SARS-COV-2: LA TERAPIA ANTIVIRALE

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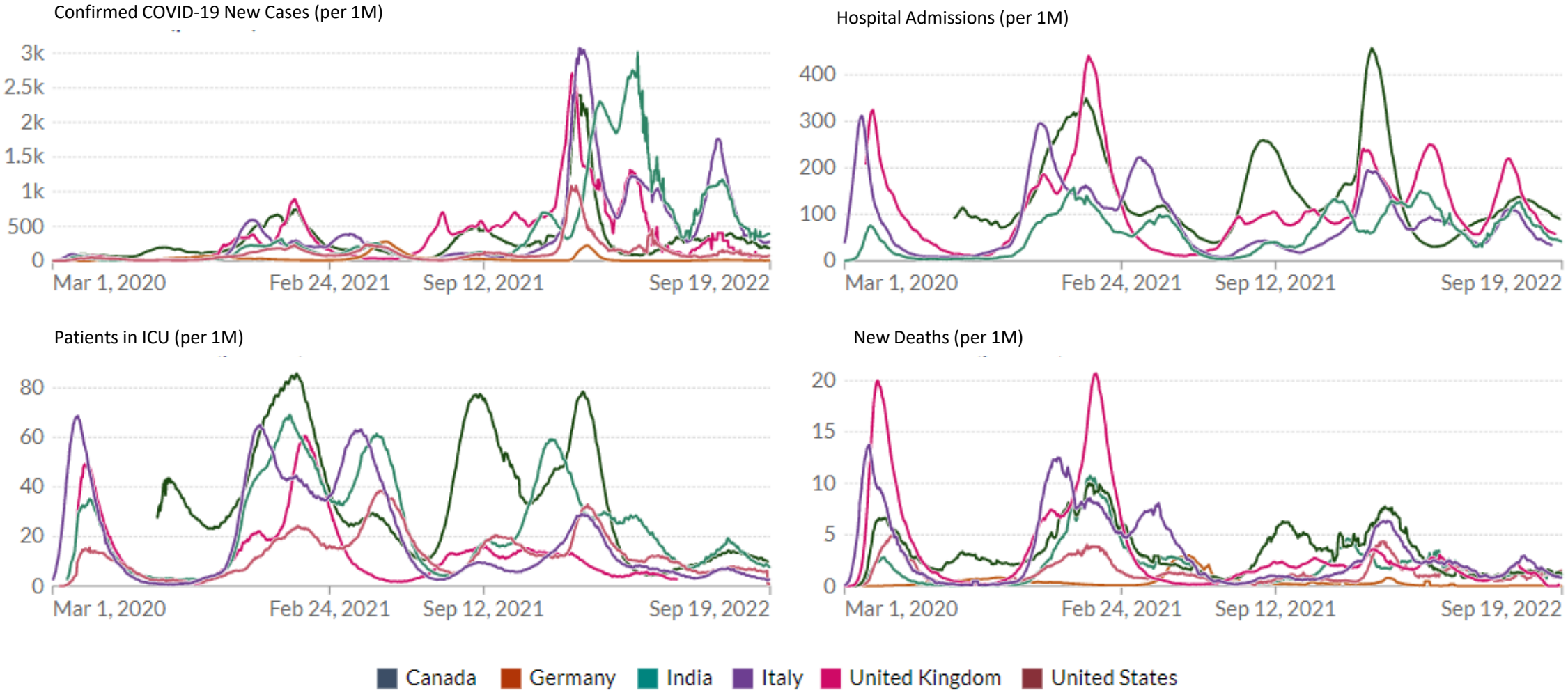
Disclosures

I have received funding for membership of Advisory Boards, for the preparation of educational materials, for research and educational grants, for membership of speaker panels and for support for travel to conferences from the following companies:

- Gilead Sciences
- Janssen-Cilag
- Viiv Healthcare
- Merck Sharp and Dohme
- Abbvie
- Angelini
- Pfizer
- GSK
- Menarini
- Astra-Zeneca

Despite Successful Immunization Strategies, Individuals Continue to test positive, get hospitalized and die



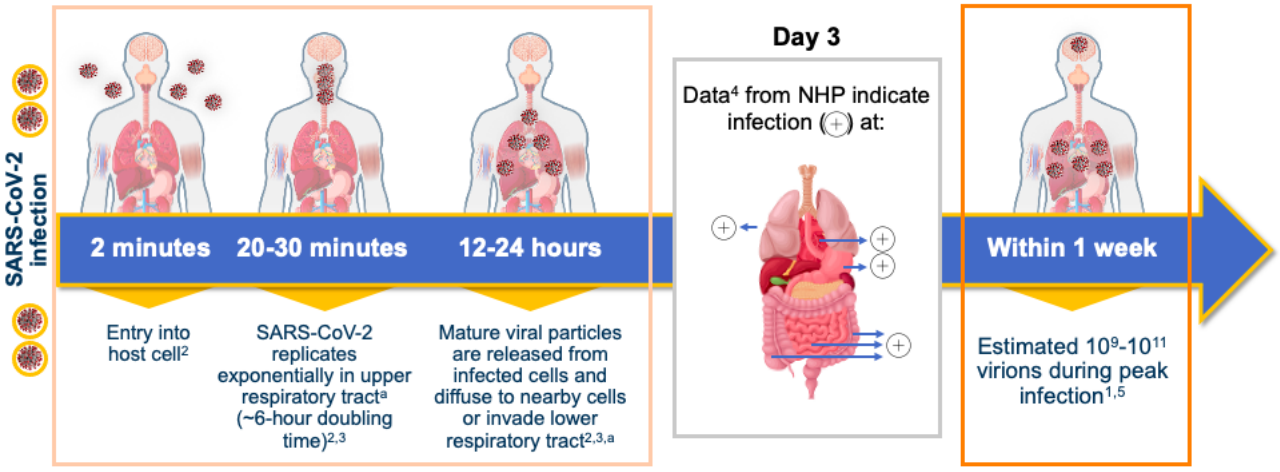
COVID-19 = coronavirus disease 2019; ICU = intensive care unit.

Our World in Data. Confirmed COVID-19 cases, deaths, hospital admissions, and patients in ICU per million people. Our World in Data website.

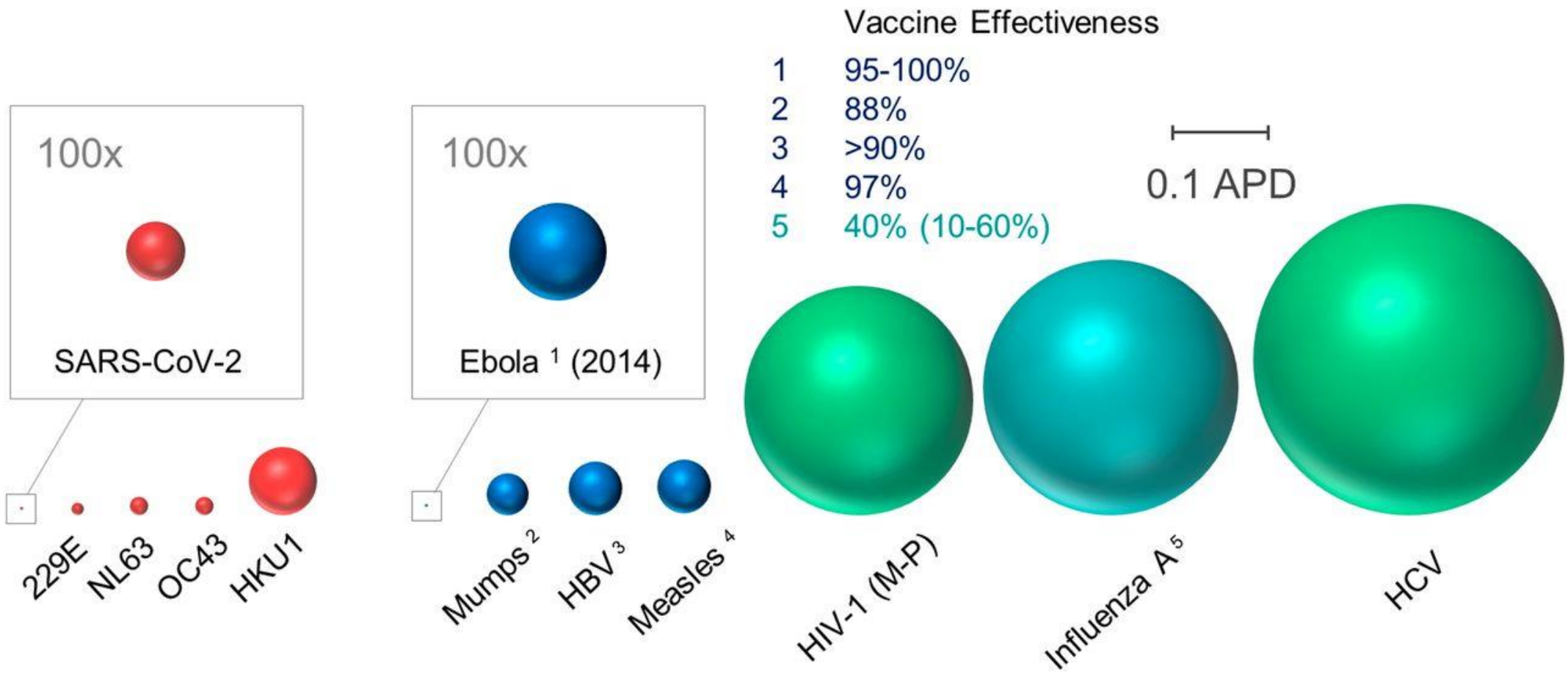
Importanza della Medicina Personalizzata per COVID-19

SARS-Cov-2 non è sempre uguale

Le diverse varianti danno una differente risposta dell'ospite e hanno diversa sensibilità ai farmaci e ai vaccini



SARS-CoV-2 exhibits an extremely low variability respect to others RNA-based viruses



Rausch et al., 2020

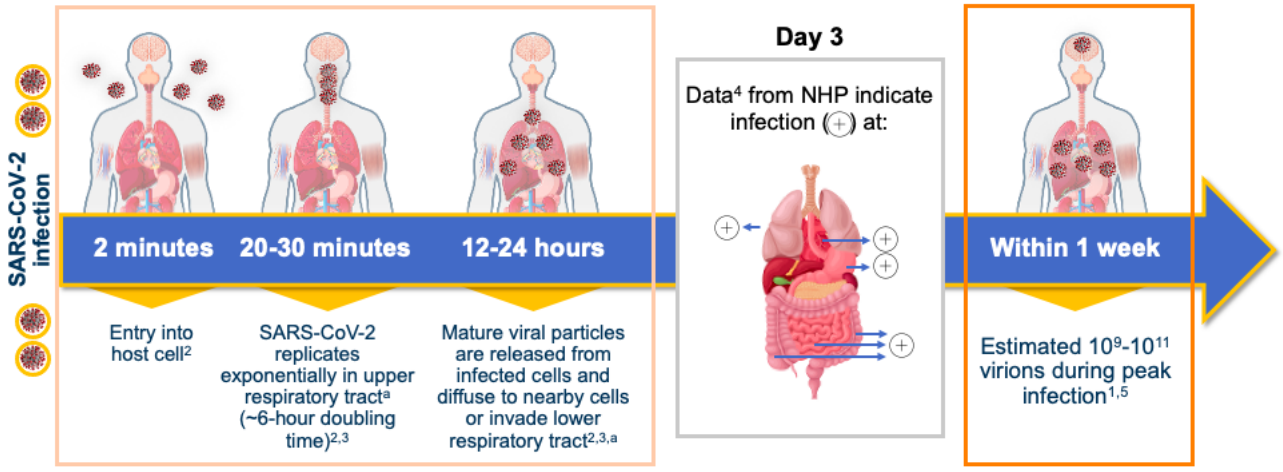
Importanza della Medicina Personalizzata per COVID-19

SARS-Cov-2 non è sempre uguale

Le diverse varianti danno una differente risposta dell'ospite e hanno diversa sensibilità ai farmaci e ai vaccini

L'ospite e la sua risposta non è sempre uguale

L'immunità dei soggetti è variabile, la risposta è diversa in funzione dell'infezione, vaccinazione e profilassi eseguita

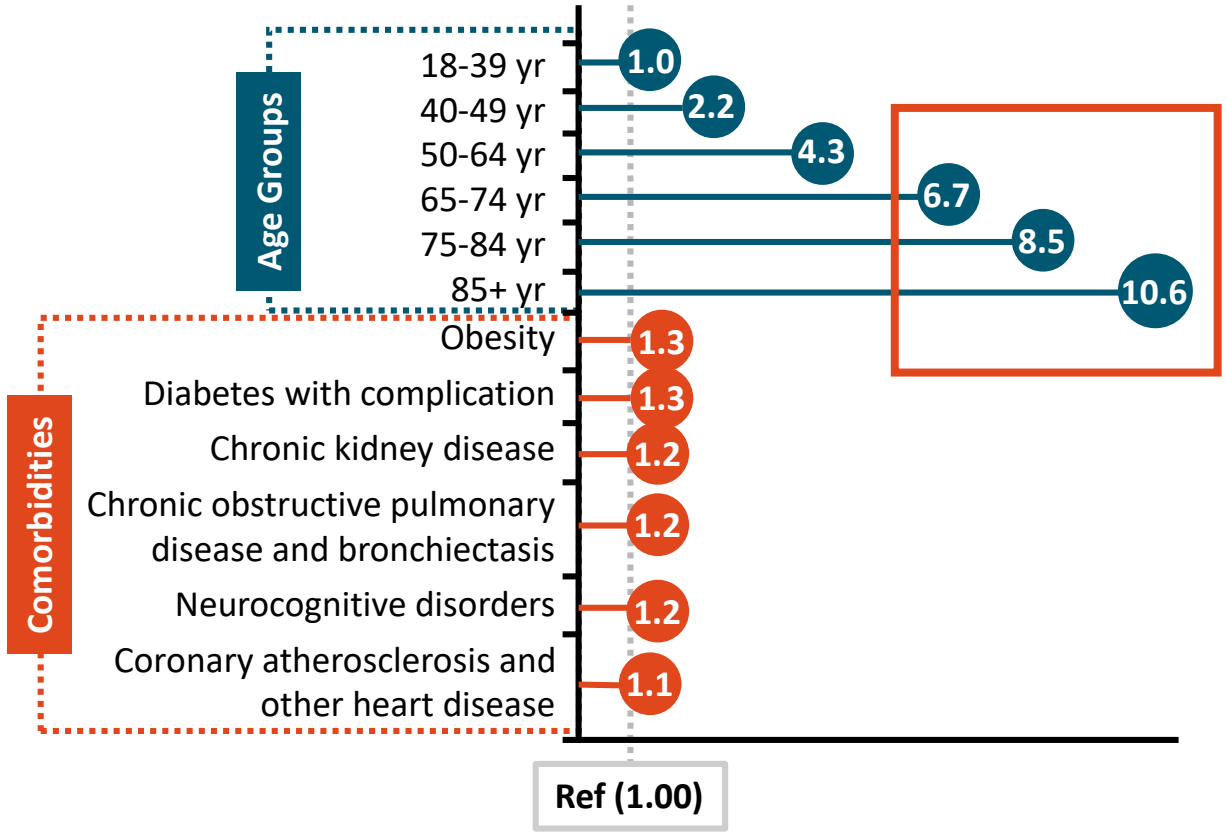


Genetic predispositions

DPP9 and FOXP4 linked to pulmonary fibrosis
Variants at the chemokine receptor genes CXCR6 and CCR9
ABO blood type
Genes involved type I interferon function
Locus 3 related Homo Neanderthal
Auto Ab against type I interferon

Age Is Strongest Risk Factor for Severe COVID-19

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

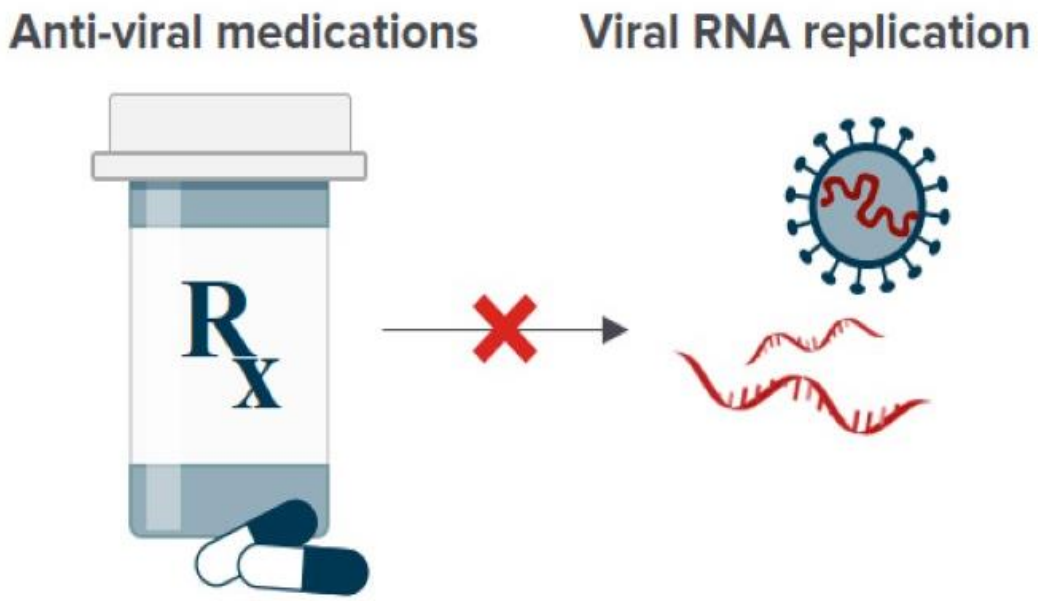


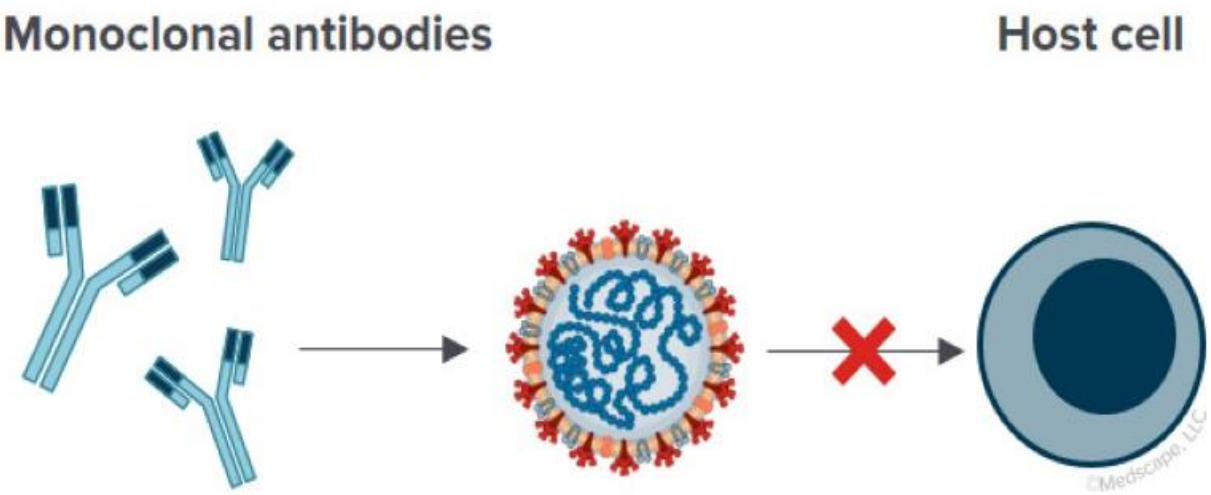
- **EPIC-HR and MOVe-OUT High-Risk Criteria**
  - ≥60 yr of age
  - Chronic pulmonary disease
  - Overweight or obese
  - Chronic kidney disease
  - Cardiovascular disease
  - Neurodevelopmental disorders
  - Medically related technologic dependence
  - Tobacco smoker
  - Immunosuppression
  - Sickle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

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

Slide credit: clinicaleducationalliance.com: cea clinical education alliance

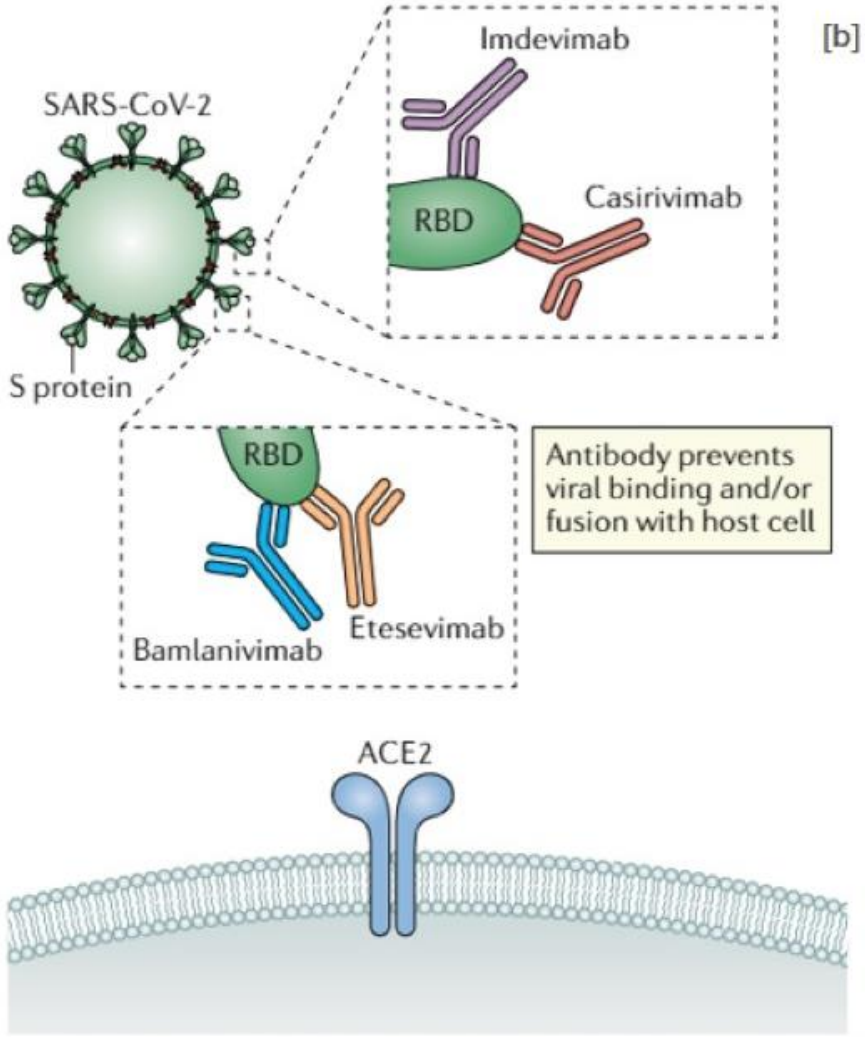
Mechanism of Action of Treatments





Mechanism of Action of mAbs – Casirivimab/Imdevimab

- SARS-CoV-2 encodes 4 structural proteins, including S protein[a]
  - S1 subunit contains the RBD region that makes direct contact with host cell receptor ACE2
    - Interaction between RBD and ACE2 is the first event in SARS-CoV-2 cellular entry
- mAbs target the S protein[b]
  - Bind the ACE2 receptor and stop the virus from entering cells
- Casirivimab and imdevimab[b]
  - Recombinant human IgG1 mAbs that target the RBD of the S protein of SARS-CoV-2



