Covid-19 Update – A Discussion

Robert Dachs, MD, FAAFP
(Conference Chair)
Director of Graduate Medical Education
Department of Emergency Medicine
Ellis Hospital, Clinical Associate Professor
Family Residency Program
Albany Medical College
Schenectady, NY

Monica Gandhi, MD
Professor of Medicine
Associate Chief
Division of HIV, Infectious Disease and Global Medicine
University of California, San Francisco (UCSF)
San Francisco, CA

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Disclosure

Dr. Dachs and Dr. Gandhi have no financial interests or relationships to disclose.

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Learning Objectives

1. Appreciate current trends in infection rates
2. Review current of Covid-19 vaccine recommendations
3. Appropriately test symptomatic patients
4. Initiate CDC guided therapy for at-risk Covid-19 infected patients

Topics

- Current status – Snapshot
- Vaccine update
- Testing
- Therapies
- Long Covid
- The future….

Big Picture: Where Are We Today?

COVID drops to 10th leading cause of death in US

Stephanie Soucheray, MA, *August 8, 2024*

Mortality in the United States — Provisional Data, 2023

Weekly / August 8, 2024 / 73(31);677–681

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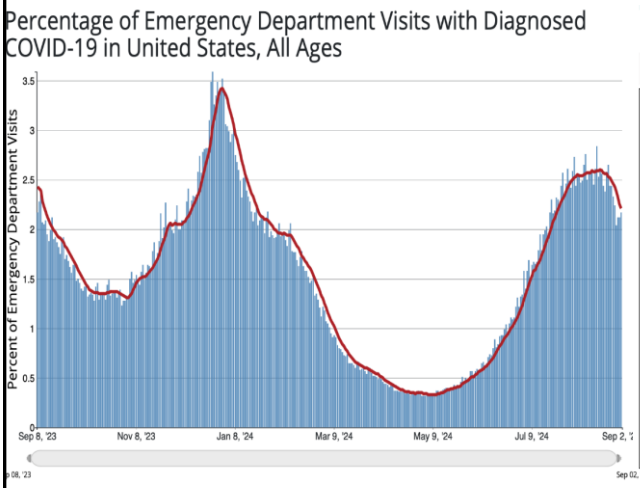
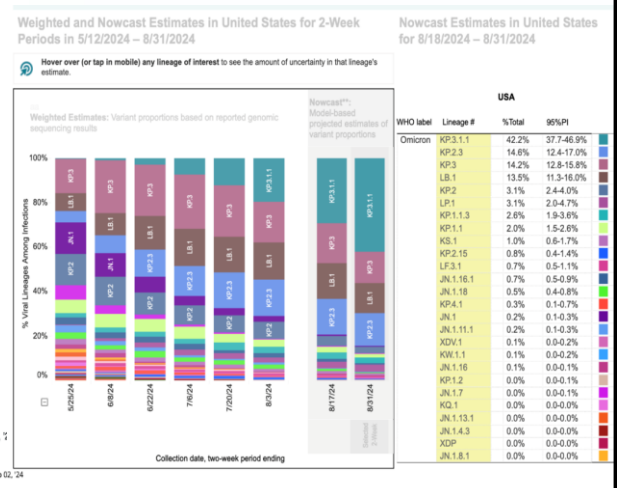
Big Picture: Where Are We Today?





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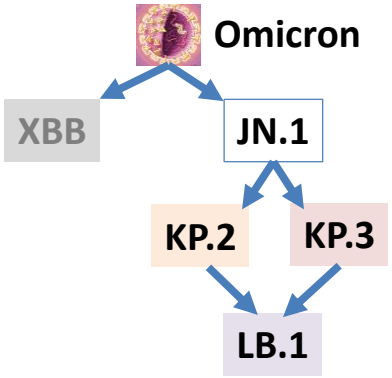
Vaccine: FDA Recommendation for Fall 2024/25

FDA Updates Advice to Manufacturers of COVID-19 Vaccines (2024-2025 Formula): If Feasible Use KP.2 Strain of JN.1-Lineage

June 13, 2024



June 6, 2024

Rubin, R, JAMA, published Aug 6, 2024

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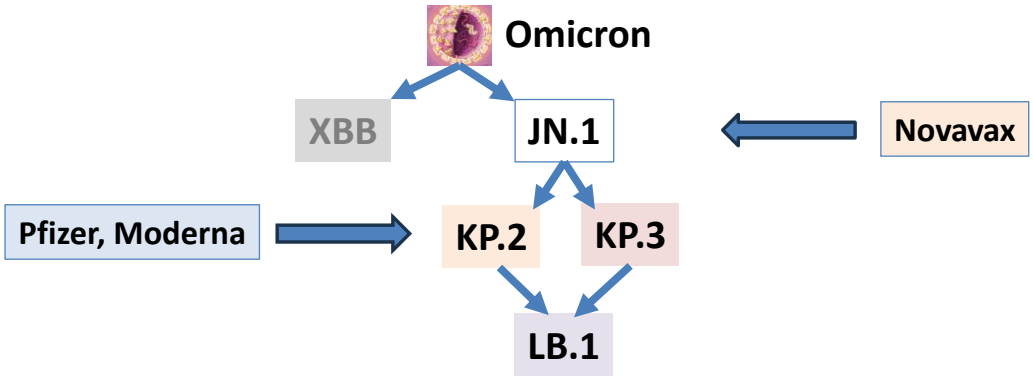
Vaccine: FDA Recommendation for Fall 2024/25

FDA approves updated Pfizer, Moderna Covid vaccines as virus surges; shots to be available within days

PUBLISHED THU, AUG 22 2024-1:36 PM EDT | UPDATED THU, AUG 22 2024-4:30 PM EDT

FDA Approves Updated Novavax COVID Vaccine Week After Approving Moderna And Pfizer's Shots

Arianna Johnson Forbes Staff



Rubin, R, JAMA, published Aug 6, 2024

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Vaccine: Past, Present and Future

22% of population received last year's updated vaccine....

Did last year's recommendation of the monovalent XBB 1.5 vaccine decrease ED visits/hospitalization?

- ED/ UC encounters was 51% (95% CI = 47%–54%) Day 7–59 and 39% (95% CI = 33%–45%) Days 60–119
- hospitalization from two CDC VE networks were: 52% (95% CI = 47%–57%) and 43% (95% CI = 27%–56%),

Interim Effectiveness of Updated 2023–2024 (Monovalent XBB.1.5) COVID-19 Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalization Among Immunocompetent Adults Aged ≥18 Years — VISION and IVY Networks, September 2023–January 2024

DuCuir J, et al. MMWR Feb 29,2024

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Vaccine: Past, Present and Future

Question: How well did we do with updated vaccine in NH residents?

Data from CDC's National Healthcare Safety Network➔

1) **40.5%** NH residents received updated 2023-24 Covid -19 vaccine (between Oct 2023 – Feb 2024)

= 5.3% hospitalization rate (1 in 20)

TABLE 2. Cumulative weekly rates of incident SARS-CoV-2 infection,* COVID-19–associated hospitalization† and percentage up to date with COVID-19 vaccination§ by facility among nursing home residents, by U.S. region¶ — National Healthcare Safety Network, United States, October 16, 2023–February 11, 2024

Region	No. of facilities	Resident-weeks	No. of SARS-CoV-2 infections	Cumulative weekly rate of SARS-CoV-2 infection (95% CI)*,**	No. of COVID-19–associated hospitalizations	Cumulative weekly COVID-19–associated hospitalization rate†,** (95% CI)	% of residents up to date with COVID-19 vaccination (95% CI)††
Overall	14,811	21,046,590	230,105	109.3 (108.9–109.8)	12,211	5.8 (5.7–5.9)	40.5 (40.4–40.6)
Northeast	2,432	4,772,100	54,229	113.6 (112.7–114.6)	2,912	5.9 (5.7–6.1)	47.3 (47.1–47.6)
South	5,508	7,956,877	74,094	93.1 (92.5–93.8)	4,002	5.0 (4.9–5.2)	32.4 (32.2–32.5)
Midwest	4,774	5,619,718	73,134	130.1 (129.2–131.1)	3,782	6.7 (6.5–6.9)	44.7 (44.5–45.0)
Mountain	547	599,880	6,799	113.3 (110.7–116.1)	328	5.5 (4.9–6.1)	41.9 (41.2–42.5)
Pacific	1,550	2,098,015	21,849	104.1 (102.8–105.5)	1,287	6.1 (5.8–6.5)	44.1 (43.7–44.5)

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Vaccine: Past, Present and Future

What Happens If a Women at Delivery Has Covid?

