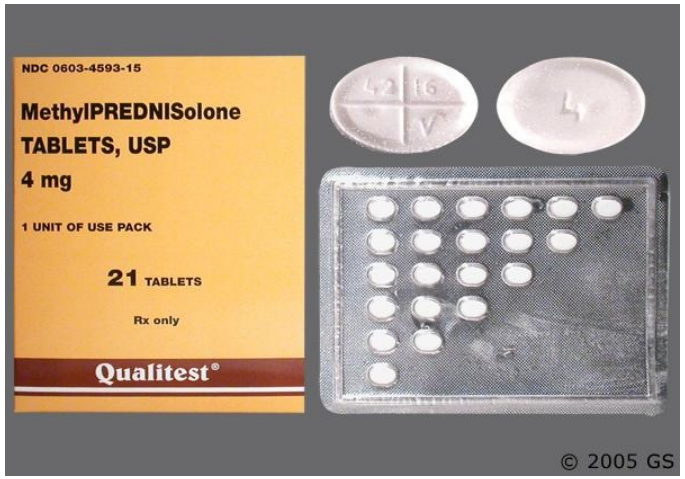
- A rapid antigen test done in the office was positive for COVID-19.

- 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 - 1

- The patient was prescribed a methylprednisolone dose pack and a five-day course of azithromycin



- Approximately 7-days later the patient presented to the emergency department in acute respiratory failure with extensive bilateral ground glass infiltrates on the chest x-ray requiring immediate intubation.
- The family withdrew treatment when transfer for ECMO was recommended.

Case History - 1

- 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.

Case History - 2

- A 41-year-old female developed nasal congestion and a dry cough after a cross country flight. She had a home rapid antigen test and the result was positive.
  - She is otherwise healthy with no chronic medical conditions.
  - She lives with her husband and two healthy children
  - As soon as the test came back positive she started wearing a mask, isolated herself in the home away from the rest of the family, and was approved by her employer to work from home.

- She calls you as her primary care provider and wants to know if she should take any treatment for COVID.

Clin Infect Dis. 2023 Jun 30;ciad400. doi: 10.1093/cid/ciad400. Online ahead of print.

Oral Nirmatrelvir and Ritonavir for Covid-19 in Vaccinated, Non-Hospitalized Adults, Ages 18-50 Years

Jeremy Samuel Faust [1], Ashish Kumar [2], Jui Shah [3], Sumanth Khadke [3], Sourbha S Dani [3], Sarju Ganatra [4], Paul E Sax [5]

Affiliations + expand

PMID: 37387690 DOI: 10.1093/cid/ciad400

Conclusion: NMV-r use in vaccinated adults aged 18-50, especially with serious comorbidities, was associated with reduced all-cause hospital visits, hospitalization, and mortality in the first 30 days of COVID-19 illness. However, NMR-r in patients without significant comorbidities or with only asthma/COPD had no association of benefit. Therefore, identifying high-risk patients should be a priority and overprescription should be avoided.

Case History - 2

- So, while the use of antiviral medications for COVID in younger patients with chronic illness and comorbidities can reduce complications of the disease, there is no good evidence of benefit in young, healthy patients.

- CDC guidance on isolation if you test positive for COVID-19:
  - Stay home for at least 5 days and isolate from others in your home.
  - Do not go places where you are unable to wear a mask.
  - Ending isolation depends on the severity of symptoms (at least 5 days and those who are sicker, at least 10 days).
  - Wear a mask when around others for at least 10 days.

https://www.cdc.gov/coronavirus/2019-ncov/your-health/isolation.html

Case History – 3

- 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

July 14, 2023 1 min read

FDA approves Veklury for COVID-19 treatment in patients with severe renal impairment

Key takeaways:

- Veklury is indicated for the treatment of COVID-19 in adult and pediatric patients in the United States.
- Approval was based on the phase 1 and phase 3 REDPINE trials.

