COVID-19: Treatment Update

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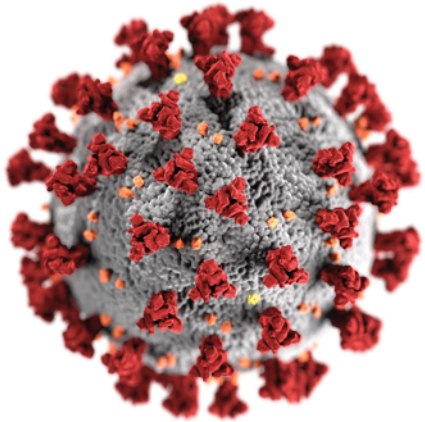
Disclosures

- None
- … except that putting this talk together was enormously difficult

COVID-19: Outline

- **What happened over the past 12 months?**
- What's new right now?



What happened since December 2020?

- Synchronous massive increase in USA December-January 2021, followed by huge rise in some countries – notably India, Brazil, South Africa
- Greater understanding of the science of SARS-CoV-2 transmission – *it's airborne*
- Widespread utilization of remdesivir and dexamethasone, +/- tocilizumab, for inpatient treatment
- Emergency use authorization of 3 vaccines and monoclonal antibodies for outpatient treatment and prevention
- Early summer 2021 with little disease activity, followed by late summer Delta surge that continues today
- Observation that vaccine effectiveness wanes over time, leading to recommendation for 3rd mRNA shots, concerns about J&J effectiveness
- Recognition of more transmissible and vaccine-evasive variants, leading to the current domination of Delta → Omicron

Daily new confirmed COVID-19 cases per million people

7-day rolling average. Due to limited testing, the number of confirmed cases is lower than the true number of infections.

Our World in Data

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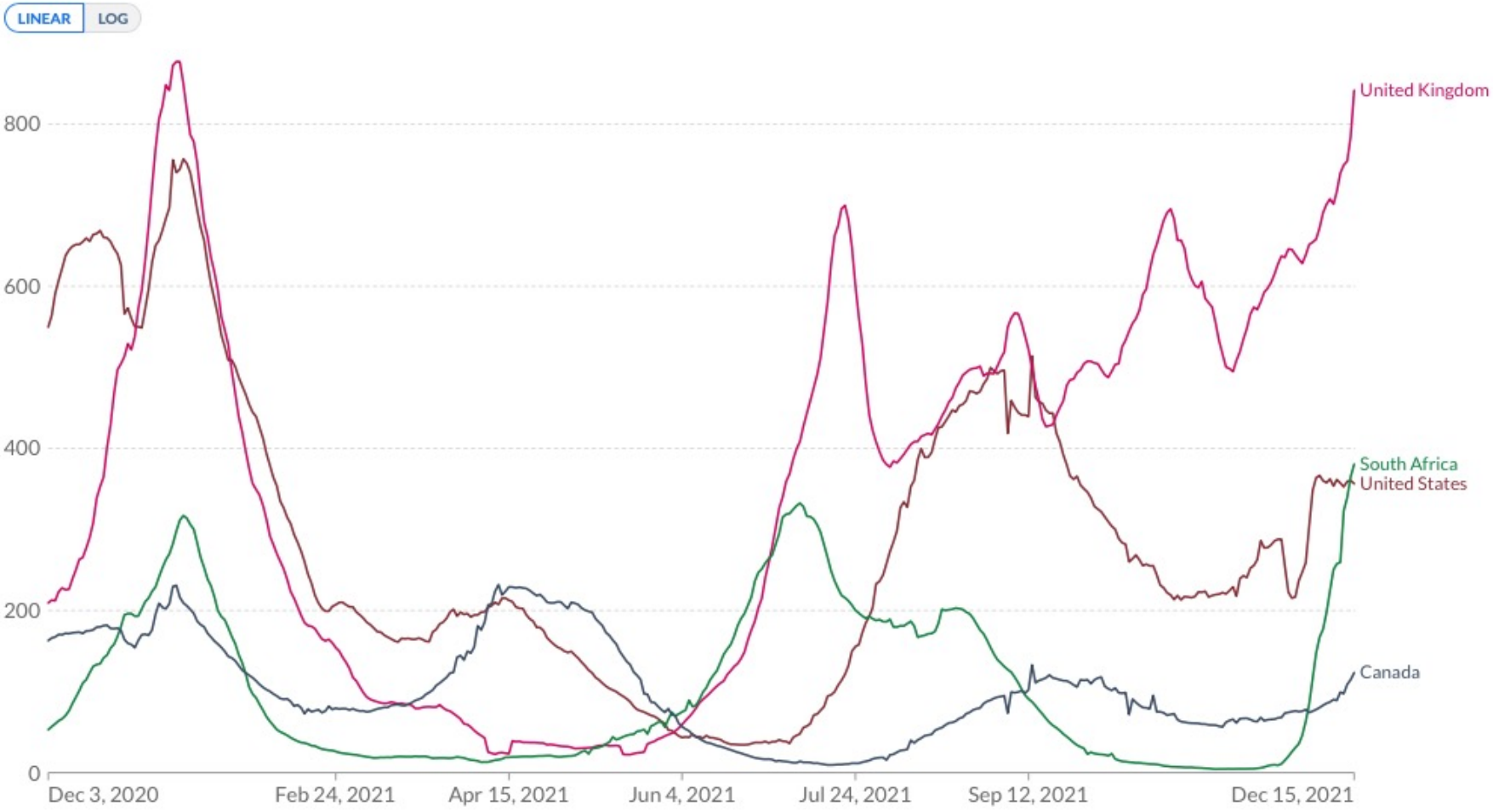
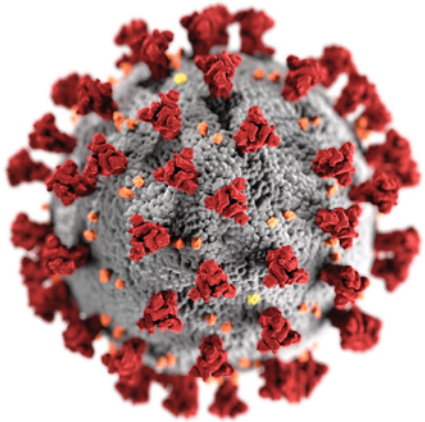
Our World in Data