Methods: observational study; data from 2,990,973 deliveries in the Premier Healthcare Database; February 2020 to August 2023

Carlson J, et al. Obstet Gynecol 2024; 143:131–8

	Pre-Delta Period		Delta Period		Omicron Period	
	COVID-19 (n=20,031)	No COVID-19 (n=1,200,927)	COVID-19 (n=10,534)	No COVID-19 (n=462,938)	COVID-19 (n=26,053)	No COVID-19 (n=1,270,490)
hypertension						
Maternal outcome						
Acute renal failure	134 (0.7)	1,893 (0.2)	161 (1.5)	820 (0.2)	119 (0.5)	2,784 (0.2)
Adverse cardiac event or outcome	148 (0.7)	3,935 (0.3)	152 (1.4)	1,641 (0.4)	118 (0.5)	4,678 (0.4)
Thromboembolic disease	81 (0.4)	1,339 (0.1)	92 (0.9)	590 (0.1)	44 (0.2)	1,326 (0.1)
ARDS	694 (3.5)	1,094 (0.1)	808 (7.7)	403 (0.1)	162 (0.6)	1,264 (0.1)
Shock	114 (0.6)	964 (0.1)	156 (1.5)	381 (0.1)	51 (0.2)	1,171 (0.1)
Sepsis	261 (1.3)	1,129 (0.1)	287 (2.7)	464 (0.1)	95 (0.4)	1,382 (0.1)
Any severe outcome*	977 (4.9)	17,849 (1.5)	860 (8.2)	7,518 (1.6)	725 (2.8)	21,305(1.7)
ICU admission	957 (4.8)	17,395 (1.4)	838 (8.0)	7,405 (1.6)	713 (2.7)	21,002 (1.7)
Mechanical ventilation	315 (1.6)	1,412 (0.1)	371 (3.5)	468 (0.1)	83 (0.3)	1,287 (0.1)
In-hospital death	34 (0.2)	79 (0.007)	51 (0.5)	28 (0.006)	7 (0.03)	69 (0.005)
Pregnancy outcome						
Any adverse pregnancy outcome†	2,788 (13.9)	112,276 (9.3)	2,140 (20.3)	44,137 (9.5)	3,244 (12.5)	123,048 (9.7)

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CDC Recommendation for Fall 2024/25

CDC recommends **everyone ages 6 months and older receive an updated 2024-2025 COVID-19 vaccine** to protect against the potentially serious outcomes of COVID-19 this fall and winter whether or not they have ever previously been vaccinated with a COVID-19 vaccine. Updated COVID-19 vaccines will be available from Moderna, Novavax, and Pfizer later this year.

ACIP Advisory Committee; June 27, 2024

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Vaccine: Past, Present and Future

Would you recommend updated vaccine this fall to…….

- **Healthy 30 y/o pregnant patient?**
- **Healthy 40 y/o?**
- **Healthy 65 y/o?**
- **55 y/o male with obesity, HTN, pre-DM?**
- **Healthy 40 y/o women caring for 80 y/o mother with dementia?**
- **Healthy 40 y/o parents caring for child with severe asthma/ immunocompromised?**

Note: 6.6% of US adults (survey 29,164 persons) stated are immunosuppressed
-3.9% take immunosuppressive drugs *Martinson ML et al. JAMA Mar 12, 2024*

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ACIP Advisory Committee; June 27, 2024

- *Was considered at ACIP*
- *WHO does not recommend "routine" revaccination*
- *Canada is "risk-based"*

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WHO Recommendation for Updated Vaccine

Table 1: Summary of the updated SAGE recommendations for COVID-19 vaccination

Vaccination status	Population	Recommendation
Never received a COVID-19 vaccine	All adults	1 dose[1]
	Children and adolescents with comorbidities	
	Health workers with direct patient contact	
	Pregnant persons	1 dose
	Any individual who is immunocompromised	2 to 3 doses[2]
Previously received at least 1 dose of a COVID-19 vaccine	Adults over 75 or 80 years old[3]	Revaccination 6 to 12 months after the most recent dose
	Adults over 50 or 60 years old[3] with comorbidities	
	Any individual who is immunocompromised	
	Adults over 50 or 60 years old[3]	Revaccination 12 months after the most recent dose
	Adults with comorbidities	
	Health workers with direct patient contact	
	Pregnant persons	Single dose in each pregnancy
	Healthy adults	Revaccination not routinely recommended
	Children and adolescents	

Legend: High priority use groups; Sub-populations with special considerations

November 2023

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Vaccine: Past, Present and Future?

Mathematical modeling suggests.....

Annals of Internal Medicine — ORIGINAL RESEARCH

Evaluation of Strategies for Transitioning to Annual SARS-CoV-2 Vaccination Campaigns in the United States

Chad R. Wells, PhD; Abhishek Pandey, PhD; Seyed M. Moghadas, PhD; Meagan C. Fitzpatrick, PhD; Burton H. Singer, PhD; and Alison P. Galvani, PhD

published online March 26, 2024

1) optimal timing between the 1st and 2nd dose for children < 2 years and adults aged > 50 yrs in an annual vaccination campaign ***was estimated to be 5 months.***

2) Compared to a single-dose campaign, a second dose booster dose =➔
- **123,869 fewer hospitalizations (95% CI; 121,994 -125,742)**
- **5524 fewer deaths (95% CI; 5434 - 5613),**
- **averting $3.63 billion (95% CI;, $3.57 - $3.69 billion) in costs over a single year.**

Current median cost of a COVID hospitalization is $11,275
Kapinos KA, et al. JAMA Network Open 2024;7(1):e2350145.

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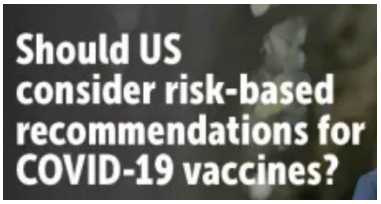
Vaccine: Past, Present and Future?



AND/ OR…


Annals of Internal Medicine ORIGINAL RESEARCH

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Chad R. Wells, PhD; Abhishek Pandey, PhD; Seyed M. Moghadas, PhD; Meagan C. Fitzpatrick, PhD; Burton H. Singer, PhD; and Alison P. Galvani, PhD

Twice a year???

- Older/immunocompromised being offered/recommended twice a year vaccination?
- Will FDA ask for a reformulated the COVID vaccine every year?
- *Two jabs in the fall (Covid + Flu)*
  - *getting them at the same time safe?*
  - *Get them in one arm or alternate?*
  - *Covid/flu "combo" vaccine in Phase 3 trials. Next year?*

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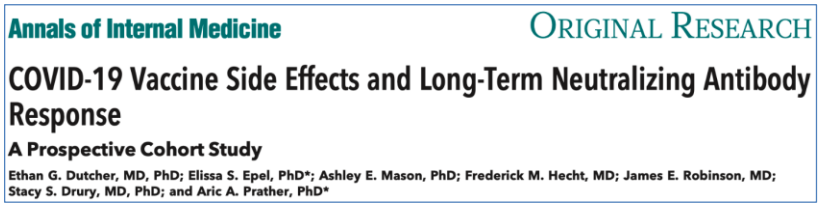
Vaccine: "It's Good to Feel Bad"


Annals of Internal Medicine ORIGINAL RESEARCH

COVID-19 Vaccine Side Effects and Long-Term Neutralizing Antibody Response

A Prospective Cohort Study

Ethan G. Dutcher, MD, PhD; Elissa S. Epel, PhD*; Ashley E. Mason, PhD; Frederick M. Hecht, MD; James E. Robinson, MD; Stacy S. Drury, MD, PhD; and Aric A. Prather, PhD*

Published ahead of print, June 11, 2024.

