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COVID-19 Real-Time Learning Network

Specialty Society Collaborators:

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

With funding from the Centers for Disease Control and Prevention, IDSA has launched the COVID-19 Real Time Learning Network, an online community that brings together information and opportunities for discussion on latest research, guidelines, tools and resources from a variety of medical subspecialties around the world.

www.COVID19LearningNetwork.org

@RealTimeCOVID19 | #RealTimeCOVID19

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Prevention

An online learning module designed with frontline healthcare personnel in mind.

PreventionCHKC.org

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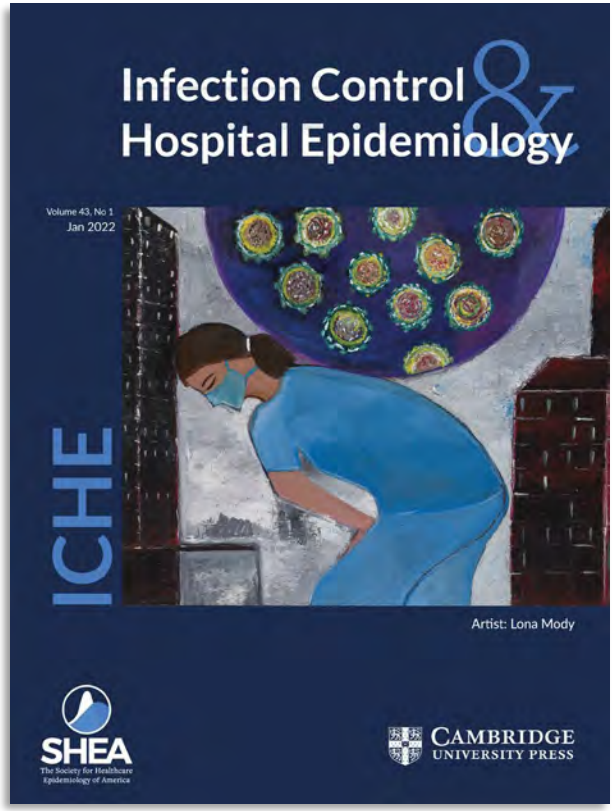
ICHE Journal – Fast Tracking COVID Article Submissions



Infection Control & Hospital Epidemiology publishes scientifically authoritative, clinically applicable, peer-reviewed research on control and evaluation of the transmission of pathogens in healthcare institutions and on the use of epidemiological principles and methods to evaluate and improve the delivery of care. Major topics covered include infection control practices, surveillance, antimicrobial stewardship, cost-benefit analyses, resource use, occupational health, and regulatory issues.

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SHEA Webinar

COVID-19 Town Hall Round 89

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House Keeping Items

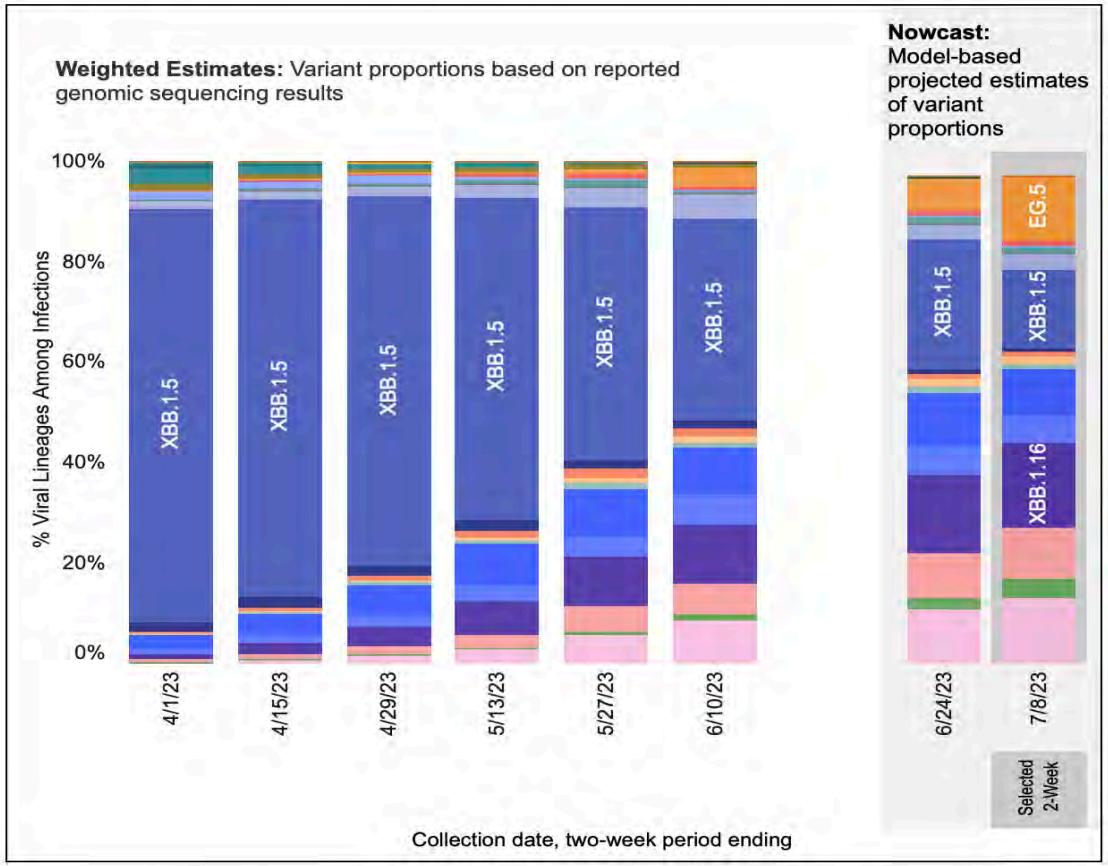
- Technical difficulties? Visit: https://support.zoom.us
- Webinar recording, PowerPoint presentation, and references available LearningCE’ s Rapid Response Program
- Streaming Live on SHEA's Facebook page
- Zoom Q&A and Chat

SHEA Town Hall 89
Overview

SARS-CoV-2 Variants, US, CDC

Weighted and Nowcast Estimates in United States for 2-Week Periods in 3/19/2023 – 7/8/2023

Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.



Nowcast Estimates in United States for 6/25/2023 – 7/8/2023

USA

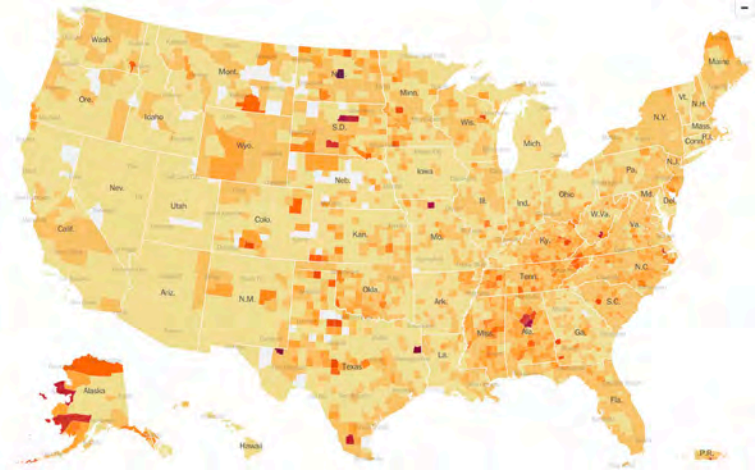
WHO label	Lineage #	%Total	95%PI
Omicron	XBB.2.3	13.4%	11.3-15.8%
	XBB.1.9.2	5.6%	4.0-7.7%
	XBB.1.9.1	9.4%	8.1-10.9%
	XBB.1.5.68	1.0%	0.6-1.9%
	XBB.1.5.59	1.6%	1.0-2.6%
	XBB.1.5.10	0.8%	0.4-1.5%
	XBB.1.5.1	0.7%	0.5-1.0%
	XBB.1.5	16.1%	13.8-18.6%
	XBB.1.16.6	4.1%	2.0-7.9%
	XBB.1.16.1	10.4%	8.4-12.8%
	XBB.1.16	17.5%	15.2-20.0%
	XBB	3.6%	2.5-5.1%
	FE.1.1	1.3%	0.6-2.7%
	FD.2	0.1%	0.1-0.3%
	EU.1.1	1.1%	0.6-1.7%
	EG.5	13.0%	7.5-21.1%
	CH.1.1	0.2%	0.1-0.4%
	BQ.1.1	0.0%	0.0-0.0%
	BQ.1	0.0%	0.0-0.0%
	BN.1	0.0%	0.0-0.0%
	BF.7	0.0%	0.0-0.0%
	BA.5	0.0%	0.0-0.0%
	BA.2.75	0.0%	0.0-0.0%
	BA.2	0.0%	0.0-0.0%
Other	Other*	0.0%	0.0-0.1%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one 2-week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all 2-week periods displayed.
# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.2.75.2, CH.1.1 and BN.1, BA.2.75 sublineages are aggregated with BA.2.75. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BF.11, BA.5.2.6, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Except the lineages shown and their sublineages, sublineages of XBB are aggregated to XBB. Except XBB.1.5.1,XBB.1.5.10,FD.2,EU.1.1, XBB.1.5.68 and XBB.1.5.59 sublineages of XBB.1.5 are aggregated to XBB.1.5. Except XBB.1.16.1, XBB.1.16.6 sublineages of XBB.1.16 are aggregated to XBB.1.16. Except FE.1.1, sublineages of XBB.1.18.1 are aggregated to XBB. For all the other lineages listed, their sublineages are aggregated to the listed parental lineages respectively. Previously, XBB.1.5.59 was aggregated to XBB.1.5 and XBB.1.16.6 was aggregated to XBB.1.16. Lineages BA.2.75.2, XBB, XBB.1.5 , XBB.1.5.1,XBB.1.5.10, FD.2, XBB.1.9.1, XBB.1.9.2, XBB.1.16, XBB.1.16.1, XBB.2.3, BN.1, BA.4.6, BF.7, BF.11, BA.5.2.6 ,BQ.1.1, EU.1.1, XBB.1.5.68, FE.1.1, XBB.1.5.59 and XBB.1.16.6 contain the spike substitution R346T.

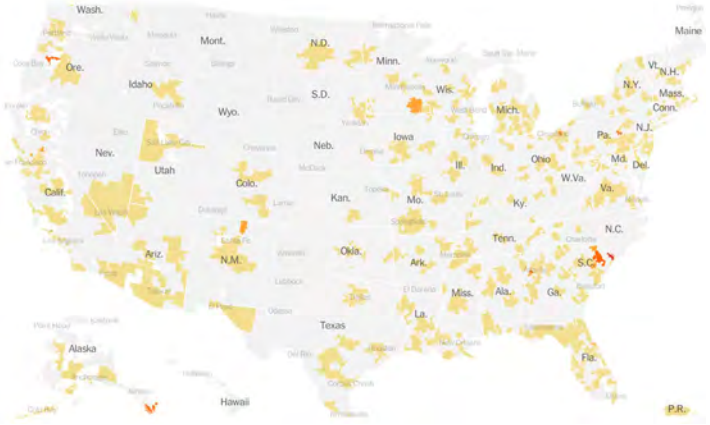
https://covid.cdc.gov/covid-data-tracker/#variant-proportions

