The End of the Pandemic

Looking back so we can continue to *look forward*
Covid Vaccines, Treatments, and Mitigation

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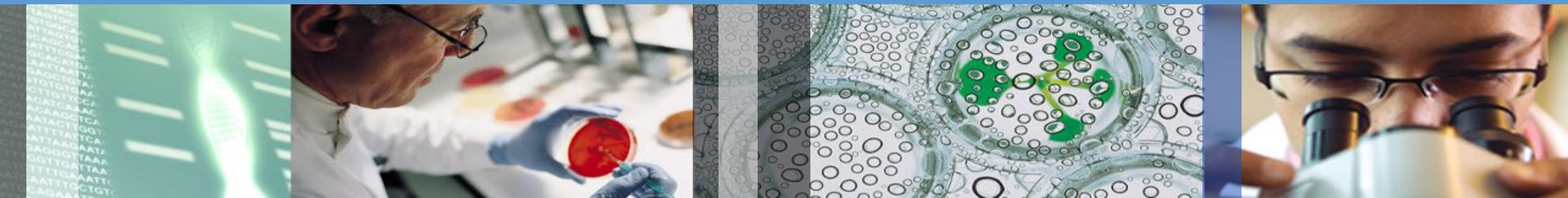
Professor of Medicine

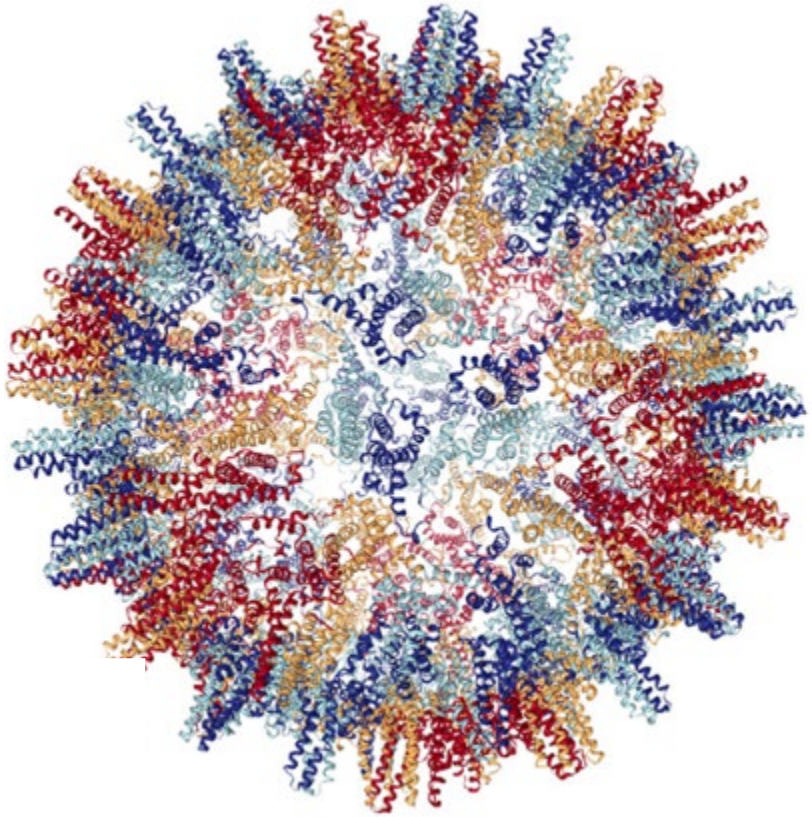
Division of Infectious Diseases

DukeMedicine

@camwolfe



DISCLOSURES – 12 months:



- DSMB (ongoing):
  - Janssen – RSV Vaccines
  - Biogen, Atea – Covid, SLE therapeutics
  - Allovir – cellular antiviral therapy
- Advisory Boards (closed):
  - AstraZeneca – Covid therapeutics
- I am a current member of the NIH COVID Treatment Guidelines Panel
  - Talk is neither endorsed by them, nor necessary reflective of their views

Outline:

- Learning Objectives:

  - Review current epidemiology of COVID19 & other respiratory viruses as we head into the fall
  - Understanding who is at risk, and how best now to treat them for COVID19
  - Updating latest information on vaccine & drug prevention for COVID19 & other respiratory viruses

- Future Directions?

Not going to discuss politics, legal or regulatory issues, or anything regarding social mitigation techniques
- *much* still to be learned there!

ProMED
INTERNATIONAL SOCIETY
FOR INFECTIOUS DISEASES

Date: 30 Dec 2019
Source: Finance Sina [machine translation]
https://finance.sina.cn/2019-12-31/detail-iihnzahk1074832.d.html?from=wap

Wuhan unexplained pneumonia has been isolated test results will be announced [as soon as available]

On the evening of [30 Dec 2019], an "urgent notice on the treatment of pneumonia of unknown cause" was issued, which was widely distributed on the Internet by the red-headed document of the Medical Administration and Medical Administration of Wuhan Municipal Health Committee.

12320 hotline staff said that what type of pneumonia of unknown cause appeared in Wuhan this time remains to be determined.

According to the above documents, according to the urgent notice from the superior, some medical institutions in Wuhan have successively appeared patients with pneumonia of unknown cause. All medical institutions should strengthen the management of outpatient and emergency departments, strictly implement the first-in-patient responsibility system, and find that patients with unknown cause of pneumonia actively adjust the power to treat them on the spot, and there should be no refusal to be pushed or pushed.

The document emphasizes that medical institutions need to strengthen multidisciplinary professional forces such as respiratory, infectious diseases, and intensive medicine in a targeted manner, open green channels, make effective connections between outpatient and emergency departments, and improve emergency plans for medical treatment.

Another piece of emergency notification, entitled "City Health and Health Commission's Report on Reporting the Treatment of Unknown Cause of Pneumonia" is also true. According to this document, according to the urgent notice from the superior, the South China Seafood Market in our city has seen patients with pneumonia of unknown cause one after another.

The so-called unexplained pneumonia cases refer to the following 4 cases of pneumonia that cannot be diagnosed at the same time: fever (greater than or equal to 38C); imaging characteristics of pneumonia or acute respiratory distress syndrome; reduced or normal white blood cells in the early stages of onset The number of lymphocytes was reduced. After treatment with antibiotics for 3 to 5 days, the condition did not improve significantly.

The early days… Lest we Forget

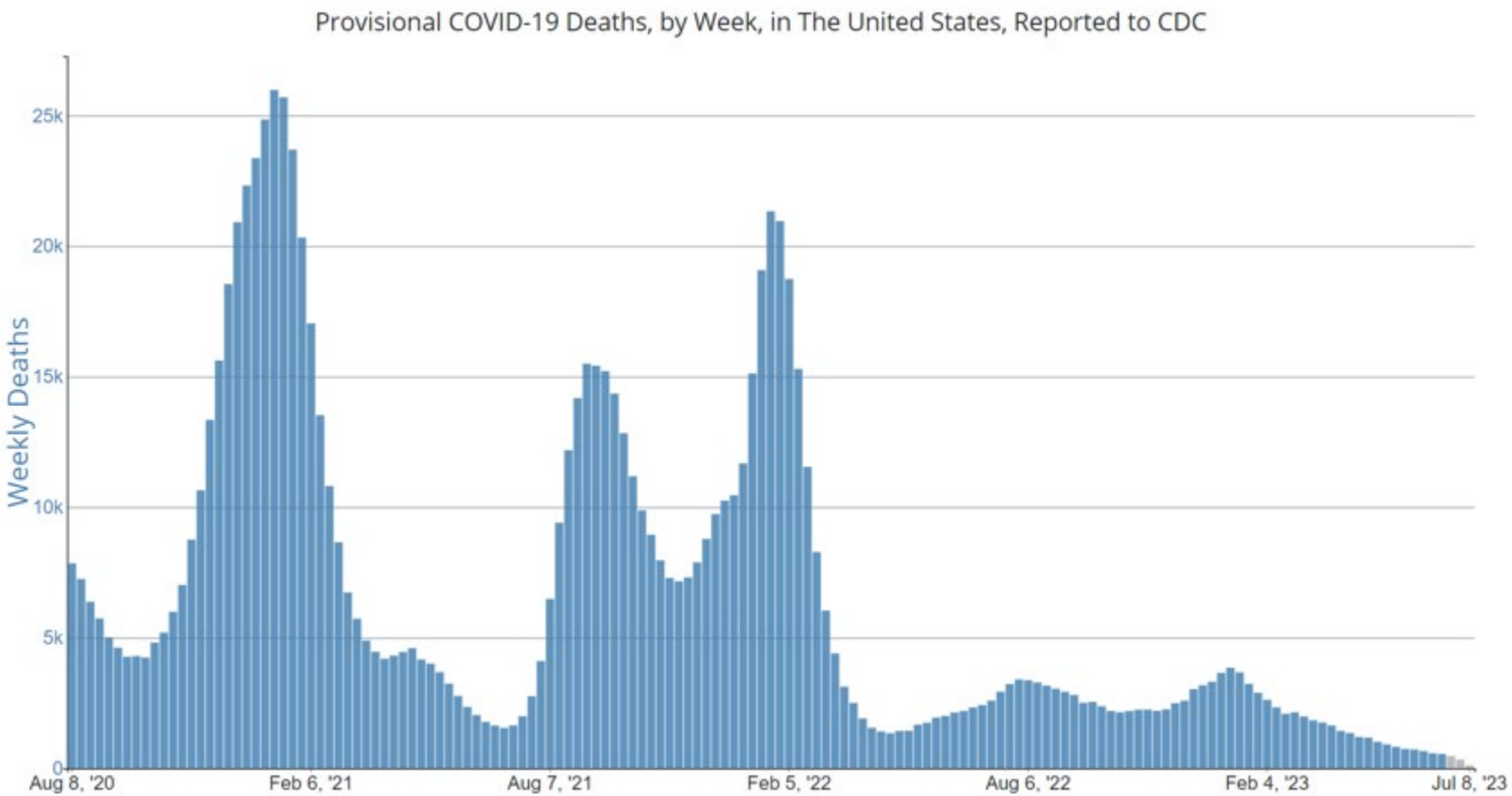
Best Guess Epidemiology

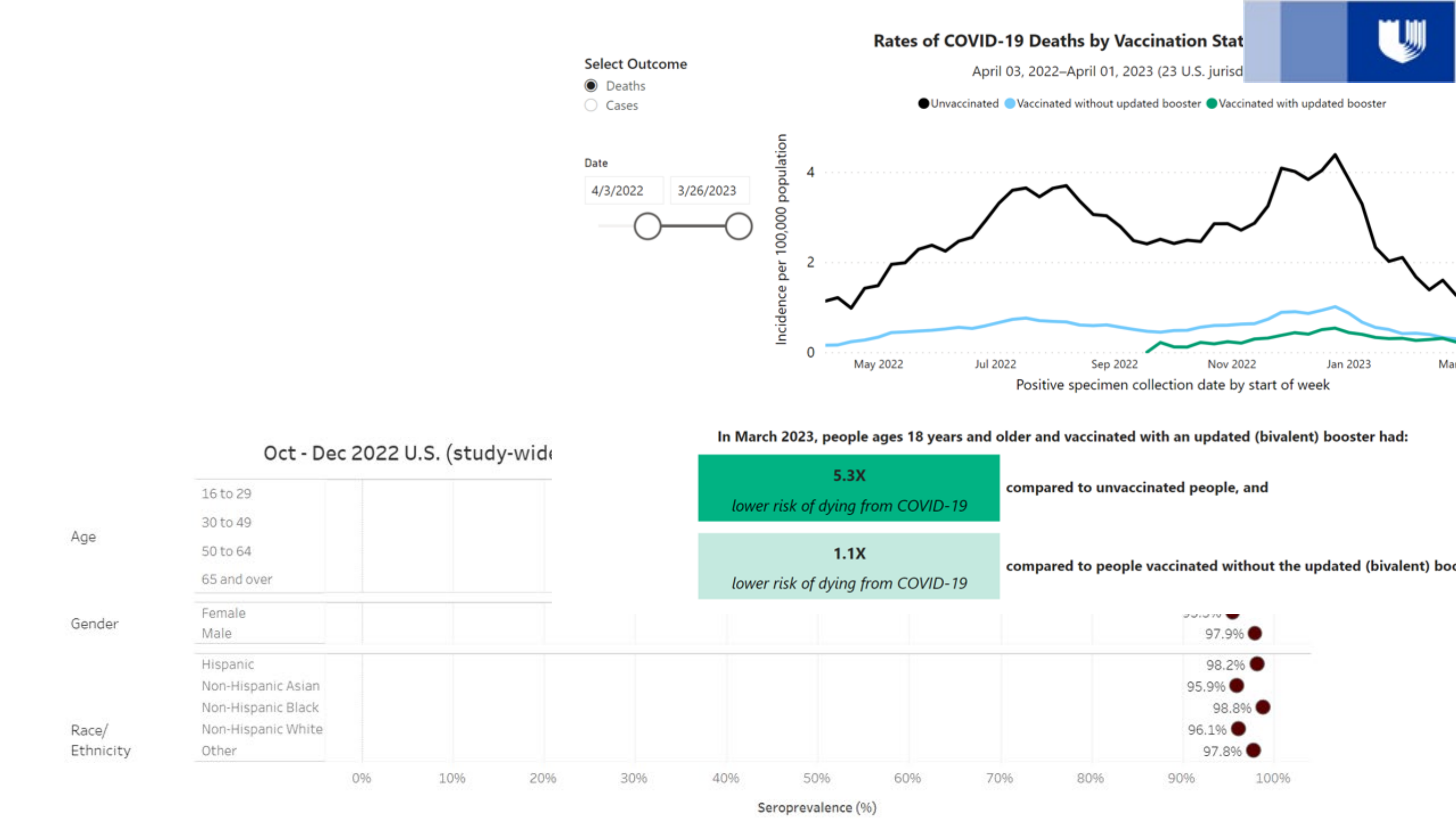
- Ro = 2.5; Doubling time 7-10 days — Community epi wave 2 months
- Community attack rate = 30-40% — US: 96 million cases
- Cases requiring hospitalization = 5% — US: 4.8 million admissions
- Cases requiring ICU care = 1-2% — US: 1.9 million ICU
- Cases requiring ventilatory support = 1% — US: 1 PPV
- CFR = 0.5% — US: 480,000 deaths

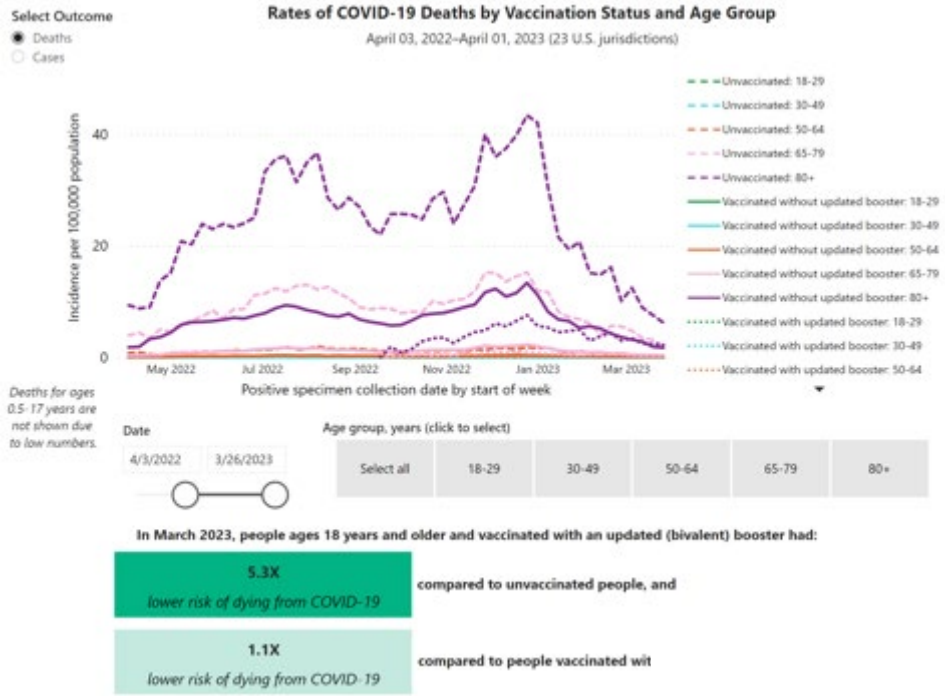
- **PREPARE FOR DISEASE BURDEN ROUGHLY 10X SEVERE FLU SEASON**

