COVID Treatment Updates

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HARVARD
MEDICAL SCHOOL

HOPE Conference
January 11, 2022

Disclosures, last 12 months (Updated 01/10/2022)

Disclaimer: Literature is vast and rapidly evolving

Thanks to Raj Gandhi, Jake Lemieux, Jonathan Li, Sarah Turbett, Scott Dryden-Peterson, Emmy Rubin

We will discuss the following off-label use in this presentation:

All treatments for COVID-19 except remdesivir (only approved medication)

<u>Industry support to myself/institution</u>:
None

<u>Scientific Advisory Board</u>:
Data Monitoring Committee, Kintor Pharmaceuticals, ACTIV-6 (AK)

<u>Speaker's Bureau:</u>
None

<u>Royalties</u>:
Uptodate

-12 °C | °F

Precipitation: 1%
Humidity: 52%
Wind: 21 km/h

Boston, MA

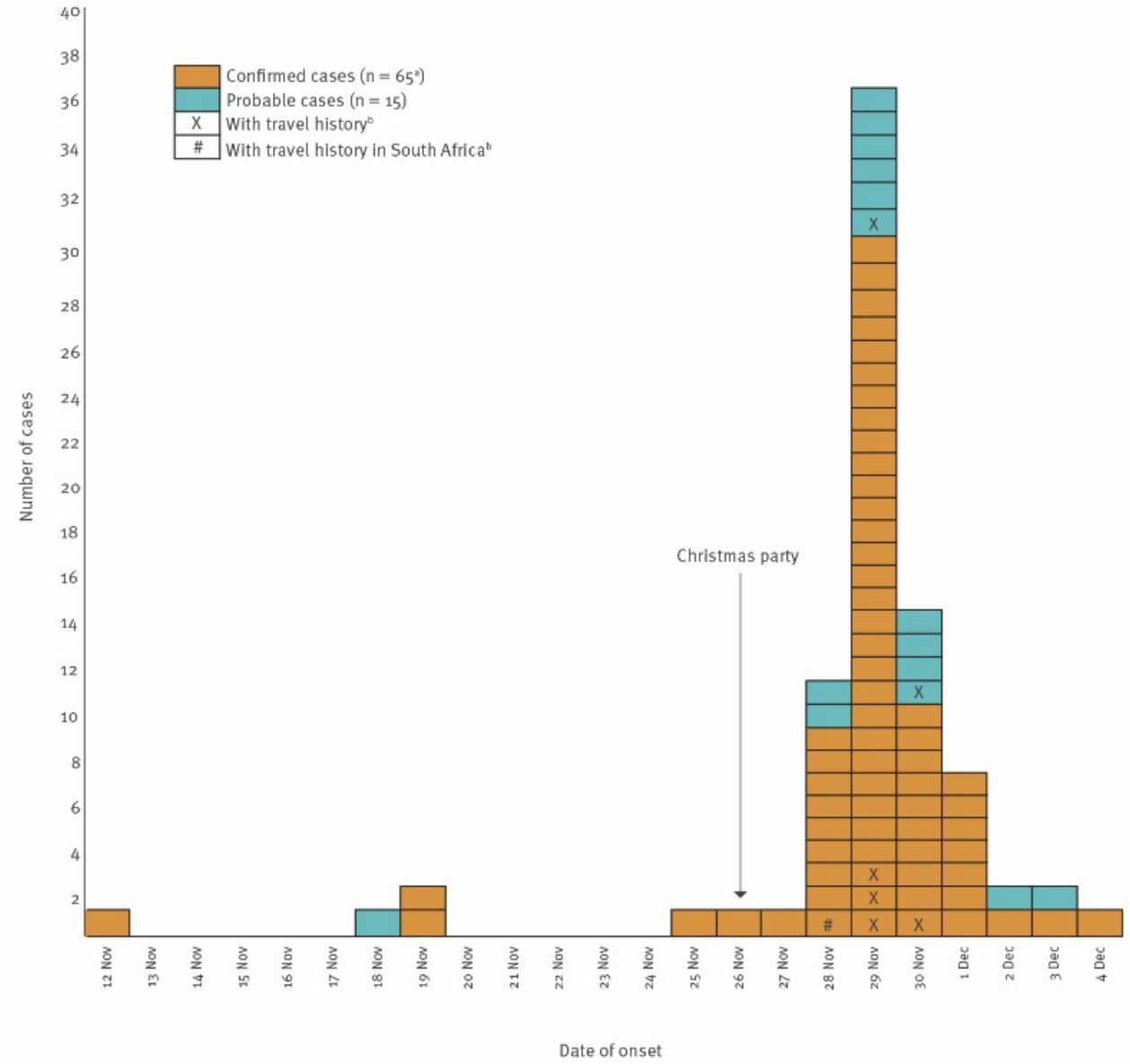
Tuesday 6:00 AM
Partly cloudy

Temperature | Precipitation | Wind

7 AM	10 AM	1 PM	4 PM	7 PM	10 PM	1 AM	4 AM
Tue	Wed	Thu	Fri	Sat	Sun	Mon	Tue
-10° -13°	3° -3°	4° -2°	1° -15°	-9° -13°	-3° -7°	2° -4°	0° -8°

Omicron's clinical picture

- □ incubation time
  - ~3d ***o*** vs. 4-6d ***δ***
- □ secondary attack rate
  - households ~31% ***o*** vs. ~21% ***δ***
- Clinical presentation differs? TBD
- Milder illness
  - UK report: for unvaccinated, omicron associated with 24% □ likelihood of hospitalization compared to prior

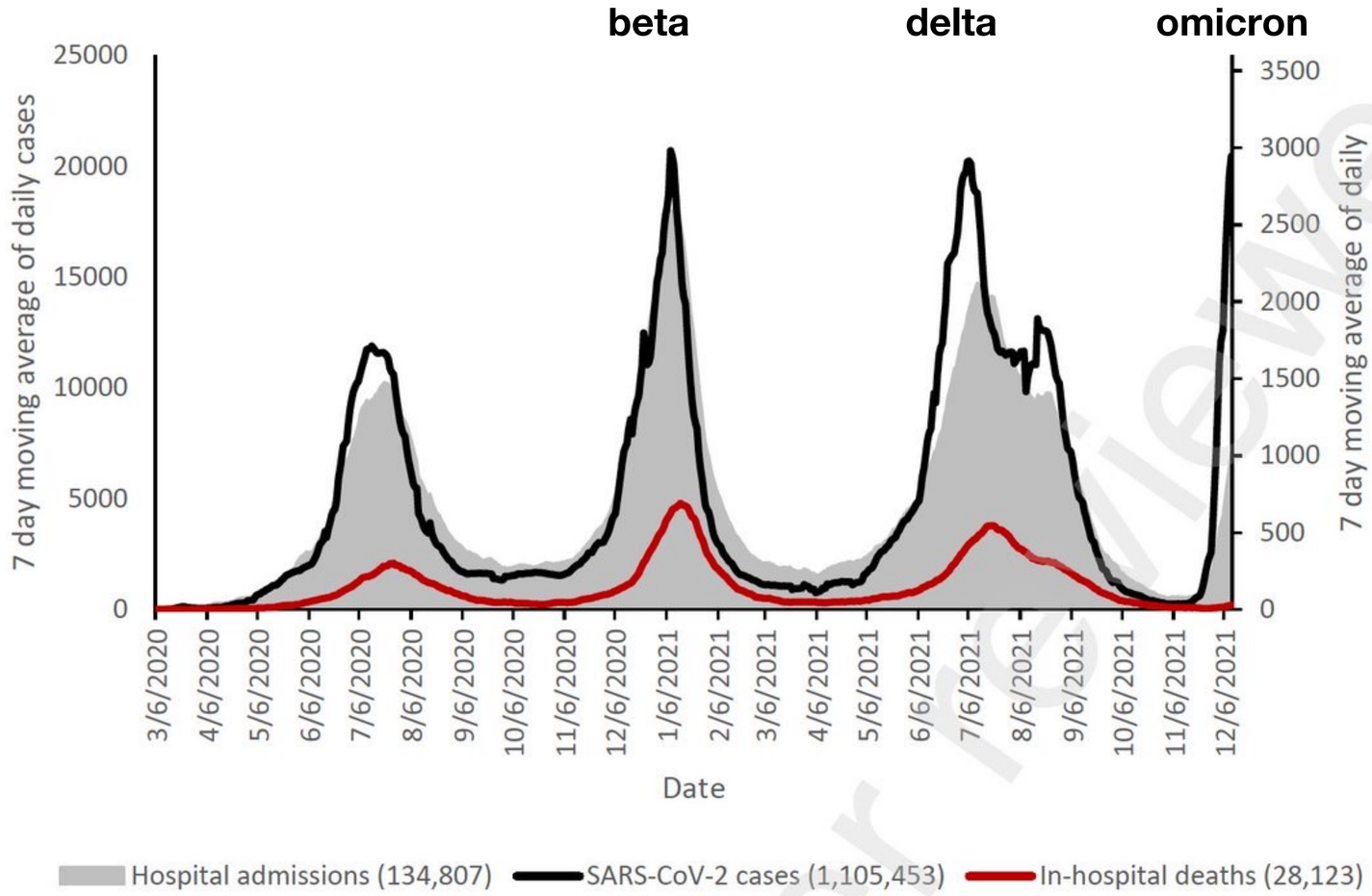


tmas Party, Eurosurveillance; Danish household study pre-print; Imperial College Report 12-22; Bhattacharyya tweet, Nebraska MMWR

Lower hospitalization rates in Gauteng during omicron surge compared to prior surges

	Beta	Delta	Omicron
Cases	41,046	33,423	133,511
Hospitalization rate	18.9%	13.7%	4.9%
% admissions w/ severe dz	60.1%	66.9%	28.8%

? generalizable to North America
much younger population
seasonal differences
preexisting immunity (vaccine or natural)



[Preprint of Clinical severity in Gauteng's 4th wave with omicron]

MGH / BWH rate of omicron versus delta

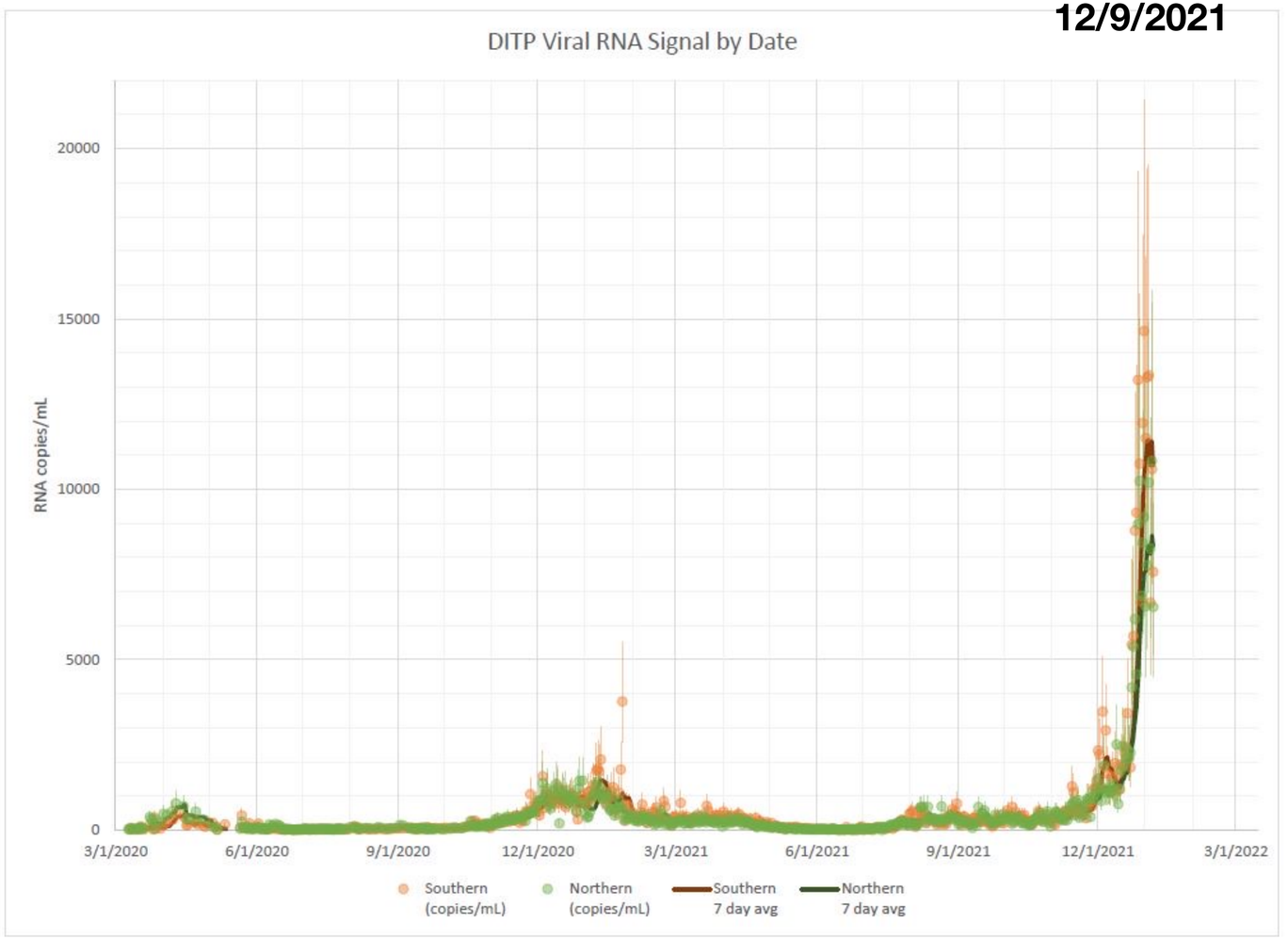
- SGTF rates
- Variant assays being validated but not yet deployed