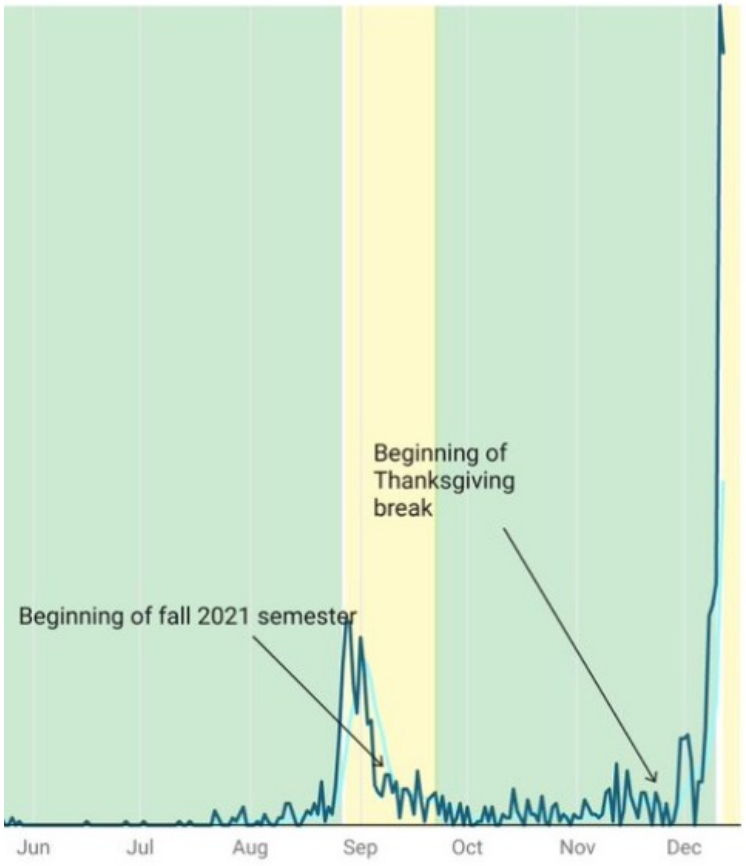
COVID-19: Outline

- What happened over the past 12 months?
- **What's new right now?**
  - **Omicron**



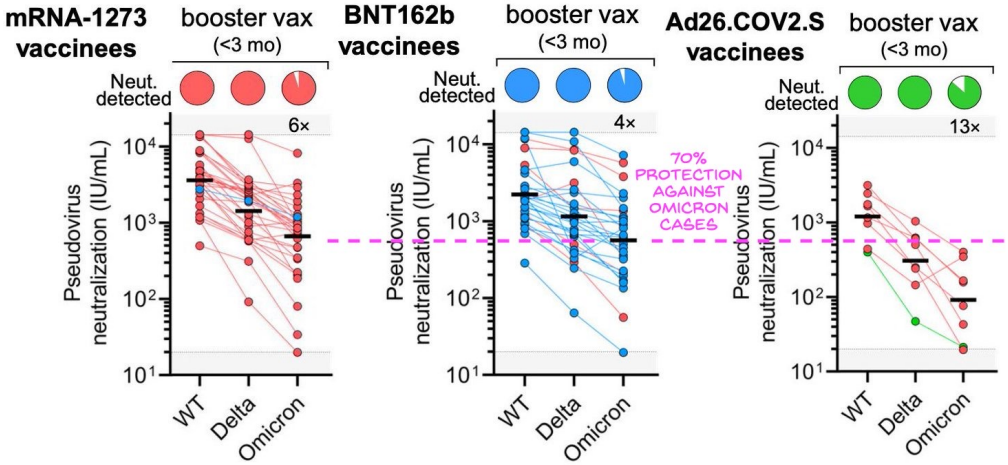
Omicron

- Greek letter of the alphabet
- Pronunciation – “Oh-muh-kron”, others
- Why different?
  - Immune evasion
  - Transmissibility
  - Severity
- What does it all mean?



Omicron – Immune evasion

- More than 50 mutations compared with ancestral strain, 30 in spike region – will lead to spike gene target failure in some PCR assays
- Has substantial implications for reinfection, vaccine effectiveness, and monoclonal antibody therapy
- Reinfections reportedly 2x higher in South Africa than previously
- Breakthrough cases also higher – partially protected by 3rd vaccine dose > J&J



Omicron – Neutralization by monoclonal antibodies

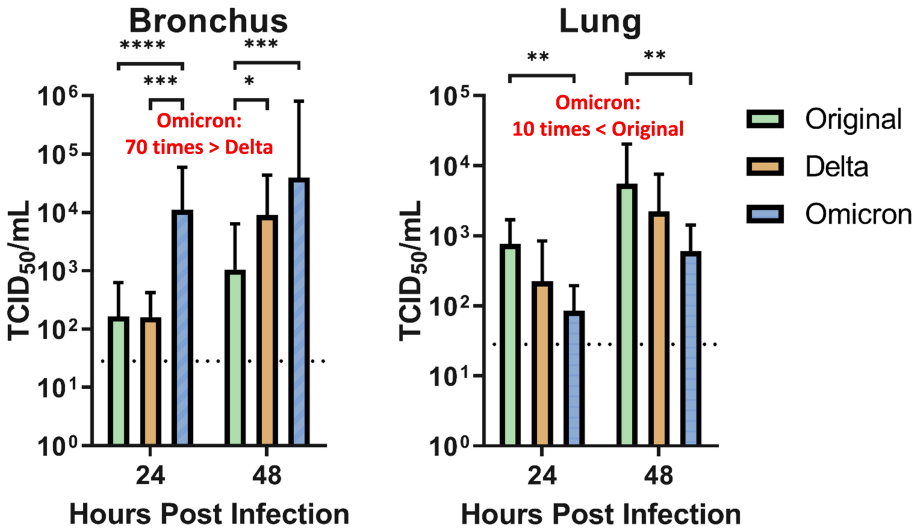
		IC_{50} (ng/mL)		
mAb	Developer	Ancestral (A.2.2)	Omicron (B.1.1.529)[1]	Fold-change
Sotrovimab	Vir Biotechnology / GSK	372	1059	2.8
Casirivimab	Regeneron	27	nn (to 1ug/mL)	N/A
Imdevimab	Regeneron	25	nn (to 1ug/mL)	N/A
Bamlanivimab	AbCellera Biologics / Eli Lilly	32	nn (to 10ug/mL)	N/A
Cilgavimab	Astra Zeneca	18	nn (to 1ug/mL)	N/A
Tixagevimab	Astra Zeneca	47	3490	73.8
Ab-3467	Burnett et al. [7]	502	nn (to 10ug/mL)	N/A