American Hospital Association™
Advancing Health in America

NETEC


Provisional COVID-19 Deaths, by Week, in The United States, Reported to CDC
Weekly Deaths
25k
20k
15k
10k
5k
0
Aug 8, '20
Feb 6, '21
Aug 7, '21
Feb 5, '22
Aug 6, '22
Feb 4, '23
Jul 8, '23


Rates of COVID-19 Deaths by Vaccination Stat
April 03, 2022–April 01, 2023 (23 U.S. jurisd
Select Outcome
Deaths
Cases
Date
4/3/2022
3/26/2023
Unvaccinated
Vaccinated without updated booster
Vaccinated with updated booster
Incidence per 100,000 population
4
2
0
May 2022
Jul 2022
Sep 2022
Nov 2022
Jan 2023
Positive specimen collection date by start of week
In March 2023, people ages 18 years and older and vaccinated with an updated (bivalent) booster had:
5.3X
lower risk of dying from COVID-19
compared to unvaccinated people, and
1.1X
lower risk of dying from COVID-19
compared to people vaccinated without the updated (bivalent) boo
Oct - Dec 2022 U.S. (study-wid
Age
16 to 29
30 to 49
50 to 64
65 and over
Gender
Female
Male
Race/
Ethnicity
Hispanic
Non-Hispanic Asian
Non-Hispanic Black
Non-Hispanic White
Other
97.9%
98.2%
95.9%
98.8%
96.1%
97.8%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Seroprevalence (%)


Select Outcome
Deaths
Cases
Rates of COVID-19 Deaths by Vaccination Status and Age Group
April 03, 2022–April 01, 2023 (23 U.S. jurisdictions)
Incidence per 100,000 population
40
20
0
May 2022
Jul 2022
Sep 2022
Nov 2022
Jan 2023
Mar 2023
Positive specimen collection date by start of week
Unvaccinated: 18-29
Unvaccinated: 30-49
Unvaccinated: 50-64
Unvaccinated: 65-79
Unvaccinated: 80+
Vaccinated without updated booster: 18-29
Vaccinated without updated booster: 30-49
Vaccinated without updated booster: 50-64
Vaccinated without updated booster: 65-79
Vaccinated without updated booster: 80+
Vaccinated with updated booster: 18-29
Vaccinated with updated booster: 30-49
Vaccinated with updated booster: 50-64
Deaths for ages 0.5-17 years are not shown due to low numbers.
Date
4/3/2022
3/26/2023
Age group, years (click to select)
Select all
18-29
30-49
50-64
65-79
80+
In March 2023, people ages 18 years and older and vaccinated with an updated (bivalent) booster had:
5.3X
lower risk of dying from COVID-19
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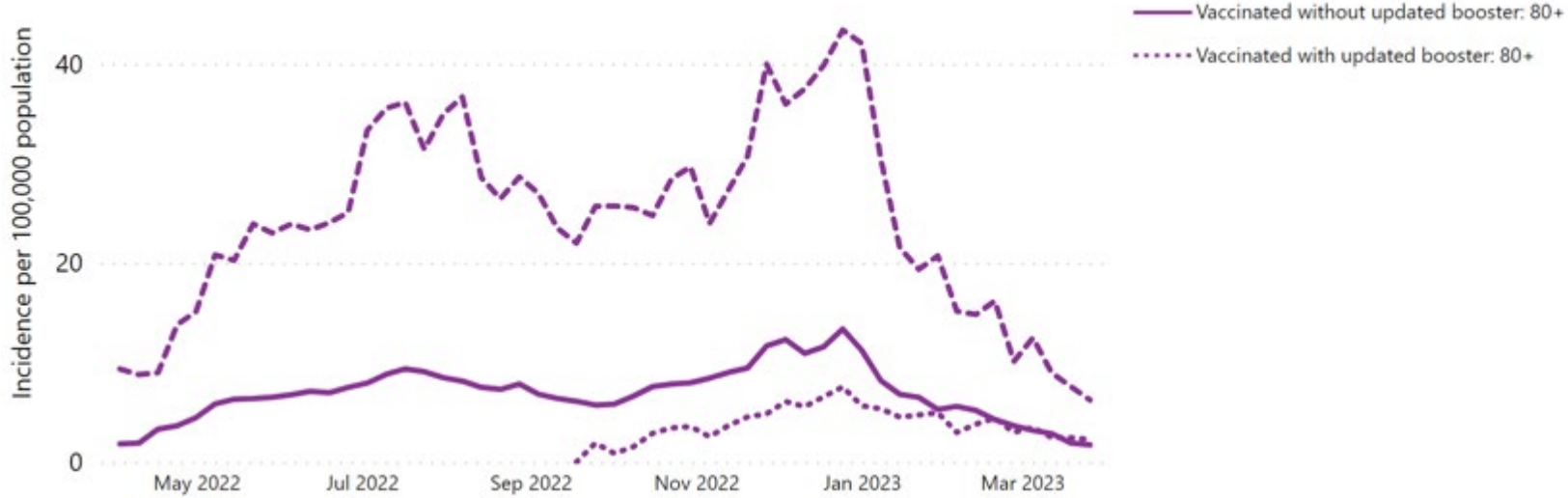
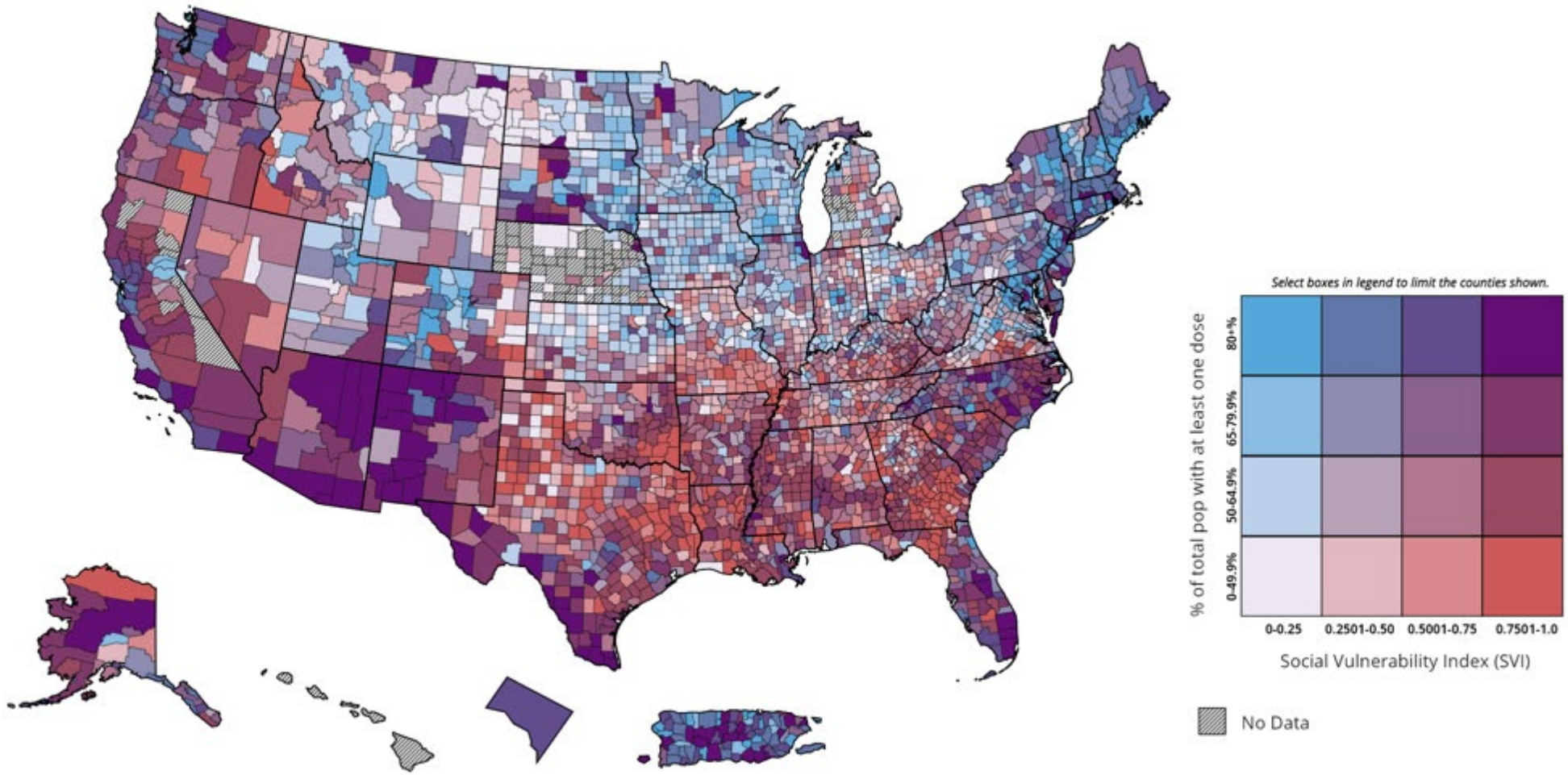
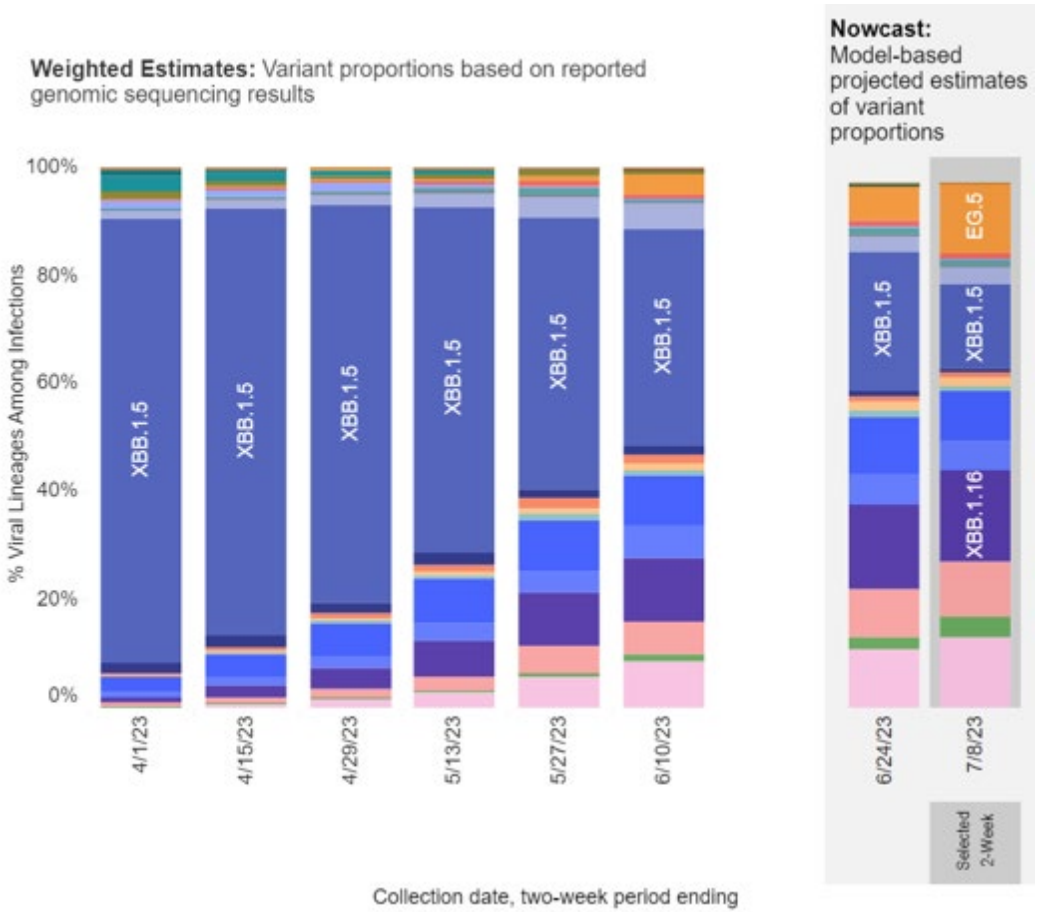

Unvaccinated: 80+
Vaccinated without updated booster: 80+
Vaccinated with updated booster: 80+
Incidence per 100,000 population
40
20
0
May 2022
Jul 2022
Sep 2022
Nov 2022
Jan 2023
Mar 2023

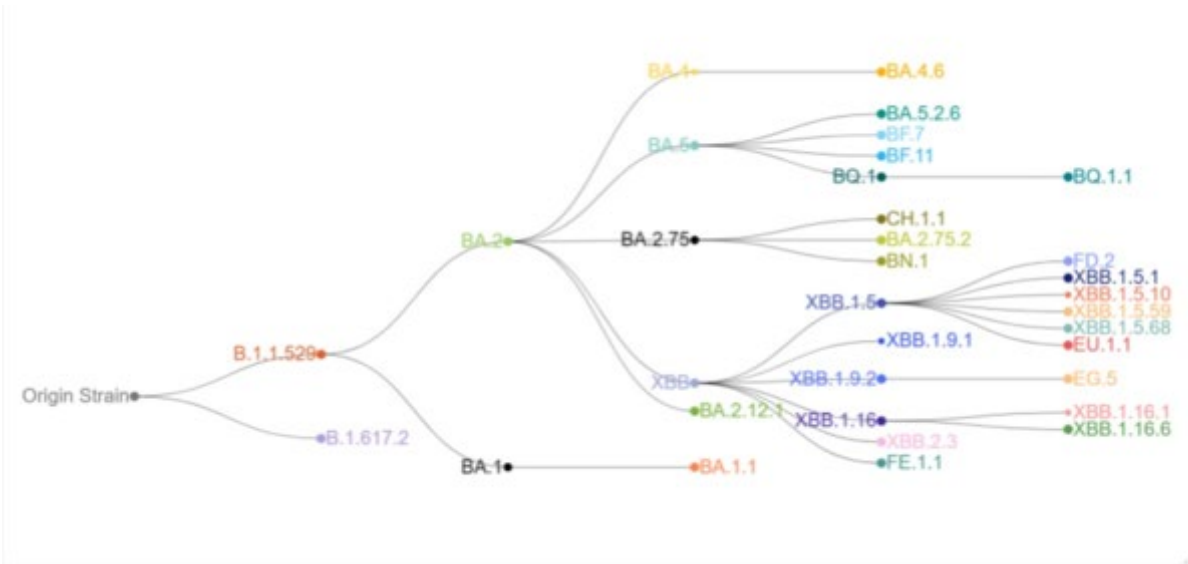
43% relative VE among adults age 50-64 ≥14 days after bivalent booster dose compared with those who received 2-4 monovalent doses only, BA.5-related sublineages
37% relative VE among adults age ≥65 ≥14 days after bivalent booster dose compared with those who received 2-4 monovalent doses only, BA.5-related sublineages

40% relative VE among adults age 50-64 ≥14 days after bivalent booster dose compared with those who received 2-4 monovalent doses only, XBB/XBB.1.5-related sublineages
43% relative VE among adults age ≥65 ≥14 days after bivalent booster dose compared with those who received 2-4 monovalent doses only, XBB/XBB.1.5-related sublineages

Outcome	Vaccine effectiveness*	Age Group	Vaccine(s)#	Population	Study period
Invasive mechanical ventilation (IMV) or death	**94%** median 60 days after 3 doses (Omicron†)	Adults	mRNA	21 U.S. medical centers	Mar 2021–Jan 2022
Death	**89.6%** against death among adults <60 days after 2nd vaccine booster dose	Adults	mRNA	19 states	March 29–July 25, 2022


Select boxes in legend to limit the counties shown.
% of total pop with at least one dose
80+%
65-79.9%
50-64.9%
0-49.9%
0-0.25
0.2501-0.50
0.5001-0.75
0.7501-1.0
Social Vulnerability Index (SVI)
No Data


Weighted Estimates: Variant proportions based on reported genomic sequencing results
100%
80%
60%
40%
20%
0%
% Viral Lineages Among Infections
XBB.1.5
4/1/23
4/15/23
4/29/23
5/13/23
5/27/23
6/10/23
Collection date, two-week period ending
Nowcast: Model-based projected estimates of variant proportions
EG.5
XBB.1.16
6/24/23
7/8/23
Selected 2-Week


Origin Strain
B.1.1.529
B.1.617.2
BA.1
BA.2
BA.1
BA.5
BA.2.75
XBB
BA.2.12.1
BA.4.6
BA.5.2.6
BF.7
BF.11
BQ.1
BQ.1.1
CH.1.1
BA.2.75.2
BN.1
XBB.1.5
XBB.1.9.1
XBB.1.9.2
XBB.1.16
XBB.2.3
FE.1.1
BA.1.1
FD.2
XBB.1.5.1
XBB.1.5.10
XBB.1.5.59
XBB.1.5.68
EU.1.1
EG.5
XBB.1.16.1
XBB.1.16.6

People who are aged 6 months and older who are moderately or severely immunocompromised may get 1 additional updated COVID-19 vaccine dose 2 or more months after the last recommended updated COVID-19 vaccine. The additional dose(s) help your immune system to better protect you against COVID-19 infection.