Methods: 363 participants, received 2 doses of mRNA vaccines
Post vaccine symptom survey done, and Ab titers @ 1 and 6 months

Results: Patients with chills, tiredness, feeling unwell, headache
(+) 1.4-1.6 higher antibody titers at 1 and 6 months

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Suspected Infection and Testing

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Suspected Infection and Testing

Annals of Internal Medicine ORIGINAL RESEARCH

Performance of Rapid Antigen Tests to Detect Symptomatic and Asymptomatic SARS-CoV-2 Infection

A Prospective Cohort Study

Methods: prospective study, US volunteers
- At home 10 Ag tests + 7 PCR tests
- Using both tests q48hrs
  (5,353 participants, 10/18/21-1/31/22)

Results: 5,199 neg(-) tests ==➔ 99.6% concordance (Ag vs. PCR)

(+) symptoms/test on Day O(nset): Ag sensitivity = 59% *(95%CI 46-71%)*
(+) symptoms/test Days 0 and 2: Ag sensitivity = 92% *(95%CI 81-97%)*
(+) symptoms/test Days 0,2,4: Ag sensitivity = 93% *(95% CI 83-98%)*

Soni, A et al. Ann Intern Med, published online July 4, 2023

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HCW's – Please Test If You Feel Sick

Methods: observational cohort study, Boston VA healthcare system

- 12/1/20 – 9/30/21
- 327 (+) HCW's

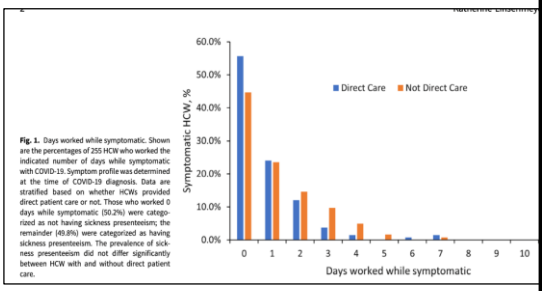

Fig. 1. Days worked while symptomatic. Shown are the percentages of 255 HCW who worked the indicated number of days while symptomatic with COVID-19. Symptom profile was determined at the time of COVID-19 diagnosis. Data are stratified based on whether HCWs provided direct patient care or not. Those who worked 0 days while symptomatic (50.2%) were categorized as not having sickness presenteeism; the remainder (49.8%) were categorized as having sickness presenteeism. The prevalence of sickness presenteeism did not differ significantly between HCW with and without direct patient care.

Results: ½ had non-specific symptoms

-allergies (37%), a "cold" (27%), migraine (23%), insufficient sleep (23%), "something else, not COVID-19" (21%), and a "mild case of COVID-19" (15%).

½ had specific symptoms – ***"took precautions"***

Linsenmeyer K, et al. Infection Control & Hospital Epidemiology (2023), 1–4

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Precautions (ie. Back to Work) After a COVID-19 Infection..

- You can go back to your normal activities when, for at least 24 hours, both are true:
  - Your symptoms are getting better overall, **and**
  - You have not had a fever (and are not using fever-reducing medication).

- When you go back to your normal activities, take added precaution over the next 5 days, such as taking additional steps for cleaner air, hygiene, masks, physical distancing, and/or testing when you will be around other people indoors.

CDC Guidance, March 2024

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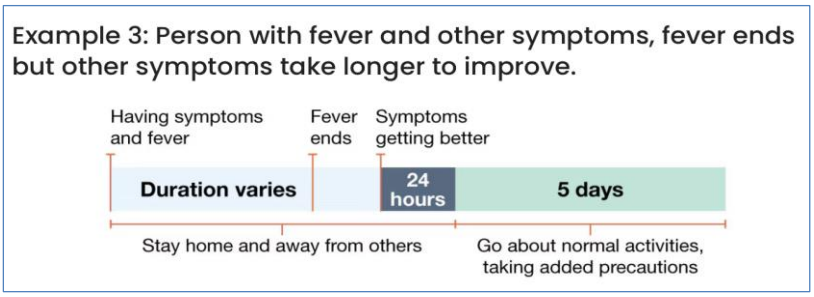
Precautions (ie. Back to Work) After a COVID-19 Infection..



- When you go back to your normal activities, take added precaution over the next 5 days, such as taking additional steps for cleaner air, hygiene, masks, physical distancing, and/or testing when you will be around other people indoors.

CDC Guidance, March 2024

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Are We Taking the Steps to Protect the Most Vulnerable?

Research Letter | Oncology

Masking Policies at National Cancer Institute–Designated Cancer Centers During Winter 2023 to 2024 COVID-19 Surge

Methods: review of websites + F/U call of 67 NCI-designated cancer centers COVID-19 policies, Jan 15, 2024.

Results: All 67 centers had COVID-19 policies
-28 (42%) required masking in "some" clinical areas
-12 (18%) had universal masking in all areas

-14 (21%) had up-to-date clinical policies
*more masking in Northeast, longer duration of NCI designation and in clinics with higher care ranking

Hoerger M, et al. JAMA Open Network, July 31, 2024; e2424999

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Treatment: Antiviral Therapy: NIH Guideline

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.

Accessed July 11, 2024

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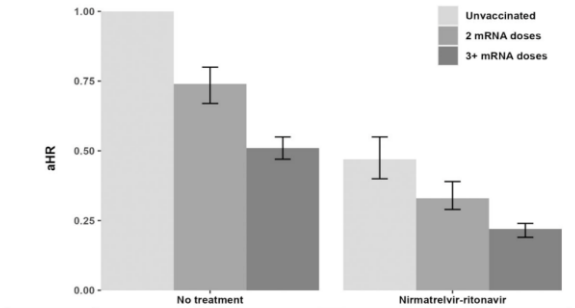
Treatment: Antiviral Therapy
Decrease Hospitalization/Death vs. Shorten Course

Methods: retrospective study, US Epic records
731,349 outpt with (+) Covid
Age > 50yrs or (+) underlying condition
4/1/22 – 8/31/22

Combined Protection of Vaccination and Nirmatrelvir-Ritonavir Against Hospitalization in Adults With COVID-19

Shah MM, et al. CID July 15 2024; 79: 108-10

Hospitalization



	Unvaccinated	2 mRNA doses	3+ mRNA doses	Unvaccinated	2 mRNA doses	3+ mRNA doses
No. of participants	141 931	114 656	199 670	35 826	42 355	130 778
No. hospitalized	1316	921	1671	180	180	481
Hospitalizations per 100 000 person-days	31.1	27.0	28.1	19.7	16.4	14.2
aHR (95% CI)	Reference	0.74 (.67–.80)	0.51 (.47–.55)	0.47 (.40–.55)	0.33 (.29–.39)	0.22 (.19–.24)

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Treatment: Antiviral Therapy
Decrease Hospitalization/Death vs. Shorten Course

Effectiveness of nirmatrelvir–ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system

Methods: outpt cohort study
Kaiser Permanente Southern Cal
4/8/22- 10/7/22…

Results: *Propensity-score matched…*	**Paxlovid (n=7,274)** (n=5,472)	**no treatment (n=126,152)** (n=84,657)
Hospitalization/death @ 30 days	**(+) decreases by 79.6% (95%CI: 34-94%)**	

Leward JA, et al. Lancet Infect Dis 2023; 23: 806-15

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Treatment: Antiviral Therapy
Decrease Hospitalization/Death vs. Shorten Course

Population-based evaluation of the effectiveness of nirmatrelvir–ritonavir for reducing hospital admissions and mortality from COVID-19

Methods: population-based cohort study
Ontario, CA 4/1/22- 8/31/22…

Results: *Propensity-score matched…*	**Paxlovid (n=8,876)**	**no treatment (n=168,669)**
Hospitalization/death @ 30 days	**2.1%**	**3.7%**
	NNT= 62 (95% CI, 43-80)	

Subgroups:
* **unvaccinated people: NNT = 28 (95% CI 7–49)**
** **those < 70 years of age: NNT = 181 (95% CI 50–312)**

Schwartz KL, et al. CMAJ; 2023; E220-6

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Treatment: Antiviral Therapy
Decrease Hospitalization/Death vs. Shorten Course

I. Complete resolution: Paxlovid =12 days
Started within 5 days placebo = 13 days

ORIGINAL ARTICLE
Nirmatrelvir for Vaccinated or Unvaccinated Adult Outpatients with Covid-19
NEJM April 4, 2024

II. Resolution 11 symptoms : simnotrelvir =6.7 days
Started within 3 days placebo = 9 days

ORIGINAL ARTICLE
Oral Simnotrelvir for Adult Patients with Mild-to-Moderate Covid-19
NEJM Jan 18, 2024

III. Resolution 5 symptoms : ensitrelvir =6.9 days
Started within 3 days placebo = 8 days

Original Investigation | Infectious Diseases
Efficacy and Safety of 5-Day Oral Ensitrelvir for Patients With Mild to Moderate COVID-19
The SCORPIO-SR Randomized Clinical Trial
JAMA Network Open Feb 9, 2024

IV. Resolution 11 symptoms: oral remdesivir = 4 days
Started within 5 days Paxlovid = 5 days

ORIGINAL ARTICLE
VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19
NEJM Feb 2, 2023

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Comparing Antivirals:
Paxlovid Tamiflu