The FDA has approved the use of Veklury for the treatment of COVID-19 in patients with severe renal impairment, including those on dialysis, according to a press release from drug manufacturer Gilead Sciences Inc.

"Patients with advanced [chronic kidney disease] CKD and end-stage kidney disease are at high risk for severe COVID with hospitalization and mortality rates remaining high, even for those who are vaccinated," **Meghan Sise, MD,** of th department of nephrology at Massachusetts General Hospital, said in the release. "This latest update to the prescribi information for remdesivir now includes patients with advanced CKD and ESKD and this is an important advance for a population that remains highly vulnerable to the impacts of COVID-19."

Remdesivir can be used in patients with severe renal disease!

The Journal of Infectious Diseases

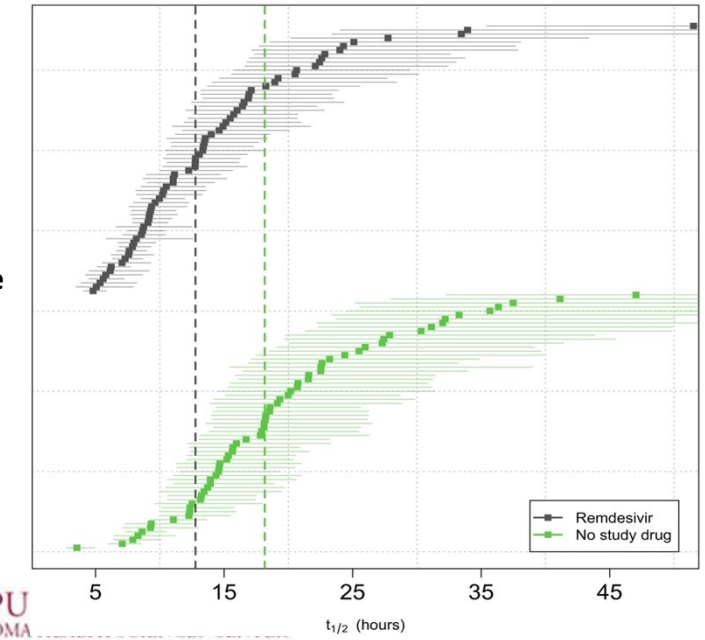
MAJOR ARTICLE

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."*

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

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 (eG
  - Note that a dose reduction is required for impairment (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 ion rate (eGFR) for certain patients after assessment on a ed on history or exam.
    - harmacists must have sufficient information available, such as through alth 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.

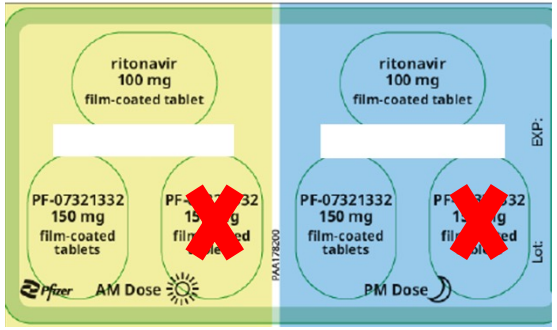
Coadministration of this drug with PAXLOVID should be avoided d/or holding of this drug, dose adjustment of this drug, or special ing is necessary. Consultation with the prescriber of the teracting drug is recommended. For further information, Care Provider Fact Sheet and the individual for the drug.

Drug-drug Interactions

The table below provides a list drug interactions, including contraindicated drugs, in addition t mitant Medications above (HMG-CoA reductase inhibitors [statins], ontaining ethinyl estradiol, and medications for HIV-1 treatment, ***gre a guide and are not considered a comprehensive list of all poss ct with PAXLOVID. The healthcare provider should consult othe h 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 on
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.

How do we explain long-COVID symptoms?

