COVID-19: from immune pathogenesis to therapy

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N ENGL J MED 382;13 NEJM.ORG MARCH 26, 2020

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Covid-19 — Navigating the Uncharted

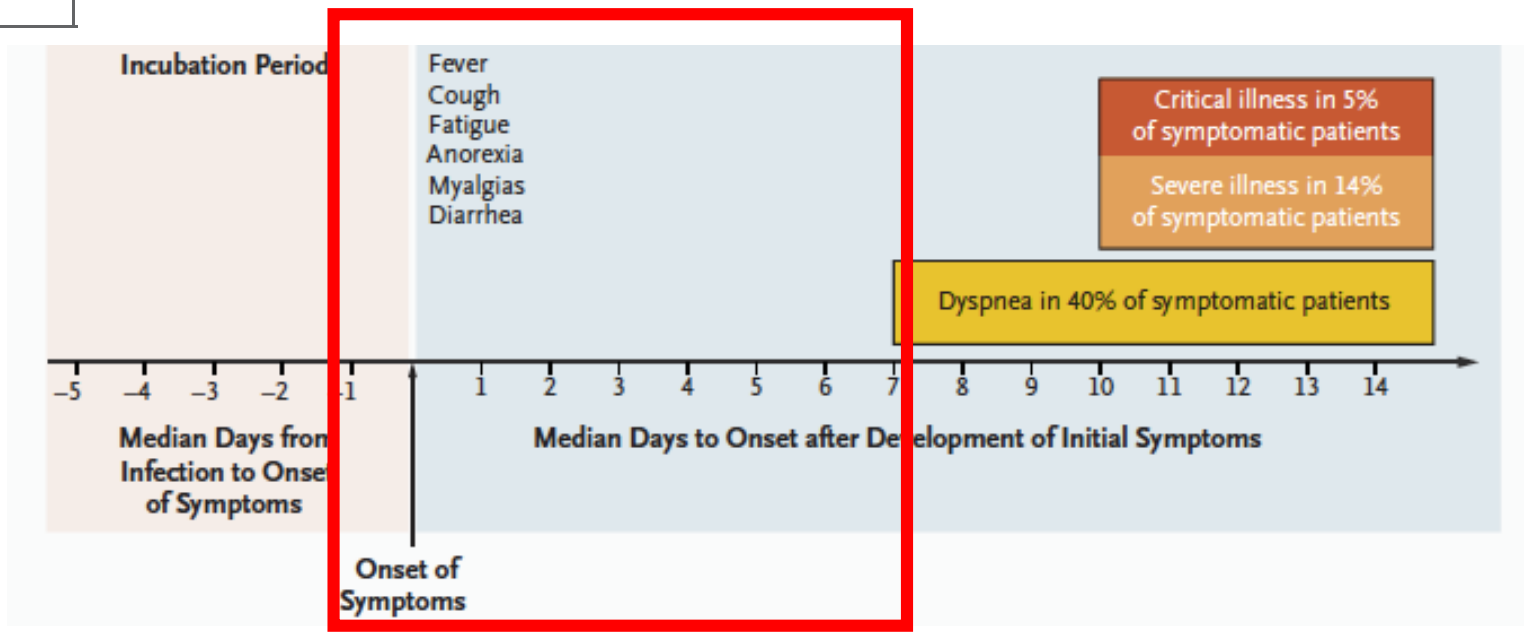
Anthony S. Fauci, M.D., H. Clifford Lane, M.D., and Robert R. Redfield, M.D.

More than 3 years later, WHO declares COVID-19 global health emergency over

By Briona Arradondo | Published May 5, 2023 | Coronavirus | FOX 13 News |

Table 1. Established and Potential Risk Factors for Severe Covid-19.*

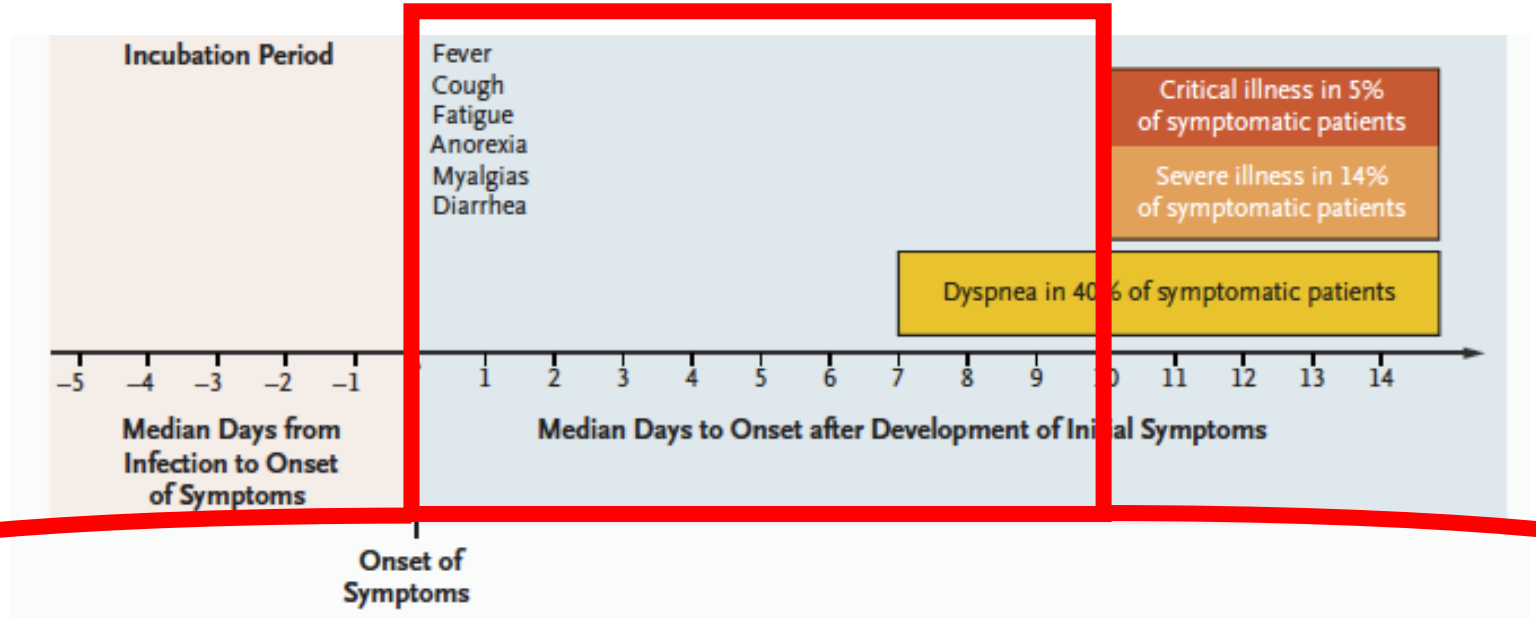
Older age (e.g., >65 years)
Chronic lung disease
Cardiovascular disease
Diabetes mellitus
Obesity
Immunocompromise†
End-stage renal disease
Liver disease



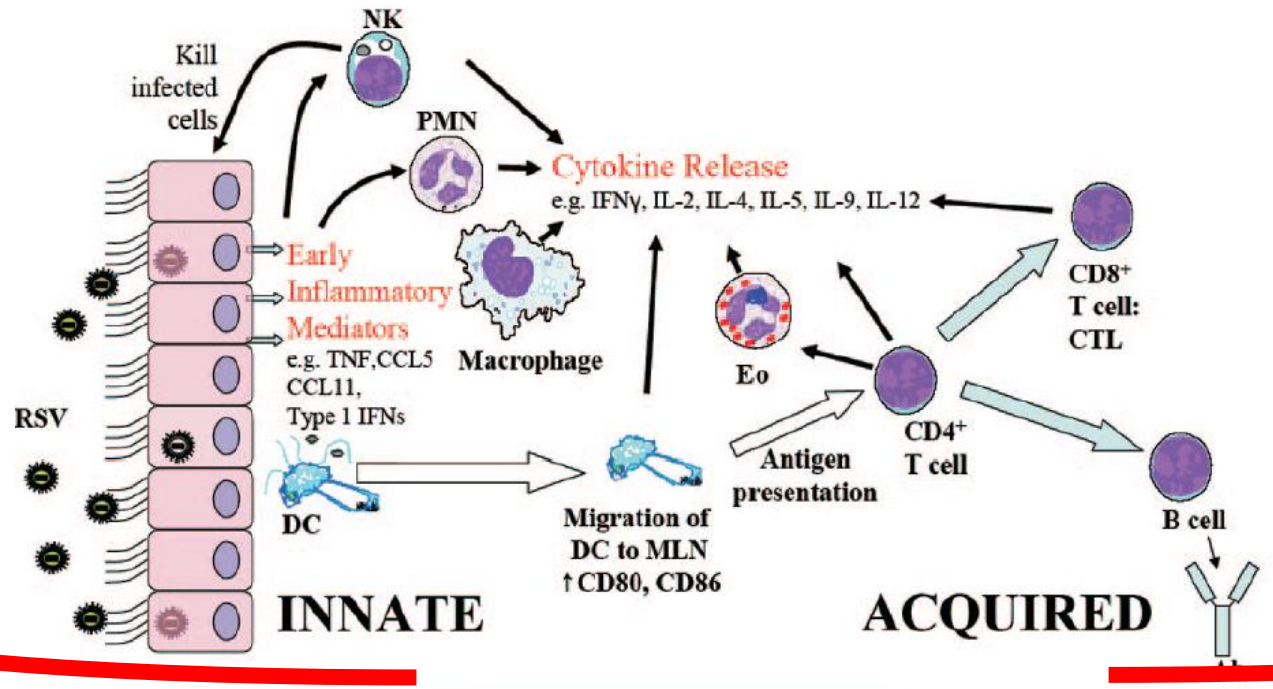
Berlin NEJM 2020

Treat as early as possible

Date of onset of first symptoms drives treatment decision making



Berlin NEJM 2020



Phase 1. active viral replication

Antivirals

Openshaw et al. Clinical Microbiolgy Reviews 2005

Treatment in the outpatient setting

Table 2a. Therapeutic Management of Nonhospitalized Adults With Mild to Moderate COVID-19 Who Do Not Require Supplemental Oxygen

Patient Disposition	Panel's Recommendations
All Patients	• All patients should be offered symptom management **(AIII)**. • The Panel recommends against the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**.
Patients Who Are at High Risk of Progressing to Severe COVID-19[b]	*Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapy. For use when the preferred therapies are not available, feasible to use, or clinically appropriate:* • **Molnupiravir**[d,f,g] **(CIIa)**
Each recommendation in the Guidelines receives 2 ratings that reflect the strength of the recommendation and the quality of the evidence that supports it. See Guidelines Development for more information.	

