ReFORMÚLaTE

ADEU COVID

ACTUALIZACIÓN DEL TRATAMIENTO DE LA COVID-19

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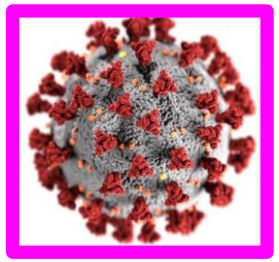
IDIBAPS



Transparency Declaration

Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from the following Pharmaceutical Companies:

Abbvie
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Gilead Sciencies
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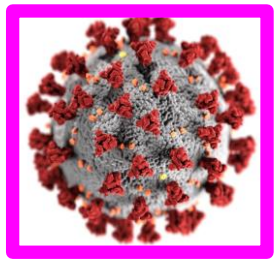

Role of antivirals and neutralizing antibodies in the prophylaxis and treatment of COVID-19

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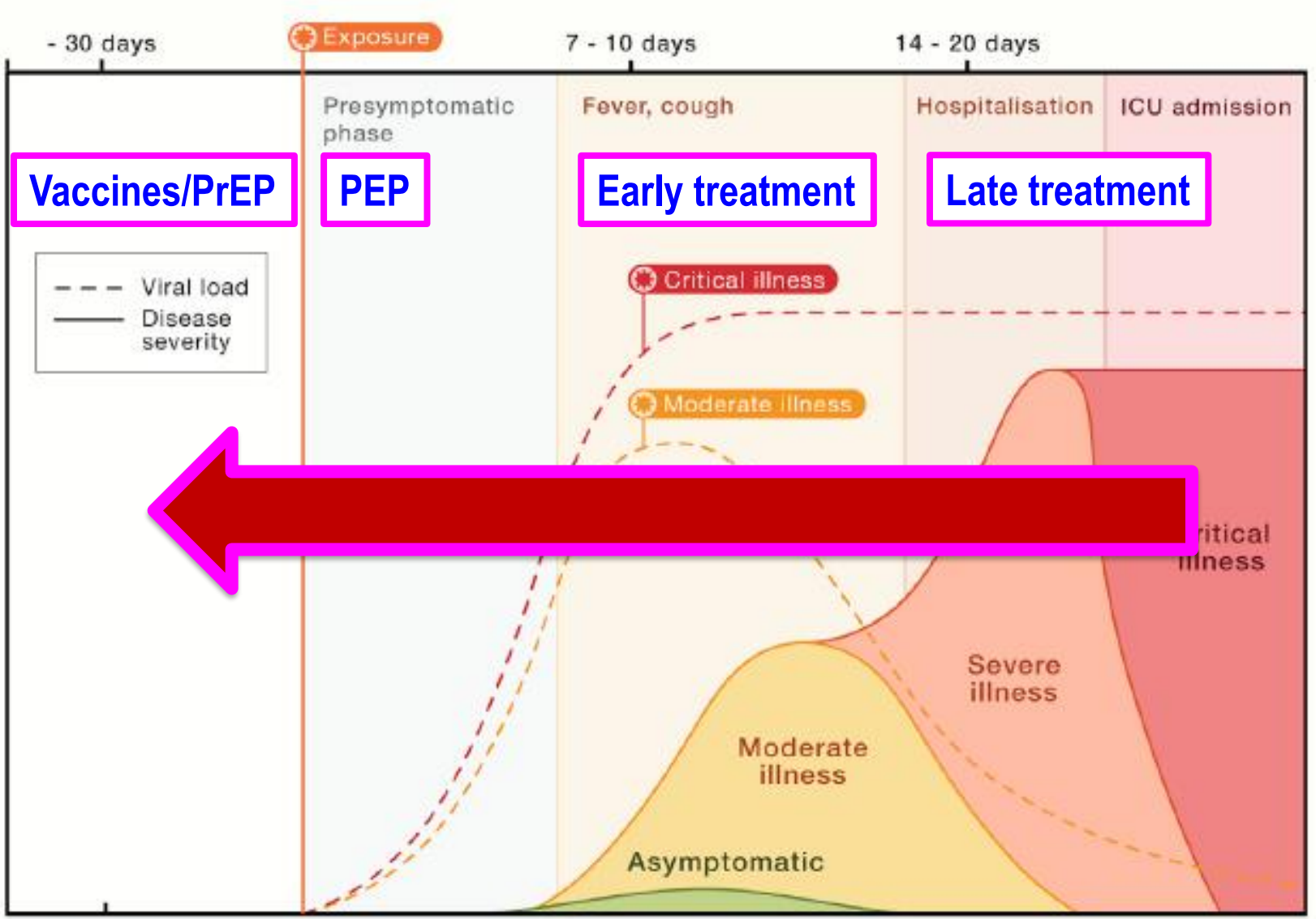
- Inpatient Treatment
- Outpatient treatment
- Pre-exposure prophylaxis (PreP)
- Take-home messages

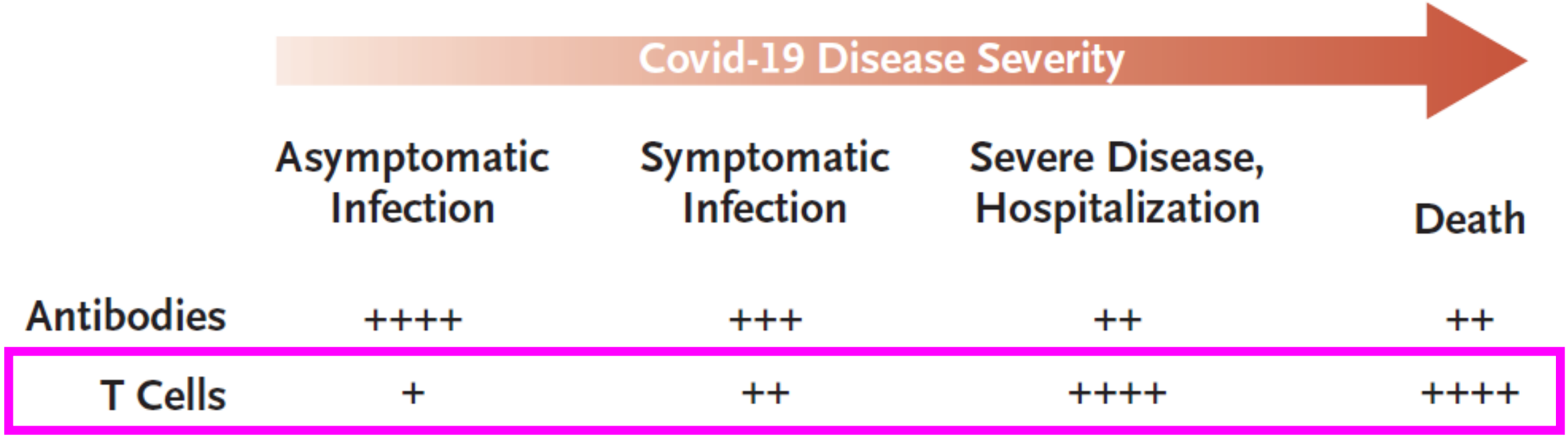
November 25th 2022

Prophylactic and Therapeutic Approaches to COVID-19

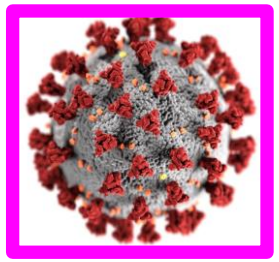


Corti D et al. Cell. August 19th 2021;184:4593-4595.

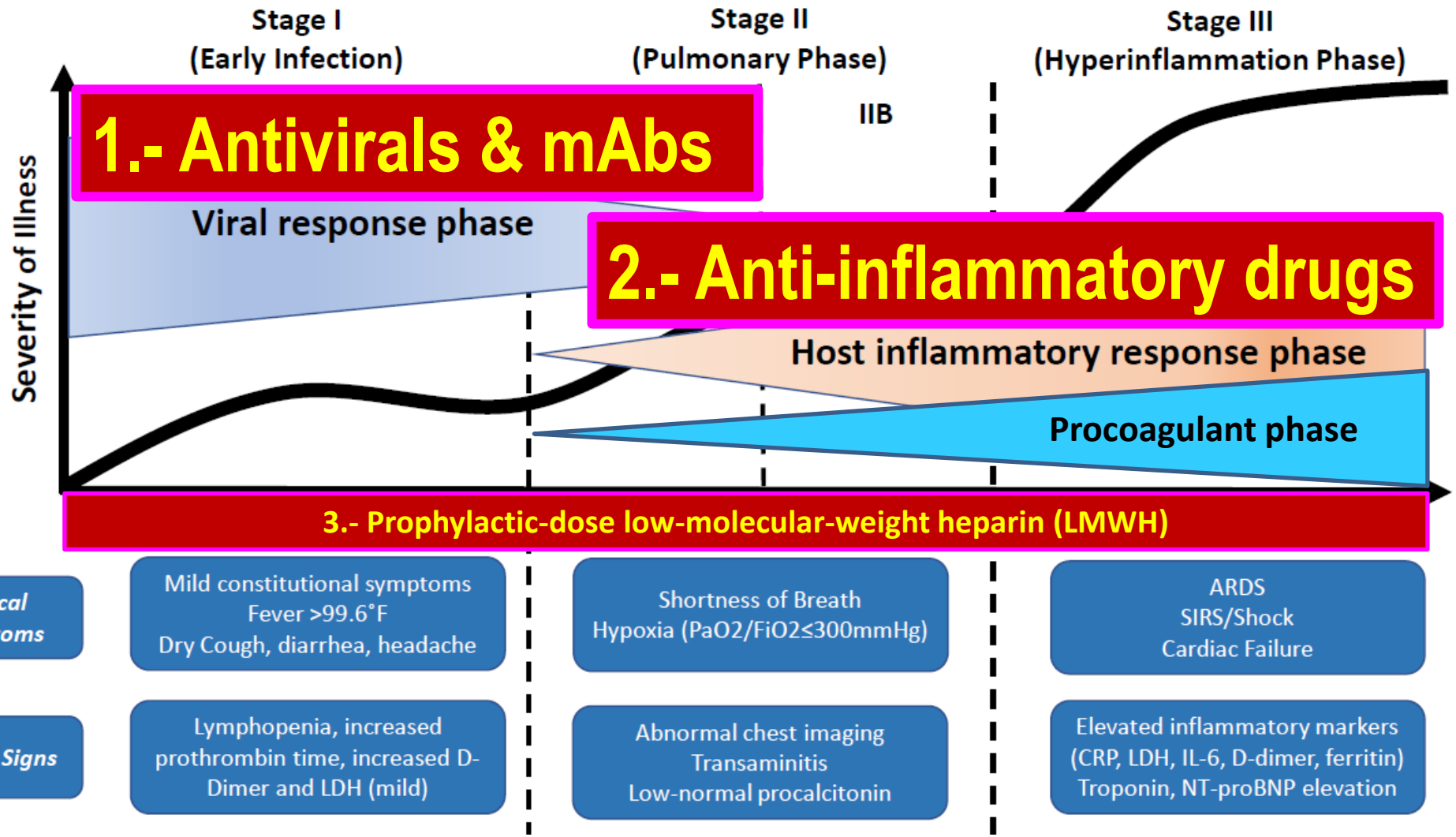
Immune Responses for Protection against Severe SARS-CoV-2



Barouch DH. N Engl J Med. Sep 15, 2022; 387:1011-1020.



