COVID-19 2023

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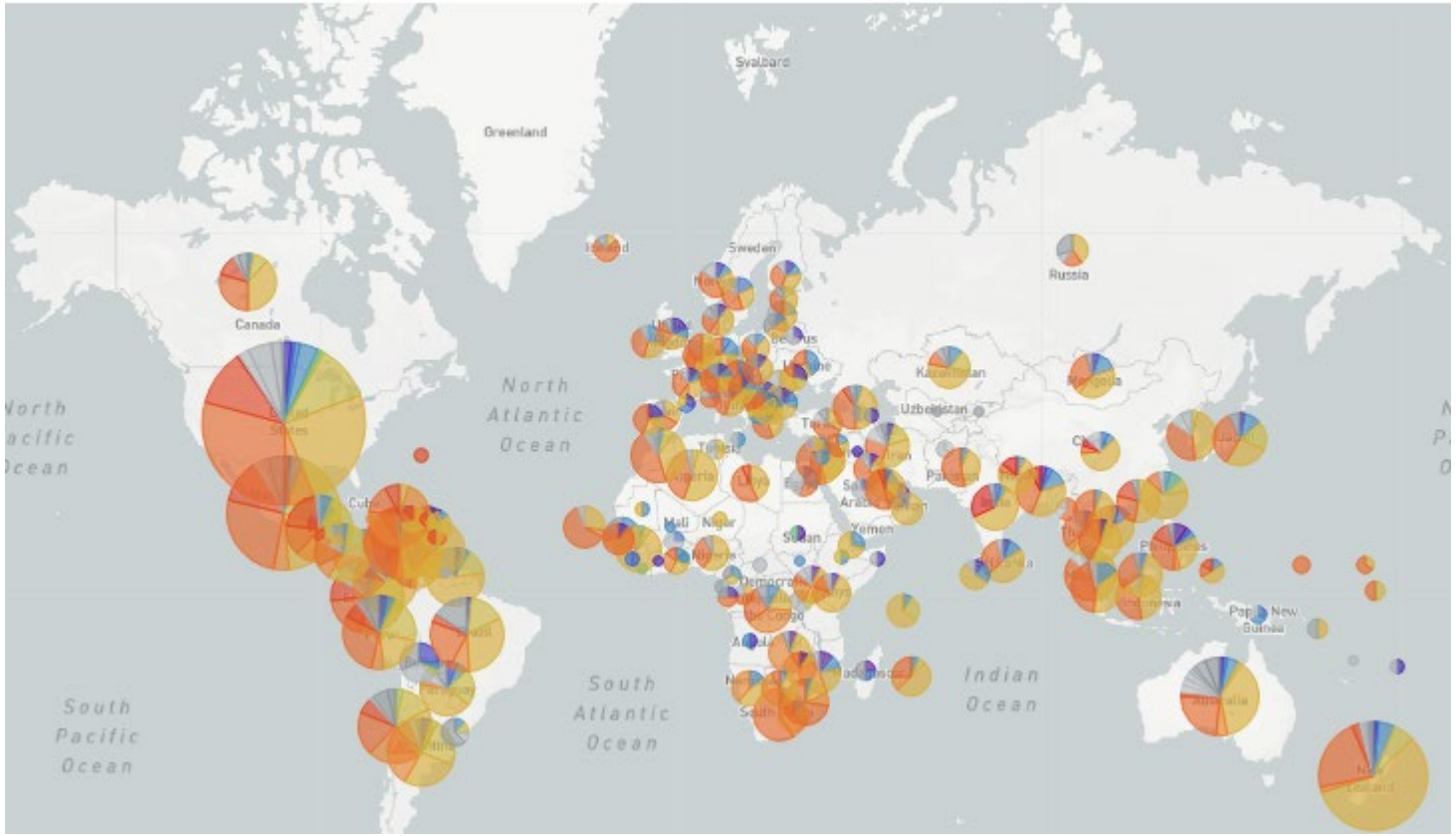
Genomic Epidemiology of SARS-CoV-2: Geography

Phylogeny

Clade

- 20H (Beta, V2)
- 20I (Alpha, V1)
- 20J (Gamma, V3)
- 21A (Delta)
- 21I (Delta)
- 21J (Delta)
- 21B (Kappa)
- 21C (Epsilon)
- 21D (Eta)
- 21F (Iota)
- 21G (lambda)
- 21H (Mu)
- 21K (Omicron)
- 21L (Omicron)
- 21M (Omicron)
- 22A (Omicron)
- 22B (Omicron)
- 22C (Omicron)
- 19A
- 19B
- 20A
- 20C
- 20G
- 20E (EU1)
- 20D
- 20F