Research

JAMA | Original Investigation

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD; Sarah E. Jolley, MD, MS; Elizabeth W. Karlson, MD, MS; Emily B. Levitan, ScD; Bruce Levy, MD; Grace A. McComsey, MD; Lisa McCorkell, MPP; Girish N. Nadkarni, MD, MPH; Sairam Parthasarathy, MD; Upinder Singh, MD; Tiffany A. Walker, MD; Caitlin A. Selvaggi, MS; Daniel J. Shinnick, MS; Carolin C. M. Schulte, PhD; Rachel Atchley-Challenner, PhD; RECOVER Consortium Authors; Leora I. Horwitz, MD; Andrea S. Foulkes, ScD; for the RECOVER Consortium

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

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***

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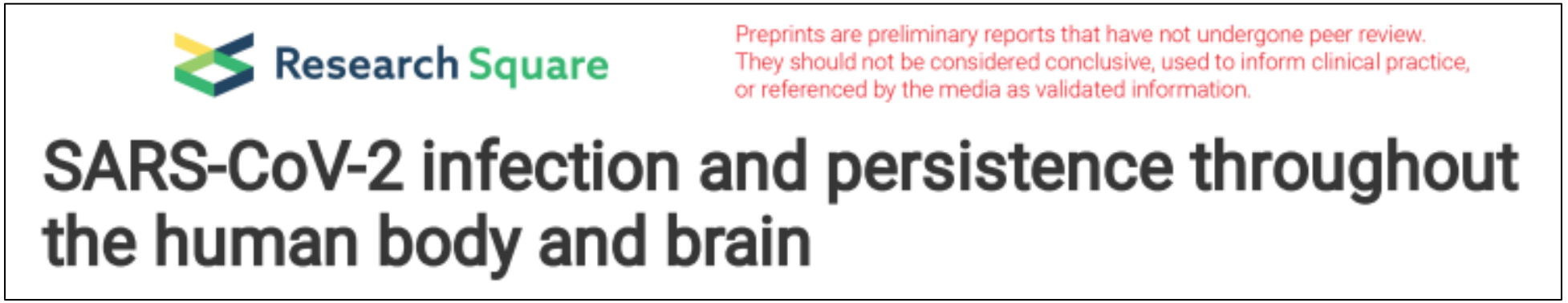
JAMA. doi:10.1001/jama.2023.8823
Published online May 25, 2023.



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

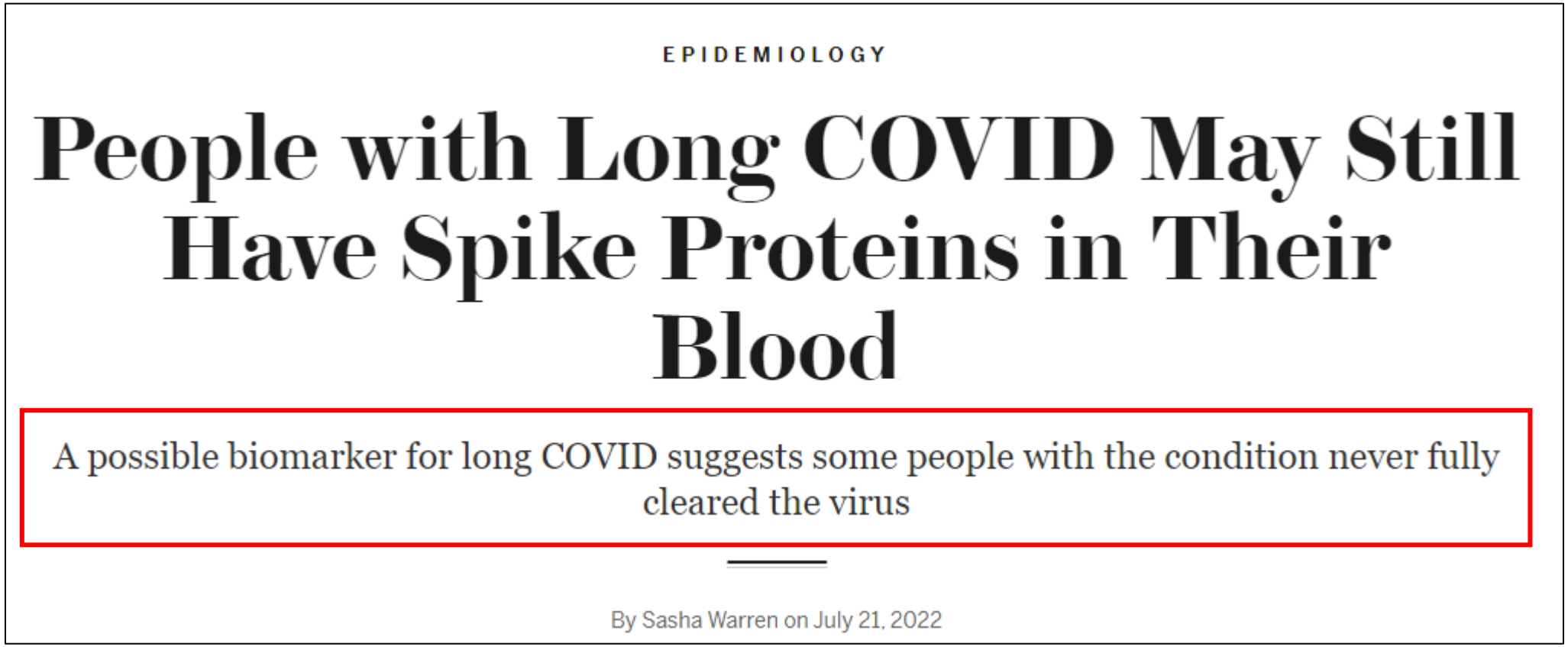
- ***Extensive tissue sampling from throughout the bodies looking for long-term persistent SARS-CoV-2 virus***