Bases of COVID-19 treatment

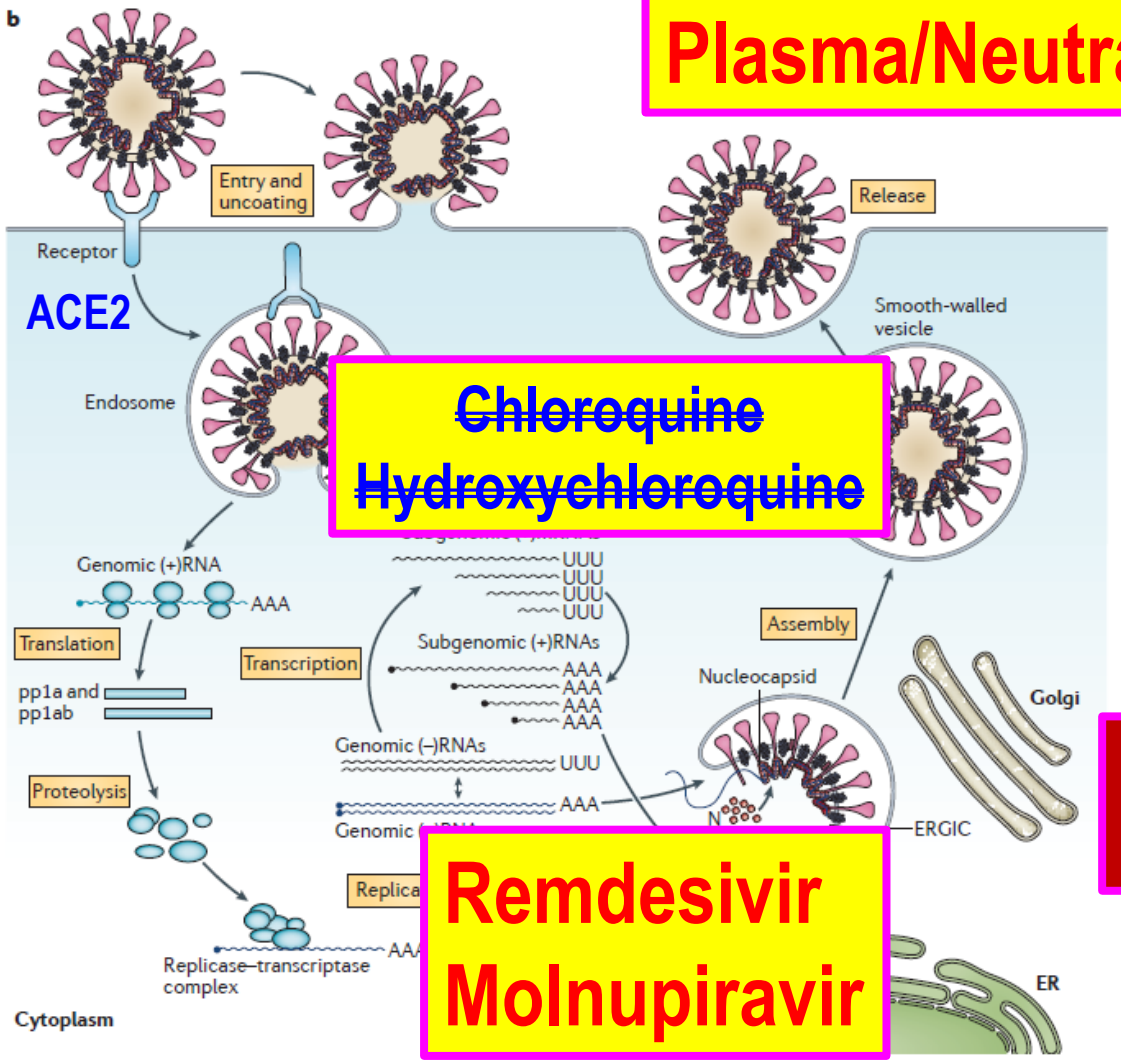


Siddiqu HK, Mehra MR. J Heart Lung Transplant. 2020 doi: 10.1016/j.healun.2020.03.012; Pericas JM, Hernandez-Meneses M et al. Eur Heart J. June 8th 2020.

SARS-CoV-2 life cycle: Antiviral targets

Entry inhibitors
hrACE2 – APN01
~~Camostat~~

Plasma/Neutralizing Antibodies



~~Chloroquine~~
~~Hydroxychloroquine~~

~~Interferon-beta~~

~~Ivermectin~~

~~Lopinavir/rtv~~
Nirmatrelvir/rtv

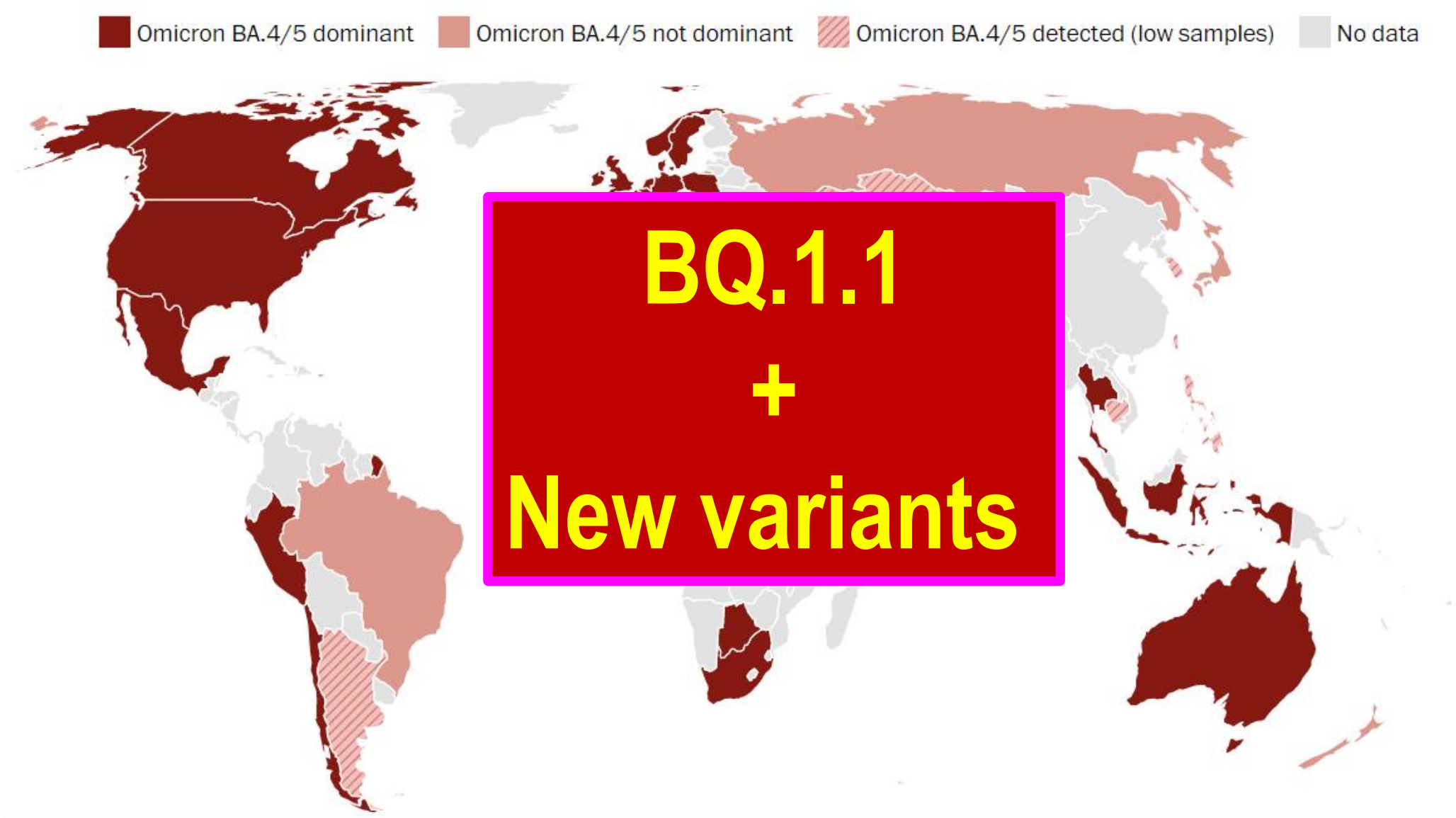
Remdesivir
Molnupiravir

Potential for combining several antiviral drugs

* Interferon induces hundreds of genes which can act on various parts of the lifecycle from potentially degrading viral RNA (OAS, RNASL) to inhibiting virus egress (BST-2)

De Wit Nature Rev Microbiol, 2016; Sanders JM, et al. JAMA. 2020 Apr 13. doi: 10.1001/jama.2020.6019.

The Omicron BA.4/5 variants now dominate worldwide



https://www.washingtonpost.com/health/interactive/2021/tracker-omicron-spread/?itid=lk_interstitial_manual_13 July 18th 2022.

Antiviral Drugs are *in vitro* Active against new Omicron Subvariants BA.2, BA.5, BA.2.75 and BA.4.6

	GS-441524, Remdesivir§	EIDD-1931, Molnupiravir¶	PF-07321332, Nirmatrelvir‖
	micromoles		
Ancestral strain (A): SARS-CoV-2/ UT-NC002-1T/ Human/2020/Tokyo	0.98 ±0.30	0.59 ±0.11	1.71 ±0.29
Omicron (BA.2): hCoV-19/Japan/UT-NCD1288-2N/2022	1.32 ±0.21	0.25 ±0.08	1.69 ±0.66
Omicron (BA.5): hCoV-19/Japan/TY41-702/2022	0.45 ±0.09	0.23 ±0.07	1.50 ±0.34
Omicron (BA.2.75): hCoV-19/Japan/ TY41-716/2022	1.52 ±0.42	0.90 ±0.18	1.78 ±0.35
Omicron BA.4.6: hCoV-19/USA/ WI-UW-12757/2022		1.95	8.38	4.43
Omicron BA.4.6: hCoV-19/USA/ WI-UW-12767/2022		0.54	2.62	1.29

Takashita E et al. NEJM. Sept 29th 2022; Takashita E et al. NEJM. Nov 16th 2022.