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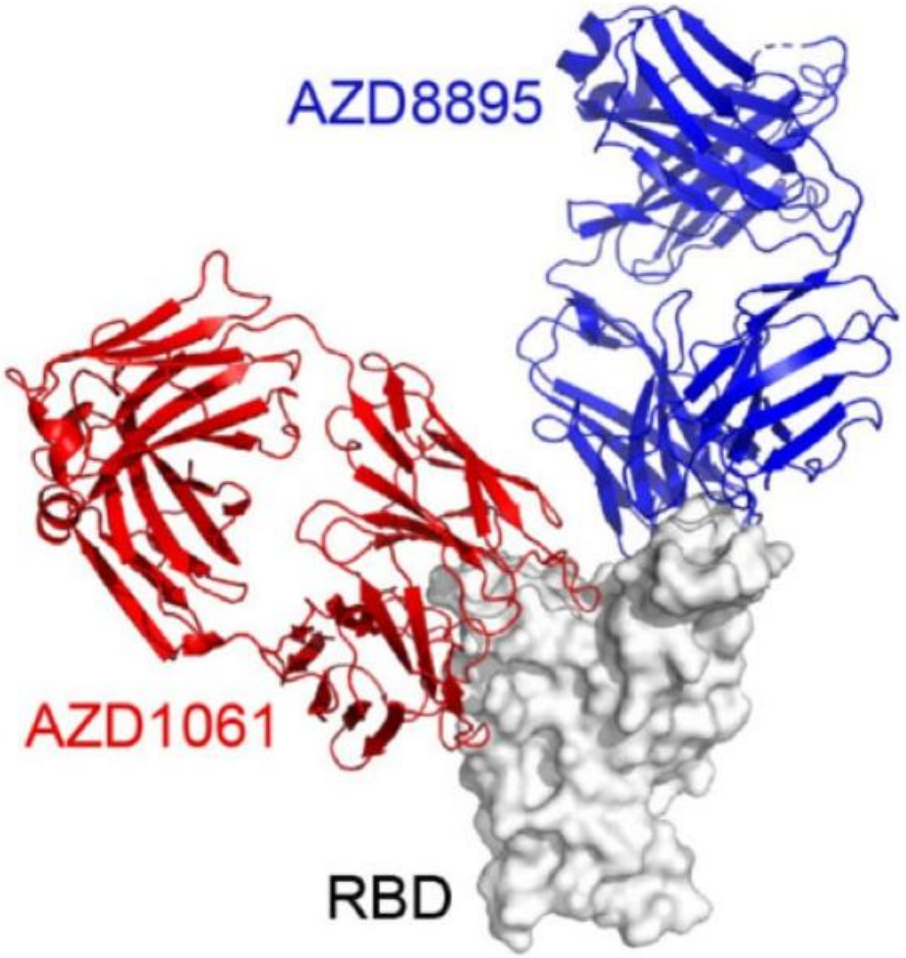
IgG, immunoglobulin G; RBD, receptor-binding domain.

a. Jackson CB, et al. Nat Rev Mol Cell Biol. 2022;23:3-20; b. Taylor PC, et al. Nat Rev Immunol. 2021;21:382-393.

Mechanism of Action of mAbs – Tixagevimab - Gilgavimab

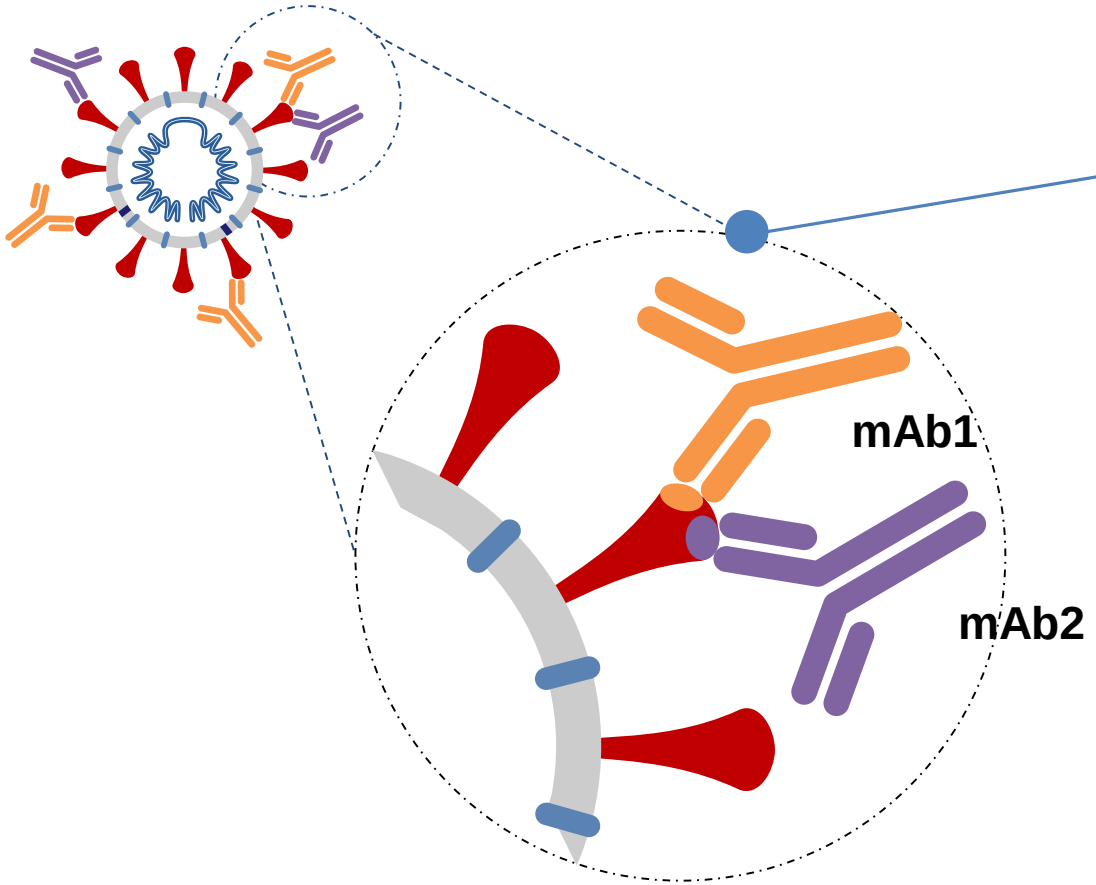


Tixagevimab (AZD8895) and cilgavimab (AZD1061) bind at separate parts of the RBD

Loo Y-M, et al. Sci Transl Med. 2022. [Epub ahead of print].

RBD: rteceptor-binding domain

A highly potent antibody cocktail targeting the SARS-CoV-2 virus



- **Two distinct antibodies bind non-competitively** to the SARS-COV2 spike
- **Prevents virus** from infecting healthy cells
- Using two antibodies **protects against emergence of resistance**

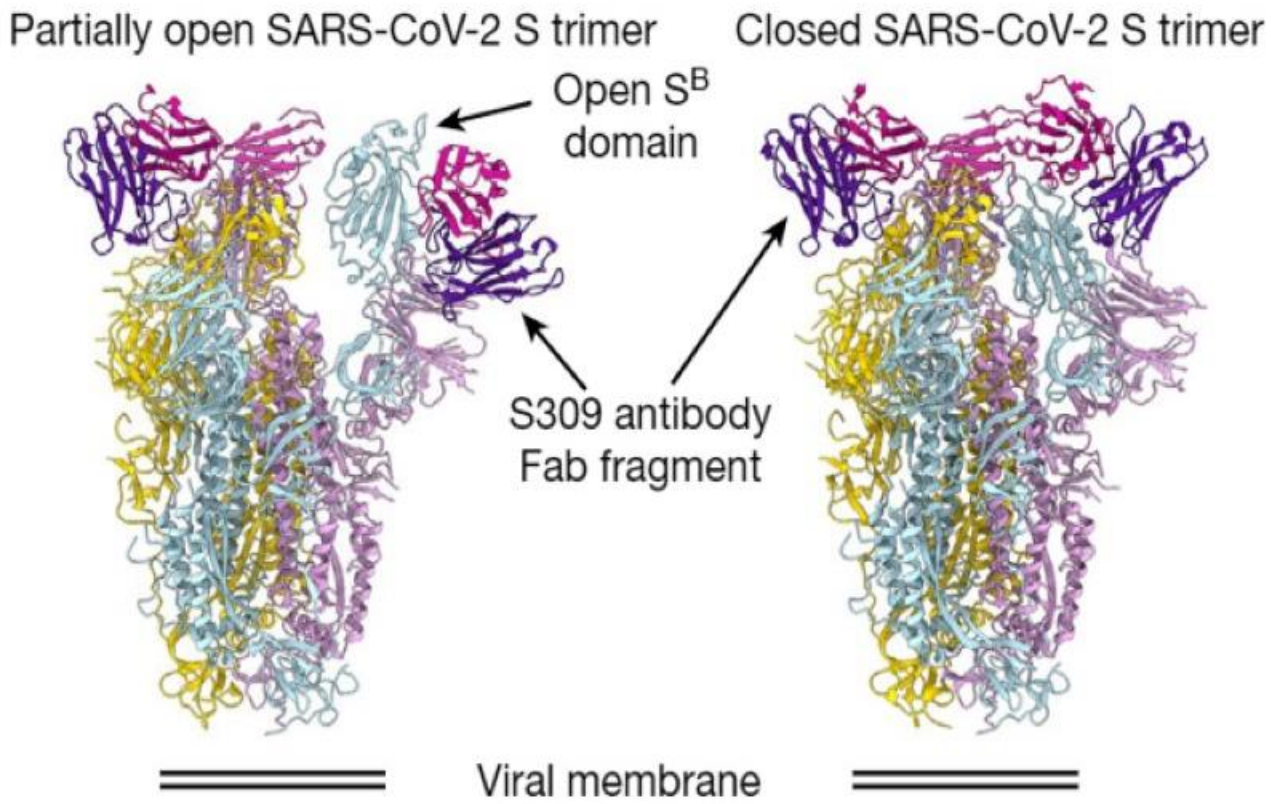
The mAbs bind to nonoverlapping epitopes of the spike protein receptor binding domain (RBD) of SARS-CoV-2, and thereby block binding to the human ACE2 receptor

ACE2: angiotensin converting enzyme 2; mAb: monoclonal antibody

Hansen. Science 2020; Baum. Science 2020; Ho, BioRxiv 2021

Mechanism of Action of mAbs – Sotrovimab

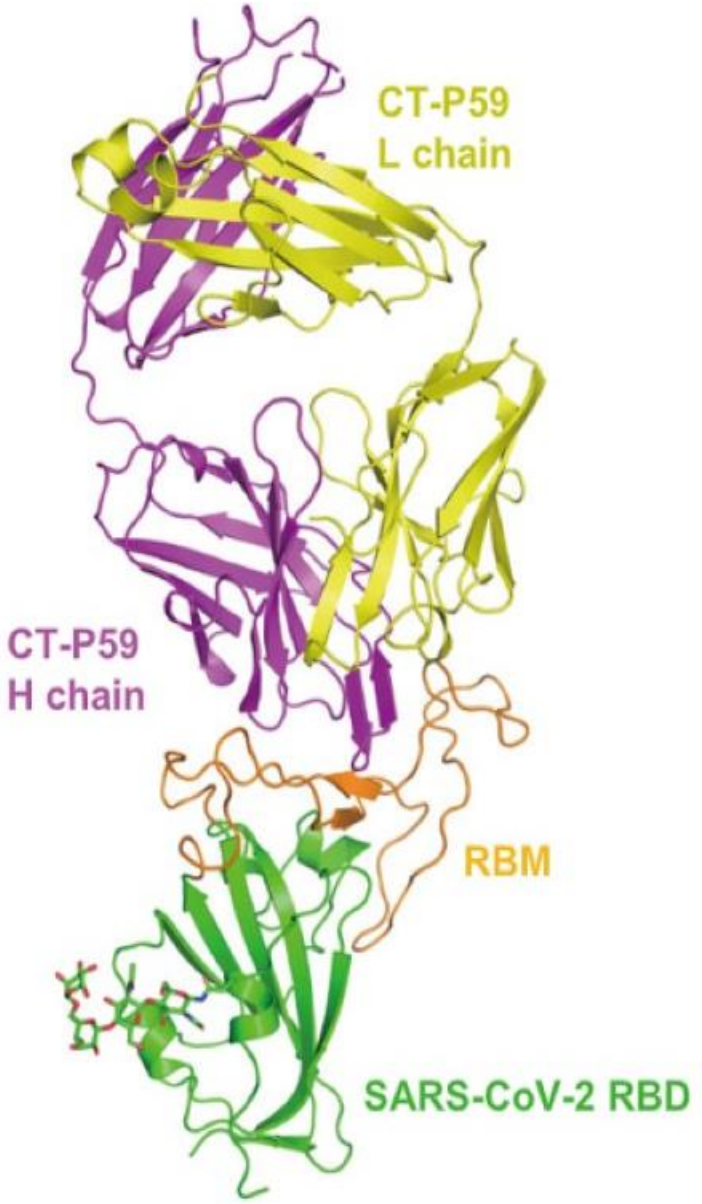
- Sotrovimab is based on the S309 antibody which neutralizes both SARS-CoV-2 and SARS-CoV by targeting a conserved epitope
- Does not target the RBD



Pinto D, et al. Nature. 2020;583:290-295.

Mechanism of Action of mAbs – Regdanvimab

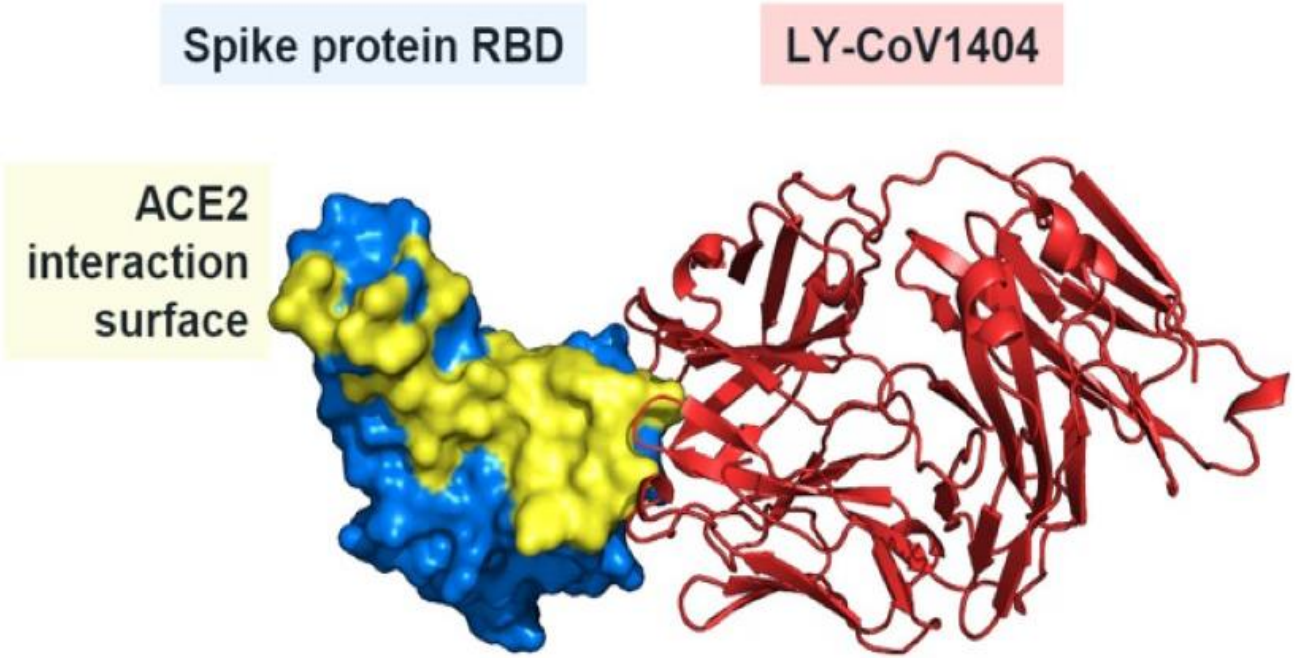
Regdanvimab binds to the RBD at a separate site compared with other antibodies



Kim C, et al. Nature Comm. 2021.;12:288.

Mechanism of Action of mAbs – Bebtelovimab (LY-CoV1404)

Bebtelovimab binds at the RBD and blocks the interaction with ACE2



Westendorf K, et al. bioRxiv. Preprint [interim data/not peer reviewed]. 2021.04.30.442182.

Popolazione Target per il trattamento di COVID19 con Mabs

Soggetti di età **>12 anni**, positivi per SARS CoV-2, **non ospedalizzati** per COVID-19, **non in ossigenoterapia** per COVID-19, con sintomi di grado lieve-moderato di recente insorgenza (e comunque da **non oltre 10 giorni**) e presenza di almeno uno dei seguenti fattori di rischio:

1. indice di massa corporea (BMI) ≥30
2. malattia renale cronica (soggetto cronicamente sottoposto a dialisi peritoneale o emodialisi)
3. diabete non controllato (HbA1c ≥9.0% o 75 mmol/mol o con complicanze croniche)
4. immunodeficienze primitive o secondarie
5. età >65 anni
6. **età ≥55 anni con:**

- malattie cardio-cerebrovascolari (inclusa ipertensione con concomitante danno d'organo) e/o
- broncopneumopatia cronica ostruttiva (BPCO) e/o altre malattie respiratori croniche

7. **età 12-17 anni con**:

a. BMI ≥ 85° percentile per età e genere
b. Anemia falciforme
c. Malattie cardiache congenite o acquisite
d. Malattia del neurosviluppo
e. Dipendenza da dispositivo tecnologico (p.es. soggetti con tracheotomia, gastrostomia, etc)
f. Asma, o altre malattie respiratorie che richiedono medicazioni giornaliere per il loro controllo.

Popolazione Target per il trattamento di COVID19 con Mabs

Oltre i 10 giorni in soggetti con immunodeficienza che presentino:

- ✓ Sierologia per SARS-COV-2 negativa
- ✓ Prolungata positività al tampone molecolare

AIFA agosto 2021

Trattamento di pazienti ospedalizzati per COVID-19, anche in ossigenoterapia supplementare (con l'esclusione dell'ossigenoterapia ad alti flussi, o in ventilazione meccanica), con sierologia negativa per gli anticorpi IgG anti- Spike di SARSCoV-2

mAbs in trials for Pre- and Post-exposure prophylaxis

Pre-Exposure prophylaxis
mAbs have been shown to reduce viral load, and therefore, may reduce transmission and prevent disease in people who would be at high risk of getting servere COVID-19

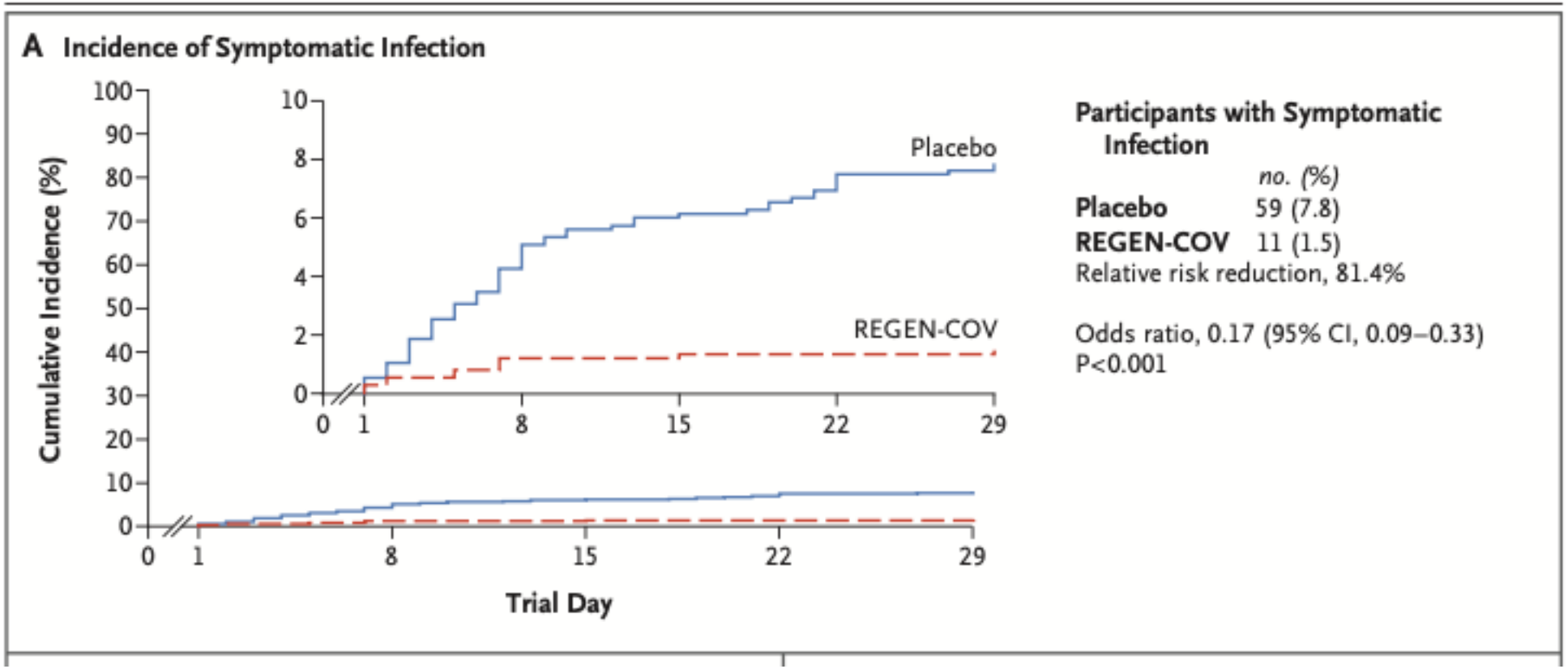
Post-Exposure prophylaxis
Trials with exposed people who would be at high risk of severe disease have reported reductions in infection and disease progression (eg. Care home setting)

Gottlieb RL, et al. *JAMA*. 2021;325:632-644; Weinreich DM, et al. *N Engl J Med*. 2021;384:238-251.