- Can decrease hospitalization and death in selected patients
- ⇩ symptoms approx. 1 day
- Under prescribing??
  - ***1 in 4 NH residents at end of 2022 were Rx antiviral[1]***

- Does <u>not</u> decrease hospitalization (including elderly)[2]
- ⇩ symptoms approx. 1 day
- Overprescribing??
  - ***606/1000 children dx[3]***

IDSA, AAP, CDC strongly recommend antiviral Rx < 5 yrs, esp < 2 yrs, regardless of the duration of their symptoms

[1]McGarry BE, et al. JAMA 2023; 330: 561-3.
[2]Hanula R, et al. JAMA Int Med 2024; 184: 18-27
[3]Antoon JW, et al. Pediatrics 2023 152: e2023061960

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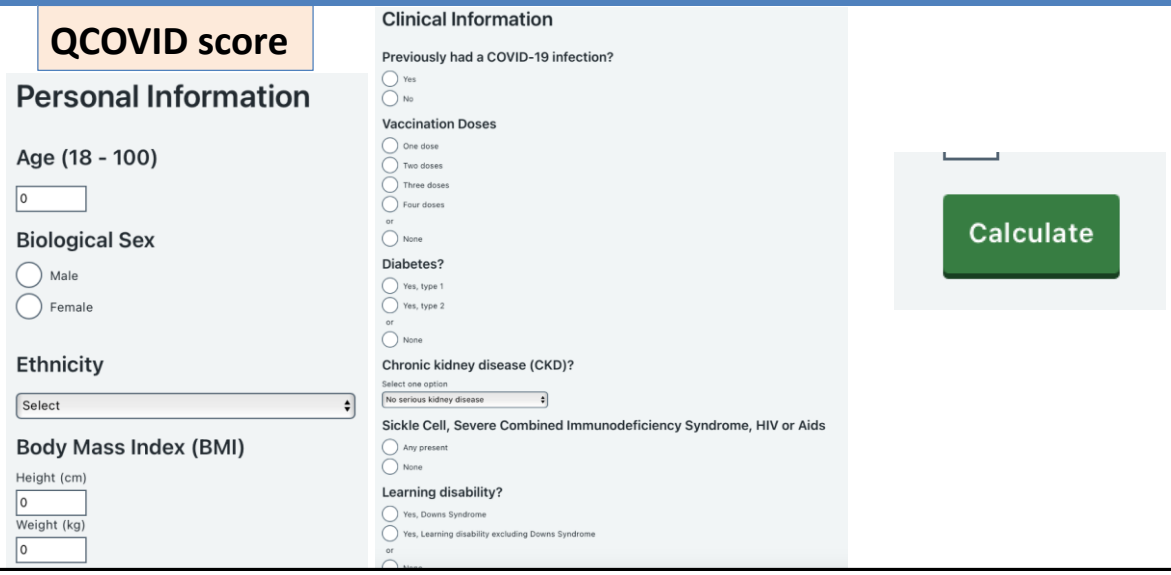
Treatment: Antiviral Therapy
Who Should We Consider for Rx?

QCOVID score



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Treatment: Antiviral Therapy
Who Should We Consider for Rx?

QCOVID score

LOCH score

Which age group are you in:

- ○ 0 to 49 years
- ○ 50 to 59 years
- ◉ 60 to 69 years
- ○ 70 years and older

- ☐ Any comorbidity (DM, HTN, asthma, COPD, CVD, CKD, liver disease, cancer)
- ☐ Patient reports dyspnea
- ☑ Patient has received 2+ Pfizer/Moderna or 1+ Janssen COVID-19 vaccinations

LOCH Risk Score (range 0-6) = 1.5 points ; moderate risk group (1 - 2.5 points).

during the Omicron wave 11/21 to 11/22 with 2+ weeks follow-up: 13/4822 outpatients (0.27%) in the moderate risk group were hospitalized.

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Options:

- **Paxlovid (nirmatrelvir/ritonavir)**
  - (+) reduction in hospitalization/death
  - Watch drug-drug interactions
  - Check GFR. Dose adjustment
- **Remdesivir** – 3-day infusion (Infusion Center)
  - When are we getting an oral option?
- **Molnupiravir** – 4 tab BID x 5 days, less effective?
- Dexamethasone --- **NO!**

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Is Molnupiravir Worthwhile?

Effectiveness and Safety of Molnupiravir in the Intended-Use Population: an Observational Cohort Study Abu-Ahmed W, et al. Clin Micro Infection published ahead of print, June 19,2024

Methods: retrospective cohort study, of ***"at-risk" patients*** (not eligible for Paxlovid) 1/22/22-2/26/23

Results: *(propensity matched)*	Molnupiravir	untreated
-hospitalization or death	70/3,957 **(1.7%)**	699/19,785 **(3.5%)**

Word of caution: Avoid in pregnancy!

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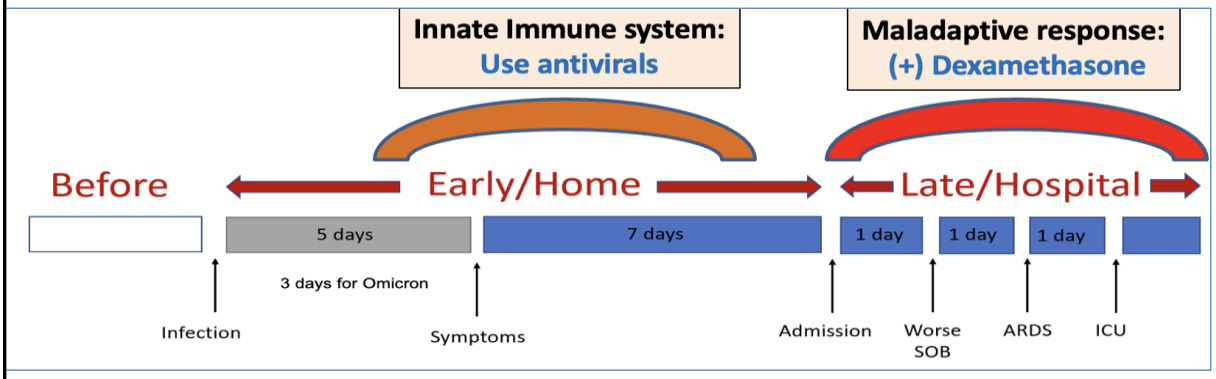
Time Course... Therapy



Please do not use dexamethasone/steroids in the first week

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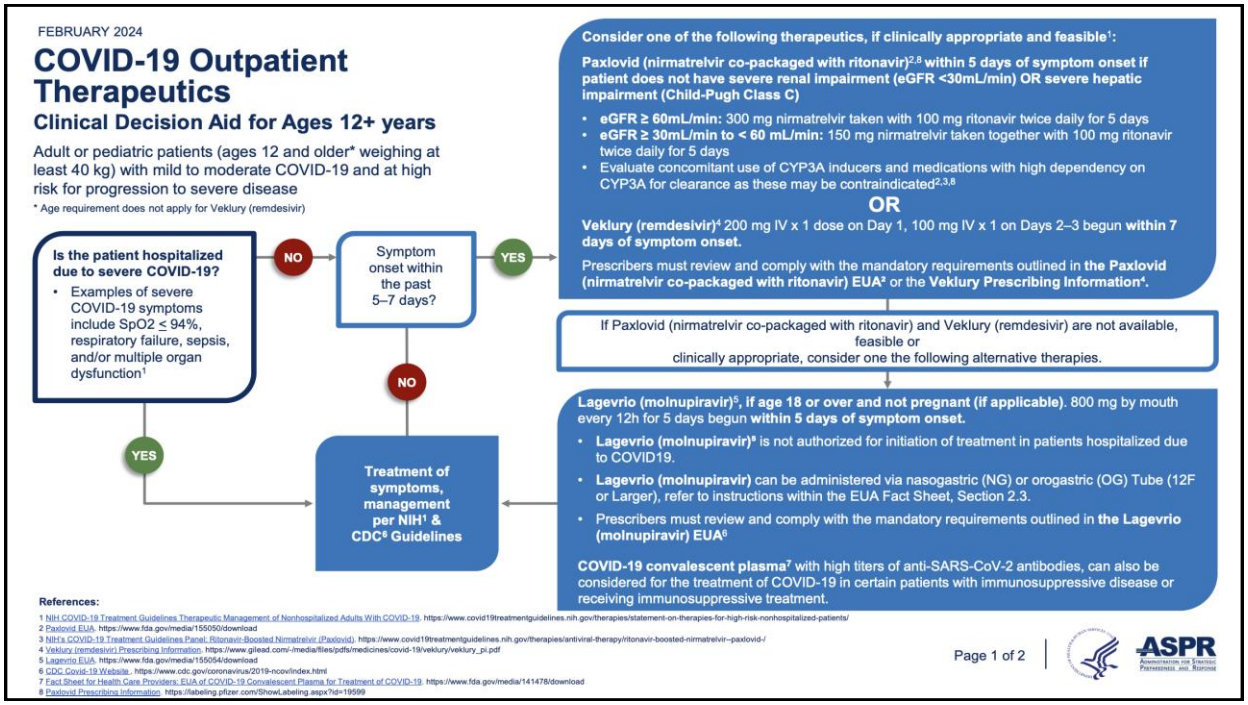

FEBRUARY 2024

COVID-19 Outpatient Therapeutics

Clinical Decision Aid for Ages 12+ years

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

* Age requirement does not apply for Veklury (remdesivir)

Is the patient hospitalized due to severe COVID-19?
- Examples of severe COVID-19 symptoms include SpO2 ≤ 94%, respiratory failure, sepsis, and/or multiple organ dysfunction[1]

NO → Symptom onset within the past 5–7 days?