The Omicron variants BA.4/5 and BA.2.75 are resistant to most neutralizing monoclonal antibodies except Bebtelovimab

Fold reducing neutralizing susceptibility to neutralizing antibodies under EUA

Test\mAb	BAM	ETE	BAM/ETE	CAS	IMD	CAS/IMD	CIL	TIX	CIL/TIX	SOT	BEB	ADI
Omicron/BA.1	>1000$_{37}$	428$_{37}$	887$_{14}$	>1000$_{44}$	>1000$_{45}$	>1000$_{18}$	272$_{40}$	264$_{42}$	50$_{28}$	3.8$_{51}$	1$_{21}$	110$_{17}$
Omicron/BA.2	>1000$_{23}$	504$_{23}$	794$_{13}$	>1000$_{29}$	259$_{28}$	387$_{16}$	2.1$_{28}$	608$_{27}$	7.8$_{24}$	23$_{38}$	1.1$_{24}$	>1000$_{15}$
Omicron/BA.2.12.1	>1000$_{9}$	432$_{9}$	776$_{6}$	>1000$_{10}$	361$_{10}$	143$_{7}$	3$_{10}$	382$_{10}$	9.5$_{7}$	19$_{11}$	1$_{10}$	>1000$_{5}$
Omicron/BA.4/5	853$_{12}$	408$_{12}$	554$_{7}$	>1000$_{15}$	488$_{15}$	387$_{9}$	9.7$_{22}$	>1000$_{22}$	33$_{18}$	26$_{24}$	1$_{20}$	968$_{8}$
Omicron/BA.2.75	705$_{5}$	333$_{5}$	554$_{3}$	221$_{5}$	>1000$_{5}$	>1000$_{3}$	19$_{5}$	30$_{5}$	25$_{3}$	13$_{5}$	3.1$_{5}$	673$_{4}$

Monoclonal antibody (mAb) abbreviations: BAM: Bamlanivimab/LY-CoV555/LY3819253, ETE: Etesevimab/LY-CoV016/JS016/CB6, CAS: Casirivimab/REGN10933, IMD: Imdevimab/REGN10987, CIL: Cilgavimab/COV2-2130/AZD1061, TIX: Tixagevimab/COV2-2196/AZD8895, SOT: Sotrovimab/Vir-7831/S309, **BEB: Bebtelovimab/LY-CoV1404/LY3853113**, REG: Regdanvimab/CT-P59, AMU: Amubarvimab/BRII-196/P2C-1f11, ROM: Romlusevimab/BRII-198/P2B-1G5, ADI: Adintrevimab/ADG20/ADG-2.

The color scheme indicates the fold-reduction in neutralization: **absence of color – <5-fold reduced susceptibility**; light blue – 5 to 24.9-fold reduced susceptibility; **dark blue – ≥25-fold reduced susceptibility.**

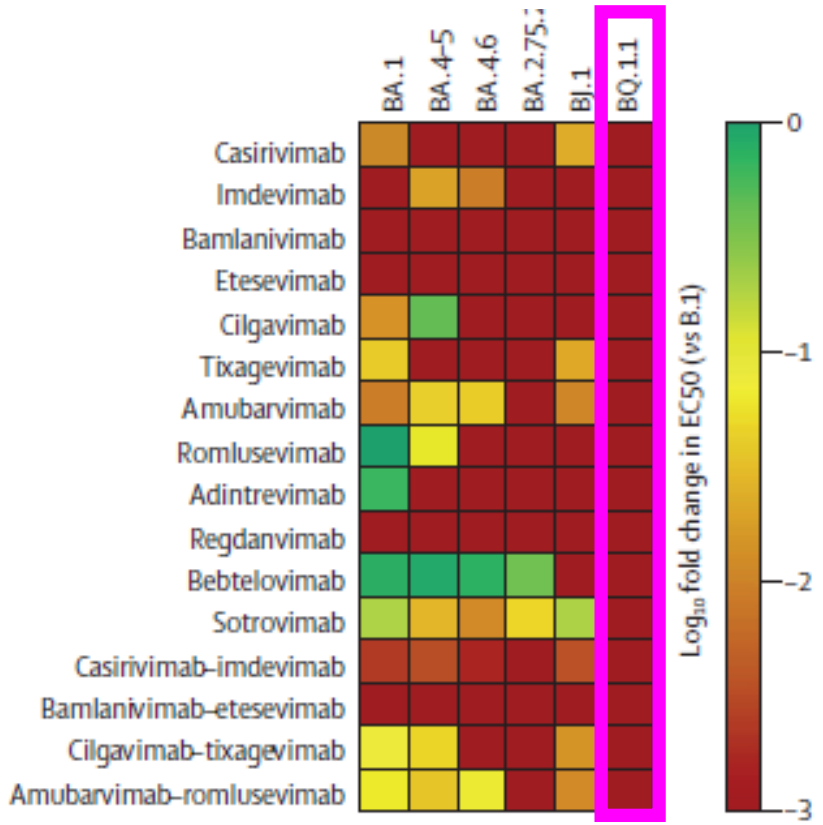
Bebtelovimab is not approved by the EMA, it is in the review phase.

https://covdb.stanford.edu/page/susceptibility-data/; **September 29th 2022**

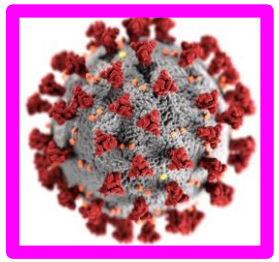
The Omicron variant BQ.1.1 is resistant to all neutralizing monoclonal antibodies (mAbs)

		B.1	BA.1	BA.4-5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Single mAbs	Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
	Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
	Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
	Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
	Tixagevimab	7	173	10090	27740	>50000	304	>50000
	Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
	Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
	Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
	Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
	Bebtelovimab	5	7	6	7	14	>50000	>50000
	Sotrovimab	157	833	5554	13000	3239	825	>50000
Cocktails of mAbs	Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
	Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab–tixagevimab	7	97	155	7131	>50000	482	>50000
	Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

EC50 (ng/ml)



Arora P et al. Lancet Infect Dis. November 18th 2022.



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November 25th 2022

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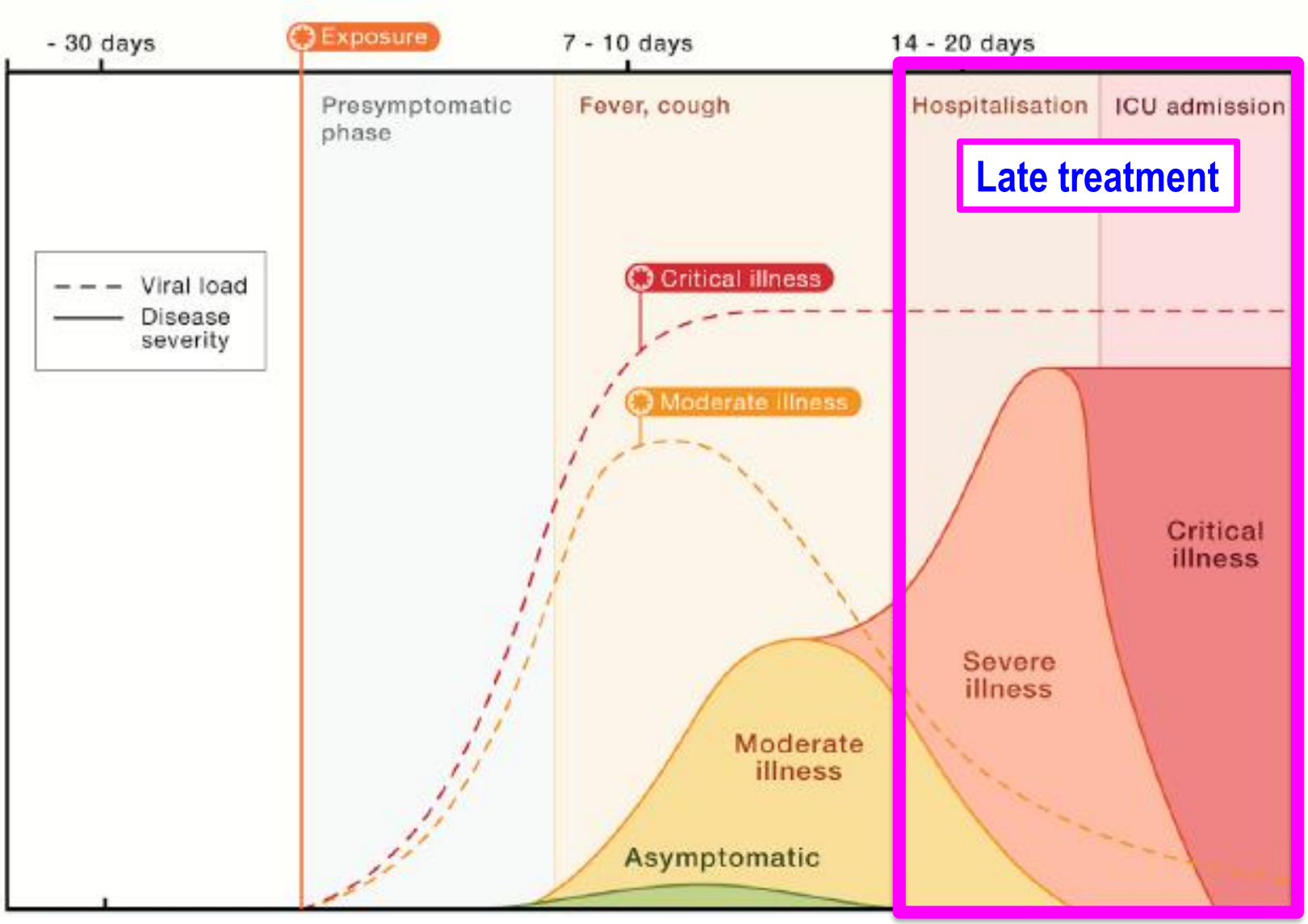


Corti D et al. Cell. August 19th 2021;184:4593-4595.

Disease stages
- **NIH stages**
- **ACTT scores**

Community	Hospital - Ward	Hospital - ICU
Asymptomatic/Mild Stages 1-2	Moderate/Severe Stages 3-5	Critical (MV, ECMO) Stages 6-7

Isolation, at least 10-14 days

Treatment
- Early antiviral therapy
- Proper timing anti-inflammatory drugs
- Prophylactic heparin

Oral antivirals are not effective in severe COVID-19

Remdesivir, IV, 5 days
Stages 4 (no oxygen) & 5 (low-flow oxygen supply)
Stage 6 plus **Baricitinib**, oral, 14 days

Parenteral mAbs**, single IV dose
Only in seronegative persons or with <260 BAU/mL.

Dexamethasone, 6 mg IV/oral, 10 d.
Stages 5-7, low/high-flow oxygen supply, MV and ECMO
Tocilizumab, single IV dose
Baricitinib, 4 mg/d, oral 10 d.

Low molecular weight heparin, SC
During the entire hospitalization period

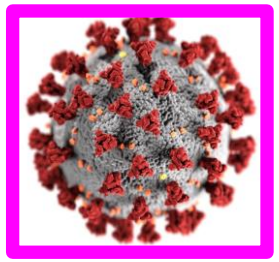
** Check variant of concern (VoC) for antiviral activity.

Miro JM, Torres A, Paredes R. Arch Bronconeumol. 2022;58 Suppl 1:8-10.