US COVID-19 HOTSPOTS

February 6, 2022



February 12, 2023



June 23, 2023

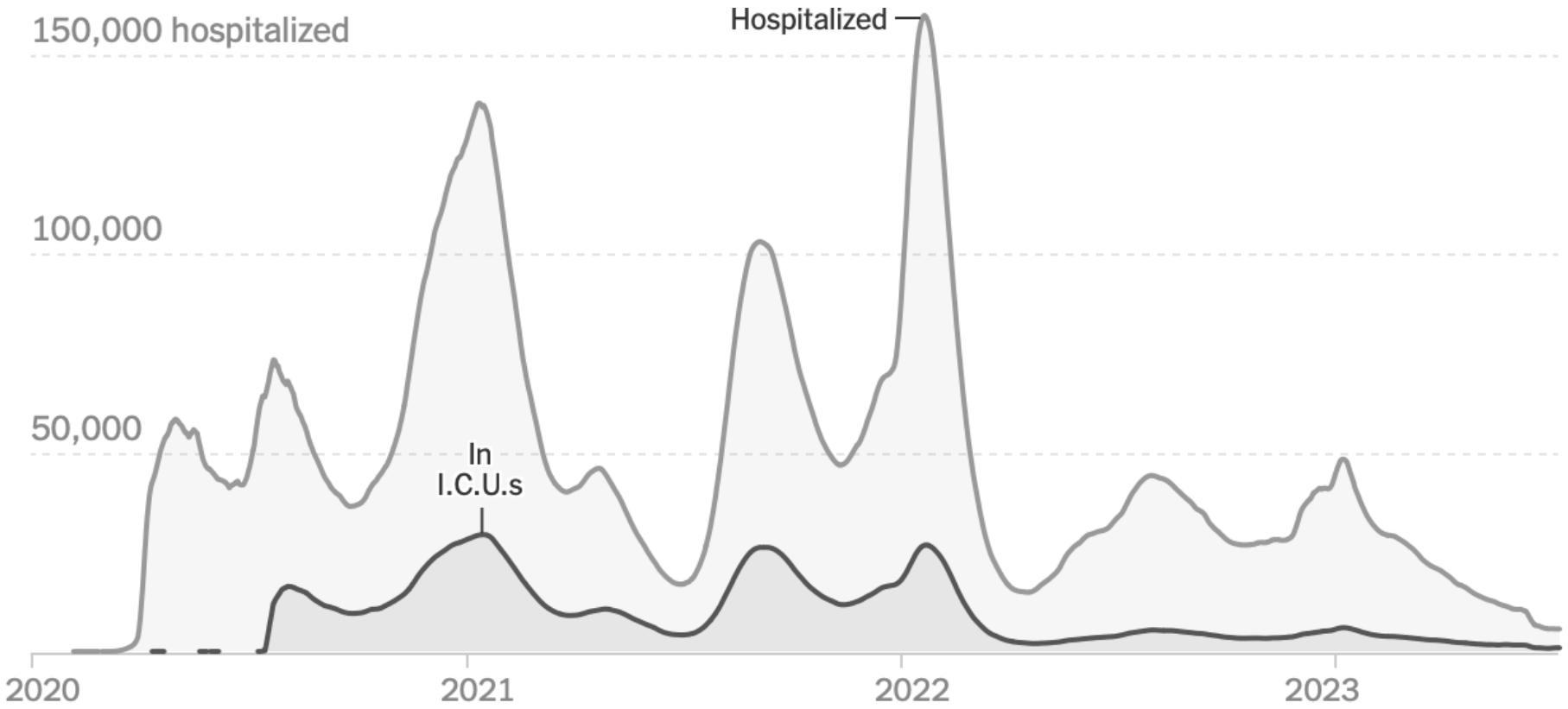
July 22, 2023

Average daily cases per 100,000 people in past week

10 30 50 70 100 250 Few or no cases

Source: New York Times https://www.nytimes.com/interactive/2023/us/covid-cases.html 7-22-2023

Hospital and ICU Admissions for COVID-19 in the United States

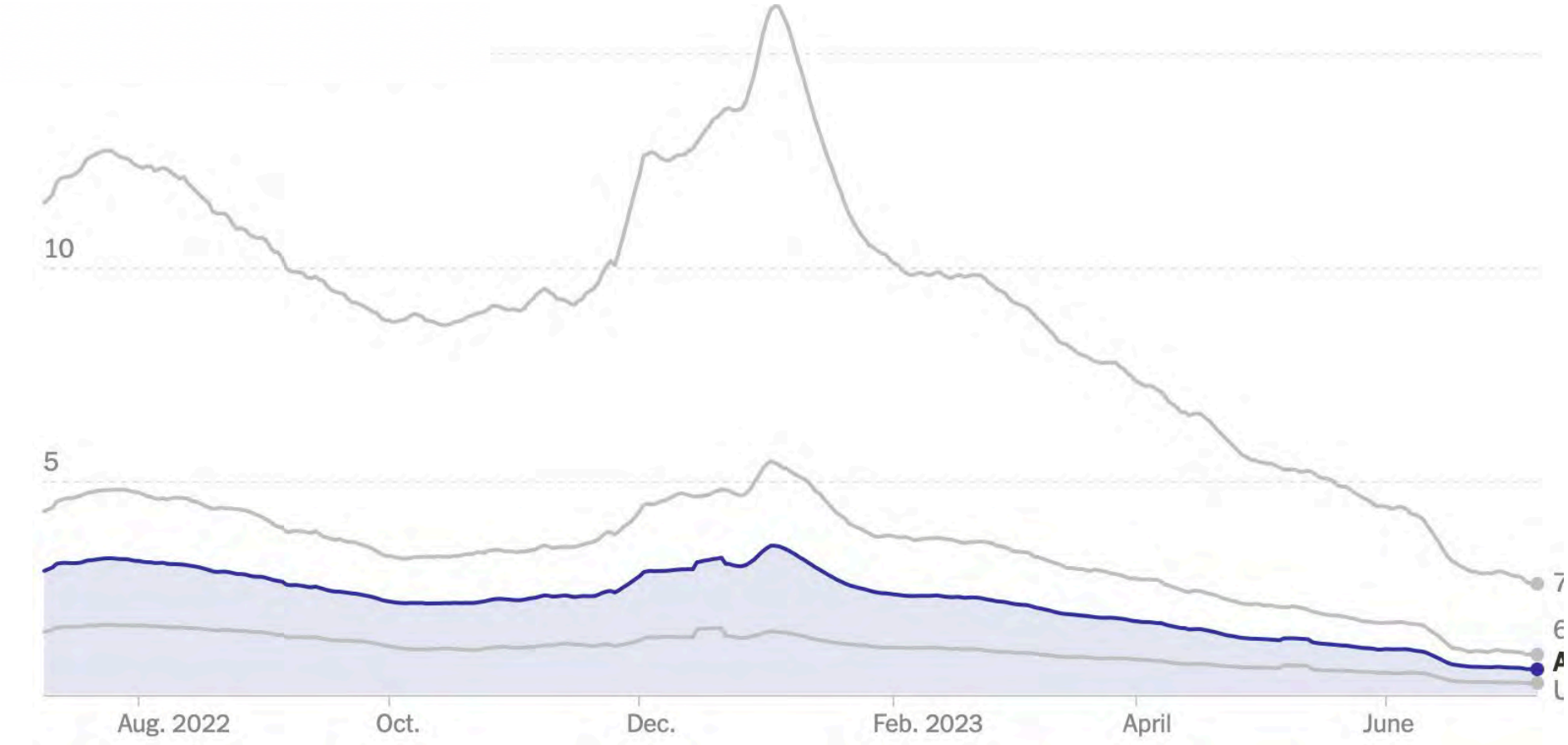


Hospitalizations decreased 9.9% from our last Town Hall

ICU admissions increased 2.4% from our last Town Hall

Source: New York Times –
https://www.nytimes.com/interactive/2023/us/covid-cases.html accessed 7-22-23

COVID-19 Daily Hospital Admissions in the United States, by Age

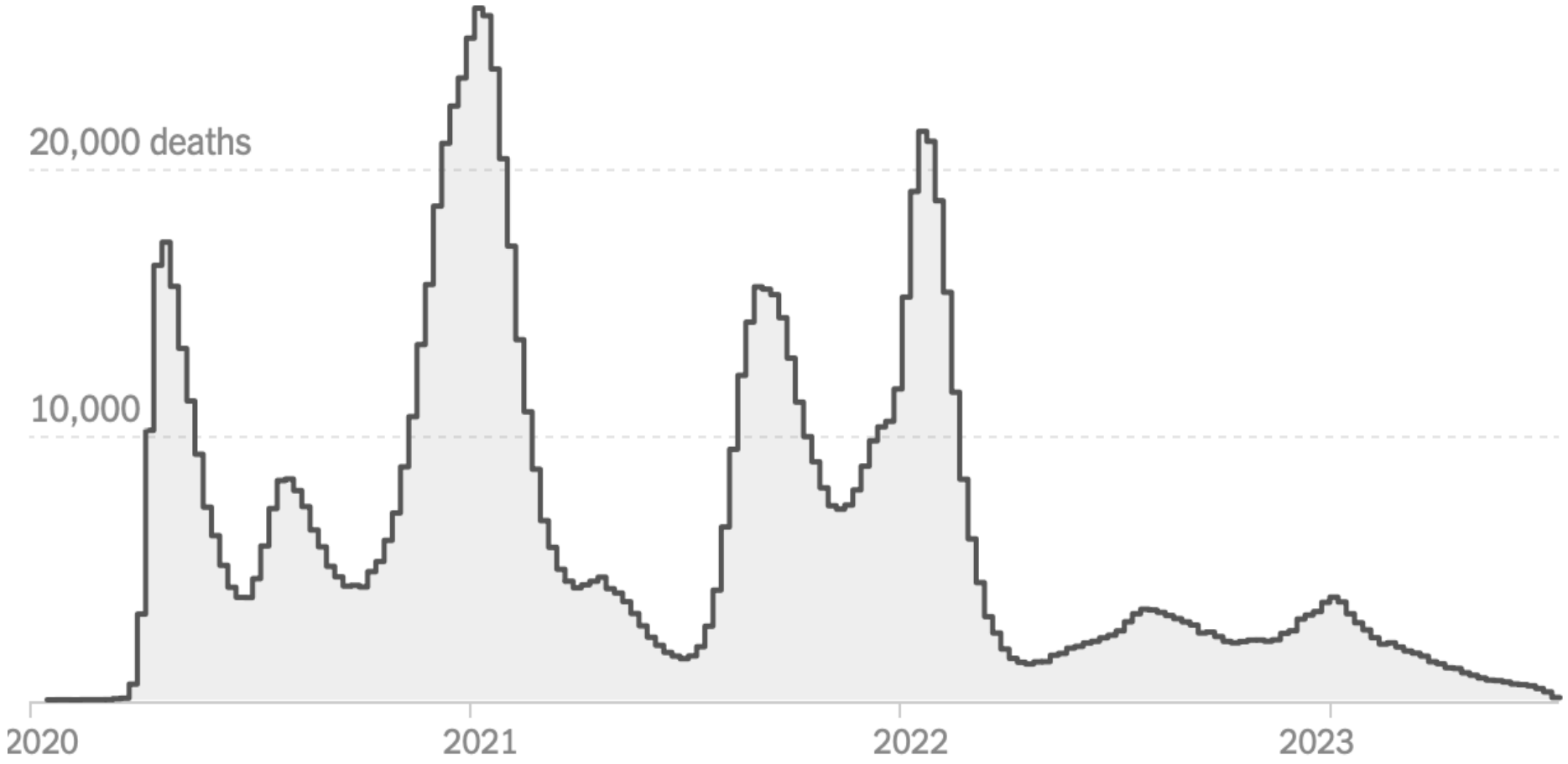


Daily hospitalizations decreased 9.4% from our last Town Hall

Source: New York Times 7-22-2023

COVID-19 Deaths in the United States

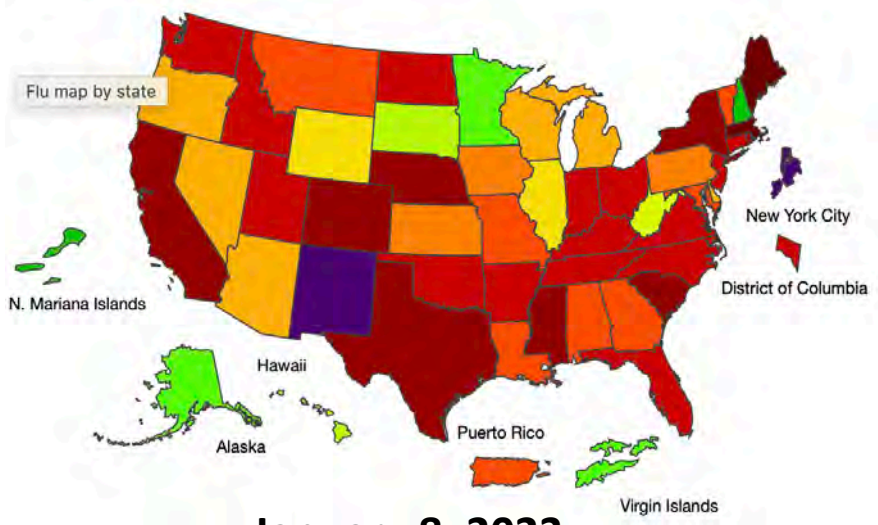
Cumulative Deaths – 1,132,206



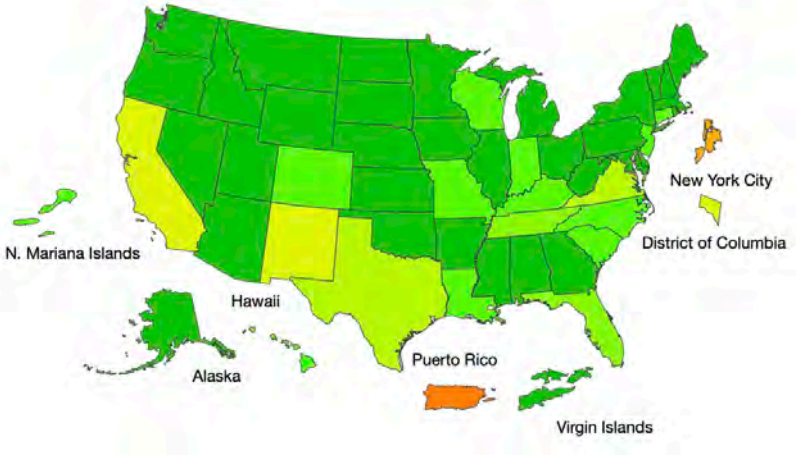
84.8% decrease from our last Town Hall

NY Times https://www.nytimes.com/interactive/2023/us/covid-cases.html **7-22-23**