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



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."

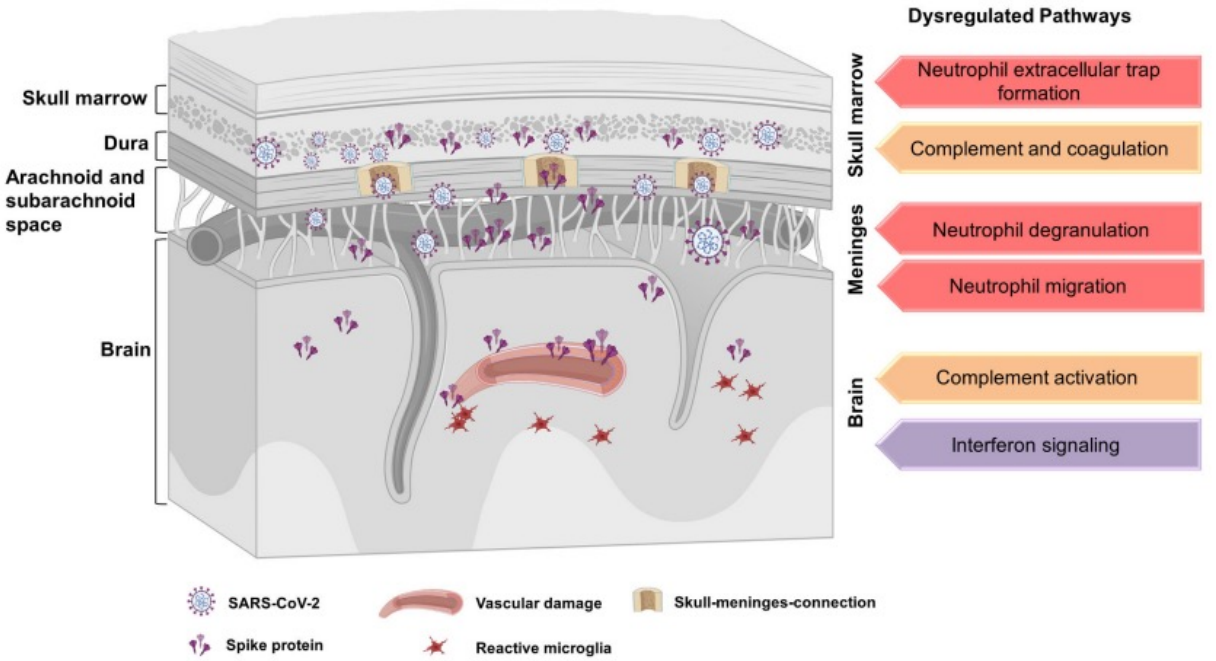
https://www.scientificamerican.com/article/people-with-long-covid-may-still-have-spike-proteins-in-their-blood1/#:~:text=The%20presence%20and%20intensity%20of,to%20blame%20for%20long%20COVID.