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

Paxlovid (nirmatrelvir co-packaged with ritonavir)[2,8] within 5 days of symptom onset if patient does not have severe renal impairment (eGFR <30mL/min) OR severe hepatic impairment (Child-Pugh Class C)
- **eGFR ≥ 60mL/min:** 300 mg nirmatrelvir taken with 100 mg ritonavir twice daily for 5 days
- **eGFR ≥ 30mL/min to < 60 mL/min:** 150 mg nirmatrelvir taken together with 100 mg ritonavir twice daily for 5 days
- Evaluate concomitant use of CYP3A inducers and medications with high dependency on CYP3A for clearance as these may be contraindicated[2,3,8]

OR

Veklury (remdesivir)[4] 200 mg IV x 1 dose on Day 1, 100 mg IV x 1 on Days 2–3 begun **within 7 days of symptom onset.**

Prescribers must review and comply with the mandatory requirements outlined in **the Paxlovid (nirmatrelvir co-packaged with ritonavir) EUA**[2] or the **Veklury Prescribing Information**[4].

NO → If Paxlovid (nirmatrelvir co-packaged with ritonavir) and Veklury (remdesivir) are not available, feasible or clinically appropriate, consider one the following alternative therapies.

YES → **Treatment of symptoms, management per NIH[1] & CDC[6] Guidelines**

Lagevrio (molnupiravir)[5], if age 18 or over and not pregnant (if applicable). 800 mg by mouth every 12h for 5 days begun **within 5 days of symptom onset.**
- **Lagevrio (molnupiravir)[5]** is not authorized for initiation of treatment in patients hospitalized due to COVID19.
- **Lagevrio (molnupiravir)** can be administered via nasogastric (NG) or orogastric (OG) Tube (12F or Larger), refer to instructions within the EUA Fact Sheet, Section 2.3.
- Prescribers must review and comply with the mandatory requirements outlined in **the Lagevrio (molnupiravir) EUA**[6]

COVID-19 convalescent plasma[7] with high titers of anti-SARS-CoV-2 antibodies, can also be considered for the treatment of COVID-19 in certain patients with immunosuppressive disease or receiving immunosuppressive treatment.

References:

1 NIH COVID-19 Treatment Guidelines Therapeutic Management of Nonhospitalized Adults With COVID-19. https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-therapies-for-high-risk-nonhospitalized-patients/
2 Paxlovid EUA. https://www.fda.gov/media/155050/download
3 NIH's COVID-19 Treatment Guidelines Panel. Ritonavir-Boosted Nirmatrelvir (Paxlovid). https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/
4 Veklury (remdesivir) Prescribing Information. https://www.gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf
5 Lagevrio EUA. https://www.fda.gov/media/155054/download
6 CDC Covid-19 Website . https://www.cdc.gov/coronavirus/2019-ncov/index.html
7 Fact Sheet for Health Care Providers: EUA of COVID-19 Convalescent Plasma for Treatment of COVID-19. https://www.fda.gov/media/141478/download
8 Paxlovid Prescribing Information. https://labeling.pfizer.com/ShowLabeling.aspx?id=19599

Page 1 of 2 | ASPR

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Treatment: Antiviral Therapy

Lingering Questions……

1. Are antivirals being underutilized?
2. Should therapy only start within first 3 days of symptoms?
3. Is 5-day duration of treatment the correct duration?
4. **Does Paxlovid (or antivirals) increase risk of "rebound"?**
5. **Do antivirals decrease the risk of "long Covid"/PASC?**

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Paxlovid and Rebound?

Pro	**Con**
1. Edelstein GE, et al. Ann Intern Med Nov 2023 **Methods:** Observational cohort study **Result:** Paxlovid Rx *(n=55):* 20.8% viral rebound No Rx: *(n=72)* 1.8% viral rebound	*1. Smith DJ, et al. MMWR Dec 22, 2023* **Methods:** 7 trials, 1 RCT,6 observational **Result:** 4 retrospective studies: no difference 3 studies (+) correlation: a. CLL patients: 9% vs. 3.6% rebound. b. *Edelstein et al….* *Rx older pts (57 vs. 39 yrs)* *Rx ⬆ immunosuppression (32% vs 9%)* c. *Smith-Jeffcoat et al….* *limited follow up time*
2. Smith-Jeffcoat et al. CID Nov 2023 **Methods:** Prospective, propensity-match **Result:** Paxlovid Rx *(n=130):* 32% symptom rebound 27% viral rebound No Rx: *(n=241)* 20% symptom rebound 7% viral rebound	

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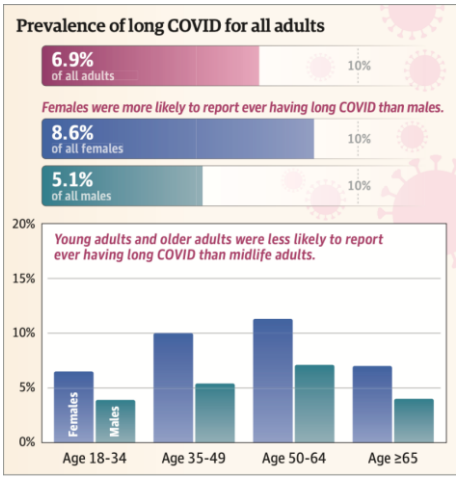
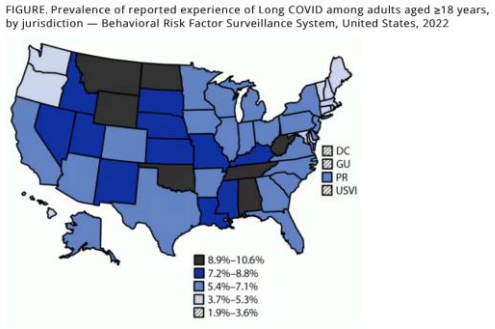
Long Covid: Prevalence in US



6.4%- 6.9% of US adults report Long COVID (defined > 3 months



- CDC analysis of 2022 BRFSS survey, 96,000 telephone interviews
- MEPS survey *(JAMA, July 2,2024)*

Ford, ND, et al MMWR, Feb 15, 2024.

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Q1: How Do You Define "Long Covid"?

- Review of 38 studies➔ 6 different definitions[1]

[1]Choe R, et al Annals Int Med, published ahead of print, May 21, 2024

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Q1: How Do You Define "Long Covid"?

- Review of 38 studies➔ 6 different definitions[1]

FROM THE NATIONAL ACADEMY OF MEDICINE

Long Covid Defined

The NEW ENGLAND JOURNAL of MEDICINE 2

Box 1. 2024 NASEM Long Covid Definition*

Long Covid is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.