People Aged 5 Years and Older

Who got their last recommended updated COVID-19 vaccine at least 2 months ago may get an additional updated **Pfizer-BioNTech or Moderna** COVID-19 vaccine.

If you or your child got:	You or your child should get:
1 original vaccine	**2 updated** Pfizer-BioNTech vaccines. • 1st updated dose at least 3 weeks after original dose. • 2nd updated dose at least 4 weeks after 1st updated dose. **More details:** Getting your 2nd dose
2 original vaccines	**1 updated** Pfizer-BioNTech vaccine at least 4 weeks after the last original vaccine.
3 original vaccines	**1 updated** Pfizer-BioNTech or Moderna vaccine at least 8 weeks after the last original vaccine.

Outpatient Management:

Patient Disposition	Panel's Recommendations
All Patients	• Symptom management should be initiated for all patients **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or other systemic corticosteroids in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives a rating for the strength of the recommendation (A, B, or C) and a rating for the evidence that supports it (I, IIa, IIb, or III). See Guidelines Development for more information.	

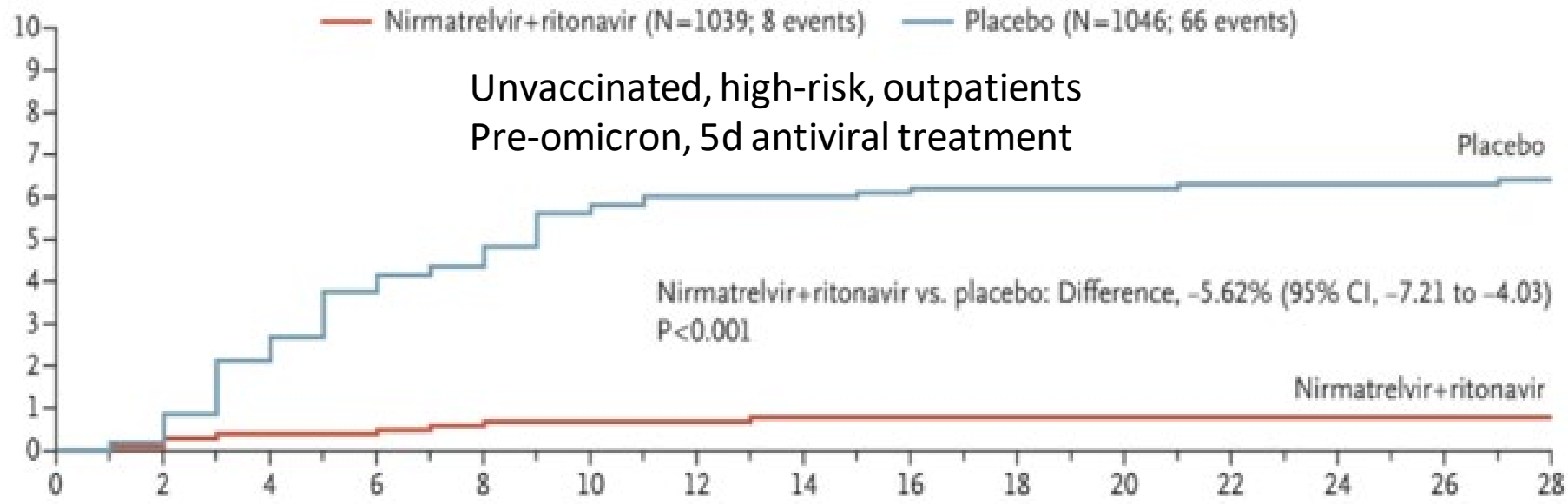
Outpatient Management – Nirmatrelvir / R:

Protease ($3CL^{Pro}$) inhibitors:

ORIGINAL ARTICLE

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

Jennifer Hammond, Ph.D., Heidi Leister-Tebbe, B.S.N., Annie Gardner, M.P.H., M.S.P.T., Paula Abreu, Ph.D., Weihang Bao, Ph.D., Wayne Wisemandle, M.A., MaryLynn Baniecki, Ph.D., Victoria M. Hendrick, B.Sc., Bharat Damle, Ph.D., Abraham Simón-Campos, M.D., Rienk Pypstra, M.D., and James M. Rusnak, M.D., Ph.D. for the EPIC-HR Investigators*



EPIC-SR: Std Risk patients: 1° Endpoint of Sx alleviation for 96hrs not met
Non-significant 51% relative risk reduction in hospitalization
(Treatment arm: 5/576; placebo: 10/569).

Outpatient Management – Nirmatrelvir / R:

Southern California Kaiser dataset, reviewing all Nirmatrelvir/R
End point of hospitalization, medical attended visit

THE LANCET
Infectious Diseases
Lewnard et al, March 2023

7274 Nirm/R recipients vs 126k SOC with + test.

Overall population:	**53·6% (95% CI 6·6–77·0**
If dispensed <5d of sxs:	**79·6% (33·9–93·8)**
If test & treat same day and <5d:	88.1% (49-97% QI)

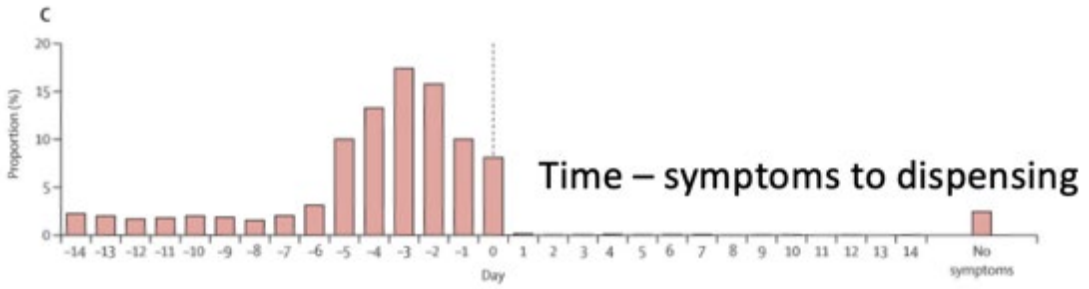
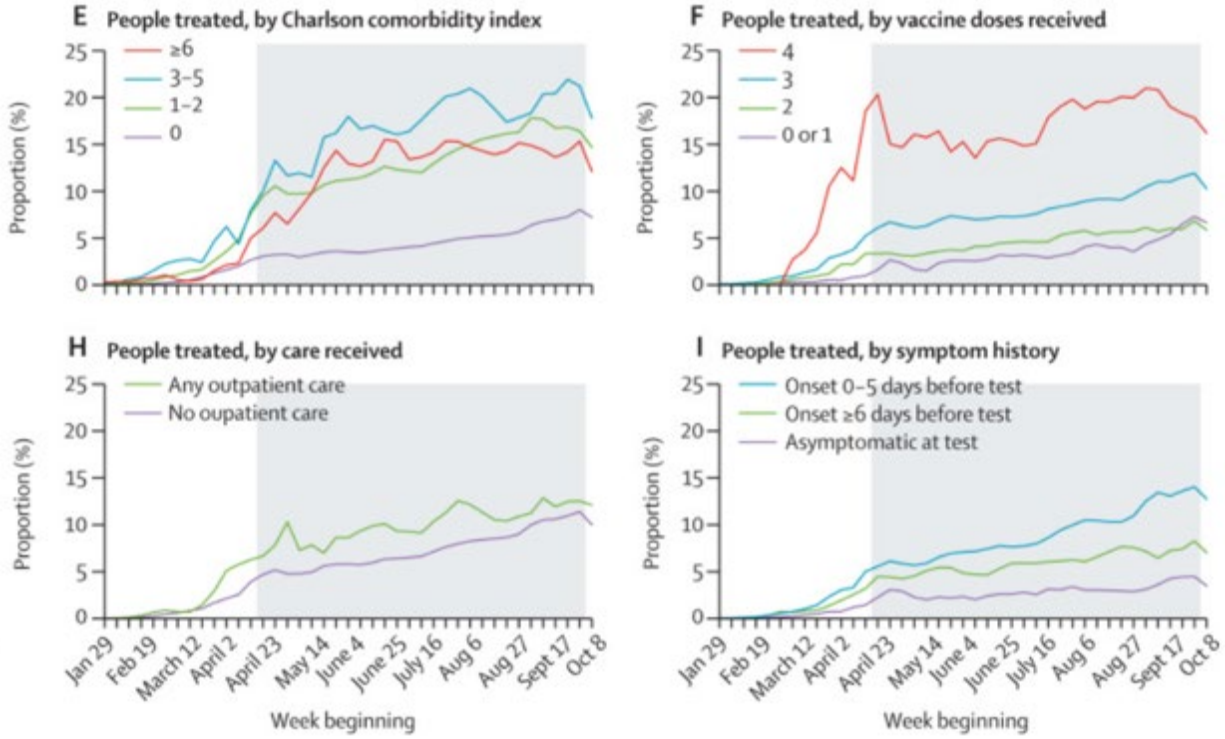
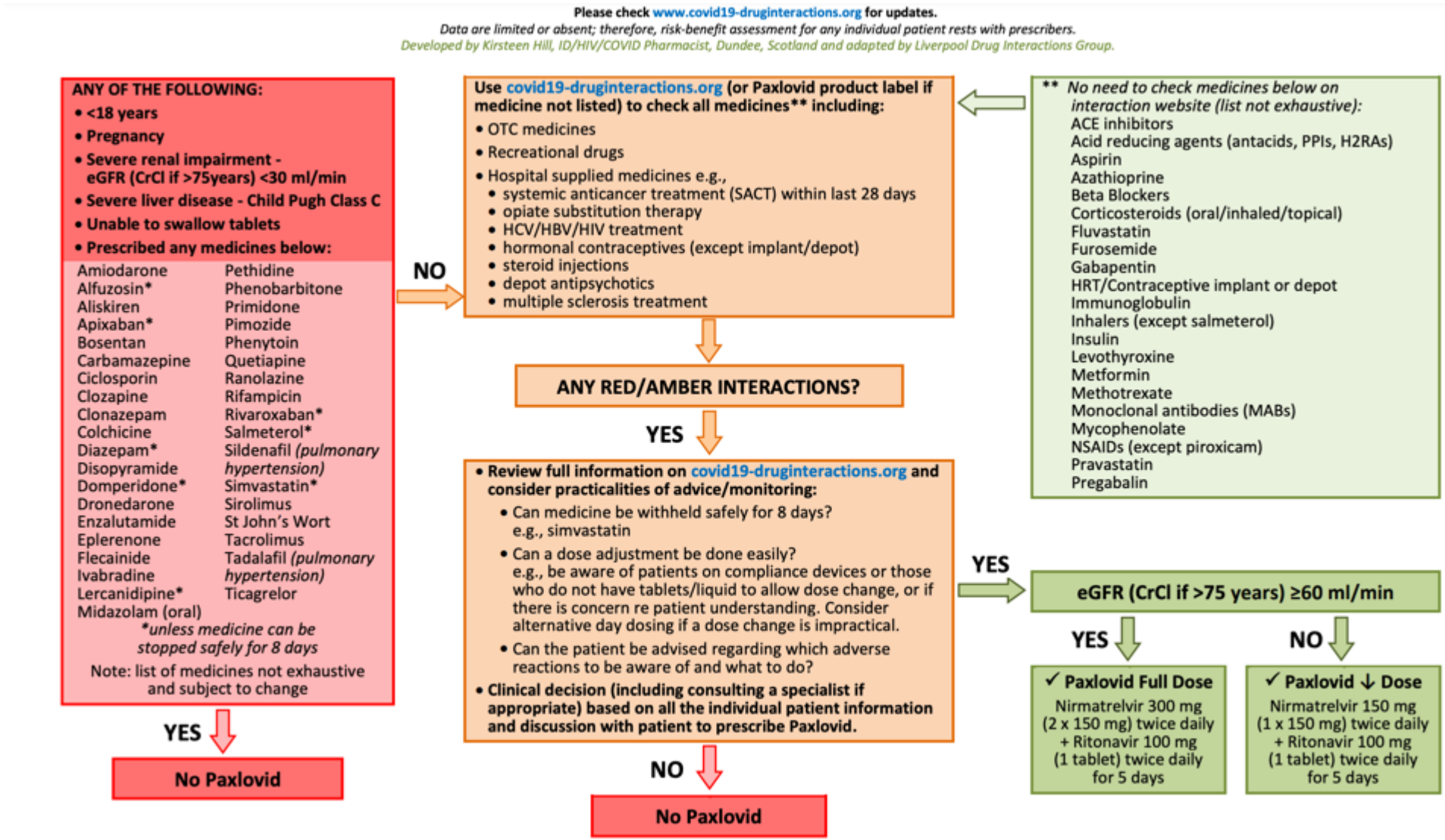


Figure 1 Timing of symptom onset (A) and nirmatrelvir–ritonavir dispensing (B) relative to date of SARS-CoV-2 testing, and timing of symptom onset relative to data of nirmatrelvir–ritonavir dispensing (C)