"……we observed the presence of spike protein in the skull of deceased patients long after their COVID-19 infection, suggesting that the spike's persistence may contribute to long-term neurological symptoms."

SARS-CoV-2 Spike Protein Accumulation in the Skull-Meninges-Brain Axis: Potential Implications for Long-Term Neurological Complications in post-COVID-19

Zhouyi Rong[1,2,15]†, Hongcheng Mai[1,2,15]†, Saketh Kapoor[1]†, Victor G. Puelles[3,4,13,14], Jan Czogalla[3,4], Julia Schädler[5], Jessica Vering[5], Claire Delbridge[6], Hanno Steinke[7], Hannah Frenzel[7], Katja Schmidt[7], Özüm Sehnaz Caliskan[9], Jochen Martin Wettengel[10], Fatma Cherif[11], Mayar Ali[1,16], Zeynep Ilgin Kolabas[1,2,16], Selin Ulukaya[1], Izabela Horvath[1,17], Shan Zhao[1], Natalie Krahmer[9], Sabina Tahirovic[11], Ali Önder Yildirim[12], Tobias B. Huber[3,4], Benjamin Ondruschka[3,5], Ingo Bechmann[7], Gregor Ebert[8], Ulrike Protzer[10], Harsharan Singh Bhatia[1,2], Farida Hellal[1,2], Ali Ertürk[1,2]*