Slide courtesy Sarah Turbett MGH Micro, Thanks to Crystal Cho, Vamsi Thiriveedhi, Seamus Carroll

Omicron arrives in Massachusetts on top of a delta surge

First omicron detection in MWRA wastewater 12/9/2021

Daily records being set in MA wastewater for community burden of SARS-CoV-2



https://www.mwra.com/biobot/biobotdata.htm

Hospitalizations in Massachusetts

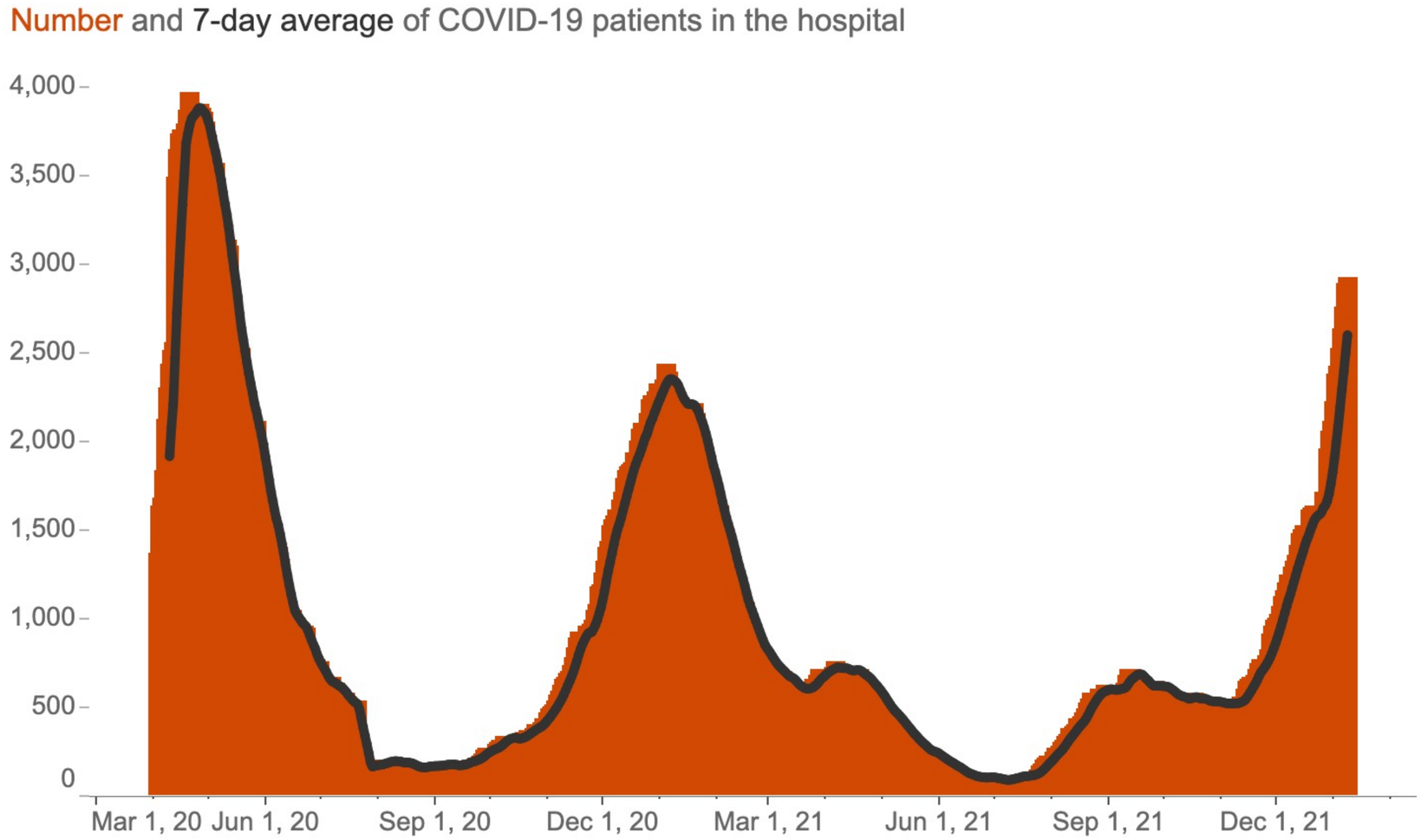
Hospitalizations

On January 9, 2022 there were 2,923 patients hospitalized for COVID-19.

Of those 2,923 patients, 1,293 were reported to be fully vaccinated for COVID-19 when they contracted COVID-19.

Select dates

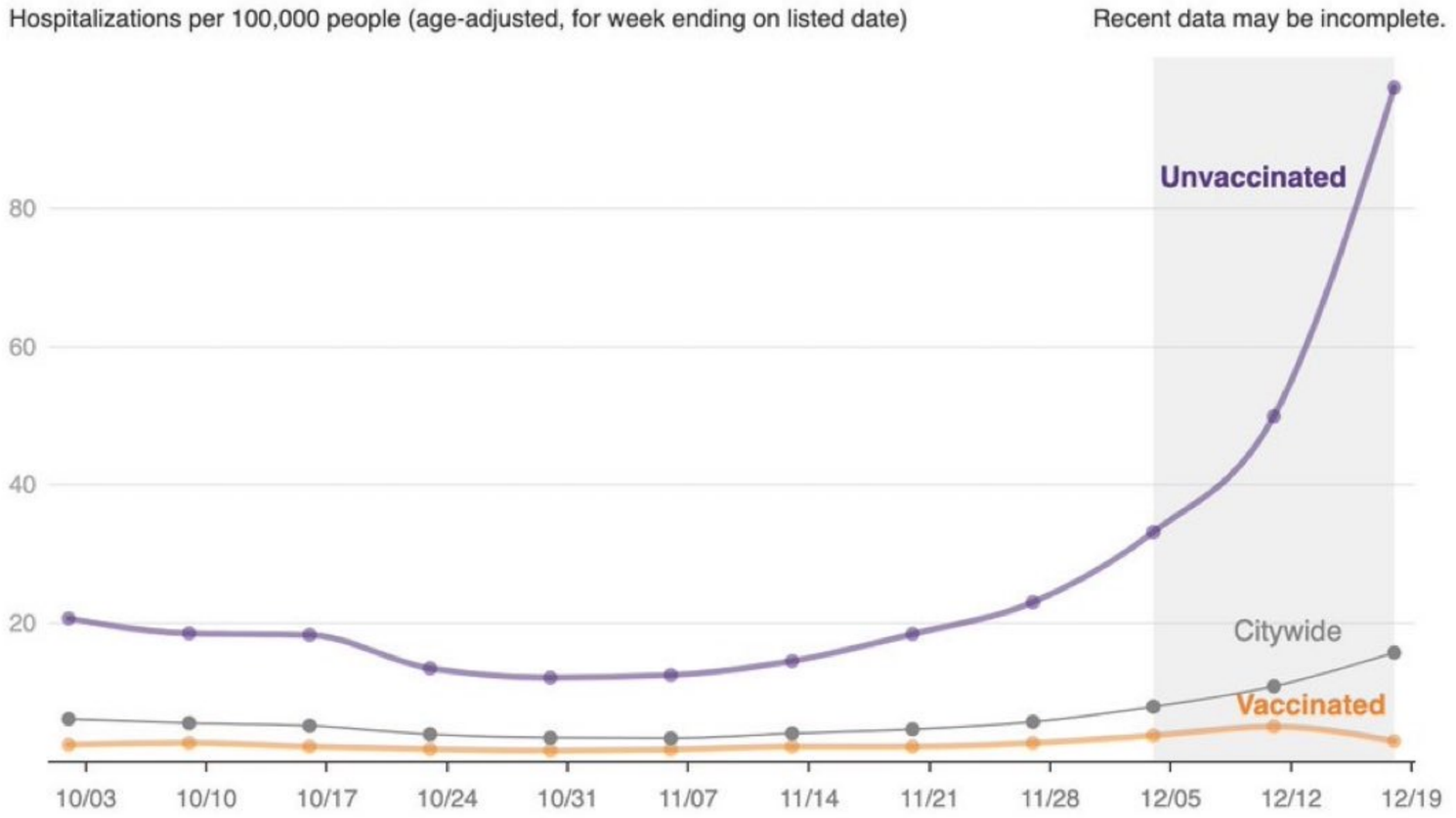
4/4/2020 — 1/9/2022



https://www.mass.gov/info-details/covid-19-response-reporting#covid-19-interactive-data-dashboard-

Is vaccination protective against hospitalization during the omicron era?

- NYC much higher hospitalization rates among unvaccinated
- UK data suggests vaccination remains protective against hospitalization; more vaccinations and more recent vaccination protective against infection



https://www1.nyc.gov/site/doh/covid/covid-19-data.page#daily; UK Technical Briefing on omicron Dec 31 2021

Clinical picture of omicron in January 2022

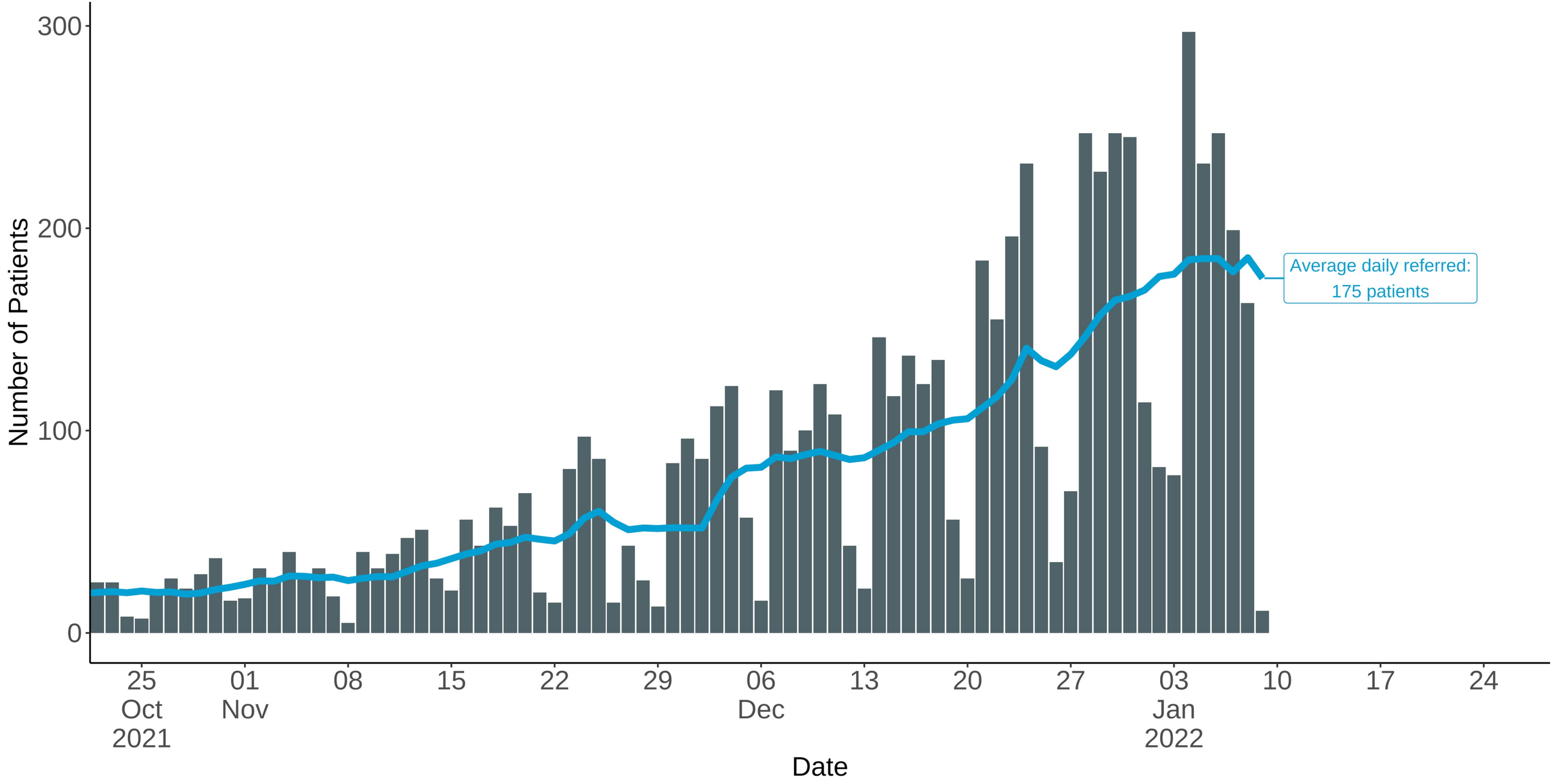
- The good:
  - Early signals suggest less severe disease
  - Vaccination remains protective versus hospitalization
    - Number and recency of vaccinations influence protection
- The bad:
  - Shorter incubation times, increased attack rates -> more transmissible
- The ugly:
  - Despite relatively high vaccination rates in resource rich settings, omicron threatens to overwhelm health systems
    - Workforce issues
  - For patients high-risk for hospitalizaton:
    - Certain countermeasures (some mAbs) are not active against omicron
    - Other countermeasures (sotrovimab, antivirals) are in short supply