[1]Choe R, et al Annals Int Med, published ahead of print, May 21, 2024
[2]Ely EW, et al. NEJM, Published July 31, 2024; DOI: 10.1056/NEJMsb2408466

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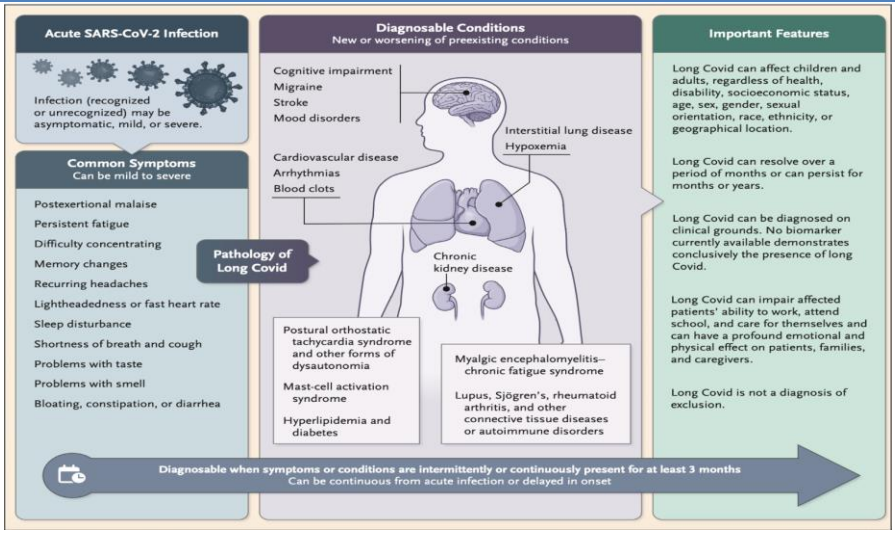
Q1: How Do You Define "Long Covid"?



Ely EW, et al. NEJM, Published July 31, 2024; DOI: 10.1056/NEJMsb2408466

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Q1: How Do You Define ”Long Covid”?

- Review of 38 studies➔ 6 different definitions[1]
- Different phenotypes➔ Neurologic (“brain fog”)
  Myalgic encephalitis/CFS
  Cardiovascular (POTS)
  Respiratory, GI, Endocrine, etc…

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Q1: How Do You Define ”Long Covid”?

- Review of 38 studies➔ 6 different definitions[1]
- Different phenotypes➔
- Varying biochemical abnormalities ➔
  - Elevated EBV and/or CMV and/or VZV serologies
  - Low cortisol without compensatory ACTH elevation
  - Anemia
  - Abnormal iron levels
  - Thrombocytopenia, lymphopenia
  - Diminished serotonin
  - Elevated ESR, CRP, bilirubin, lipase, LDH

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Annals of Internal Medicine ORIGINAL RESEARCH

Differentiation of Prior SARS-CoV-2 Infection and Postacute Sequelae by Standard Clinical Laboratory Measurements in the RECOVER Cohort

Erlandson KM, et al
Ann Intern Med; published online August 13, 2024

CAUTION: No evidence any of 25 common lab values is a useful biomarker of PASC (ie. no lab value confirms the diagnosis!)

- Varying biochemical abnormalities ➔
  - Elevated EBV and/or CMV and/or VZV serologies
  - Low cortisol without compensatory ACTH elevation
  - Anemia
  - Abnormal iron levels
  - Thrombocytopenia, lymphopenia
  - Diminished serotonin
  - Elevated ESR, CRP, bilirubin, lipase, LDH

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Q2: Theories Behind "Long Covid"?

- Review of 38 studies➔ 6 different definitions[1]
- Different phenotypes➔
- Varying biochemical abnormalities ➔
- Various theories➔ ongoing immune activation
  remnant viral RNA or protein
  dysbiosis (gut microfora)
  mitochondrial dysfunction
  neural (vagal n.) dysfunction

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Q3: Is There Going to Be an Rx "Long Covid"?

- Review of 38 studies➔ 6 different definitions[1]
- Different phenotypes➔
- Varying biochemical abnormalities ➔
- Various theories➔
- Variety of attempted Rx:
  - Melatonin
  - SSRI, SNRI
  - Probiotics
  - Vaccination after infection
  - Exercise
  - Hyperbaric oxygen

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Q4: Does Anything Help Decrease Risk of "Long Covid"?

- Vaccination[1] + booster[2]

Methods: VA database 441,583 pts, PASC @ 1yr

Results: Omicron era….
Unvaccinated: 7.7%
Vaccinated: 3.5%

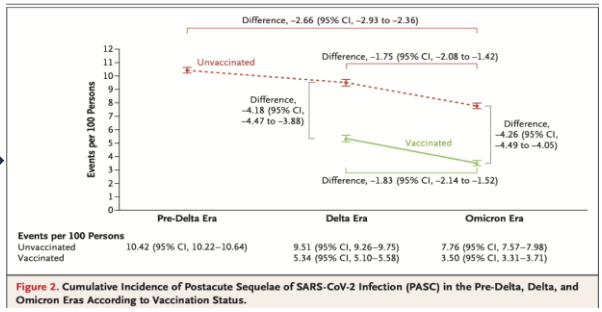

Figure 2. Cumulative Incidence of Postacute Sequelae of SARS-CoV-2 Infection (PASC) in the Pre-Delta, Delta, and Omicron Eras According to Vaccination Status.

Xie Y, et al. NEJM 391: Aug 8, 2024; 515-5

[1]Watanabe A, et al. Vaccine 2023; 41: 1783-90
[2]Xie Z, et al Vaccine https://doi.org/10.1016/j.vaccine.2024.04.070

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Q2: Does Anything Help Decrease Risk of "Long Covid"?

- Vaccination[1] + booster[2]
- **Antivirals????**

Systematic review

The efficacy of antivirals, corticosteroids, and monoclonal antibodies as acute COVID-19 treatments in reducing the incidence of long COVID: a systematic review and meta-analysis

Gangqiang Sun [1], Ke Lin [1], Jingwen Ai [1, 2, *], Wenhong Zhang [1, 2, 3]

14 papers investigating acute COVID-19 antiviral treatment conclude➔

(+) protective efficacy against long COVID

(OR, 0.61; 95% CI, 0.48–0.79; p 0.0002)

Clin Microbiol Infect. 2024 Jul 14:S1198-743X(24)00335-5. doi: 10.1016/j.cmi.2024.07.006. Online ahead of print.

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Question: Is It "Long Covid" OR.... "Long Post-viral Infection"?

JAMA Network Open

Original Investigation | Public Health

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome After SARS-CoV-2 Infection

This study asks the question:

Is it COVID or does this happen with other Covid-like illnesses?

Methods: prospective, multi-center, longitudinal study, adults ages 18-64
Presenting with SARS-CoV-2 like symptoms

Results:	(+) Covid (n=2418)	(-) Covid (n=2,320)
(+) ME/CFS @ 3 months	3.4%	3.7%
@ 3-12 months	No difference	

Unger ER, et al . Published online July 24, 2024

50

Final Questions… the Future???

- What are the chances of Omicron mutating (ie. to a new Greek letter?)
- The next pandemic… influenza, coronavirus, other???
- Are we prepared for the next pandemic?


The pathogens that could spark the next pandemic

The World Health Organization has updated its list of most dangerous viruses and bacteria.

Nature, Published online August 2, 2024


The NEW ENGLAND JOURNAL of MEDICINE

PERSPECTIVE

Déjà Vu All Over Again — Refusing to Learn the Lessons of Covid-19

Sinha, MS et al. NEJM 391: Aug 8, 2024

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Thank You for Your Time and Attention

Time for Your Questions….

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Supplemental Slides/Studies

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How Best to Message Vaccines?

Constructing vaccination slogans in the late stage of vaccine launch: an experimental study based on the framing effect theory

Gong Z et al. Jour Public Health published online Sept 4, 2024

Egoistic:

Altruistic:

Loss-framing:

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How Best to Message Vaccines?

Constructing vaccination slogans in the late stage of vaccine launch: an experimental study based on the framing effect theory

Gong Z et al. Jour Public Health published online Sept 4, 2024

Egoistic: *"Vaccination can make you develop antibodies against COVID-19, thus reducing the likelihood of contracting COVID-19 and developing severe symptoms after infection"*

Altruistic: *'Vaccination can promote the formation of community herd immunity, thereby reducing the likelihood of community members getting infected with COVID-19 and developing severe symptoms after infection'*

Loss-framing: *'If you are not vaccinated, you will not develop antibodies to COVID-19, and thus you will be more susceptible to COVID-19 and more likely to develop severe symptoms after infection'*

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How Best to Message Vaccines?

Methods: Survey 1085 participants in China, one of 4 groups

Constructing vaccination slogans in the late stage of vaccine launch: an experimental study based on the framing effect theory

Gong Z et al. Jour Public Health published online Sept 4, 2024

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Loss-framing: *'If you are not vaccinated, you will not develop antibodies to COVID-19, and thus you will be more susceptible to COVID-19 and more likely to develop severe symptoms after infection'*

+ Control Group (no message)

Asked: how likely are you to receive Covid vaccine?

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How Best to Message Vaccines?