Graphical Summary

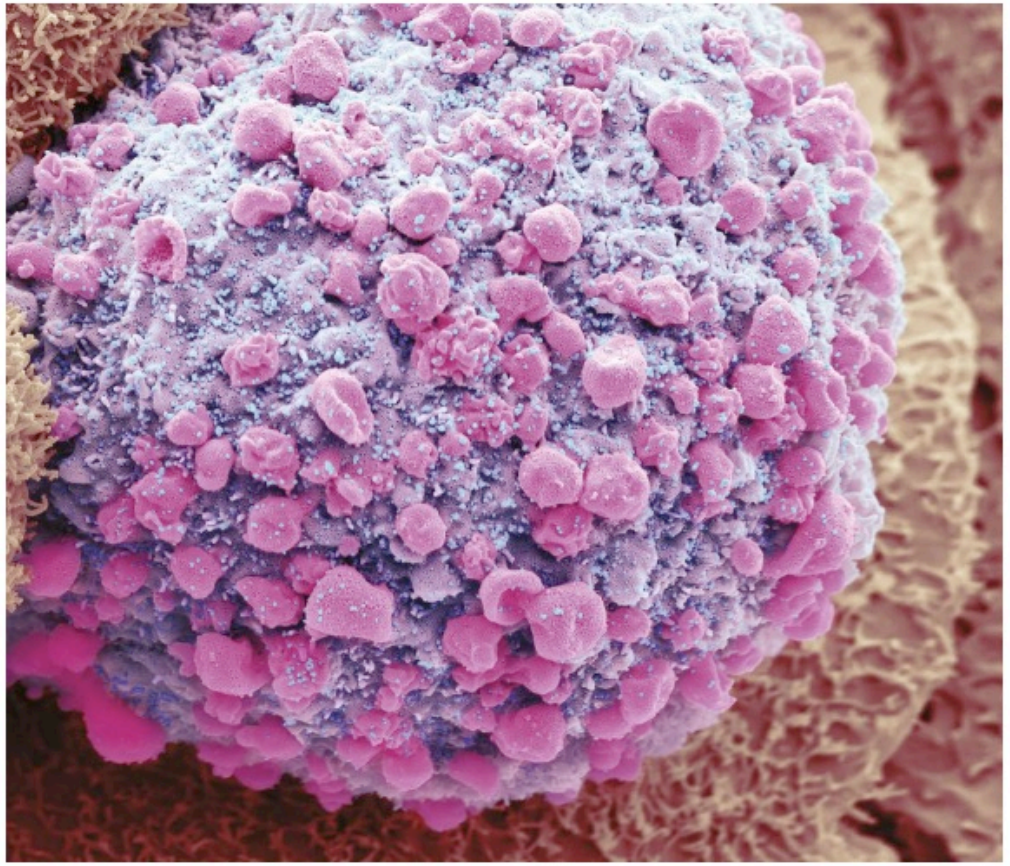


https://www.biorxiv.org/content/10.1101/2023.04.04.535604v1.full.pdf

".....both teams published results last month suggesting that pieces of SARS-CoV-2 can linger in the gut for months after an initial infection. The findings add to a growing pool of evidence supporting the hypothesis that persistent bits of virus — coronavirus "ghosts", Bhatt has called them — could contribute to the mysterious condition called long COVID."

Natarajan, A. et al. Med https://doi.org/10.1016/j.medj.2022.04.001 (2022).
Zollner, A. et al. Gasteroenterology https://doi.org/10.1053/j.gastro.2022.04.037 (2022)

News in focus



Particles of SARS-CoV-2 (blue; artificially coloured) bud from a dying intestinal cell.

CORONAVIRUS 'GHOSTS' CAN LINGER FOR MONTHS IN THE GUT

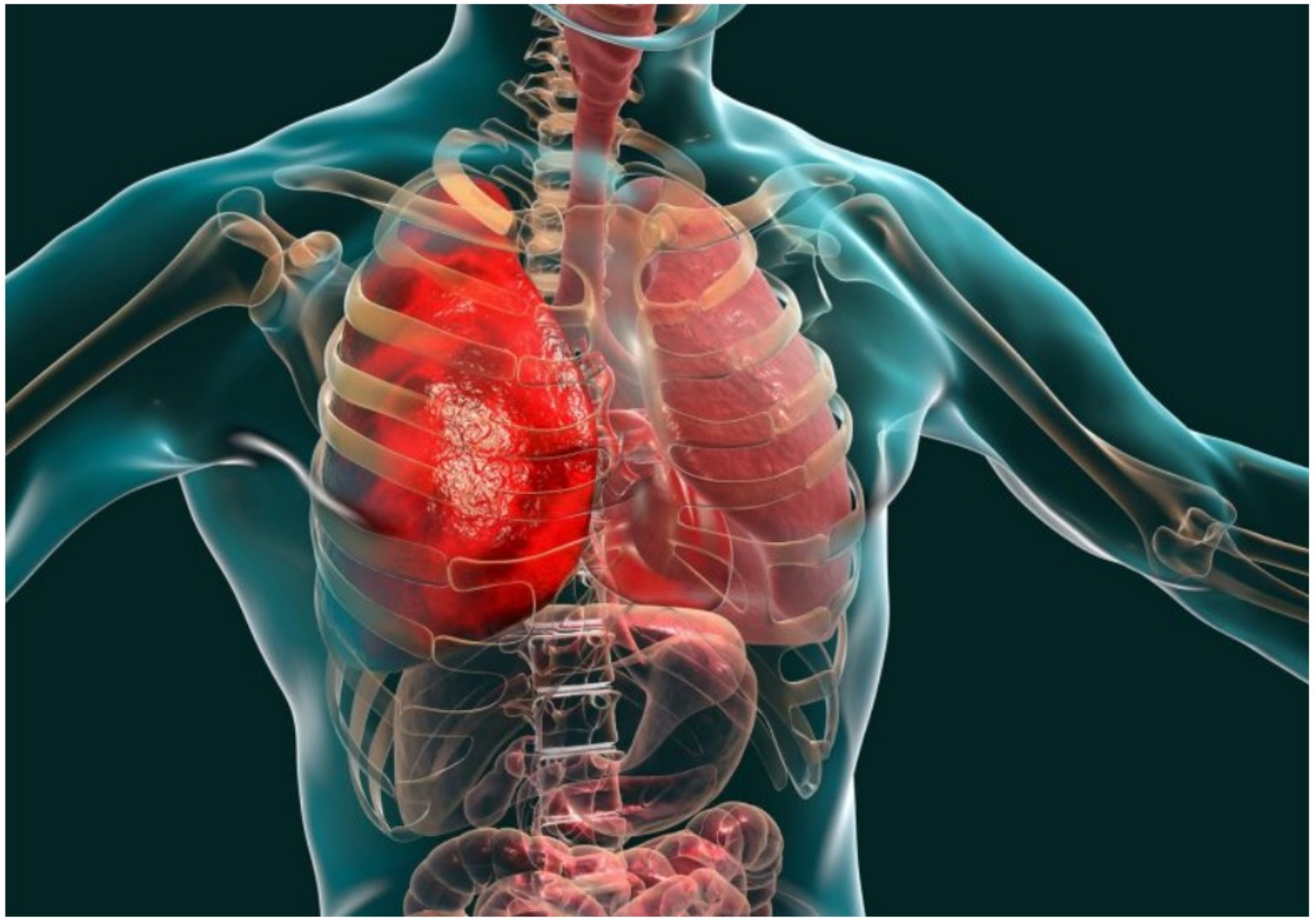
Scientists are studying whether long COVID could be linked to viral fragments that persist in various tissues.