Outpatient therapies being operationalized

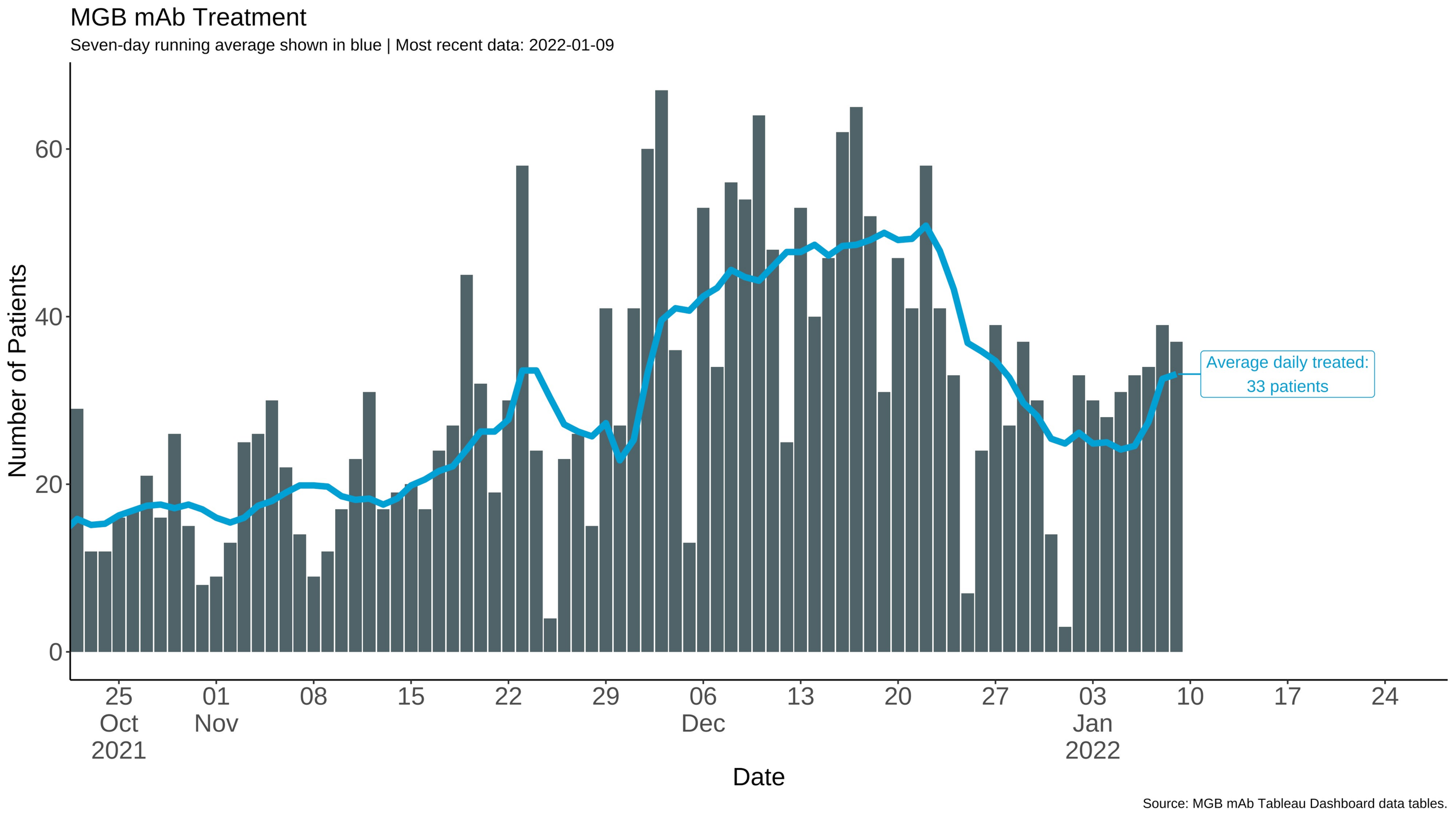
	Sotrovimab	Remdesivir	PAXLOVID	Molnupiravir	Tixagevimab & Cilgavimab (Evusheld)
Treatment of symptomatic illness	High-risk Unvaccinated or unlikely to have vaccine responses	High-risk Unvaccinated or unlikely to have vaccine responses	High-risk Unvaccinated or unlikely to have vaccine responses	High-risk Unvaccinated or unlikely to have vaccine responses	No
Window to apply treatment	10d	7d	5d	5d	N/A
Post-exposure prophylaxis	No	No	No	No	No
Pre-exposure prophylaxis	No	No	No	No	High-risk / unlikely to have vaccine responses
Route of administration	IV x1 (IM@FDA)	IV x 3 days	PO x 5 days	PO x 5 days	IM

MGB mAb Referrals

Seven-day running average shown in blue | Most recent data: 2022-01-09



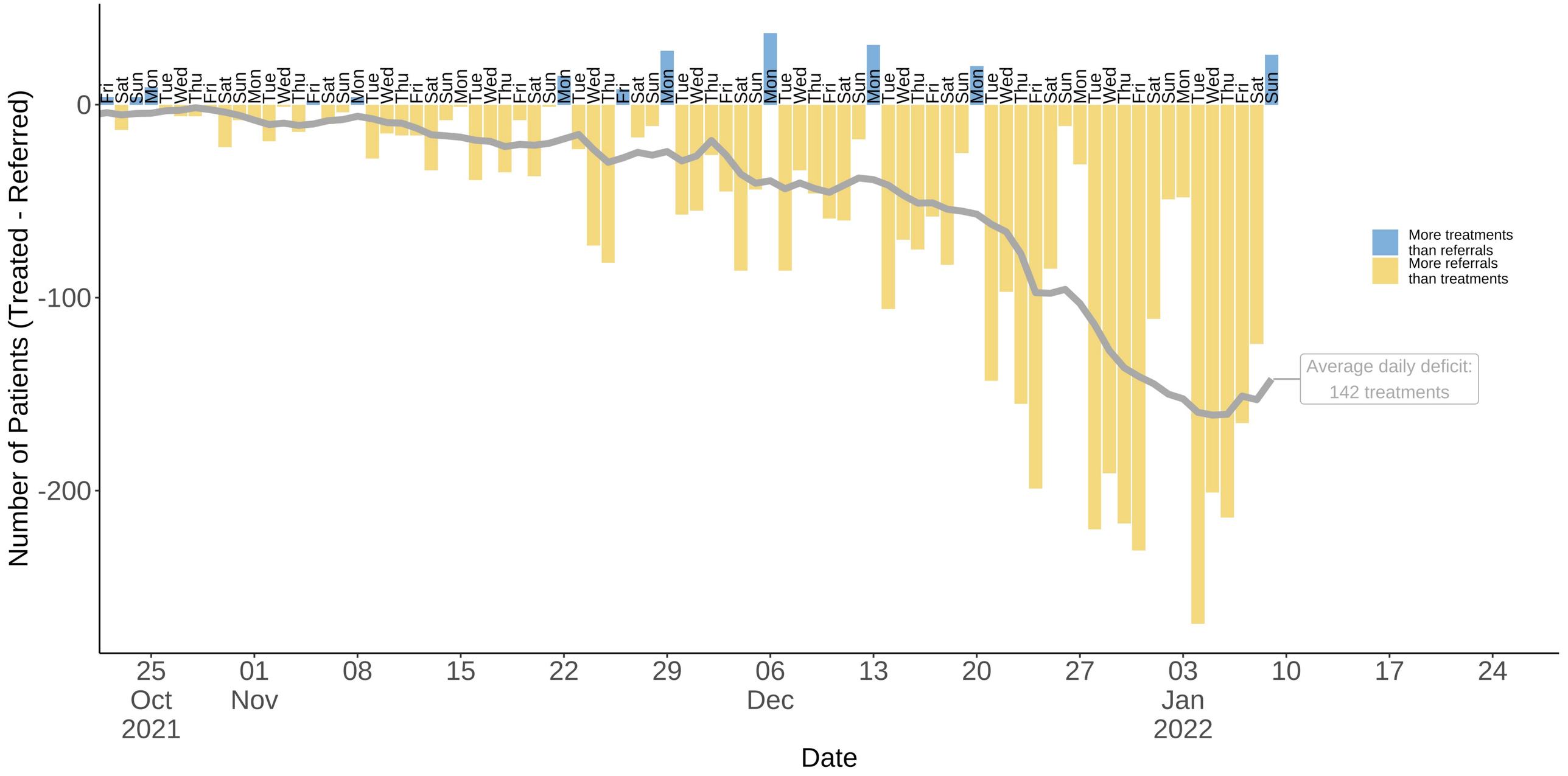
Source: MGB mAb Tableau Dashboard data tables.



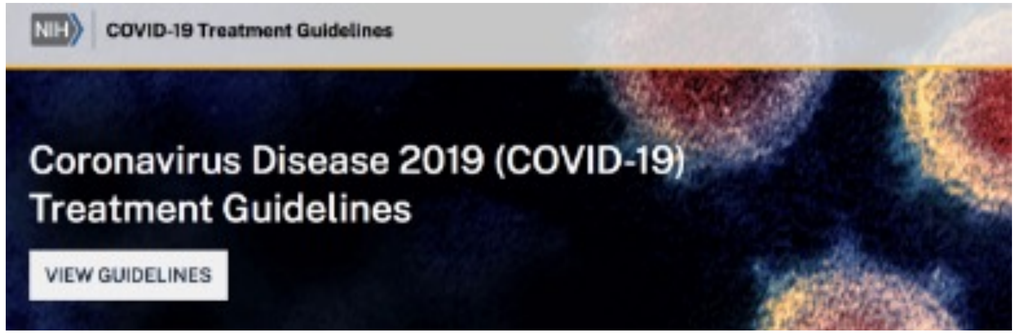
Source: MGB mAb Tableau Dashboard data tables.

Daily Alignment of Provided Treatment to Need

Referrals of prior day compared with treatments given | Seven-day running average shown in grey | Most recent data: 2022-01-09



Source: MGB mAb Tableau Dashboard data tables. Unique referrals calculated as 'Pending' referrals of the prior day subtracted from sum of 'Pending', 'No response', 'Scheduled', and 'Ineligile'



The COVID-19 Treatment Guidelines Panel's Interim Statement on Patient Prioritization for Outpatient Anti- SARS-CoV-2 Therapies or Preventive Strategies When There Are Logistical or Supply Constraints

Last Updated: December 23, 2021

https://www.covid19treatmentguidelines.nih.gov/

Tier	Risk group
1	Immunocompromised individuals regardless of vaccine status **or** Unvaccinated individuals age ≥75 y or age ≥65 y with additional risk factors*
2	Unvaccinated individuals age ≥65 y or age <65 y with risk factors*
3	Vaccinated individuals age ≥75 y or age ≥65 y with additional risk factors*
4	Vaccinated individuals age ≥65 y or age <65 y with risk factors*

Risk factors for progressing to severe COVID include advanced age, cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromised, obesity, pregnancy, sickle cell disease, other conditions

*https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

Who is receiving sotrovimab these days

- Population is VERY broad (many immunocompromised patients)
- Subprioritization to the most likely to benefit
- Addition of CDC social vulnerability index; randomization if necessary
- ? incorporation of point-of-care omicron/delta testing to allow use of CAS/IMV - not possible at this time

MGB Prioritization Framework for SARS-CoV-2 Monoclonal Antibody Therapy

Patients are offered therapy in available locations in order of clinical prioritization. Within a clinical priority tier, patients are ranked by CDC social vulnerability index (highest quartile zip codes, then all others) and then in randomized order. Last updated: December 23, 2021.

Clinical Priority 1	
Not fully vaccinated	**Fully vaccinated**
Age ≥70 BMI >40 Severe immunocompromise[4] Sickle cell disease Chronic kidney disease with GFR <30 or dialysis Cystic fibrosis Receiving chronic oxygen supplementation OR: Age >55 **and** ▪ Diabetes mellitus ▪ Cardiovascular disease[1] ▪ Chronic lung disease[2] ▪ BMI >30 ▪ Chronic kidney disease, GFR 30–59 ▪ Immunosuppression or immune deficiency ▪ Chronic liver disease[3] ▪ Cerebrovascular disease (including stroke) ▪ Dementia or other neurologic conditions	Severe immunocompromise[4] Receiving chronic oxygen supplementation

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/

MGB Policy / Prioritization Framework - pulse website

Who are eligible for EVUSHELD?