Corticosteroids

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ORIGINAL ARTICLE

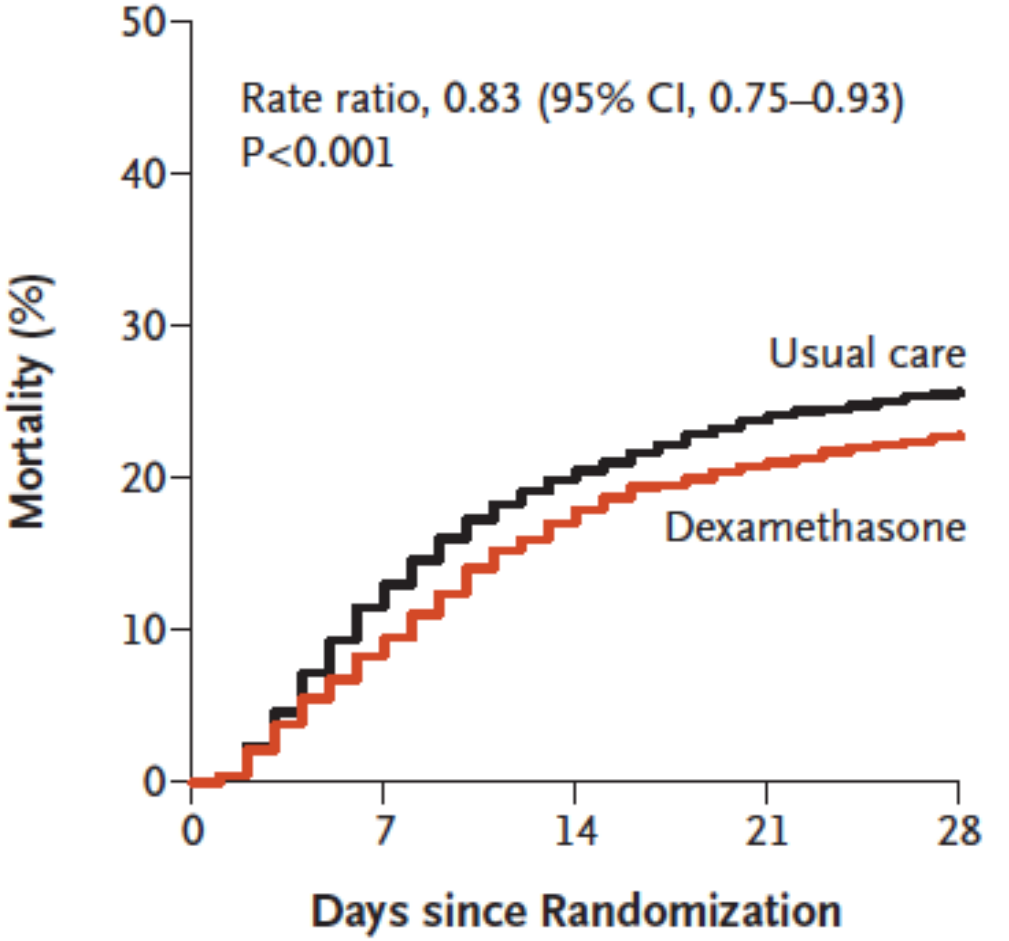
Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Randomized, controlled, open label, adaptive, platform trial designed to evaluate a range of treatments for COVID-19 including dexamethasone

Dexamethasone 6 mg PO or IV once daily (n=2104) x 10 days vs usual care (n=4321)

A All Participants (N=6425)



No. at Risk					
Usual care	4321	3754	3427	3271	3205
Dexamethasone	2104	1903	1725	1659	1621

Primary outcome: mortality at day 28

Overall: 22.9% vs 25.7% (p<0.001)

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

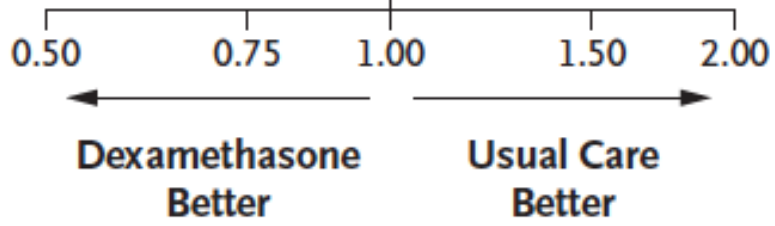


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Treatment in the outpatient setting

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EPIC-HR Study: Evaluation of Protease Inhibition for COVID-19 in High Risk patients

Phase 2-3 randomised double-blind in unvaccinated high risk patients, under delta VOC

Symptoms 5 days before

NMV 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 hours for 5 days

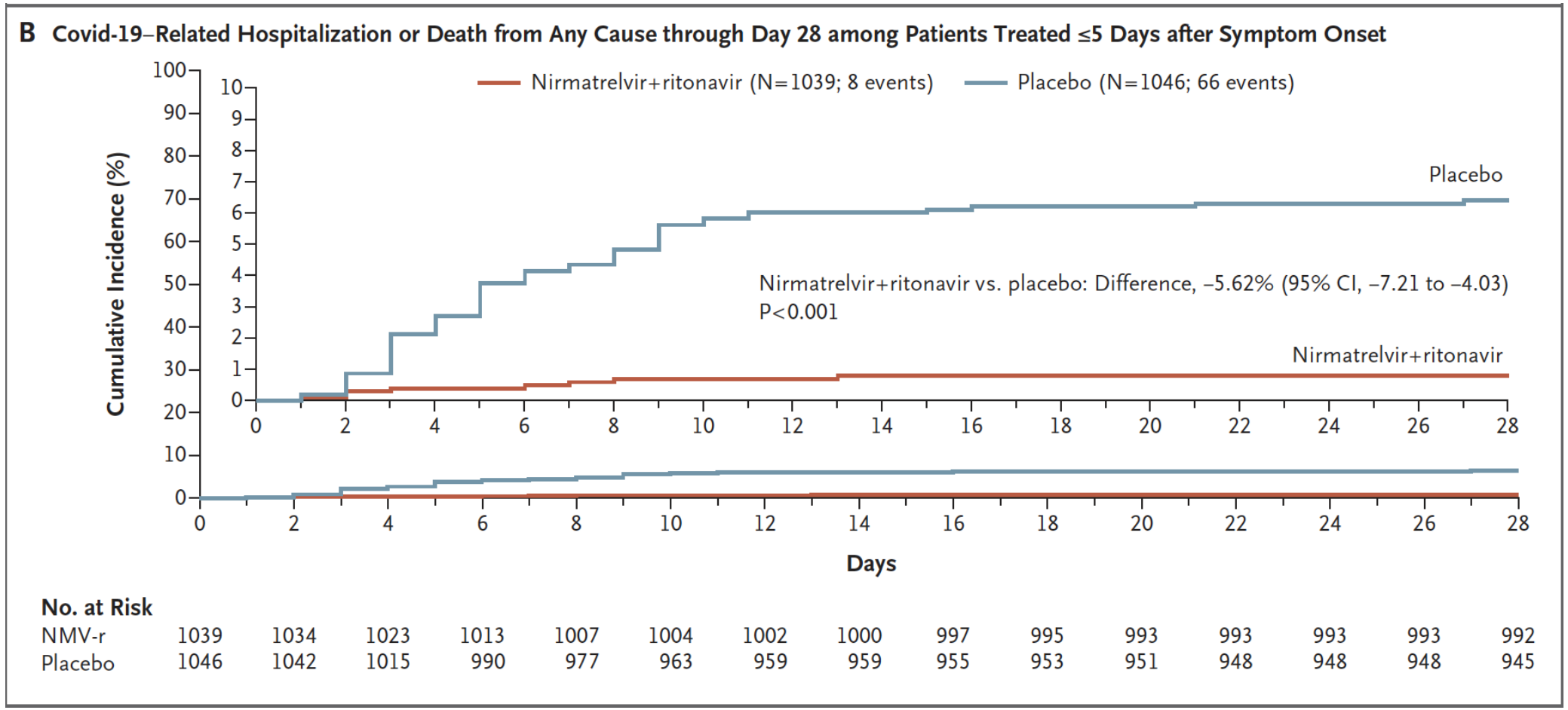
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 14, 2022 VOL. 386 NO. 15

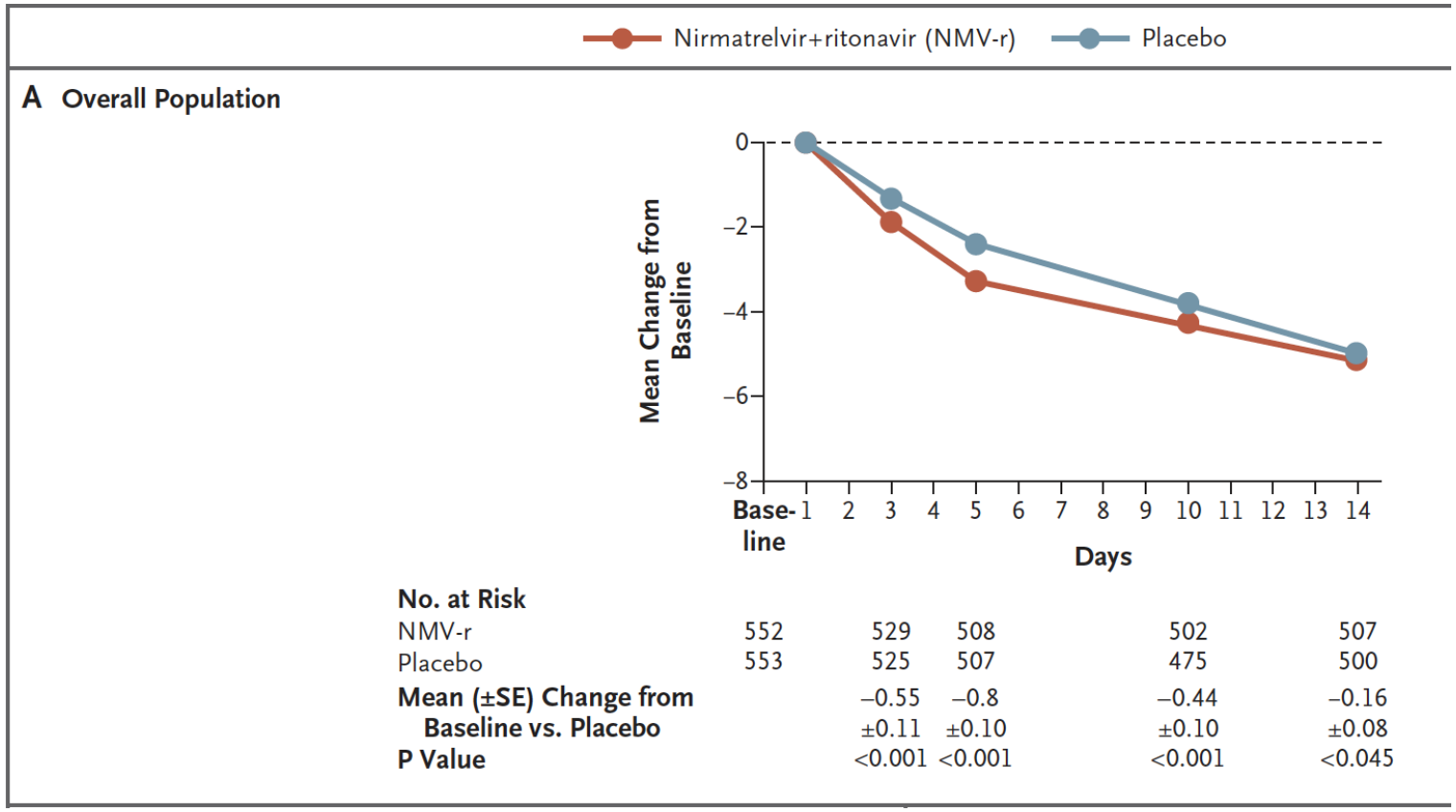
Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