New Immunomodulatory Therapies in Hospitalized Patients

Trial	Target population	Outcomes
Brensocatib (DPP-1; an enzyme responsible for the activation of neutrophil serine proteases) plus SoC. STOP-COVID RCT*	Hospitalized patients with at least one risk factor for severe disease	**Did not improve clinical status**
Baricitinib (4 mg/d 14 d) plus remdesivir. ACTT-4 RCT**	Hospitalized patients with low-flow (≤15 L/min), high-flow (>15 L/min) or non-invasive mechanical ventilation	**Same efficacy as dexamethasone plus remdesivir but better safety profile**
High-Dose (20 mg/d) vs. Low-Dose (6 mg/d) **Dexamethasone**. COVIDICUS RCT***	ICU patients	**Did not improve survival**
Vilobelimab (anti-C5a antibody) plus SoC. PANAMO RCT****	Mechanically ventilated patients	**Improved survival**

*Keir HR et al. Lancet Respir Med. Sep 2, 2022; S2213-2600(22)00261-2; ** Wolfe CR et al. Lancet Respir Med. 2022 Sep; 10:888-899; ***Bouadma L et al. JAMA Intern Med. Sep 1, 2022; 182:906-916; ****Vaar APJ et al. Lancet Respir Med. Sep 7 2022; S2213-2600(22)00297-1.



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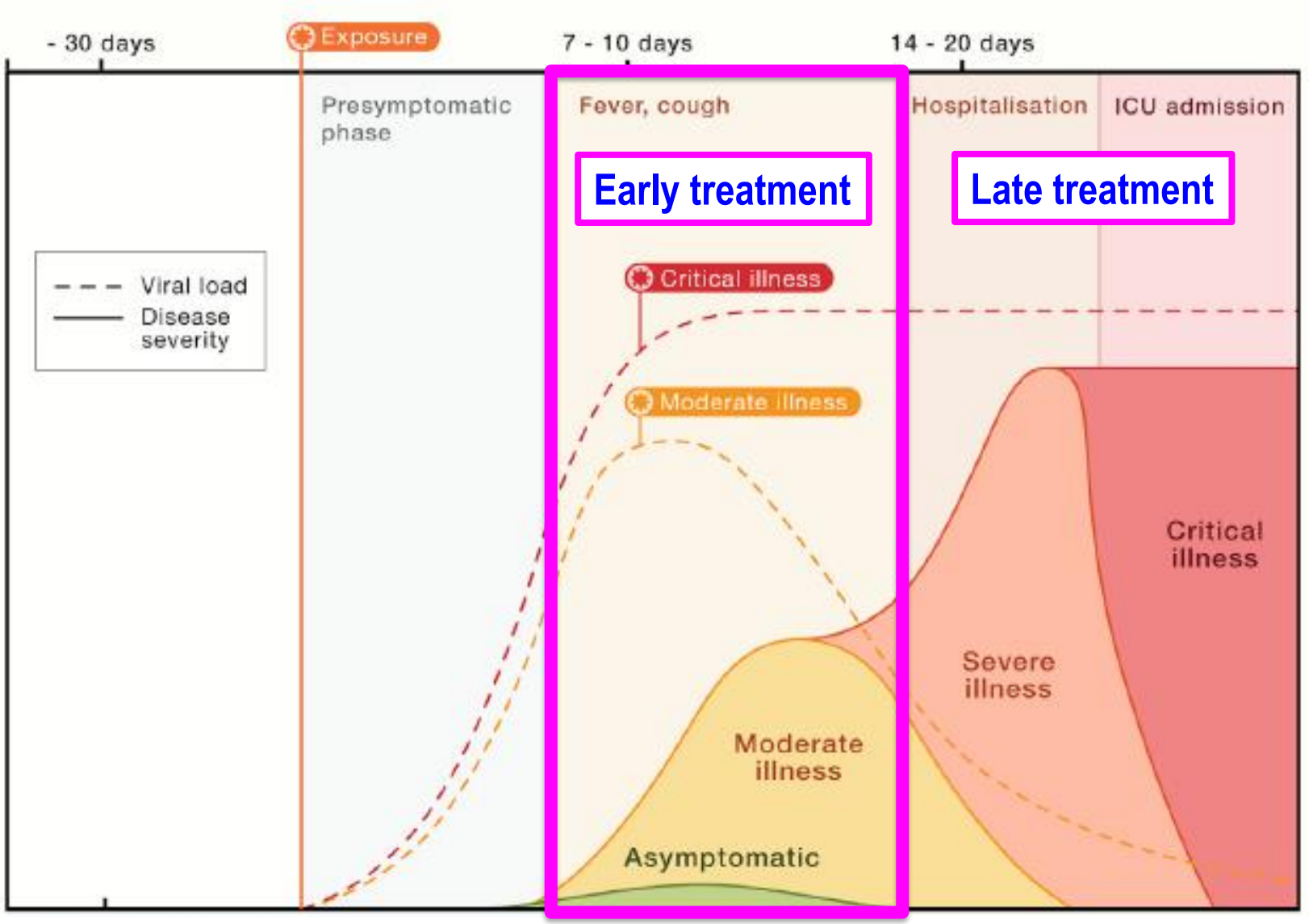


Corti D et al. Cell. August 19th 2021;184:4593-4595.

There was a need for oral antivirals for early COVID-19 treatment in the community to avoid hospitalization

Aim: STOP Hospitalization

Treat early* to target population

- Elderly individuals
- Comorbidities
- Immunosuppressed

Rambla de Catalunya, Barcelona, Spain

*≤7days

Remdesivir – PINETREE RCT in non-vaccinated patients

- Phase 3 (GS-US-540-9012) double-blind, randomized, placebo-controlled trial compared the efficacy and safety of **3 days of IV remdesivir (N=279)** to standard of care (N=283) in **non-hospitalized, non-vaccinated, high-risk participants with confirmed COVID-19.**
- 562 participants were randomly assigned 1:1 to receive IV RDV (**200 mg on day 1, 100 mg on days 2 to 3**) or placebo **≤7 days of symptoms onset**.
- Overall, 52% were male, 44% were Hispanic/Latino ethnicity and **30% were ≥ 60 years old**. **The most common comorbidities were diabetes mellitus** (62%), **obesity** (56%; median BMI, 30.7) and **hypertension** (48%).
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.

	Remdesivir N=279	**Placebo** N=283	*P*-value
- Hospitalization/all-cause death	0.7%	5.3%	0.008
- Medical visits/all-cause death	1.6%	8.3%	0.002
- Grade ≥3 TRAEs	3.6%	7.1%	-

- **No deaths occurred in either arm by day 28.** Biomarkers associated with inflammation and coagulation, including LDH and procalcitonin, were prognostic for COVID-19 related hospitalization or all-cause death. **RDV improved by day 3 of treatment, peripheral lymphopenia, monocyte count, and decreased neutrophil-to-lymphocyte ratio compared to placebo.**

→ Remdesivir reduced hospital admission/death by 87%.

Gottlieb RL, et al. NEJM. Dec 22 2021; Pan DZ et al. CROI 2022; Poster H-01; Webb B et al. CROI 2022; Poster H-01; *Lingas G et al. CROI 2022; Poster-H01.

Molnupiravir: MOVe-OUT RCT in non-vaccinated patients

- Phase 3, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of treatment with **oral molnupiravir (800 mg BID for 5 days) started within 5 days** after the onset of signs or symptoms in non-hospitalized, unvaccinated adults **with mild-to-moderate, laboratory-confirmed Covid-19** and **at least one risk factor for severe COVID-19 illness:** age >60 years; active cancer; chronic kidney disease; COPD; obesity BMI ≥30; serious heart conditions; or diabetes mellitus. **Exclusion criteria**; dialysis or eGFR <30 ml/min, pregnancy, unwillingness to use contraception, severe neutropenia (ANC<500/mL), platelets <100,000/uL, and **SARS-CoV-2 vaccination**
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 29**.

	Molnupiravir N=709	**Placebo N=699**	*P*-value
Outcomes at 29 days			
- Hospitalization/death	6.8%	9.7%	0.022
- Mortality	**One death**	**9 deaths**	

→ Molnupiravir reduced the risk of hospitalization/death by 30%.

Molnupiravir is not approved by the EMA, it is in the review phase.

Caraco Y et al. 31st ECCMID July 9-12 2021 P#4700; MSD Press release October 1st 2021; Bernal AJ et al, N Engl J Med. Dec 16, 2021; doi: 10.1056/NEJMoa2116044.

Oral Nirmatrelvir/rtv in non-vaccinated patients

- **EPIC-HR** (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) is a multinational randomized, double-blind study of **non-hospitalized non-vaccinated adult patients** with COVID-19, who are at high risk of progressing to severe illness.
- 2,246 eligible participants with at least **one underlying medical condition** and a **mild/moderate confirmed diagnosis of SARS-CoV-2 infection (within 5 days)** were randomized (1:1) to receive **oral nirmatrelvir/ritonavir** or placebo orally **every 12 hours** for **5 days.**
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.
- **The study was stopped** after the first interim analysis with 1,219 adults enrolled by September 29, 2021 was performed.

At 28 days	**Nirmatrelvir** N=1,039	**Placebo** N=1,046	*P*-value
- Hospitalization/death	0.8%	6.3%	<0.001
- Death	No deaths	**12 deaths**	-
- D/C due to TRAEs	2.1%	4.2%	-

→ Nirmatrelvir/ritonavir reduced hospital admission/death by 87%.

Hammond J, et al. N Engl J Med. Feb 16 2022. Online ahead of print.

Antivirals for early COVID-19 treatment in non-vaccinated patients

	Remdesivir	Molnupiravir	Nirmatrelvir/ ritonavir
Efficacy	**87%**	**30-65%**	**87%**
Administration	Intravenous (IV), 3 d.	Oral, 5 d. (40 tablets)	Oral, 5 d. (30 tablets)
Advantages	Highly efficacious Studied in pregnancy Few/No DDI	No DDI	Highly efficacious Ritonavir safe in pregnancy
Disadvantages	**IV infusion** for 3 days	**Lowest efficacy** Not recommended in pregnancy/children	Important **DDI**
NNT	**18**	**31/36**	**18**

*Relative risk reduction hospitalization/death; NNT=Number needed to treat; DDI = Drug-drug interactions.

Adapted from Gandhi RT et al. JAMA. 2022; 327:617-618; Bernal AJ et al, N Engl J Med. Dec 16, 2021; Gottlieb RL, et al. NEJM. Dec 22 2021; Hammond J, et al. N Engl J Med. Feb 16 2022.

Real-world effectiveness studies of early antiviral treatments

- Israel
- Hong Kong

Nirmatrelvir/rtv Use and Severe Covid-19 Outcomes during the Omicron Surge in Israel: Only effective among patients 65 years of age or older

- Data were obtained for all members of Clalit Health Services who were 40 years of age or older during the omicron surge (January 9 to March 31, 2022). A total of **109,254 patients met the eligibility criteria**, of whom 3902 (4%) received nirmatrelvir.
- **Endpoints**: hospitalization and death due to Covid-19, with adjustment for sociodemographic factors, coexisting conditions, and previous SARS-CoV-2 immunity status.