The NEW ENGLAND JOURNAL of MEDICINE

Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19

We randomly assigned, in a 1:1 ratio, participants (≥12 years of age) who were enrolled within 96 hours after a household contact received a diagnosis of SARS- CoV-2 infection to receive a total dose of 1200 mg of REGEN-COV or matching placebo administered by means of subcutaneous



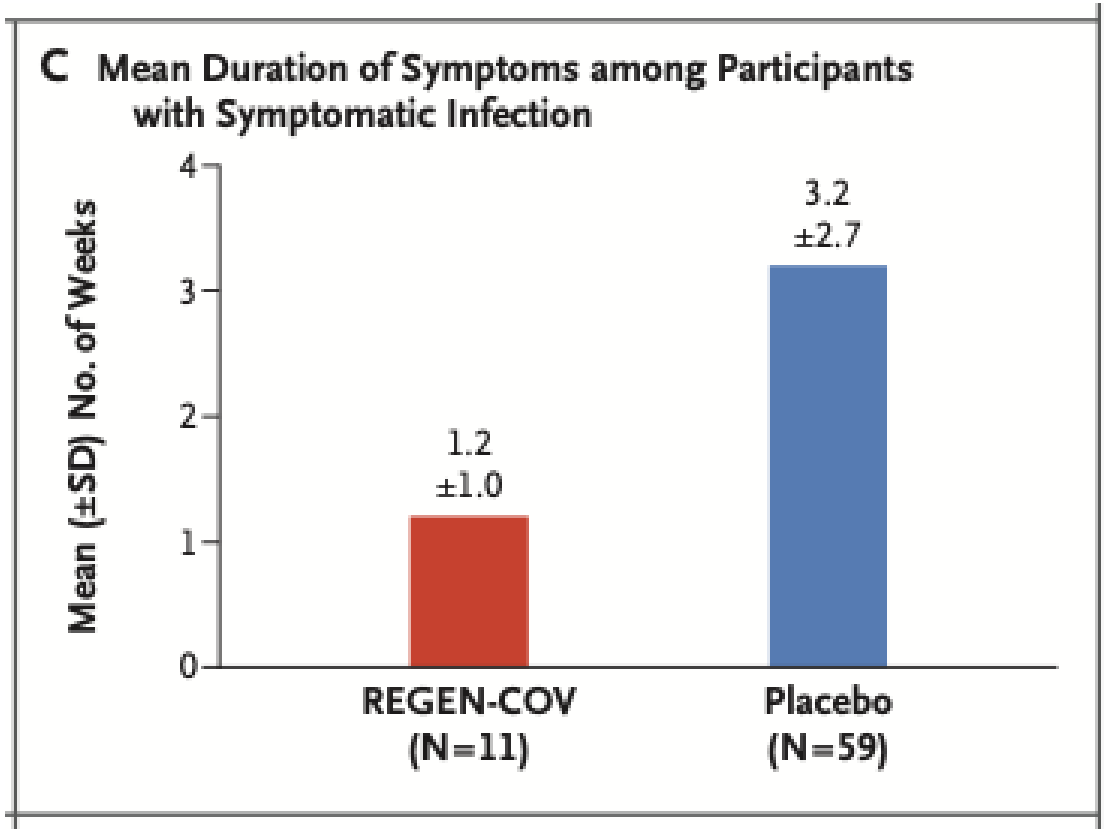
Symptomatic SARS-CoV-2 infection developed in 11 of 753 participants in the REGEN-COV group (1.5%) and in 59 of 752 participants in the placebo group (7.8%) (relative risk reduction 81.4%; P<0.001)

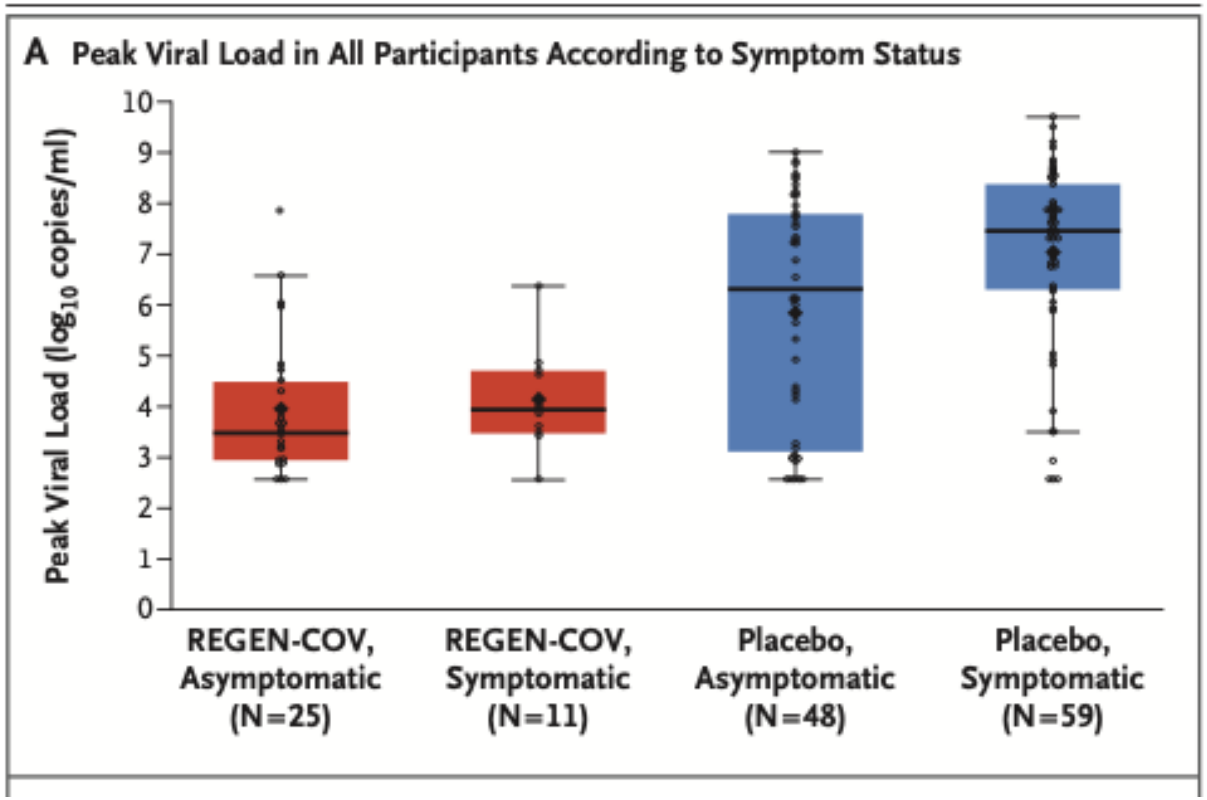
600 mg di casirivimab e 600 mg di imdevimab somministrati in un'unica infusione endovenosa oppure mediante iniezione sottocutanea.

M.P. O'Brien; N Engl J Med 2021;385:1184-95.

The NEW ENGLAND JOURNAL of MEDICINE

Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19





Among symptomatic infected participants, the median time to resolution of symptoms was 2 weeks shorter with REGEN-COV than with placebo (1.2 weeks and 3.2 weeks, respectively).

The duration of a high viral load (>104 copies per milliliter) was shorter (0.4 weeks and 1.3 weeks, respectively)

M.P. O'Brien; N Engl J Med 2021;385:1184-95.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

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

N Engl J Med. 2022 Apr 20. doi: 10.1056/NEJMoa2116620. Online ahead of print.

6-Month Data EXTENDED FOLLOW-UP:

PROVENT: Phase III Randomized, Double-Blind, Placebo-Controlled Study of AZD7442 for Pre-exposure Prophylaxis in 5197 Participants[1,2]

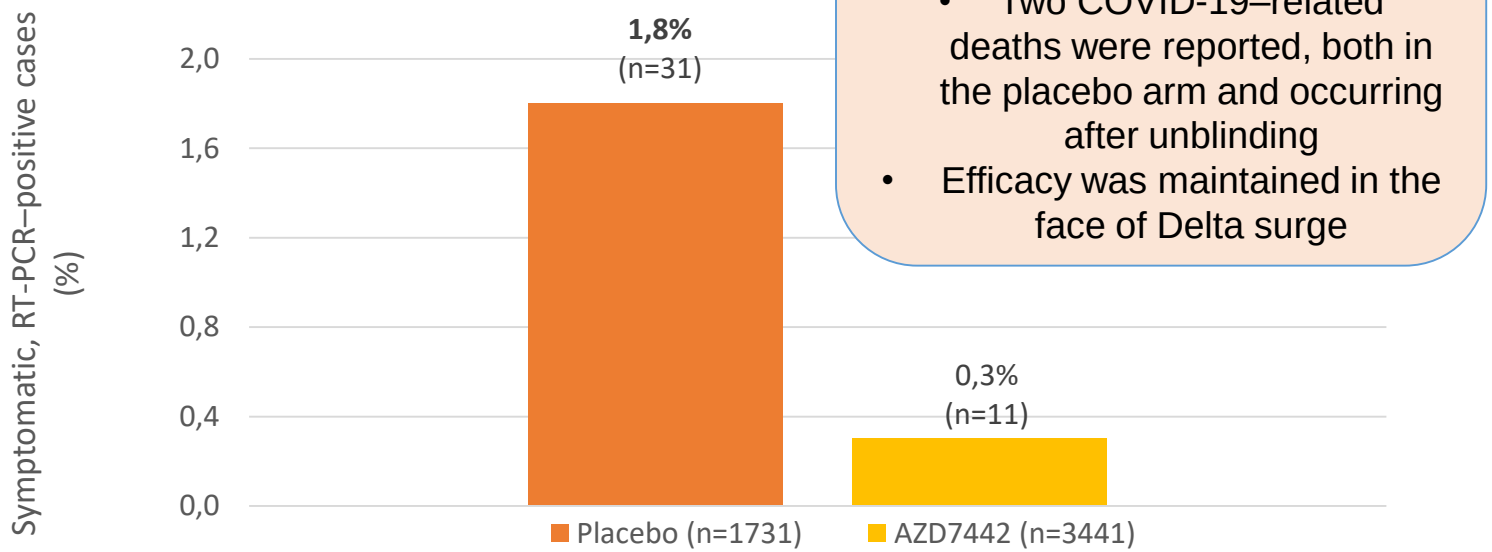
ClinicalTrials.gov identifier: NCT04625725
Status: active, not recruiting
Completion date: June 2022

Primary outcome measures[1]

- Incidence of the first case SARS-CoV-2 RT-PCR–positive symptomatic illness
- Safety and tolerability of AZD7442 (incidence of AEs, SAEs, MAAEs, AESIs)

Reduction in the incidence of symptomatic COVID-19 with AZD7442 compared with placebo—6-month (median) follow-up[1,3]

RRR: 82.8%
(95% CI: 66-91; *P* < 0.001)[a]

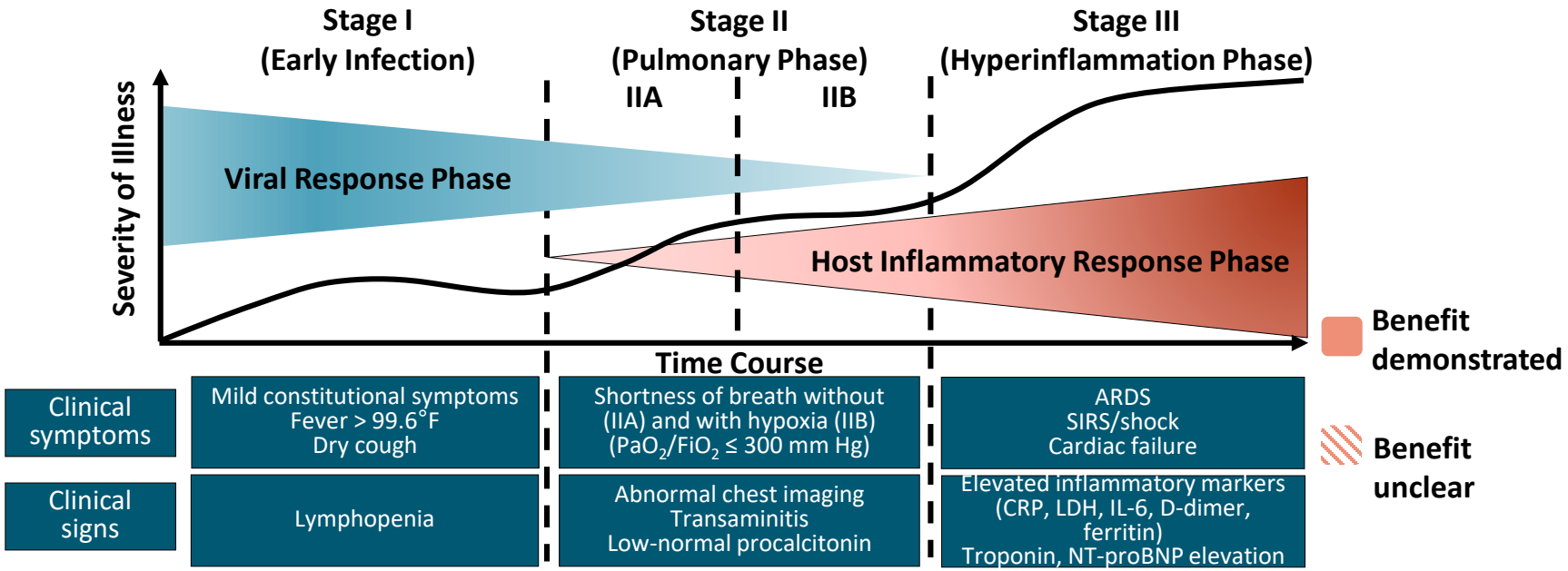


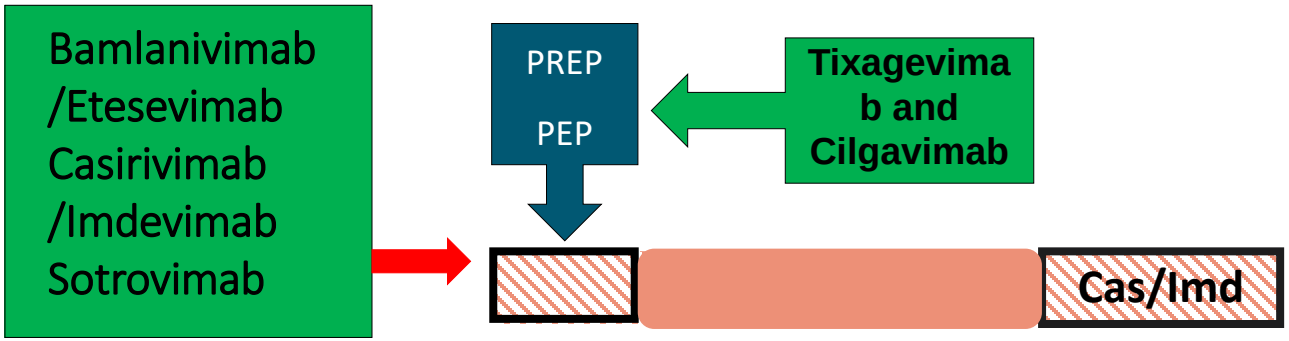
- There were 5 cases of severe COVID-19 in the placebo arm and none in the AZD7442 arm
- Two COVID-19–related deaths were reported, both in the placebo arm and occurring after unblinding
- Efficacy was maintained in the face of Delta surge

AE = adverse event; AESI = adverse event of special interest; COVID-19 = coronavirus disease 2019; MAAE = medically attended adverse event; RT-PCR = reverse transcriptase–polymerase chain reaction; SAE = severe adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

1. AstraZeneca Pharmaceuticals LP press release. Published August 20, 2021; 2. Study NCT04625725. ClinicalTrials.gov website; 3. Levin M et al. Presentation at: IDWeek 2021; September 29-October 3, 2021; virtual conference.

COVID-19 Therapies Predicted to Provide Benefit at Different Stages





Siddiqi. J Heart Lung Transplant. 2020;39:405.

Origin of «D614G» variant

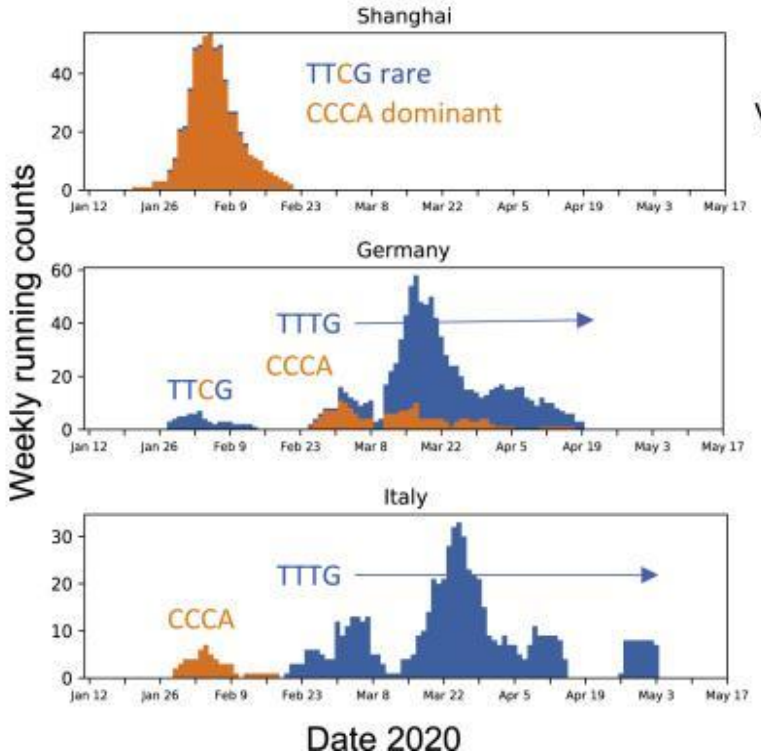
Cell

Tracking Changes in SARS-CoV-2 Spike: Evidence that D614G Increases Infectivity of the COVID-19 Virus

This «change» was firstly described by **Korber et al (Cell, 2020).**

- It was suggested an independent event occurred in several geographic regions.
- **The first report in sequences was in China (Zhejiang), on 24 January 2020**.
- A variant circulated in Shanghai had the D614G mutation (spike) but not the other 3 mutations that characterize the D614G variant.

A



B

G-clade mutations (C3037T, C14408T, A23403G) CCA -> TTG
Plus the linked mutation in the UTR: C241T CCCA -> TTTG

11805	TTG	(72.03%)	9692	TTTG	(71.65%)
4582	CCA	(27.96%)	3835	CCCA	(28.35%)

Variants:

53	CTG		51	TCTG	5 CTCG
39	TCG		32	TTCG	4 CCTA
16	CCG		13	CTTG	3 TCTA
9	TTA		11	TCCA	2 CTTA
8	CTA		9	TCCG	2 CTCA
5	TCA		7	CCCG	1 TTCA
1	ACA		6	TTTA	1 CCTG

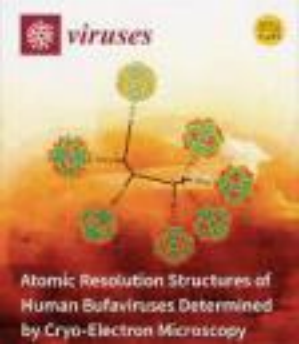
Earliest examples in GISAID:

TTCG: Germany, Jan 2020: cluster of cases late Jan.-Feb.
One example: Germany/BavPat1/EPI_ISL_406862|2020-01-28

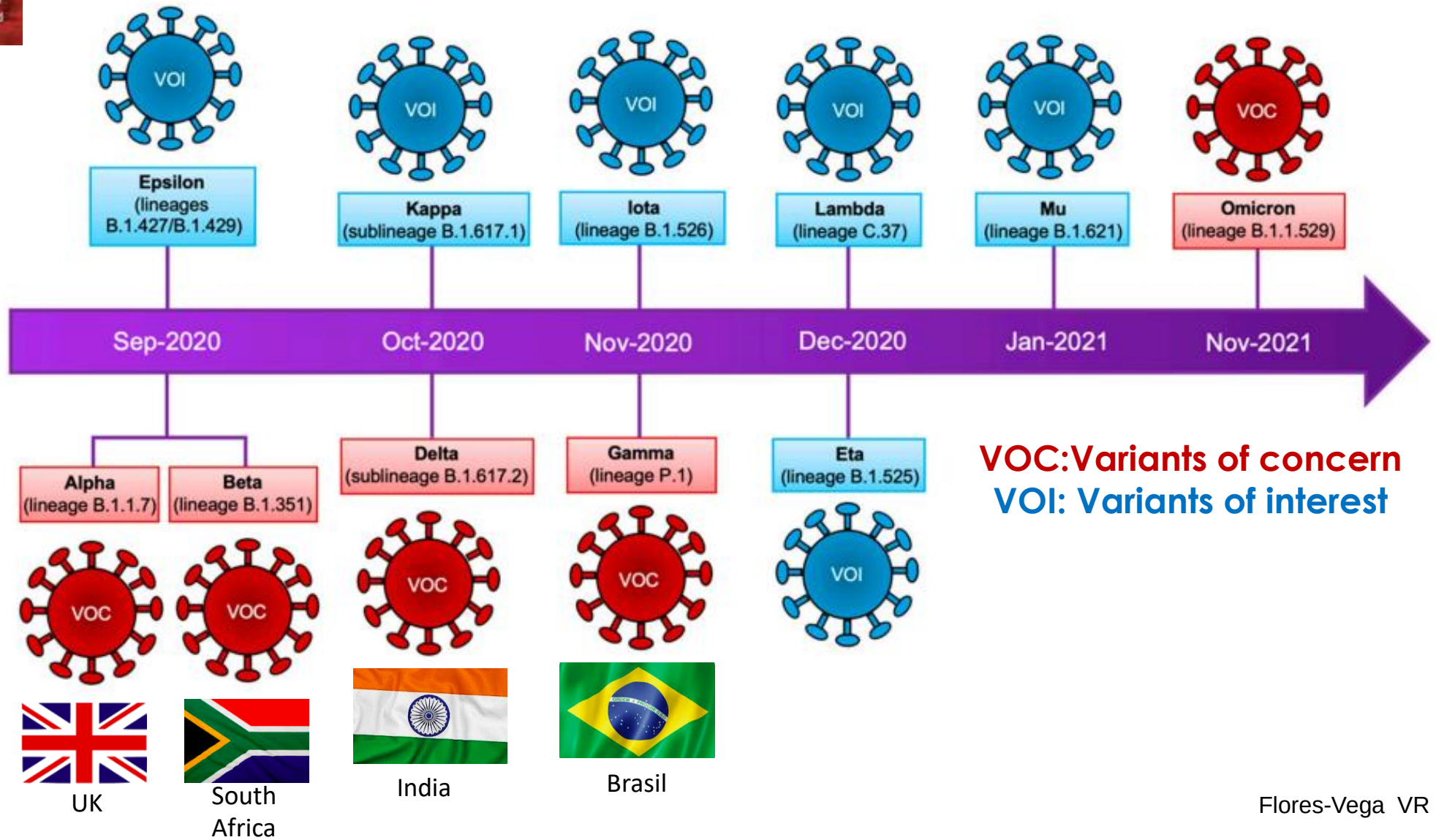
TTCG: Sampled several times in China, *e.g.*:
Sichuan/SC-PHCC1-022/EPI_ISL_451345|2020-01-24
Shanghai/SH0025/EPI_ISL_416334|2020-02-06
Guangzhou/GZMU0019/EPI_ISL_429080|2020-02-05

CCCG: Sampled twice in early Feb., Wuhan and Thailand
Thailand/Samut_prakarn_840/EPI_ISL_447919|2020-02-04
Wuhan/HBCDC-HB-06/EPI_ISL_412982|2020-02-07

TTTG: First identified in Italy; within 10 days sampled in many in countries in Europe, the USA, Mexico
First sample: Italy/CDG1/2020|EPI_ISL_412973|2020-02-20



Why so many SARS-CoV-2 variants?