Influenza Activity by State in the United States



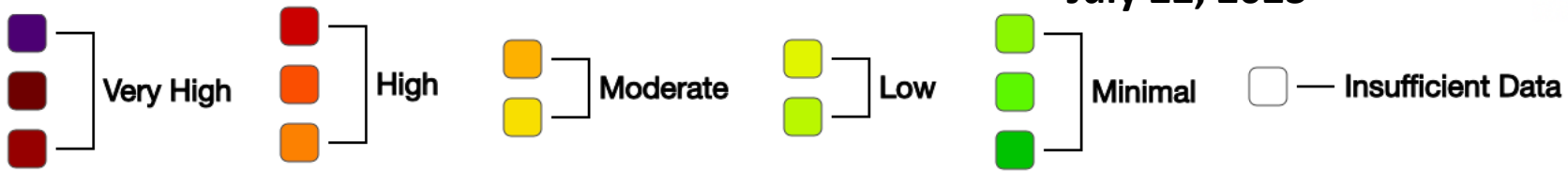
January 8, 2023



May 6, 2023

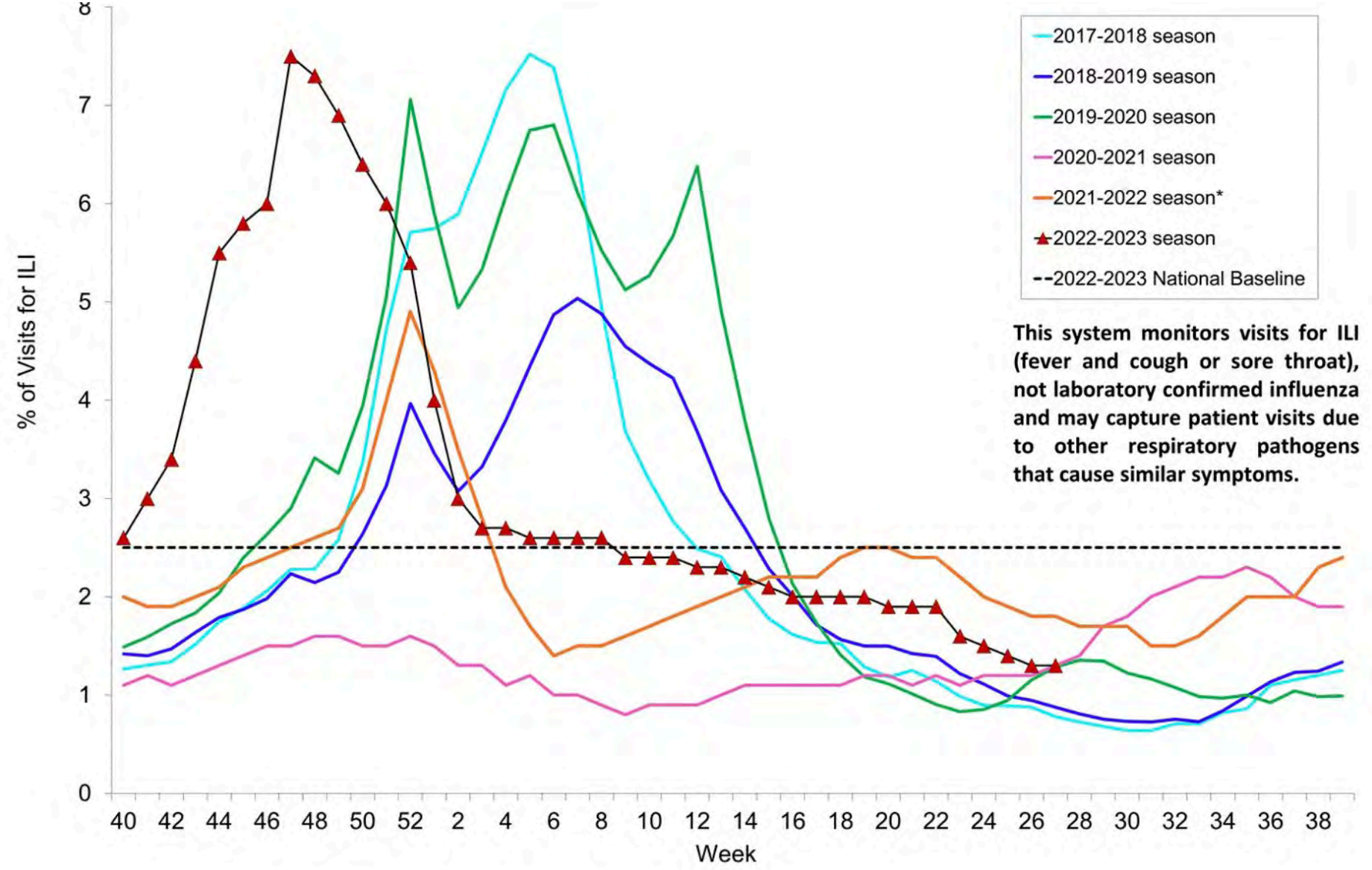
June 23, 2023

July 22, 2023



Source: CDC https://www.cdc.gov/flu/weekly/usmap.htm 7-22-23

Percentage of Outpatient Visits for Influenza-Like Illness



Source: CDC – https://www.cdc.gov/flu/weekly/index.htm – 7-22-2023

This Month's Emerging Infectious Disease News

1. A **JAMA** study of extended care facilities between May and December 2021 found that more than 40% of the facilities never administered either monoclonal antibodies or antiviral agents and also found evidence that structural barriers likely contributed to underuse and disparities..
2. A **JAMA** study from England found no evidence of an increased risk of stroke in the 21 days immediately after vaccination with either of the 2 mRNA COVID-19 bivalent BA.1 vaccines.
3. Another **JAMA** study found that time to recovery from COVID-19 pneumonia among hospitalized participants was not significantly affected by administration of abatacept, cenicriviroc, or infliximab when compared with standard care .
4. A **JAMA Pediatrics** study reported significant developmental delay in children exposed to the pandemic .
5. A **JAMA Network Open** paper found that, despite having better chronic risk factor profiles, patients admitted during the pandemic for heart failure, COPD, or asthma in Ontario and Alberta exhibited poorer outcomes (more required ICU admission and more died).
6. Another **JAMA Network Open** paper found that mRNA vaccines administered in pregnancy provoked an IgG response for the mother-infant dyad for 6 months after birth; post-vaccination systemic symptoms may indicate a more robust immune response, without adverse outcomes.
7. Another **JAMA Network Open** study performed a secondary analysis of placebo recipients in four randomized vaccine trials. finding that exposure history and demographic factors had the strongest outcome associations.
8. A scholarly article in **The Annals of Internal Medicine** addresses approaches to the societal management of viral medical rumors and false or misleading information.

References available in the chat

This Month's Emerging Infectious Disease News

9. A series of letters to the editor [and the Editor-in-Chief's response] in the July issue of **The Annals of Internal Medicine** address the limitations of a recently published study comparing masks and n95 respirators during care of COVID-19 patients .
10. Two opinion pieces published online together in **Clinical Infectious Diseases** provide point and counterpoint for routine COVID screening at admission.
11. A Brazilian study published in **Infection Control and Hospital Epidemiology** described the adverse effects on the pandemic on a national initiative to decrease healthcare-associated infections in ICUs
12. An opinion piece published in **Infection Control and Hospital Epidemiology** makes the case that to address vaccine hesitancy effectively, one has to have cultural competencies
13. A **Science Advances** paper describes the development and successful Phase 1 testing of a conjugated Influenza A and COVID-19 vaccine.
14. A **Lancet** paper just published online found that early initiation of Paxlovid was associated with a significantly reduced risk of all-cause mortality by day 28 when compared to molnupiravir, both in the overall population and in patient subgroups, including those fully vaccinated with the booster dose.
15. A **Nature** paper identified paper identified a common HLA allele associated with rapid clearance of SAR-CoV-2 (and therefore is associated with asymptomatic infection)
16. Two pieces in the past month in the **New York Times** provide outgoing CDC Director, Rochelle Walensky's, insights about the Nation's pandemic response as well her view of what needs to be done to prepare us for the next pandemic.

References available in the chat

Panelists:

Dr. David Henderson
NIH Consultant

Dr. Sarah Haessler
Baystate Health

Dr. Kristina Bryant
University of Louisville

Dr. David Weber
UNC School of Medicine

COVID-19 UPDATE
FOCUS ON LONG COVID-19: PREVENTION AND THERAPIES

David J. Weber, MD, MPH, FIDSA, FSHEA, FRSM (London)
Sanders Distinguished Professor of Medicine, Pediatrics and Epidemiology
Associate Chief Medical Officer
Medical Director, Hospital Epidemiology
University of North Carolina, Chapel Hill, NC

UNC
SCHOOL OF MEDICINE

Disclosures: Consultancy; Pfizer, Merck, PDI, BD, Germitec, Wellair
All drugs/vaccines issues discussed consistent with FDA approvals or authorizations

LONG COVID-19

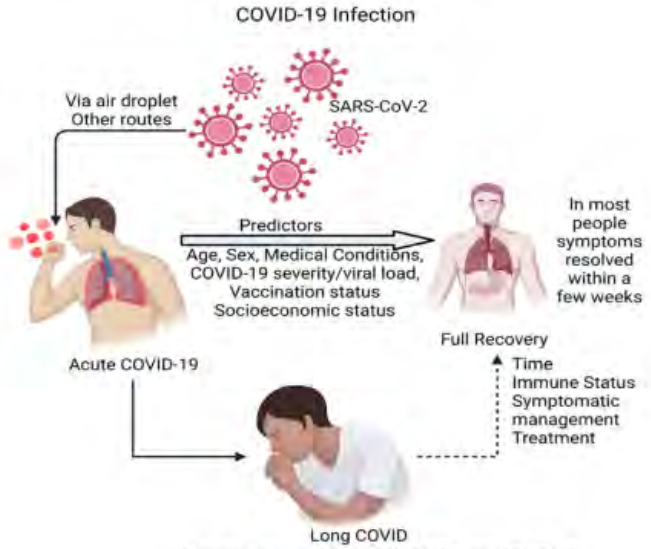


Figure 1: Long Covid as sequelae of acute Covid-19.
Initial hypotheses regarding COVID-19 postulated that age, sex, preexisting comorbidities, and severity of Covid-19 can raise the likelihood of long Covid. However, subsequent studies suggest long Covid can occur regardless of prior comorbidities or severity of acute Covid-19.