- Population is VERY broad (many immunocompromised patients)
- Subprioritization to the most likely to benefit
- ? incorporation of anti-spike testing

- NIH interim recommendations for subprioritization:
- Patients who are within 1 year of receiving B-cell depleting therapies (e.g., rituximab, ocrelizumab, ofatumumab, alemtuzumab)
- Patients receiving Bruton tyrosine kinase inhibitors
- Chimeric antigen receptor T cell recipients
- Post-hematopoietic cell transplant recipients who have chronic graft versus host disease or who are taking immunosuppressive medications for another indication
- Patients with hematologic malignancies who are on active therapy
- Lung transplant recipients
- Patients who are within 1 year of receiving a solid-organ transplant (other than lung transplant)
- Solid-organ transplant recipients with recent treatment for acute rejection with T or B cell depleting agents
- Patients with severe combined immunodeficiencies
- Patients with untreated HIV who have a CD4 T lymphocyte cell count <50 cells/mm3

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies/

Antivirals at MGB

- Outpatient RDV - reimbursement code provided for Medicaid/Medicare, unclear commercial insurer coverage, strong consideration for operationalization if sotrovimab / PAXLOVID shortage persists
- Oral antivirals - allocations to MA found on ASPR website: 1120 PAXLOVID courses, 5000+ molnupiravir (and more to come shortly)
- Most states elected selected pharmacy deployment, first-come first-serve
  - Unknown subprioritization within EUA population
  - NYC ran out of PAXLOVID in ~3 days
  - Project minimal impact on hospitalizations
- MA is (only?) state trying to centralize distribution outside of commercial pharmacies
  - Molnupiravir ~900 courses arrived January 10 — more to update next time!

https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Paxlovid/Pages/default.aspx
https://www.phe.gov/emergency/events/COVID19/investigation-MCM/molnupiravir/Pages/default.aspx

Phased deployment of oral antivirals based on supply

2-3 mos for molnupiravir
Several mos for PAXLOVID

Drug supply	Extreme shortage	Moderate shortage	No shortage
Target population	Highest risk	Higher risk	Those willing to take
Goal(s)	↓ hospitalizations	↓ hospitalizations	↓ hospitalizations, ↓ symptoms, ↓ contagion, ?↓ PAS-C
Method to target allocation	Central / lottery	Central / key high-volume locales	Pharmacies Test and treat

Equity will be considered at all stages

Take-home messages re: treatment

- When drugs in short supply, treat highest risk out patients to reduce hospitalizations
- As omicron takes over, among mAbs sotrovimab left for treatment
- Antivirals
  - Remdesivir promising, but difficult to deploy
  - PAXLOVID more robust, but many drug interactions
  - Molnupiravir less efficacious, genotoxicity concerns - high-risk individuals when above therapies are not available
- Other therapies - off-label and not EUA - if above therapies not available and with shared decision-making
- Worldwide access to novel therapies should be accelerated to address inequities

COVID-19 Therapeutics for Non-Hospitalized Patients (as of January 11, 2022 At 7 AM US EST)

Rajesh T. Gandhi, MD

Director, HIV Clinical Services and Education, Massachusetts General Hospital

Co-Director, Harvard University Center for AIDS Research

Disclosures (past 2 years):
Member, NIH & Infectious Diseases Society of America COVID-19 Treatment Guidelines Panels;
Recommendations in this talk are my own and not necessarily those of the Panels

Acknowledgments: Arthur Kim, Jon Li, Annie Luetkemeyer, Alison Han, Safia Kuriakose, Alice Pau, Efe Airewele

COVID-19 Therapeutics: Key Questions

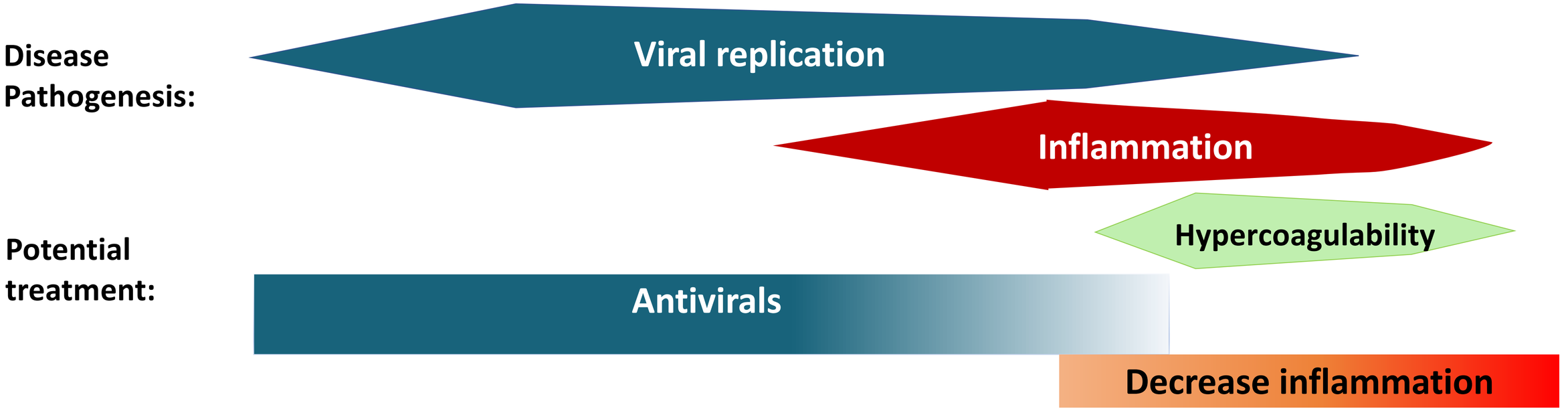
What are treatment options for high-risk non-hospitalized individuals with mild to moderate COVID-19?

Which treatments are preferred – and why?

What are future directions in outpatient therapies?

Treatment Across the COVID-19 Spectrum

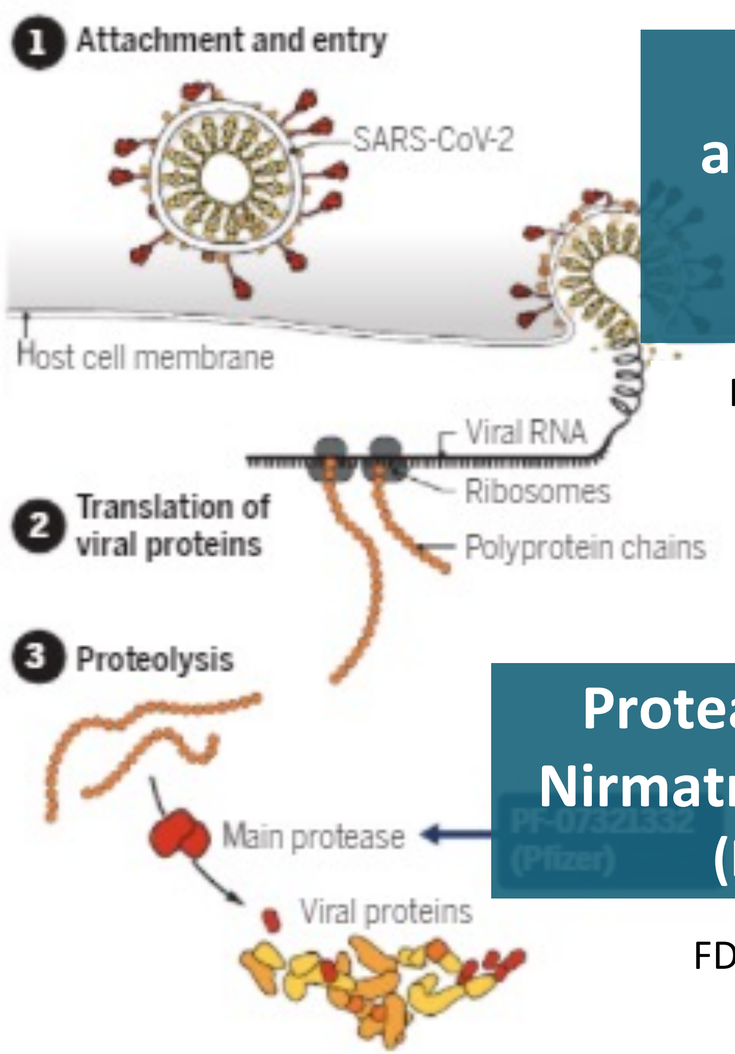
Stage/ Severity:	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (eg fever, cough, taste/smell changes); no dyspnea	O_2 saturation >=94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure



Gandhi RT, CID, 2020

Gandhi RT, Lynch J, del Rio C. NEJM 2020

SARS CoV-2 Antivirals

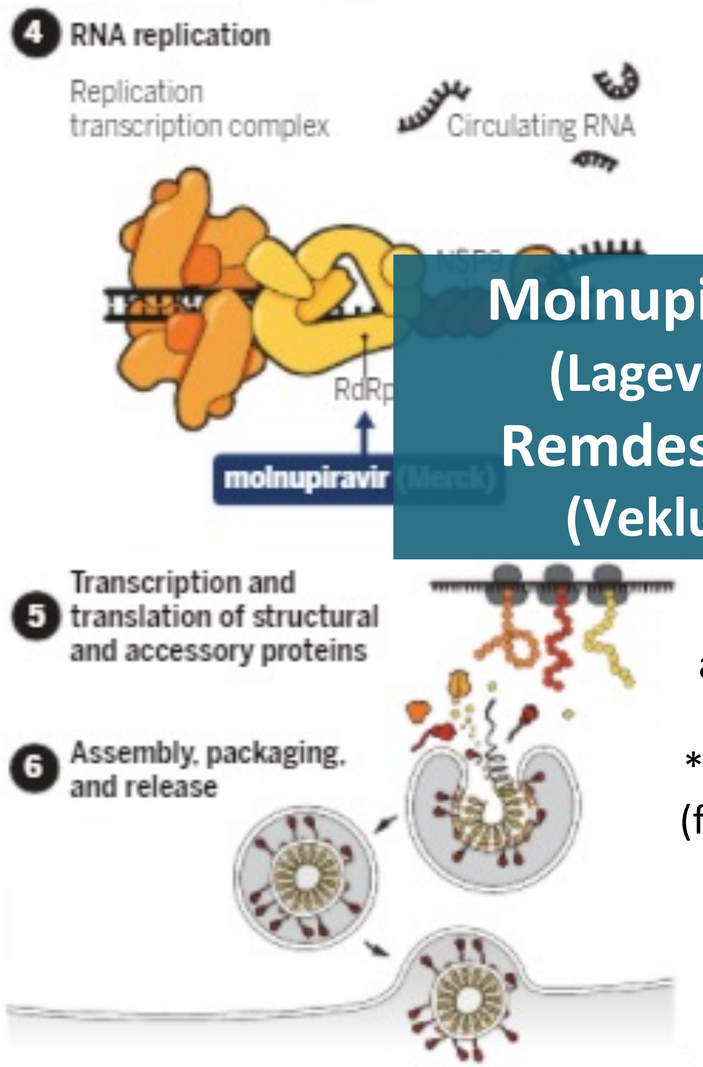


Anti-spike antibodies, eg sotrovimab (Xevudy)

FDA authorization: May 26, 2021

Protease inhibitor: Nirmatrelvir/ritonavir (Paxlovid)

FDA authorization: Dec 22, 2021



Molnupiravir* (Lagevrio), Remdesivir (Veklury)**

*FDA authorization: Dec 23, 2021
**FDA approval (for hospitalized patients): Oct 20, 2020

Rx options | Preferred rx | Supply / demand | Future

Modified from https://www.science.org/doi/epdf/10.1126/science.acx9605

Anti-SARS-CoV-2 Monoclonal Abs for Treatment

- Phase 3 placebo-controlled trials in non-hospitalized patients with mild to moderate COVID and ≥1 risk factor for severe disease

Antibody	% Reduction Hospitalization/Death
Bamlanivimab/etesevimab*	70%
Casirivimab/Imdevimab*	70%
Sotrovimab*	85%
BRII-196/BRII-198**	78%
Tixagevimab/Cilgavimab† (600 mg IM)	Sx ≤7 d: 50%; ≤3 d: 88%†
Regdanvimab††	72%††

*Authorized in US; **Interim analysis; †Reduction in severe COVID-19 or death in those with 3 d or less of symptoms; ††Approved in South Korea, authorized in European Union

Dougan M et al, NEJM, 2021; Weinreich et al., NEJM 2021; Gupta A et al, NEJM, 2021; Evering T et al, IDWeek 2021; https://www.astrazeneca.com/media-centre/press-releases/2021/azd7442-phiii-trial-positive-in-covid-outpatients.html; https://www.astrazeneca-us.com/content/az-us/media/press-releases/2021/new-analyses-of-two-AZD7442-COVID-19-Phase-III-trials-in-high-risk-populations-confirm-robust-efficacy-and-long-term-prevention.html; Ison MG et al, IDWeek 2021

Tixagevimab/cilgavimab Authorized for Pre-Exposure Prophylaxis

- People who are not currently infected and who have not had known recent exposure and:
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and** may not mount an adequate immune response to COVID-19 vaccination **or**
  - For whom vaccination with any available COVID-19 vaccine is not recommended due to history of severe adverse reaction

- May be re-dosed every 6 months

https://www.fda.gov/media/154701/download

PROVENT: Phase 3 Pre-exposure Prophylaxis Trial

IM Tixagevimab/cilgavimab (AZD7442) 300 mg vs. Placebo

Selection criteria
(N=5973 screened)

Key inclusion criteria:

- Adults age ≥18 years at increased risk for inadequate response to vaccination or SARS-CoV-2 infection
- Negative point-of-care SARS-CoV-2 serology test and unvaccinated at screening

Key exclusion criteria:

- History of laboratory-confirmed SARS-CoV-2 infection or positive SARS-CoV-2 result based on available data, history of SARS or MERS
- Prior vaccine or mAb/biologic for COVID-19

N=5197
Randomized and dosed

AZD7442
300 mg single dose (×2 IM injections of 1.5 mL each)
n=3460

Placebo (normal saline)
single dose (×2 IM injections of 1.5 mL each)
n=1737

Primary endpoints

Efficacy endpoint:
SARS-CoV-2 RT-PCR–positive symptomatic illness prior to 183 days post dose (Full Pre-exposure Analysis Set)

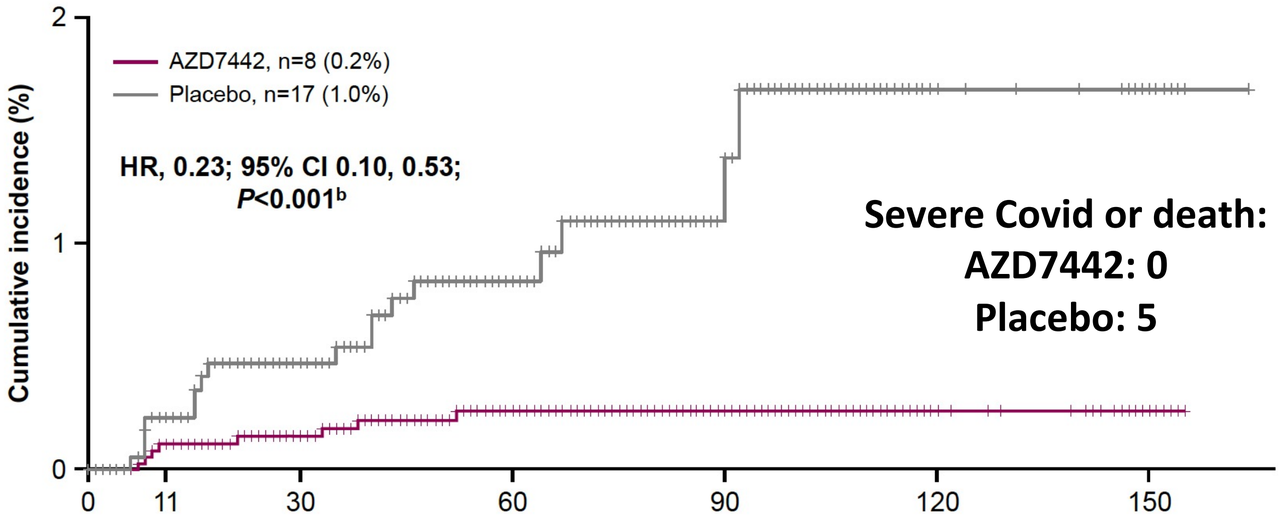
Safety endpoint:
AEs through 457 days (15 months) post dose (Safety Analysis Set)

Who was in PROVENT (n=5172)?