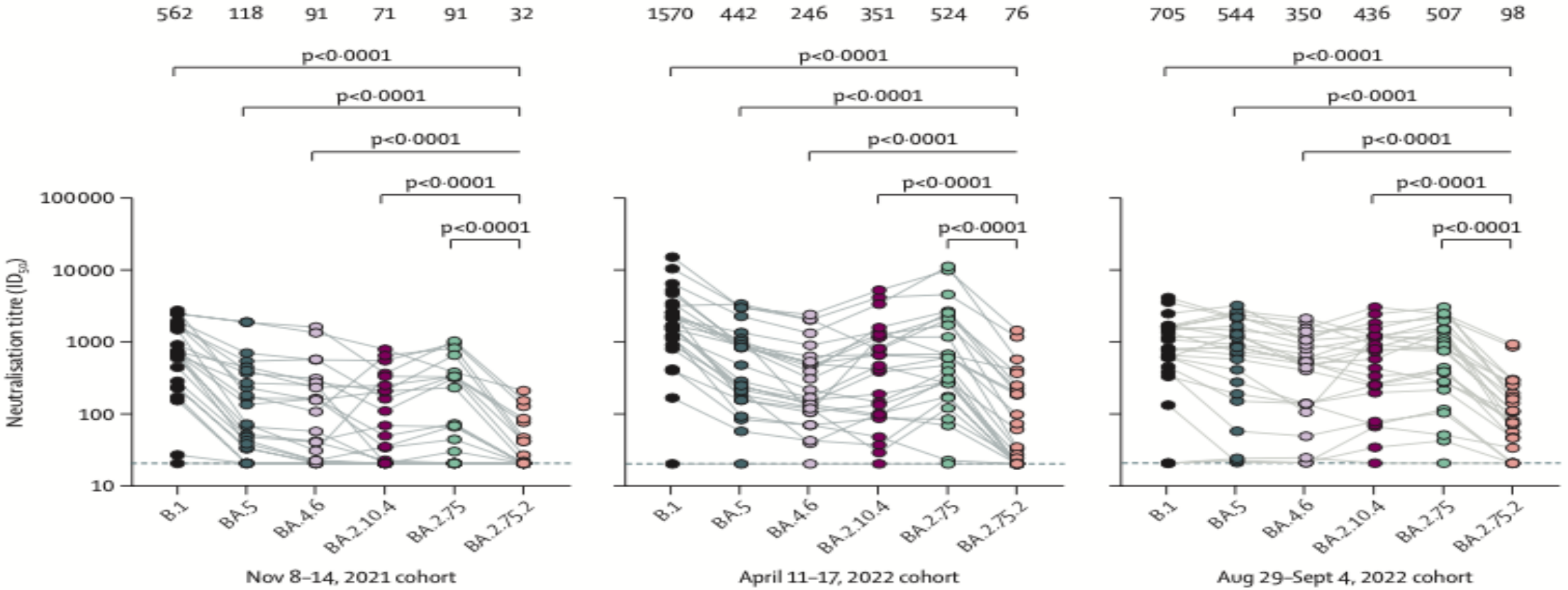
VOC:Variants of concern

VOI: Variants of interest

Flores-Vega VR et al., Viruses 2022

Omicron sublineage BA.2.75.2 exhibits extensive escape from neutralising antibodies

Sensitivity to neutralisation by serum from random blood donors in Stockholm, including a cohort sampled Nov 8–14, 2021 (before the emergence of the omicron variant, figure C),; a cohort sampled April 11–17, 2022 (after both a large wave of infections driven by BA.1 then BA.2and the rollout of third vaccine doses, figure D); and a cohort sampled Aug 29 to Sept 4, 2022 after the spread of BA.5, figure E).



***Lancet Infect Dis* 2022** October 13, 2022

Omicron Has Chenged the Monoclonal Antibody Landscape

SARS-CoV-2 neutralizing activity of mAbs (BA.1)

Antibody	Antibody IC_{50}				
	Wu01	Alpha	Delta	Beta	Omicron
Bamlanivimab	0.0031	0.0043	>10	>10	>10
Etesevimab	0.0194	0.9139	0.0019	>10	>10
REGN10933	0.0019	0.0006	0.0009	1.8303	>10
REGN10987	0.0094	0.0006	0.0454	0.0011	>10
C102	0.0524	0.6460	0.0169	>10	>10
P2B-2F6	0.1088	0.0081	>10	>10	>10
Sotrovimab/S309	1.9642	0.1154	0.2188	0.0335	0.0950
Fab2-36	0.1186	0.0437	0.0375	0.0987	>10
DZIF-10c	0.0014	0.0003	2.9103	0.0326	0.0346

IC_{50} ($\mu g\ ml^{-1}$)

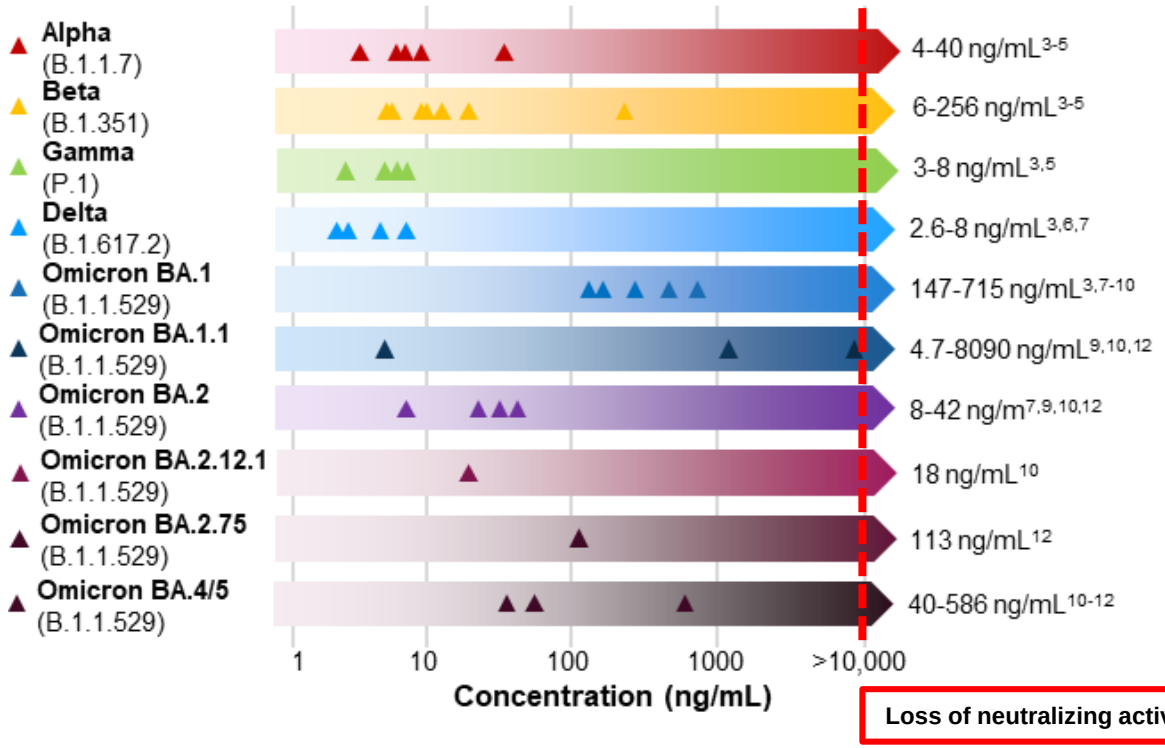
- <0.02
- 0.02–0.2
- 0.2–2
- 2–10
- >10

REGN10933, casirivimab; REGN10987, imdevimab.

Gruell H, et al. Nat Med. 2022. [Epub ahead of print].

Tixagevimab/Cilgavimab binds to Distinct, Non-overlapping Neutralizing Epitopes and Neutralizes VOC, Including Omicron (B.1.1.529)

EVUSHELD retains neutralizing activity against VOC, including Omicron based on IC_{50} (ng/mL)[a]



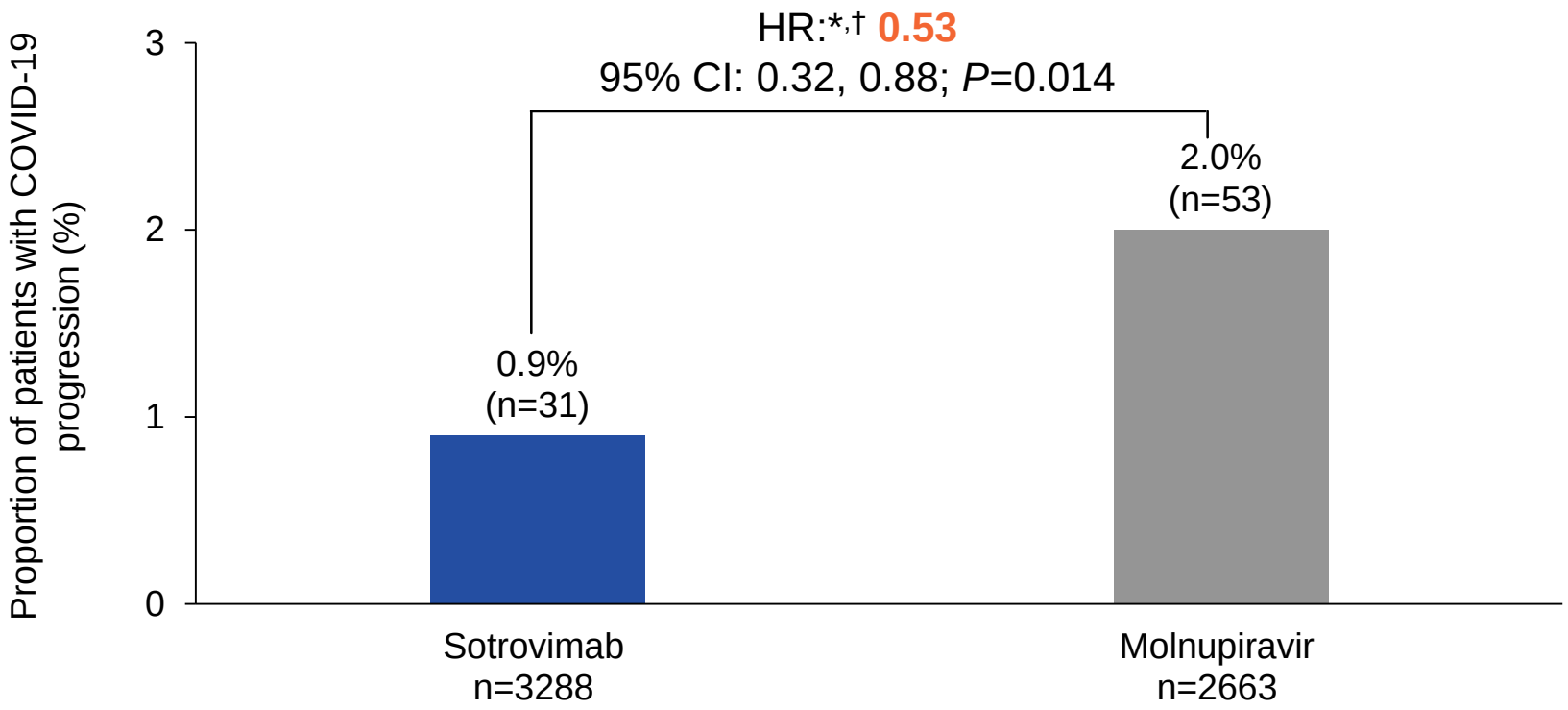
- EVUSHELD maintains neutralization against all Omicron sub-lineages
- Although neutralization against BA.1 is lower, EVUSHELD's neutralization of BA.2 is comparable to the original strain

10. National Center for Advancing Translational Sciences. Evusheld: tixagevimab (tixagevimab) and cilgavimab (cilgavimab) mAbs for SARS-CoV-2 antiviral resistance information (version 5). National Center for Advancing Translational Sciences website. https://opendata.ncats.nih.gov/variant/datasets?id=107. Accessed June 17, 2022;
11. Dejnirattisai W, Zhou D, Supasa P, et al. Antibody evasion by the P.1 strain of SARS-CoV-2. *Cell*. 2021;184:2939-2954.e9;
12. Chen RE, Zhang X, Case JB, et al. Resistance of SARS-CoV-2 variants to neutralization by monoclonal and serum-derived polyclonal antibodies. *Nat Med*. 2021;27:717-726; **13.** Liu C, Ginn HM, Dejnirattisai W, et al. Reduced neutralization of SARS- CoV-2 B.1.617 by vaccine and convalescent serum. *Cell*. 2021;184:4220-4236.e13; **14.** Bruel T, Hadjadj J, Maes P, et al. Serum neutralization of SARS-CoV-2 Omicron sublineages BA.1 and BA.2 in patients receiving monoclonal antibodies. *Nat Med*. 2022; 28:1297–1302. Accessed May 9, 2022. **15.** VanBlargan LA, Errico JM, Halfmann PJ, et al. An infectious SARS-CoV-2 B.1.1.529 Omicron virus escapes neutralization by therapeutic monoclonal antibodies. *Nat Med*. 2022;28:490-495; **16.** Case JB, Mackin S, Errico J, et al. Resilience of S309 and AZD7442 monoclonal antibody treatments against infection by SARS-CoV-2 Omicron lineage strains [preprint published online March 18, 2022]. *bioRxiv*. 2022. https://doi.org/10.1101/2022.03.17.484787. Accessed June 17, 2022; **17.** Cao Y, Yisimayi A, Jian F, et al. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection [published online ahead of print June 17, 2022]. *Nature*. 2022. https://doi.org/10.1038/s41586-022-04980-y. Accessed June 17, 2022; **18.** Tuekprakhon A, Huo J, Nutalai R, et al. Further antibody escape by Omicron BA.4 and BA.5 from vaccine and BA.1 serum [preprint published online May 23, 2022]. *bioRxiv*. 2022. https://www.biorxiv.org/content/10.1101/2022.05.21.492554v1. Accessed June 17, 2022.

Data are emerging from treatment with sotrovimab in a real-world setting

Comparative effectiveness – sotrovimab vs molnupiravir (Omicron BA.1 variant)

Sotrovimab treatment was associated with lower risk of 28-day COVID-19–related hospitalisation/death compared with molnupiravir treatment during the Omicron variant surge



*Sensitivity analyses were based on the fully-adjusted stratified Cox model; †results of stratified Cox regression were adjusted for demographic variables, ten high-risk cohort categories, vaccination status, calendar week, BMI category and other comorbidities.

AIDS, acquired immunodeficiency syndrome; AV, antiviral; BMI, body mass index; CI, confidence interval; CMA, conditional market authorization; CVD, cardiovascular disease; EHR, electronic health record; EUA, emergency use authorization; HIV, human immunodeficiency virus; HR, hazard ratio; mAb, monoclonal antibody; NHS, National Health Service; OAV, oral antiviral; RW, real world; SD, standard deviation.

Zheng B, et al. medRxiv (preprint). 23 May 2022. doi:10.1101/2022.05.22.22275417v1.

Data are emerging from treatment with sotrovimab in a real-world setting

Comparative effectiveness – sotrovimab vs antivirals (Omicron BA.1 and BA.2 variants)

Patients treated with sotrovimab who were infected with Omicron BA.1 and BA.2 showed a statistically significant decrease in viral load between Day 1 and Day 7[1]

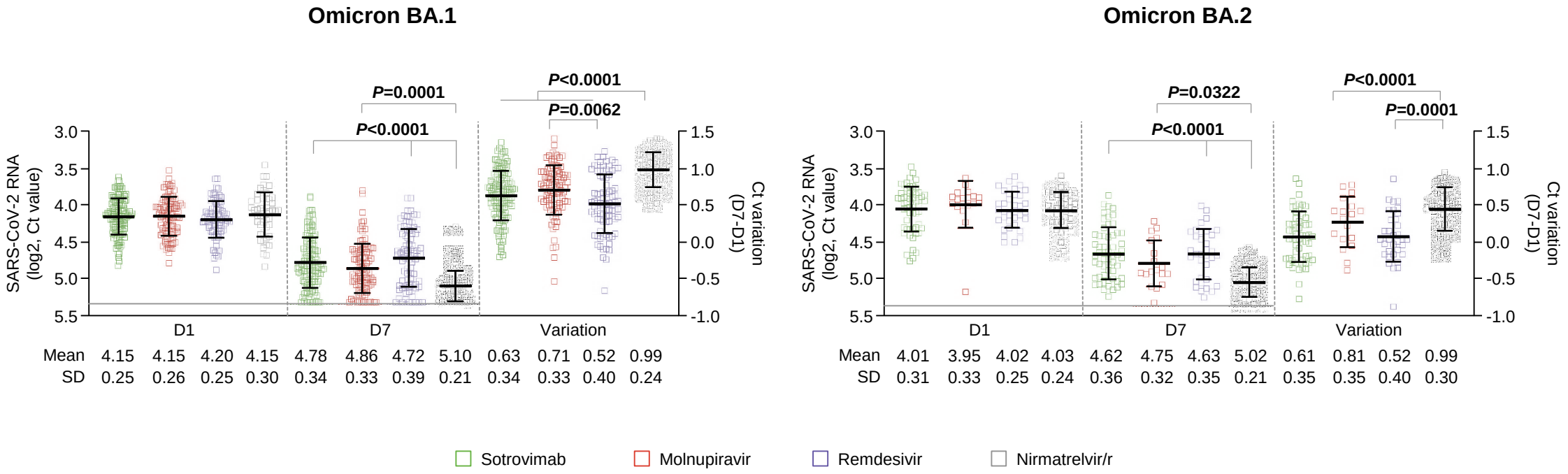


Figure adapted with permission from Mazzotta V, et al. medRxiv (preprint). 23 June 2022. doi: 10.1101/2022.06.23.22276509v1; Mazzotta V, et al. J Med Virol 2022; Oct 2:10.1002/jmv.28186. doi: 10.1002/jmv.28186.

AIFA, Agenzia italiana del farmaco (Italian Medicines Agency); BMI, body mass index; Ct, cycle threshold; IQR, interquartile range; mAb, monoclonal antibody; MASS, monoclonal antibody screening score; N/A, not applicable; NP, nasopharyngeal; OAV, oral antiviral; SD, standard deviation.

1. Mazzotta V, et al. medRxiv (preprint). 23 June 2022. doi:10.1101/2022.06.23.22276509v1; Mazzotta V, et al. J Med Virol 2022; Oct 2:10.1002/jmv.28186. doi: 10.1002/jmv.28186. 2. Gupta A, et al. *JAMA*. 2022;327(13):1236-1246.

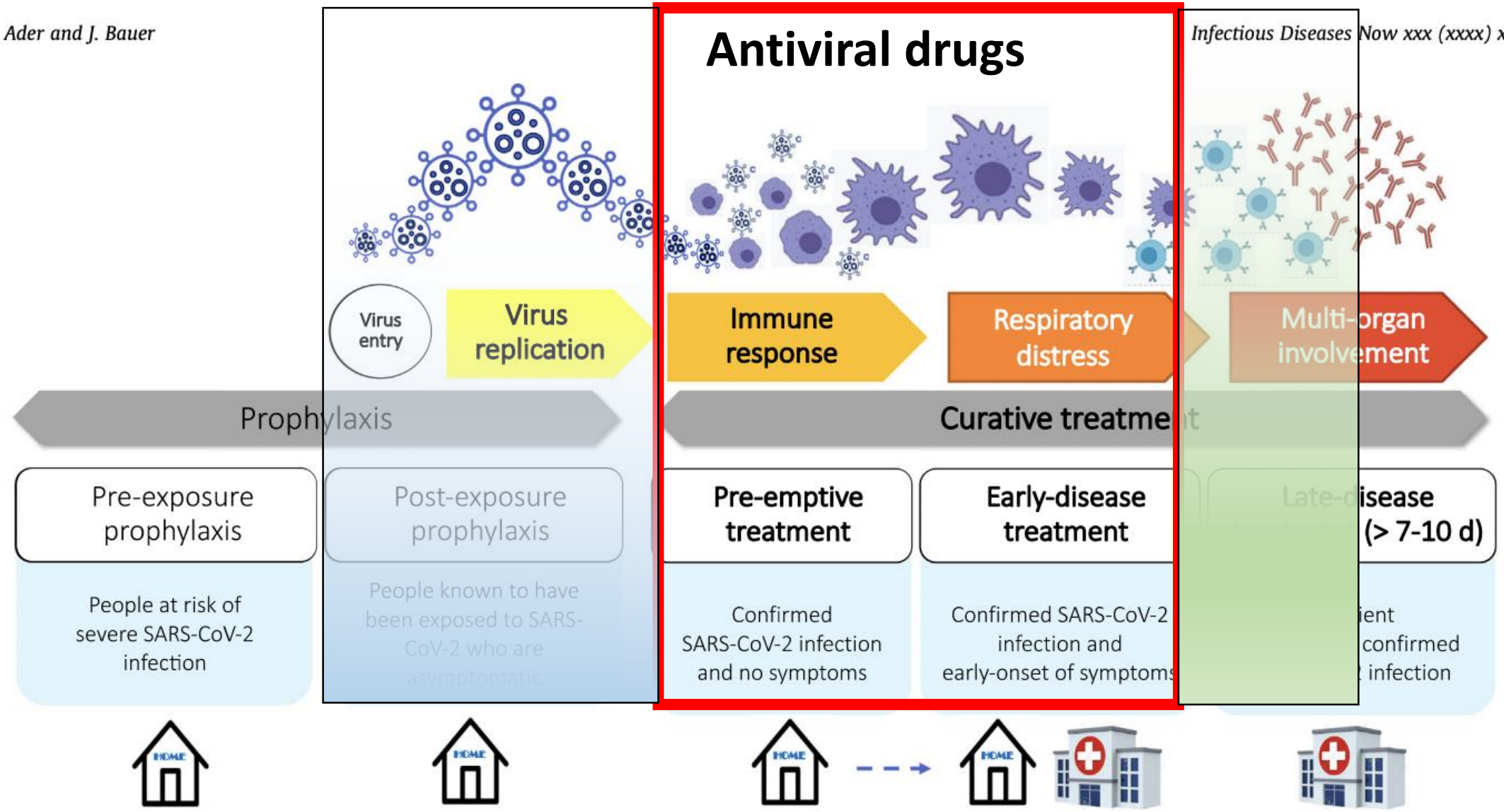
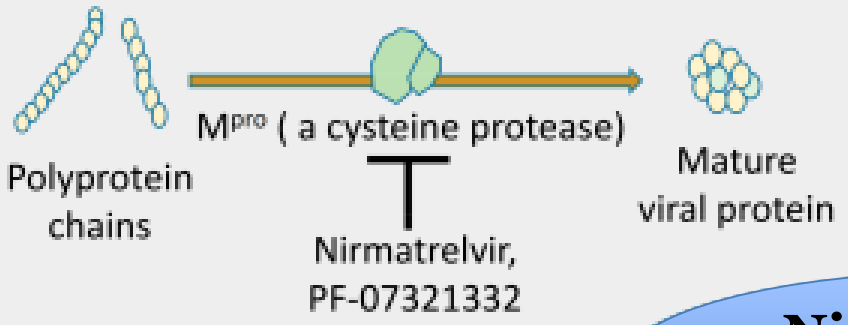


Fig. 1. COVID-19 therapeutic strategy according to the different stages of the disease.