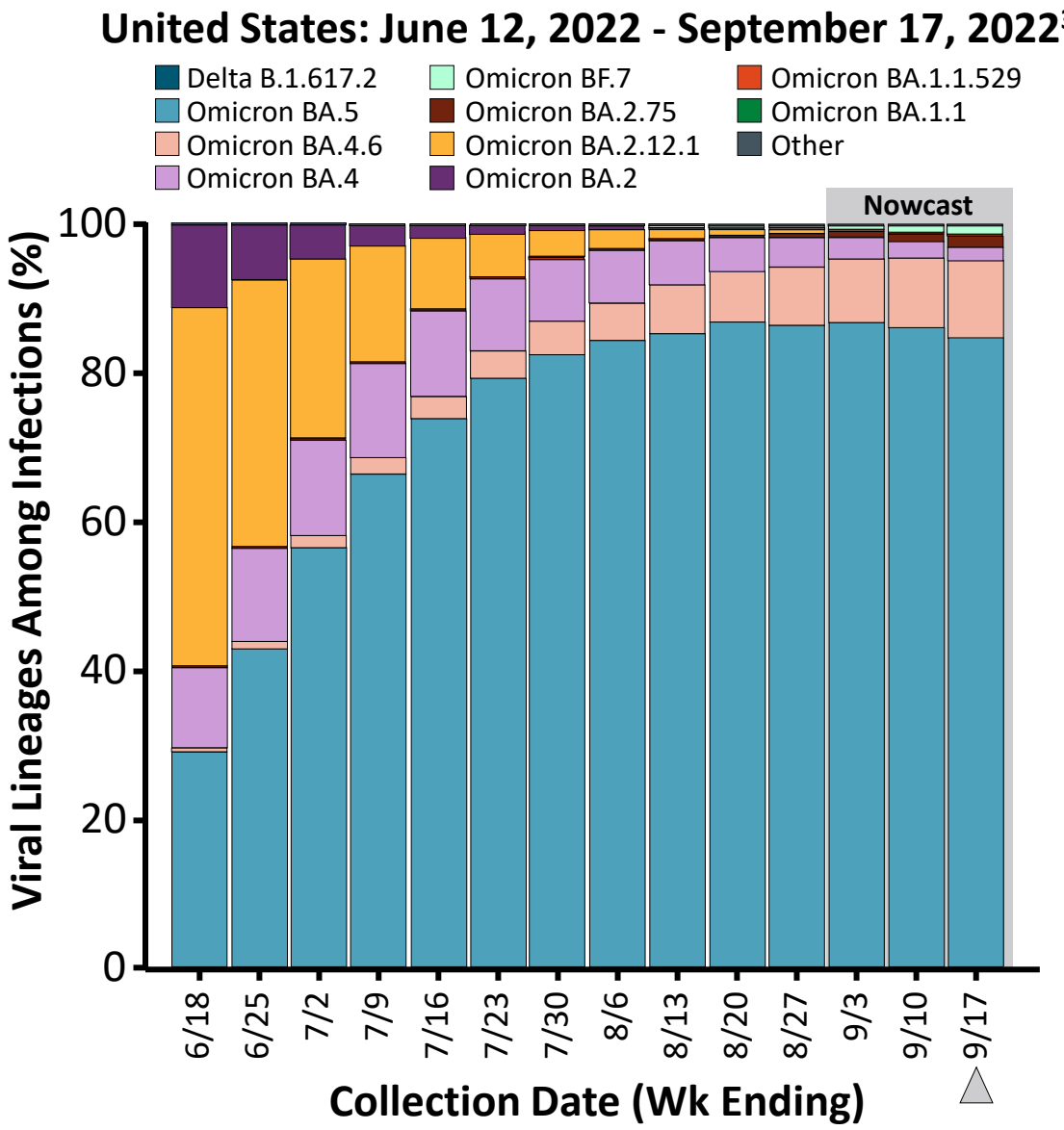


GISAID. Updated September 21, 2022. gisaid.org/phylodynamics/global/nextstrain/.

Slide credit: clinicaleducationalliance.com:

Omicron: Transmissibility

- Omicron spreads rapidly[1,2]
  - Increased transmissibility[1]
    - Secondary attack rate in households with **omicron** vs **delta**: **31%** vs **21%**
    - Unvaccinated individuals have higher transmissibility compared with fully vaccinated individuals
    - **Omicron** is 2.7-3.7 times more transmissible than delta among vaccinated individuals[1]
  - **Immune evasion**



1. Lyngse. medRxiv. 2021;[Preprint]. Note: This study has not been peer reviewed.
2. cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html.
3. covid.cdc.gov/covid-data-tracker/#variant-proportions.

CDC: COVID-19 Vaccine and Booster Recommendations

- **6 mo - 4 yr of age**: receive all COVID-19 primary series doses
- **5 yr of age or older**: all primary series doses and recommended booster dose(s)
  - 5-11 yr of age should receive monovalent booster
- People with immunocompromise have different primary series and booster recommendations

Bivalent Booster (Pfizer or Moderna)
12 yr of age or older who have received all primary series doses and people who have previously received 1 or more original (monovalent) boosters
12-17 yr of age can receive only Pfizer bivalent booster
Recommendations may be updated as CDC continues to monitor latest data

cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html. Last updated September 8, 2022.
cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html.
Last updated September 2, 2022.