- Age ≥60 yrs: 43%
- Obese: 41.7%. CVD: 8%; COPD 5%; CKD: 5%; Liver disease 4.6%
- Immunosuppressed: 3.8%

Symptomatic COVID-19: 77% Reduction

Updated Nov 18, 2021. Median follow-up, 6 m:
83% reduction
Authorized for pre-exposure prophylaxis, Dec 8, 2021



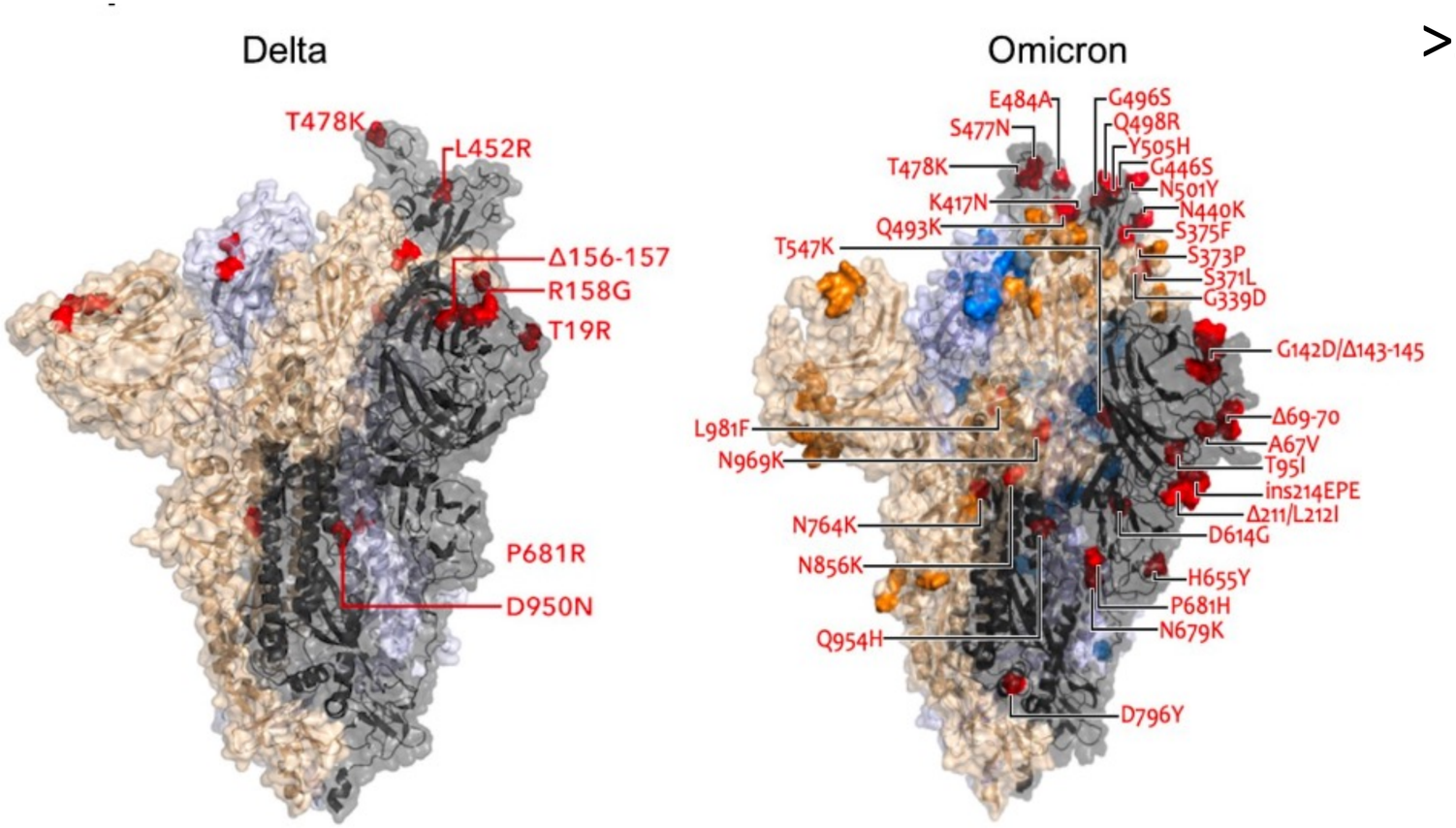
Levin M et al, IDWeek 2021, LB5
https://www.astrazeneca-us.com/content/az-us/media/press-releases/2021/new-analyses-of-two-AZD7442-COVID-19-Phase-III-trials-in-high-risk-populations-confirm-robust-efficacy-and-long-term-prevention.html

Populations to consider for Tixagevimab/cilgavimab

- Active treatment for cancer
- Solid-organ transplant recipient and taking immunosuppressive therapy
- Receipt of CAR-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency
- Advanced or untreated HIV infection (CD4 cell count <200; history of AIDS defining illness without immune reconstitution; clinical manifestations of symptomatic HIV)
- High-dose corticosteroids, alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapy, TNF blockers, other immunosuppressive/immunomodulatory agents (e.g., B-cell depleting agents)

https://www.fda.gov/media/154701/download

Omicron and anti-SARS CoV-2 monoclonal antibodies

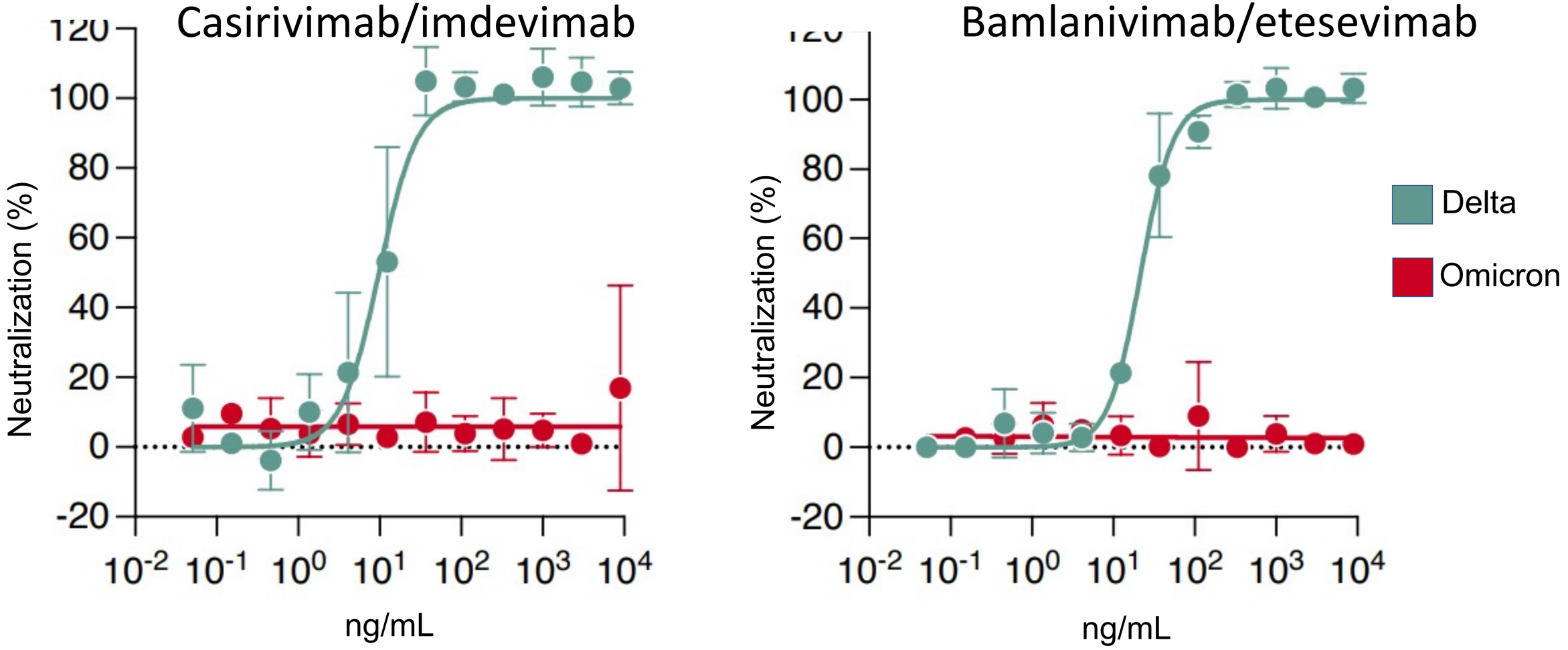


>50 amino acid changes; ~30 in spike

Modified from slide from Dr. Arthur Kim

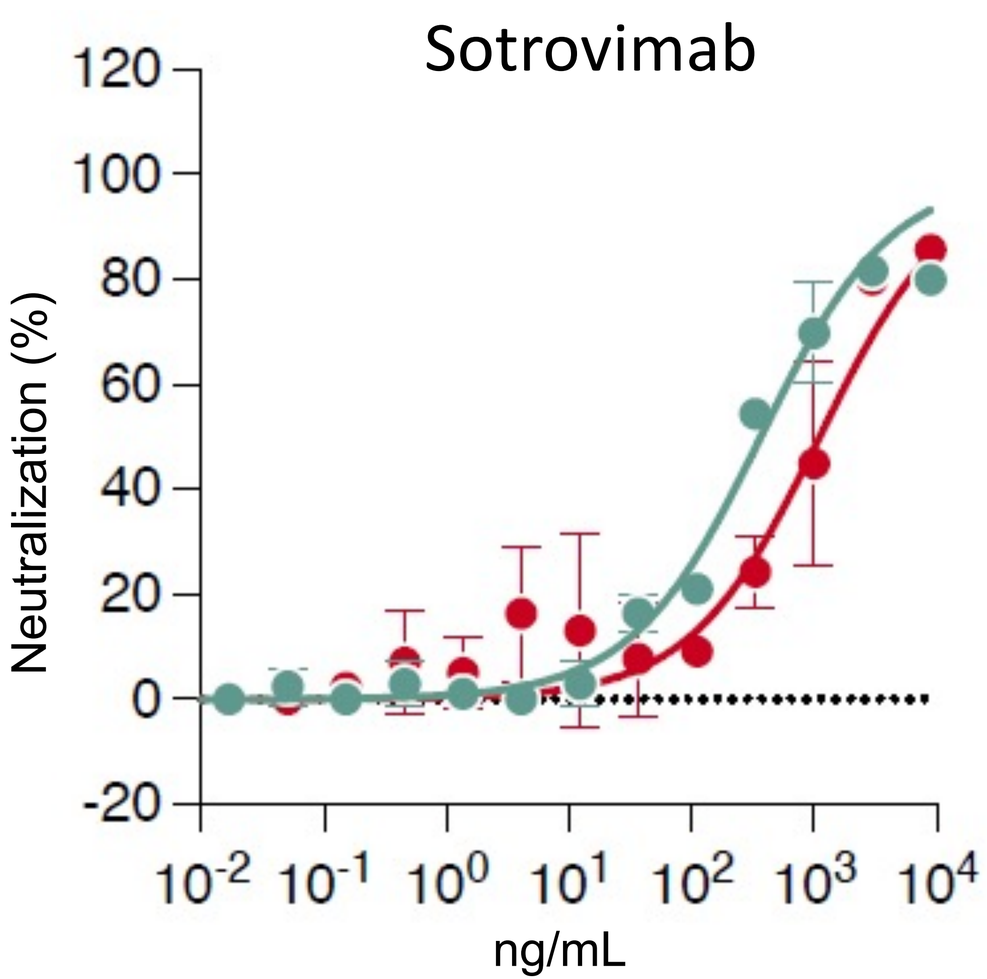
https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html