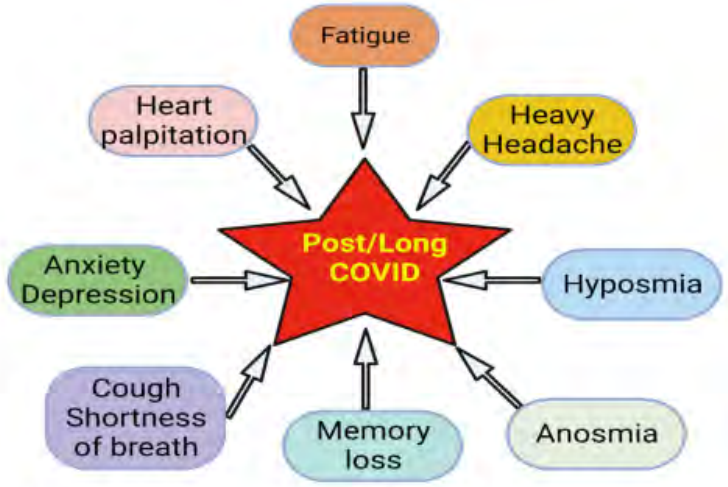


Figure 3:
Major clinical complications in long Covid after 12 weeks of initial infection

Figure 2:
Covid-19 infection affects almost all organs and organ systems are affected resulting in different pathophysiology. Few of the key symptoms and outcome results are shown. This is primarily due to the sequelae of cytokine storm.

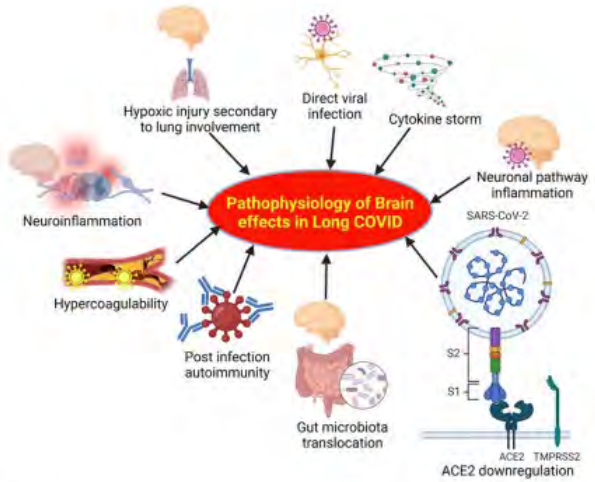


Figure 4:
Major factors post Covid in the underlying pathophysiology of brain effects in long Covid.

Zadeth FH, et al
Arch Micrbiol Immunol
2023;7:36-61

CONSEQUENCES OF COVID-19

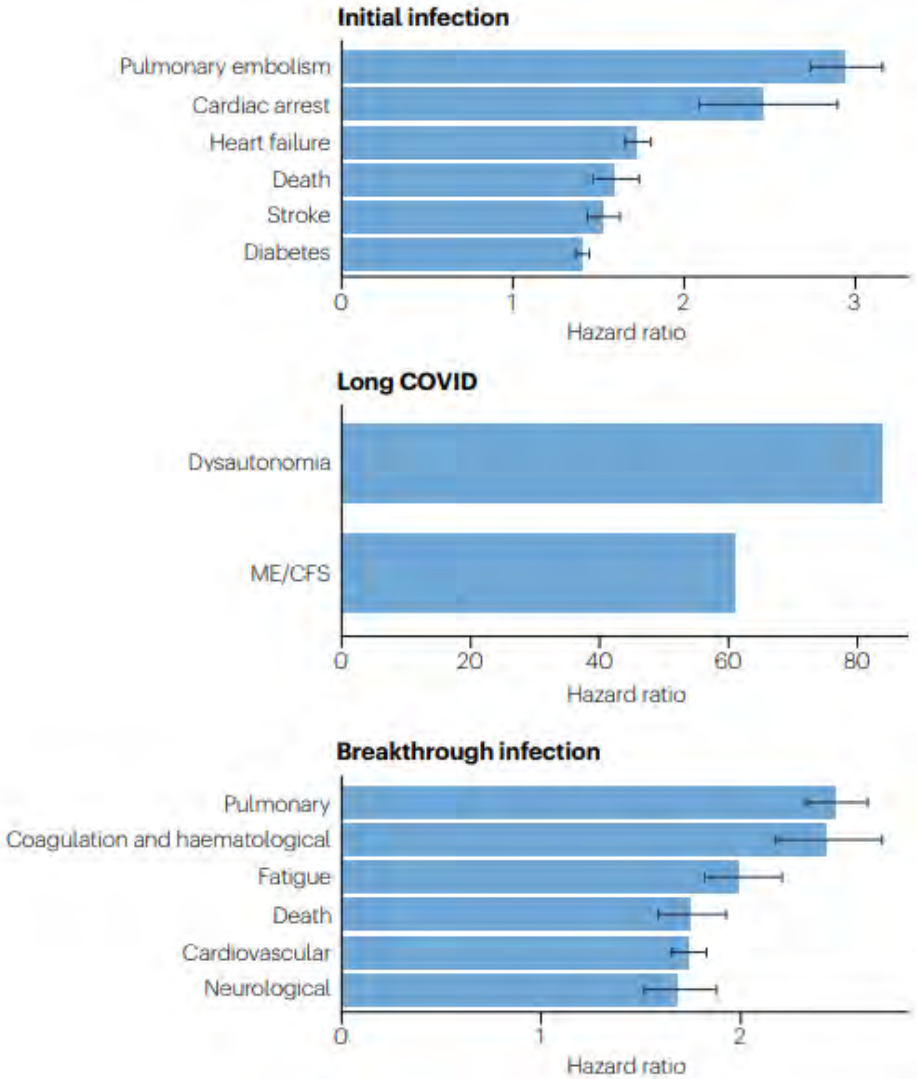


Fig. 2 | SARS-CoV-2 infection, COVID-19 and long COVID increases the risk of several medical conditions. Because diagnosis-specific data on large populations with long COVID are sparse, outcomes from general infections are included and a large proportion of medical conditions are expected to result from long COVID, although the precise proportion cannot be determined. One year after the initial infection, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections increased the risk of cardiac arrest, death, diabetes, heart failure, pulmonary embolism and stroke, as studied with use of US Department of Veterans Affairs databases. Additionally, there is clear increased risk of developing myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and dysautonomia. Six months after breakthrough infection, increased risks were observed for cardiovascular conditions, coagulation and haematological conditions, death, fatigue, neurological conditions and pulmonary conditions in the same cohort. The hazard ratio is the ratio of how often an event occurs in one group relative to another; in this case people who have had COVID-19 compared with those who have not. Data sources are as follows: diabetes[9], cardiovascular outcomes[8], dysautonomia[12,201], ME/CFS[10,202] and breakthrough infections[4].

Systematic Review of the Prevalence of Long COVID

Methods. We searched key registers and databases from 1/1/20-11/2/21, limited to publications in English and studies with at least 100 participants

Results. One hundred twenty studies in 130 publications were included. Length of follow-up varied between 12 weeks and 12 months. Few studies had low risk of bias. All complete and subgroup analyses except 1 had I2 ≥90%, with prevalence of persistent symptoms range of 0%–93% (pooled estimate [PE], 42.1%; 95% prediction interval [PI], 6.8% to 87.9%). Studies using routine healthcare records tended to report lower prevalence (PE, 13.6%; PI, 1.2% to 68%) of persistent symptoms/pathology than self report (PE, 43.9%; PI, 8.2% to 87.2%). However, studies systematically investigating pathology in all participants at follow up tended to report the highest estimates of all 3 (PE, 51.7%; PI, 12.3% to 89.1%). Studies of hospitalized cases had generally higher estimates than community-based studies.

Conclusions. The way in which Long COVID is defined and measured affects prevalence estimation. Given the widespread nature of SARS-CoV-2 infection globally, the burden of chronic illness is likely to be substantial even using the most conservative estimates

Woodrow M, et al. Open Forum ID 2023;3 May 2023

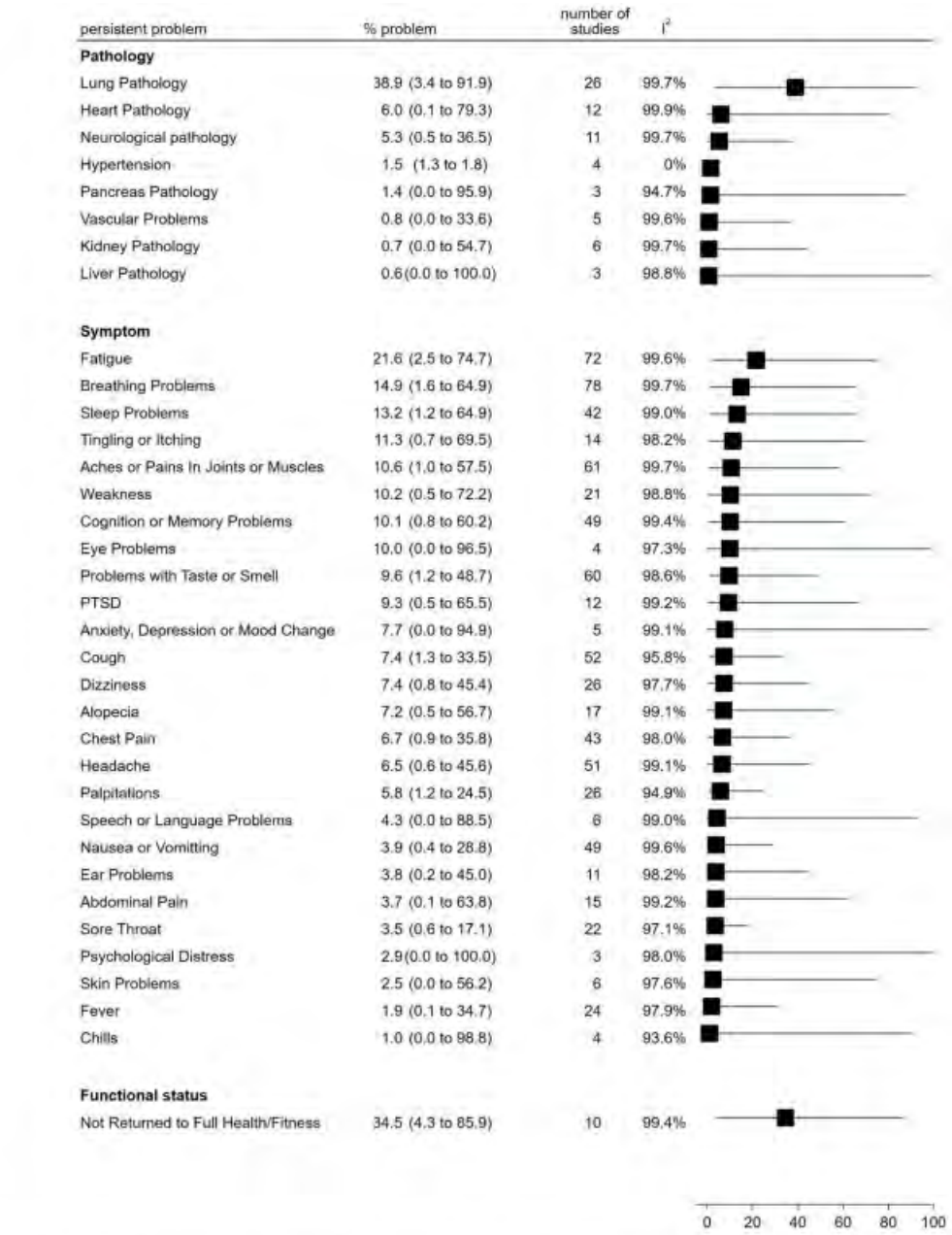
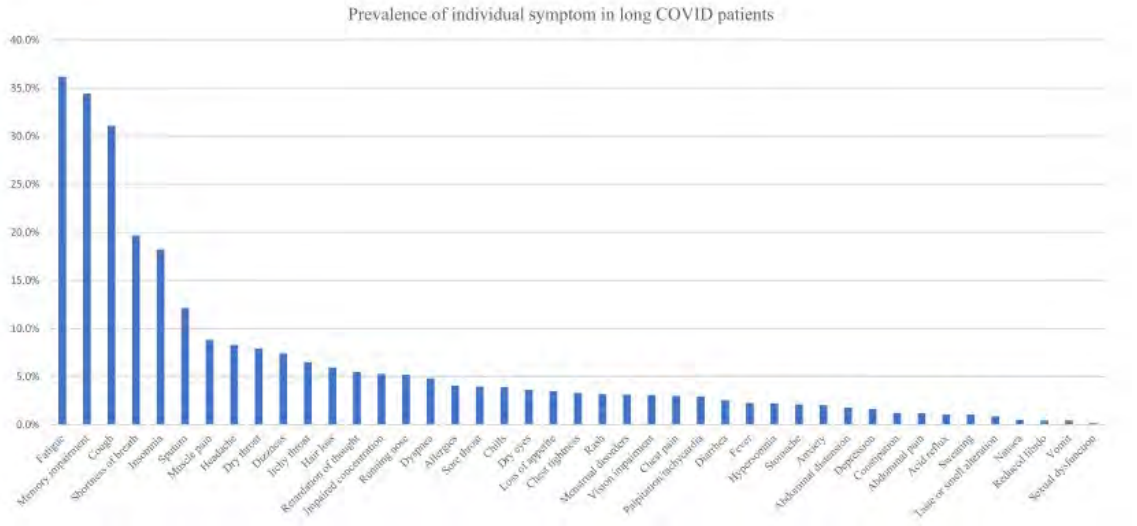


Figure 3. Forest plot of individual symptoms, pathology, and functional disability identified in the included studies, with 95% prediction intervals.