Hazard Ratios (HR [95%CI]) for Hospitalization Due to Covid-19 According to Immunity Status and Age Group

All Patients		Patients without Previous Immunity		Patients with Previous Immunity	
40–64 yr (N=66,433)	≥65 yr (N=42,821)	40–64 yr (N=20,555)	≥65 yr (N=3318)	40–64 yr (N=45,878)	≥65 yr (N=39,503)
0.74 (0.35 to 1.58)	0.27 (0.15 to 0.49)	0.23 (0.03 to 1.67)	0.15 (0.04 to 0.60)	1.13 (0.50 to 2.58)	0.32 (0.17 to 0.63)

Arbel R et al. N Engl J Med. Sep 1st, 2022; 387:790-798.

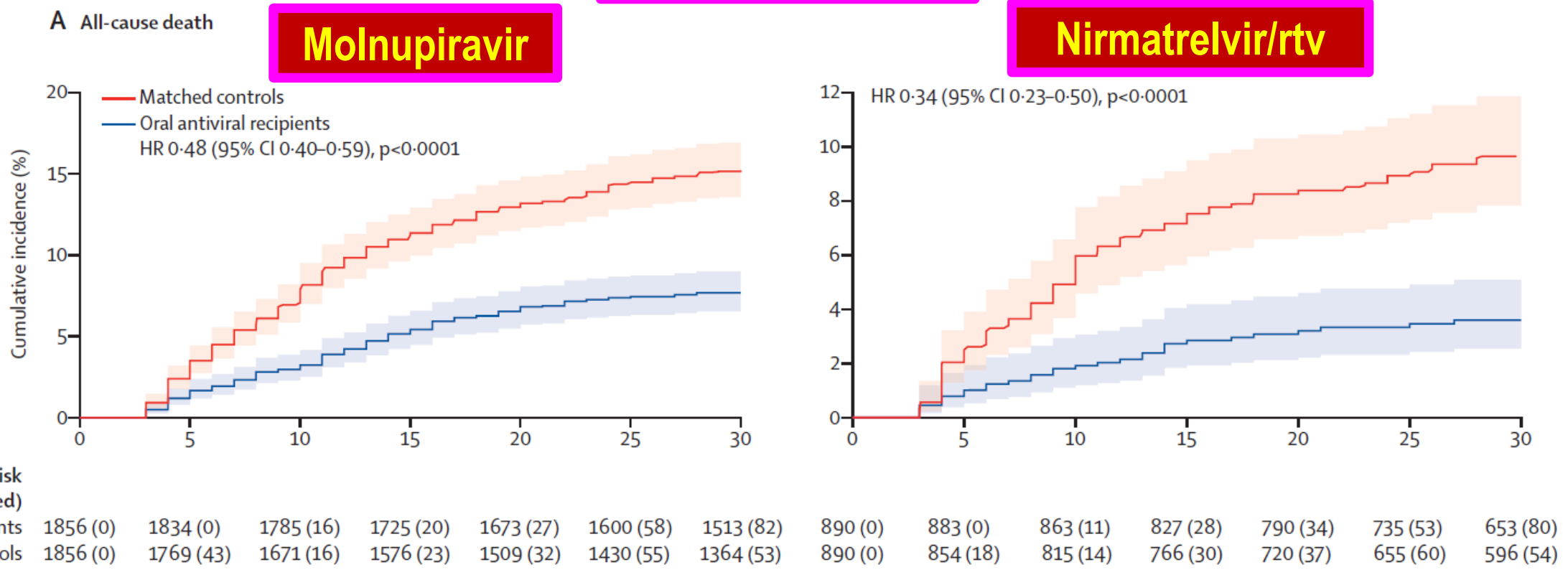
Early molnupiravir and nirmatrelvir treatment was effective in mild hospitalized (no O2) patients during the BA.2 Surge in Hong Kong

- Patients who received the oral antivirals molnupiravir or nirmatrelvir–ritonavir were matched with controls using **propensity-score matching in a ratio of 1:1**. 1856 molnupiravir recipients and 1856 matched controls, and 890 nirmatrelvir-ritonavir recipients and 890 matched controls were included.
- Primary outcome was all-cause mortality.

All-cause death

Molnupiravir

Nirmatrelvir/rtv



Number at risk (number censored)													
Molnupiravir recipients	1856 (0)	1834 (0)	1785 (16)	1725 (20)	1673 (27)	1600 (58)	1513 (82)	890 (0)	883 (0)	863 (11)	827 (28)	790 (34)	735 (53)	653 (80)
Controls	1856 (0)	1769 (43)	1671 (16)	1576 (23)	1509 (32)	1430 (55)	1364 (53)	890 (0)	854 (18)	815 (14)	766 (30)	720 (37)	655 (60)	596 (54)

Molnupiravir is not approved by the EMA, it is in the review phase.

Wong CKH, et al. Lancet Infect Dis. August 24th 2022.

The answer: The PANORAMIC Trial

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

- **The PANORAMIC trial has the same design as Move-Out**
- **Same primary efficacy endpoint (hospitalization/death)**
- **SARS-CoV-2 vaccinated persons included** and trial conducted during the **Omicron wave**.
- **Original sample size calculation:** 10,600 patients (3% SoC arm *vs.* 2% Molnupiravir arm). **Final sample size: 25,000 patients** included by April 27th 2022. Follow-up ended on May 27th 2022.
- Expected results very soon ...

https://www.panoramictrial.org/

PANORAMIC trial: Molnupiravir fails to prevent COVID-19 hospitalization in vaccinated patients in UK

- **Same design, criteria and dosage as in the MOVE-OUT** but this was an open-label RCT: **oral Molnupiravir for 5 days** *vs.* Standard of Care (SoC)
  → **93% of individuals had received a booster COVID-19 vaccine.**
- **The primary efficacy endpoint hospitalization or all-cause death by day 29**.

	Molnupiravir N=12,516	**SoC N=12,600**	*P*-value
Outcomes at 29 days			
- Hospitalization/Death	103 (0.8%)	96 (0.8%)	0.340
- Mortality	2	5	

→ **Molnupiravir did not reduce hospitalization/death in COVID-19 vaccinated individuals**

Molnupiravir is not approved by the EMA, it is in the review phase.

Butler CC on behalf the PANORAMIC Trial Investigators. SSRN, Oct . 6th 2022

Nirmatrelvir/rtv results according to the baseline SARS-CoV-2 serology

- **EPIC-HR** (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) is a multinational randomized, double-blind study of **non-hospitalized adult patients** with COVID-19, who are at high risk of progressing to severe illness.
- 2,246 eligible participants with at least **one underlying medical condition** and a **mild/moderate confirmed diagnosis of SARS-CoV-2 infection (within 5 days)** were randomized (1:1) to receive nirmatrelvir/ritonavir or placebo orally **every 12 hours** for **5 days.**
- **The primary efficacy endpoint was composite COVID-19 hospitalization or all-cause death by day 28**.
- **Patients with previous SARS-CoV-2 infection or COVID-19 vaccination were excluded.**

	Nirmatrelvir	Placebo	RR	NNT
At 28 days				
Seronegative, no.	487	505		
- Hospitalization/death	**1.4%**	**11.5%**	**↓88%**	**10**
Seropositive, no.	540	528		
- Hospitalization/death	**0.2%**	**1.5%**	**↓87%**	**77**

→ **Baseline serological status influences clinical benefit!**

Hammond J, et al. N Engl J Med. Feb 16 2022.

Bebtelovimab = Nirmatrelvir-ritonavir for treating mild COVID-19 during Omicron BA.2 surge in USA

- Retrospective cohort study of 3,607 high risk patients treated with Bebtelovimab or Nirmatrelvir-ritonavir during BA.2 surge.
- **Bebtelovimab was given as single IV infusion of 175 mg over 1 minute within 7 days of symptom onset.**
- Median age of 66.2 years (IQR, 52.5–74.7 years); 58.4 were female, 94.9% were white and 96% were non-Hispanic. The most common comorbid conditions were hypertension (46.3%), diabetes mellitus (19.4%), and immunosuppression (16.3%).
- **Endpoint**: **Severe outcome** (WHO Ordinal Scale of 4 [hospitalized and oxygen supplementation by mask or nasal prongs] or greater).

Outcome	Patients, No. (%) Bebtelovimab (n = 2833)	Nirmatrelvir-Ritonavir (n = 774)	*P* Value
Severe outcome[a]	41 (1.4)	9 (1.2)	.55
ICU admission	14 (0.5)	2 (0.3)	.38
Death	6 (0.2)	0 (0.0)	.20

Abbreviation: ICU, intensive care unit.

[a]Severe outcome is defined according to the World Health Organization classification of 4 (hospitalization and oxygen supplementation) or higher (including death).

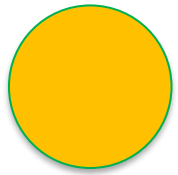
Bebtelovimab is not approved by the EMA, it is in the review phase.

Razonable RR et al. J Infect Dis. Sep 17 2022; jiac346. doi: 10.1093/infdis/jiac346.

What do we know about anti-inflammatory and anticoagulant treatment in the community?

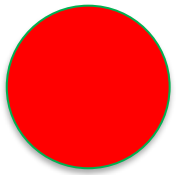
Anti-inflammatory treatment

- Colchicine, oral
- Fluvoxamine, oral
- Budesonide, inhaled



Anticoagulant treatment

- Aspirin, oral
- Apixaban, oral
- Heparin, SC low molecular weight



Tardif JC et al. Lancet Respir Med. 2021; 9:924-932; Lenze EJ et al. JAMA, Nov 12, 2020; Reis G et al. Lancet Glob Health; October 27, 2021; Yu LM et al. Lancet 2021; 398: 843–55; Connors JM et al. JAMA October 11, 2021; Cools F, et al. Lancet Haematol. Jun 29th 2022; Barco S, et al. Lancet Haematol. Jun 29th 2022; Bramante CT et al. N Engl J Med. Aug 18, 2022; 387:599-610..

Disease stages
- **NIH stages**
- **ACTT scores**

Community	Hospital - Ward	Hospital - ICU
Asymptomatic/Mild Stages 1-2	Moderate/Severe Stages 3-5	Critical (MV, ECMO) Stages 6-7

Isolation, at least 10-14 days

Treatment
- Early antiviral therapy
- Proper timing anti-inflammatory drugs
- Prophylactic heparin

Symptomatic treatment.
Close monitoring for early detection of progression.
In seronegative older or high risk persons consider*:
- **Parenteral mAbs** (IM/IV)**
- **Nirmatrelvir/rtv, oral 5-d**
- **Remdesivir (IV), IV 3-d**
- **Molnupiravir, oral 5-d**

Remdesivir, IV, 5 days
Stages 4 (no oxygen) & 5 (low-flow oxygen supply)
Stage 6 (non-invasive MV)

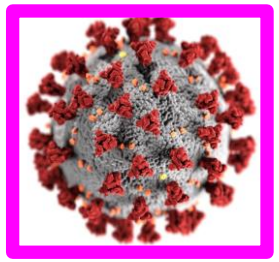
Parenteral mAbs**, single IV dose
Only in seronegative persons and susceptible SARS-CoV-2

Dexamethasone***, 6 mg IV/oral, 10d
Stages 5-7, low/high-flow oxygen supply, MV and ECMO
Tocilizumab***, single IV dose
Baricitinib***, 4 mg/d, oral 14 d.