[1] *nn, non-neutralising at highest concentration tested*

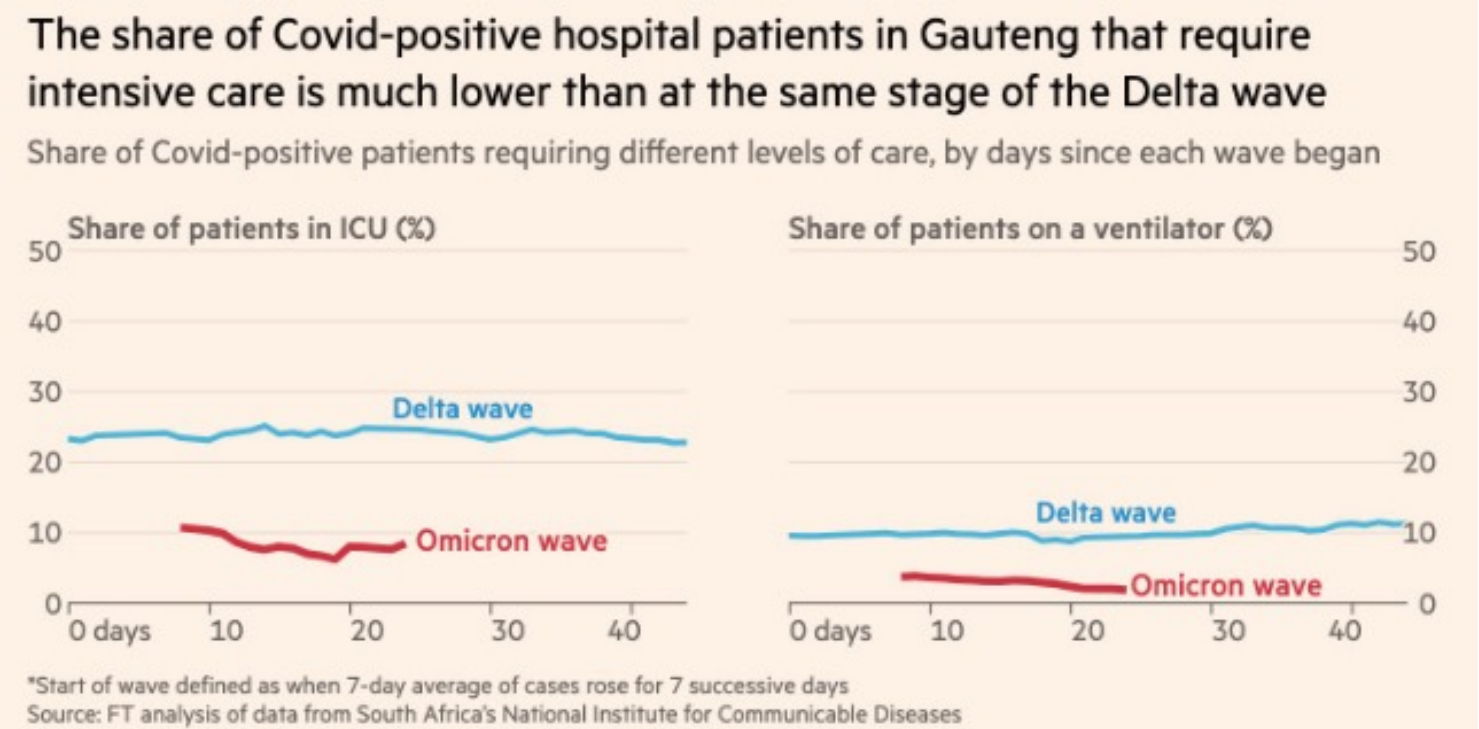
Table 2: Neutralisation of SARS-CoV-2 omicron variant by commercially developed monoclonal antibodies and the class 4 Ab-3467.

Omicron – Transmissibility

- Steep growth curves in all regions Omicron has entered
- Superspreader events occurring among vaccinated people
- Transmission in Hong Kong hotel despite isolation
- Growth of Omicron 70X faster in bronchus cells than delta – but slower in lungs



Omicron – Severity



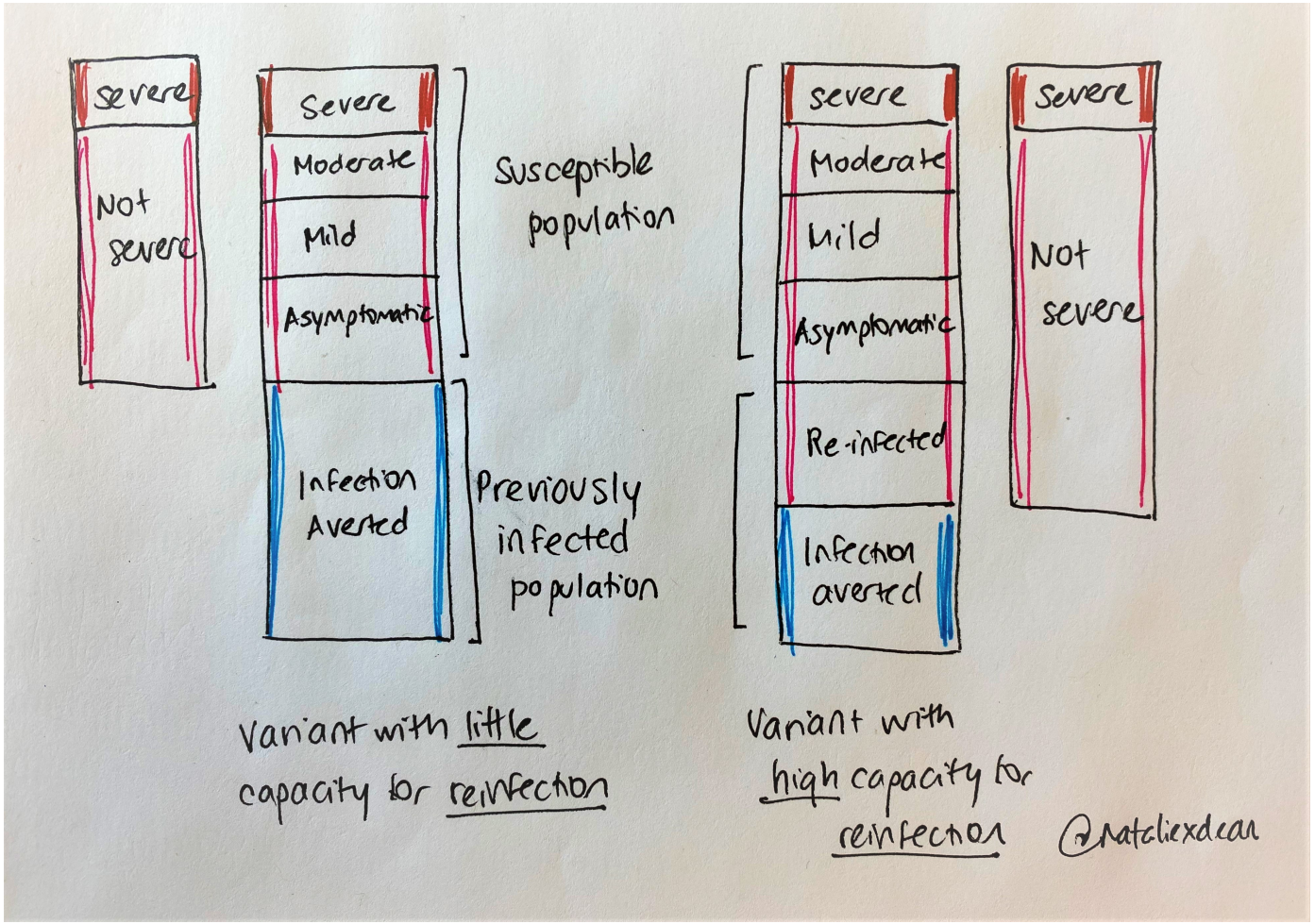


Figure: Natalie Dean, PhD

Omicron – What does it all mean?