The NEW ENGLAND JOURNAL of MEDICINE

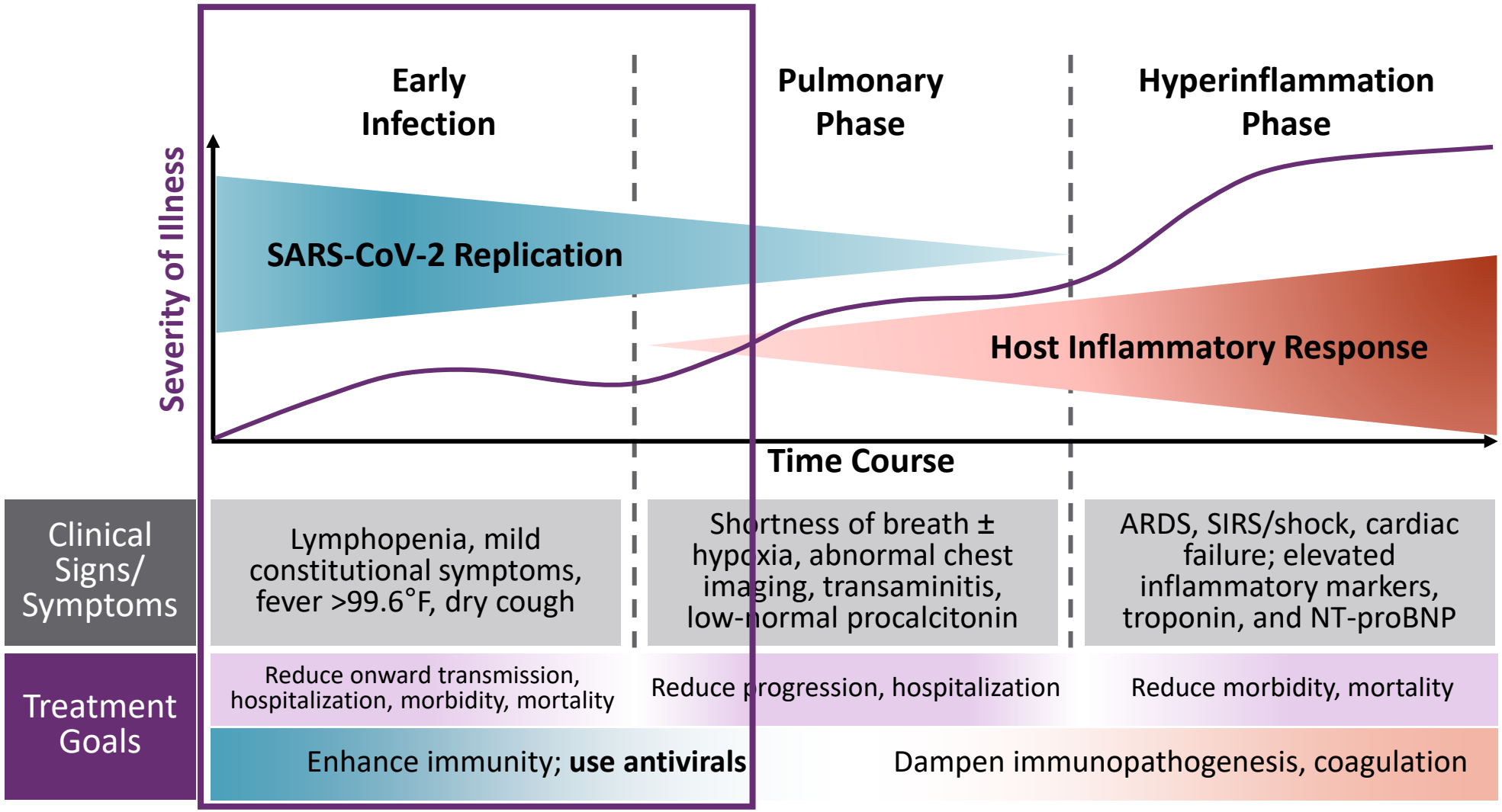
ORIGINAL ARTICLE

Intramuscular AZD7442 (Tixagevimab–Cilgavimab) for Prevention of Covid-19

M.J. Levin, A. Ustianowski, S. De Wit, O. Launay, M. Avila, A. Templeton, Y. Yuan, S. Seegobin, A. Ellery, D.J. Levinson, P. Ambery, R.H. Arends, R. Beavon, K. Dey, P. Garbes, E.J. Kelly, G.C.K.W. Koh, K.A. Near, K.W. Padilla, K. Psachoulia, A. Sharbaugh, K. Streicher, M.N. Pangalos, and M.T. Esser, for the PROVENT Study Group*

N Engl J Med . 2022 Apr 20

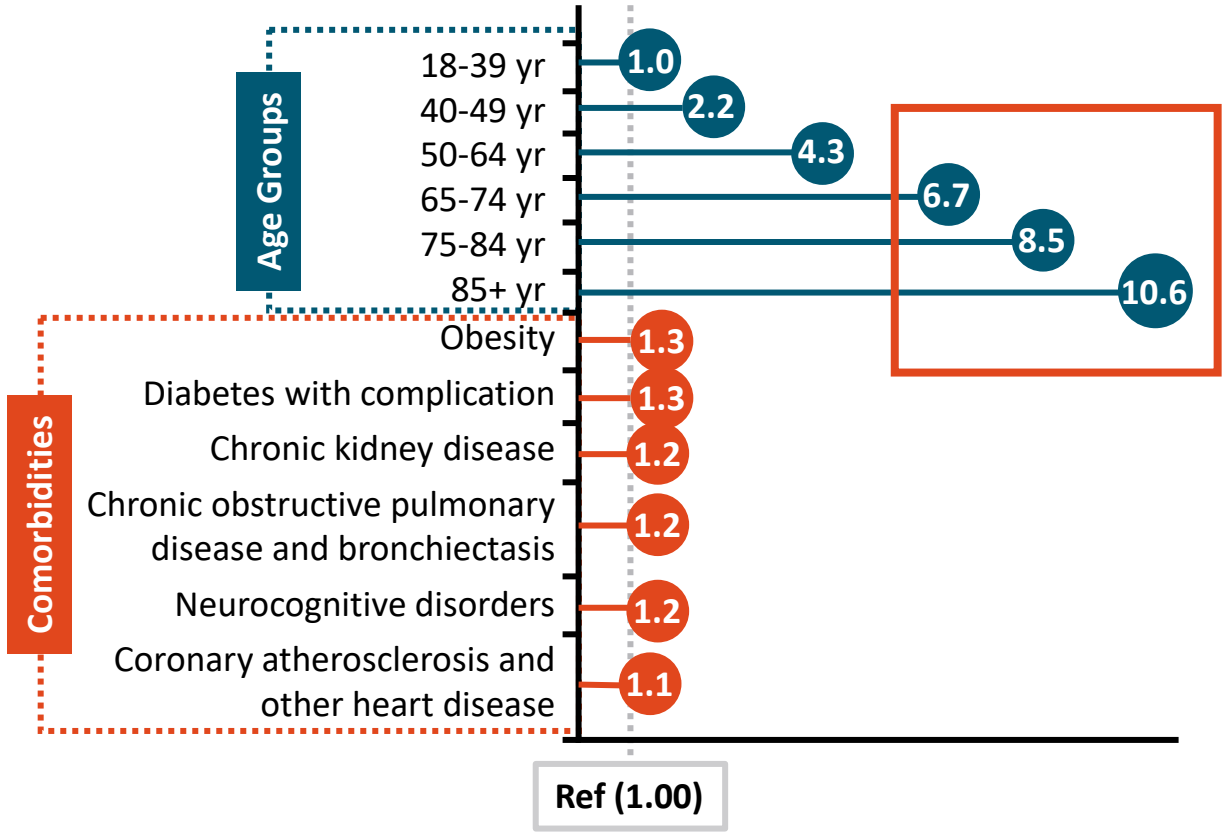
Benefit of Early Outpatient Antiviral Treatment



NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated August 8, 2022.
Siddiqi. J Heart Lung Transplant. 2020;39:405.