Low molecular weight heparin, SC
During the entire hospitalization period

***Few data in previously infected or vaccinated patients.**
**** Check variant of concern (VoC) for antiviral activity.**
***** All three may be combined.**

Miro JM et al. Arch Bronconeumol. April 2022; WHO. BMJ Sep 4 2022.

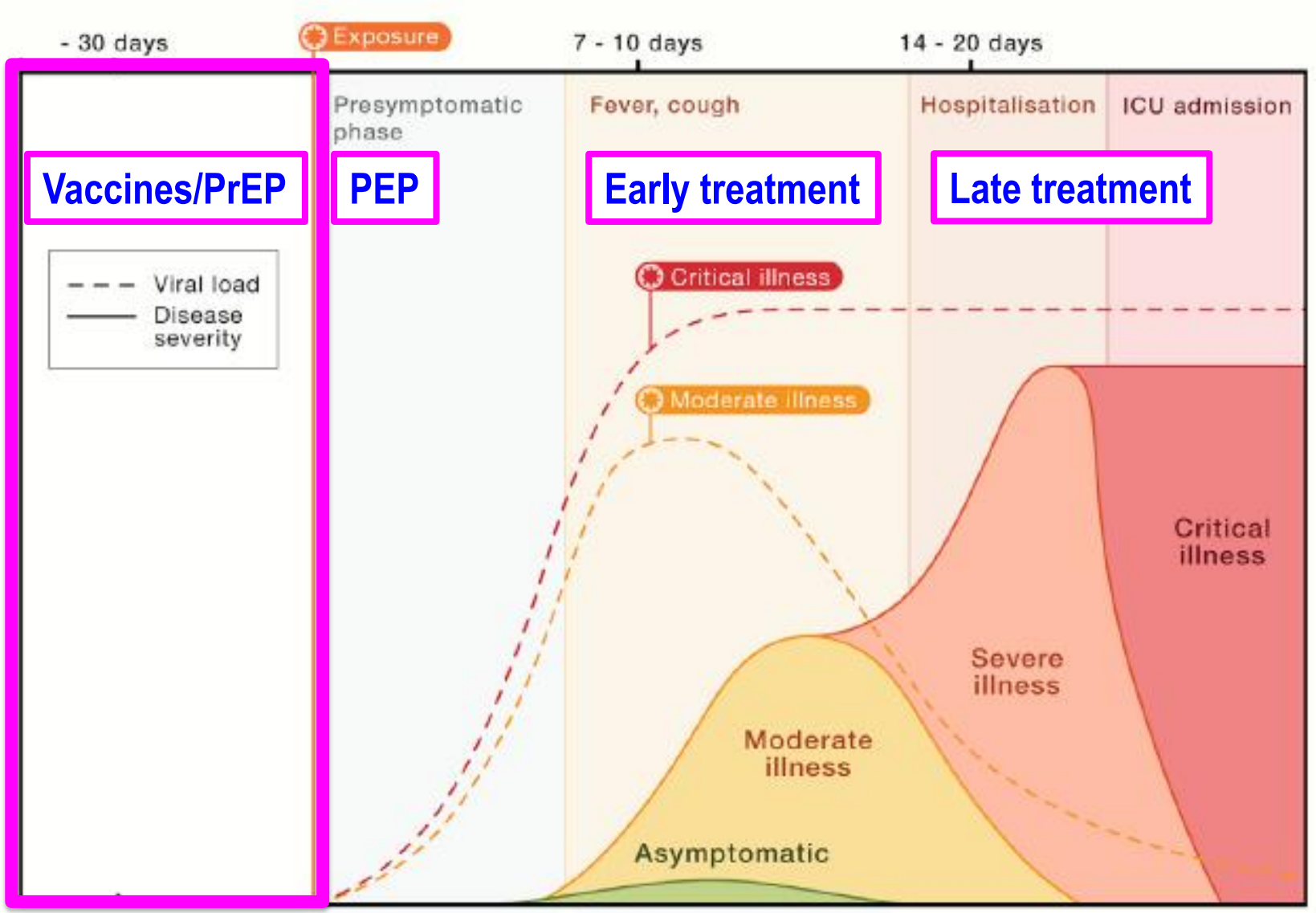


Role of antivirals and neutralizing antibodies in the prophylaxis and treatment of COVID-19

- Introduction
- Inpatient Treatment
- Outpatient treatment
- **Pre-exposure prophylaxis (PreP)**
- Take-home messages

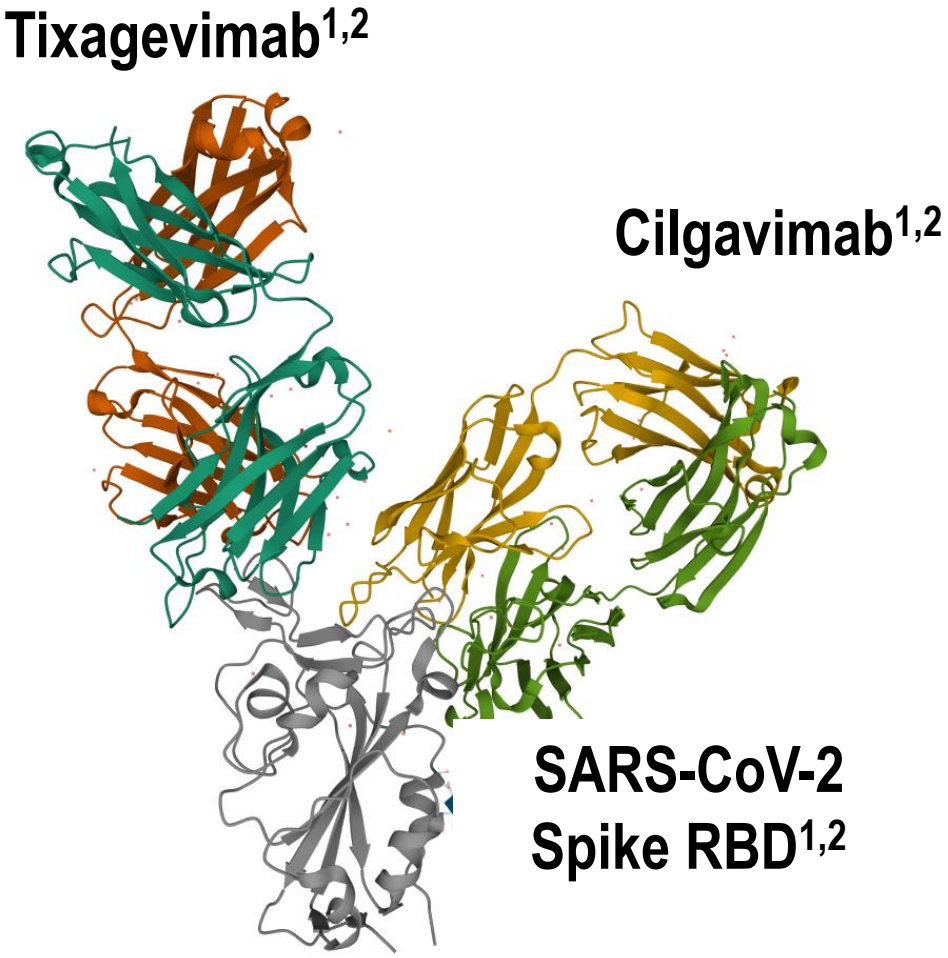
November 25th 2022

Prophylactic and Therapeutic Approaches to COVID-19



Corti D et al. Cell. August 19th 2021;184:4593-4595.

PrEP for COVID-19: Tixagevimab and Cilgavimab (Evusheld®)

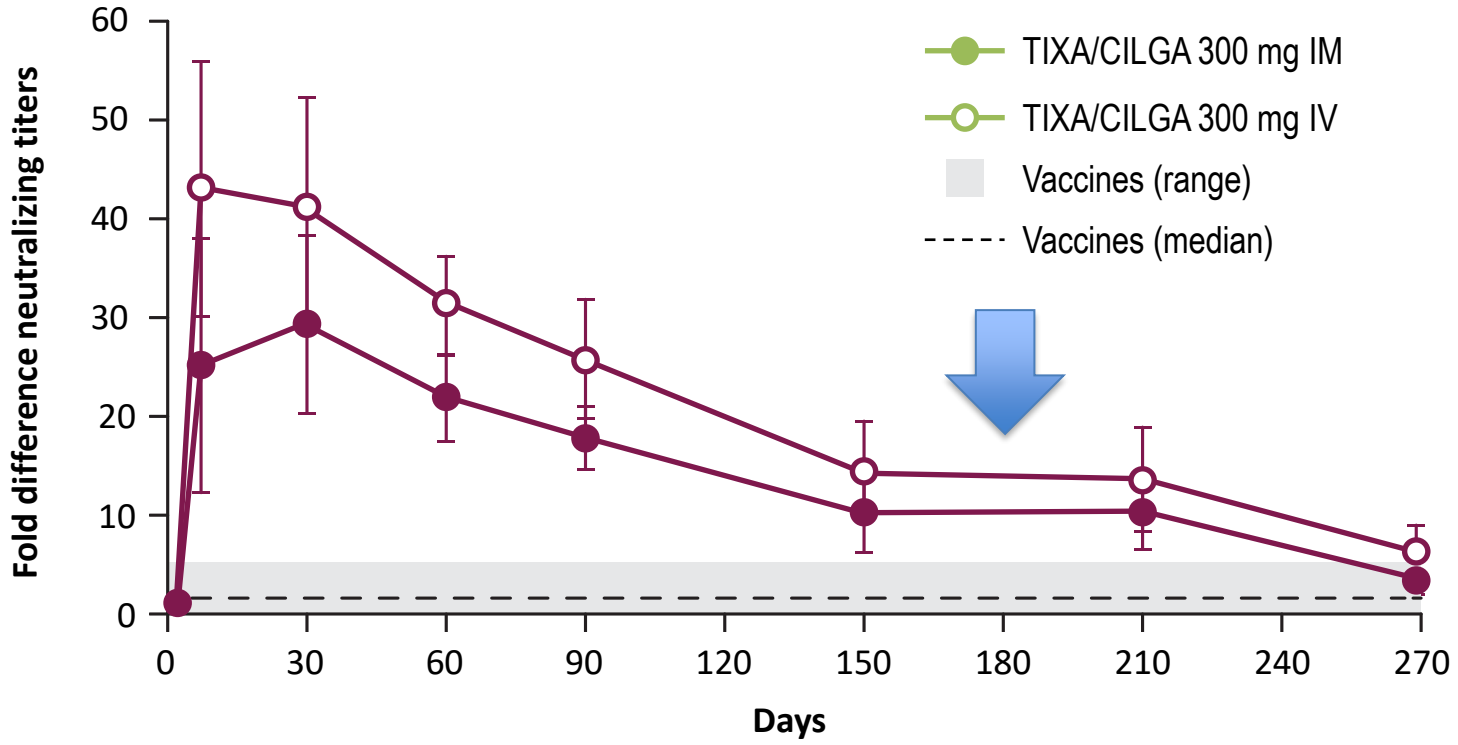


- **Two human mAbs binding two distinct epitopes[3]**
- Highly potent[4]
- Retained neutralizing activity against variants of concern[3,5]
- **Extended half-life (YTE modification)[5]**
- Favorable safety profile[6]
- **Efficacy was shown for pre-exposure prophylaxis in non-vaccinated high-risk populations[5,6]**

1. Sehnal D et al. Nucleic Acids Res. 2021;49:W431-W437; 2. Protein Data Bank. https://www.rcsb.org/. 7L7E. Accessed November 10, 2021; 3. Loo YM et al. Online ahead of print. Sci Transl Med. 2022; 4. Zost SJ et al. Nature. 2020;584:443-4493; 5. Fact sheet for healthcare providers. Emergency Use Authorization (EUA) of EVUSHELD™ (tixagevimab co-packaged with cilgavimab). 2022; 6. Levine MJ et al. N Engl J Med. Jun 9 2022; 386: 2188-2200.