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

Relative risk reduction of hospitalization or death at day 28: 89.1%

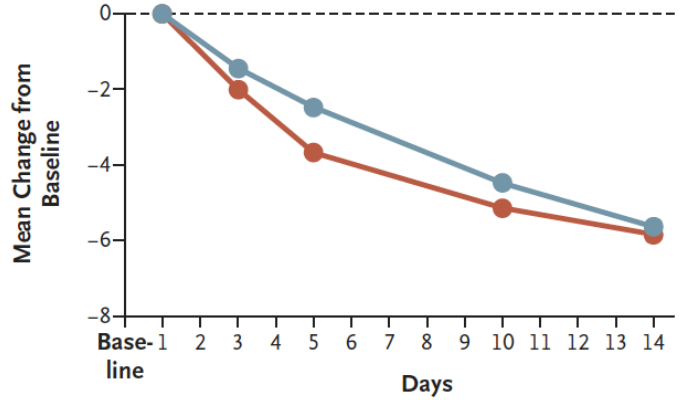


Viral load reduction



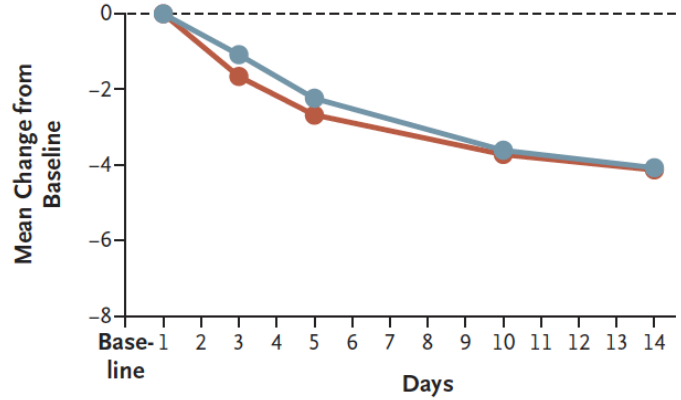
No. at Risk					
NMV-r	552	529	508	502	507
Placebo	553	525	507	475	500
Mean (±SE) Change from Baseline vs. Placebo		−0.55 ±0.11	−0.8 ±0.10	−0.44 ±0.10	−0.16 ±0.08
P Value		<0.001	<0.001	<0.001	<0.045

B Seronegative



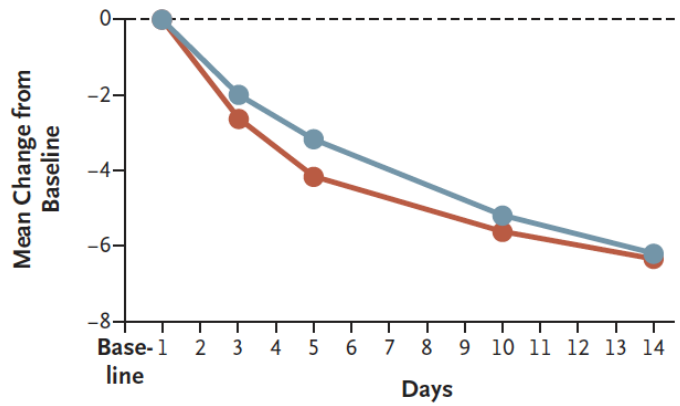
No. at Risk					
NMV-r	318	304	297	296	293
Placebo	312	294	284	267	273
Mean (±SE) Change from Baseline vs. Placebo		−0.56 ±0.14	−1.20 ±0.13	−0.67 ±0.14	−0.21 ±0.12
P Value		<0.001	<0.001	<0.001	0.07

C Seropositive



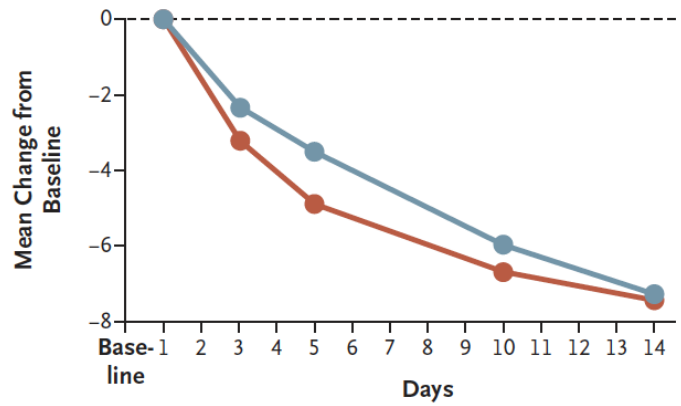
No. at Risk					
NMV-r	231	222	208	203	211
Placebo	233	223	215	200	219
Mean (±SE) Change from Baseline vs. Placebo		−0.58 ±0.18	−0.44 ±0.16	−0.11 ±0.12	−0.06 ±0.11
P Value		0.001	0.01	0.37	0.60

D Baseline Viral Load >10^4 copies/ml



No. at Risk					
NMV-r	443	424	408	408	408
Placebo	442	419	402	379	396
Mean (±SE) Change from Baseline vs. Placebo		−0.66 ±0.12	−1.00 ±0.12	−0.43 ±0.12	−0.15 ±0.10
P Value		<0.001	<0.001	<0.001	0.13

E Baseline Viral Load >10^7 copies/ml



No. at Risk					
NMV-r	224	213	209	204	208
Placebo	202	191	185	171	176
Mean (±SE) Change from Baseline vs. Placebo		−0.88 ±0.16	−1.39 ±0.15	−0.73 ±0.17	−0.16 ±0.14
P Value		<0.001	<0.001	<0.001	0.25

Intravenous remdesivir (200 mg on day 1 and 100 mg on days 2 and 3)

Randomised double-blind in unvaccinated high risk patients.

Symptoms in the previous 7 days

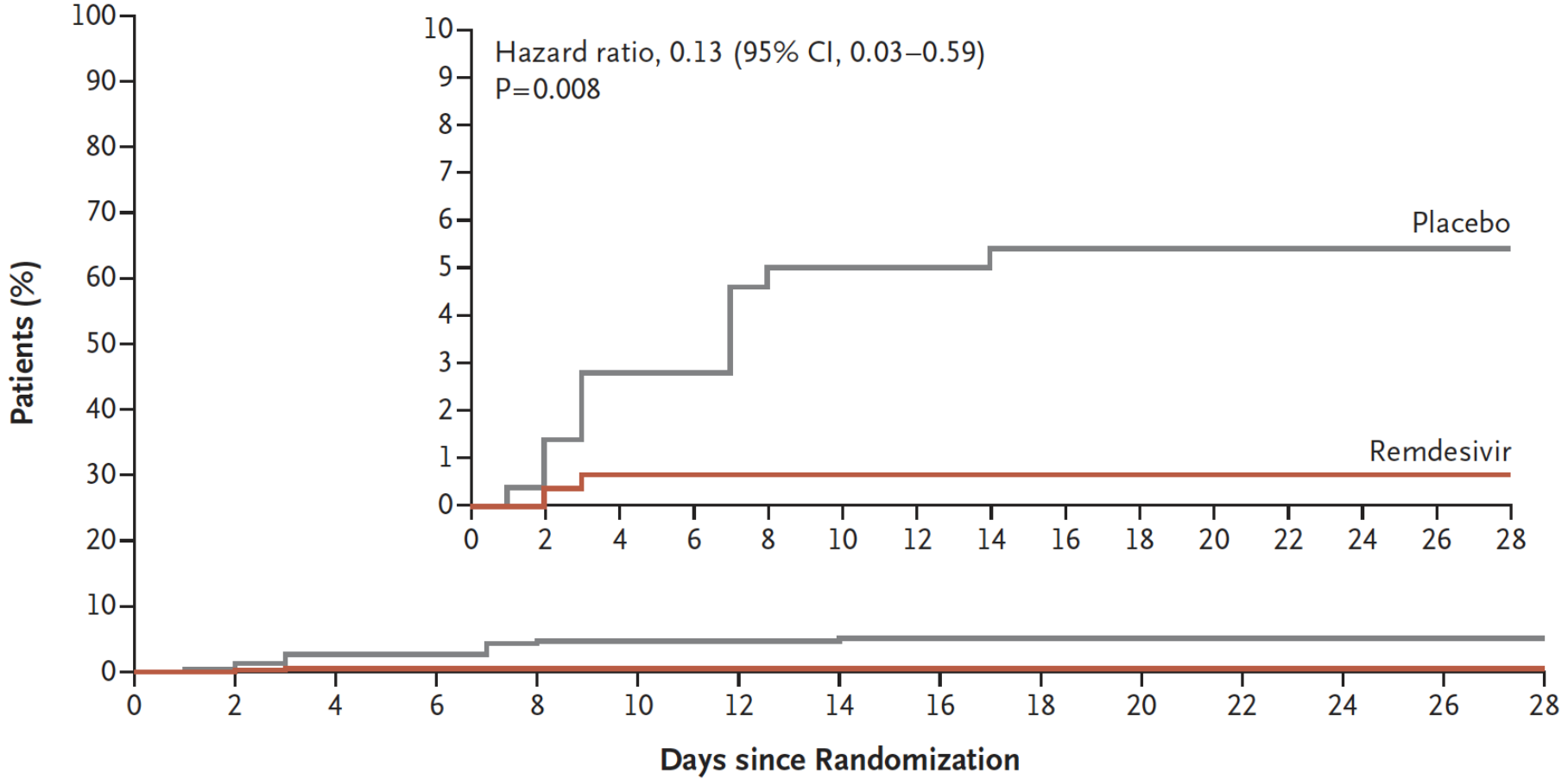
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 27, 2022 VOL. 386 NO. 4

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

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012 (PINETREE) Investigators†

A Covid-19–Related Hospitalization or Death from Any Cause



No. at Risk

Placebo	283	280	272	271	265	264	264	263	262	261	261	260	256	250	227
Remdesivir	279	276	272	272	271	268	268	268	264	264	264	264	260	252	226

800 mg of molnupiravir or placebo twice daily for 5 days.