Prevalence and risk factors of long COVID 6–12 months after infection with the Omicron variant among non-hospitalized patients in Hong Kong

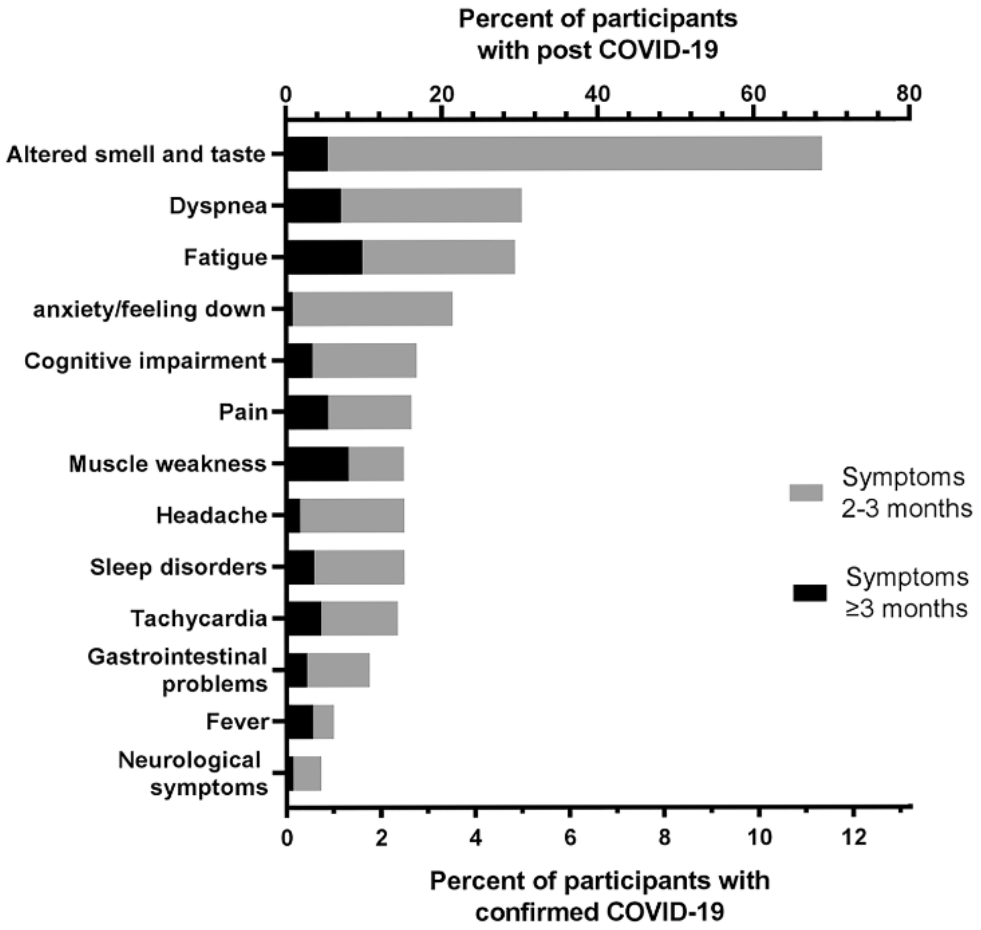
Long COVID has been reported among patients with COVID-19, but little is known about the prevalence and risk factors associated with long COVID 6–12 months after infection with the Omicron variant. This is a large-scale retrospective study. A total of 6242 out of 12 950 non-hospitalized subjects of all ages with SARS-CoV-2 infection (confirmed by polymerase chain reaction/rapid antigen test) during the Omicron dominant outbreak (December 31, 2021–May 6, 2022) in Hong Kong were included. Prevalence of long COVID, frequencies of symptoms, and risk factors were analyzed. Three thousand four hundred and thirty (55.0%) subjects reported at least one long COVID symptom. The most reported symptom was fatigue (1241, 36.2%). Female gender, middle age, obesity, comorbidities, vaccination after infection, having more symptoms, and presenting fatigue/chest tightness/headache/diarrhea in the acute stage of illness were identified as associated risk factors for long COVID. Patients who had received three or more doses of vaccine were not associated with a lower risk of long COVID (adjusted odds ratio 1.105, 95% confidence interval 0.985–1.239, p=0.088). Among patients with at least three doses of vaccine, there was no significant difference in the risk of long COVID between the CoronaVac vaccine and BNT162b2 vaccine (p > 0.05). Omicron infection can lead to long COVID in a significant proportion of non-hospitalized patients 6–12 months after infection. Further investigation is needed to uncover the mechanisms underlying the development of long COVID and determine the impact of various risk factors such as vaccines.



Luo J, et al. J Med Virol 2023;2 June

Post COVID-19 symptoms are common, also among young adults in the general population

Post coronavirus disease-19 (post COVID-19) is mainly studied in clinical populations and less is about post COVID-19 in a young general population. The aim of the study is to investigate the prevalence and symptoms of post COVID-19 and its potential risk factors in young adults. Participants from the Swedish population-based birth cohort BAMSE were included (n = 2022, mean age 26.5 years). Post COVID-19 was assessed through a questionnaire and defined as symptoms after confirmed COVID-19 (registry-based or self-reported positive test) lasting for ≥ 2 months. In total, 681 participants had had confirmed COVID-19. Among them, 112 (16.5%) fulfilled the definition of post COVID-19 (17.8% in females, 14.5% in males, p = 0.26). The most common post COVID-19 symptoms were altered smell and taste (68.8%), dyspnea (33.7%) and fatigue (30.4%). Overall, no major risk factors for post COVID-19 were identified except for being bedbound during COVID-19. However, asthma and rhinitis were associated with the post COVID-19 symptom dyspnea, migraine with altered smell and taste, and lower self-rated health with fatigue. In conclusion, post COVID-19 symptoms are common, also among young adults in the general population. Although not life-threatening, it could have a considerable impact on public health due to the high prevalence and long-term symptoms.



Mogensen I, et al. Nature Scientific Reports 2023;13:11300

EFFECTIVENESS OF ANTIVIRALS TO REDUCE RISK OF SEVERE COVID-19

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Randomized Trial of Metformin, Ivermectin, and Fluvoxamine for Covid-19

METHODS: In this phase 3, double-blind, randomized, placebo-controlled trial, we used a 2-by-3 factorial design to test the effectiveness of three repurposed drugs — metformin, ivermectin, and fluvoxamine — in preventing serious SARS-CoV-2 infection in non-hospitalized adults who had been enrolled within 3 days after a confirmed diagnosis of infection and less than 7 days after the onset of symptoms

RESULTS: The adjusted odds ratio for a primary event was 0.84 (95% confidence interval [CI], 0.66 to 1.09; P = 0.19) with metformin, 1.05 (95% CI, 0.76 to 1.45; P = 0.78) with ivermectin, and 0.94 (95% CI, 0.66 to 1.36; P = 0.75) with fluvoxamine. In prespecified secondary analyses, the adjusted odds ratio for emergency department visit, hospitalization, or death was 0.58 (95% CI, 0.35 to 0.94) with metformin, 1.39 (95% CI, 0.72 to 2.69) with ivermectin, and 1.17 (95% CI, 0.57 to 2.40) with fluvoxamine. The adjusted odds ratio for hospitalization or death was 0.47 (95% CI, 0.20 to 1.11) with metformin, 0.73 (95% CI, 0.19 to 2.77) with ivermectin, and 1.11 (95% CI, 0.33 to 3.76) with fluvoxamine.

CONCLUSIONS: None of the three medications that were evaluated prevented the occurrence of hypoxemia, an emergency department visit, hospitalization, or death associated with Covid-19.

Bramante CT, et al. NEJM 2022;387:599

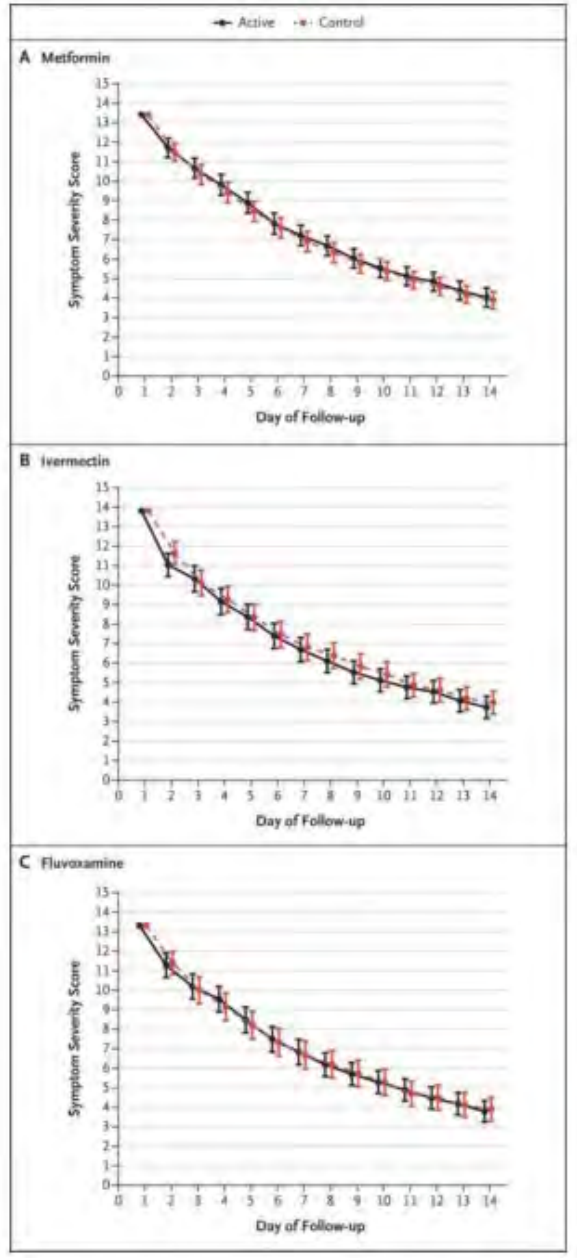


Figure 2. Total Scores on a Symptom Severity Scale during a 14-Day Period.

Real-world effectiveness of molnupiravir and Paxlovid against mortality, hospitalization, and in-hospital outcomes among community-dwelling, ambulatory patients with confirmed SARS-CoV-2 infection during the omicron wave in Hong Kong: an observational study

Methods: Observational study, 2/26/22-7/26/22; period when Omicron BA.2.2. dominant. Retrospective cohort design as primary analysis, and a case-control design.

Results: Molnupiravir use was associated with lower risks of death (HR 0·76 [95% CI 0·61–0·95]) and in-hospital disease progression (0·57 [0·43–0·76]) than non-use was, where a risk of hospitalization was similar in both groups (0·98 [0·89–1·06]). Nirmatrelvir plus ritonavir use was associate with lower risks of death (0·34 [0·22–0·52]), hospitalization (0·76 [0·67–0·86]), and in-hospital disease progression (0·57 [0·38–0·87]) than non-use was. We consistently found reduced risks of mortality and hospitalization associated with early oral antiviral use among older patients.

Conclusions: Early initiation of novel oral antivirals was associated with reduced risks of mortality and in-hospital disease progression. Nirmatrelvir plus ritonavir use was additionally associated with a reduced risk of hospitalization.