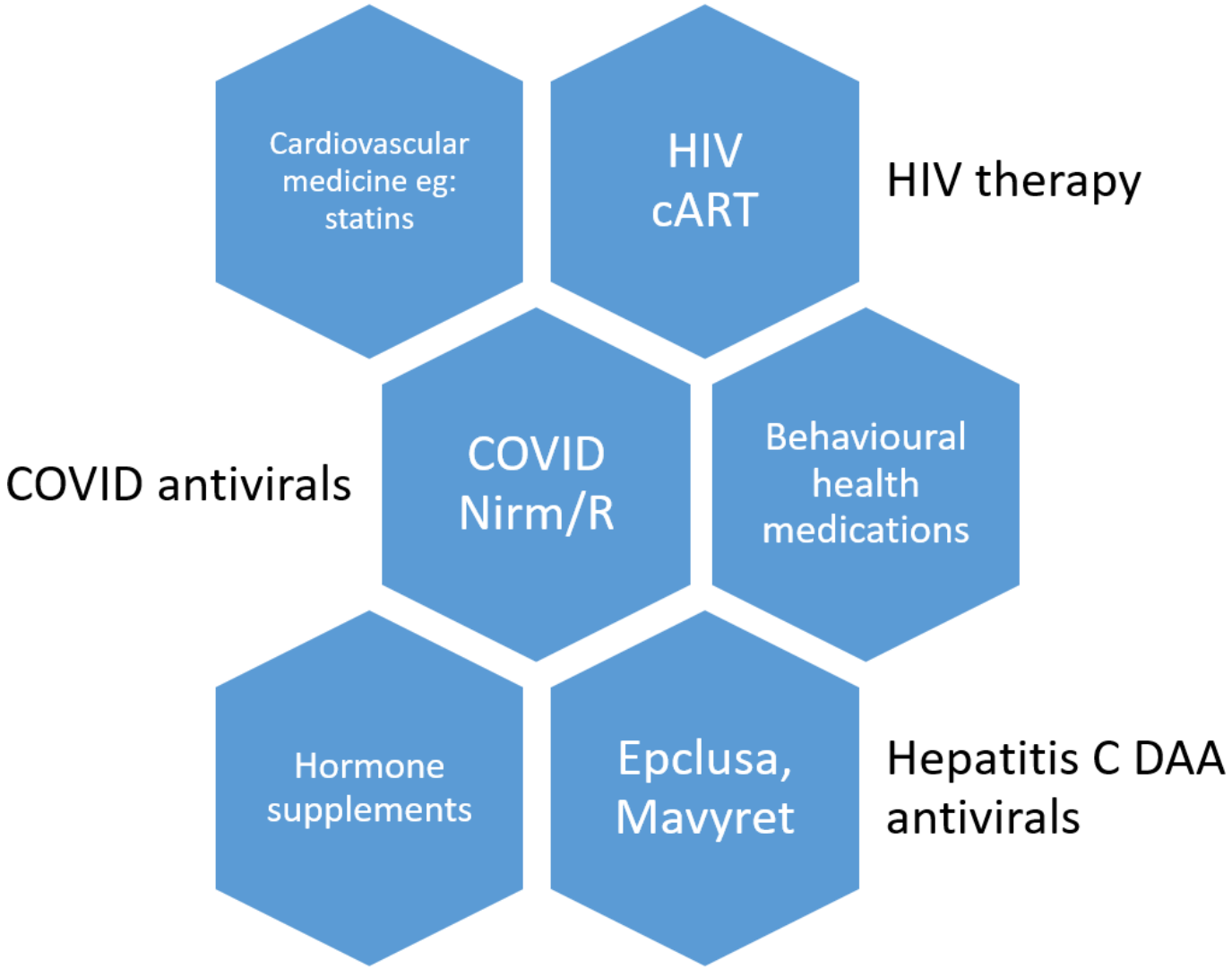


Outpatient Management – Nirmatrelvir / R:



https://www.covid19-druginteractions.org/checker

Outpatient Management – Nirmatrelvir / R:



Outpatient Management

RNA-dependent RNA polymerase Rd-Rp inhibitors - Molnupiravir:

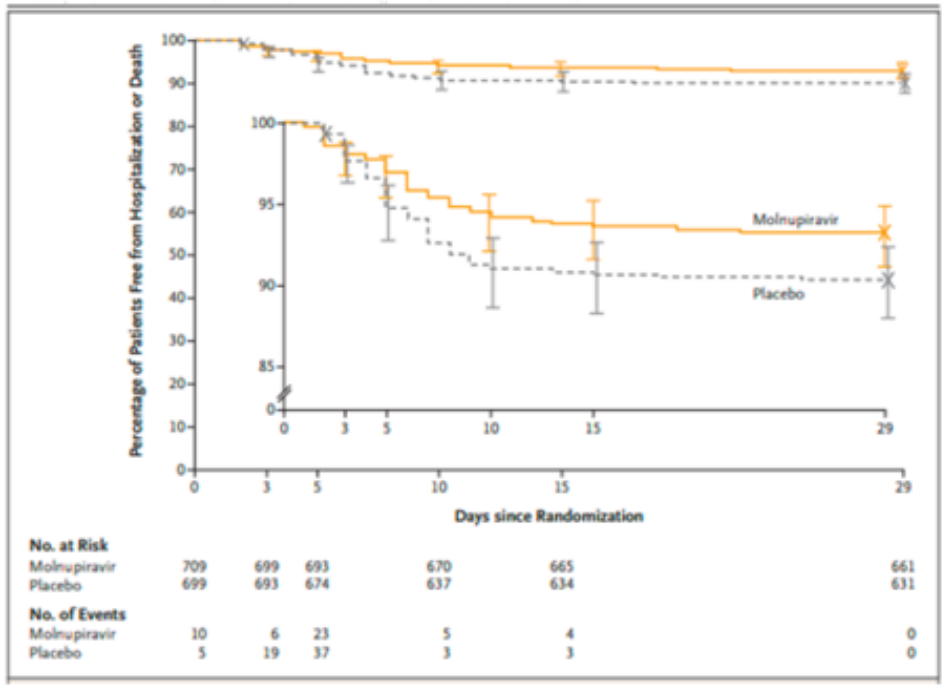
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez,

Move-OUT



Pre-omicron, unvaccinated, high-risk adults
Endpoint: Hospitalization or Death:
Molnu 6.8% vs Placebo 9.7% (**30% relative reduction**)
Deaths: 1 vs 9

Activity: increases frequency of viral RNA mutations, impairing SARS-CoV-2 replication. Induces accelerated RNA mutagenesis by the viral RNA-dependent RNA polymerase (RdRp)

Virus	EC_{50} (µM)	CC_{50} (µM)	Selectivity Index	Assay
CHKV	1.0	338	≥ 300	Plaque reduction assay in Vero cells
VEEV	1.4	> 500	≥ 300	Plaque reduction assay in Vero cells
WEEV	0.73	247	≥ 300	Neutral Red CPE assay in Vero 76 cells
EEEV	0.93	123	132	Visual CPE assay in Vero 76 cells
Human-CoV	0.20	224	≥ 1100	Neutral Red CPE assay in HEL cells
SARS-CoV	< 0.4	139	≥ 300	Neutral Red CPE assay in Vero 76 cells
MERS-CoV	< 0.8	20	>25	$TCID_{50}$ viral titer reduction assay in Vero E6 cells
Ebola	4.7	>100	>21	Plaque reduction assay in Vero cells
RSV	2.5	> 300	> 120	Replicon assay in Huh-7 cells
Enterovirus-68	2.3	52	23	Neutral Red CPE assay in RD cells
Enterovirus-71	2.3	48	21	Neutral Red CPE assay in Vero 76 cells
Rhinovirus	0.48	44	92	Neutral Red CPE assay in HeLa cells
Influenza A (H1N1)	1.1	> 300	> 270	HAU titer assay in MDCK cells
Influenza B (Yamagata)	0.015	> 100	≥ 6000	HAU titer assay in MDCK cells

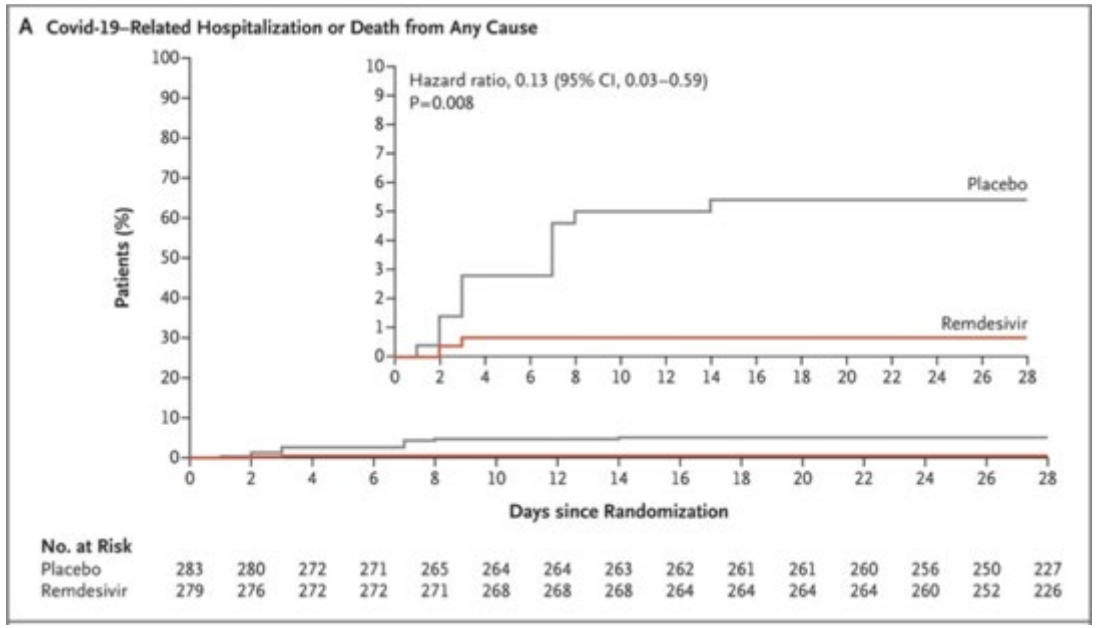
Outpatient Management

RNA-dependent RNA polymerase Rd-Rp inhibitors - Remdesivir:

The NEW ENGLAND JOURNAL of MEDICINE

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

Robert L. Gottlieb, M.D., Ph.D., Carlos E. Vaca, M.D., Roger Paredes, M.D., Ph.D., Jorge Mera, M.D., Brandon J. Webb, M.D., Gilberto Perez, M.D., Godson Oguchi, M.D., Pablo Ryan, M.D., Ph.D., Bibi U. Nielsen, M.D., Michael Brown, Ph.D., F.R.C.P., Ausberto Hidalgo, M.D., Yessica Sachdeva, M.D., et al., for the GS-US-540-9012 (PINETREE) Investigators†



- Practical Issues:
  - Initially not supported by insurance
  - Requires an outpatient facility
    - suitable infection control support
  - Requires nursing staff / clinical team members
  - Home health options remains limited

Outpatient Mx – Real world efficacy:

THE LANCET

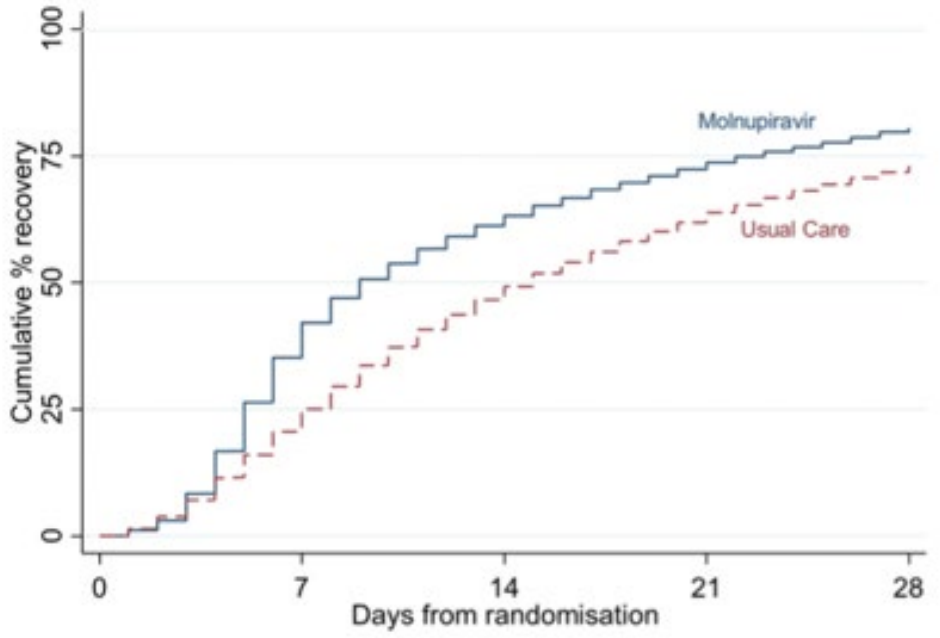
ARTICLES | VOLUME 401, ISSUE 10373, P281-293, JANUARY 28, 2023

Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial

PANORAMIC
Platform Adaptive trial of NOvel antiviRals for eArly treatMent of COVID-19 In the Community

Pragmatic UK outpatient trial, >50yrs or >18 with RF's
>12,000 participants, heavily vaccinated (AZ, mRNA)
Mean age 56y

No difference in hospital admission rate (1% each)
Reduced time to recovery; d7 VL undetectable 21% vs 3%

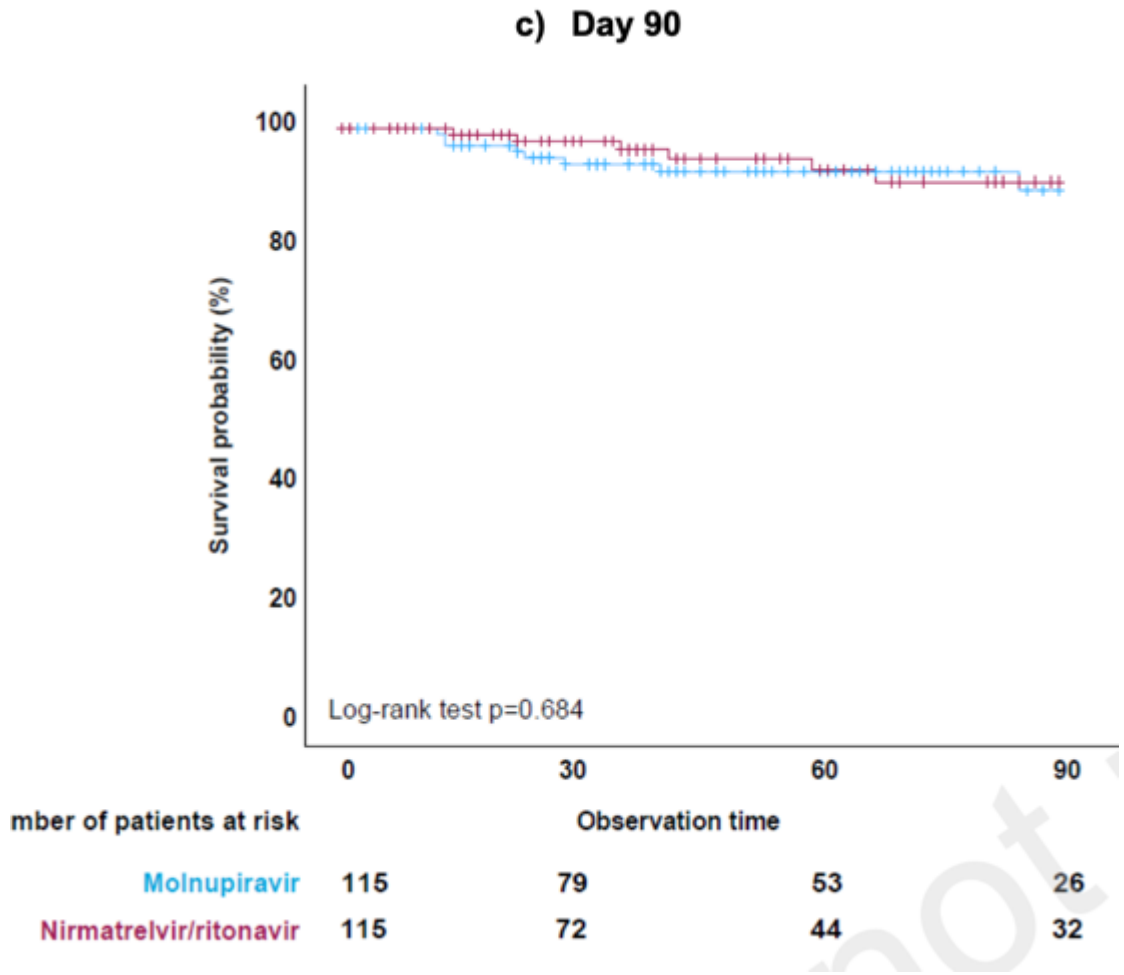


Cumulative number not yet recovered (recovered)					
Molnupiravir	12432 (0)	7948 (5179)	4670 (7734)	3228 (8966)	2173 (9741)
Usual Care	12151 (0)	9415 (2993)	6124 (5788)	4177 (7393)	2776 (8376)