Age Is Strongest Risk Factor for Severe COVID-19

COVID-19 Death Risk Ratio for Select Age Group and Comorbid Conditions



- **EPIC-HR and MOVe-OUT High-Risk Criteria**
  - ≥60 yr of age
  - Chronic pulmonary disease
  - Overweight or obese
  - Chronic kidney disease
  - Cardiovascular disease
  - Neurodevelopmental disorders
  - Medically related technologic dependence
  - Tobacco smoker
  - Immunosuppression
  - Sickle cell disease
  - Diabetes
  - Active cancer

cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Slide credit: clinicaleducationalliance.com: cea clinical education alliance

Timely Tests for SARS-CoV-2: Rapid Antigen Test (RAT)

- Use RAT for symptomatic individuals and close contacts of individuals who are positive for COVID-19
  - RATs have higher rate of false-negative results compared with PCR tests
  - PCR tests are definitive diagnostic test
- ANY positive test should be interpreted as definitive and positive
  - Long-standing positive test results >10 days following infection may represent noninfectious viral particles
- In event of negative COVID-19 test, perform repeat RAT in 2-3 days

cdc.gov/coronavirus/2019-ncov/hcp/testing-overview.html. Last updated August 25, 2022.

Outpatient Antivirals: Reduced Hospitalization or Death

- Early use of antiviral agents significantly reduces risks of hospitalization or death compared with placebo
- Important to test and treat in timely fashion to maximize benefit

Study (Drug)	Start Date After Symptom Onset (Days)	RRR in Hospitalization or Death (%) Compared With Placebo	*P* Value
MOVe-OUT (molnupiravir)[1]	5	30	.0218
EPIC-HR (nirmatrelvir/ritonavir)[2]	3	89	<.001
	5	88	
PINETREE (remdesivir)[3]	7	87	.008

1. Bernal. NEJM. 2022;386:509. 2. Hammond. NEJM. 2022;386:1397. 3. Gottlieb. NEJM. 2022;386:305.

Current treatment options in non-hospitalized adults for prevention of hospitalization/death

Recommended	Major limitations	Use in pregnancy
Nirmatrelvir/ritonavir (NMV/r)	Drug-drug interactions, advanced kidney and liver disease, dysgeusia	✓
Remdesivir (RDV)	IV x 3 days, advanced kidney disease	✓

Alternative	Major limitations	Use in pregnancy
Molnupiravir (MOV)	Lower efficacy, concern for mutagenicity, bone and cartilage risk <18	✗

- Placebo-controlled efficacy trials: pre-Omicron, unvaccinated
- Eligible: high risk for progression to severe COVID-19 – *who is high risk today?*
- Positive test no longer required if COVID-19 suspected

K Chew. CROI 2023

Hammond, NEJM 2022; Kuriakose Abstract 515 (NMV/r DDIs); Gottlieb, NEJM 2022; Jayk Bernal, NEJM 2022; NIH COVID-19 Treatment Guidelines, www.covid19treatmentguidelines.nih.gov

Nirmatrelvir + Ritonavir: CYP3A Metabolism

Select Recommendations	
Contraindicated	**Use With Caution**
↑ alfuzosin ↑ piroxicam ↑ ranolazine ↑ amiodarone ↑ anticancer drugs (eg, apalutamide) ↑ rivaroxaban ↑ colchicine ↑ glecaprevir/pibrentasvir ↑ salmeterol ↑ sildenafil ↑ midazolam ↓ voriconazole	↑↓ warfarin (monitor INR) ↑ apixaban ↑ dabigatran ↓ bupropion ↑ trazadone ↑ anti-HIV protease inhibitor (eg, darunavir) ↓ raltegravir ↑ clarithromycin/erythromycin ↑ rifabutin ↑ quetiapine ↑ digoxin ↓ ethinyl estradiol (use add'l contraception) ↑ immunosuppressants (eg, tacrolimus) ↑ corticosteroid (eg, prednisone) ↑ fentanyl ↓ methadone
Phenytoin, carbamazepine, rifampin, St John's wort all ↓ nirmatrelvir + ritonavir	*Hold if giving to avoid increase: lovastatin, simvastatin, atorvastatin, rosuvastatin, bosentan*

- Review patient's medications and supplements
- Nirmatrelvir + ritonavir = CYP3A inhibitor, so may increase levels of other drugs
- When used with CYP3A inducers, may not achieve adequate levels of nirmatrelvir

fda.gov/media/155050/download

Potential Symptom Rebound Following Nirmatrelvir + Ritonavir Use

- Retrospective review of patients at Mayo Clinic Rochester who received nirmatrelvir + ritonavir for mild to moderate SARS-CoV-2 infection
  - Median age: 63 yr; 56% female; 93% fully vaccinated
  - Time from positive SARS-CoV-2 test to nirmatrelvir + ritonavir prescription: 1 day (IQR: 1-2 days)
- Rebound defined as recurrence of COVID-19 symptoms following completion of 5 days of nirmatrelvir + ritonavir
- 4 of 483 patients (0.8%) experienced rebound
  - All were fully vaccinated
- Median time to rebound after nirmatrelvir + ritonavir treatment: 9 days (IQR: 7.0-14.5 days)
- All resolved **without** hospitalization or additional COVID-19–directed therapy

Raganath. Clin Infect Dis. 2022;[Epub].