Randomised double-blind in unvaccinated high risk patients.

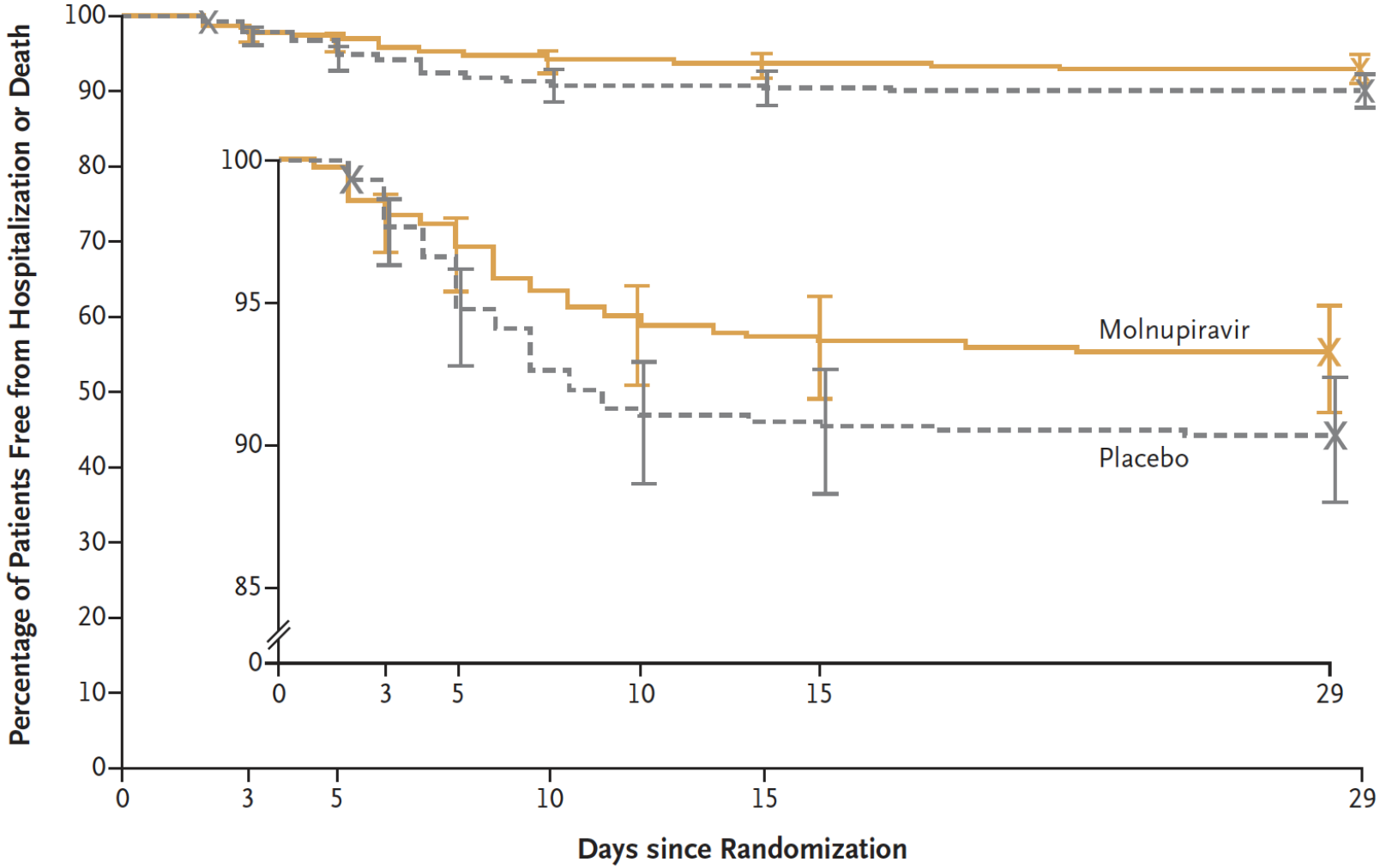
Symptoms in the previous 5 days

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 10, 2022 VOL. 386 NO. 6

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*



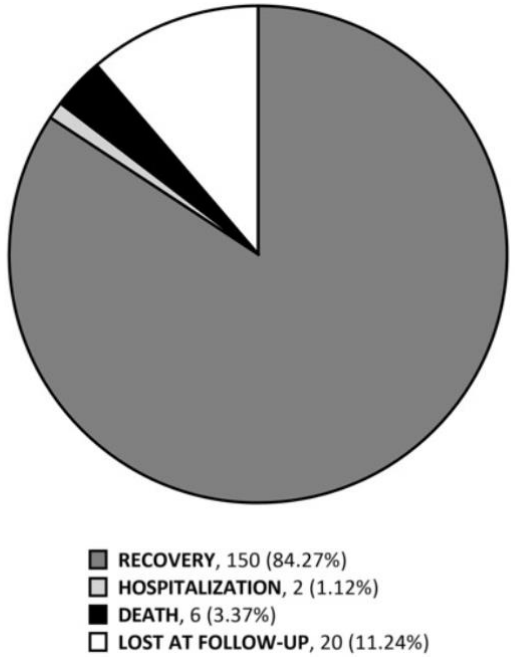
No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

Beringheli, Bai et al, HIV Glasgow 2022 *and manuscript in preparation*

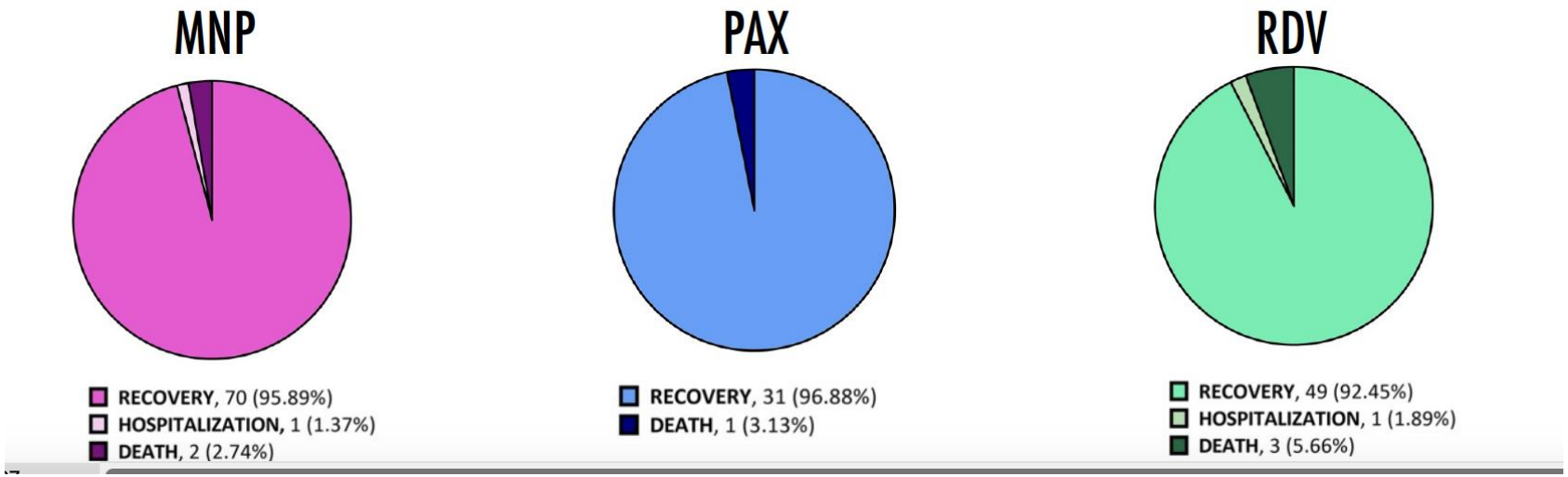
Real life data

178 PATIENTS

- MNP, 78 (43.82%)
- PAX, 44 (24.7%%)
- RDV, 66 (31.46%)



Graphic.2 - Outcomes for each treatment, n (%)



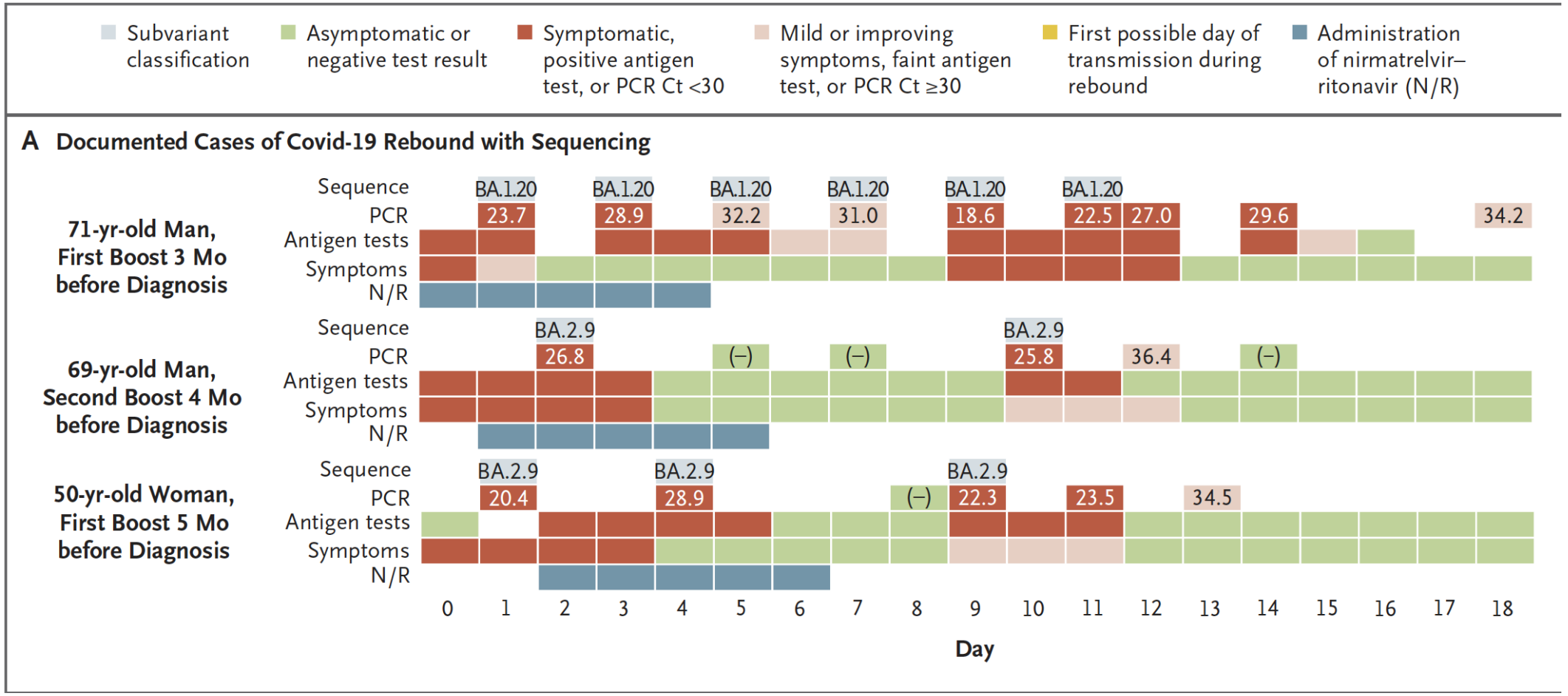
Factors associated to viral clearance at day 7