Outpatient Mx – Comparative efficacy:

MOLNUPIRAVIR COMPARED TO NIRMATRELVIR/RITONAVIR FOR COVID-19 IN HIGH-RISK PATIENTS WITH HAEMATOLOGICAL MALIGNANCY IN EUROPE. A MATCHED-PAIRED ANALYSIS FROM THE EPICOVIDEHA REGISTRY

- 18+yrs, baseline 'active' heme malignancy at any point 5 years prior
- Lab confirmed COVID, treated with either molnu OR n/R
  - No other antivirals allowed (dexa or CCP allowed)
- Oct 2021 – Jan 2023
  - 29/30 tested in each arm, Omicron variant
- 116 molnu cases matched to 116 n/R controls
  - Matched by age, sex, malignancy status at diagnosis of covid
- 40% Italy, 15% Czech, 14% Spain



Preprints with THE LANCET

papers.ssrn.com/sol3/cf_dev/AbsByAuth.cfm?per_id=4739137

Outpatient Mx – Comparative efficacy:

THE LANCET

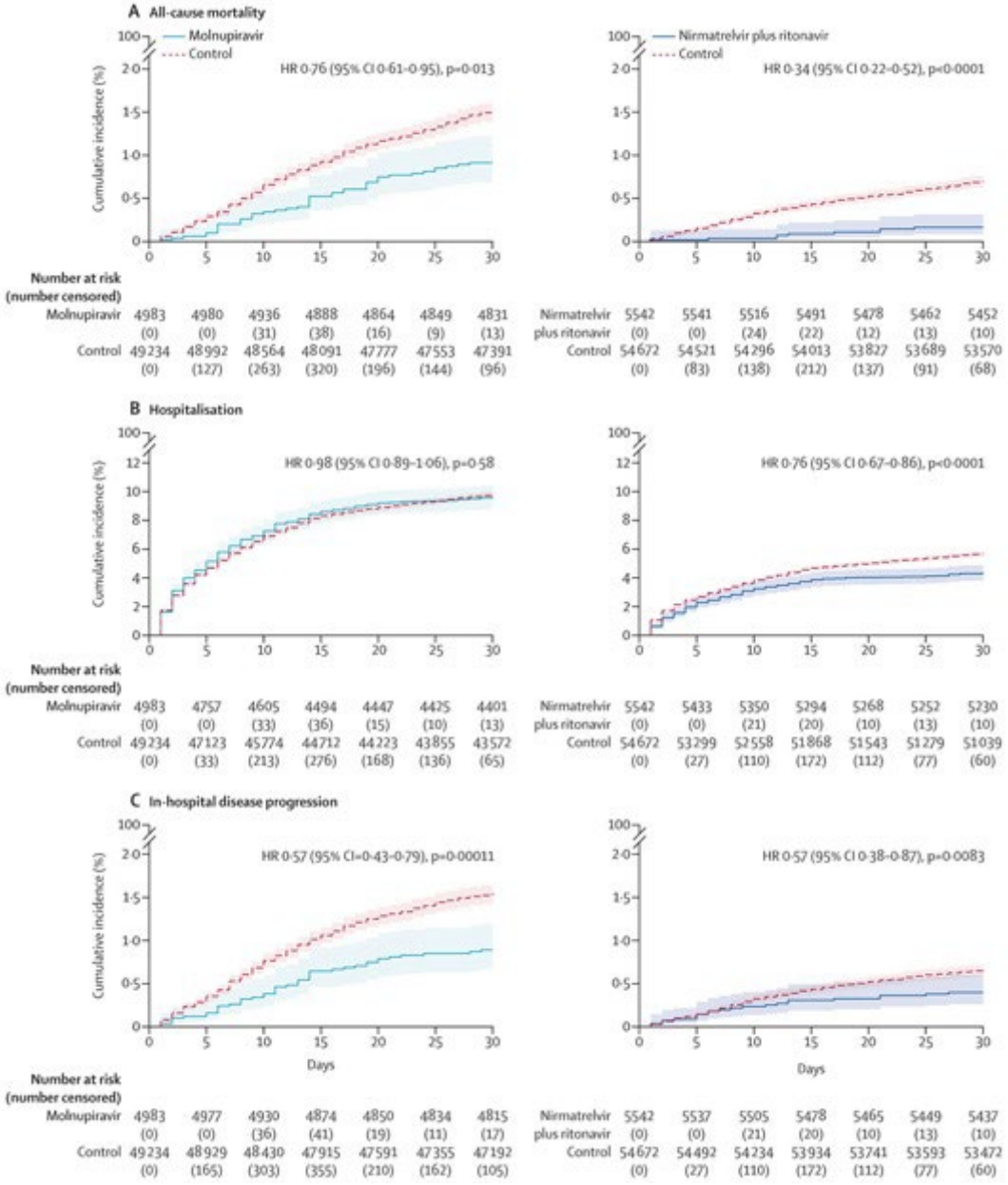
ARTICLES | VOLUME 400, ISSUE 10359, P1213-1222, OCTOBER 08, 2022

Real-world effectiveness of molnupiravir and nirmatrelvir plus ritonavir against mortality, hospitalisation, 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

Carlos K H Wong, PhD • Ivan C H Au, BSc • Kristy T K Lau, MSc • Eric H Y Lau, PhD • Prof Benjamin J Cowling, PhD • Prof Gabriel M Leung, MD

Hong Kong, Omicron
BA2.2 dominant phase
Feb-Jun 2022

Retrospective cohort design



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Outpatient Management: What doesn't work?

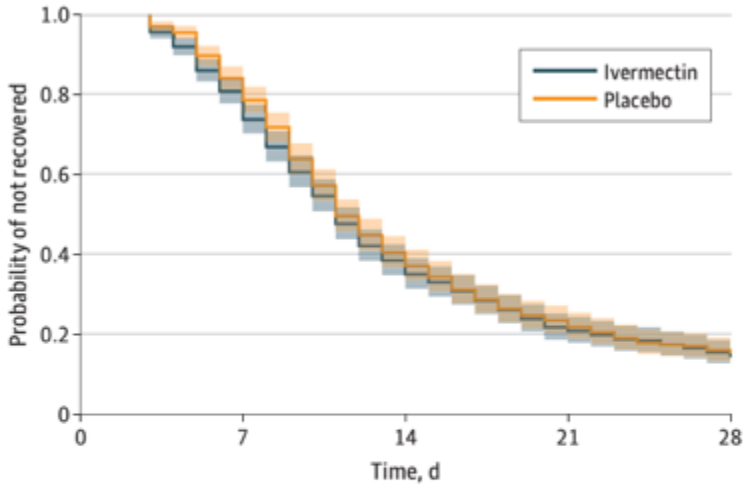
Outpatient Management: What doesn't work?

JAMA | Original Investigation

Effect of Higher-Dose Ivermectin for 6 Days vs Placebo on Time to Sustained Recovery in Outpatients With COVID-19 A Randomized Clinical Trial

Susanna Naggie, MD, MHS; David R. Boulware, MD, MPH; Christopher J. Lindsell, PhD; Thomas G. Stewart, PhD;

Figure 3. Primary Outcome of Time to Sustained Recovery



No. of patients at risk

Ivermectin	602	487	232	131	92
Placebo	604	508	244	142	95

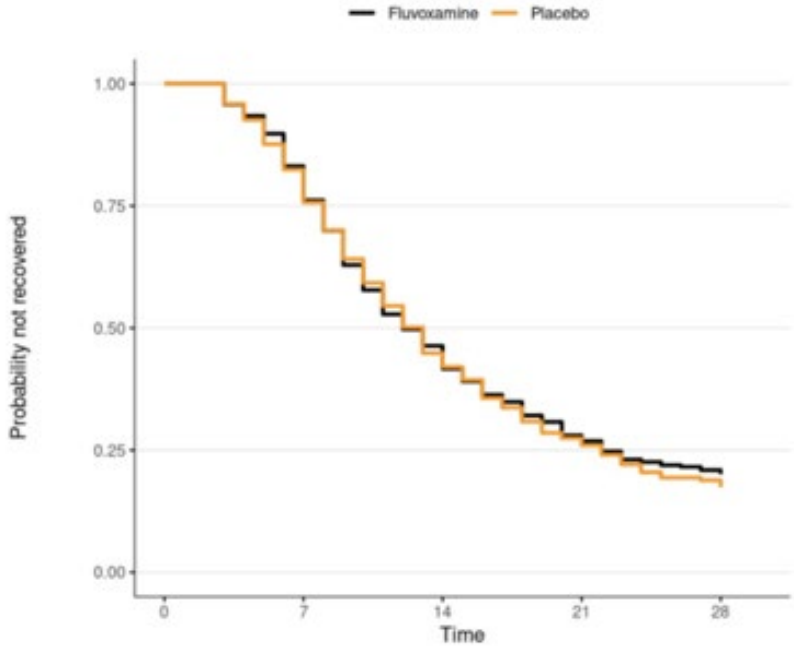
Recovery was defined as the third of 3 consecutive days without symptoms. Four participants were censored for nonresponse and all others were followed up until recovery, death, or the end of short-term 28-day follow-up. Median (IQR) time to recovery was 11 (11-12) days in the ivermectin group and 11 (11-12) days in the placebo group. Shaded regions denote the pointwise 95% CIs.

medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES

Fluvoxamine for Outpatient Treatment of COVID-19:A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial

Matthew W. McCarthy, Susanna Naggie, David R. Boulware, Christopher J. Lindsell, Thomas G. Stewart, G. Michael Felker, Dushyantha Jayaweera, Mark Sulkowski, Nina Gentile, Carolyn Bramante, Upinder Singh, Rowena J. Dolor, Juan Ruiz-Unger, Sybil Wilson, Allison DeLong, April Remaly, Rhonda Wilder, Sean Collins, Sarah E. Dunsmore, Stacey J. Adam, Florence Thicklin, George Hanna, Adit A. Ginde, Mario Castro, Kathleen McTigue, Elizabeth Shenkman, Adrian F. Hernandez, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group

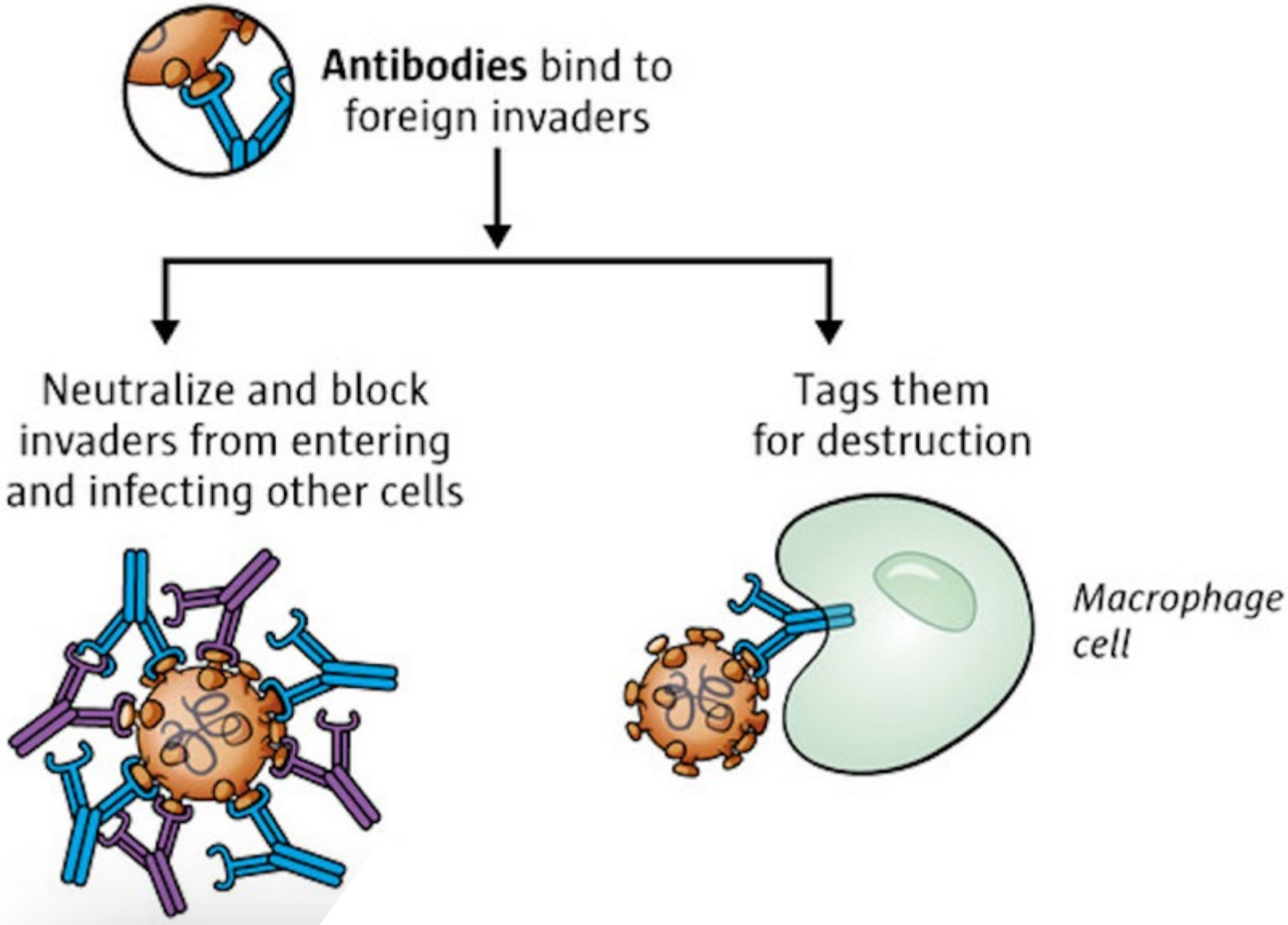
Figure 3. Kaplan-Meier for primary outcome of time to sustained recovery



No. at risk

Fluvoxamine	650	524	287	171	125
Placebo	588	477	254	153	104

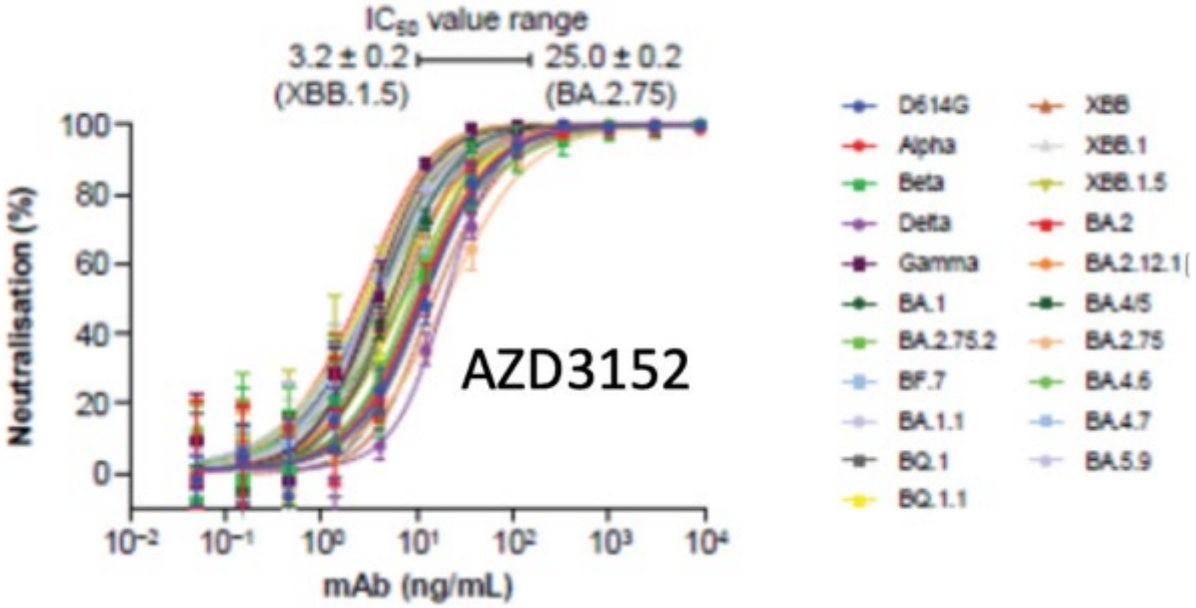
Outpatient Management - Monoclonals:

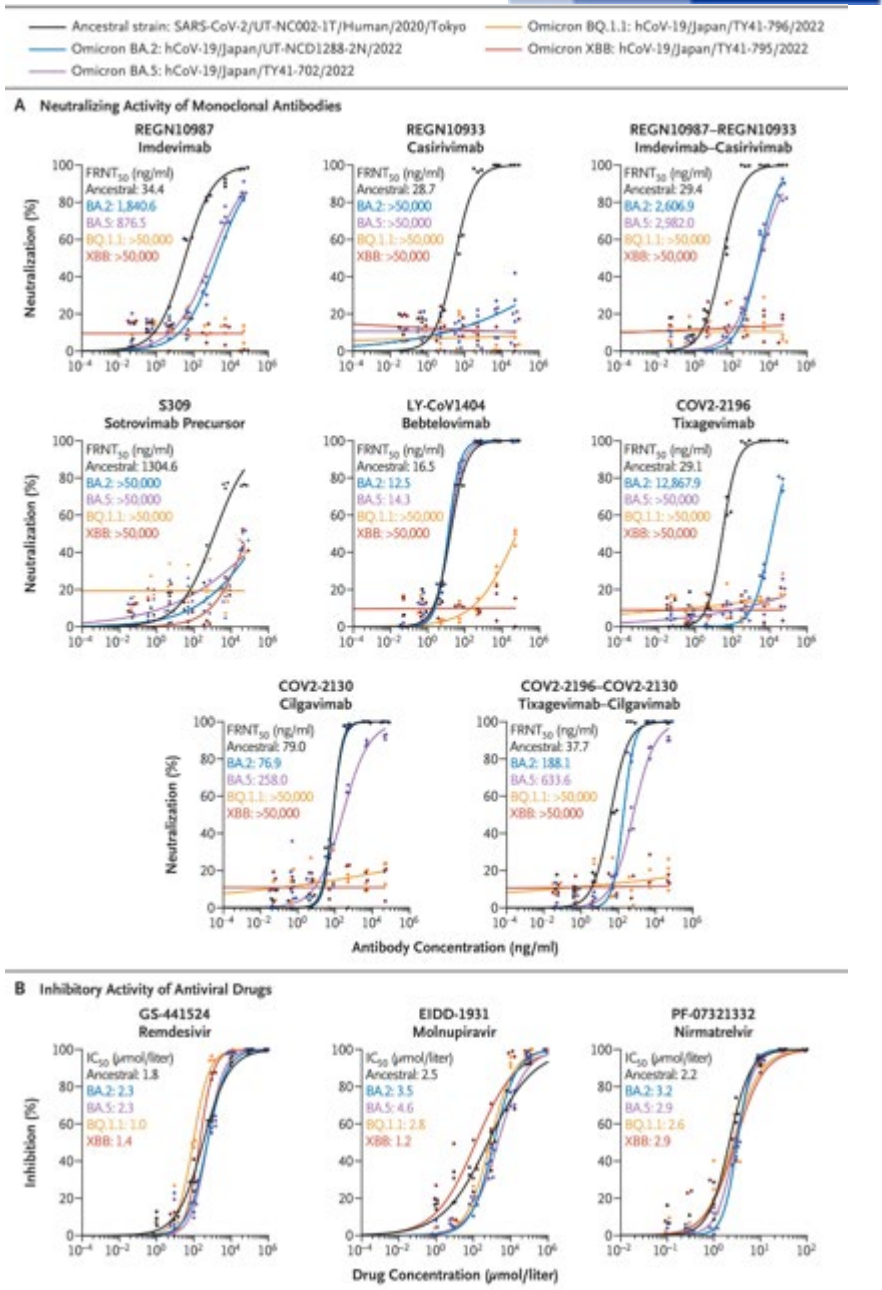


TxID
Duke Transplant/ Immunocompromised Host Infectious Diseases

Outpatient Management - Monoclonals:

Bamlanivimab	– outpatient Rx
Etesevimab	- outpatient Rx
Casirivimab-Imdevimab	- outpatient Rx, prevention
Sotrovimab	- outpatient Rx, prevention
Bebtelovimab	- outpatient Rx,
Tixagevimab-Cilgavimab	- prevention, ?treatment





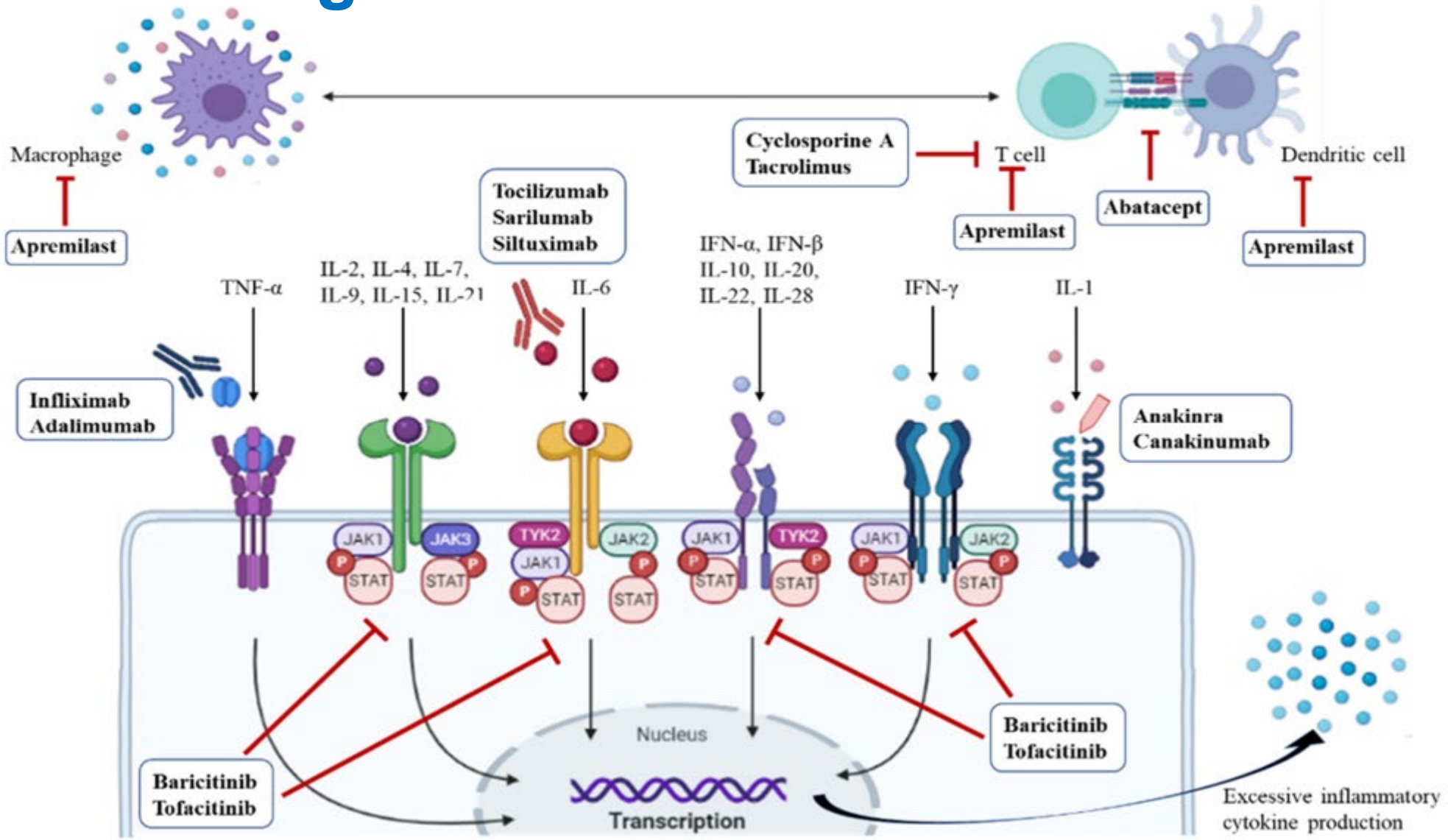
Inpatient Therapy:

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a,b]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone** (AIIa) or other systemic corticosteroids (AIII) for the treatment of COVID-19.[c]	
	Patients who are at high risk of progressing to severe COVID-19[a,b]	**Remdesivir**[d] (BIII)	
Hospitalized and Requires Conventional Oxygen[e]	Patients who require minimal conventional oxygen	**Remdesivir**[d,f] (BIIa)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[h] (CIIa) For other patients: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[f] (BIIa). If remdesivir cannot be obtained, use **dexamethasone** (BI).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[g] (BIIa) or **IV tocilizumab**[g] (BIIa) to 1 of the options above.	
Hospitalized and Requires HFNC Oxygen or NIV	All patients	**Dexamethasone** should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in order of preference): • **PO baricitinib**[g,i] (AI) • **IV tocilizumab**[g,i] (BIIa) Add **remdesivir** to 1 of the options above in certain patients (CIIa).[j]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation (BIII).
Hospitalized and Requires MV or ECMO	All patients	**Dexamethasone** should be administered to all patients (AI). If the patient has not already received a second immunomodulator, promptly add 1 of the following (listed in alphabetical order): • **PO baricitinib**[g,i] (AI) • **IV tocilizumab**[g,i] (BIIa)	

Antiviral Strategy

Anti-inflammatory Strategy

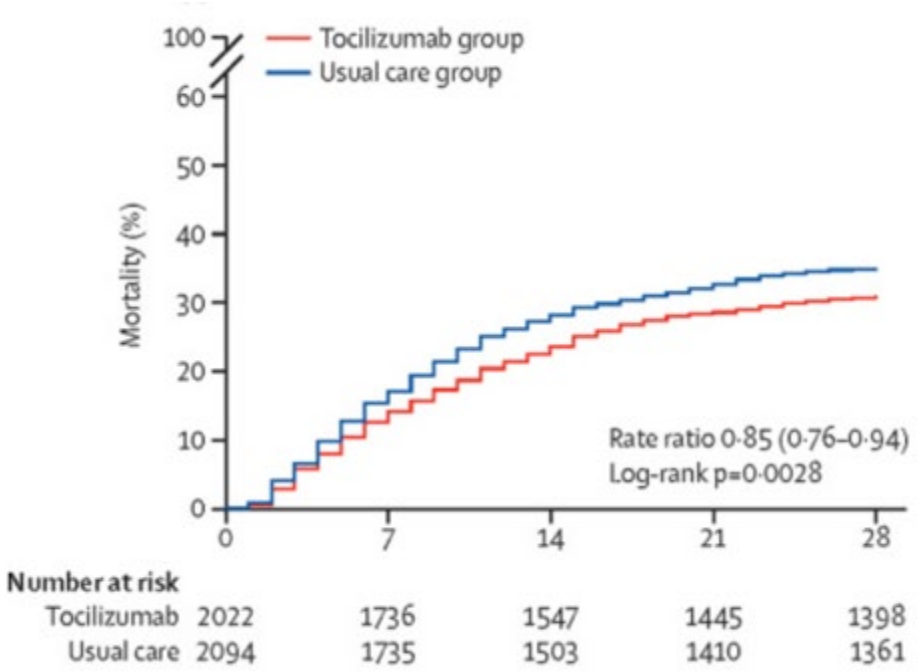
Inpatient Management – Immune Modulation

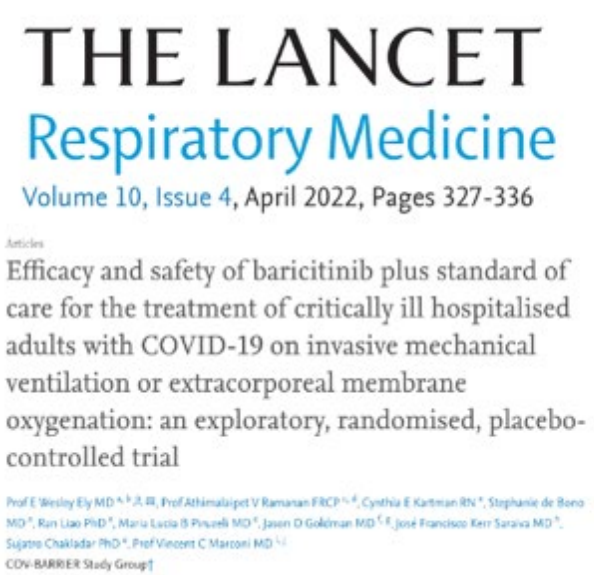


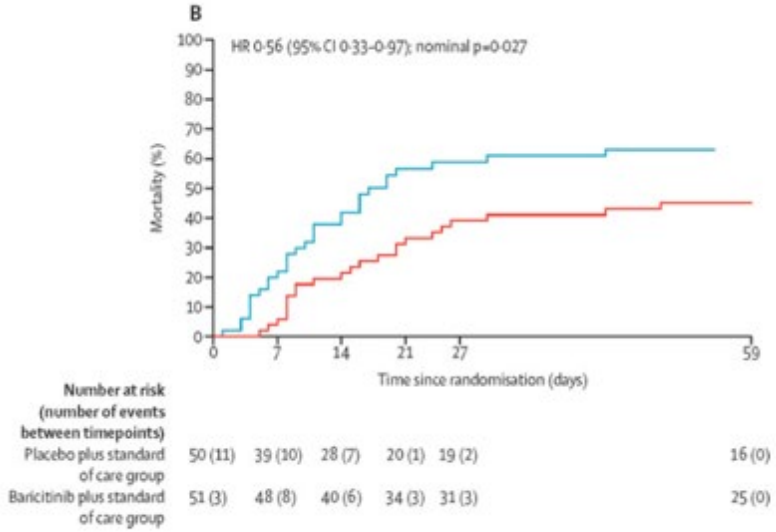
Nature Reviews Immunology **volume 21**, pages 694–703 (2021)

Pharmaceuticals **2021**, *14*(12), 1256;
https://doi.org/10.3390/ph14121256

Inpatient Management – Immune Modulation

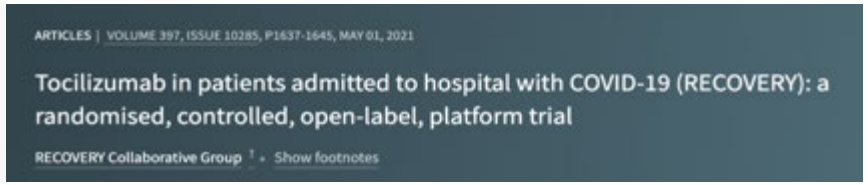






- Although “ranked” equal by NIH, we end up preferentially using Baricitinib b/c:
  - Shorter I/S half life
  - More safety data in RCT’s
  - Cheaper
- Other I/modulators, data less complete, inc: infliximab, abatacept, anakinra, vimbelomab

RECOVERY
Randomised Evaluation of COVID-19 Therapy



Inpatient Management – Passive Immune therapy

The NEW ENGLAND JOURNAL of MEDICINE

Randomized Controlled Trial > N Engl J Med. 2021 Feb 18;384(7):610-618.
doi: 10.1056/NEJMoa2033700. Epub 2021 Jan 6.