COVID-19 Rebound Summary

- Occurs at low frequency but warrants prevention[1-3]
- Patients still may be infectious during rebound period[1]
  - Positive cultures can persist after treatment course
- COVID-19 rebound is not easily explained by impaired immunity or resistance mutations[2,3]

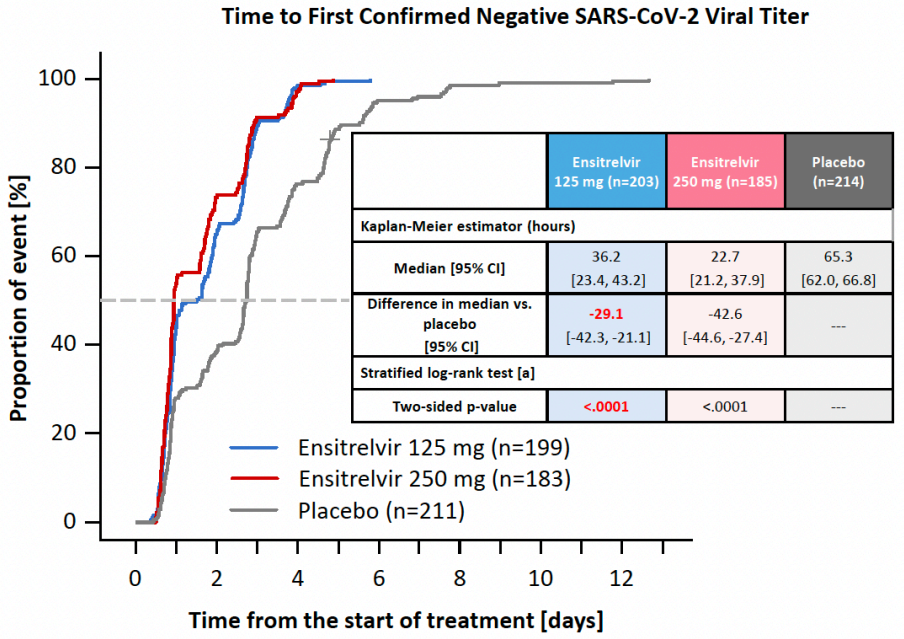
1. Boucau. Clin Infect Dis. 2022;[Epub]. 2. Carlin. Clin Infect Dis. 2022;[Epub].
3. Epling. medRxiv. 2022[Preprint]. Note: this study has not been peer reviewed.

COVID at CROI 2023

Ensitrelvir (SCORPIO-SR)

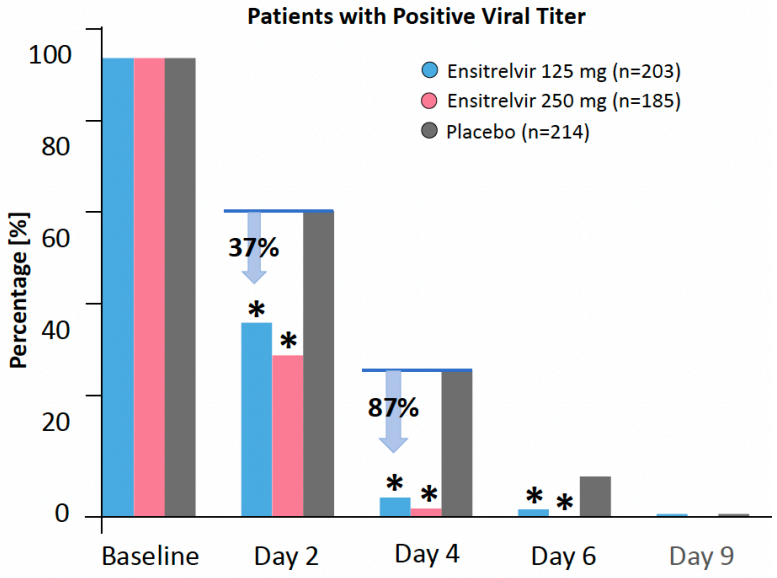
- SARS-CoV-2 protease inhibitor, no booster, once daily, 42-48h half-life
- Phase 3 RCT, Japan/Asia, Feb-Nov 2022 (early Omicron)
- Mixed risk, >90% vaccinated, within 72h of symptoms (primary)
- Ensitrelvir once daily × 5 days vs blinded placebo

Ensitrelvir 125 mg shorten the time to cessation of SARS-CoV-2 viral shedding by 29 hours (median) compared with placebo.
Ensitrelvir 125mg showed 87% reduction of patient with positive viral titer at Day 4 compared with placebo.



	Ensitrelvir 125 mg (n=203)	Ensitrelvir 250 mg (n=185)	Placebo (n=214)
Kaplan-Meier estimator (hours)			
Median [95% CI]	36.2 [23.4, 43.2]	22.7 [21.2, 37.9]	65.3 [62.0, 66.8]
Difference in median vs. placebo [95% CI]	-29.1 [-42.3, -21.1]	-42.6 [-44.6, -27.4]	---
Stratified log-rank test [a]			
Two-sided p-value	<.0001	<.0001	---