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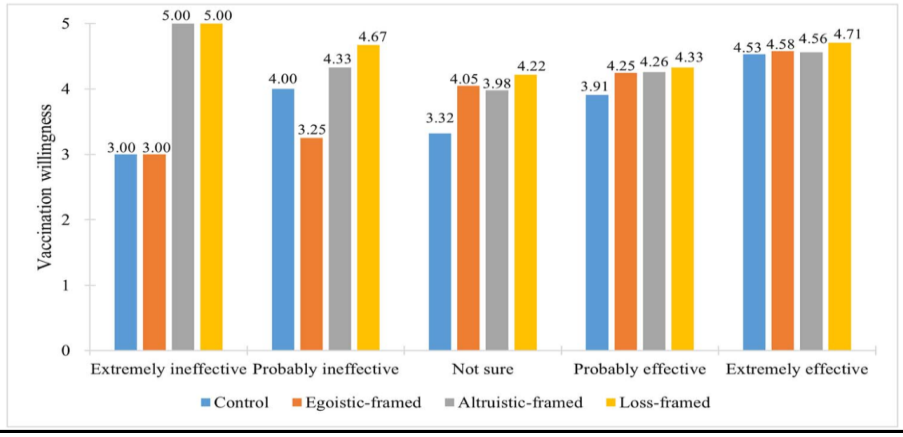
Gong Z et al. Jour Public Health published online Sept 4, 2024



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Vaccine: Past, Present and Future
Should We Encourage Children Be Vaccinated?

Background: Yes..illness tends to be mild in children

Morbidity and Mortality Weekly Report

SARS-CoV-2 Epidemiology and COVID-19 mRNA Vaccine Effectiveness Among Infants and Children Aged 6 Months–4 Years — New Vaccine Surveillance Network, United States, July 2022–September 2023

Question: Will vaccination be worthwhile (ie. decrease hospitalization) in children?

Methods: Observational study of children receiving 0, 1 or 2 doses of vaccine July 1, 2022–September 30, 2023

Results: 2 vaccine doses reduced hospitalization 40% (95% CI, 8-60%)

Tannis A, et al . MMWR, December 1, 2023

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Vaccine: Past, Present and Future
Was the Updated XBB1.5 Vaccine Safe?

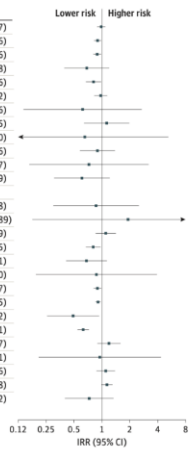
902,803 US adults => mRNA XBB1.5

No signal of adverse events in 28-day follow up

Andersson NW, et al. JAMA 2024; 331:105-58

Figure. 28-Day Risk of Adverse Events Following Vaccination With an XBB.1.5-Containing Vaccine

Outcome	No. of events/person-years: XBB.1.5-containing vaccine (risk period)	Reference period	IRR (95% CI)
Ischemic cardiac event	436/65 600	7730/1 090 799	0.96 (0.87-1.07)
Any cerebrovascular event	577/65 890	10 778/1 094 496	0.88 (0.81-0.96)
Cerebral infarction only (including TIA)	477/66 237	8993/1 100 022	0.87 (0.79-0.96)
Arterial thromboembolism	14/68 755	301/1 139 844	0.67 (0.38-1.18)
Deep vein thrombosis	125/67 853	2800/1 125 709	0.79 (0.66-0.96)
Pulmonary embolism	176/68 056	2993/1 128 940	0.95 (0.81-1.12)
Myocarditis	2/68 823	40/1 140 975	0.60 (0.14-2.66)
Pericarditis	15/68 772	214/1 140 221	1.10 (0.63-1.95)
Cerebral venous thrombosis	1/68 828	25/1 141 057	0.64 (0.08-5.20)
Thrombocytopenia and coagulative disorders	24/68 694	486/1 138 928	0.88 (0.57-1.36)
Guillain–Barré syndrome	2/68 825	41/1 141 000	0.71 (0.16-3.17)
Bell palsy	9/68 748	229/1 139 799	0.59 (0.30-1.19)
Transverse myelitis	0/68 834	5/1 141 141	NE
Encephalomyelitis or encephalitis	4/68 817	78/1 140 884	0.85 (0.29-2.48)
Narcolepsy	1/68 830	8/1 141 083	1.89 (0.17-20.89)
Appendicitis	75/68 434	1131/1 135 095	1.08 (0.84-1.39)
Aseptic arthritis	133/67 725	2884/1 123 716	0.79 (0.66-0.95)
Type 1 diabetes	17/68 280	449/1 132 265	0.67 (0.40-1.11)
Subacute thyroiditis	2/68 818	59/1 140 914	0.85 (0.19-3.90)
Heart failure	476/66 452	9217/1 102 898	0.88 (0.79-0.97)
Arrhythmia	1219/60 369	23 520/1 008 312	0.89 (0.84-0.95)
Acute liver failure	10/68 776	335/1 140 206	0.48 (0.25-0.92)
Acute kidney failure	216/67 836	5387/1 125 135	0.61 (0.53-0.71)
Acute pancreatitis	58/68 576	909/1 137 104	1.17 (0.88-1.57)
Erythema multiforme	2/68 830	23/1 141 064	0.93 (0.20-4.31)
Seizure	89/68 219	1398/1 131 107	1.08 (0.86-1.36)
Arterial aneurysm	245/ 67 519	3792/1 120 767	1.11 (0.97-1.28)
Uveitis	12/68 692	372/1 138 915	0.71 (0.39-1.32)



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Treatment: Antiviral Therapy
Decrease Hospitalization/Death vs. Shorten Course

Methods: systematic review
All studies 12/21-3/31/23

American Journal of Therapeutics 31, e246–e257 (2024)

OPEN

Effectiveness of Nirmatrelvir-Ritonavir for the Prevention of COVID-19–Related Hospitalization and Mortality: A Systematic Literature Review

Results: 18 real-world studies. All retrospective… 12/18 studies in Omicron era
- compared to no Rx (n=15), molnupiravir (n=5), sotrovimab (N=2), remdesivir (n=1)

6 studies➔ decrease hospitalization (21-89%)
2 studies ➔ decrease mortality (66-85%)
4 studies ➔ composite hospitalization/death (54-92%)

Cha-Siva AS, et al. Am J Ther 2024; e246-257

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Vaccine: Past, Present and Future

Note #1: Does not include pts not hospitalized (DNR/DNI, hospice) and this is all self-reporting (mandated) – ? underestimates #'s and morbidity

Note #2: as of March 2024, CDC no longer recommends that members of the public isolate for 5 days after onset of COVID-19 symptoms,
this guidance does not apply to residents of long-term care facilities

= 5.3% hospitalization rate (1 in 20)

2) TABLE 2. Cumulative weekly rates of incident SARS-CoV-2 infection,* COVID-19–associated hospitalization† and percentage up to date with COVID-19 vaccination§ by facility among nursing home residents, by U.S. region¶ — National Healthcare Safety Network, United States, October 16, 2023–February 11, 2024

Region	No. of facilities	Resident-weeks	No. of SARS-CoV-2 infections	Cumulative weekly rate of SARS-CoV-2 infection (95% CI)*,**	No. of COVID-19–associated hospitalizations	Cumulative weekly COVID-19–associated hospitalization rate†,** (95% CI)	% of residents up to date with COVID-19 vaccination (95% CI)††
Overall	14,811	21,046,590	230,105	109.3 (108.9–109.8)	12,211	5.8 (5.7–5.9)	40.5 (40.4–40.6)
Northeast	2,432	4,772,100	54,229	113.6 (112.7–114.6)	2,012	5.9 (5.7–6.1)	47.3 (47.1–47.6)
South	5,508	7,956,877	74,094	93.1 (92.5–93.8)	4,002	5.0 (4.9–5.2)	32.4 (32.2–32.5)
Midwest	4,774	5,619,718	73,134	130.1 (129.2–131.1)	3,782	6.7 (6.5–6.9)	44.7 (44.5–45.0)
Mountain	547	599,880	6,799	113.3 (110.7–116.1)	328	5.5 (4.9–6.1)	41.9 (41.2–42.5)
Pacific	1,550	2,098,015	21,849	104.1 (102.8–105.5)	1,287	6.1 (5.8–6.5)	44.1 (43.7–44.5)

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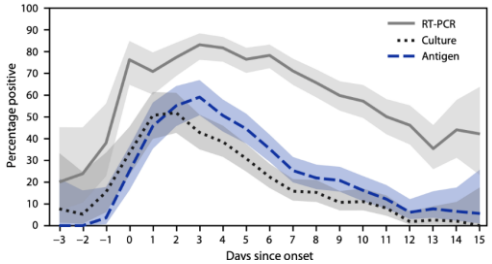
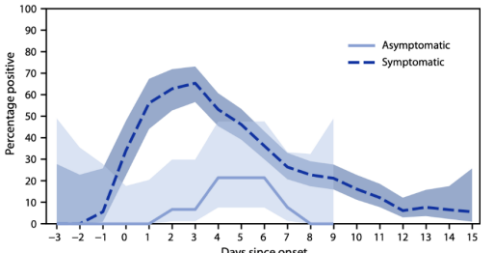
Suspected Infection and Testing

Methods: prospective study, household members of (+) family patient
- At home daily antigen test, PCR and viral cultures x 10 days
- (354 participants in 129 households, 11/22 - 5/23)

Result: antigen test = 47% sensitivity (compared to RT-PCR)





Smith-Jeffcoat SE, et al. MMWR April 25, 2024

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If My Clinic Only Has a Rapid Antigen Test.....