	Molnupiravir (n=4983)		Control (n=49 234)		Molnupiravir vs control	
	Crude incidence rate (events per 100 000 person-days)		Crude incidence rate (events per 100 000 person-days)		HR (95% CI)*	p value
	Estimate (95% CI)	Person-days	Estimate (95% CI)	Person-days		
All-cause mortality	17·9 (14·3–22·0)	492 995	22·1 (20·9–23·4)	5 134 524	0·76 (0·61–0·95)	0·013
Hospitalisation	107·6 (98·2–117·6)	450 697	104·0 (101·1–107·0)	4 740 249	0·98 (0·89–1·06)	0·58
In-hospital disease progression	10·2 (7·5–13·4)	491 635	16·8 (15·7–18·0)	5 115 217	0·57 (0·43–0·76)	0·0001
In-hospital death	7·3 (5·1–10·1)	492 995	12·9 (11·9–13·9)	5 134 524	0·53 (0·38–0·75)	0·0002
Invasive mechanical ventilation	1·4 (0·6–2·9)	492 609	3·4 (2·9–3·9)	5 127 257	0·40 (0·19–0·84)	0·016
Intensive care unit admission	3·5 (2·0–5·5)	491 635	4·4 (3·8–5·0)	5 116 681	0·74 (0·45–1·21)	0·24

HR=hazard ratio. *HRs greater than 1 indicate that molnupiravir users had higher risk of outcome compared with the matched control group.

Table 2: **Outcomes for outpatient molnupiravir users versus matched controls**

	Nirmatrelvir plus ritonavir (n=5542)		Control (n=54 672)		Nirmatrelvir plus ritonavir vs control	
	Crude incidence rate (events per 100 000 person-days)		Crude incidence rate (events per 100 000 person-days)		HR (95% CI)*	p value
	Estimate (95% CI)	Person-days	Estimate (95% CI)	Person-days		
All-cause mortality	4·2 (2·6–6·3)	528 328	11·6 (10·8–12·6)	5 471 588	0·34 (0·22–0·52)	<0·0001
Hospitalisation	48·5 (42·6–54·9)	507 655	61·0 (58·9–63·2)	5 221 023	0·76 (0·67–0·86)	<0·0001
In-hospital disease progression	4·6 (2·9–6·8)	526 844	7·5 (6·8–8·3)	5 462 351	0·57 (0·38–0·87)	0·0083
In-hospital death	1·5 (0·7–3·0)	528 328	5·8 (5·2–6·4)	5 471 588	0·25 (0·12–0·50)	0·0001
Invasive mechanical ventilation	0·8 (0·2–1·9)	527 944	1·2 (0·9–1·5)	5 468 815	0·62 (0·23–1·72)	0·36
Intensive care unit admission	3·2 (1·9–5·2)	526 926	1·9 (1·6–2·3)	5 463 019	1·58 (0·95–2·63)	0·078

HR=hazard ratio. *HRs greater than 1 indicate that nirmatrelvir plus ritonavir users had higher risk of outcome compared with the matched control group.

Table 3: **Outcomes for outpatient nirmatrelvir plus ritonavir users versus matched controls**

Wong CKH, et al. Lancet 2022;400:1213

Table 2: Public health impact and number needed to treat to avert COVID-19 cases, hospitalizations, and deaths with bivalent COVID-19 vaccine strategies.

	COVID-19 cases			COVID-19 hospitalizations			COVID-19 deaths		
	NNT	Total Averted	% Averted	NNT	Total averted	% Averted	NNT	Total averted	% Averted
Everyone									
Strategy 1 *Everyone*[a]	100 (83 – 130)	326,111 (249,538 – 393,601)	28.3% (21.7 – 34.2)	2,025 (1,707 – 2,881)	15,995 (11,241 – 18,975)	31.7% (22.3 – 37.6)	10,854 (8,304 – 14,560)	2,983 (2,224 – 3,899)	45.0% (33.5 – 58.8)
Vaccine group-based strategies									
Strategy 2 *Previously vaccinated*	128 (97 – 205)	200,588 (125,016 – 264,472)	17.4% (10.9 – 23.0)	2,212 (1,749 – 3,615)	11,561 (7,074 – 14,621)	22.9% (14.0 – 29.0)	14,619 (10,368 – 22,180)	1,749 (1,153 – 2,466)	26.4% (17.4 – 37.2)
Strategy 3 *Unvaccinated*[a]	55 (50 – 61)	125,524 (113,288 – 136,562)	10.9% (9.8 – 11.9)	1,537 (1,289 – 2,076)	4,433 (3,281 – 5,283)	8.8% (6.5 – 10.5)	5,523 (4,321 – 7,316)	1,233 (931 – 1,576)	18.6% (14.0 – 23.8)
Strategy 4 *Primary Series Only*	137 (105 – 214)	85,429 (54,515 – 111,943)	7.4% (4.7 – 9.7)	2,197 (1,785 – 3,005)	5,308 (3,881 – 6,533)	10.5% (7.7 – 13.0)	14,742 (11,278 – 19,598)	791 (595 – 1,034)	11.9% (9.0 – 15.6)
Age group-based strategies									
Strategy 5 *75+ years*	106 (81 – 172)	14,318 (8,837 – 18,870)	1.2% (0.8 – 1.6)	387 (311 – 608)	3,920 (2,491 – 4,882)	7.8% (4.9 – 9.7)	1,410 (1,118 – 1,957)	1,074 (774 – 1,355)	16.2% (11.7 – 20.4)
Strategy 6 *65+ years*	130 (99 – 211)	29,100 (17,951 – 38,341)	2.5% (1.6 – 3.3)	661 (531 – 1,040)	5,707 (3,628 – 7,106)	11.3% (7.2 – 14.1)	2,714 (2,134 – 3,811)	1,390 (990 – 1,768)	21.0% (14.9 – 26.7)
Strategy 7 *50+ years*	130 (98 – 211)	68,747 (42,169 – 91,094)	6.0% (3.7 – 7.9)	1,144 (912 – 1,832)	7,778 (4,858 – 9,763)	15.4% (9.6 – 19.4)	5,458 (4,192 – 7,845)	1,630 (1,134 – 2,122)	24.6% (17.1 – 32.0)

[a]For unvaccinated persons, we assumed the vaccine administered was a monovalent dose following current clinical guidance for the primary series.
All analyses compared perfect vaccine uptake to baseline coverage of bivalent vaccines.
All age group-based strategies (Strategies 5-7) excluded the unvaccinated population when targeting vaccines to older age groups.
NNT; number needed to treat.

Table 3: Public health impact and number needed to treat for nirmatrelvir-ritonavir during COVID-19 infection to avert hospitalizations and deaths.

	COVID-19 hospitalizations			COVID-19 deaths		
	NNT	Total averted	% Averted	NNT	Total averted	% Averted
Age group-based strategies *Based on current eligibility*						
Strategy 1 (50+ years)	19 (16-27)	9,699 (6,882 – 11,611)	19.2% (13.9 – 22.7)	79 (65 - 126)	2,323 (1,458 – 2,866)	35.0% (22.5 – 41.8)
Strategy 2 (65+ years)	15 (12 – 21)	8,218 (5,745 – 9,941)	16.3% (11.5 – 19.5)	54 (44 – 87)	2,160 (1,339 – 2,661)	32.6% (20.5 – 39.3)
Strategy 3 (75+ years)	11 (9 – 15)	5,644 (3,947 – 6,826)	11.2% (7.9 – 13.4)	35 (29 – 55)	1,669 (1,053 – 2,038)	25.2% (15.8 – 30.5)

All analyses compared current uptake (30% in eligible COVID-19 cases without medical contraindications) to 100%.

Methods: This modeling study used person-level data from the California Department of Public Health on COVID-19 cases, hospitalizations, deaths, and vaccine administration from July 23, 2022 to January 23, 2023.

Results: : For both bivalent vaccines and nirmatrelvir -ritonavir, the most efficient strategy (based on NNT) for averting severe COVID-19 was targeting the 75+ years group. We predicted that perfect coverage of bivalent boosters in the 75+ years group would avert 3,920 hospitalizations (95%UI: 2,491-4,882; 7.8% total averted; NNT 387) and 1,074 deaths (95%UI: 774-1,355; 16.2% total averted; NNT 1,410). Perfect uptake of nirmatrelvir-ritonavir in the 75+ years group would avert 5,644 hospitalizations (95%UI: 3,947-6,826; 11.2% total averted; NNT 11) and 1,669 deaths (95%UI: 1,053-2,038; 25.2% total averted; NNT 35).

Park HJ, et al.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10246024/pdf/nihpp-2023.05.18.23289533v1.pdf

THERAPEUTICS DEMONSTRATED TO REDUCE RISK OF POST-COVID-19 SEQUELAE

COVID-19 Vaccine

Paxlovid

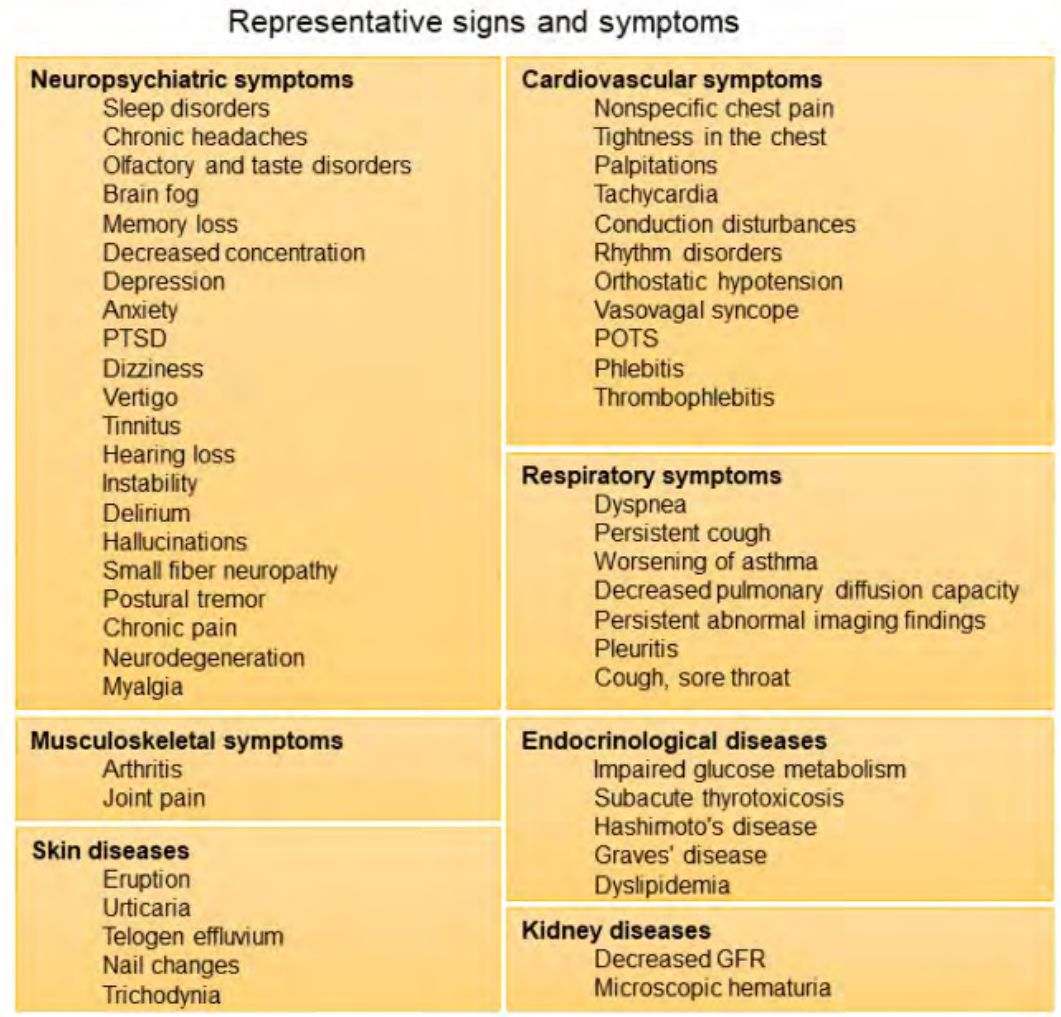
Mulnupiravir

UNC SCHOOL OF MEDICINE

POST COVID-19 SEQUELAE

Nomenclature of post-COVID-19 conditions

- Post-COVID condition (WHO, CDC)
- Long COVID syndrome Long COVID
- Long-haul COVID Post-acute COVID-19
- Long-term effects of COVID Chronic COVID
- Post-acute sequelae of SARS-CoV-2 infection (PASC)
- Post-COVID Neurological Syndrome (PCNS)