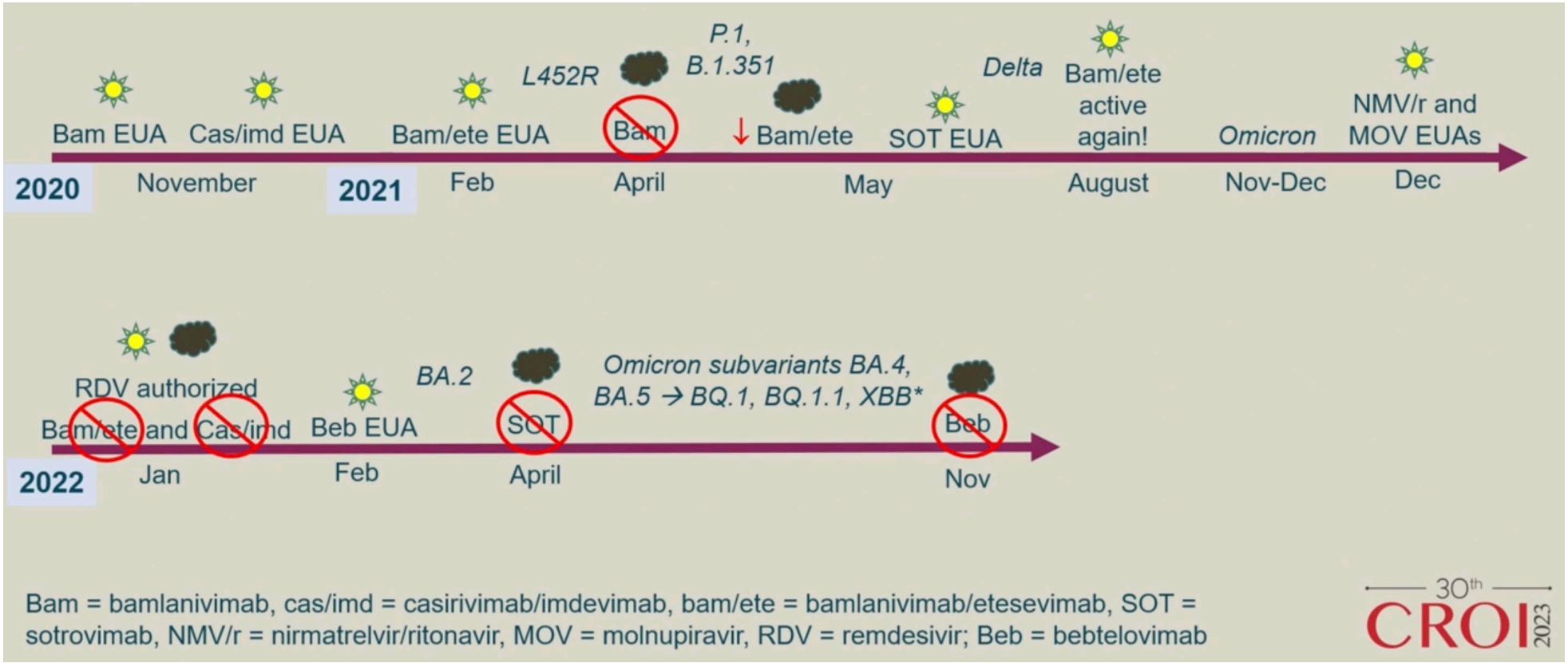
Analysis in the Modified Intention-to-Treat Population (All Pretreatment RT-PCR-Positive Patients with Detectable SARS-CoV-2 Viral Titers at Baseline) with any observations after the start of treatment, CI = Confidence Interval
[a] Adjusted for SARS-CoV-2 vaccination status



vs Placebo *< 0.05
Mantel-Haenszel test stratified by SARS-CoV-2 vaccination history
Viral titer negative (<0.75 $\log_{10}$ ($TCID_{50}$/mL))
Viral titer positive (≥0.75 $\log_{10}$ ($TCID_{50}$/mL))

COVID at CROI 2023

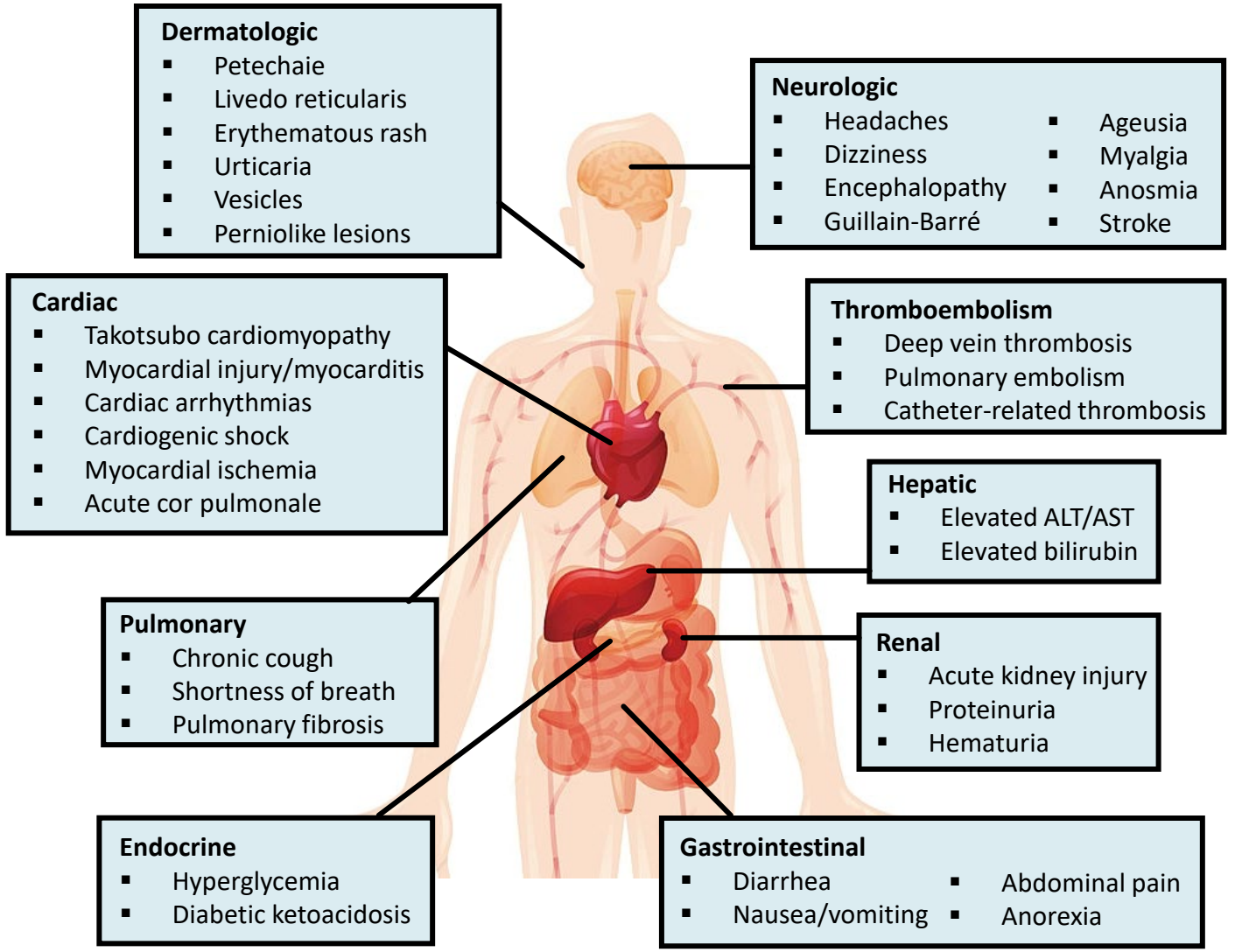
The rise and fall of monoclonal antibodies for the treatment of COVID-19