Original Investigation | Infectious Diseases

COVID-19 Rapid Antigen Tests With Self-Collected vs Health Care Worker–Collected Nasal and Throat Swab Specimens
A Randomized Clinical Trial

Methods: Multicenter, randomized clinical trial, compared 2,674 patients:

		Sensitivity compared to RT-PCR	
Health care worker:	Nasal = 57.9%.	Throat = 69.4%	Combined = 81%
Self obtained:	Nasal = 60.0%.	Throat = 53.7%	Combined = 73%

Todsen T, et al. JAMA Network Open 2023;6(12):e2344295.

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Treatment: Antiviral Therapy
Decrease Hospitalization/Death vs. Shorten Course

Nirmatrelvir/ritonavir and remdesivir against symptomatic treatment in high-risk COVID-19 outpatients to prevent hospitalization or death during the Omicron era: a propensity score-matched study

Methods: high-risk outpatients
Tertiary care center, Mexico City
1/1/22- 7/31/23
Propensity-score matched…

Results:	**Paxlovid (n=332)**	**remdesivir (n=451)**	**no treatment (n=783)**
Hospitalization/death @ 30 days	**5 (1.5%)**	**27 (5.9%)**	**136 (17.3%)**

Rajme-Lopez, S, et al. Ther Adv Infect Dis 2024; 11:1-8

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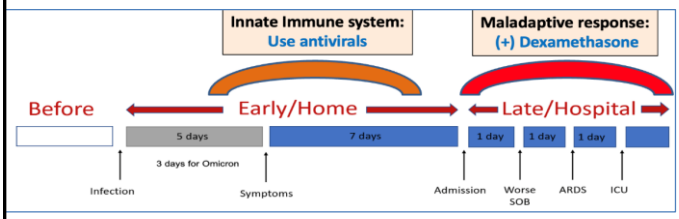
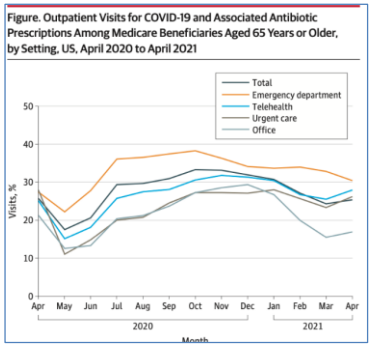
Reminder: Please Do NOT

A. (Outpatient) Steroids



B. (Outpatient) Antibiotics



Azithromycin = 50%

Tsay SV, et al. ; 327: JAMA 2022: 2018-9

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Remdesivir Decreases Mortality for In-patients

*Methods: retrospective, observational multi-center study, 12/20 – 4/22 propensity match hospitalized patients (*not requiring oxygen*):

Results:	(+) remdesivir (n= 58,188)	no remdesivir (n= 17,574)
- Death at 14 days.	5.4%	7.3%
- Death at 28 days	8.0%	9.8%

**Similar result for hospitalized patients requiring oxygen
***JAMA study with positive results also, less robust

*Mozaffari E, et al. Open Forum Infectious Dis, 2024
**Mozaffari E, et al. Open Forum Infectious Dis, 2023
Both studies: manufacture supported study
***Chokkalingam AP et al. JAMA Network Open, 2022;5(12):e2244505.

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Q3: What the Etiology of Long Covid?
(Pathophysiology Theories/Studies of Interest)

- Autoimmune?
- Cognitive dysfunction:
  - viral persistence?
  - activation of complement and platelet aggregation ➔ microthrombosis?
  - neuroinflammation and impaired neurogenesis?
  - low-serotonin–induced dysfunction in vagal signaling?
- Reactivation of EBV?

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Big Picture: Where Are We Today?

Covid-19 vs. Influenza vs. RSV

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COVID-19 vs. RSV vs. Influenza

Methods: prospective cohort study
Adults admitted to 25 US hospitals
(+) RSV ***or*** (+) Covid-19 ***or*** (+) influenza
2/1/22 – 5/31/23

JAMA Network Open
Original Investigation | Infectious Diseases
Severity of Respiratory Syncytial Virus vs COVID-19 and Influenza Among Hospitalized US Adults
Surie D, et al JAMA Open Network 2024

Results:	**RSV** (n=484)	**Covid-19** (n=6422) (n=5000 vaccinated)	**Influenza** (n=1092) (n=393 vaccinated)
Death/IMV	12%	14.1% (no vax) 9.2% (+ vax) *p=.03*	10.3% (no vax) 5.1% (+ vax) *p<0.01*

Conclusion: hospitalization for RSV is less common than Covid-19 or influenza
*RSV is more severe than vaccinated Covid or influenza pts

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COVID-19 and RSV vs. Influenza

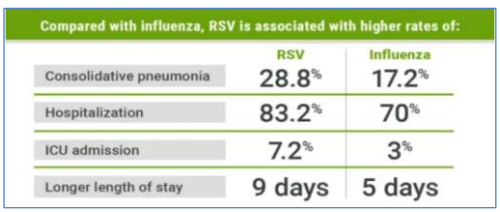
Clinical Outcomes of US Adults Hospitalized for COVID-19 and Influenza in the Respiratory Virus Hospitalization Surveillance Network, October 2021–September 2022
Kojima N, et al OFID 2023

	Omicron era: n=1,451	Influenza n=2,363
Vaccinated:	70%	56%
ICU:	15.5%	13.3%
Vasopressors	8.2%	4.8%. *p<0.5*
Death	4.6%	2.6%. *P <0.5*

Respiratory Syncytial Virus vs Influenza Virus Infection: Mortality and Morbidity Comparison Over 7 Epidemic Seasons in an Elderly Population

Single-center retrospective study
All patients age > 75

Recto CG, et al JID published online Apr 2, 2024



Death @ 28 days: 9.6%. 9.7%

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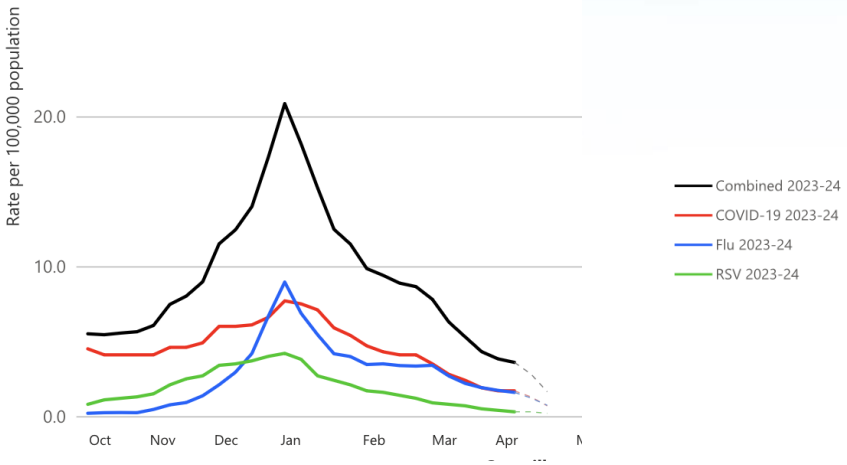
COVID-19 and RSV vs. Influenza

Hospitalizations



CDC RESP-NET Dashboard

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A New York county banned face masks in public. Disabled people are suing.

Nassau County passed a law this month that bans people from wearing face masks in public. Violators could face up to $1,000 in fines or jail time.

Washington Post, Aug 27, 2024

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