Parameters	OR	95%CI	p values	AOR	95%CI	p values
Antiviral treatment:						
Molnupiravir	1		0.059	1		0.157
Paxlovid	0.314	0.121-0.816	0.017	2.783	0.977-7.928	0.055
Remdesivir	0.690	0.308-1.547	0.368	1.425	0.633-3.206	0.392
Age, each year more	1.021	0.998-1.043	0.069	0.987	0.963-1.011	0.274
Gender,						
Female	1					
Male	1.196	0.592-2.416	0.619			
COVID-19 vaccination:						
No	1					
Yes (complete schedule, <120 days)	1.303	0.513-3.308	0.578			
Unknown						
Calendar period:						
Jan-Feb 22	1		0.032			
Mar- Apr 22	1.110	0.472-2.609	0.810			
May-Jun 22	0.364	0.150-0.883	0.025			
Risk factor for progression:						
No immunodeficiency	1	0.351-2.699	0.959	1	0.424-2.587	0.920
Immunodeficiency	0.974			1.047		
Symptoms:						
None	1					
Yes	1.730	0.437-6.846	0.435			
Setting:						
Outpatient service	1					
Hospitalization for diseases other than COVID-19	0.772	0.311-1.920	0.578			
Days from symptoms onset to antiviral treatment, each day more	0.825	0.665-1.025	0.082			

LEGEND

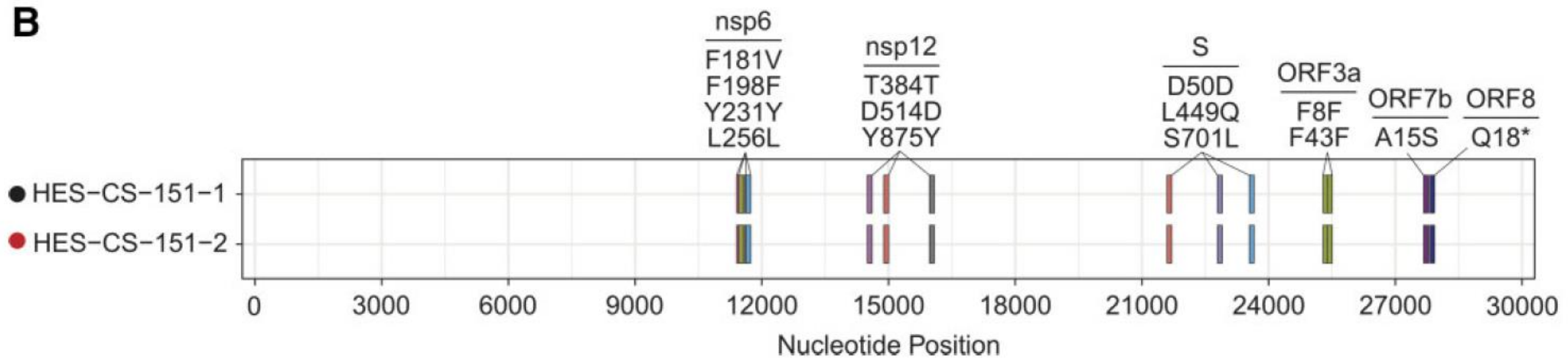
OR, odds ratio; AOR, adjusted odds ratio; 95%CI, 95% confidence interval. Univariable and multivariable logistic regression analysis; in the multivariable analysis the association between antiviral treatment and virological clearance at day 7th after treatment is adjusted for age and immunodeficiency.

Covid-19 rebound after Paxlovid – Omicrom VOC



Charness et al NEJM 2022

No viral resistence at rebound



Epling et al, CID 2022

Immune maturation at rebound

Fig 1A. Blood examination and SARS CoV-2 determination on nasopharyngeal swabs

	T1 (April, 20)	T2 (April, 27)	T3 (May, 2)	T4 (May, 16)
RBC (10^6/uL)	4.06	3.98	3.95	4.06
Hb (g/dl)	**12.3**	**11.9**	**11.8**	**12.2**
PTL (10^3/uL)	226	234	220	338
WBC (10^3/uL)	**7.55**	**4.74**	**5.75**	**6.65**
Lymphocytes (10^3/uL)	660	1170	810	1136
Monocytes (10^3/uL)	**970**	**550**	**790**	**610**
CRP (mg/L)	<5.0	5.0	<5.0	<5.0
LDH (U/L)	**250**	**200**	**205**	**180**
SARS CoV-2 (Ct)	E = 23 RdRp/S = 26 N = 20	NOT DETECTED	E = 21 RdRp/S = 25 N = 21	NOT DETECTED
SARS CoV-2 (VOC)	**B.1.1.529 BA.2 (Omicron)**	**NA**	**B.1.1.529 BA.2 (Omicron)**	**NA**

Fig 1B. Innate response

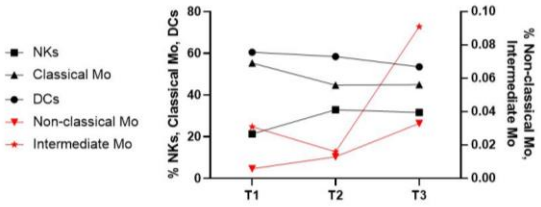


Fig 1C. SARS-CoV-2-specific CD4+ T cells

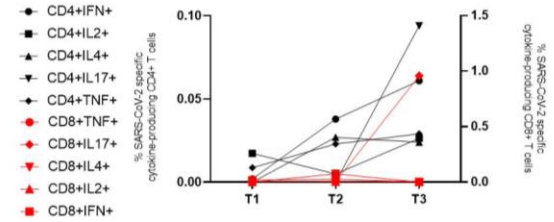


Fig 1D. Th1 - CD4+ polyfunctionality

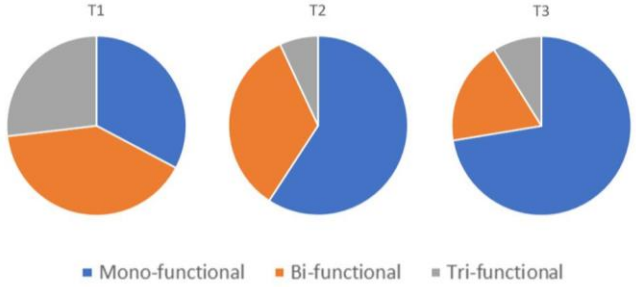
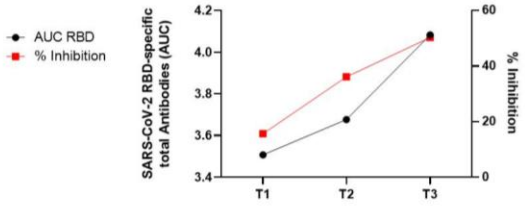


Fig 1E. SARS-CoV-2-specific Abs

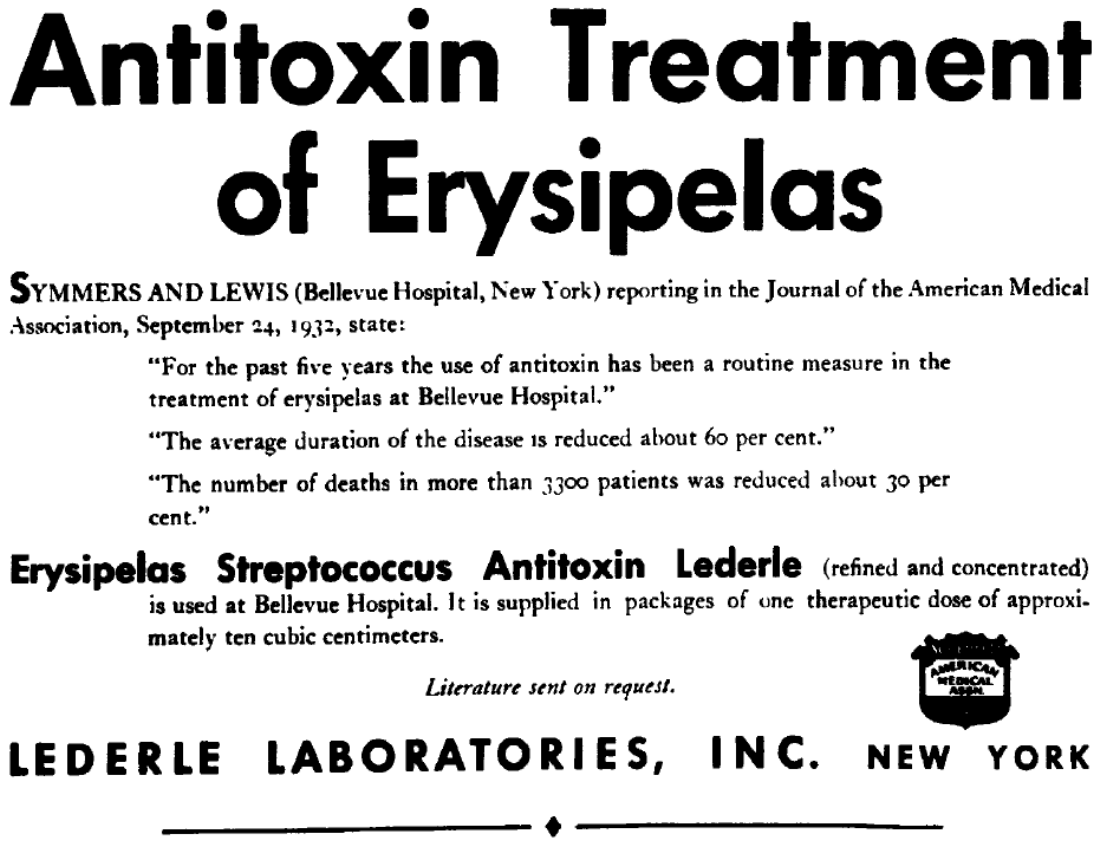


Marchetti, Rovito et al, Clinical Microbiology and Infection 2023

– also Epling et al. CID 2022

Antivirals

- Antivirals
- Convalescent plasma
- Monoclonal antibodies
- Intravenous immune globulins



Antitoxin Treatment of Erysipelas

SYMMERS AND LEWIS (Bellevue Hospital, New York) reporting in the Journal of the American Medical Association, September 24, 1932, state:

"For the past five years the use of antitoxin has been a routine measure in the treatment of erysipelas at Bellevue Hospital."