PrEP for COVID-19: Tixagevimab and Cilgavimab (Evusheld®)

Neutralizing Antibody Titers Following Evusheld® Administration Compared to Antibody Titers Associated With Vaccinated Individuals



Concentration of neutralizing antibodies afforded by vaccines ranged from 0.5-fold to 4.0-fold

Neutralizing antibody titer levels from TIXA/CILGA remain at or above levels reported for COVID-19 vaccines **up to 9 months**

Evusheld® has been recommended by the EMA to know its marketing authorization

From The Medical Letter on Drugs and Therapeutics. JAMA, January 25th 2022; 327:384-385.

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

- **Not vaccinated**

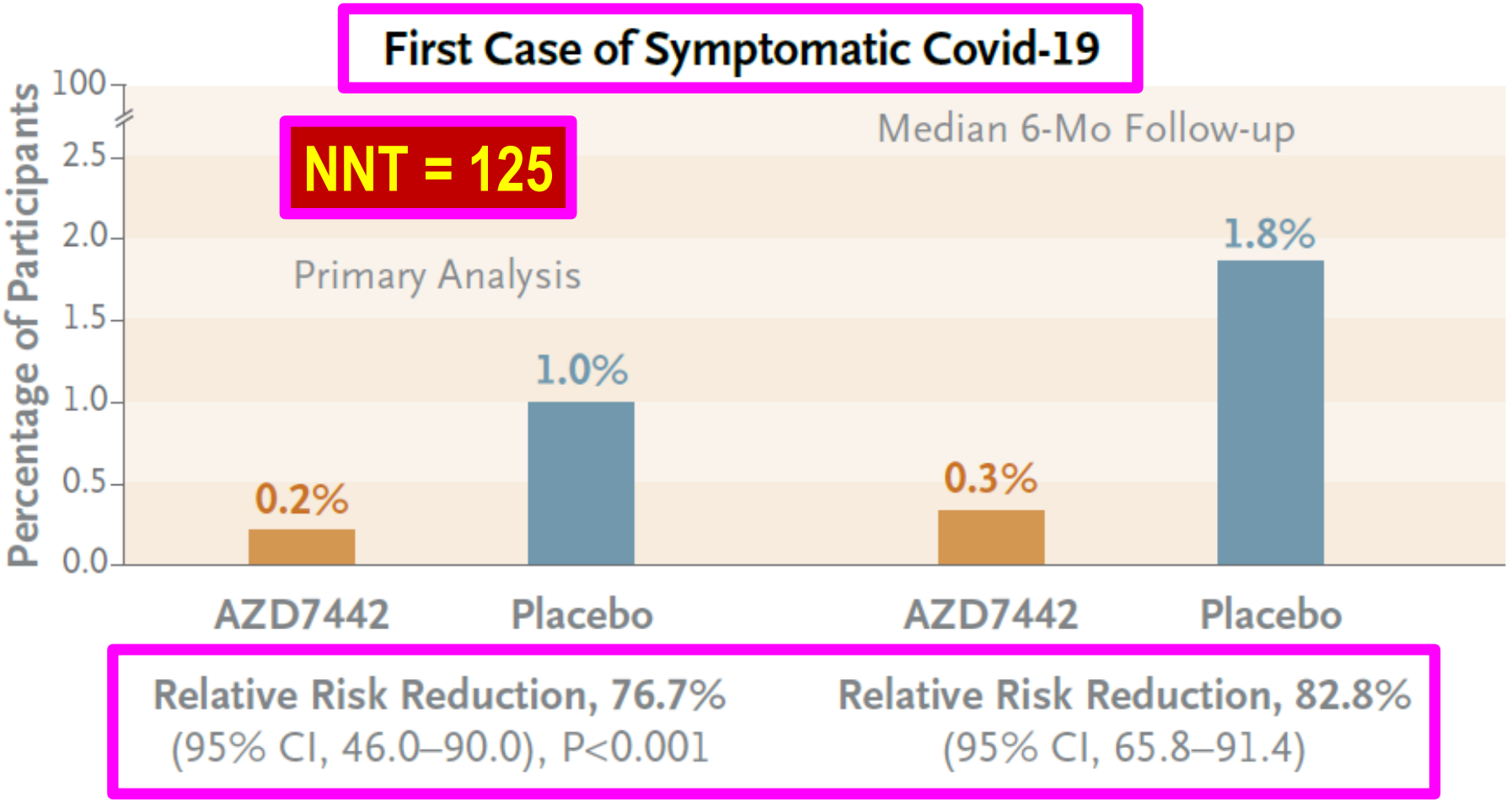
Risk factors for an inadequate response to Covid-19 vaccination

- Age ≥60 years
- Obesity
- Immunocompromised status
- Inability to receive vaccines without adverse effects
- Congestive heart failure
- Chronic obstructive pulmonary disease
- Chronic kidney disease
- Chronic liver disease

Evusheld® has been recommended by the EMA to know its marketing authorization

Levine MJ et al. N Engl J Med. Jun 9 2022; 386: 2188-2200.

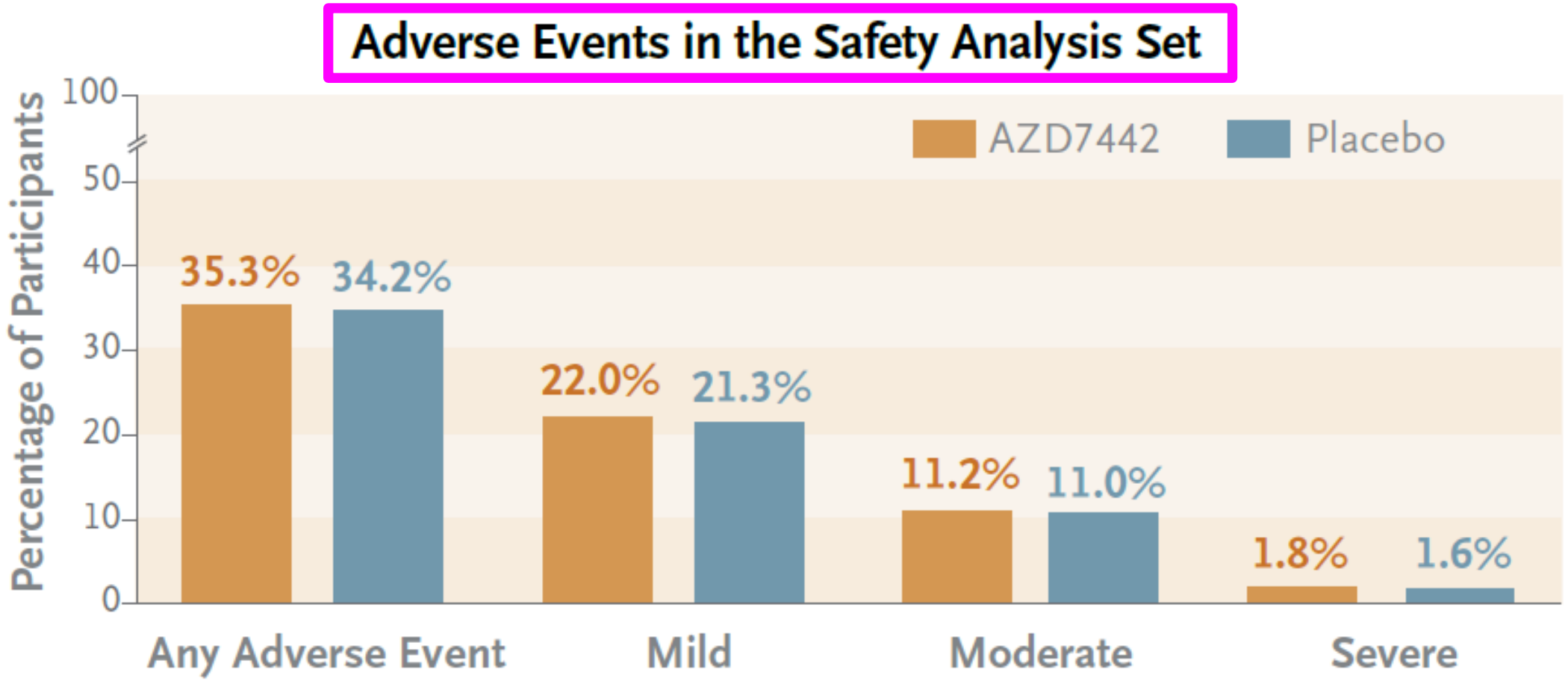
Intramuscular Tixagevimab–Cilgavimab (Evusheld®) for Prevention of Covid-19 (RCT, 2:1; N=5,197)



Subjects were randomized 2:1 to receive either **150 mg of tixagevimab plus 150 mg of cilgavimab IM** (1.5 mL) or placebo **every six months.**

Levine MJ et al. N Engl J Med. Jun 9 2022; 386: 2188-2200..

Intramuscular Tixagevimab–Cilgavimab (Evusheld®) for Prevention of Covid-19 (RCT, 2:1; N=5,197)



- The most common adverse effects were headache (6%) and fatigue (4%). **In the post-hoc analysis**, the incidence of **serious cardiac adverse events** (e.g., myocardial infarction, cardiac failure, arrhythmia) was higher in the antibody group than in the placebo group (0.6% *vs*. 0.2%).

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Levine MJ et al. N Engl J Med. Jun 9 2022; 386: 2188-2200..