Early High–Titer Plasma Therapy to Prevent Severe Covid–19 in Older Adults

JAMA Oncology

June 17, 2021

Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19

Michael A. Thompson, MD, PhD[1]; Jeffrey P. Henderson, MD, PhD[2]; Pankil K. Shah, MD, MSPH[3]; et al

Leukemia

Article | Published: 01 February 2022

IMMUNOTHERAPY

Convalescent plasma improves overall survival in patients with B-cell lymphoid malignancy and COVID-19: a longitudinal cohort and propensity score analysis

Thomas Hueso, Anne-Sophie Godron, Emilie Lanoy, Jérôme Pacanowski, Laura I. Levi, Emmanuelle Gras, Laure Surgers, Amina Guemriche, Jean-Luc Meynard, France Pirenne, Salim Idri, Pierre Tiberghien, Pascal Morel, Caroline Besson, Rémy Duléry, Sylvain Lamure, Olivi
Gagneux-Brunon, Nathalie Freymond, Sophie Grabar & Karine Lacombe

Leukemia **36**, 1025–1034 (2022) | Cite this article

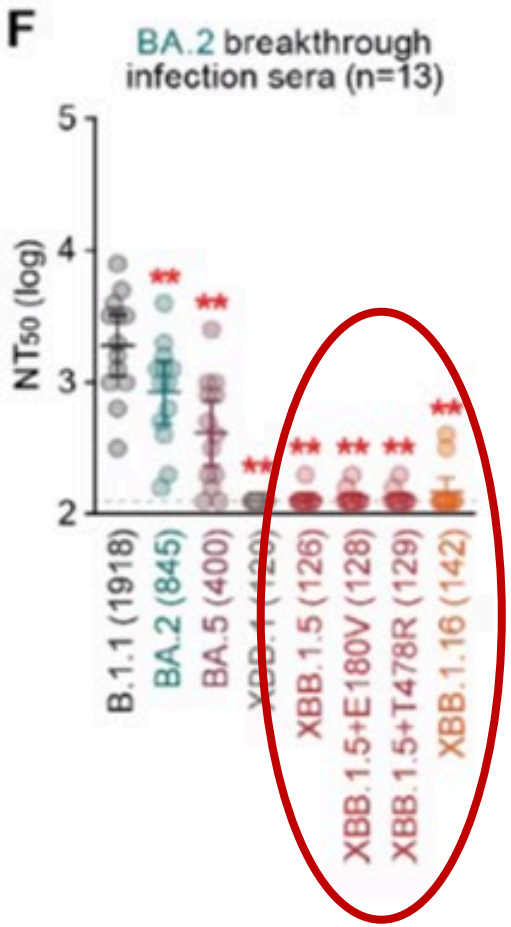
The NEW ENGLAND JOURNAL of MEDICINE

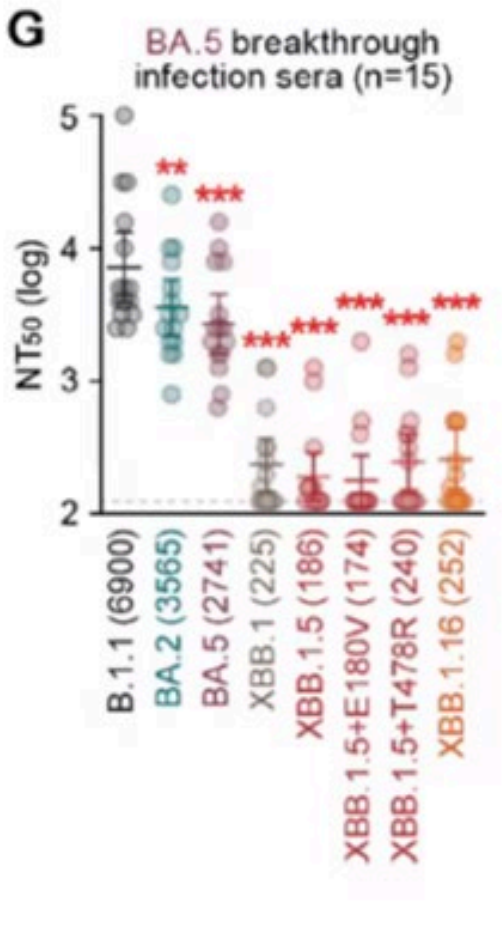
Early Outpatient Treatment for Covid-19 with Convalescent Plasma

David J. Sullivan, M.D., Kelly A. Gebo, M.D., M.P.H., Shmuel Shoham, M.D., Evan M. Bloch, M.B., Ch.B., Bryan Lau, Ph.D., Aarthi G. Shenoy, M.D., Giselle S. Mosnaim, M.D., Thomas J. Gniadek, M.D., Ph.D., Yuriko Fukuta, M.D., Ph.D., Bela Patel, M.D., Sonya L. Heath, M.D., Adam C. Levine, M.D., M.P.H., et al.

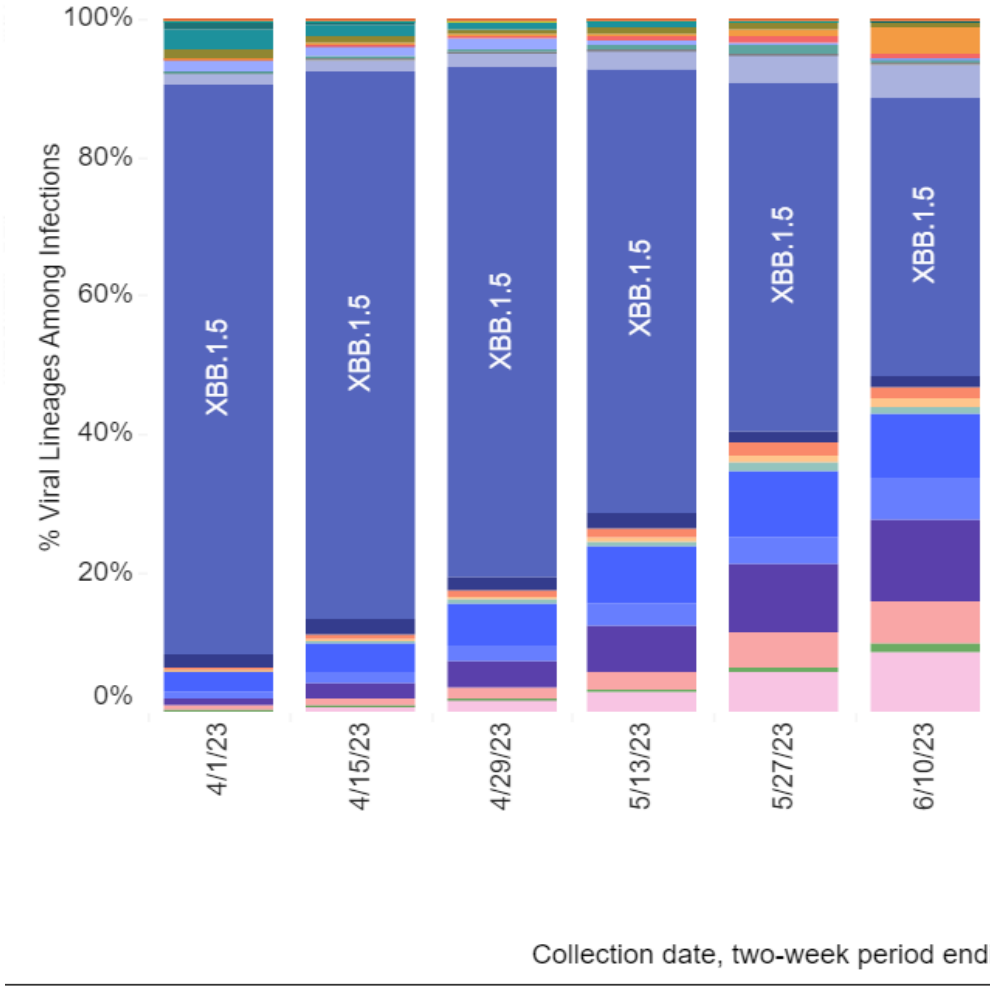
Virological characteristics of the SARS-CoV-2 Omicron XBB.1.16 variant

Daichi Yamasoba[1,2#], Keiya Uriu[1,3#], Arnon Plianchaisuk[1#], Yusuke Kosugi[1,3#], Lin Pan[1,4#], Jiri Zahradnik[5], The Genotype to Phenotype Japan (G2P-Japan) Consortium, Jumpei Ito[1,6], Kei Sato[1,3,4,6,7,8,9*]

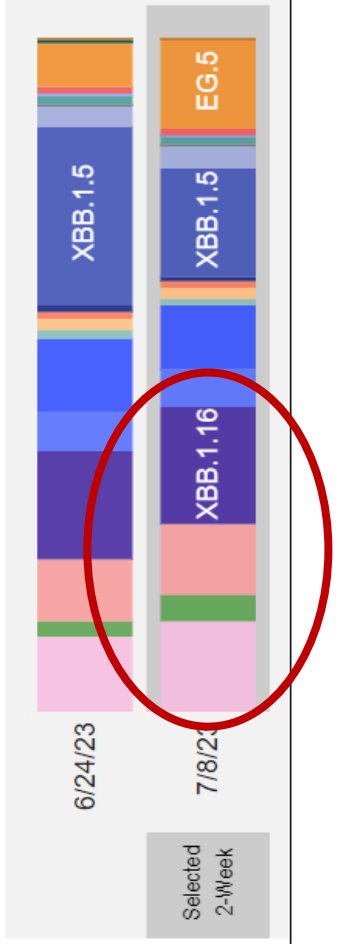




Weighted Estimates: Variant proportions based on reported genomic sequencing results



Nowcast: Model-based projected estimates of variant proportions



STRIVE
ACTIV INSIGHT018

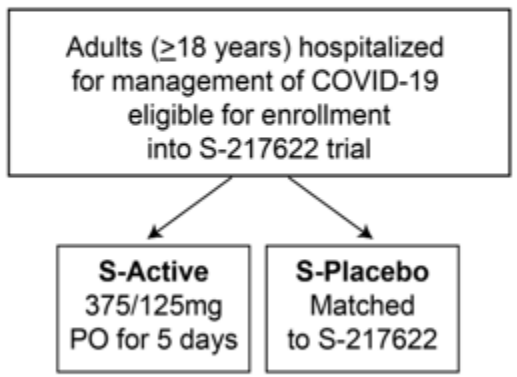
Strategies & Treatments for Respiratory Infections & Viral Emergencies (STRIVE)

- New clinical trials platform, launched in 2022.
- Global footprint
- Funded by US National Institutes of Health (NIH) and other stakeholders
- Purpose:
  - Identify better treatments for severe respiratory infections
  - Maintain agile clinical trials infrastructure for pandemic preparedness
- Patient population: hospitalized pts with acute respiratory infection
- Scope:
  - COVID-19 – initial focus
  - Influenza
  - Other known respiratory pathogens
  - Emerging pathogens

STRIVE Trial #1 Design

Study Design:

Randomized (1:1) placebo-controlled



Primary Outcome:

- Days-to-Recovery Scale through Day 60

Trial Population: ~1500

- Hospitalized for COVID-19 and Sx onset ≤14 days
- Signs and/or Sx of lower respiratory tract infection

Approach to Remdesivir:

- Remdesivir permitted, use pre-specified prior to enrollment
- Subgroup analysis of treatment effect +/- RDV in SOC

Approach to Corticosteroids:

- Dexamethasone prohibited due to DDI with S-217622
- Corticosteroid options: **prednisolone or prednisone**

Approach to other SOC:

- Other immunomodulatory agents permitted
- Other SOC permitted, as specified per local guidance

Unique issues with our current best data?

- Many of the best trials were pre-vaccination
- Few trials systematically enrolled immunosuppressed patients
- Most RCT's enrolled pre-omicron
- Many trials enrolled at sites with variable SOC backgrounds, and SOC was changing
- No trials I'm aware of were specific to HIV, in fact many excluded.

- Quandaries?
  - How many people *really* need augmented immunomodulation with potentially less pathogenic variants
  - What does augmentation of immunosuppression mean if you have HIV and are controlled or not?
  - Can we not reach a place where your individualized treatment is guided by more than simply the O2%?
    - Eg: inflammation, viral kinetics
  - How do we study new agents with hospitalization / mortality reduced?

Unique issues for the Immunocompromised?

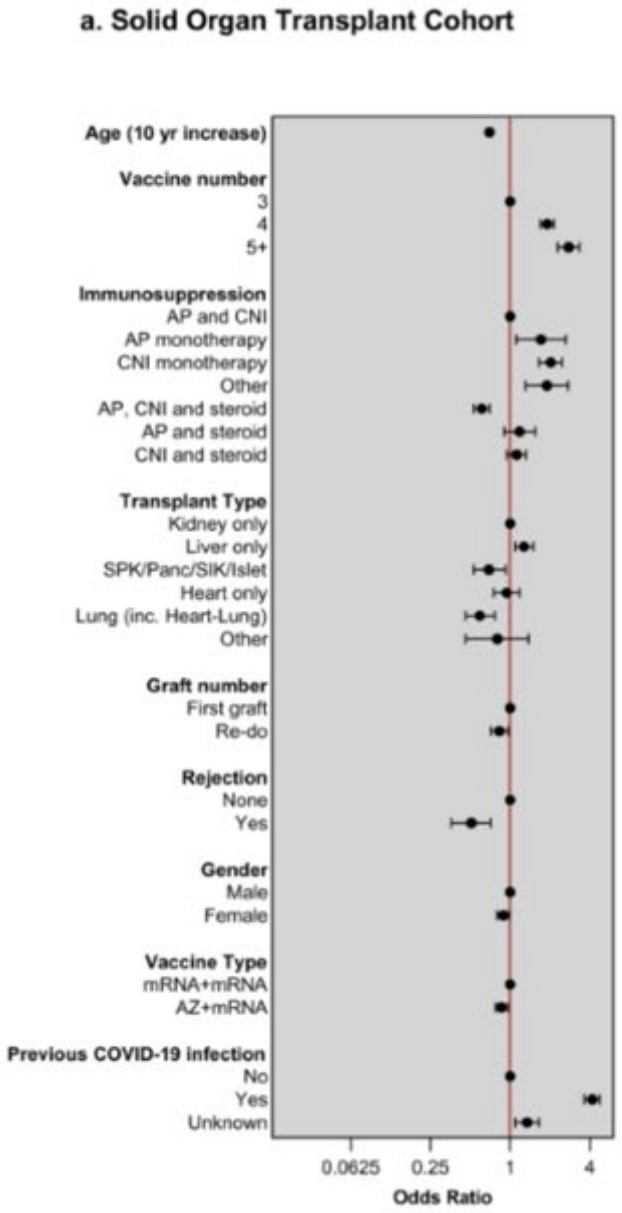
- MORE virus
- MORE drug-interactions
- MORE resistance risk
- LESS vaccine response
- LESS vaccine longevity
- Rarely included in trials
- Collateral damage
  - Eg: acute, chronic organ rejection
  - Increased rates of co-infection