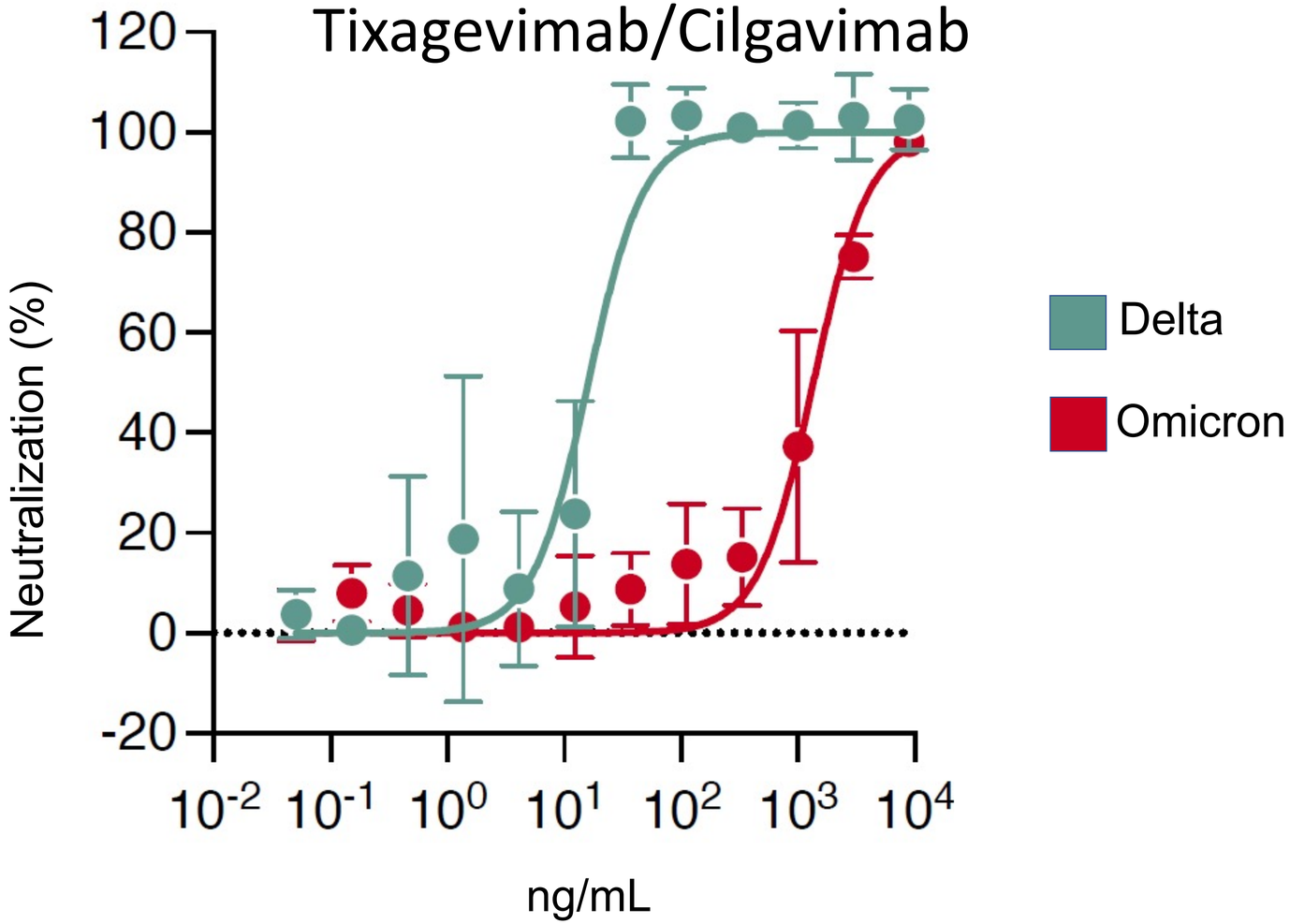
Casirivimab/Imdevimab and Bamlanivimab/Etesevimab markedly lower neutralization activity against Omicron



Planas D et al
https://www.biorxiv.org/content/10.1101/2021.12.14.472630v1.full.pdf

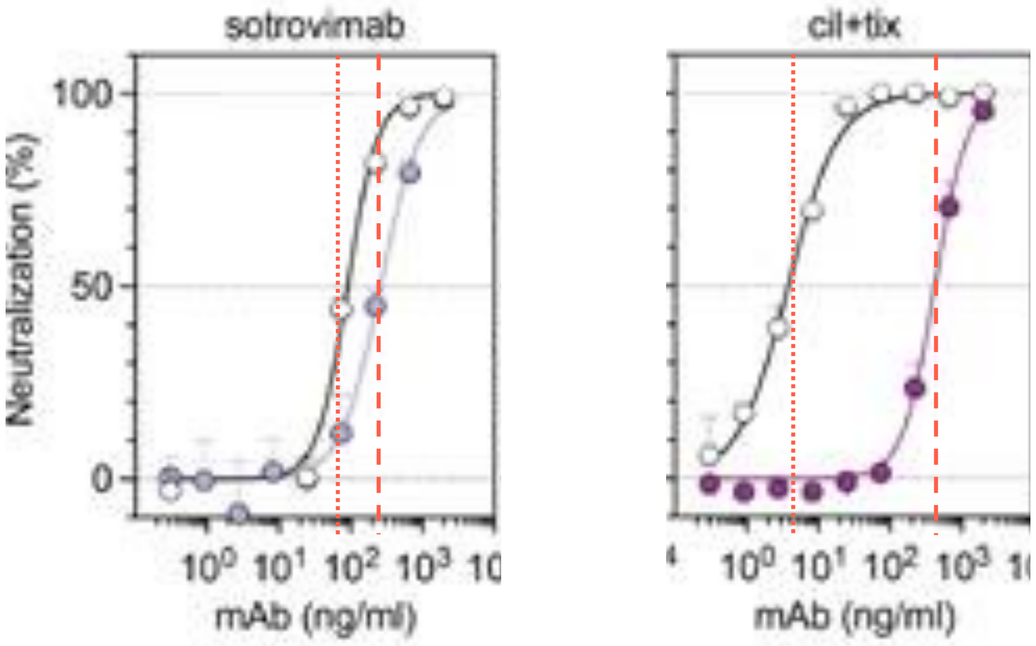
Sotrovimab and Tixagevimab/Cilgavimab neutralization activity against Omicron

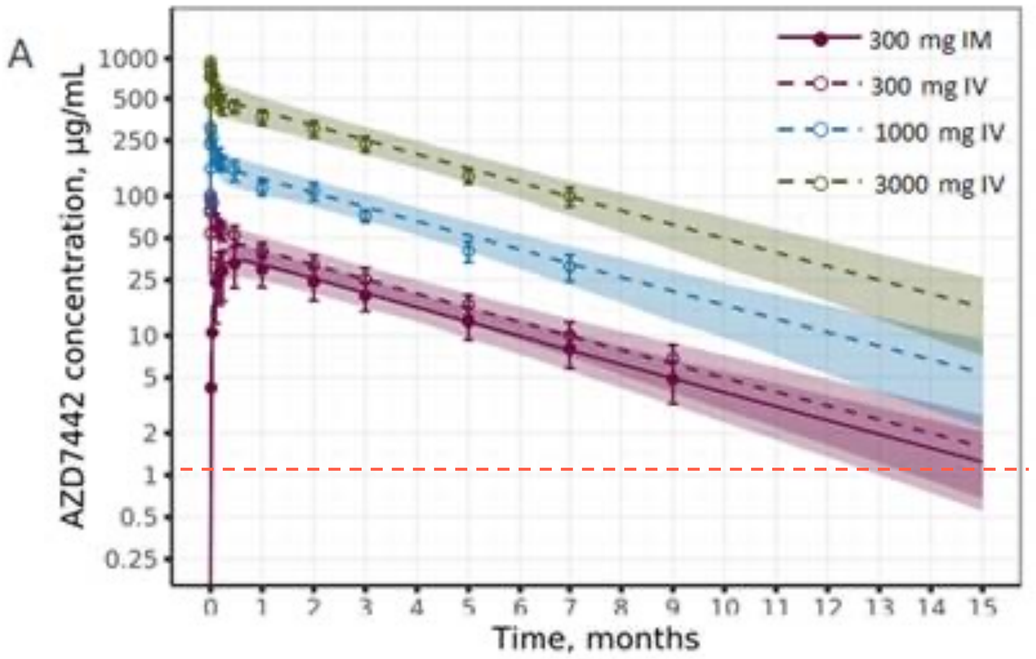




Planas D et al
https://www.biorxiv.org/content/10.1101/2021.12.14.472630v1.full.pdf

Pseudovirus neutralization
Open white circles: Wuhan-Hu-1
Purple closed circles: Omicron





Cameroni et al, https://www.biorxiv.org/content/10.1101/2021.12.12.472269v1
Loo YM et al, https://www.medrxiv.org/content/10.1101/2021.08.30.21262666v2

h.t. Dr. Jon Li

Omicron and Amubarvimab/Romlusevimab

- In a study done prior to Omicron:
  - 80% reduction in hospitalization/death in non-hospitalized COVID-19 patients at high risk of clinical progression to severe disease.
  - Deaths: amubarvimab/romlusevimab (0), placebo (9) (p=0.0037)
- Press release from Brii:
  - Pseudovirus neutralization data: substantial drop in activity of amubarvimab; romlusevimab not affected

EUA application currently under review by the US FDA

Evering T et al, IDWeek 2021;
https://www.briibio.com/news-detial.php?id=512#news

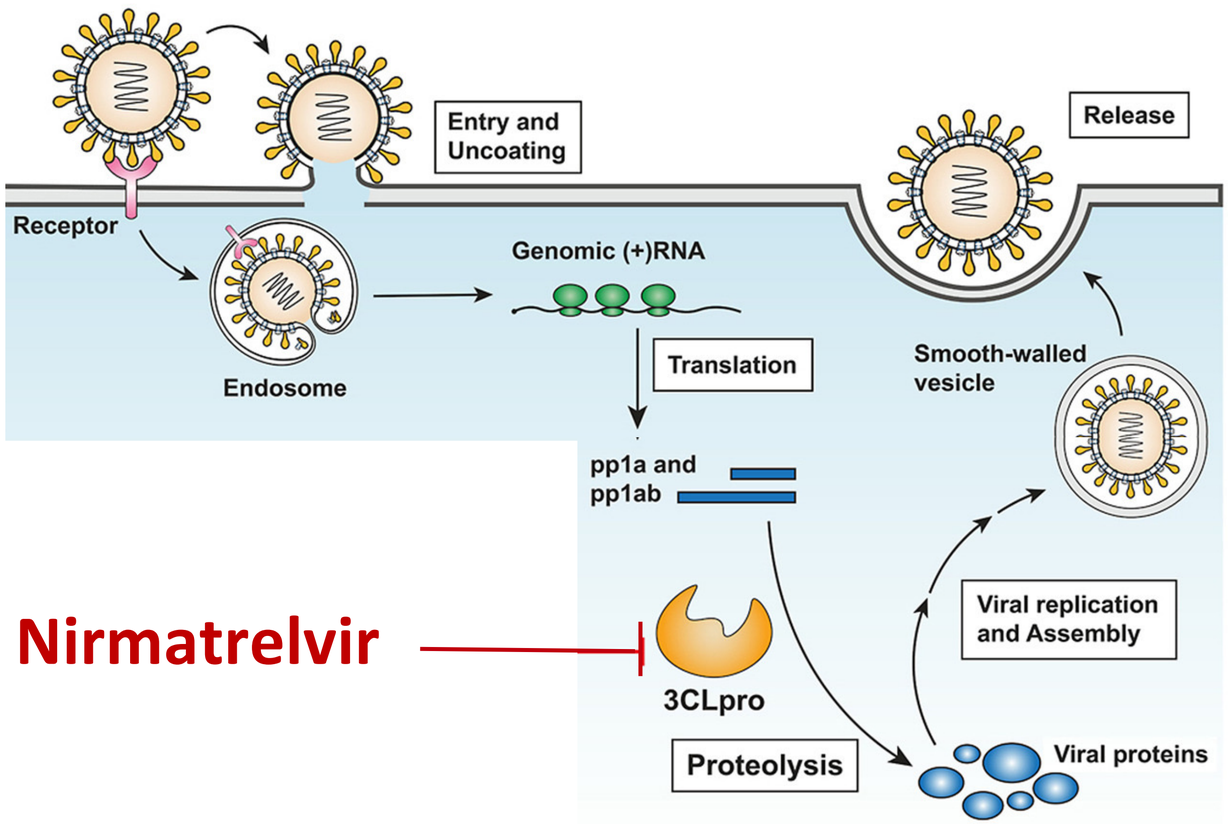
Intramuscular (IM) Sotrovimab

- COMET-TAIL: randomized trial of IM vs. IV administration of sotrovimab (500 mg) in high risk, non hospitalized adults and adolescents (> 12 yo) up to 7 days after symptom onset (n=983)
- Progression to hospitalization or death: 2.7% (IM) vs 1.3% (IV)
- IM sotrovimab non-inferior to IV sotrovimab
- <1% rates of serious adverse events and Grade 3-4 adverse events in both groups

https://www.gsk.com/en-gb/media/press-releases/primary-endpoint-met-in-comet-tail-phase-iii-trial-evaluating-intramuscular-administration-of-sotrovimab-for-early-treatment-of-covid-19/

SARS CoV-2 Protease Inhibitor: Nirmatrelvir

- SARS CoV-2 polyproteins cleaved by the viral main protease enzyme at 11 sites → non-structural proteins essential for viral replication
- Nirmatrelvir: oral SARS CoV-2 protease inhibitor
  - Co-packaged with ritonavir (RTV): inhibits CYP3A metabolism of nirmatrelvir
  - Must be given with RTV to achieve therapeutic levels



Chiou WC et al, Biochemical and Biophysical Res Comm, 2021;
Owen DR et al, Science 2021

Nirmatrelvir/ritonavir in High-Risk Patients with COVID-19

- Phase 2/3 EPIC HR: unvaccinated non-hospitalized patients at high risk for progression to severe COVID-19 and within 5 days of symptom onset
- Participants (n=2246) randomized to nirmatrelvir/ritonavir twice daily or placebo for 5 d
- About 10-fold reduction in viral load at day 5 relative to placebo

≤5 days of symptom onset	Hospitalization or death	% Reduction
NTV/rtv	**8/1039 (0.8%) 0 deaths**	**88% P<0.0001**
Placebo	**66/1046 (6.3%) 12 deaths**	

Participants ≥65 years	Hospitalization or death	% Reduction
NTV/rtv	**1/94 (1.1%) 0 deaths**	**94% P<0.0001**
Placebo	**16/98 (16.3%) 6 deaths**	

https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-additional-phase-23-study-results

Who is Authorized to Receive Nirmatrelvir/rtv?