"The average duration of the disease is reduced about 60 per cent."

"The number of deaths in more than 3300 patients was reduced about 30 per cent."

Erysipelas Streptococcus Antitoxin Lederle (refined and concentrated) is used at Bellevue Hospital. It is supplied in packages of one therapeutic dose of approximately ten cubic centimeters.

Literature sent on request.

AMERICAN MEDICAL ASSN

LEDERLE LABORATORIES, INC. NEW YORK

Figure 1. Lederle advertisement for erysipelas antiserum that appeared in the 15 March 1933 issue of the *New York State Journal of Medicine*. The data cited were published in [37].

Table 1. Infectious diseases that were treated with antibody-based therapies in the preantibiotic era.

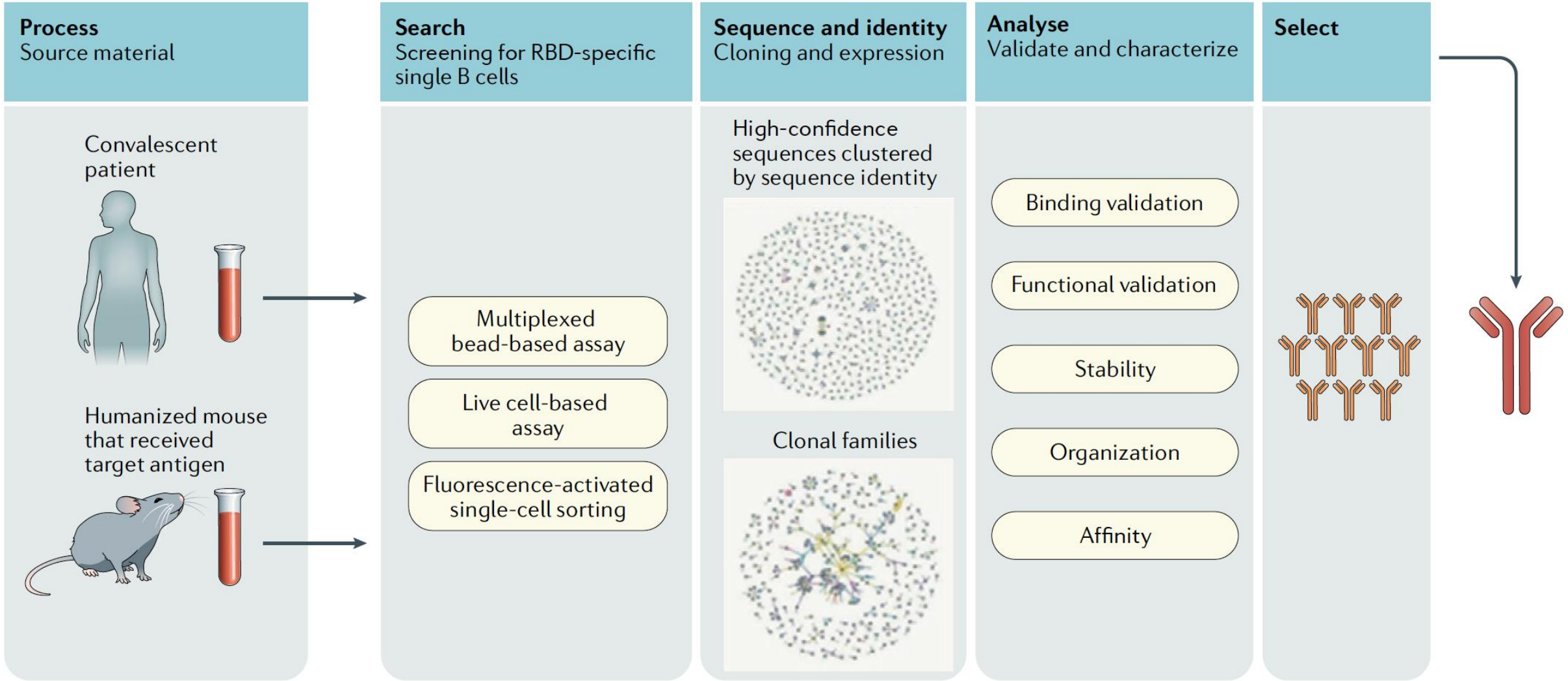
References	Disease	Class, organism
		Bacteria
[7]	Pneumonia	*Streptococcus pneumoniae*
[7]	Meningitis	*Neisseria meningitidis*
[8–10]	Meningitis	*Haemophilus influenzae*
[11–17]	Erysipelas; scarlet fever	Group A *Streptococcus*
[18–20]	Whooping cough	*Bordetella pertussis*
[21]	Anthrax	*Bacillus anthracis*
[22]	Botulism	*Clostridium botulinum*
[16]	Gas gangrene	*Clostridium perfringens*
[23, 24]	Tetanus	*Clostridium tetani*
[25]	Brucellosis	*Brucella abortus*
[26,27]	Dysentery	*Shigella dysenteriae*
[28]	Tularemia	*Francisella tularensis*
[11]	Diphtheria	*Corynebacterium diphtheriae*
		Viruses
[29, 30]	Measles	Measles
[31, 32]	Poliomyelitis	Poliomyelitis
[33, 34]	Mumps	Mumps
[33, 35]	Chickenpox	Varicella zoster

Table 2. Opportunistic pathogens for which experimental data suggest a potential role for antibody-based therapies.

References	Pathogen
[145[	*Pneumocystis carinii*
[146]	*Cryptosporidium parvum*
[142]	*Toxoplasma gondii*
[135, 136, 147]	*Cryptococcus neoformans*
[148]	*Candida albicans*
[149]	Herpes simplex virus
[71, 150]	Cytomegalovirus
[151, 152]	*Pseudomonas aeruginosa*

The rise and fall of monoclonal antibodies (mAb) in COVID-19

mAb: the rise



Review. Taylor PC et al, Nat Rev Immunol. 2021 Jun;21(6):382-393.

Classification of mAbs

Name	RBD site
Sotrovimab (VIR-7831)[1,2] **VIR-7832[1,2]**	Class 3
REGN-COV2 (REGN10933 and REGN10987, not co-formulated)[3,4,5]	Class 1 Class 2
LY-CoV555 and LY-CoV16[6,7]	Class 2
AZD7442[8] (cocktail of AZD8895 and AZD1061)	Class 1 Class 2

Only sotrovimab† binds to a Class 3 RBD site, distinct from the RBM (ACE2 binding site)[1,2]

1. Barnes CO, et al. *Nature* 2020;588:682–7; 2. Pinto D, et al. *Nature* 2020;583:290–5; 3. Baum A, et al. *Science* 2020;369:1014–18; 4. Baum A, et al. *Science* 2020;370:1110–5; 5. Hansen J, et al. *Science* 2020;369:1010–14; 6. Jones BE, et al. *bioRxiv preprint* 2020; doi: https://doi.org/10.1101/2020.09.30.318972; 7. Shi R, et al. *Nature* 2020;584:120–4; 8. Zost SJ, et al. *Nature* 2020;584:443–9.

mAbs: main RCT

Methods	Results	Limitations and Interpretation
BLAZE-1: Double-Blind RCT of Bamlanivimab 700 mg Plus Etesevimab 1,400 mg in Nonhospitalized Patients With Mild to Moderate COVID-19 in the United States and Puerto Rico[1]		

Key Inclusion Criteria
• Aged ≥12 years
• At high risk for severe COVID-19 or hospitalization
Interventions
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  • BAM 700 mg plus ETE 1,400 mg (n = 511)
  • Placebo (n = 258)
Primary Endpoint
• COVID-19-related hospitalization (defined as ≥24 hours of acute care) or death from any cause by Day 29
	Participant Characteristics
	• Median age 56 years; 30% aged ≥65 years; 53% women
	• 87% White, 27% Hispanic/Latinx, 8% Black/African American
	• Mean duration of symptoms was 4 days
	• 76% with mild COVID-19, 24% with moderate COVID-19
	Primary Outcomes
	• COVID-19-related hospitalizations or all-cause deaths by Day 29: 4 (0.8%) in BAM plus ETE arm vs. 15 (5.8%) in placebo arm (change of -5.0%; 95% CI, -8.0% to -2.1%; $P < 0.001$)
	• All-cause deaths by Day 29: 0 in BAM plus ETE arm vs. 4 (1.6%) in placebo arm
		Key Limitation
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation
		• Compared to placebo, BAM plus ETE significantly reduced the number of COVID-19-related hospitalizations and all-cause deaths in high-risk patients

BLAZE-4, Treatment Arms 9–11: Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2]		

Key Inclusion Criteria
• Aged 18–64 years
• No risk factors for progression to severe COVID-19
Key Exclusion Criteria
• ≥1 of the following:
  • SpO_2 ≤93% on room air
  • Respiratory rate ≥30 breaths/min
  • Heart rate ≥125 bpm
	Participant Characteristics
	• Median age 35 years; 56% women
	• 36% Hispanic/Latinx, 19% Black/African American
	• Mean duration of symptoms prior to enrollment was 3.6 days
	Primary Outcomes
	• Proportion with PHVL:
	  • 13% in BAM plus ETE plus BEB arm vs. 21% in placebo arm ($P = 0.098$), with a relative reduction of 38% (95% CI, -9% to 65%)
		Key Limitations
		• Only low-risk patients included
		• Not powered to assess hospitalizations and deaths
		• Conducted before widespread circulation of the Omicron VOC
		Interpretations
		• There were no differences in the proportion of patients with PHVL across the arms.