Nirmatrelvir/ritonavir may decrease hospitalization and mortality rates and prevent virus transmission, and has good oral bioavailability.

Mechanism: an inhibitor of M^{pro}, a protease critical in viral replication



Efficacy: reduce hospitalization rate and mortality

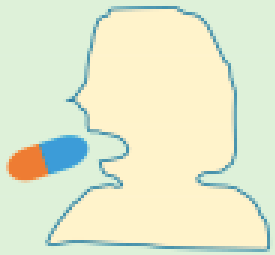
6.3% (66/1046) of the control group were hospitalized with **12** subsequent deaths

vs.

0.3% (8/1039) of the Paxlovid™ group were hospitalized with **no** deaths

Nirmatrelvir/ Ritonavir

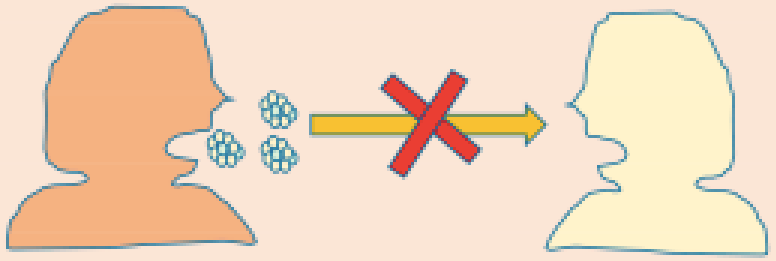
Convenience: orally bioavailable



Oral bioavailability (F) = **50%** in rat

Fraction of oral dose absorbed from the gastrointestinal tract (Fa x Fg) = **95%** in rat

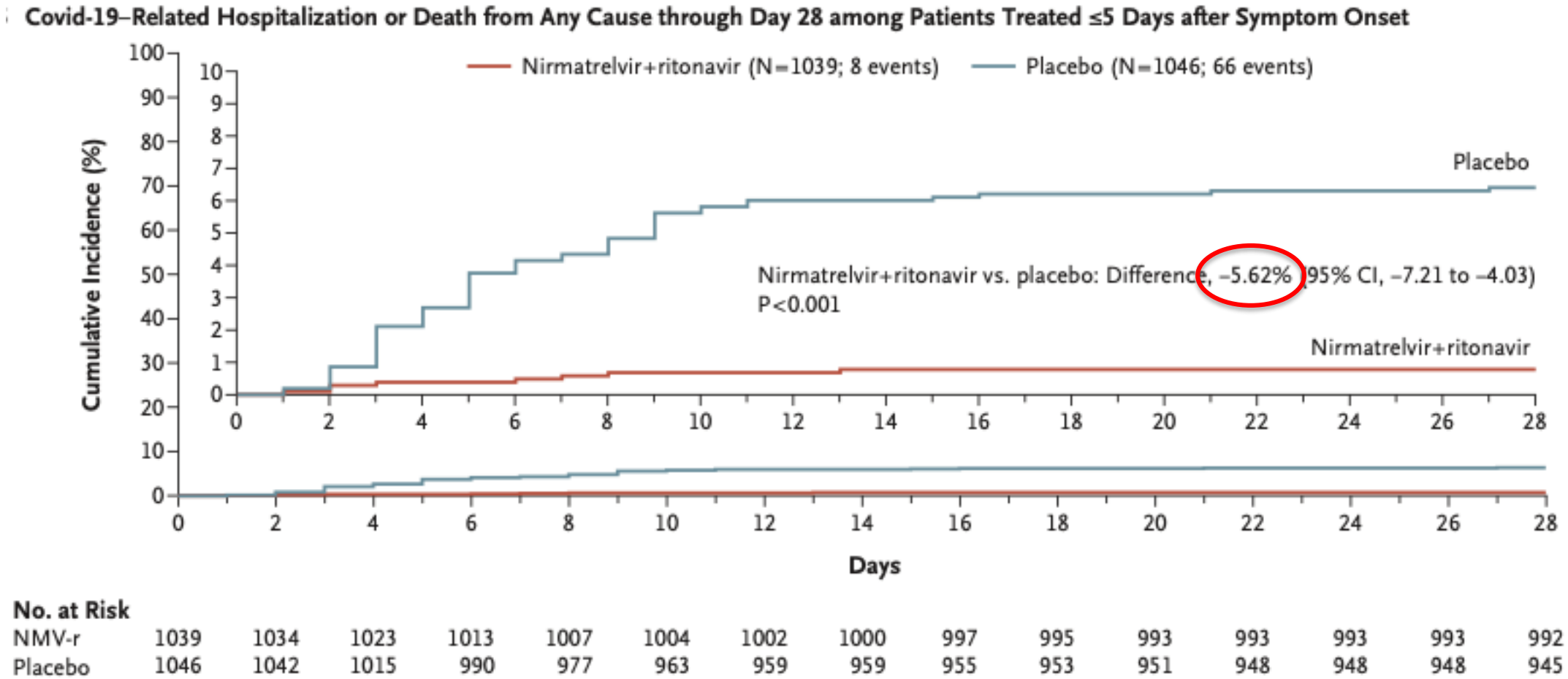
Prevention: prevent transmission to untreated sentinels



Yuan-Pin Hung *Antibiotics* **2022**, *11*, 220

The NEW ENGLAND JOURNAL of MEDICINE

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



L'efficacia è stata mantenuta nell'analisi finale su 1.379 pazienti (mITT) con una differenza di -5,62 punti percentuali (IC95%: -7,78 - -3,84; p<0.001) con riduzione del rischio relativo: 88,9%.

Tutti i 13 decessi si sono verificati nel gruppo placebo

Hammond J NEJ April 14, 2022 vol. 386 no.

Nirmatrelvir + Ritonavir: CYP3A Metabolism

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

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

fda.gov/media/155050/download

Slide credit: clinicaleducationalliance.com: cea clinical education alliance

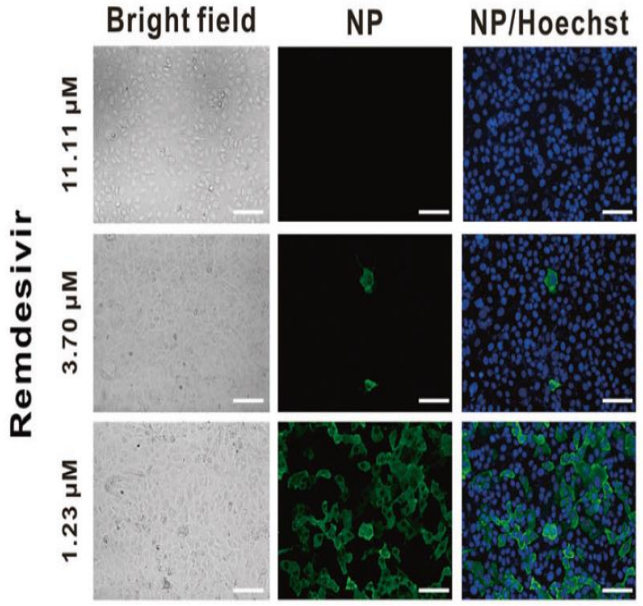
Antiviral Efficacy of Remdesivir Against SARS-CoV2 In Vitro

Prodrug of a nucleoside analog that is intracellularly metabolized to an analog of adenosine triphosphate which inhibits viral RNA polymerases

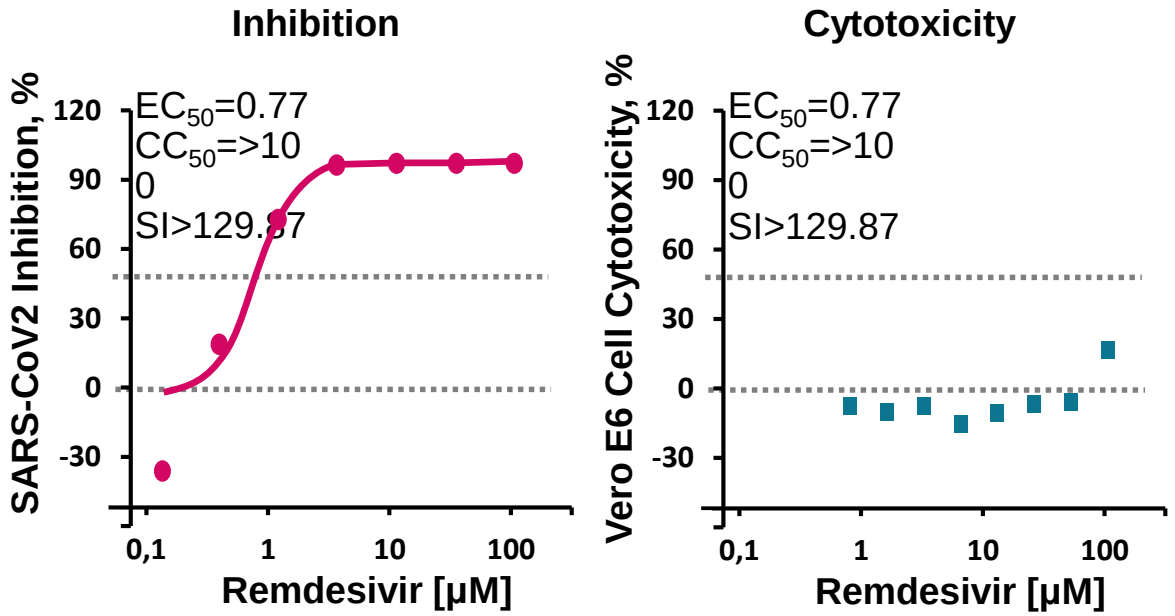
Broad spectrum activity against several viral families including filoviruses (e.g. Ebola) and coronaviruses (e.g. SARS-CoV and MERS-CoV)

In Vitro Assays in Vero E6 cells to measure the effects of remdesivir on the cytotoxicity, virus yield and infection rate of SARS-CoV2

Immunofluorescence microscopy of virus infection in Vero E6 cells upon treatment of remdesivir



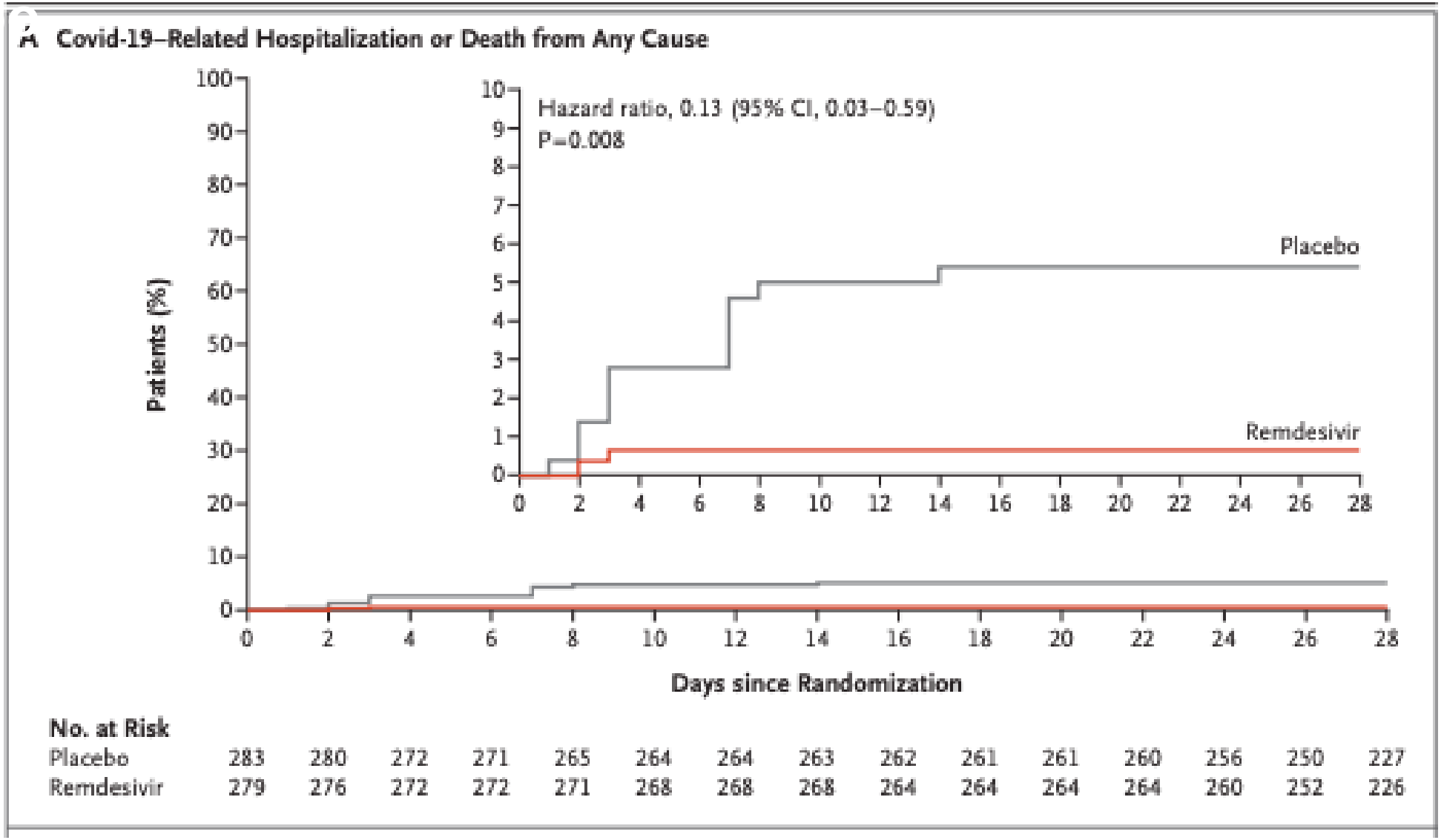
Virus yield and cytotoxicity in SARS-CoV2-infected Vero E6 cells treated with remdesivir



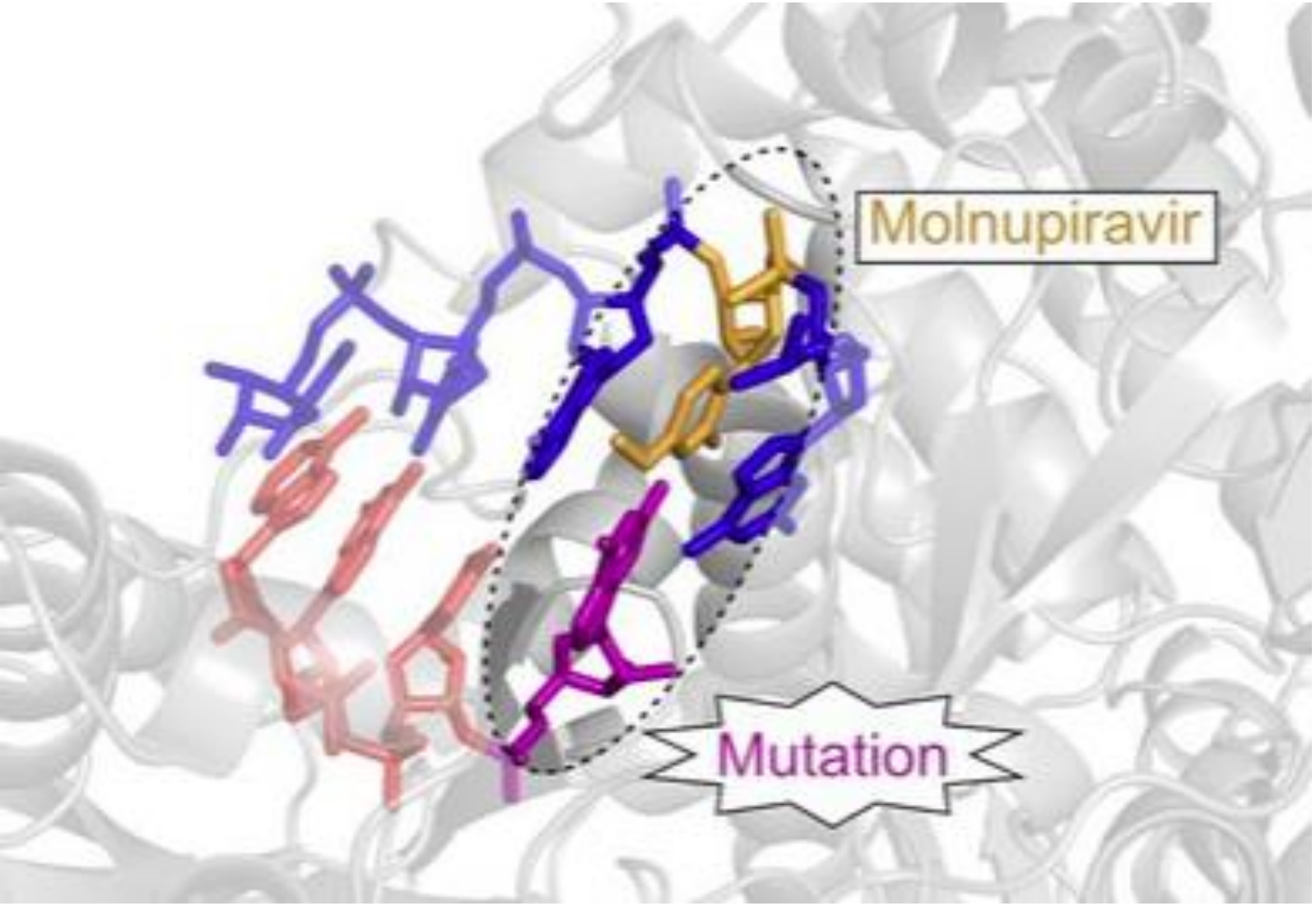
Remdesivir is effective in SARS-CoV2 inhibition with low Vero E6 cell cytotoxicity

Wang et al., *Cell Research*, 2020

A 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than



Molnupiravir is an oral form of a potent ribonucleoside analogue that hinders the replication of various ribonucleic acid (RNA) viruses such as SARS-CoV-2.



The molnupiravir's active triphosphate form (NHC-TP) **is incorporated into the viral RNA, where it leads to mutations (purple) that ultimately prevent the virus from replicating**

supporting a mechanism of lethal mutagenesis in CoV.