Takao M, Ohira M. Psychiatry Clin Neurosci 2023;77:72-83

Molnupiravir and risk of post-acute sequelae of covid-19: cohort study

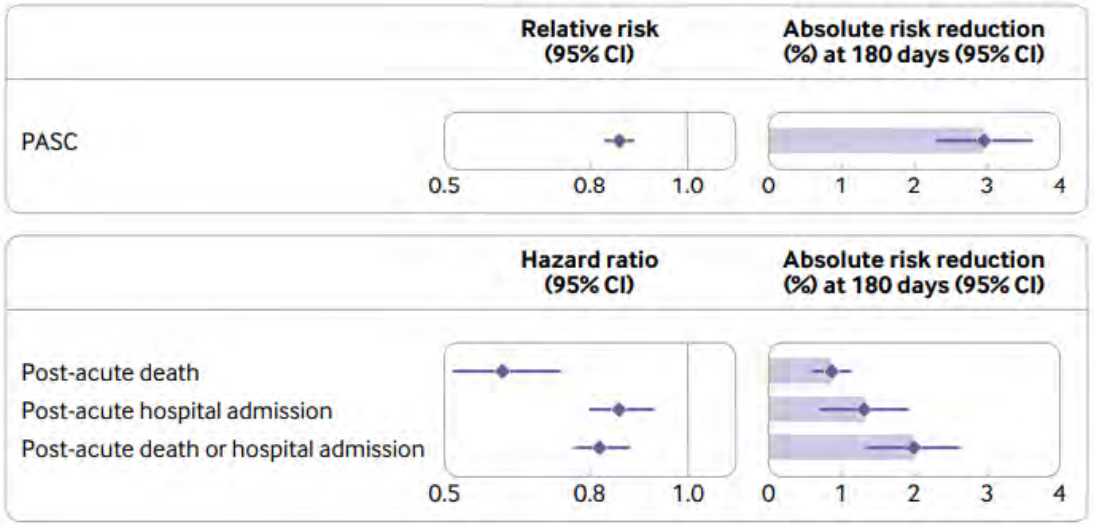
WHAT IS ALREADY KNOWN ON THIS TOPIC

Among people with SARS-CoV-2 infection, molnupiravir use within five days of symptom onset has been shown to reduce the risk of hospital admission or death in people at risk of progression to severe covid-19

WHAT THIS STUDY ADDS

In people with SARS-CoV-2 infection and at least one risk factor for progression to severe covid-19, compared with no treatment, molnupiravir use during the first five days after a positive SARS-CoV-2 test result was associated with reduced risk of post-acute sequelae of SARS-CoV-2

The reduced risk in the molnupiravir group was evident in those who had not received a covid-19 vaccine, received at least one vaccine dose, and had received a booster dose, and in those with primary SARS-CoV-2 infection and reinfection



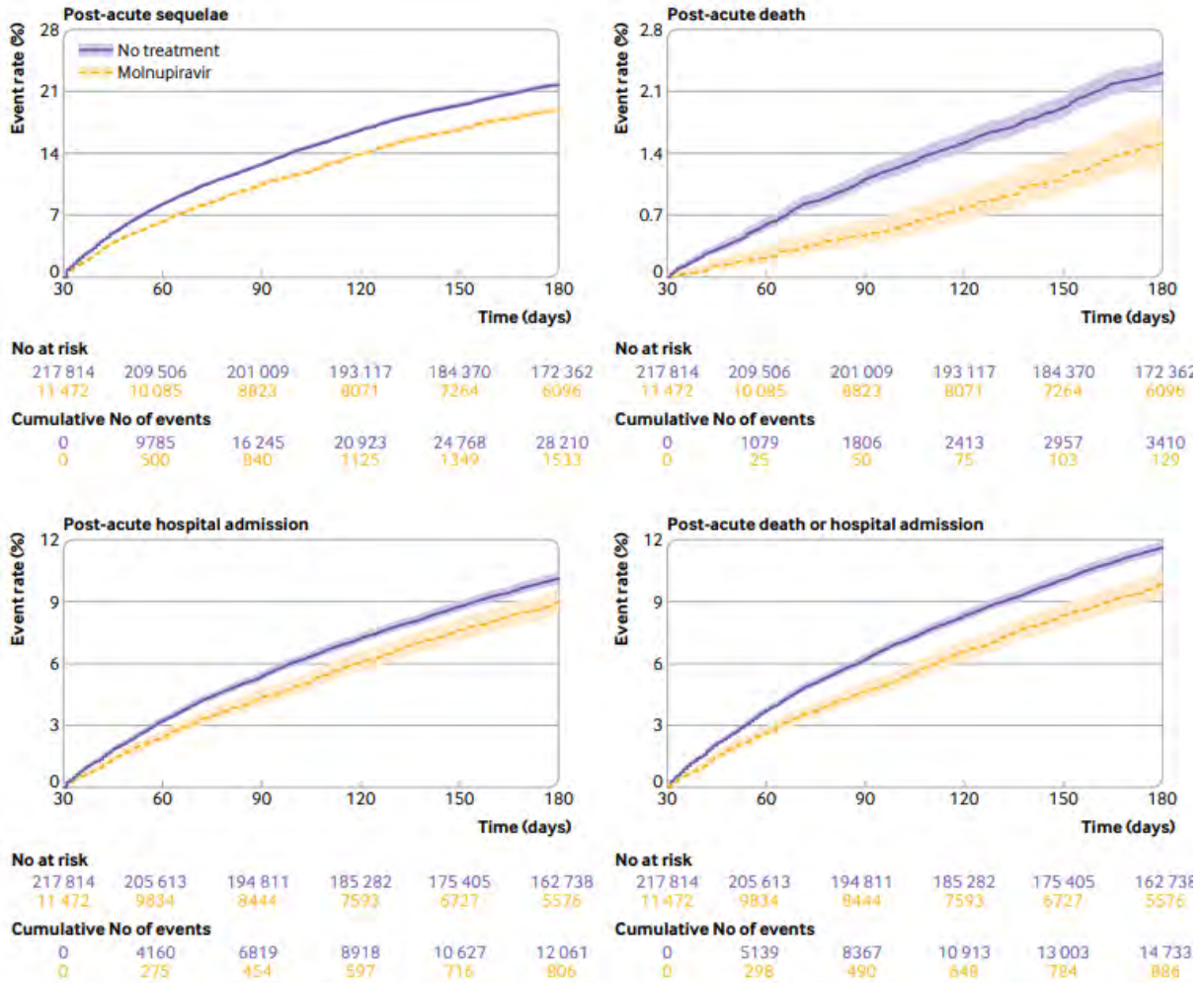


Fig 2 | Event rates of post-acute sequelae in molnupiravir group (n=11 472) and no treatment group (n=217 814). Post-acute outcomes were ascertained 30 days after a first SARS-CoV-2 positive test result between 5 January 2022 and 15 January 2023 until end of follow-up. Event rates were estimated based on inverse probability weighting method. Shading represents 95% confidence intervals (CIs)

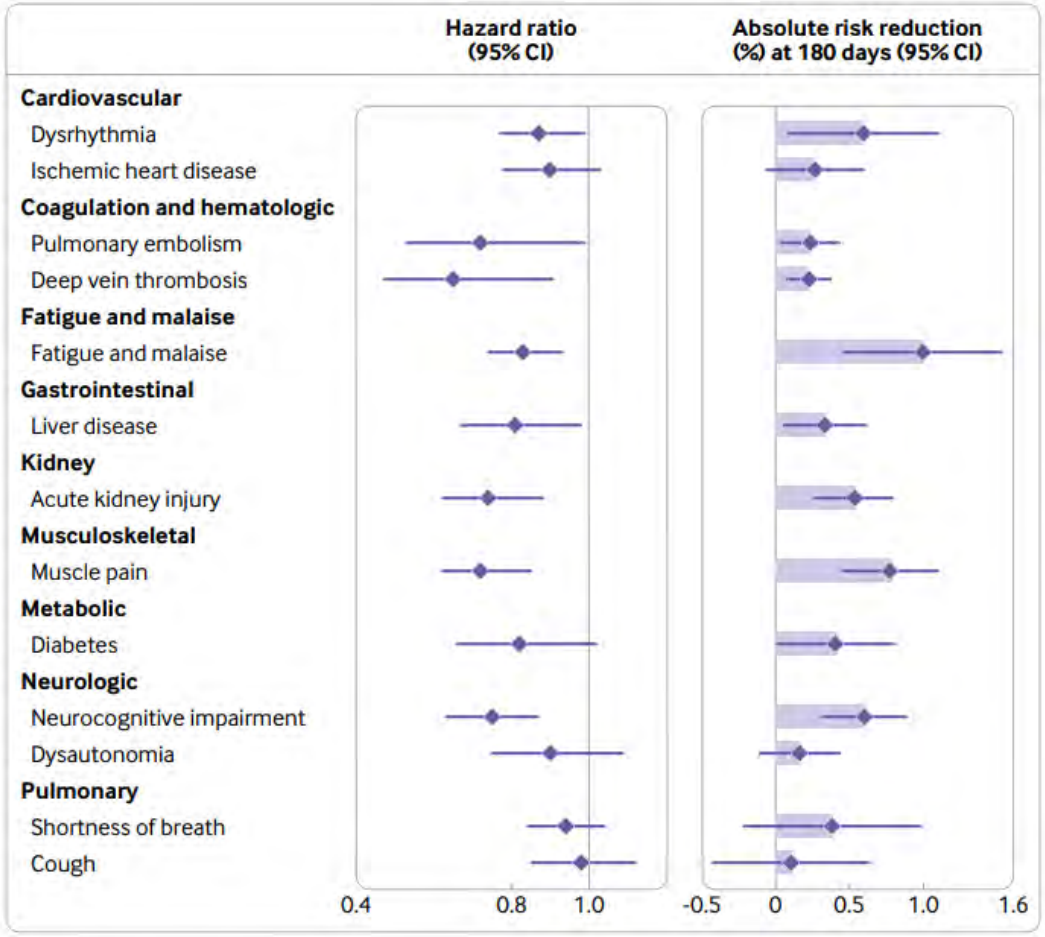
Xie Y, et al. BMJ 2023;381:e074572

Molnupiravir and risk of post-acute sequelae of covid-19: cohort study

Methods: Cohort study in US VA. 229286 participants who tested positive for SARSCoV-2 between 1/5/22-1/15/23, had at least one risk factor for progression to severe covid-19, and survived the first 30 days after testing positive were enrolled.

Results: Compared with no treatment, molnupiravir use within five days of a positive SARS-CoV-2 test result was associated with reduced risk of PASC (relative risk 0.86 (95% confidence interval 0.83 to 0.89); absolute risk reduction at 180 days 2.97% (95% confidence interval 2.31% to 3.60%)), post-acute death (hazard ratio 0.62 (0.52 to 0.74); 0.87% (0.62% to 1.13%), and post-acute hospital admission (0.86 (0.80 to 0.93); 1.32% (0.72% to 1.92%)). Molnupiravir was associated with reduced risk of eight of the 13 postacute sequelae: dysrhythmia, pulmonary embolism, deep vein thrombosis, fatigue and malaise, liver disease, acute kidney injury, muscle pain, and neurocognitive impairment. Molnupiravir was also associated with reduced risk of PASC in people who had not received a covid-19 vaccine, had received at one or two vaccine doses, and had received a booster dose, and in people with primary SARS-CoV-2 infection and reinfection.

Xie Y, et al. BMJ2023;381:e074572



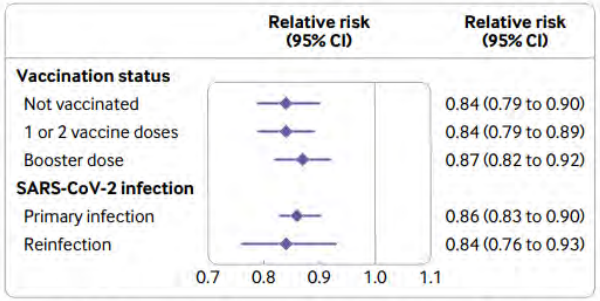


Fig 4 | Relative risk of molnupiravir compared with no treatment on post-acute sequelae of covid-19 according to vaccination status and primary SARS-CoV-2 infection or reinfection. Outcomes were ascertained 30 days after a first SARS-CoV-2 positive test result between 5 January 2022 and 15 January 2023 until end of follow-up. CI=confidence interval

Outpatient treatment of Covid-19 with metformin, ivermectin, & fluvoxamine and the development of Long Covid over 10-month follow-up.