Chew. CROI 2023

Long COVID (PASC)

- Postacute sequelae of COVID-19
- New symptoms that affect everyday function, emerge within 4 wk to 3 mo after first being infected, and last for ≥2 mo
  - Symptoms may fluctuate over time
  - Overlap with prolonged symptoms post hospitalization

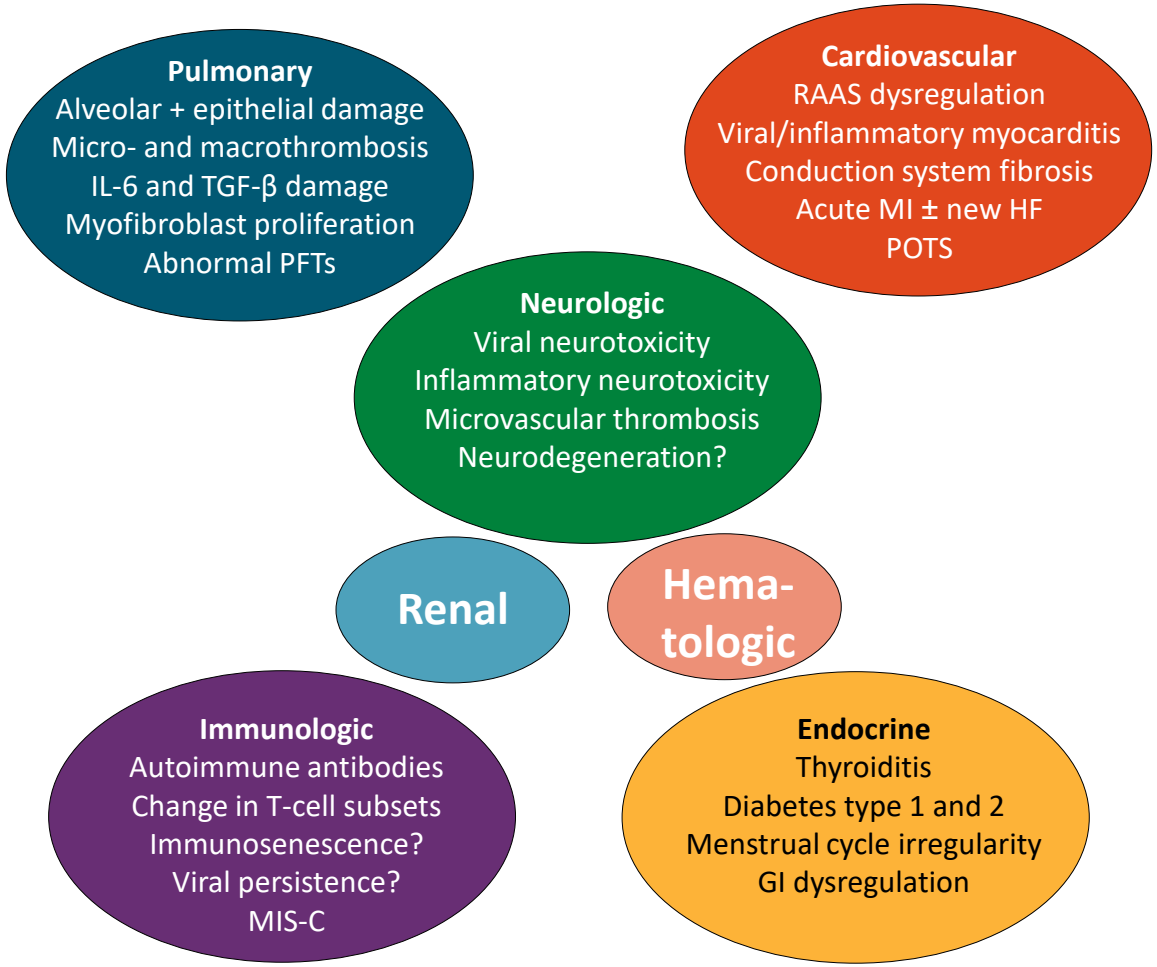


who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html.