Treatment of mild-to-moderate COVID-19 in adult and pediatric patients (age 12 and older, ≥40 kg) who are at high risk for progression and within 5 days of symptom onset

Dosing considerations:

- Nirmatrelvir 300 mg (2 x 150 mg tablets) + 100 mg (1 tablet) ritonavir twice daily for 5 d, with or without food
- Moderate renal insufficiency (eGFR ≥30 but < 60): nirmatrelvir 150 mg + ritonavir 100 mg twice daily for 5 days
- Not recommended if severe renal insufficiency or severe hepatic impairment

Nirmatrelvir/ritonavir: Potential Drug Drug Interactions

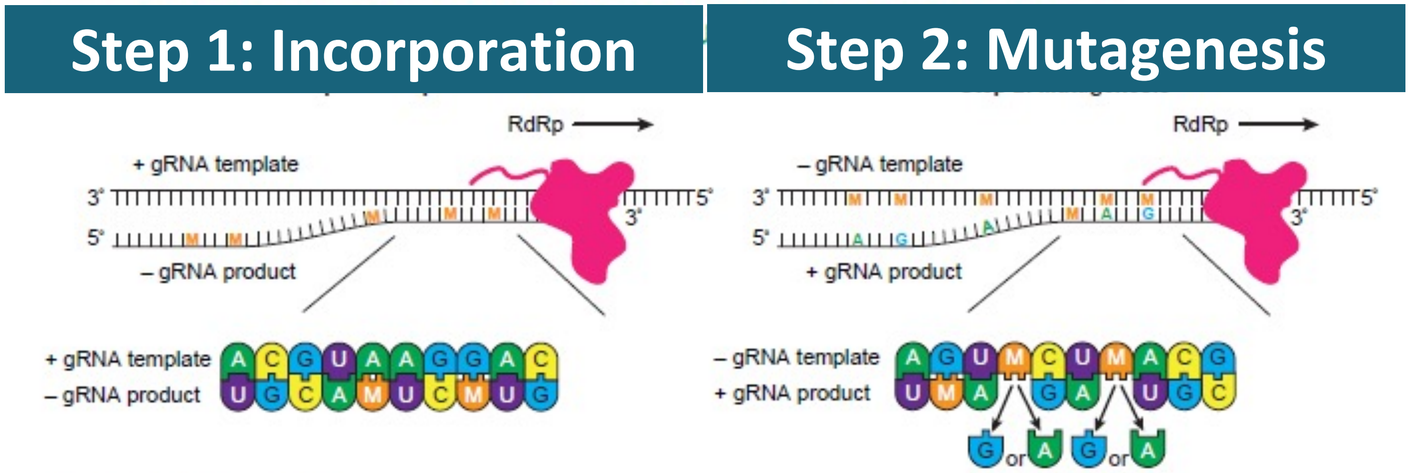
- Ritonavir inhibits CYP3A: affects metabolism of many medications
  - Some medicines should not be coadministered, eg amiodarone, clopidogrel, rifampin, rivaroxaban
  - Others may need dose reduction/monitoring, eg calcineurin inhibitors
  - Other medications may be temporarily stopped: eg, atorvastatin, rosuvastatin
- Useful resources:
  - NIH COVID-19 Treatment Guidelines
  - Univ. of Liverpool COVID-19 Drug Interaction Checker

Rx options | Preferred rx | Supply / demand | Future

https://www.covid19treatmentguidelines.nih.gov/
https://www.covid19-druginteractions.org/

Small Molecule Antiviral for SARS-CoV-2: Molnupiravir (MOV)

- Oral ribonucleotide prodrug
- Converted into Beta-D-N4 hydroxycytidine (NHC)
- Inhibits SARS CoV-2 replication by inducing RNA mutagenesis



Adapted from Kabinger et al, 2021.

- Accumulation of multiple mutations beyond a tolerable threshold in the viral genome is known as viral error catastrophe, resulting in significant impairment or complete loss of viral replication

Strizki et al, IDWeek 2021, Abstract #511,

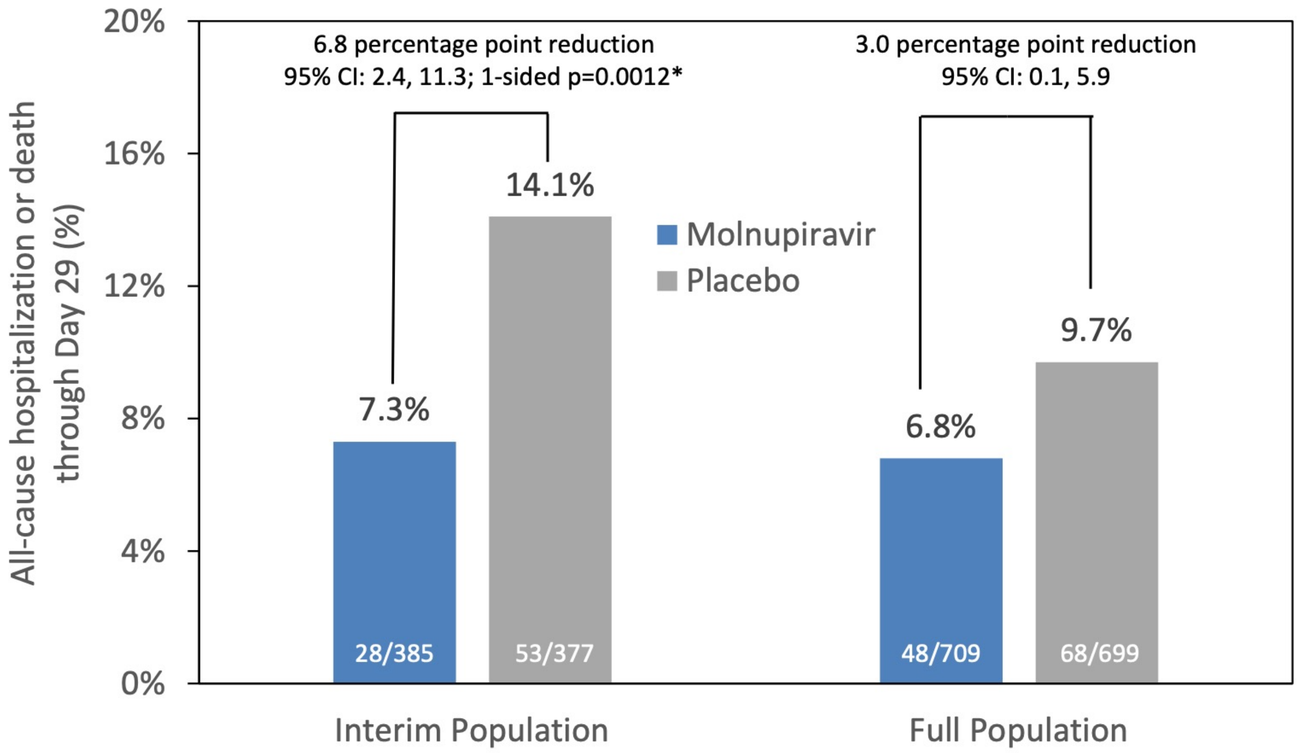
Molnupiravir Reduces Hospitalization/Death by 30%

MOVe-OUT (n=1433):

- Non-hospitalized unvaccinated adults, mild to moderate COVID
- ≥1 risk factor for severe disease
- Symptom onset within 5 days of study randomization
- Randomized to molnupiravir 800 mg (four 200 mg pills) twice a day or placebo for 5 days

Interim analysis (n=762): 48% reduction in hospitalization/death

Final analysis (n=1408): 30% reduction in hospitalization/death



9 deaths in placebo group, 1 in MOV group

Bernal AJ et al, NEJM, Dec 16, 2021

Molnupiravir: Mutagenicity Evaluations

Evidence for mutagenicity:

- Hypoxanthine phosphoribosyltransferase gene mutation assay in Chinese Hamster Ovary cells exposed to NHC for 32 days

No or equivocal evidence for mutagenicity:

- In vivo rodent mutagenicity assays: equivocal results in Pig-a assay; negative in Big Blue assay
- In vivo rat micronucleus assay: negative

FDA conclusion: “low risk for genotoxicity”

Zhou S et al, JID, 2021; Troth S et al, JID, 2021; https://www.fda.gov/media/155054/download

Who Is Authorized to Receive Molnupiravir?

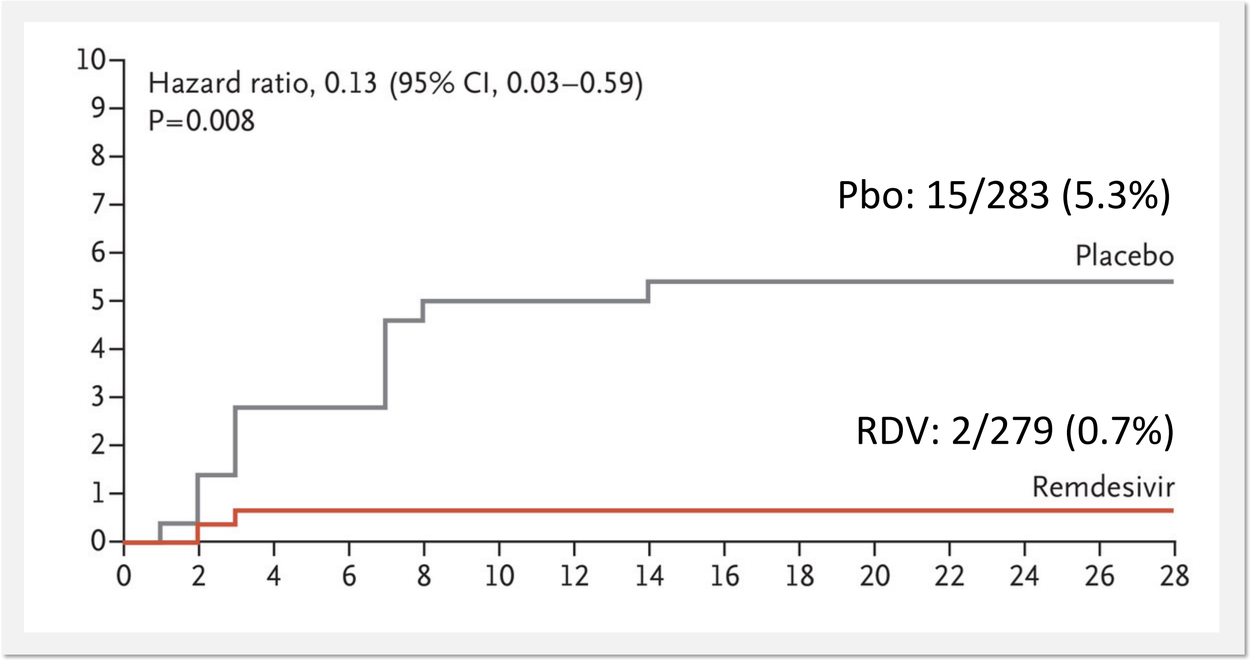
- Adults with mild-to-moderate COVID at high risk for progression and ≤5 days of symptom onset only if other treatments not accessible or clinically appropriate
- Not recommended during pregnancy (animal studies: possibility of fetal harm)
- Not authorized for children (may affect bone and cartilage growth)
- Individuals of child-bearing potential should use contraception during treatment and for 4 days after last dose
- Males of reproductive potential who are sexually active with females of child-bearing potential: use contraception during treatment and for ≥3 months after last dose

https://www.fda.gov/media/155054/download

PINETREE trial: Remdesivir in Non-Hospitalized Individuals

- Nucleotide prodrug: inhibits viral RNA polymerase: chain terminator
- FDA approved for treating hospitalized patients with COVID-19 pneumonia
- Randomized trial in non-hospitalized patients (n=562)
  - High risk, unvaccinated, symptoms ≤7 d
  - RDV IV infusion x 3 days vs. placebo
  - Stopped early: administrative reasons