Intramuscular Tixagevimab–Cilgavimab (Evusheld®) for Prevention of Covid-19 (RCT, 2:1; N=5,197)

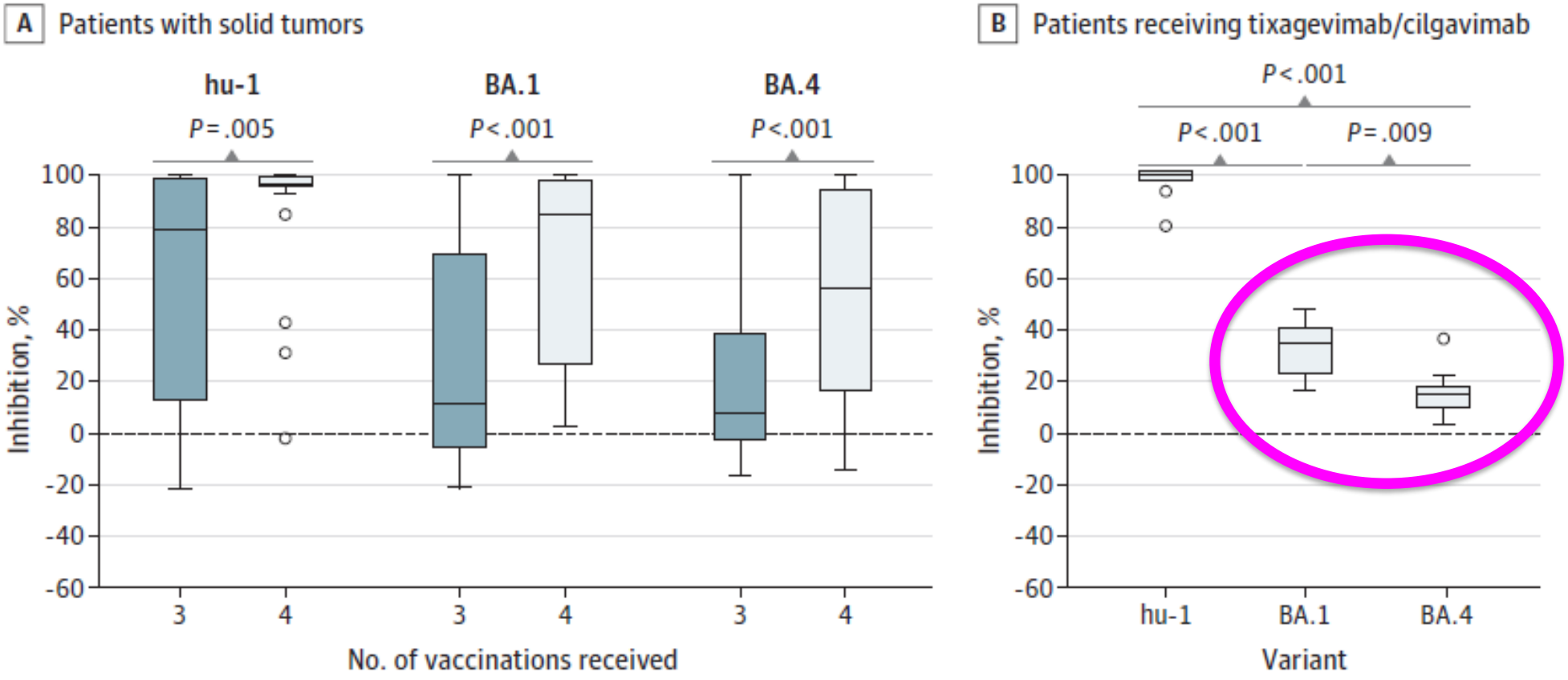
- Enrollment occurred between November 2020 and March 2021. When Covid-19 vaccines became available, participants who wanted to consider vaccination could become aware of their randomized assignment, and **data were censored after unblinding or vaccination**.
- **Few Covid-19 cases occurred in key subgroups**, including **immunocompromised persons**, **so efficacy in these groups could not be estimated**.
- These data are from the period **before the delta and omicron waves**; thus, **activity against those and new variants have not been assessed**.

Evusheld® has been recommended by the EMA to know its marketing authorization

Levine MJ et al. N Engl J Med. Jun 9 2022; 386: 2188-2200..

Inhibition of SARS-CoV-2 Omicron BA.1 and BA.4 After 4th Vaccination or Tixagevimab and Cilgavimab Administration in Patients With Cancer

Receptor-Binding Domain and Angiotensin-Converting Enzyme 2 Interaction Inhibition in (A) Patients With Solid Tumors and (B) Patients Receiving Tixagevimab and Cilgavimab

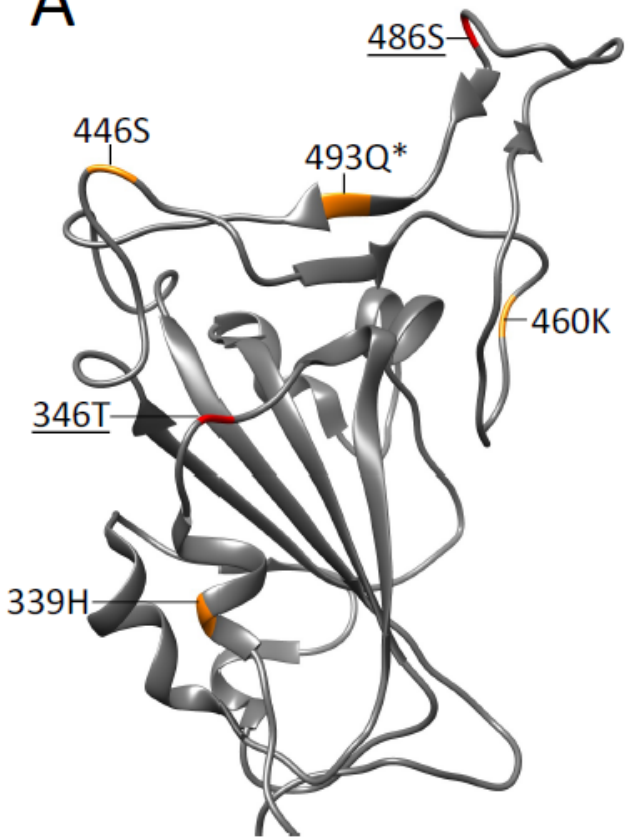


Evusheld® has been recommended by the EMA to know its marketing authorization

Mair MJ, et al. JAMA Oncol. Sept 22, 2022.

Tixagevimab–Cilgavimab have poor activity against new Omicron variants except B.1

A



B

IC50 (ng/ml)	B.1	BA.5	BA.4.6	BA.2.10.4	BA.2.75.2
S309 (sotrovimab)	119	559	925	560	442
Cilgavimab	12	71	>1000	168	>1000
Tixagevimab	4	>1000	>1000	>1000	>1000
Evusheld	6	120	>1000	816	>1000
LY-CoV1404 (bebtelovimab)	4	1	2	3	2
REGN10933 (casivirimab)	14	>1000	>1000	>1000	>1000
REGN10987 (imdevimab)	10	>1000	>1000	>1000	>1000
LY-CoV016 (etesevimab)	29	>1000	>1000	>1000	>1000
LY-CoV555 (bamlanivimab)	9	>1000	>1000	>1000	>1000
ADG-20	56	>1000	>1000	>1000	>1000
S2E12	4	>1000	>1000	>1000	>1000
S2K146	18	118	78	207	62
A23-58.1	6	>1000	>1000	>1000	>1000

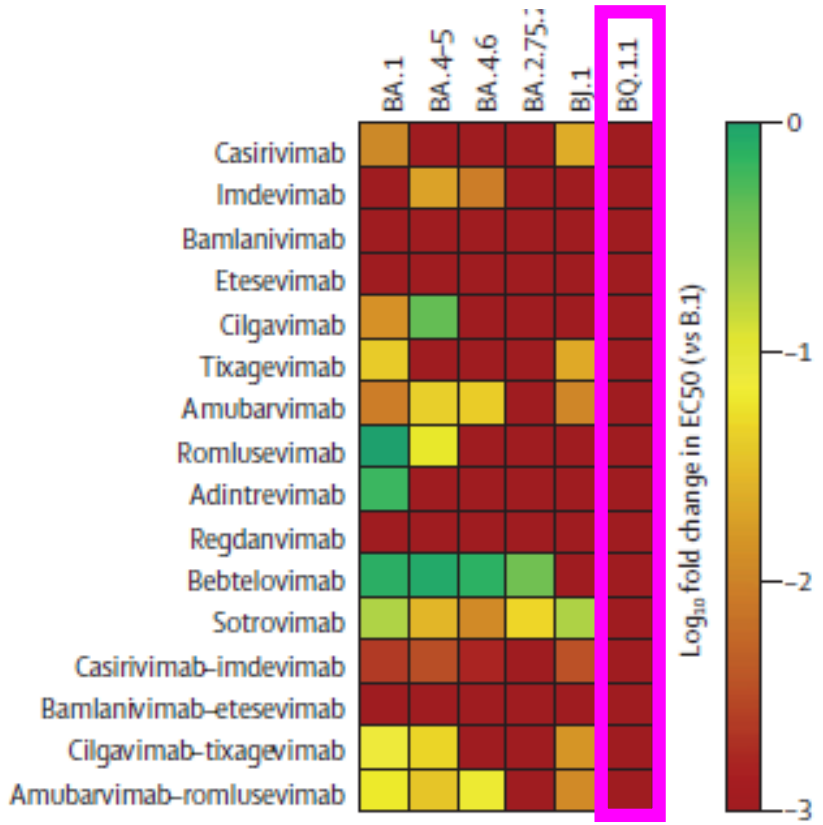
Evusheld® has been recommended by the EMA to know its marketing authorization

Sheward DJ et al. bioRxiv. September 19, 2022.

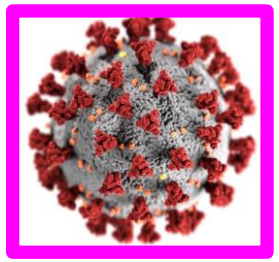
The Omicron variant BQ.1.1 is resistant to all neutralizing monoclonal antibodies (mAbs)

		B.1	BA.1	BA.4-5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Single mAbs	Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
	Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
	Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
	Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
	Tixagevimab	7	173	10090	27740	>50000	304	>50000
	Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
	Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
	Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
	Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
	Bebtelovimab	5	7	6	7	14	>50000	>50000
	Sotrovimab	157	833	5554	13000	3239	825	>50000
Cocktails of mAbs	Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
	Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab–tixagevimab	1	97	155	7131	>50000	482	>50000
	Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

EC50 (ng/ml)



Arora P et al. Lancet Infect Dis. November 18th 2022.



Role of antivirals and neutralizing antibodies in the prophylaxis and treatment of COVID-19

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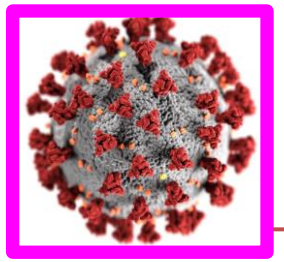
- **Take-home messages**

November 25th 2022

Take-home messages

- Early antiviral treatment of COVID-19 in the community in non-vaccinated people at risk reduced hospital admissions.
- Molnupiravir was not effective in vaccinated individuals.
- Parenteral monoclonal antibodies are as effective as antivirals in the community in non-vaccinated individuals, but their activity depends on the circulating SARS-CoV-2 variant.
- The treatment of severe COVID-19 in hospitalized patients is standardized by clinical practice guidelines and is highly effective.



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To all front-line health-care workers

To our patients and their families

November 25th 2022

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Sociedad Española
de Farmacia Hospitalaria

Gracias por su atención

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Grazas pola súa atención