✓Immune evasion

Get boosted – 4-month interval rather than 6?

Don’t rely on monoclonal antibody treatments

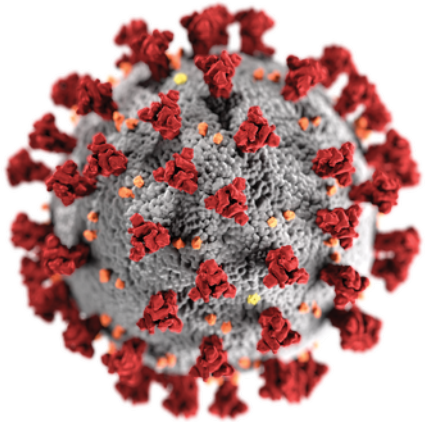
✓Transmissibility

Enhance our non-pharmaceutical interventions – ventilation and indoor masking, improve quality of masks, rapid testing

Severity of Omicron vs prior variants unknown – confounded by prior immunity

COVID-19: Outline

- What happened over the past 12 months?
- **What's new right now?**
  - Omicron
  - **Antiviral therapy**

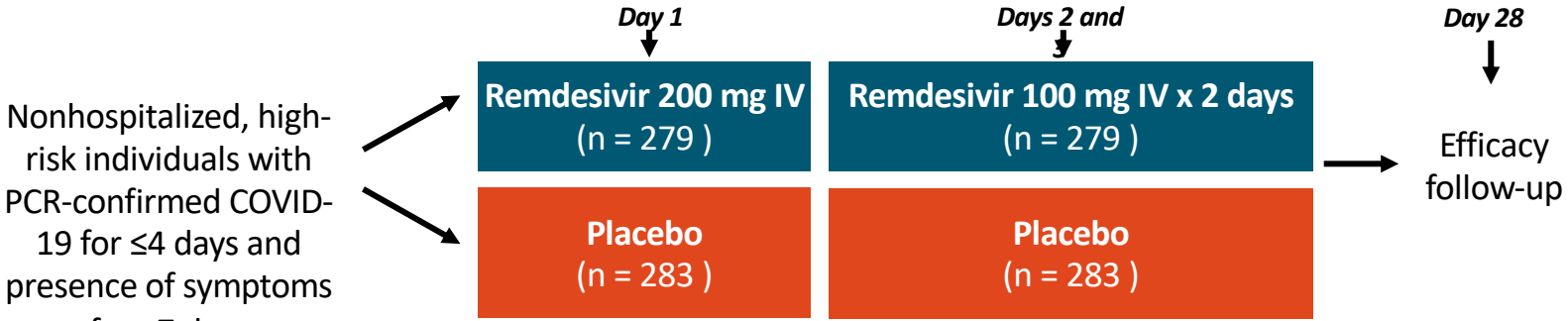


Antiviral therapy

- Outpatient remdesivir
- Molnupiravir
- Nirmatrelvir plus ritonavir (Paxlovid)

PINETREE: Remdesivir in outpatients

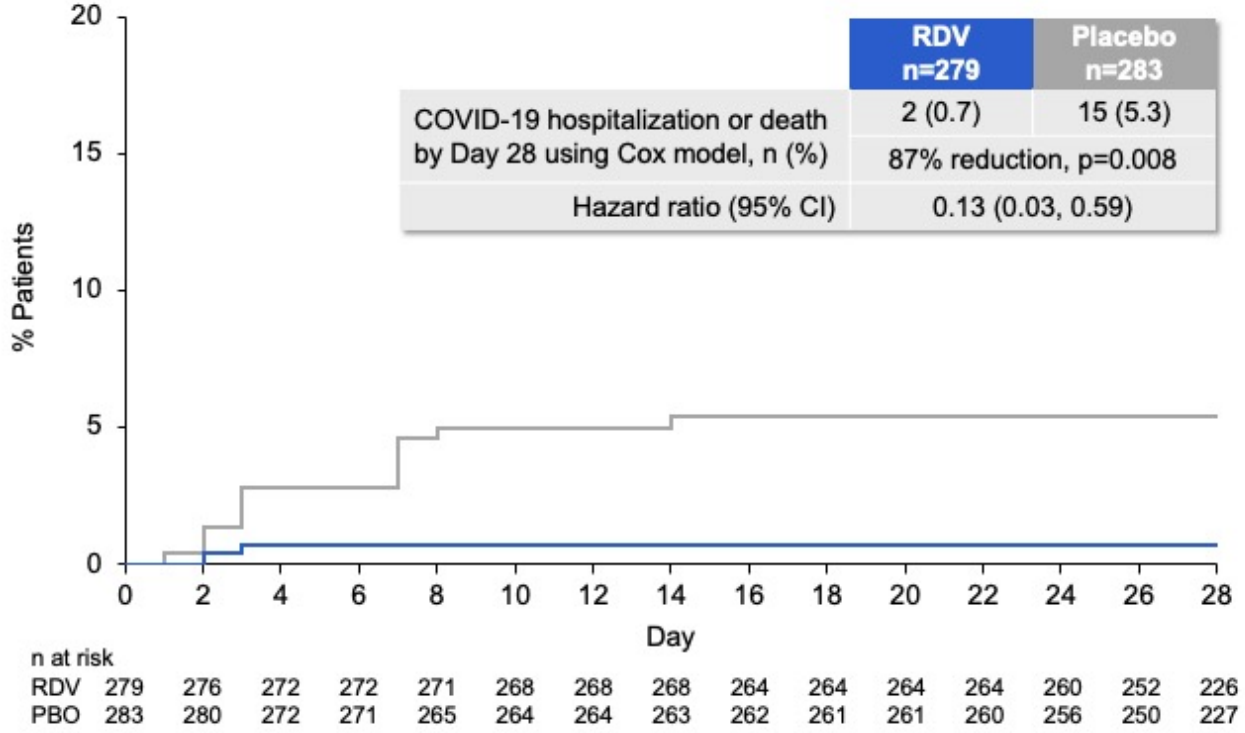
- Randomized, double-blind, placebo-controlled phase III trial at 64 sites in US, Spain, Denmark, and UK



*Study enrollment was terminated early for administrative reasons (slowing enrollment); 562 patients received ≥1 dose of study drug.

- Primary efficacy endpoint: composite COVID-19 hospitalization or all-cause mortality by Day 28
- Primary safety endpoint: proportion with treatment-emergent adverse events

Hill. IDWeek 2021. Abstr LB1.



- No death occurred in either group by Day 28

Hazard ratio, 2-sided 95% CI, and p-value estimated using Cox regression with baseline stratification factors as covariates.