Methods: This was a decentralized, remotely delivered trial in the US of 1,125 adults age 30 to 85 with overweight or obesity, fewer than 7 days of symptoms, and enrolled within 3 days of a documented SARS-CoV-2 infection. Multi-site, phase 3, randomized, quadruple-blinded placebo-controlled clinical trial.

Result: The median age was 45 years (IQR 37 to 54), 56% female of whom 7% were pregnant. Two percent identified as Native American; 3.7% as Asian; 7.4% as Black/African American; 82.8% as white; and 12.7% as Hispanic/Latino. The median BMI was 29.8 kg/m2 (IQR 27 to 34); 51% had a BMI >30kg/m2 . Overall, 8.4% reported having received a diagnosis of Long Covid from a medical provider: 6.3% in the metformin group and 10.6% in the metformin control; 8.0% in the ivermectin group and 8.1% in the ivermectin control; and 10.1% in the fluvoxamine group and 7.5% in the fluvoxamine control. The Hazard Ratio (HR) for Long Covid in the metformin group versus control was 0.58 (95% CI 0.38 to 0.88); 0.99 (95% CI 0.592 to 1.643) in the ivermectin group; and 1.36 in the fluvoxamine group (95% CI 0.785 to 2.385).

Conclusions: There was a 42% relative decrease in the incidence of Long Covid in the metformin group compared to its blinded control in a secondary outcome of this randomized phase 3 trial.

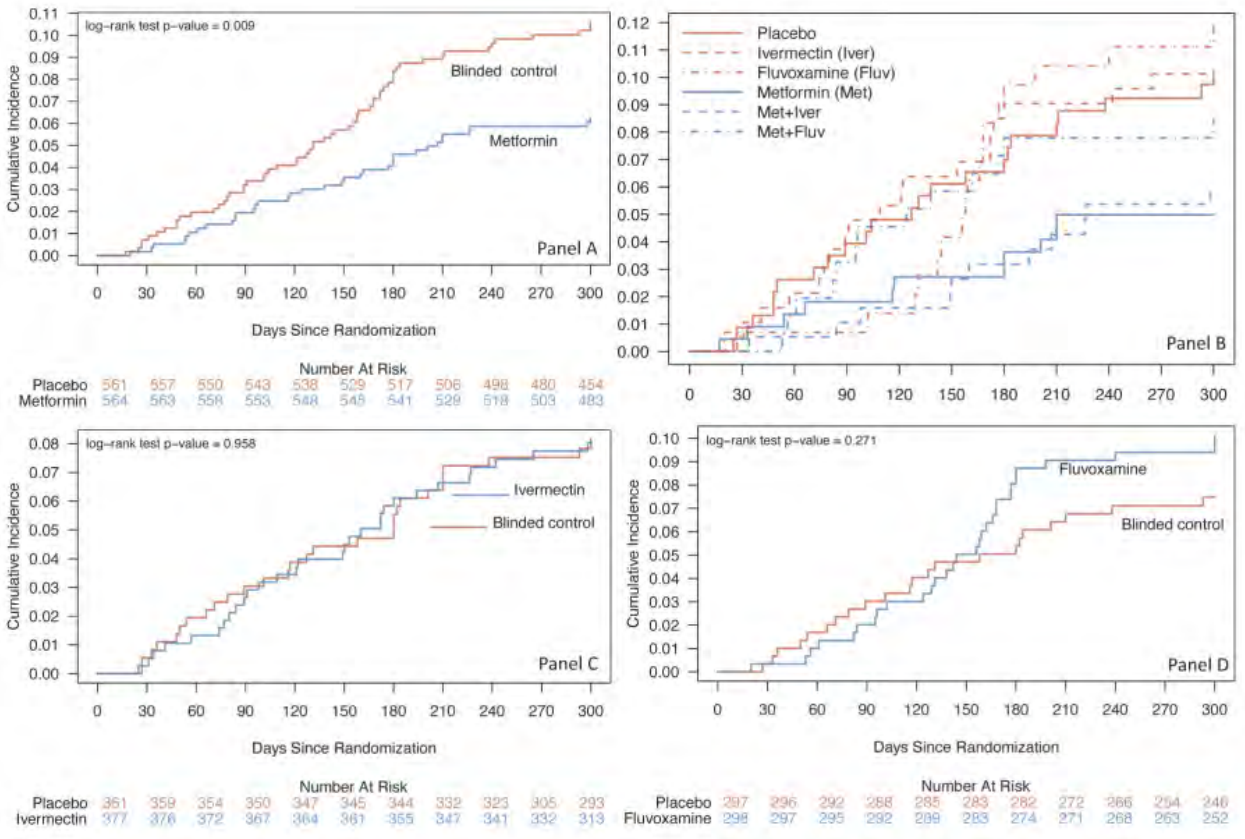


Figure 2. Cumulative incidence of "Long Covid," post-acute sequelae of SARS-CoV-2 infection (PASC), diagnosed by a medical provider over 10 months after randomization. Panel A is metformin; Panel B is all 6 arms in the trial; Panel C is ivermectin; Panel D is fluvoxamine. In this factorial design trial, each participant received two types of pills. Every participant received a pill that looked like metformin -- either metformin or an exact-matching metformin placebo. The second pill was active fluvoxamine or ivermectin, or their exact matching placebo.

Bramante CT, et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9810227/pdf/nihpp-2022.12.21.22283753v1.pdf

Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicenter, randomized, quadruple-blind, parallel-group, phase 3 trial

Results: Overall, 93 (8·3%) of 1126 participants reported receipt of a long COVID diagnosis by day 300. The cumulative incidence of long COVID by day 300 was 6·3% (95% CI 4·2–8·2) in participants who received metformin and 10·4% (7·8–12·9) in those who received identical metformin placebo (hazard ratio [HR] 0·59, 95% CI 0·39–0·89; p=0·012). The metformin beneficial effect was consistent across prespecified subgroups. When metformin was started within 3 days of symptom onset, the HR was 0·37 (95% CI 0·15–0·95). There was no effect on cumulative incidence of long COVID with ivermectin (HR 0·99, 95% CI 0·59–1·64) or fluvoxamine (1·36, 0·78–2·34) compared with placebo.

Conclusion: Outpatient treatment with metformin reduced long COVID incidence by about 41%, with an absolute reduction of 4·1%, compared with placebo. Metformin has clinical benefits when used as outpatient treatment for COVID-19 and is globally available, low-cost, and safe.

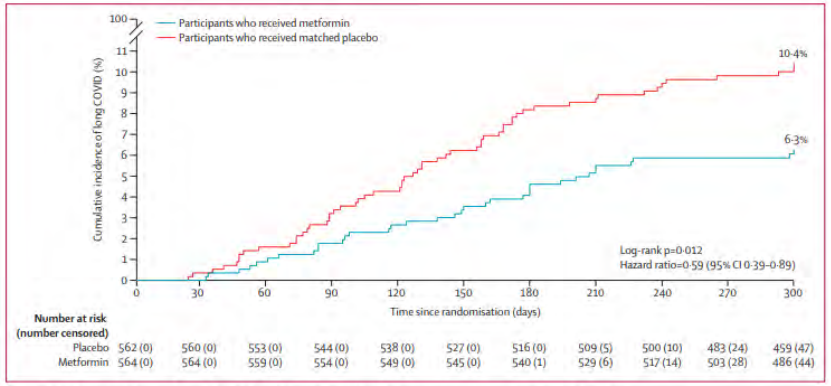


Figure 2: **Cumulative incidence of post-COVID-19 condition (long COVID) diagnoses over 10 months after randomisation**
The absolute risk reduction for metformin compared with matched placebo was 4·1% (95% CI 0·9–7·4).

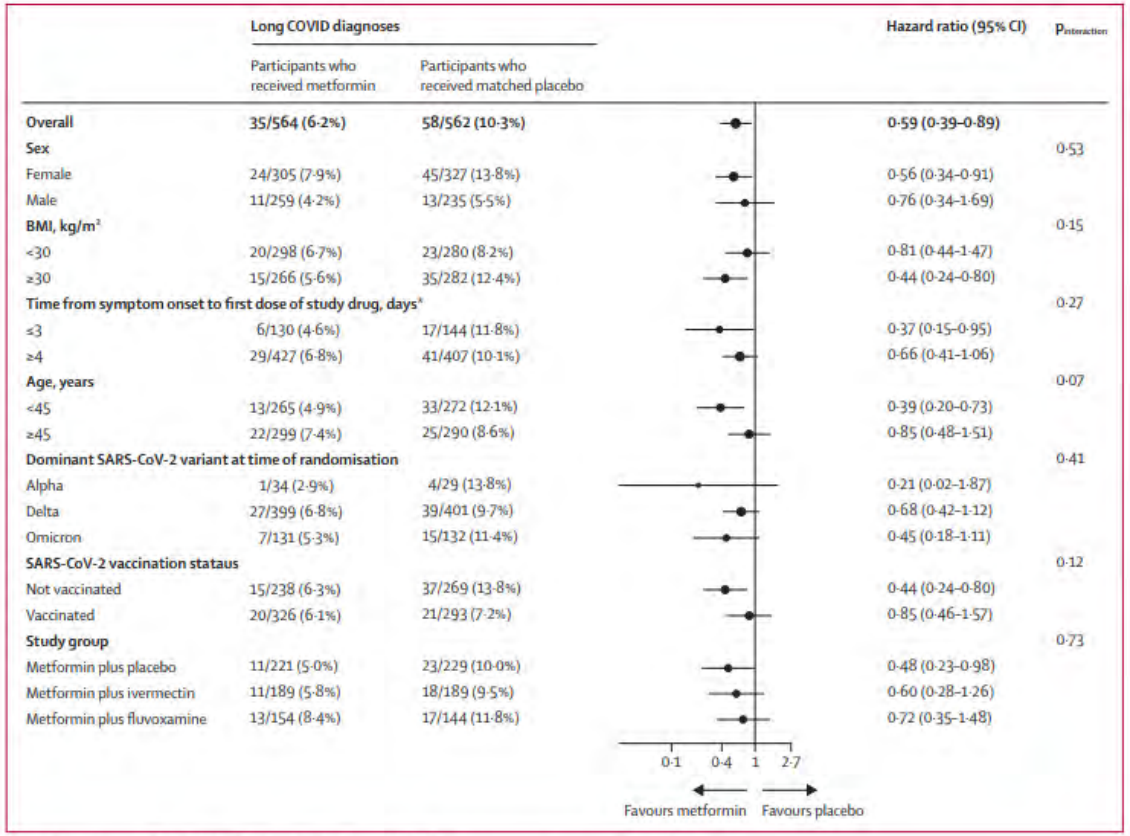


Figure 3: **Incidence of post-COVID-19 condition (long COVID) diagnoses across prespecified subgroups**
Error bars are 95% CIs. *For 18 (1·6%) of the 1126 participants, the timing of study drug initiation was not known.

Bramante CT, et al. Lancet ID 2023;June 8

CONCLUSIONS

- COVID-19 vaccination demonstrated to reduce risk of severe COVID-19 and post-acute sequelae of COVID-19. Caveats:
  - Bivalent vaccine more effective than ancestral vaccine. However, effectiveness against XBB variants reduced.
  - Impact of vaccine lower at present due to waning of vaccine induced immunity, lower virulence of XBB variants, and high prevalence of natural immunity
  - XBB univalent booster will be available in the Fall
- Paxlovid effective in reducing risk of severe COVID-19 in all subgroups (e.g., vaccinated, older, immunocompromised) and effective in reducing risk of long COVID-19. Paxlovid now FDA approved
  - Major limitation is use is drug interactions. Cost may also be a factor
- Mulnupiravir also effective in reducing risk of severe COVID-19 and reducing risk of long COVID-19, but effectiveness lower than Paxlovid (see Saravatz LD, et al. Clin Infect Dis 2023;76:165)
- Metformin likely effective in reducing risk of long COVID-19
  - Effectiveness in reducing risk of severe COVID-19 not defined – likely major limitation in use compared to Paxlovid and Mulnupiravir
- Oral antivirals need to be administered within 5 days of onset of symptoms.
- At the present, best protection offered by being up-to-date with COVID-19 vaccines (i.e., receipt of bivalent vaccine) plus use of Paxlovid for patients at high risk for severe COVID-19 and/or PASC.
- No proven therapies for Long COVID-19 (need RCTs). Novel therapies for long COVID-19 should be explored