Slide credit: clinicaleducationalliance.com:

Potential Causes of Long COVID

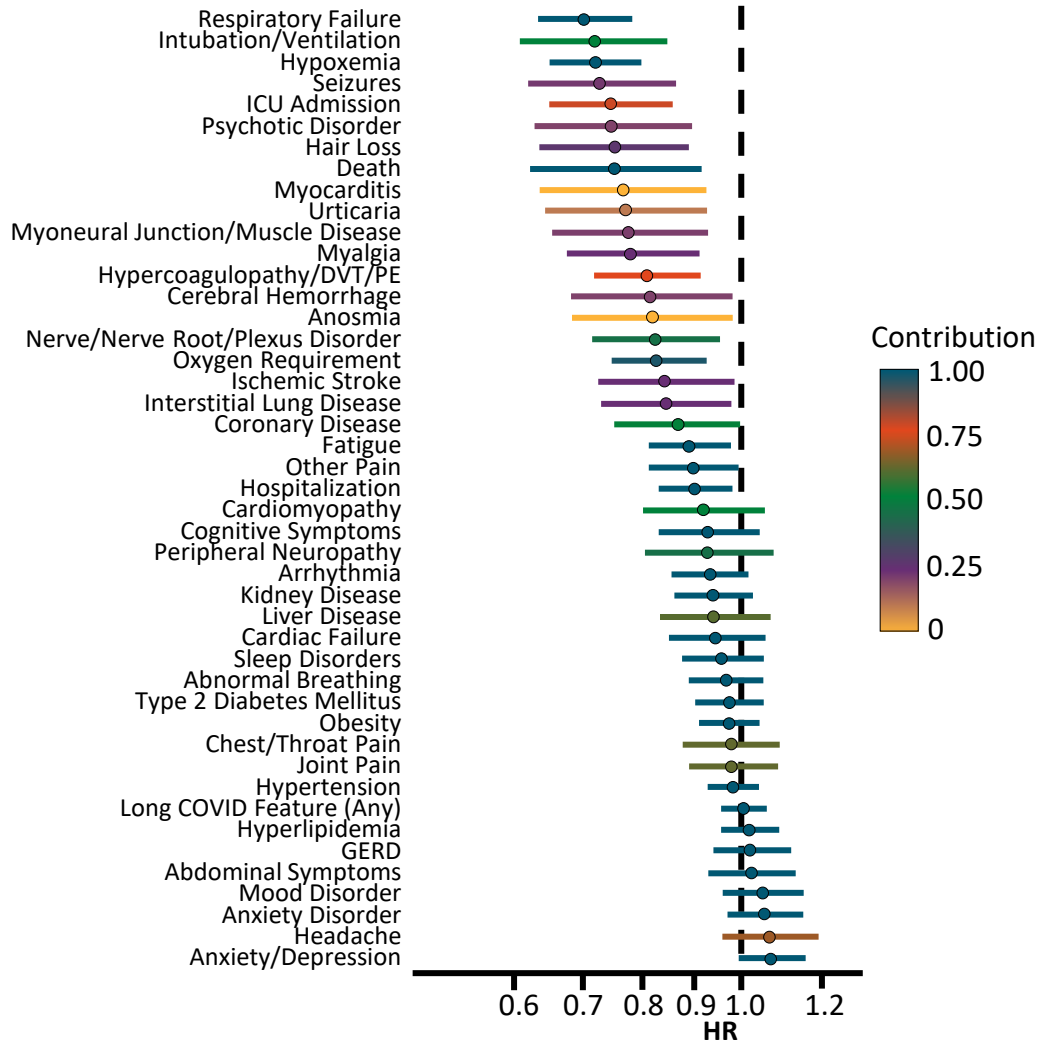
- Direct neuro-invasion
- Dysregulated immune response
- Auto-inflammation
- Post-ICU syndrome
- Lingering virus in immunologically privileged sites
- Endothelial injury, ongoing endothelial dysfunction



Akselrod. IDWeek 2021. Chasing the Sun presentation.
sciline.org/covid-19/emerging-challenges. Proal. Front Microbiol. 2021;12:698169.

Long COVID and COVID-19 Vaccination

- Long COVID can occur after breakthrough infection, but rates are consistently lower in vaccinated vs unvaccinated persons
- 2 doses of SARS-CoV-2 vaccine are protective against *some* postacute sequelae of COVID-19, but not all



Kuodi. medRxiv. 2022;[Preprint]. Note: this study has not been peer reviewed.
Taquet. Brain Behav Immun. 2022;103:154.

Can Early Antiviral Use Prevent Long COVID?

- Anti-SARS-CoV-2 vaccination is best way to prevent long COVID[1]
- Researchers hypothesize that early antiviral use may prevent or ease long COVID symptoms[2]
  - Decrease viral reservoir

- PANORAMIC trial[3]: **molnupiravir**
  - Collecting data at 3 and 6 mo post treatment
- Solidarity trial[4]: **remdesivir** in hospitalized patients
    - Soon to have 1-yr follow-up data
- **Nirmatrelvir/ritonavir**[2]
    - Several ongoing studies will assess data 6 mo post treatment

1. Ayoubkhani. medRxiv. 2022[Preprint]. 2. nature.com/articles/d41586-022-02140-w.
3. panoramictrial.org. 4. who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments.

Take-home Points

- COVID-19 is still causing mortality and morbidity in US
  - Prompt diagnosis with rapid antigen tests and PCR are essential for timely treatment
- Symptoms and risk stratification determine eligibility for treatment of selected ambulatory patients
  - Patients with immunocompromise require specialty consultation
- Guideline-preferred effective treatments include antivirals nirmatrelvir/ritonavir and remdesivir
  - Early treatment within 5 days is associated with optimal outcomes
- Alternative treatments include antiviral molnupiravir
- Ensiltrvir in Japan
- More mAbs in development, especially for PREVENTION