Implications of PINETREE study

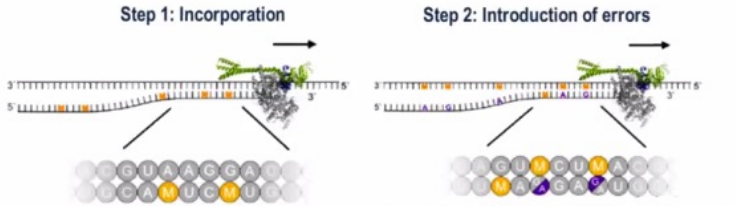
- Outpatient remdesivir could fill the gap left by ineffective monoclonal antibodies in the face of Omicron
- Problem: How to do it?
  - Virtually zero experience in clinical practice
  - Patients maximally infectious
  - Setting up IV therapy rapidly a major challenge
  - Three days required

Molnupiravir

- Oral ribonucleotide pro-drug
- Inhibits SARS-CoV-2 replication by inducing RNA mutagenesis
- Two unsuccessful studies in inpatients – MOVE-IN study and second trial conducted in India
- MOVE-OUT study results led to 13-10 vote by FDA advisory committee, and approval in Great Britain

Molnupiravir (MOV)

RNA analogue pro-drug
-> N-hydroxycytidine (NHC)



https://www.fda.gov/media/154421/download

MOVe-OUT Phase 3 Study

- Outpatients, O2 sat ≥93%,
  - One or more risk factors for severe COVID including age>60, obesity, diabetes, CAD
  - Unvaccinated (20% Ab+)
- Symptom onset w/in 5 days
  - ≈ 50% with symptom onset ≤3d
- 800mg BID x 5 days vs Placebo
- Generally well tolerated
- Activity across variants (Gamma, Delta, Mu)
- Interim analysis-> early termination

Interim analysis (n=762, mITT)

	Hospitalization or death	Relative Reduction
MOV	28/385 **(7.3%)** 0 Deaths	**48%** **(p=0.0012)**
Placebo	53/377 **(14%)** 8 deaths	

Full data set (n=1433, mITT)

	Hospitalization or death	Relative Reduction
MOV	48/709 **(6.8%)** 1 Death	**30%** **(p=0.02)**
Placebo	68/699 **(9.7%)** 9 deaths	

Merck Press releases 10/1/2021, 11/26/2021, Johnson MG et al, ASTMH, Nov 17-21, 2021, 11/30/2021 FDA briefing

Molnupiravir – What are the concerns?

- Why did efficacy drop in full analysis?
- How can we ensure prompt diagnosis and treatment?
- Safety – conflicting in vitro data on mutagenesis
  - Restriction on use in pregnancy or during breastfeeding expected
  - What about male sexual partners of women who may conceive?

Nirmatrelvir

- Oral protease inhibitor boosted with ritonavir, “Paxlovid”
- 3 tablets (2 x 150 mg NRM, 1 x 100 RTV)) twice daily x 5 days
- Studied in three trials
  - Higher risk outpatients, unvaccinated
  - Standard risk patients
  - Post-exposure prophylaxis
- Results released on first two studies

NIRMATRELVIR?

… that’s almost as bad as bamlanivimab

Nirmatrelvir: EPIC-HR study design

- Eligible
  - Risk factor for severe disease
  - 5 or fewer days of symptoms
  - Unvaccinated
- Randomized to Paxlovid or matching placebos
- Planned to enroll 3000, stopped early due to a highly significant benefit of treatment

Nirmatrelvir: EPIC-HR results

- Hospitalization, PAX vs placebo: 0.7% (5/697) vs 6.5% (44/682), $p<0.0001$
- Death, PAX vs placebo: 0 vs 12
- 88% reduction of risk of hospitalization if treated within 5 days of symptom onset; 94% reduction in study participants 65 or older
- 10-fold viral load reduction with treatment
- Fewer treatment-related adverse events in PAX group

Nirmatrelvir: EPIC-SR study design and results

- “Standard risk” – either unvaccinated with no risk factors for severe disease, or vaccinated with one high-risk factor
- Interim analysis of 80% of enrolled subjects
  - No difference in symptom resolution (primary endpoint)
  - Hospitalization, PAX vs placebo: 0.7% (3/428) vs 2.4% 10/426 (p= 0.051)
  - 10-fold viral load drop with treatment

Nirmatrelvir – What are the concerns?

- Drug interactions
- GI side effects
- Supply
- Need to start therapy within 5 days of symptoms
- How are we going to pronounce this beast of a word?

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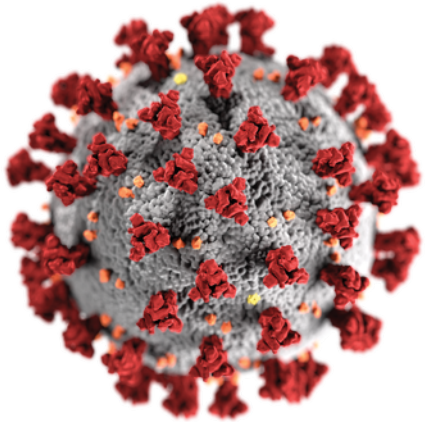
  - **Monoclonal antibodies for prevention and treatment**

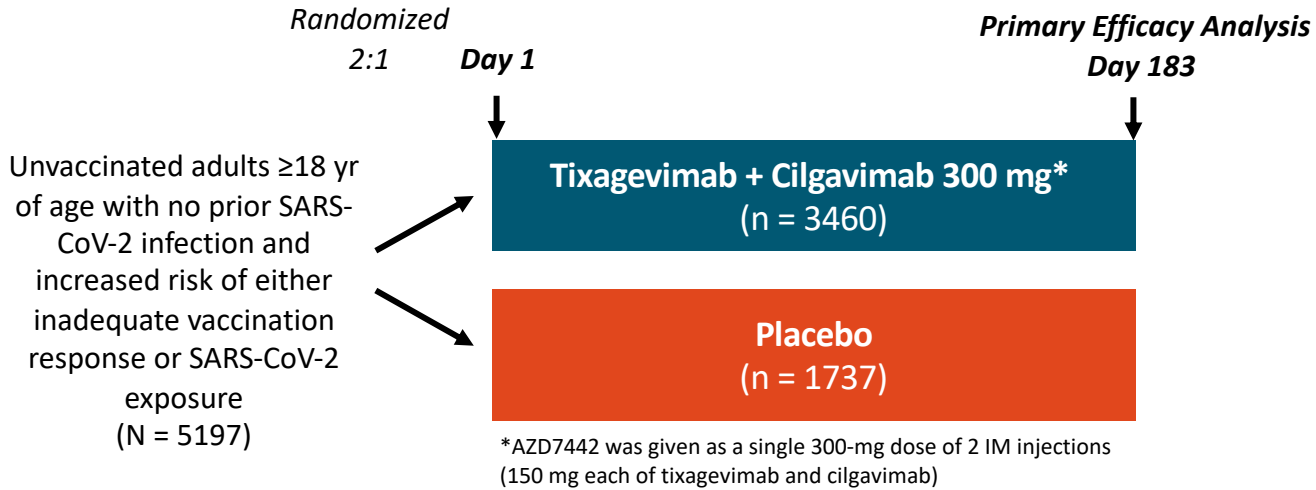


Monoclonal antibodies for prevention and treatment

- PrEP
- PEP
- Treatment of outpatients
- Treatment of inpatients

PROVENT: Tixagevimab + Cilgavimab (AZD7442) as Pre-Exposure Prophylaxis of COVID-19

- Randomized, double-blind, placebo-controlled phase III study of long-acting mAb combination



- Primary endpoints: first SARS-CoV-2 RT-PCR–positive symptomatic illness prior to Day 183, safety

Levin. IDWeek 2021. Abstr LB5.