Methods	Results	Limitations and Interpretation
BLAZE-4, Treatment Arms 9–11: Double-Blind RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab Versus Bebtelovimab Alone Versus Placebo in Low-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		

Interventions
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
  • BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 127)
  • BEB 175 mg (n = 125)
  • Placebo (n = 128)
Primary Endpoint
• Proportion of patients with PHVL (defined as SARS-CoV-2 VL >5.82 $\log_{10}$ by Day 7)
Key Secondary Endpoints
• Mean change in VL from baseline to Days 3, 5, 7, and 11
• COVID-19-related hospitalization or death from any cause by Day 29
• Time to sustained symptom resolution
	• 14% in BEB arm vs. 21% in placebo arm ($P = 0.147$), with a relative reduction of 34% (95% CI, -15% to 62%)
	Secondary Outcomes
	• Mean decline in VL greater in mAb arms vs. placebo arm at Day 5 but not at Days 3, 7, or 11
	• COVID-19-related hospitalizations or all-cause deaths by Day 29:
	  • 3 (2.4%) in BAM plus ETE plus BEB arm, including 1 death
	  • 2 (1.6%) in BEB arm
	  • 2 (1.6%) in placebo arm
	• Median time to sustained symptom resolution:
	  • 7 days in BAM plus ETE plus BEB arm vs. 8 days in placebo arm ($P = 0.289$)
	  • 6 days in BEB arm vs. 8 days in placebo arm ($P = 0.003$)
		• Few COVID-19-related hospitalizations or deaths from any cause occurred by Day 29 across the arms, as is expected for a population of individuals who were at low risk of severe COVID-19
		• Compared to placebo, the median time to sustained symptom resolution was shorter in the BEB arm.

BLAZE-4, Treatment Arms 12 and 13: Open-Label RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab and Bebtelovimab Alone in High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2]		

Key Inclusion Criteria
• Aged ≥12 years
• Weight ≥40 kg
• ≥1 risk factor for progression to severe COVID-19
Key Exclusion Criteria
• ≥1 of the following:
  • SpO_2 ≤93% on room air
  • Respiratory rate ≥30 breaths/min
  • Heart rate ≥125 bpm
Interventions
• Within 3 days of a positive SARS-CoV-2 test result, single infusion of:
	Participant Characteristics
	• Median age 50 years; 52% women
	• 18% Hispanic/Latinx, 18% Black/African American
	• Mean duration of symptoms prior to enrollment was 4.7 days
	• 21% had at least 1 dose of COVID-19 vaccine
	Efficacy Outcomes
	• COVID-19-related hospitalization or death from any cause by Day 29: 2 (4%) in BAM plus ETE plus BEB arm vs. 3 (3%) in BEB arm
	• Mean decline in VL greater in BAM plus ETE plus BEB arm vs. BEB arm at Day 5 but not at Days 3, 7, or 11
		Key Limitations
		• Open-label study
		• No placebo arm
		• Not powered to assess hospitalizations and deaths
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation
		• There was no difference in the proportion of patients who were hospitalized or who died between the arms.

Methods	Results	Limitations and Interpretation
BLAZE-4, Treatment Arms 12 and 13: Open-Label RCT of Bamlanivimab Plus Etesevimab Plus Bebtelovimab and Bebtelovimab Alone in High-Risk, Nonhospitalized Patients With Mild to Moderate COVID-19[2], continued		
• BAM 700 mg plus ETE 1,400 mg plus BEB 175 mg (n = 50) • BEB 175 mg (n = 100) **Efficacy Endpoints** • COVID-19-related hospitalization or death from any cause by Day 29 • Mean change in VL from baseline to Days 3, 5, 7, and 11		
Double-Blind RCT of Casirivimab Plus Imdevimab in Nonhospitalized Patients With Mild to Moderate COVID-19[3]		

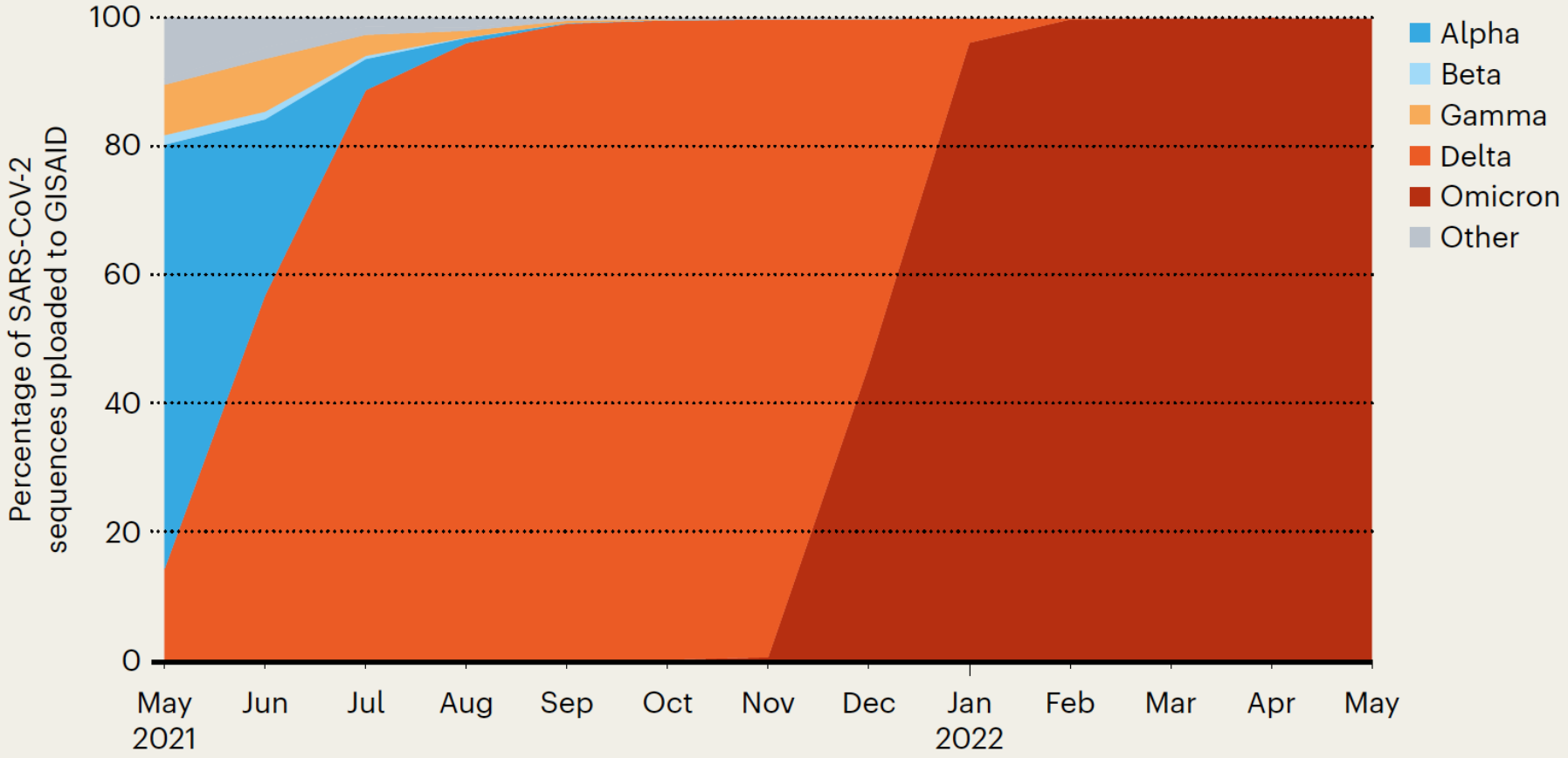
Key Inclusion Criteria
• Aged ≥18 years
• Laboratory-confirmed SARS-CoV-2 infection
• Symptom onset within 7 days of randomization
• For patients included in the modified full analysis only:
  • ≥1 risk factor for severe COVID-19
  • Positive SARS-CoV-2 RT-PCR result at baseline
Interventions
• Single IV infusion of:
  • CAS 600 mg plus IMD 600 mg (n = 736) or placebo (n = 748)
  • CAS 1,200 mg plus IMD 1,200 mg (n = 1,355) or placebo (n = 1,341)
Primary Endpoint
• ≥1 COVID-19-related hospitalization or death from any cause by Day 29
	Participant Characteristics
	• Median age 50 years
	• 35% Hispanic/Latinx, 5% Black/African American
	• Median duration of symptoms prior to enrollment was 3 days
	Primary Outcomes
	• COVID-19-related hospitalizations or all-cause deaths through Day 29:
	  • 7 (1.0%) in CAS 600 mg plus IMD 600 mg arm vs. 24 (3.2%) in placebo arm ($P = 0.002$)
	  • 18 (1.3%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 62 (4.6%) in placebo arm ($P < 0.001$)
	• All-cause deaths:
	  • 1 (0.1%) in CAS 600 mg plus IMD 600 mg arm vs. 1 (0.1%) in placebo arm
	  • 1 (< 0.1%) in CAS 1,200 mg plus IMD 1,200 mg arm vs. 3 (0.2%) in placebo arm
		Key Limitation
		• Conducted before widespread circulation of the Omicron VOC
		Interpretation
		• Compared to placebo, CAS 600 mg plus IMD 600 mg and CAS 1,200 mg plus IMD 1,200 mg reduced the risk of COVID-19-related hospitalizations or all-cause deaths in patients with mild to moderate COVID-19.

Methods	Results	Limitations and Interpretation
COMET-ICE: Double-Blind RCT of Sotrovimab in Nonhospitalized Patients With Mild to Moderate COVID-19 in Brazil, Canada, Peru, Spain, and the United States[4]		
Key Inclusion Criteria • Aged ≥18 years • ≥1 comorbidity or aged ≥55 years • Positive SARS-CoV-2 RT-PCR or antigen test result • Symptom onset ≤5 days before enrollment **Key Exclusion Criteria** • Hospitalized or required supplemental oxygen • Severely immunocompromised **Interventions** • SOT 500 mg IV (n = 528) • Placebo (n = 529) **Primary Endpoint** • Hospitalization or death from any cause by Day 29	**Participant Characteristics** • Median age 53 years; 20% aged ≥65 years; 54% women • 65% Hispanic/Latinx, 8% Black/African American • 63% with obesity; 22% with DM; 17% with moderate to severe asthma **Primary Outcome** • Hospitalizations or all-cause deaths by Day 29: 6 (1%) in SOT arm vs. 30 (6%) in placebo arm, including 2 deaths (adjusted relative risk 0.21; 95% CI, 0.09–0.50; absolute difference -4.53%; 95% CI, -6.70% to -2.37%; $P < 0.001$)	**Key Limitation** • Conducted before widespread circulation of the Omicron VOC **Interpretation** • Compared to placebo, SOT reduced the incidence of all-cause hospitalizations and deaths among patients with mild to moderate COVID-19.