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

Article

SARS-CoV-2 is associated with changes in brain structure in UK Biobank

https://doi.org/10.1038/s41586-022-04569-5

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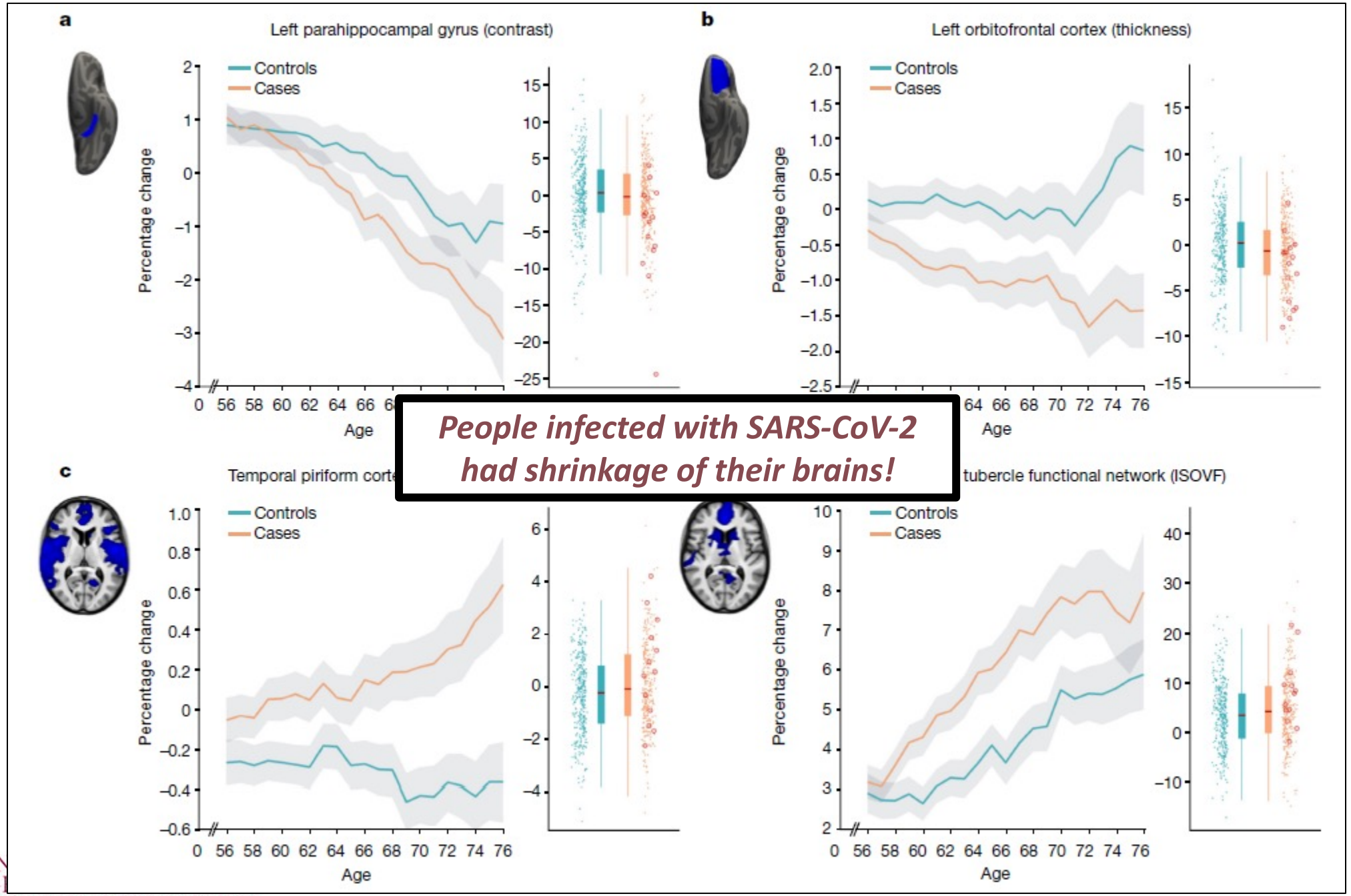
Published online: 7 March 2022