Accumulation of multiple errors (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

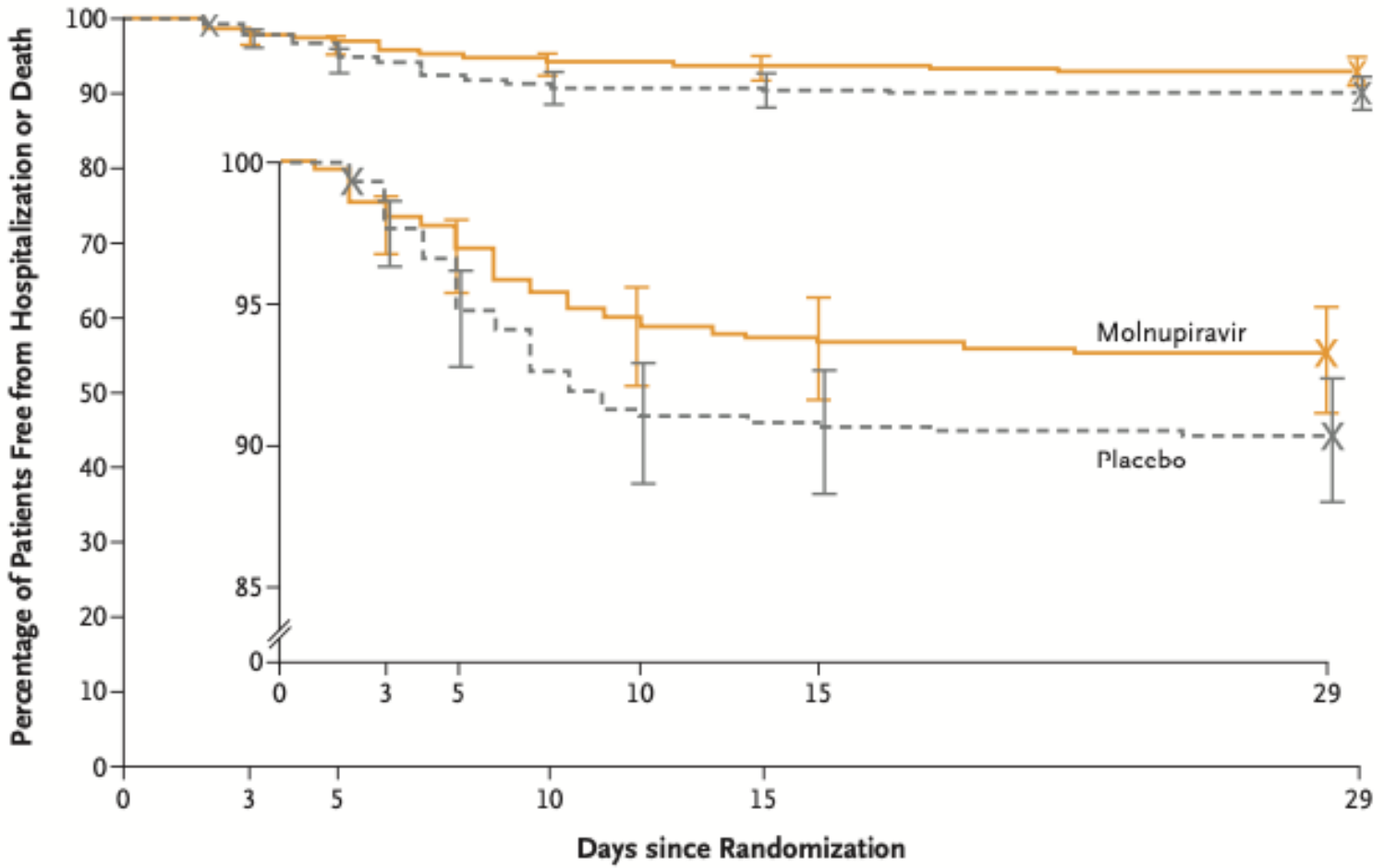
Molnupiravir (MK-4482): In Vitro and Animal Data

- MK-4482 is an orally administered prodrug of a small molecule nucleoside with **broad-spectrum antiviral activity against a range of RNA viruses**
  - Active *in vitro* against 3 key coronaviruses: SARS-1 (SARS-CoV), MERS, and SARS-CoV-2
  - Activity against other RNA viruses: influenza (seasonal, pandemic, avian subtypes), RSV, filoviruses (Ebola), Flaviviruses (Zika, Dengue), chikungunya, and alphaviruses (e.g., Venezuelan Equine encephalitis Virus [VEEV])

- Antiviral activity verified in animal models of SARS-1, MERS, influenza, RSV, VEEV, CHKV, and Ebola
  - Active in **both prophylactic and therapeutic settings** in mice infected with SARS-1 and MERS

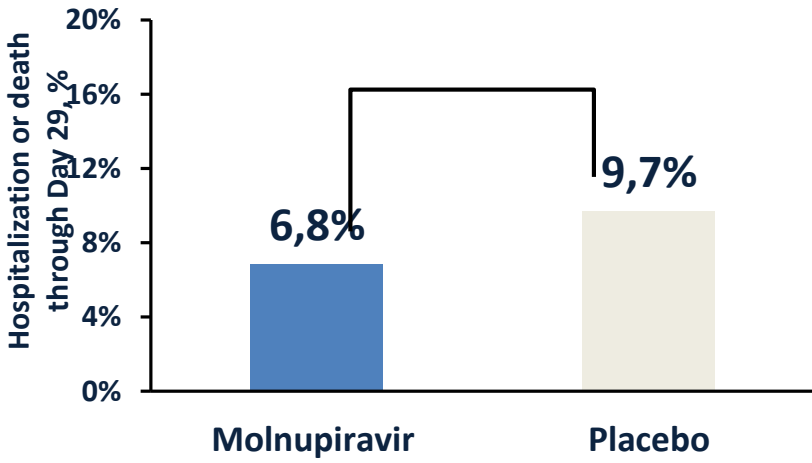
Sheahan et al. *Sci Transl Med*. 2020.

Time-to-Event Analysis of Hospitalization or Death through Day 29 in the Modified Intention-to-Treat Population.



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

The percentage of participants hospitalized or died was:
molnupiravir group: 6.8% [48 of 709]
placebo group: 9.7% [68 of 699]



A. J. Bernal. NEJM December 2022;386:509

Outpatient Antivirals: Reduced Hospitalization or Death

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

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

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

Antiviral Considerations

Anti–SARS-CoV-2 Therapy	Nirmatrelvir + Ritonavir	Molnupiravir	Remdesivir
Mechanism of action	SARS-CoV-2-3CL protease inhibitor	Nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis	Adenosine nucleotide prodrug that inhibits SARS-CoV-2 RNA-dependent RNA polymerase
Drug interactions	Common—CYP3A	None identified	Chloroquine phosphate and hydroxychloroquine sulfate
Timing of use	ASAP **within 5 days** of symptom onset		ASAP **within 7 days** of symptom onset
Pill burden	3 tablets twice daily x 5 days	4 capsules every 12 hr x 5 days	N/A
Adverse events	Dysgeusia, diarrhea (administer with food), hypertension, and myalgia	None greater than placebo	Nausea, increased ALT, increased AST
Use in pregnancy	Not studied, RTV safe, NIH panel "would not withhold if benefits outweigh risks"	Avoid use: possible teratogen Childbearing potential: assess if pregnant; contraception recommendations for males and females	Not studied, pregnancy registry for patients exposed to remdesivir during pregnancy
Use in renal dysfunction	Adjust eGFR 30-59 mL/min Not recommended if eGFR <30 mL/min	No adjustment needed	Not recommended if eGFR <30 mL/min
Use in liver dysfunction	Do not use if Child-Pugh C	No adjustment needed	Perform hepatic laboratory testing prior to use

covid19treatmentguidelines.nih.gov/therapies/statement-on-patient-prioritization-for-outpatient-therapies. fda.gov/media/155050/download. fda.gov/media/155054/download. gilead.com/-/media/files/pdfs/medicines/covid-19/veklury/veklury_pi.pdf.

Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study

Carlos K H Wong, Ivan C H Au, Kristy T K Lau, Eric H Y Lau, Benjamin J Cowling, Gabriel M Leung

	Molnupiravir recipients (n=1856)			Controls (n=1856)			Molnupiravir recipients *vs* controls	
	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Hazard ratio or mean difference (95% CI)†	p value
All-cause mortality	150 (8·1%)	75 065	19·98 (16·91 to 23·45)	295 (15·9%)	77 495	38·07 (33·85 to 42·67)	0·48 (0·40 to 0·59)	<0·0001
Invasive mechanical ventilation	7 (0·4%)	74 982	0·93 (0·38 to 1·92)	17 (0·9%)	77 343	2·20 (1·28 to 3·52)	0·42 (0·17 to 1·01)	0·052
Intensive care unit admission	1 (0·1%)	75 047	0·13 (0·00 to 0·74)	2 (0·1%)	77 462	0·26 (0·03 to 0·93)	NA	NA
Need for oxygen therapy	192 (11·8%)	60 447	31·76 (27·43 to 36·59)	260 (16·4%)	58 631	44·35 (39·12 to 50·08)	0·69 (0·57 to 0·83)	0·0001
Composite disease progression outcome‡	306 (16·5%)	68 782	44·49 (39·64 to 49·76)	481 (25·9%)	68 846	69·87 (63·76 to 76·40)	0·60 (0·52 to 0·69)	<0·0001
Low viral burden§	274 (17·0%)	18 794	145·79 (129·04 to 164·12)	209 (12·9%)	20 850	100·24 (87·11 to 114·79)	1·38 (1·15 to 1·64)	0·0005
Length of hospital stay, days¶	NA	NA	10·82 (10·41 to 11·23)	NA	NA	11·50 (11·03 to 11·98)	−0·68 (−1·31 to −0·06)	0·033

NA=not applicable. *Crude incidence rates (events per 10 000 person-days) are presented for all outcomes except length of hospital stay, for which the mean is shown. †Hazard ratios are presented for all outcomes with at least two events in each group, except length of hospital stay, for which mean difference is shown; a hazard ratio >1 indicates that molnupiravir recipients had a higher risk of the specified outcome or a shorter time to low viral burden than the matched control group, and vice versa. ‡Includes all-cause mortality, invasive mechanical ventilation, intensive care unit admission, and need for oxygen therapy. §Defined as a cycle threshold value of 30 or higher. ¶Number of participants for this analysis (including only those who were discharged alive) was 1667 for the molnupiravir group and 1681 for the control group.

Table 2: **Clinical and virological outcomes for molnupiravir recipients compared with matched controls**

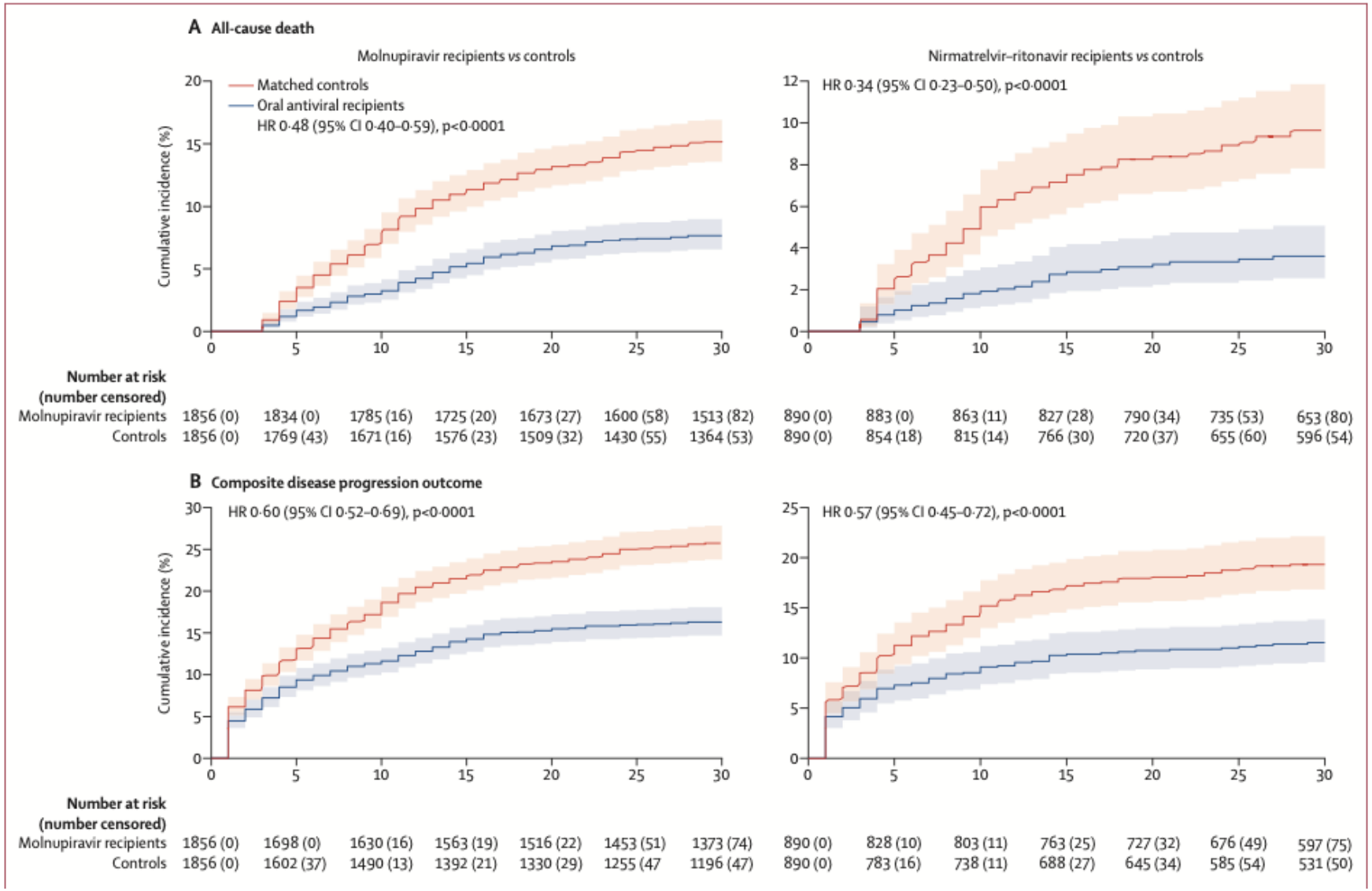
	Nirmatrelvir–ritonavir recipients (n=890)			Controls (n=890)			Nirmatrelvir–ritonavir recipients *vs* controls	
	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Cumulative incidence of new events (%)	Person-days	Crude incidence rate per 10 000 person-days or mean (95% CI)*	Hazard ratio or mean difference (95% CI)†	p value
All-cause mortality	32 (3·6%)	31 123	10·28 (7·03 to 14·51)	92 (10·3%)	34 762	26·47 (21·34 to 32·46)	0·34 (0·23 to 0·50)	<0·0001
Invasive mechanical ventilation	6 (0·7%)	31 035	1·93 (0·71 to 4·21)	6 (0·7%)	34 745	1·73 (0·63 to 3·76)	0·97 (0·31 to 3·03)	0·96
Intensive care unit admission	0	31 123	0·00	1 (0·1%)	34 750	0·29 (0·01 to 1·60)	NA	NA
Need for oxygen therapy	79 (10·1%)	25 057	31·53 (24·96 to 39·29)	102 (13·6%)	26 676	38·24 (31·18 to 46·42)	0·73 (0·54 to 0·97)	0·032
Composite disease progression outcome‡	101 (11·3%)	28 827	35·04 (28·54 to 42·57)	173 (19·4%)	31 468	54·98 (47·09 to 63·81)	0·57 (0·45 to 0·72)	<0·0001
Low viral burden§	136 (19·0%)	7269	187·10 (156·97 to 221·31)	105 (14·6%)	8438	124·44 (101·78 to 150·64)	1·38 (1·07 to 1·79)	0·013
Length of hospital stay, days¶	NA	NA	9·59 (9·06 to 10·12)	NA	NA	10·02 (9·35 to 10·69)	−0·43 (−1·29 to 0·42)	0·32

NA=not applicable. *Crude incidence rates (events per 10 000 person-days) are presented for all outcomes except length of hospital stay, for which the mean is shown. †Hazard ratios are presented for all outcomes with at least two events in each group, except length of hospital stay, for which mean difference is shown; a hazard ratio >1 indicates that nirmatrelvir–ritonavir recipients had a higher risk of the specified outcome or a shorter time to low viral burden than the matched control group, and vice versa. ‡Includes all-cause mortality, invasive mechanical ventilation, intensive care unit admission, and need for oxygen therapy. §Defined as a cycle threshold value of 30 or higher. ¶Number of participants for this analysis (including only those who were discharged alive) was 783 for nirmatrelvir–ritonavir group and 772 in the control group.

Table 3: **Clinical and virological outcomes for nirmatrelvir–ritonavir recipients compared with matched controls**

Lancet Infect Dis 2022

Cumulative incidence of all-cause mortality and composite disease progression outcome for molnupiravir and mirmatrelvir/rotonavir recipients



Composite disease progression: all-cause mortality, invasive mechanical ventilation, intensive care unit admission

Lancet Infect Dis 2022

Molnupiravir Real World Evidence

Preprint Data	Published Data	Congress Poster Data
• Severe COVID-19 Prevention (UK) Zheng et al. • Outpatient Effectiveness (Hong Yip et al. • Outpatient Effectiveness (Hor Wong et al. • Kidney Transplant Recipients Gleeson et al. • COVID-19 Rebound (US) Wang et al. • Hospitalized Elderly Patients Gonda et al. • Kidney Transplant Recipients Villamarin et al. • Mid and Moderate COVID (Ita Gentile et al. • Early MOV + Usual Care vs Us Adults at Increased Risk (Unit Butler et al. • MOV Use and Severe COVID-19 Surge (Israel) Arbel et al.	• Solid Organ Transplant Recipients (US) Radcliffe et al.	• Immunocompromised Outpatients (Spain) Alvarez Marin et al. h-Risk Patients (Italy) OVID-19 (Italy) Between Molnupiravir and D-19 (Italy) g Risk of Hospitalization clonal Antibodies and Italy) ntiviral Agents (Italy) MOV in patients with MM e)

In a population of vaccinated participants with COVID-19 at increased risk for severe COVID-19 outcomes, **MOV did not reduce the already low hospital admission but resulted in shorter time to recovery, sustained recovery, reduced contact with GP services, and reduced viral detection and viral load.**

COVID-19 Rebound After Paxlovid and Molnupiravir During January-June 2022

Methods

- Retrospective cohort study using electronic health records from TriNetX, which contains patient-level health records from 93 million unique patients from 67 healthcare organizations across all 50 US states.

Study Population

- Adult patients (aged ≥18) who contracted COVID-19 between January 1, 2022 and June 8, 2022 who were treated with NMT/RIT or MOV within 5 days of their COVID-19 infection

Outcomes

- Occurrence of COVID-19 rebound **within 7 days and 30 days after the last day of MOV or NMT/RIT treatment**, defined as:
  - COVID-19 infection, defined by lab-confirmed SARS-CoV-2 infection or COVID-19 diagnosis
  - COVID-19-related symptoms, defined by ICD-10 codes, including fever, chills, cough, shortness of breath, fatigue, muscle aches, headache, loss of taste or smell, sore throat, nasal congestion, vomiting, diarrhea, and skin rashes
  - Hospitalization, defined by CPT code
- Characteristics of patients who experienced COVID-19 rebound and those who did not experience rebound within 30 days for both MOV and NMT/RIT

CPT, Current Procedural Terminology; ICD, International Classifications of Diseases; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

Wang et al. 2022. *medRxiv 2022.*

Select Patient Characteristics

Select Patient Characteristics Before Propensity-Score Matching

Characteristic	NMT/RIT (N = 11,270)	MOV (N = 2,374)
Age in years (mean, SD)	56 (16.4)	62 (15.6)
Ethnicity (%)		
Hispanic/Latinx	22.0	2.8
Not Hispanic/Latinx	61.5	86.8
Unknown	16.6	10.4
Race (%)		
Asian	2.5	0.9
Black	8.2	5.3
White	82.2	89.3
Unknown	6.8	4.5
Adverse socioeconomic determinants of health (%)[a]	9.0	23.0
Pre-existing medical conditions and treatments (%)		
Heart diseases	13.0	28.3
Cancer	43.6	58.6
Hypertension	46.4	67.1
Cerebrovascular diseases	8.8	19.6
Chronic lower respiratory diseases	30.2	41.4

Characteristic	NMT/RIT (N = 11,270)	MOV (N = 2,374)
Pre-existing medical conditions and treatments (%) *[continued]*		
Chronic kidney diseases	9.0	32.7
Chronic liver diseases	12.6	19.9
Overweight and obesity	30.4	37.7
Type 2 diabetes	19.1	36.2
Disorders involving the immune mechanisms	4.4	7.2
Congenital disorders	13.6	22.6
Mood disorders including depression	28.4	42.7
Psychotic disorders	1.9	4.7
Substance use disorders	15.4	24.3
HIV	2.4	5.6
Organ transplant	0.8	3.6
Tobacco smoker	8.1	13.8
Immunosuppressants	6.5	9.5
COVID-19 vaccine documented in EHR (%)	19.9	12.7

Before propensity score matching adjustment, relative to the NMT/RIT cohort, the MOV cohort was:

- Older
- More socioeconomically disadvantaged
- More likely to have comorbidities

Propensity score matching was utilized to increase comparability between the NMT/RIT and MOV cohorts. The two cohorts were matched 1:1 on

- demographics,
- adverse socioeconomic
- determinants of health,
- comorbidities,
- immunosuppressant usage,
- organ transplantation
- COVID-19 vaccination status.

[a]a composite variable comprising education, employment, occupational exposure, housing, and physical, social, and psychosocial environment.

EHR, electronic health record; HIV, human immunodeficiency virus; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir; SD, standard deviation.

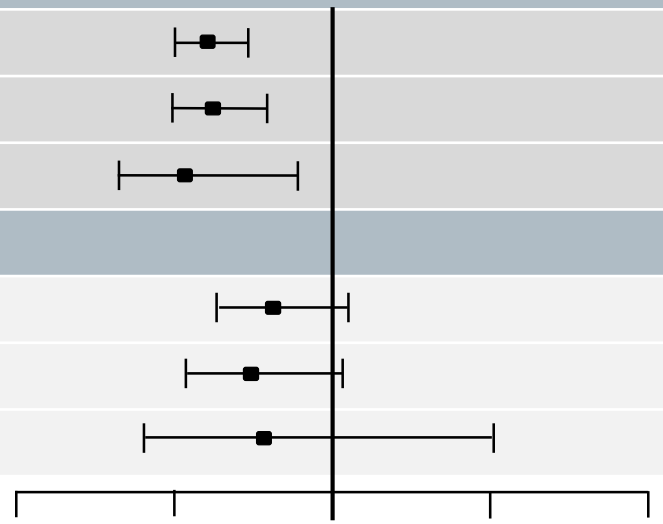
Wang et al. 2022. *medRxiv 2022.*

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV

7-Day Risk for COVID-19 Rebounds

(Before and After Propensity-Score Matching)

Rebound Outcome	NMT/RIT	MOV	HR (95% CI)
Before Matching			
COVID infections	3.53% (398/11270)	5.86% (139/2374)	0.60 (0.50−0.73)
COVID symptoms	2.31% (260/11270)	3.75% (89/2374)	0.62 (0.49−0.79)
Hospitalizations	0.44% (50/11270)	0.84% (20/2374)	0.53 (0.32−0.89)
After Matching			
COVID infections	4.54% (101/2226)	5.95% (132/2226)	0.81 (0.63−1.05)
COVID symptoms	2.61% (58/2226)	3.77% (84/2226)	0.74 (0.53−1.03)
Hospitalizations	0.67% (15/2226)	0.90% (20/2226)	0.78 (0.40−1.51)



HR, hazard ratio; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

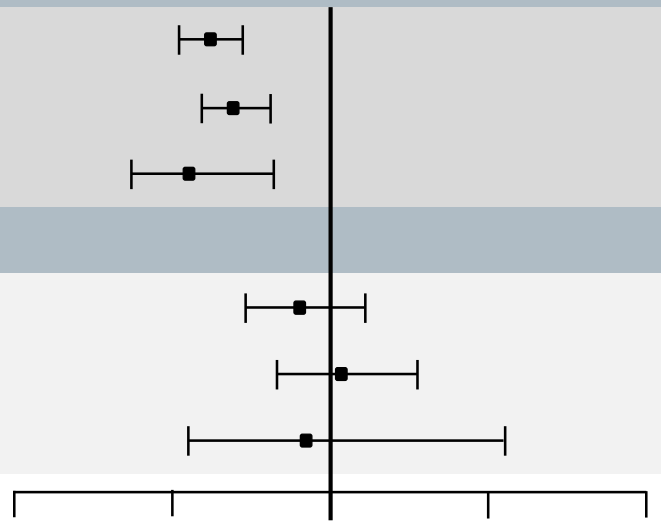
Wang et al. 2022. *medRxiv 2022.*

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV (*continued*)

30-Day Risk for COVID-19 Rebounds

(Before and After Propensity-Score Matching)

Rebound Outcome	NMT/RIT	MOV	HR (95% CI)
Before Matching			
COVID infections	5.40% (609/11270)	8.59% (204/2374)	0.62 (0.52−0.72)
COVID symptoms	5.87% (662/11270)	8.21% (195/2374)	0.69 (0.59−0.81)
Hospitalizations	0.77% (87/11270)	1.39% (33/2374)	0.55 (0.37−0.82)
After Matching			
COVID infections	7.14% (159/2226)	8.49% (189/2226)	0.90 (0.73−1.11)
COVID symptoms	7.55% (168/2226)	8.00% (178/2226)	1.03 (0.83−1.27)
Hospitalizations	1.21% (27/2226)	1.39% (31/2226)	0.92 (0.55−1.55)



HR, hazard ratio; MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

Wang et al. 2022. *medRxiv 2022.*

Study Results: Rates and Relative Risks for COVID-19 Rebound After NMT/RIT vs MOV (*continued*)

- Before propensity score matching, patients treated with MOV were significantly more likely to experience rebound COVID-19 infection, symptom, and hospitalization relative to NMT/RIT-treated patients during the 7-day follow-up and during the 30-day follow-up.
- After propensity score matching, there was no significant difference between the two cohorts regardless of the duration of follow-up.
- Incidence of rebound increased with the duration of follow-up in both cohorts.