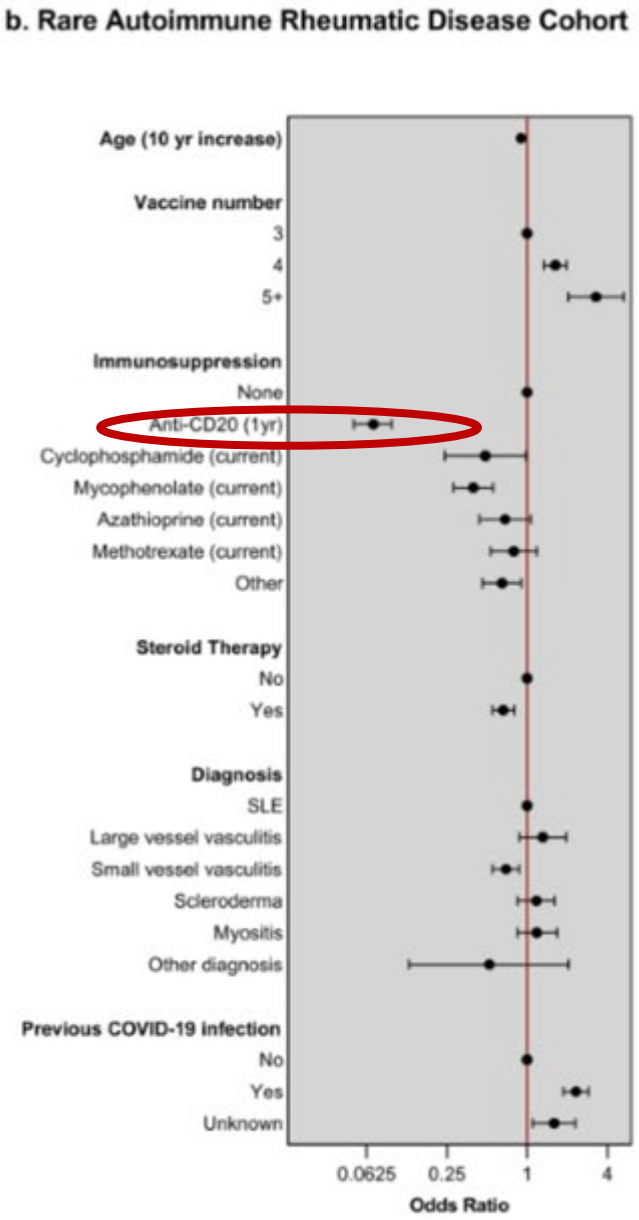
<u>Management approach</u>

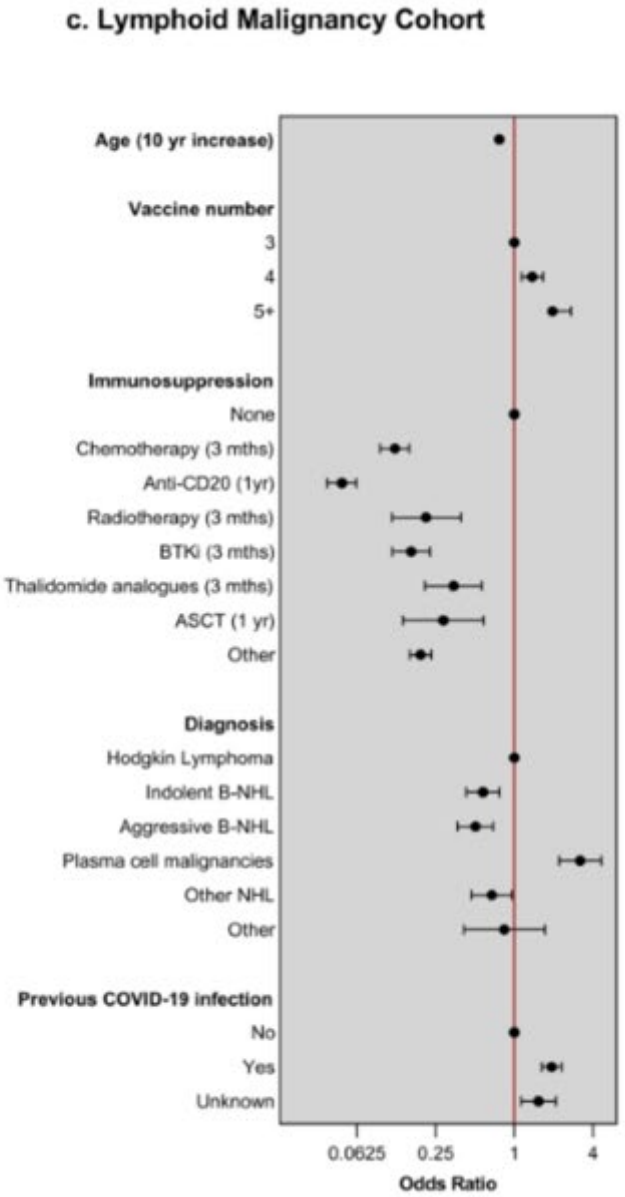
- Dual therapy?
- Prolonged antiviral treatment?
- Later initiation of AV likely ok
- More vaccine, more frequently
- Perhaps preventative mAb's

- Likely different endpoints in trials

What about our most at-risk?



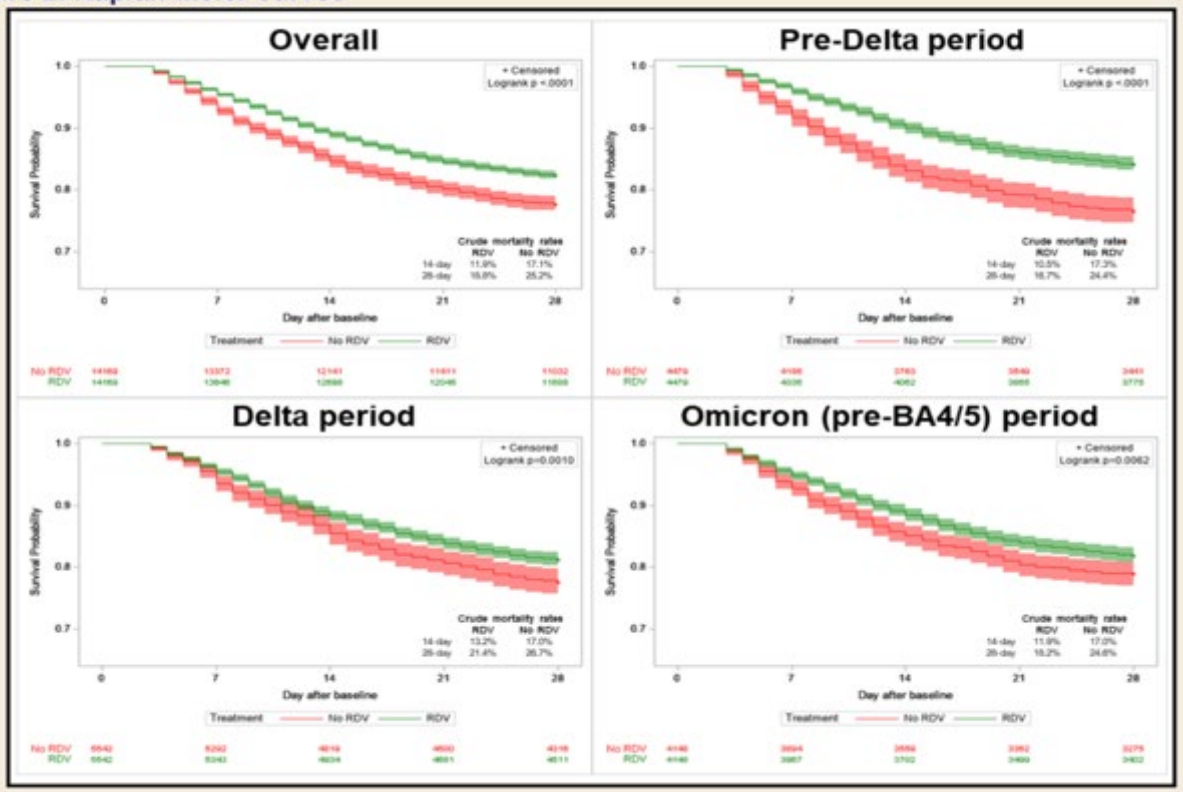




Remdesivir in Immunocompromised

- Data source: PINC AI Healthcare Database (formerly Premier Healthcare Database)
  - U.S. hospital-based, service-level, all-payer (Commercial, Medicare, Medicaid, others) database
  - Covers ~25% of all US hospitalizations from 48 states
  - Includes information on billed services and activities for each day of the hospitalization
  - >50,000 hospitalizations with a primary diagnosis of COVID-19 and an immunocompromised condition from 819 hospitals during the study period

Figure 2. Kaplan-Meier curves



Note: Number of non-RDV patients are not of unique patients but weighted numbers since matching with replacement approach was used.
RDV, remdesivir

14,169 patients, with matched non-RDV cohort
59% >65yrs
79% baseline no oxygen or low flow

- Lower mortality rate observed across all VOC periods (log-rank test: p<0.05) (**Figure 2**):

	14-day mortality		28-day mortality	
	RDV	Non-RDV	RDV	Non-RDV
Overall	11.9%	17.1%	18.8%	25.2%
Pre-Delta	10.5%	17.3%	16.7%	24.4%
Delta	13.2%	17.0%	21.4%	26.7%
Omicron	11.9%	17.0%	18.2%	24.6%

- This lower mortality rate was also observed for patients on "room air"/NSOc and across all baseline supplemental oxygen requirements:

	14-day mortality		28-day mortality	
	RDV	Non-RDV	RDV	Non-RDV
NSOc	7.4%	10.4%	11.5%	14.5%
LFO	9.0%	15.3%	14.9%	22.2%
HFO/NIV	21.7%	24.3%	34.4%	37.3%
IMV/ECMO	30.4%	37.3%	47.0%	51.2%

High-Flow Oxygen/Non-invasive ventilation; IMV/ECMO: Invasive Mechanical Ventilation/ Extracorporeal Membrane Oxygenation; LFO: Low-Flow Oxygen; HFO/NIV; N
supplemental oxygen charges; RDV, remdesivir

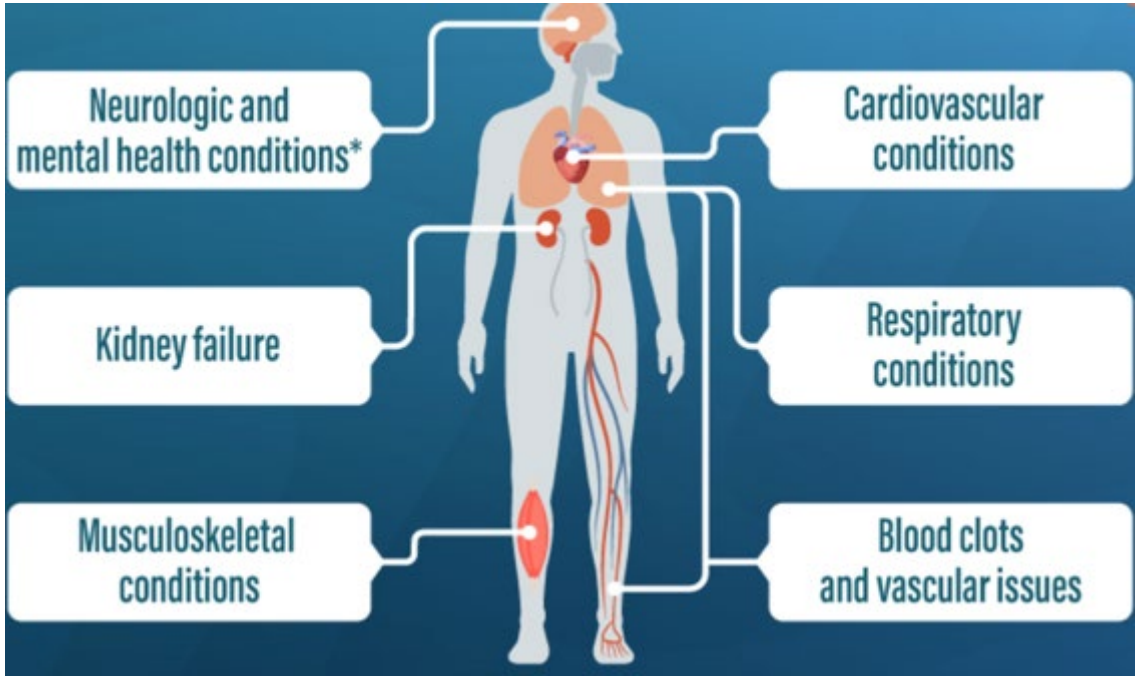
Mozaffari et al, CROI Feb 2023, Seattle, Poster 557,

Long-COVID:

<u>Overall rate falling:</u>

8-17% in UK cohorts 2020
5-10% in Australian estimates

32% *lower* during Omicron



NIAID funded cohort[1], 309 patients followed, SARS-Cov-2 confirmed
Increased risk for PASC if:

- Type 2 diabetes
- Reactivated EBV Viraemia
- Auto-antibodies – both new and evolved

Other risk factors?

- No Covid vaccine[2], obesity, asthma,
- those who developed MIS-C, older age, female sex

[1]Su et al, *Cell*, *185*(5), 881-895.e20, Jan 2022
[2]Antonelli, Lancet Infect Dis. 2021 Sep 1:

Long-COVID– What to do?

- 1) Avoid! Vaccination
- 2) Perhaps early treatment can help minimize risk?

CROI
Conference on Retroviruses and Opportunistic Infections

Preprints with THE LANCET

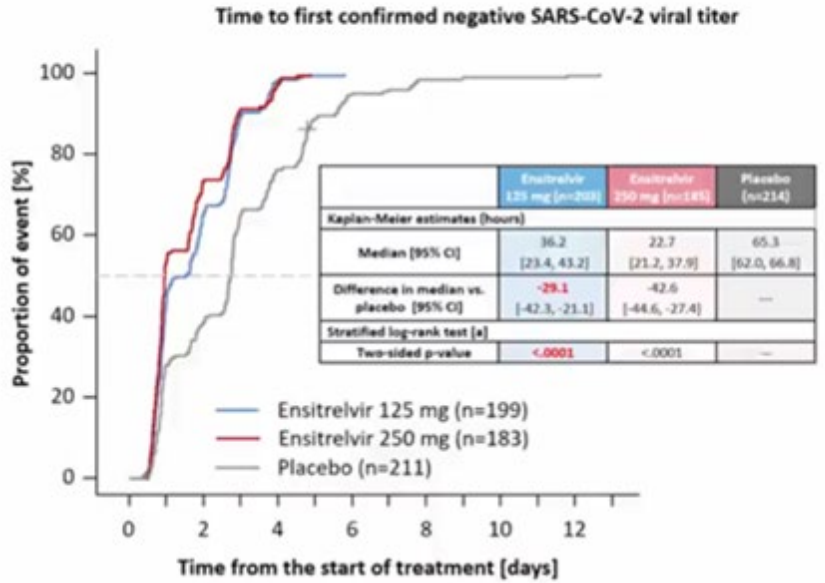
Sub-analysis of COVID-OUT trial
Treatment with fluvox, ivermectin, metformin
for adults with mild/moderate COVID

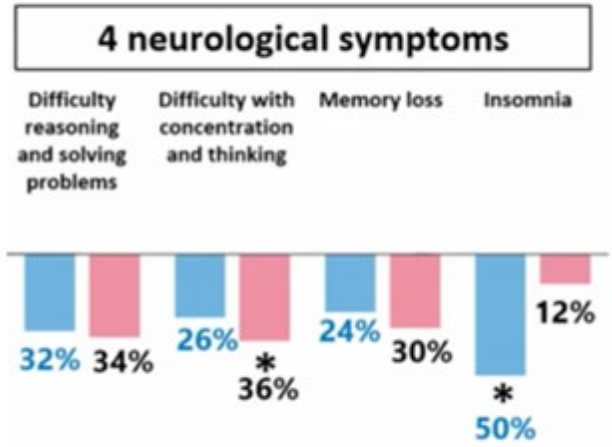
Long COVID counted if dx by medical provider
1125 followed long term
8.4% overall diagnosed

Metformin 42% relative decrease and 4.3%
absolute decrease in the Long COVID incidence

(ivermectin, fluvox unhelpful)

Sub-analysis of SCORPIO-SR trial
5 days of ensitrelvir for adults with mild/moderate COVID
Long COVID measured by PASC score
Those with high symptom scores 26-45% reduction in PASC





*: P value by Fisher's exact test <0.05

Long-COVID – future research opportunities?

- Who is at highest risk of developing PASC?
  - Data suggests vaccination is protective
  - Do different variants confer different risk?
  - Can you get PASC if you are re-infected?
- Does viral persistence contribute to symptoms?

Special Reports > Exclusives

Stanford Study of Paxlovid for Long COVID Stopped Early

— Enrollment was halted earlier than planned after interim analysis

Trends in 2023 onwards?

a) Expect less binding from old antibodies generated through vaccines and/or native immunity, as variants continue to drift. Monoclonals and CCP with unclear path forward

b) Yes antivirals currently approved, and hopefully more to come largely remain effective

c) No signal for increased severity, so drift towards hospitalized patients being older and more infirm, more immunocompromised.

d) More patients admitted *with* COVID, rather than *because* of COVID, in so far as respiratory illness at least

Questions?