PROVENT: Results

Outcome	Tixagevimab + Cilgavimab (n = 3441)	Placebo (n = 1731)	Relative Risk Reduction, % (95% CI)	*P* Value
First SARS-CoV-2 RT-PCR–positive **symptomatic illness,*** n (%)	8 (0.2)	17 (1.0)	**77** (46.1-90.0)	<.001

*Censored at unblinding and/or treatment with any COVID-19 preventive product (full pre-exposure analysis set).

Paul Sax 
@PaulSaxMD

Monoclonal PrEP for Covid19 has huge implications for people who are immunosuppressed -- many of whom have been living very isolated lives since the pandemic started, and cannot be guaranteed protection from our current vaccines.

h/t @LCalabreseDO

fda.gov
Coronavirus (COVID-19) Update: FDA Authorizes New Long-Acting Monoclo...
The FDA authorized new long-acting monoclonal antibodies for the pre-exposure prevention of COVID-19 in certain adults and pediatric individuals.

4:15 PM · Dec 8, 2021 · Twitter Web App

Omicron – Neutralization by monoclonal antibodies

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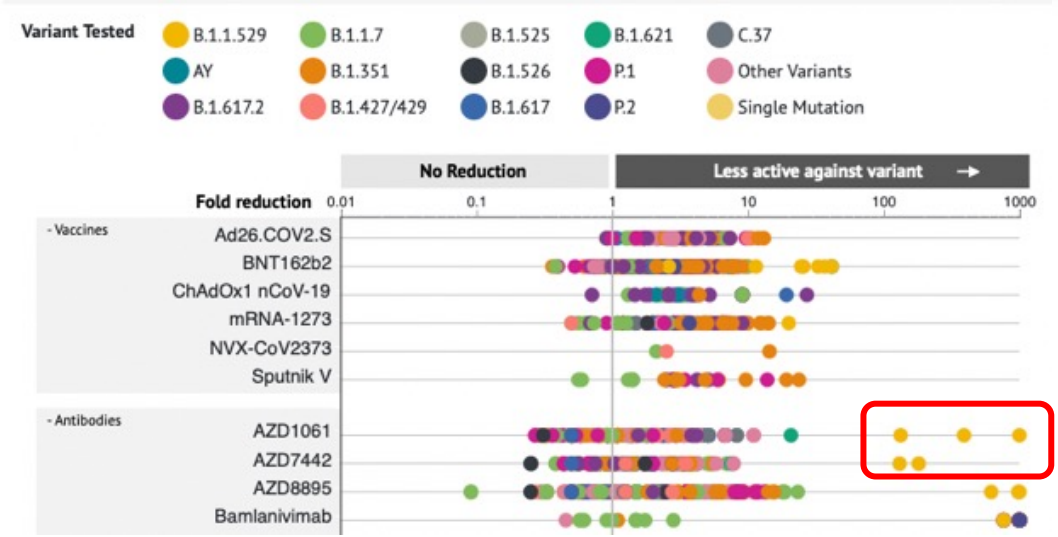
Table 2: Neutralisation of SARS-CoV-2 omicron variant by commercially developed monoclonal antibodies and the class 4 Ab-3467.

Evusheld long-acting antibody combination retains neutralising activity against Omicron variant in independent FDA study

PUBLISHED
16 December 2021



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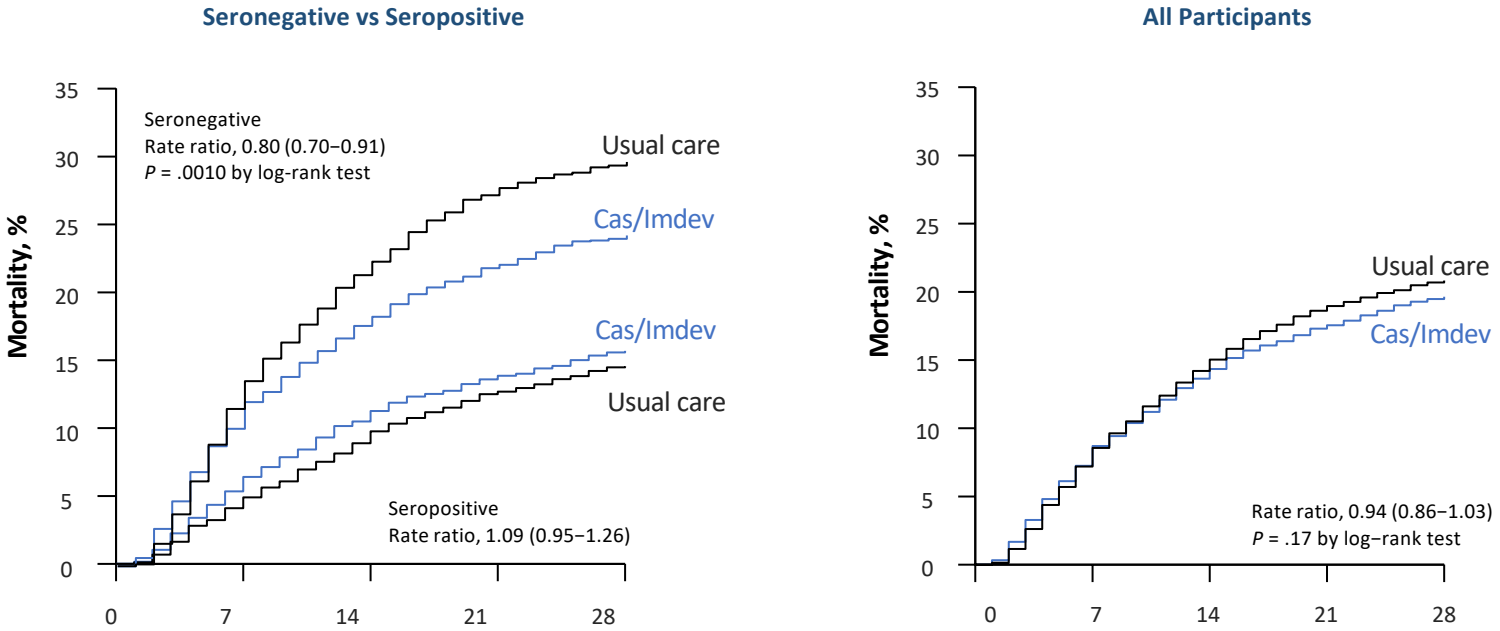
RECOVERY: Casirivimab/imdevimab for **inpatients** with COVID-19 improved survival for seronegatives