MOV, molnupiravir; NMT/RIT, nirmatrelvir/ritonavir.

Persistent COVID-19 high tract respiratory infection

- **COVID19 patients with clinical and virological evidence of persistent respiratory tract infection** could define a new target of COVID patients
- All items should be present:
  1. COVID patients with **prolonged persistent respiratory symptoms or compartmentalized low respiratory infection** well after acute respiratory syndrome
  2. Usually patients with previous **hematological/oncological/neurological disorders**, few of them previously treated with **anti CD20 monoclonal agents**
  3. **Microbiological evidence** of persistent positive NPS or biological samples representative of low respiratory tract (spontaneous or induced sputum/BAL/BAL)
  4. **Negative or low-titer serological** evidence against **SARS-CoV-2 at day 20 since infection**

- In these COVID patients a **combined treatment using Sars-CoV-2 monoclonal antibodies against S protein and antivirals** can be used under off-label and/or compassionate use program

Risk Factors for Severe COVID-19 Breakthrough Infections

A nationwide retrospective cohort of 110,760 veterans who received the primary COVID-19 vaccination series and subsequently developed laboratory-confirmed SARS-CoV-2 between December 2020 to February 2022

- **Older age** had the **strongest association** with severe breakthrough infection
- Immunocompromising medications and conditions were associated with increased risks of severe breakthrough infection
- Receipt of a **vaccine booster** was associated with **50% lower risk** of severe breakthrough infection

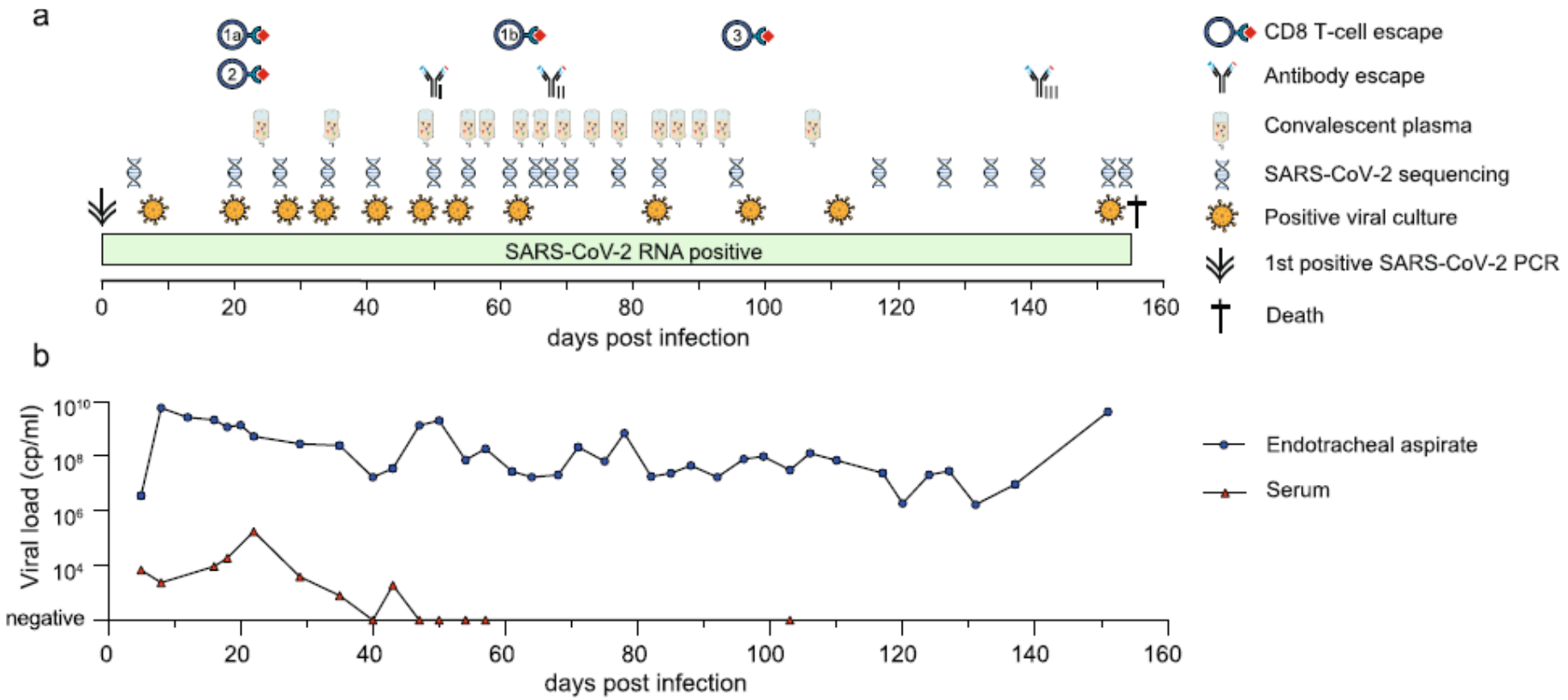
Risk Factors	Adjusted Odds Ratio (95% CI)	
Age		
≥50 (per 5-year increase)	1.42 (1.40 – 1.44)	
≥80 yrs (relative to patients aged 45-50 yrs)	16.1 (13.1 – 19.9)	
Selected Immunocompromising Medications and Conditions		
Cytotoxic chemotherapy after vaccination	2.71 (2.27 – 3.24)	
Glucocorticoid use after vaccination	2.34 (2.18-2.5)	
Leukemia or lymphoma	1.87 (1.61 – 2.17)	
Chronic Comorbid Conditions		
Heart failure	1.74	1.61 – 1.88
Dementia	2.01	1.83 – 2.20
Chronic kidney disease	1.59	1.49 – 1.69
Vaccine booster dose	0.50	

Branch-Elliman. IDWeek 2022. Abstr 788.

nature communications

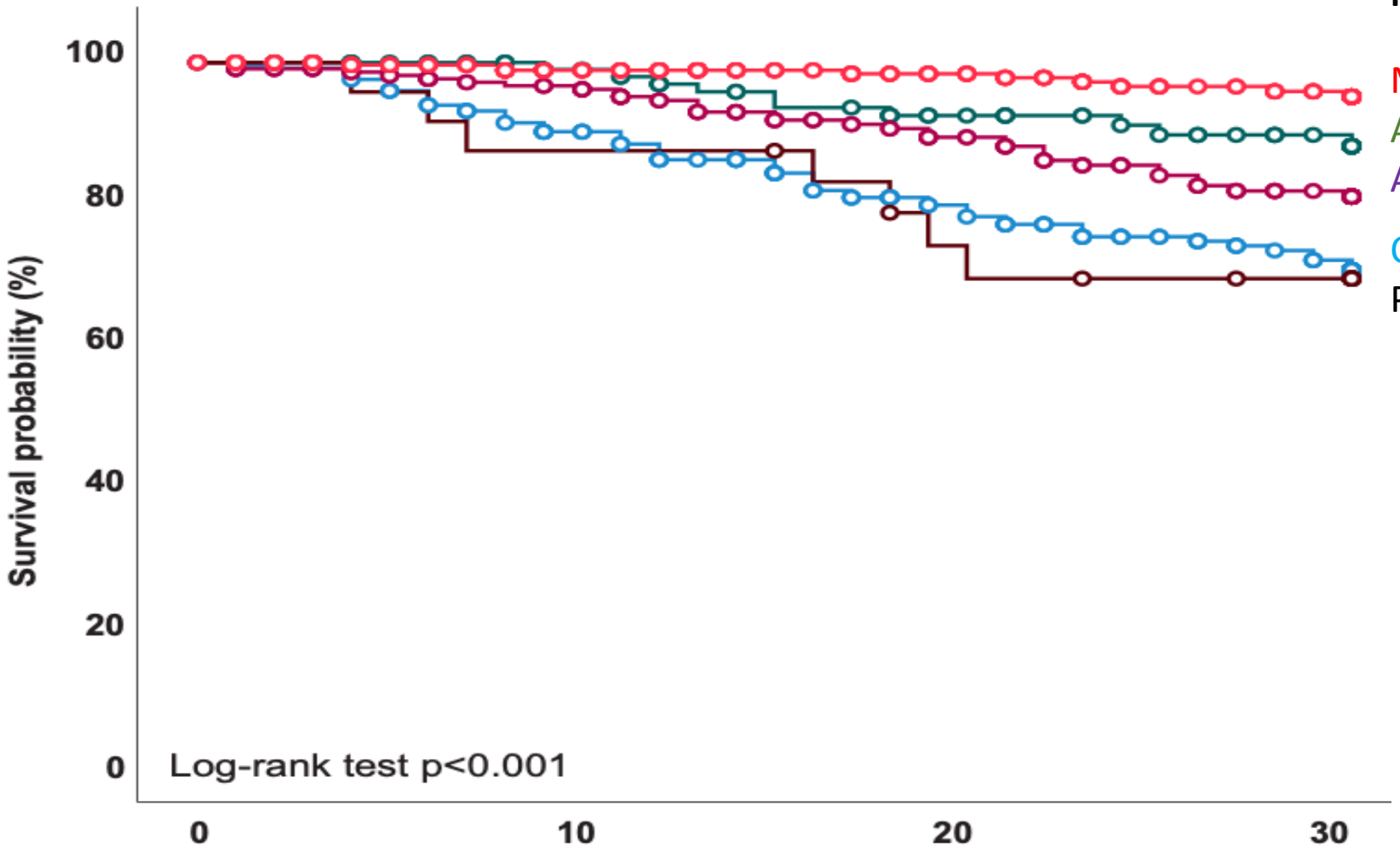
Accumulation of mutations in antibody and CD8 T cell epitopes in a B cell depleted lymphoma patient with chronic SARS-CoV-2 infection

SARS- CoV-2 sequences in a B cell-depleted lymphoma patient: three mutations in the spike protein that dampen convalescent plasma-mediated neutralization of SARS-CoV-2. Additionally, four mutations emerge in non-spike regions encoding three CD8 T cell epitopes, including one nucleoprotein epitope affected by two mutations.



Khatamzas et al, Nat Commun 09.22

Breakthrough COVID-19 in vaccinated patients with hematologic malignancies: results from EPICOVIDEHA survey



Number patients at risk

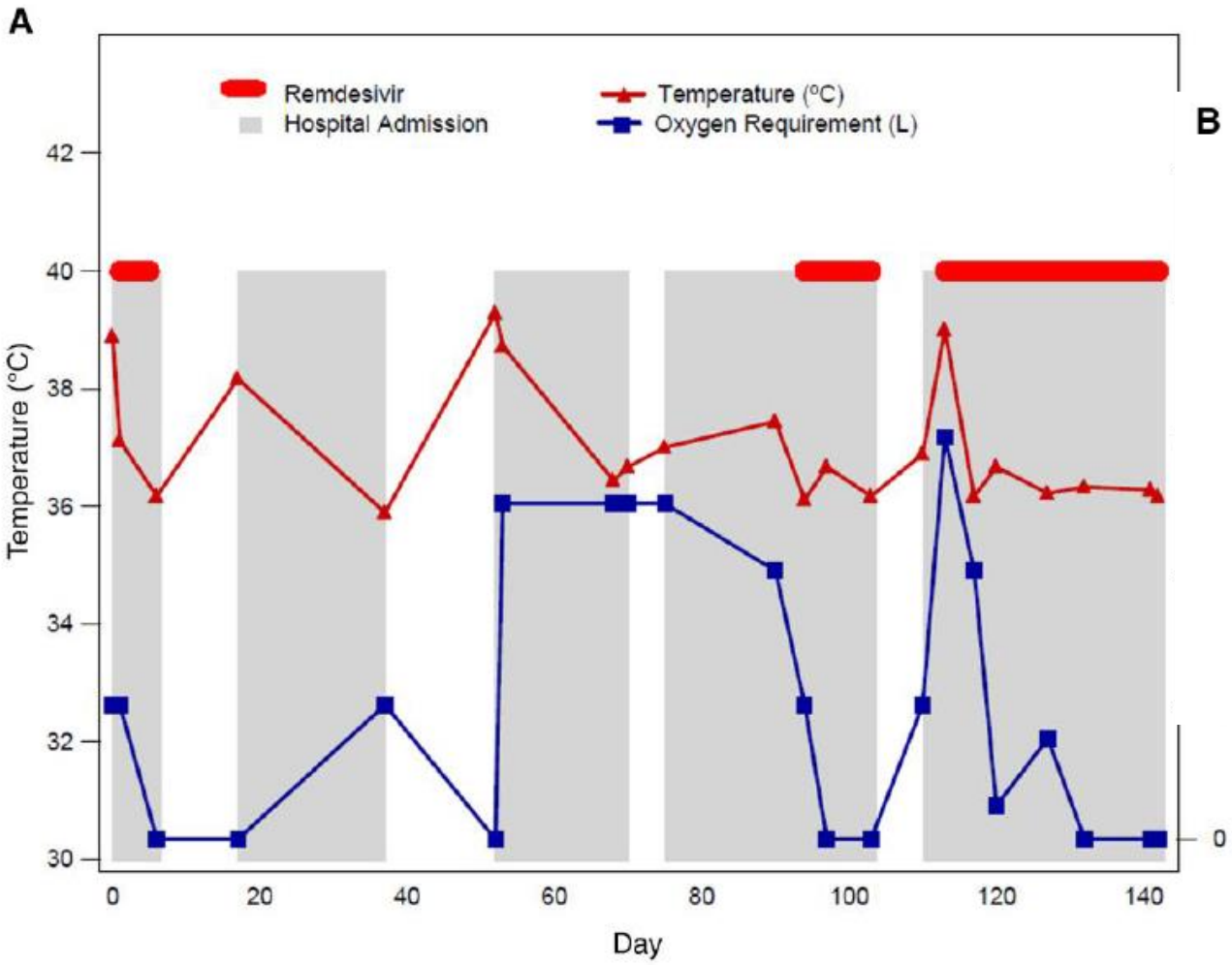
Monoclonal antibodies	311
Antivirals + MoAb	108
Antivirals	218
Corticosteroids	246
Plasma	23

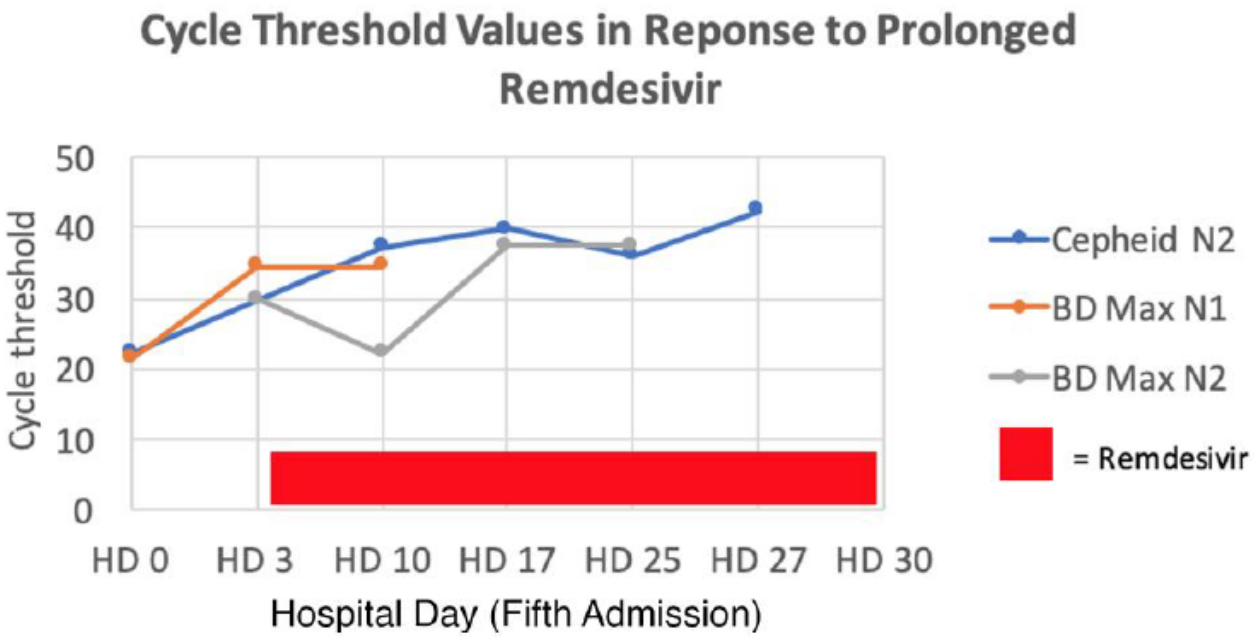
A total of 1,548 cases were included from several EU countries from 01. 2021 to 03. 2022 with a CFR in HM patients with breakthrough COVID-19 is about 9%, lower than in the pre-vaccination era. Patients who received monoclonal antibodies, alone or combined with antivirals, show a better clinical outcome

Pagano L Blood 11.222

Extended Remdesivir Infusion for Persistent Coronavirus Disease 2019 Infection

Open Forum Infectious Diseases



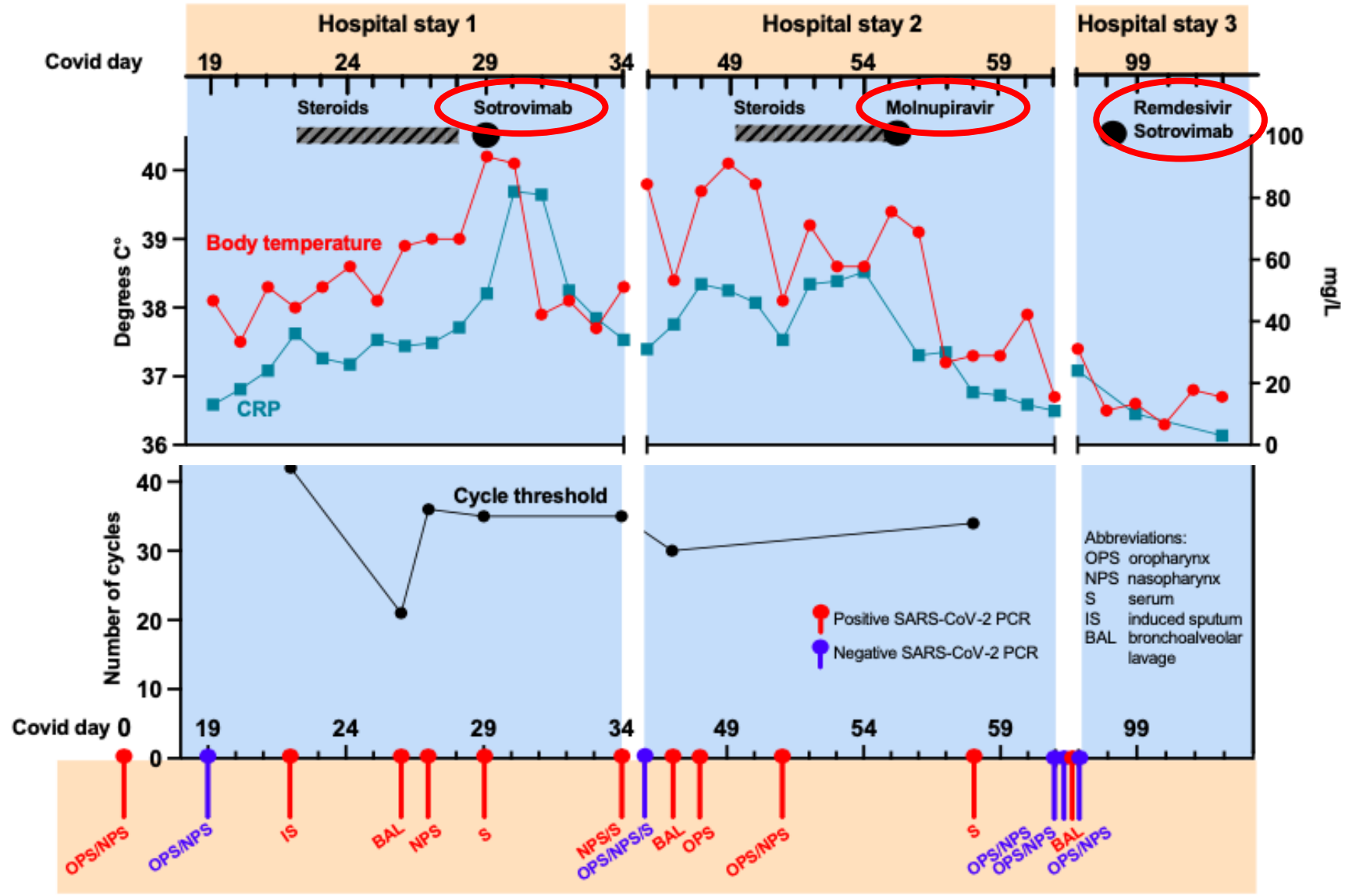


5-month persistent COVID19 in a **44 male granulomatosis with polyangiitis and secondary hypogamma** successfully treated **with 30 days of remdesivir**, desametasone e IVG. Ab Mono not available in August 2020

Martinez OFID 07.22

Case Report

Persistent Fever and Positive PCR 90 Days Post-SARS-CoV-2 Infection in a Rituximab-Treated Patient: A Case of Late Antiviral Treatment

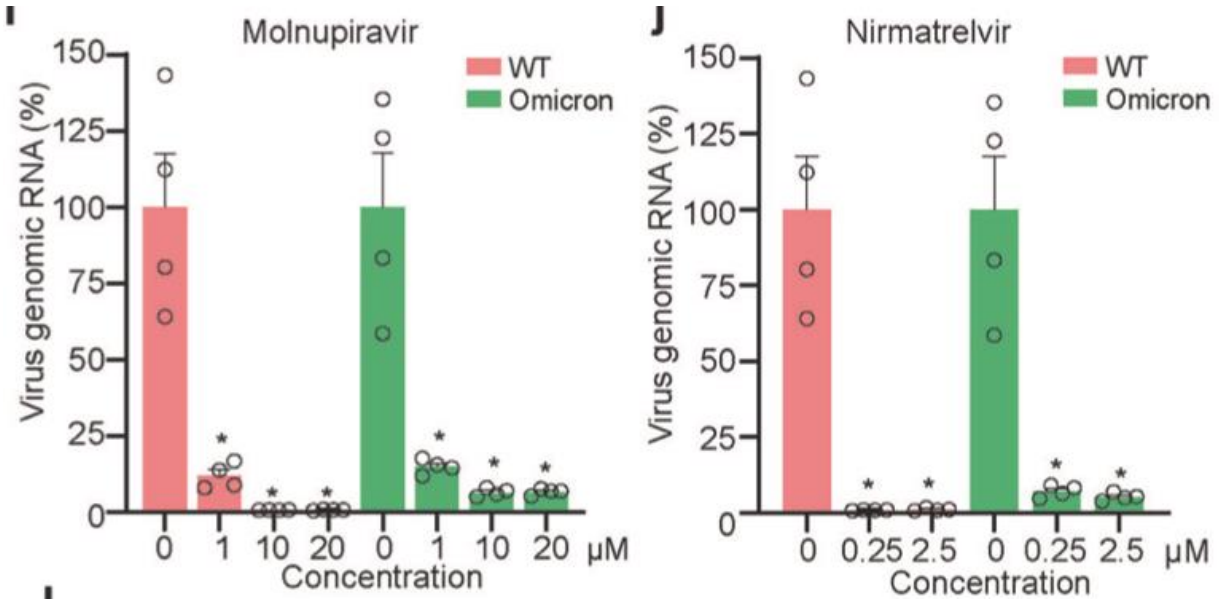


We present a case of 96 days of persistent fever and SARS-CoV-2 infection in a patient receiving B cell depletion therapy for multiple sclerosis.
The patient was hospitalized three times, with transient improvement after late antiviral treatment and full recovery 6 months post-rituximab infusion.