Open access

Gwenaëlle Douaud[1]✉, Soojin Lee[1], Fidel Alfaro-Almagro[1], Christoph Arthofer[1], Chaoyue Wang[1], Paul McCarthy[1], Frederik Lange[1], Jesper L. R. Andersson[1], Ludovica Griffanti[1,2], Eugene Duff[1,3], Saad Jbabdi[1], Bernd Taschler[1], Peter Keating[4], Anderson M. Winkler[5], Rory Collins[6], Paul M. Matthews[7], Naomi Allen[6], Karla L. Miller[1], Thomas E. Nichols[8] & Stephen M. Smith[1]

Here we investigated brain changes in 785 participants of UK Biobank (aged 51–81 years) who were imaged twice using magnetic resonance imaging, including 401 cases who tested positive for infection with SARS-CoV-2 between their two scans—with 141 days on average separating their diagnosis and the second scan—as well as 384 controls.


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
tubercle functional network (ISOVF)
Controls
Cases
Percentage change
Age

…….We identified significant longitudinal effects when comparing the two groups, including (1) a greater reduction in grey matter thickness and tissue contrast in the orbitofrontal cortex and parahippocampal gyrus; (2) greater changes in markers of tissue damage in regions that are functionally connected to the primary olfactory cortex; and (3) a greater reduction in global brain size in the SARS-CoV-2 cases. The participants who were infected with SARS-CoV-2 also showed on average a greater cognitive decline between the two time points.

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)
  - At 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
- Multiple clinical trials are ongoing to define treatments for long COVID symptoms

Final thoughts…..

- The virus has not stopped mutating:
  - **EG.5** is currently predominating in the US
    - Highly transmissible and has mutations that may decrease protection from prior vaccination and prior infection
    - Cases and hospitalizations have increased over the past few weeks
  - **BA.2.68** has been identified in multiple countries including 3 US states
    - Highly mutated (36 mutations)
    - Real concern that this variant may dodge the body's immune defenses from prior infection or vaccination
    - It is unknown if the fall booster will prevent infection with this variant
    - Will we see another Omicron-like surge????

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