Among seronegative patients, casirivimab/imdevimab monoclonal antibody therapy reduced deaths by 20% (*P* = .001)

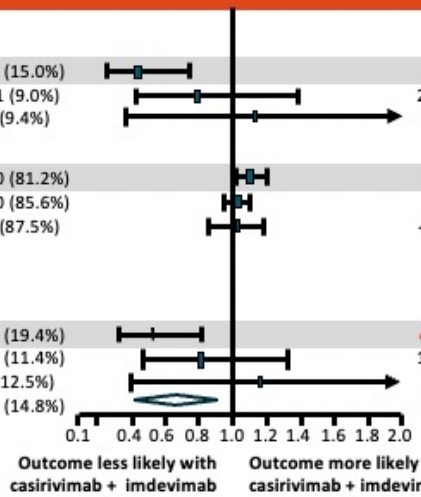
UK, United Kingdom. RECOVERY Collaborative Group, et al. *medRxiv* [Preprint]. 2021.06.15.21258542.

Casirivimab + Imdevimab for Hospitalized Patients With COVID-19: Virologic and Clinical Efficacy

- In mFAS*, casirivimab + imdevimab reduced:
  - Viral load by Day 7 in seronegative patients vs placebo (LS mean change -0.28 $\log_{10}$ copies/mL; SE 0.12; *P* =.017)
  - **Risk of death or mechanical ventilation on Days 1-29 vs placebo in:**
    - **Seronegative patients (RRR 47.0%; *P* =.006†)** and overall population (RRR 30.9%; *P* =.021†)

Clinical Outcomes in Patients Hospitalized With Low Flow/No Supplemental Oxygen*

Outcome:	Casirivimab + Imdevimab Groups	Placebo	Relative Risk (95% CI)	Relative Risk Reduction (95% CI)	*P* Value (Nominal)
Death Within 28 days					
▪ Seronegative	24/360 (6.7%)	24/160 (15.0%)		55.6% (24.2%, 74%)	0.003
▪ Seropositive	26/369 (7.0%)	18/201 (9.0%)		21.3% (-40.0%, 55.8%)	0.315
▪ Sero-unknown	9/75 (12.0%)	3/32 (9.4%)		-28.0% (NA%, 62.9%)	1.000
Discharged Alive					
▪ Seronegative	324/360 (90.0%)	130/160 (81.2%)		-10.8% (-20.2%, -2%)	0.007
▪ Seropositive	323/369 (87.5%)	170/210 (85.6%)		-2.3% (-9.6%, 4.5%)	0.364
▪ Sero-unknown	67/75 (89.3%)	28/32 (87.5%)		-2.1% (-18.9%, 12.3%)	0.749
Death or Mechanical Ventilation					
▪ Seronegative	37/360 (10.3%)	31/160 (19.4%)		**47.0%** (17.7%, 65.8%)	**0.006**
▪ Seropositive	34/369 (9.2%)	23/201 (11.4%)		19.5% (-32.8%, 51.2%)	0.301
▪ Sero-unknown	11/75 (14.7%)	4/32 (12.5%)		-17.3% (NA, 59.6%)	1.000
▪ **Overall**	82/804 (10.2%)	58/393 (14.8%)		**30.9%** (5.4%, 49.5%)	**0.021**



***Modified full analysis set: both dose groups (2.4 g IV and 8.0 g IV) and on low flow or no supplemental oxygen (n = 804).** †Nominal *P* value.

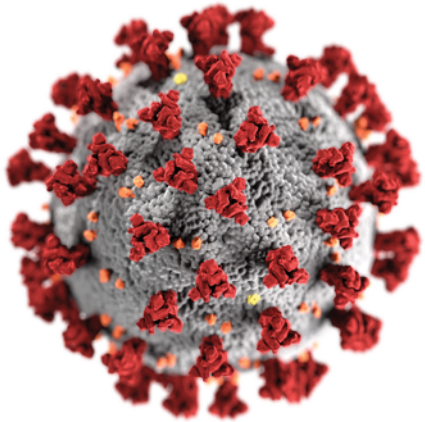
Mylonakis. IDWeek 2021. Abstr LB4.

Inpatient monoclonal antibody treatment: Not yet, but soon?

- Despite benefits seen in seronegative participants in RECOVERY trial, inpatient therapy not yet available
- Dose higher than outpatient trials – uncertain what recommended inpatient dose might be
- Possible signal of harm for seropositives
- Variants (esp Omicron) might make this all moot
- To implement:
  - Change in emergency use authorization EUA
  - On-site anti-spike antibody testing with rapid turnaround
  - Wider distribution to inpatient pharmacies

COVID-19: Outline

- What happened over the past 12 months?
- **What's new right now?**
  - Omicron
  - Antiviral therapy
  - Monoclonal antibodies for prevention and treatment
  - **Repurposed drugs**



Repurposed drugs

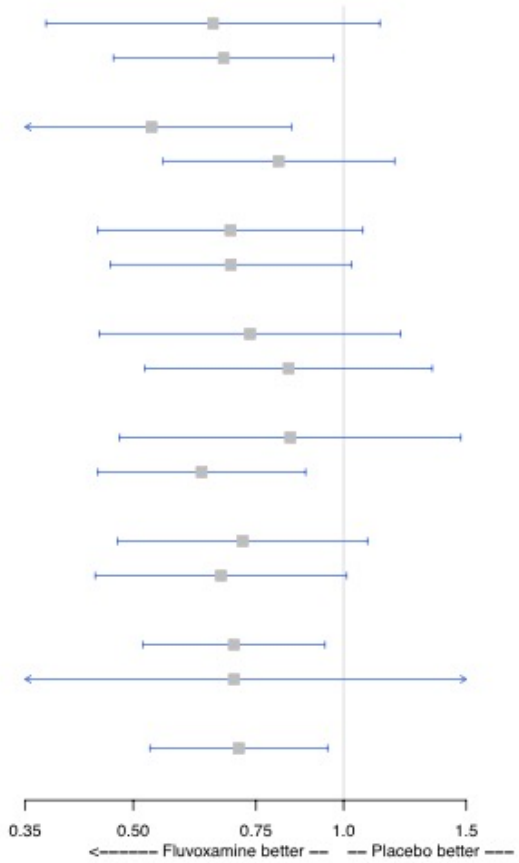
- Fluvoxamine
- Ciclesonide

TOGETHER Trial: Fluvoxamine for mild-moderate COVID-19

- Placebo-controlled trial in adults with COVID-19 and at least 1 risk factor for severe disease randomized to fluvoxamine 100 mg twice daily or placebo
- Primary endpoint: ER observation > 6h or hospitalization
- Results
  - RR of endpoint 0.71 for fluvoxamine (95% CI 0.54-0.93); 0.36 if taking 80% or more of medication
  - Per-protocol analysis of deaths, fluvoxamine vs placebo: 1 vs 12
  - Results consistent across subgroups

Reis G, et al. Lancet Global Health 2021.