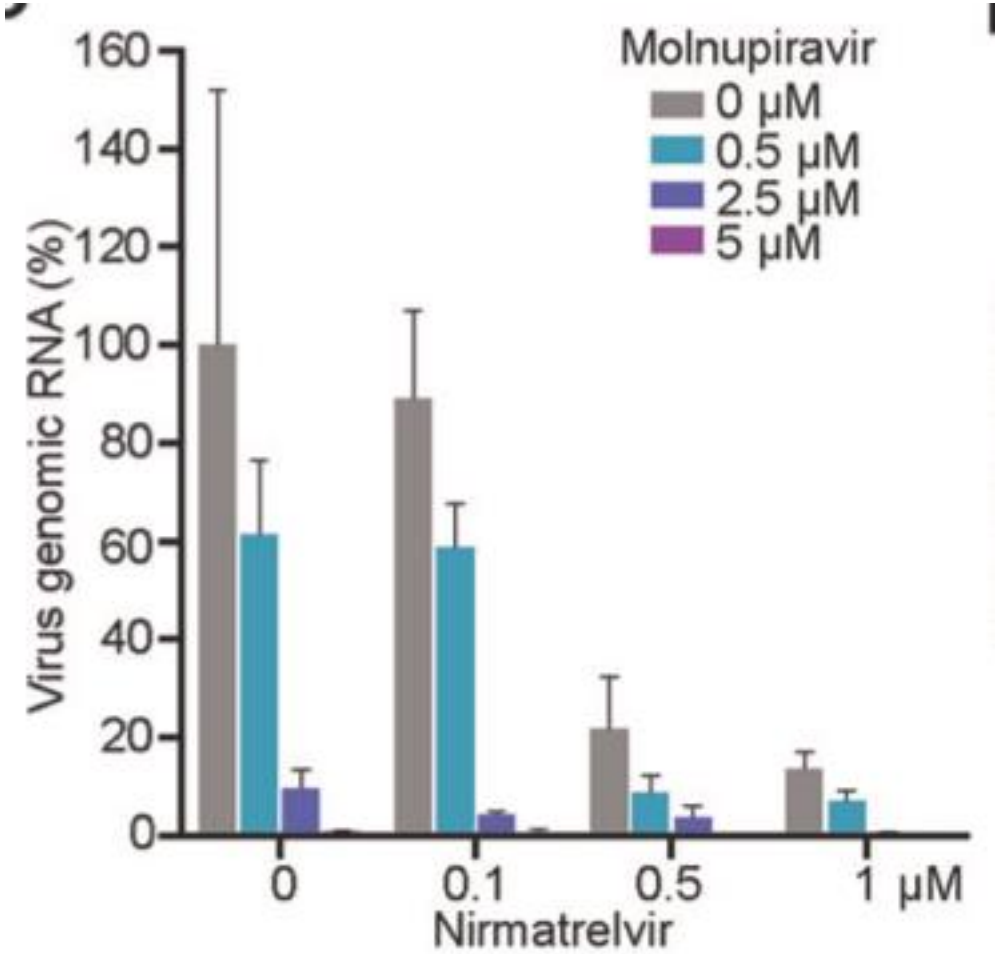
LETTER TO THE EDITOR OPEN

SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination

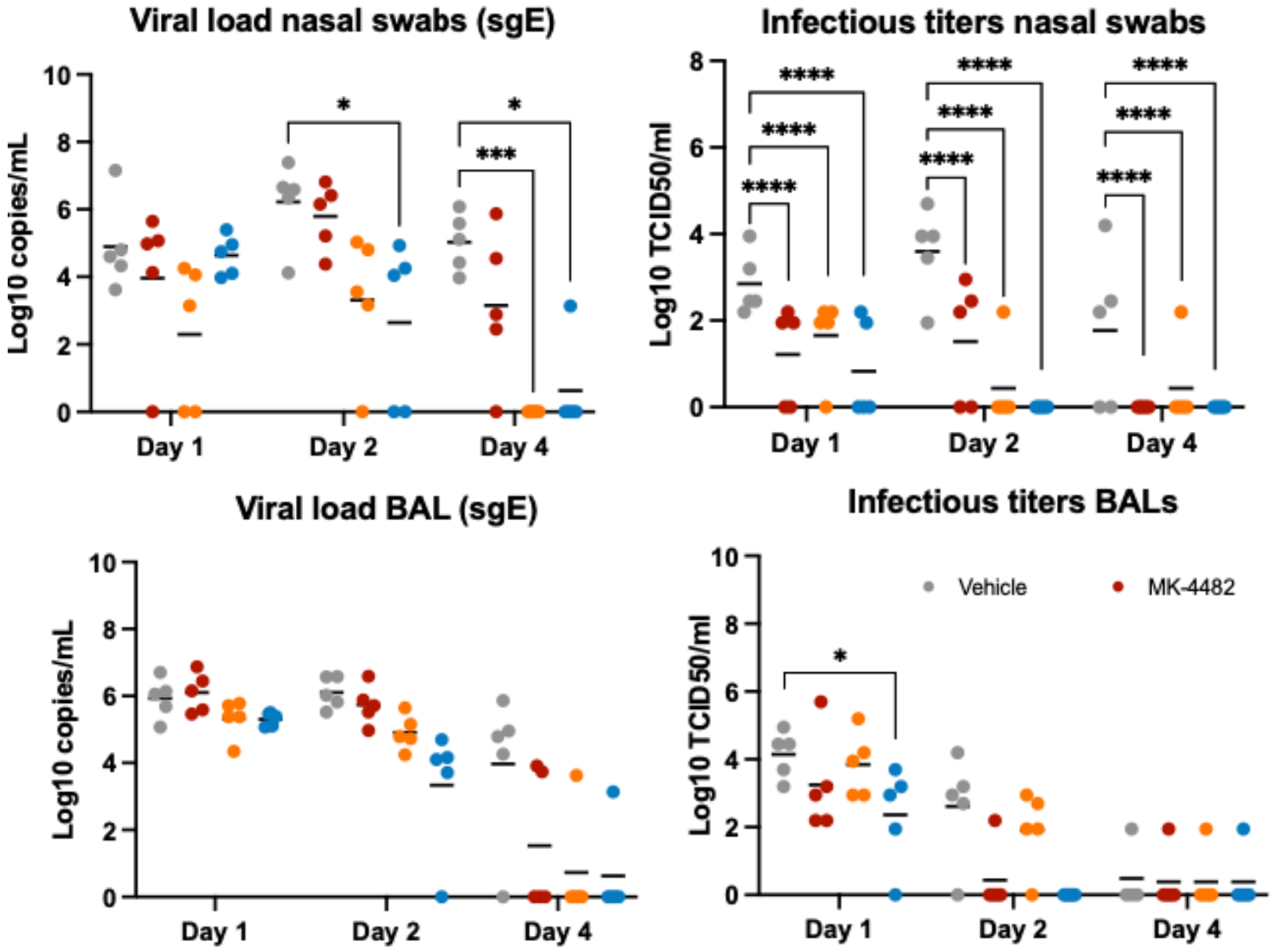
The effects of molnupiravir (n = 4) and nirmatrelvir (n = 4) on intracellular viral RNA levels of WT and Omicron SARS-CoV-2 in hAOs.



The antiviral effects of **combining molnupiravir and nirmatrelvir in Omicron** SARS-CoV-2 infected cells



Combined Molnupiravir and Nirmatrelvir Treatment Improves the Inhibitory Effect on SARS-CoV-2 in Rhesus Macaques

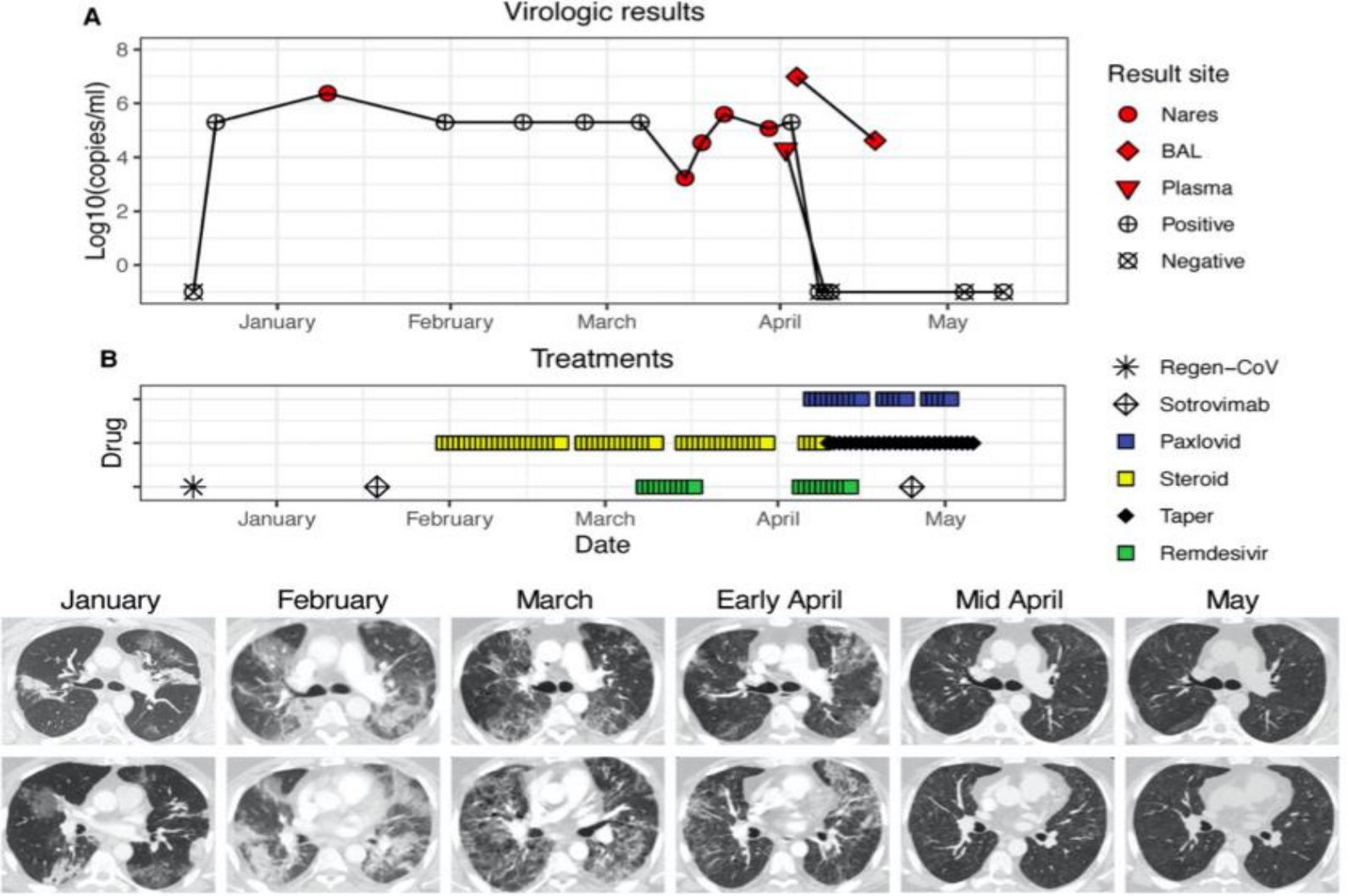


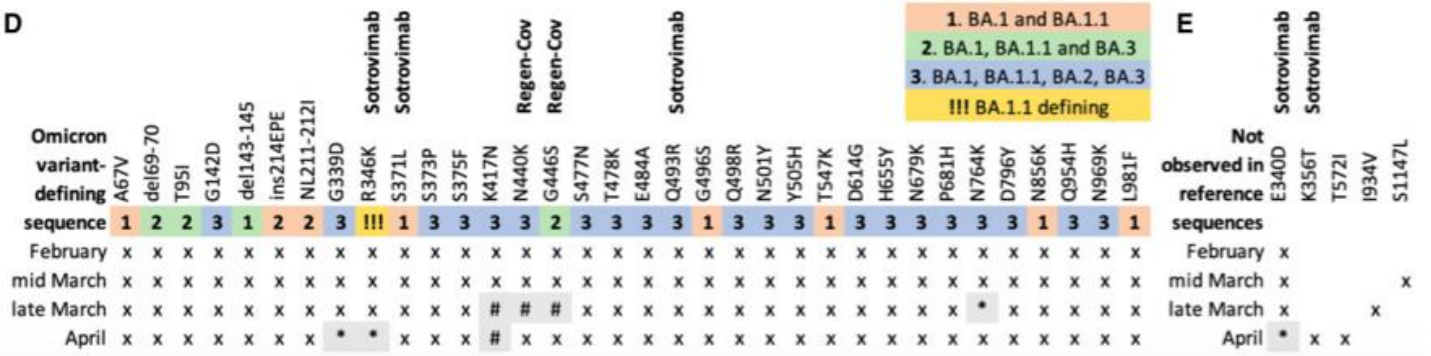
Combination therapy of MK-4482 and PF-07321332 529 **significantly reduced virus replication in the respiratory tract of SARS-CoV-2 infected rhesus macaques.**

Viral load and infectious titre in nasal swabs

Viral load and infectious titre in BAL.

Rosenke K BioRxiv 10.22





IDSA Infectious Diseases Society of America
hivma hiv medicine association
OXFORD
Clinical Infectious Diseases

Successful treatment of prolonged, severe COVID-19 in a B-cell ALL patient with an extended course of remdesivir & nirmatrelvir/ritonavir

ES Ford CID 3 November 2022

Globally, ~43% of Individuals With SARS-CoV-2 Infection Experience Long-term, Health-Related Consequences of COVID-19[1]

The burden of long COVID is substantial, despite current management measures

54%
of hospitalized COVID-19 patients experience long COVID[1]

34%
of non-hospitalized COVID-19 patients experience long COVID[1]

Most prevalent long COVID symptoms are the following:[1]

Fatigue | Memory problems | Dyspnea | Sleep problems | Joint pain

Long COVID can occur regardless of disease severity[1,2]

The duration of long COVID varies, with some individuals experiencing symptoms at least 2 years after initial infection[2]

45.6% of patients with long COVID symptoms reported working reduced hours[3]

Vaccination reduces the risk of developing long COVID sequelae by only 15%[4]

COVID-19 = coronavirus disease 2019; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.
[a]The primary outcome was the prevalence of post–COVID-19 condition and symptoms at least 28 days after the index date. Post–COVID-19 condition was defined as having (1) any symptoms or (2) at least 1 new or persisting symptom during the follow-up time.

1. Chen C et al. In press-corrected proof. *J Infect Dis*. 2022; 2. Huang L et al. *Lancet Respir Med*. 2022;10(9):863-876; 3. Davis HE et al. *EClinicalMedicine*. 2021;38:101019; 4. Al-Aly Z et al. *Nat Med*. 2022;28(7):1461-1467.

NIH Guidelines: Recommended Treatment Based on Availability and Patient Considerations

- For **nonhospitalized** patients with mild to moderate COVID-19 who are at high risk of progression to severe disease, consider these agents (**listed in order of preference**)

Anti–SARS-CoV-2 Treatment	Population	Clinical Considerations	Evidence Ranking
Nirmatrelvir + ritonavir orally PO BID x 5 days	Aged ≥12 yr and weighing ≥40 kg	**Use within 5 days of symptom onset** Drug interactions Renal dosing if eGFR 30-59 mL/min HIV activity of ritonavir	Strong
Remdesivir IV daily x 3 days	Aged ≥12 yr*	**Use within 7 days of symptom onset** Must be administered in a healthcare setting	Strong

*Consider treatment for children aged <12 yr based on age and other risk factors.

- **Unvaccinated patients** likely to derive most benefit from COVID-19 antiviral agents

covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management.
covid19treatmentguidelines.nih.gov/tables/therapeutic-management-of-nonhospitalised-children.

NIH Guidelines: Alternative Treatment Options

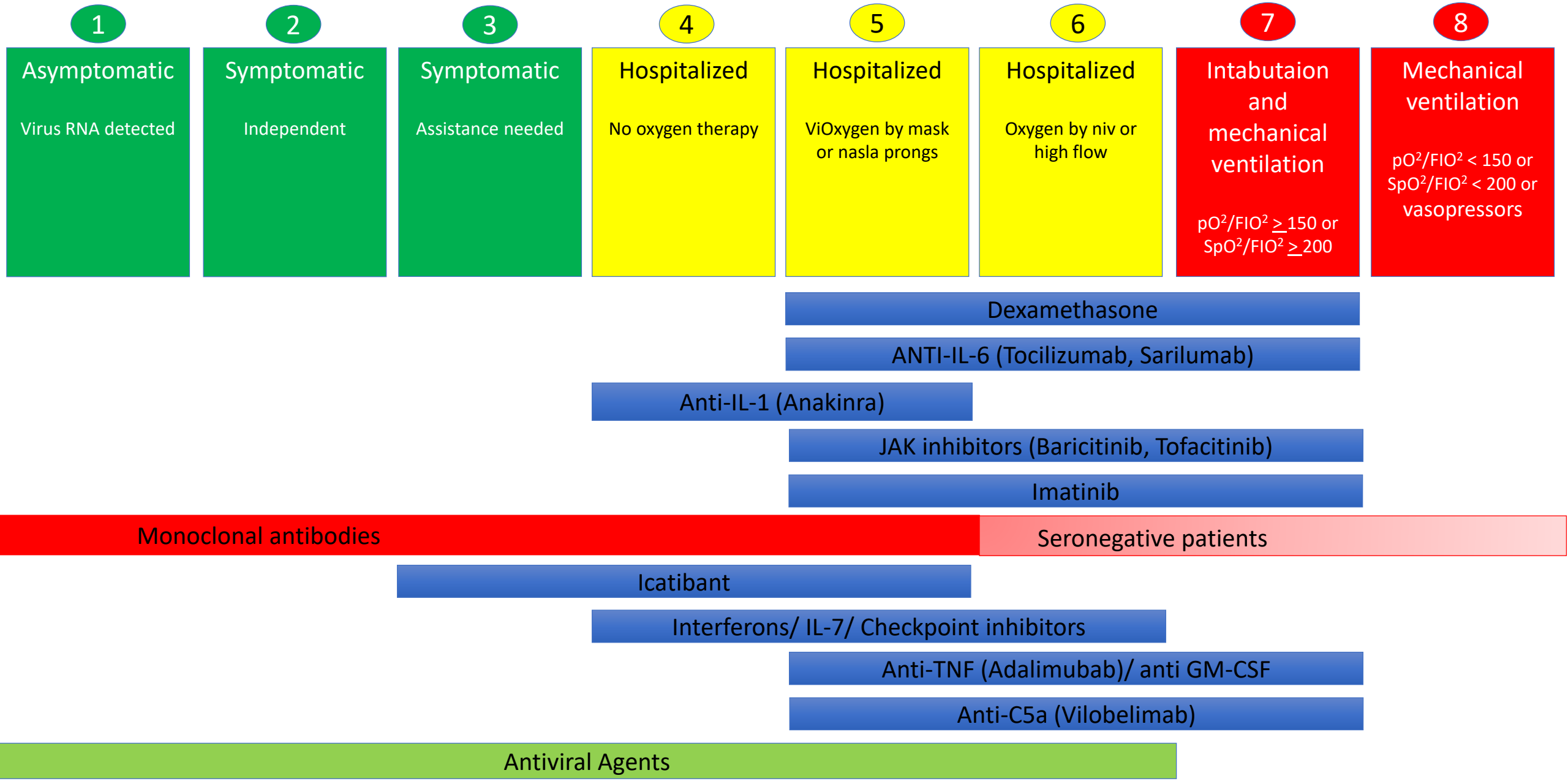
- If neither of the preferred therapies for high-risk, nonhospitalized patients is available, feasible to administer, or clinically appropriate for the individual, consider these agents (**listed alphabetically**)

Anti–SARS-CoV-2 Treatment	Population	Clinical Considerations	Evidence Ranking
Bebtelovimab IV x 1 dose	Aged ≥18 yr*	**Use within 7 days of symptom onset** Data come from in vitro studies Insufficient data on hospitalization and mortality outcomes	Optional *(RCTs or subgroup analyses)*
Molnupiravir orally every 12 hr x 5 days	Aged ≥18 yr	**Use within 5 days of symptom onset** Lower efficacy in clinical trials Caution if childbearing potential Do not use in pregnant women	Optional *(expert opinion)*

*Insufficient evidence to recommend for or against for children aged 12-17 yr.

covid19treatmentguidelines.nih.gov/management/clinical-management/nonhospitalized-adults--therapeutic-management

Immunomodulatory Treatment Options According to WHO Clinical Progression Score



Nat Med 2022; 28:39-50