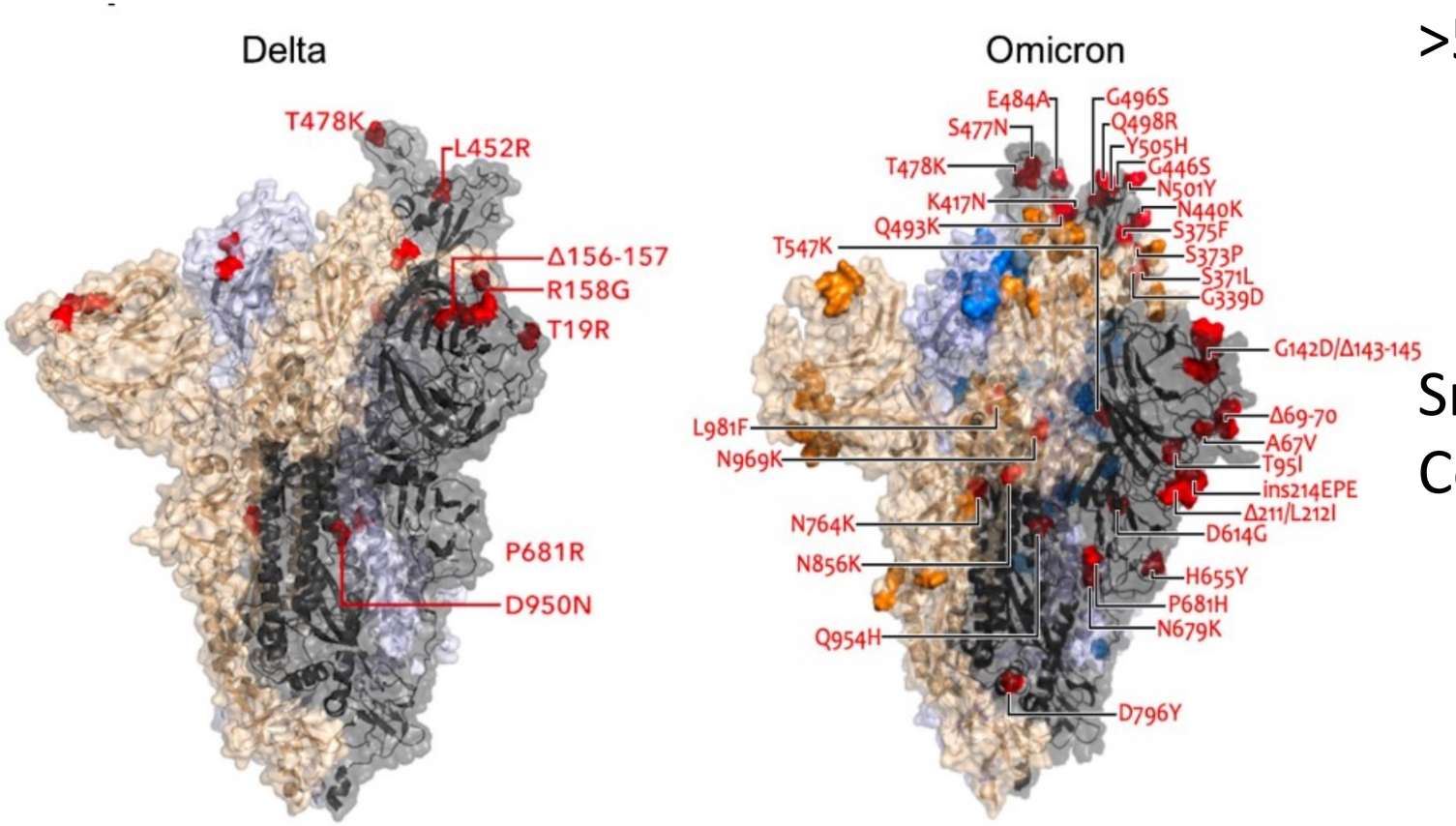
COVID-19 Hospitalization/death by d 28



- RDV: 87% reduction in hospitalization
- No deaths in either group

Gottlieb RL et al, NEJM, Dec 22, 2021

Omicron and Outpatient Therapeutics



- >50 amino acid changes; ~30 in spike
  - Of mAbs authorized for treatment, only sotrovimab anticipated to be active
- Small molecule antivirals target SARS CoV-2 replicase:
  - Data from cell cultures: preserved activity of nirmatrelvir/ritonavir, molnupiravir, remdesivir against Omicron

Modified from slide from Dr. Arthur Kim

https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html
Vangeel L et al, bioRxiv preprint doi: https://doi.org/10.1101/2021.12.27.474275

How do the therapies stack up?

	1) Nirmatrelvir/r	2) Sotrovimab	3) Remdesivir	4) Molnupiravir
Efficacy (prevention hospitalization or death)	•**Relative risk reduction: 88%** •Absolute risk: 6.3%→0.8% •NNT: 18	•**Relative risk reduction: 85%** •Absolute risk: 7%→ 1% •NNT: 17	•**Relative risk reduction: 87%** •Absolute risk: 5.3%→0.7% •NNT: 22	•**Relative risk reduction: 30%** •Absolute risk: 9.7%→6.8% •NNT: 35
Pros	•Highly efficacious •Oral regimen •Ritonavir studied (safe) in pregnancy	•Highly efficacious •Monoclonals typically safe in pregnancy •Few/no drug interactions	•Highly efficacious •Studied in pregnancy •Few/no drug interactions	•Oral regimen •Not anticipated to have drug interactions
Cons	•Drug drug interactions	•Requires IV infusion followed by 1 hour observation	•Requires IV infusion on 3 consecutive days	•Low efficacy •Concern: mutagenicity •Not recommended in pregnancy/children

Bringing it All Back Home: Outpatient Treatment Options for COVID-19

Option	Patient Population
Nirmatrelvir/ ritonavir	•Patient not on interacting medications •As soon as possible and within 5 days of symptom onset
Sotrovimab	•Patient on interacting medication/able to come to health care facility •As soon as possible and within 10 days of symptom onset
Remdesivir	•Patient in health care facility or through home infusion service •As soon as possible and within 7 days of symptom onset
Molnupiravir	•Patient not able to be treated with one of the options above •Not pregnant (if given during pregnancy, shared decision making) •As soon as possible and within 5 days of symptom onset

Fluvoxamine: TOGETHER trial

- Placebo controlled randomized adaptive platform trial in Brazil
- Participants with risk factors for severe COVID-19 (n≈1500) and within 7 days from symptom onset
- Fluvoxamine 100 mg bid or placebo, 10 d
- Primary endpoint (composite of hospitalization or ED observation >6 hours): 11% (fluvoxamine) vs. 16% (placebo) (relative risk 0.68)

	Intention-to-treat analysis		
	N	n (%)	Relative risk (95% BCI)
Fluvoxamine	741	79 (11%)	0·68 (0·52–0·88)
Placebo	756	119 (16%)	1 (ref)

- No difference in hospitalizations (10% vs. 13%), duration of hospitalization, death (2% vs. 3%), viral clearance

Reis G et al, Lancet Global Health, 2021

Inhaled Steroids: Jury Still Out

- **Inhaled budesonide**
  - PRINCIPLE (n=1856): open label randomized control trial
    - Improved time to recovery
    - Hospitalization/death: 6.8% vs. 8.8% (OR 0.75, 95% Bayesian CrI 0.55-1.03)

- **Ciclesonide** (30 days) (n=400): placebo controlled randomized clinical trial
  - Days to alleviation of symptoms: 19 days vs. 19 days
  - ED visit/hospitalization: 2/197 (1%) (ciclesonide) vs. 11/203 (5.4%) (placebo) (p=0.03)
  - Hospitalization/death: 3/197 (1.5%) vs. 7/203 (3.4%) (p=0.26, not significant)

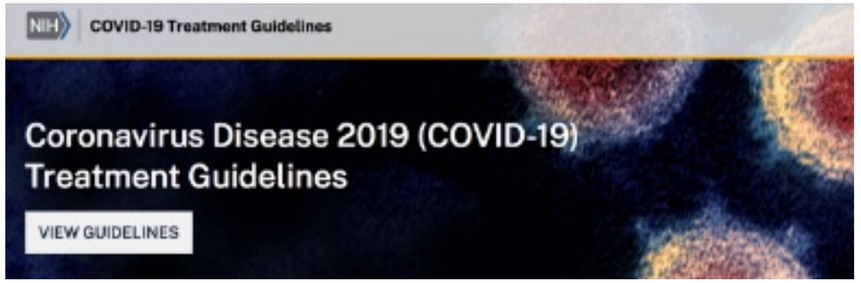
Ramakrishnan S et al, Lancet Resp Med, 2021; Yu LM et al, Lancet, 2021; Clemency BM et al. Medrxiv 2021

COVID-19 Treatment Guidelines: What Not to Use and Areas of Uncertainty

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19

Published by IDSA on 4/11/2020. Last updated, 12/2/2020

Adarsh Bhimraj*, Rebecca L. Morgan**, Amy Hirsch Shumaker, Valery Lavergne**, Lindsey Baden, Vincent Chi-Chung Cheng, Kathryn M. Edwards, Rajesh Gandhi, Jason Gallagher, William J. Muller, John C. O'Horo, Shmuel Shoham, M. Hassan Murad**, Reem A. Mustafa**, Shahnaz Sultan**, Yngve Falck-Ytter**



Not recommended or suggested:

- Hydroxychloroquine
- Azithromycin
- Lopinavir/ritonavir
- Convalescent plasma in hospitalized patients (IDSA)

Insufficient data:

- Ivermectin
- Fluvoxamine
- Inhaled steroids
- Vitamin C, Zinc
- Colchicine

Future Directions in Outpatient COVID-19 Therapy

- What is the benefit of therapies in lower risk patients (vaccinated, infected with Omicron)?
- Will monotherapy select for viral resistance? Role of combination Rx?
  - Concern greatest for severely immunocompromised.
- Should these oral therapies, mAbs be used in hospitalized patients?
  - Only if patient admitted for non-COVID reason and otherwise meets EUA criteria
- Does early treatment prevent long COVID?

Desiderata: “Things Wanted or Needed”

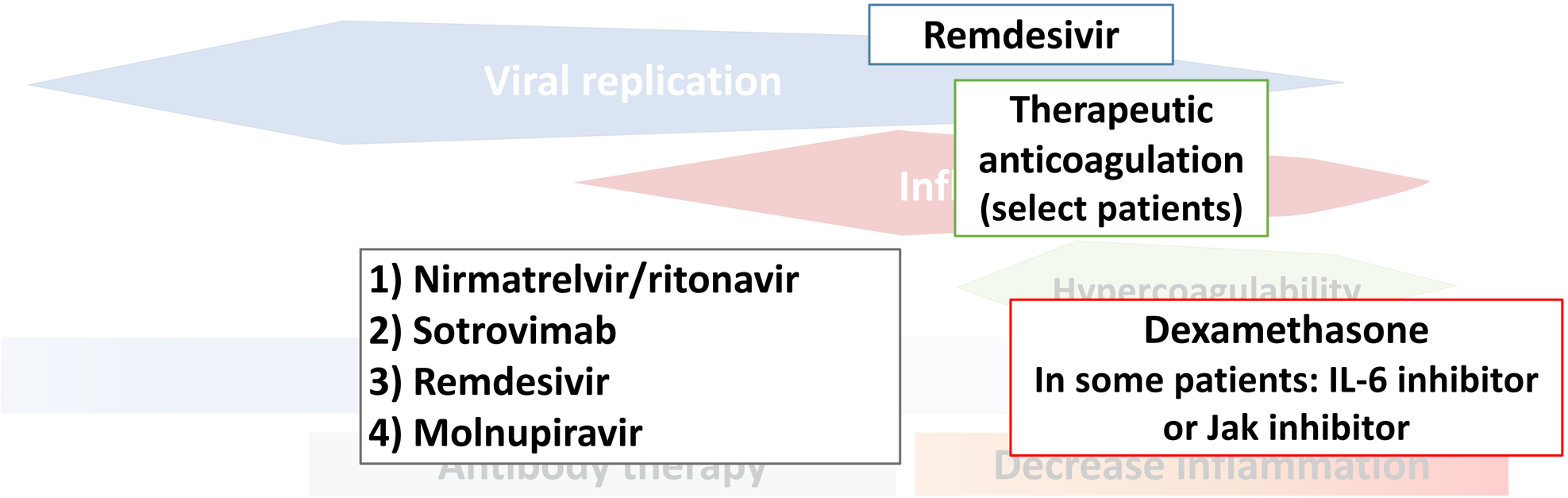
Need	Optimal Drug	Nirmatrelvir	Sotrovimab	Remdesivir	Molnupiravir
Efficacy	✓✓✓	✓✓✓	✓✓✓	✓✓✓	✓
Ease of delivery	✓✓✓	✓✓✓	X	XXX	✓✓✓
Drug Interactions	✓✓✓	XXX	✓✓	✓✓	✓✓
Safety during pregnancy	✓✓✓	✓	✓	✓✓	XXX
Authorized in children (>12)	✓✓✓	✓✓	✓✓	✓✓✓	XX
Supply/Access	✓✓✓	XXX	XXX	✓	XX

Conclusion: We Don’t Yet Have the Optimal Drug

Prophylaxis and Treatment Across the COVID-19 Spectrum

Exposure	Asymptomatic/ Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical illness
	+ SARS-CoV-2 test but no symptoms	Mild symptoms (e.g., fever, cough, taste/smell changes); no dyspnea	O_2 saturation ≥ 94%, lower respiratory tract disease	O_2 saturation <94%, respiratory rate >30/min; lung infiltrates >50%	Respiratory failure, shock, multi-organ dysfunction/failure

Pre-exposure prophylaxis: COVID-19 VACCINES Tixagevimab/ Cilgavimab



Gandhi RT, CID, 2020
Gandhi RT, Lynch J, del Rio C. NEJM 2020

COVID-19 Therapeutics for Non-Hospitalized Patients: Summary

- Multiple therapies coming on-line for treatment of high-risk non-hospitalized patients with COVID-19
- In order of preference: nirmatrelvir-ritonavir (if no significant drug interactions), sotrovimab, remdesivir, molnupiravir
- Treatment most likely to be effective when started early; testing and treatment need to go hand in glove
- When demand outstrips supply (as it does now), prioritize patients at highest risk; monitor and ensure equitable access