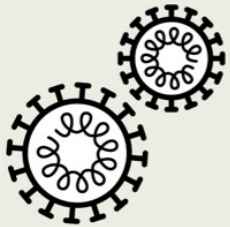
Subgroup	N Placebo (N events)	N Treatment (N events)	HR [95% CI]
Age (years)			
<=50	367 (32)	367 (21)	0.65 [0.38; 1.13]
>50	318 (70)	324 (50)	0.67 [0.47; 0.97]
Sex			
Female	438 (53)	407 (27)	0.53 [0.33; 0.84]
Male	295 (55)	330 (50)	0.81 [0.55; 1.18]
BMI (kg/m2)			
<30	360 (49)	354 (34)	0.69 [0.44; 1.07]
>=30	359 (58)	371 (42)	0.69 [0.46; 1.03]
Time from onset of symptoms			
0–3 days	296 (35)	317 (28)	0.73 [0.45; 1.21]
4–7 days	249 (38)	241 (31)	0.83 [0.52; 1.34]
Diabetes mellitus			
N	365 (27)	354 (22)	0.84 [0.48; 1.47]
Y	367 (81)	382 (55)	0.63 [0.44; 0.88]
Cardiovascular disease			
N	444 (54)	442 (39)	0.72 [0.48; 1.08]
Y	289 (54)	295 (38)	0.67 [0.44; 1.01]
Lung disease			
N	711 (102)	716 (73)	0.70 [0.52; 0.94]
Y	21 (6)	20 (4)	0.70 [0.20; 2.47]
Use of corticoid therapy			
N	724 (106)	729 (77)	0.71 [0.53; 0.95]
Y	7 (1)	6 (0)	



RCT: Efficacy of Inhaled Ciclesonide for Outpatient Treatment of Symptomatic COVID-19

POPULATION

179 Males, 221 Females



Nonhospitalized adolescents and adults with symptomatic COVID-19

Mean (range) age, 43 (13-87) y

SETTINGS / LOCATIONS

10 Sites in the US

INTERVENTION

400 Participants randomized

197 Ciclesonide MDI
Ciclesonide metered dose inhaler (MDI), 160 µg per actuation, 2 actuations twice daily for 30 d

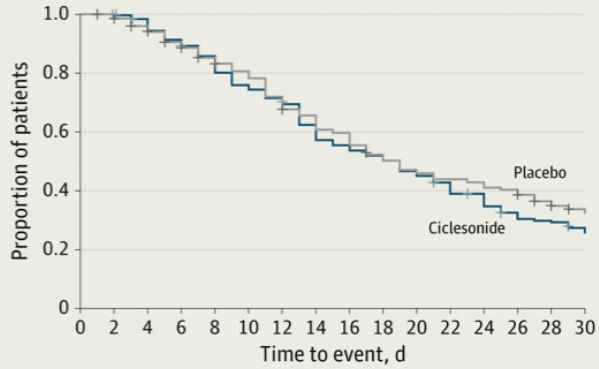
203 Placebo MDI
Placebo MDI, 2 actuations twice daily for 30 d

PRIMARY OUTCOME

Time to alleviation of COVID-19–related symptoms, defined as days until complete absence of symptoms for ≥24 h as recorded in an electronic symptom diary

FINDINGS

No significant difference in time to alleviation of COVID-19–related symptoms with the use of ciclesonide MDI vs placebo MDI



Median time to alleviation of COVID-19–related symptoms:

Ciclesonide MDI: 19.0 (95% CI, 14.0-21.0) d

Placebo MDI: 19.0 (95% CI, 16.0-23.0) d

Clemency BM, Varughese R, Gonzalez-Rojas Y, et al. Efficacy of inhaled ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. *JAMA Intern Med.* Published online November 22, 2021. doi:10.1001/jamainternmed.2021.6759

Table 2. Secondary Efficacy Outcomes

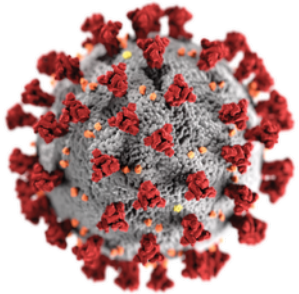
Secondary efficacy end point	No. (%) Ciclesonide (n = 197)	No. (%) Placebo (n = 203)	Results, ciclesonide vs placebo, OR (95% CI)	*P* value
Participants with subsequent emergency department visit or hospital admission for reasons related to COVID-19 by day 30, %	2 (1.0)	11 (5.4)	0.18 (0.04-0.85)	.03
Participants with hospital admission or death by day 30, %[a]	3 (1.5)	7 (3.4)	0.45 (0.11-1.84)	.26
All-cause mortality by day 30	0	0	NA	NA
COVID-19-related mortality by day 30	0	0	NA	NA
Participants with alleviation of COVID-19-related symptoms by day 7, %	28 (14.2)	29 (14.3)	0.92 (0.51-1.66)	.79
Participants with alleviation of COVID-19-related symptoms by day 14, %	81 (41.1)	76 (37.4)	1.19 (0.78-1.81)	.43
Participants with alleviation of COVID-19-related symptoms by day 30, %	139 (70.6)	129 (63.5)	1.28 (0.84-1.97)	.25

	Molnupiravir (Merck)	Paxlovid (Pfizer)	Fluvoxamine
Efficacy in high-risk patients, reduction of hospitalizations/deaths at 28 days	30% 9.7% vs 6.8%	88% 6.5% vs 0.8%	26% 64% if took >80% of medicine
Deaths in placebo vs. drug	9 vs.1	12 vs. 0	12 vs. 1 who took medicine
N	1418 mITT	2085 mITT	2196 ITT
Duration of therapy (twice daily)	5 days	5 days	10 days
Published Double-Blind Randomized Placebo-Controlled Trials	0	0	2
Drug interactions (CYP3A4)	Minimal	Yes, such as statins, blood thinners	Yes, such as caffeine, statins, blood thinners
Repurposed	Yes, Equine encephalitis Planned to test for RSV, influenza, redirected	No, Covid specific New chemical entity adapted from an anti-SARS molecule	Yes, SSRI antidepressant - >25 years of safety data
Mechanism	Nucleoside analog; Induces mutations	Inhibits Mpro, not mutagenic	Anti-inflammatory, sigma-1 receptor.
Given with co-drug to promote half-life	No	Yes, ritonavir	No
Cost	~$710	~$529	$5
Available Today?	No	No	Yes

David Boulware

Take-home points: COVID-19 treatment

- Omicron arrival will likely greatly increase case numbers
- Protection against severe disease likely with vaccination (especially 3 doses) and/or prior infection
- Activity of monoclonal antibodies aside from sotrovimab uncertain
- Remdesivir efficacy best in early, outpatient therapy – how to operationalize?
- Nirmatrelvir highly promising
- Fluvoxamine, inhaled ciclesonide may have role



THANK YOU!