mAb: the fall

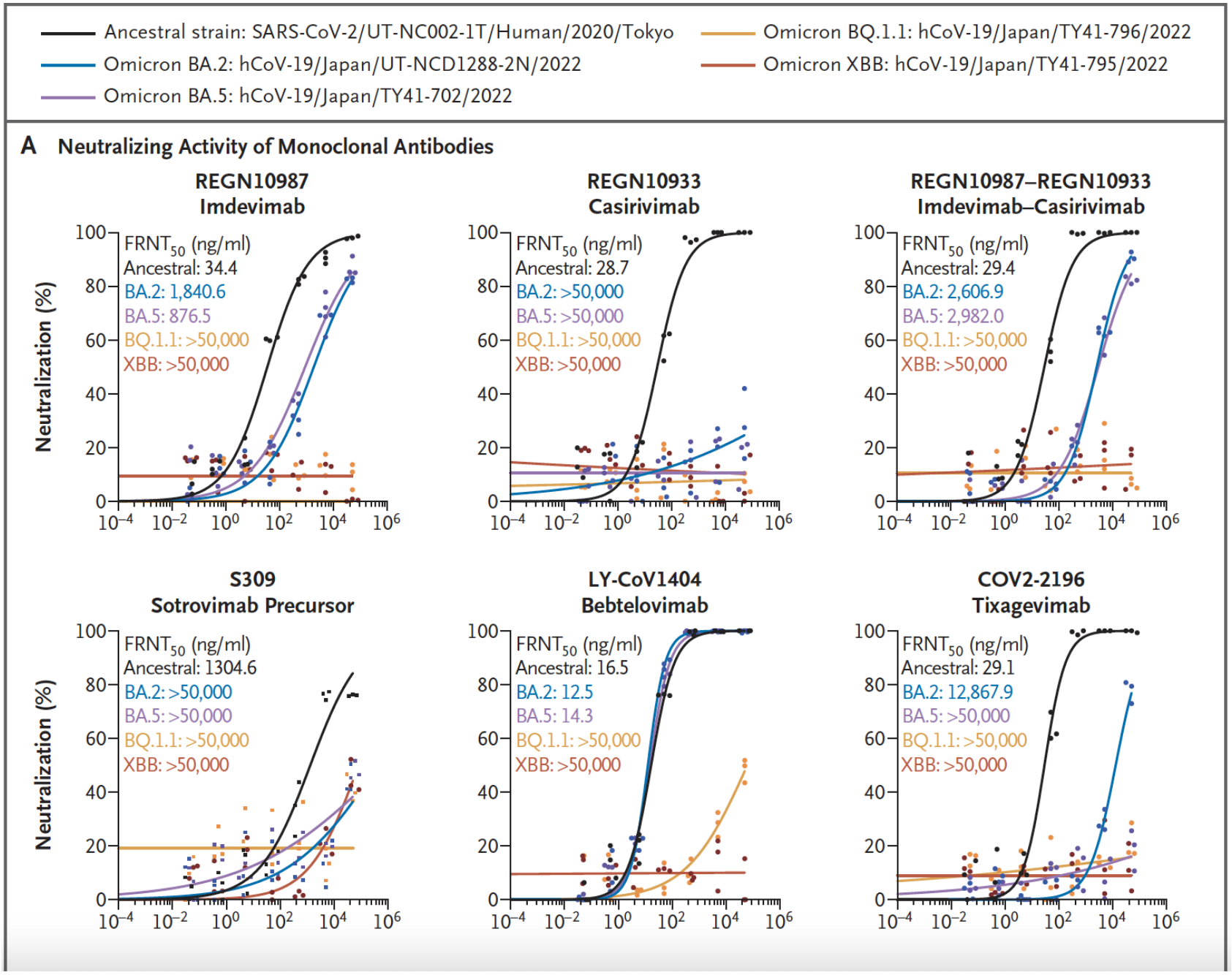
EVOLUTION OF A VIRUS

Variants of the SARS-CoV-2 coronavirus arise constantly as it evolves. But so far, only five have met the World Health Organization's criteria to be called variants of concern. By definition, these variants are much more transmissible, virulent or able to escape an immune response than the versions that came before them. Researchers can watch the evolution of SARS-CoV-2 by tracking genomic sequences submitted to data platforms such as GISAID.



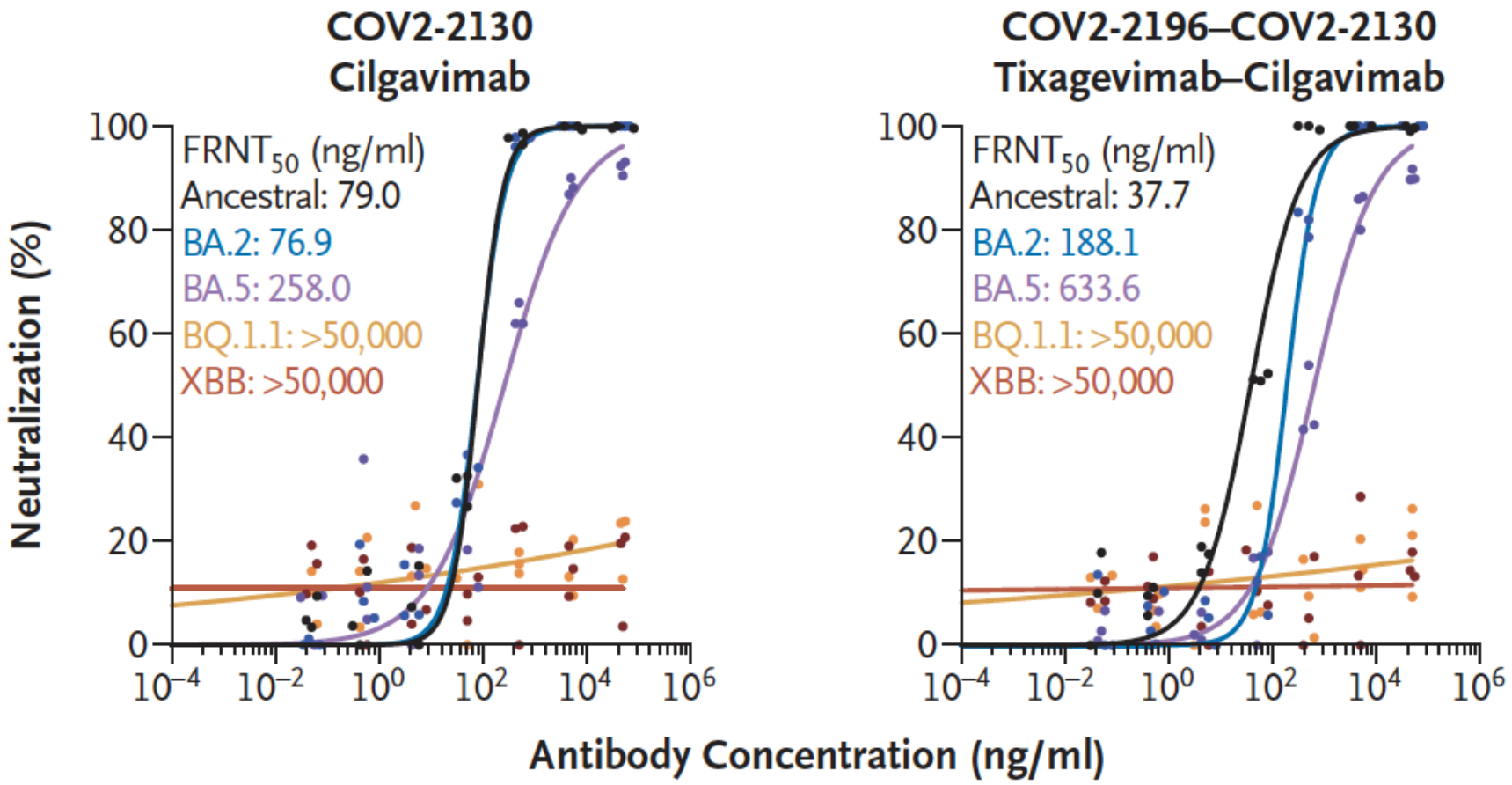
SOURCE: GISAID

Nature, May 2022



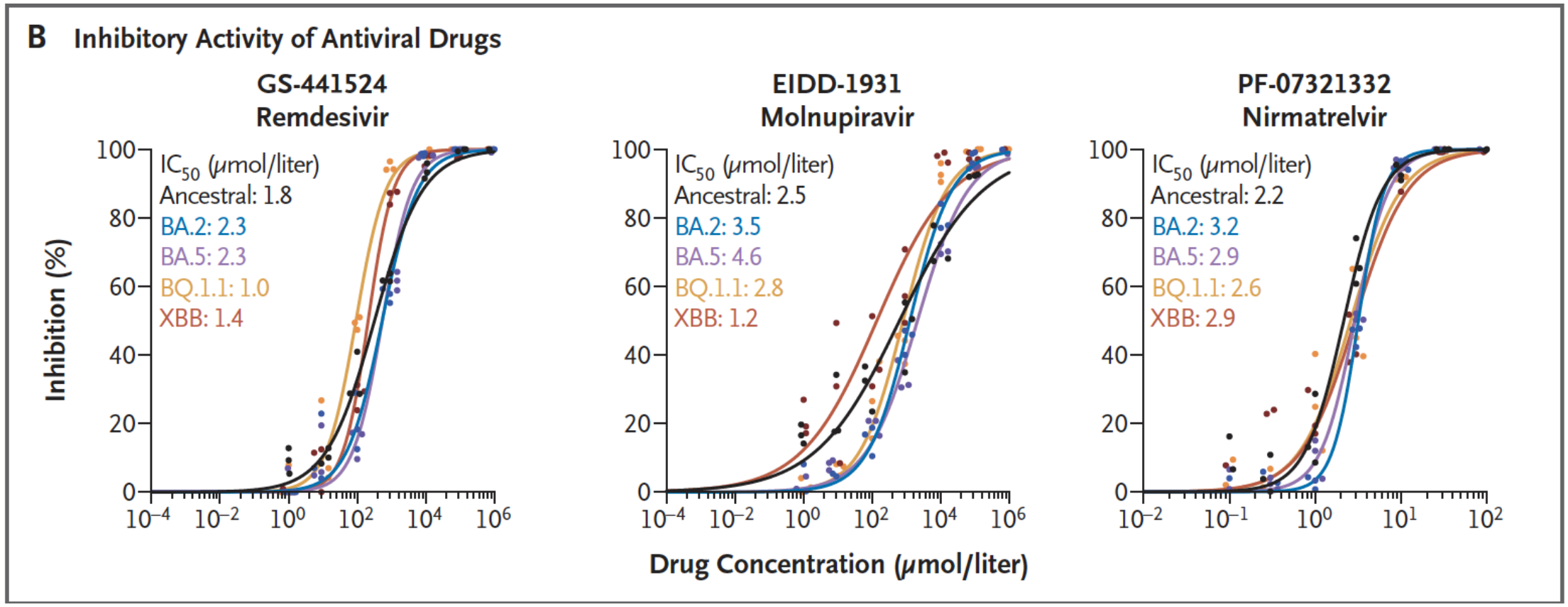
Live virus neutralization assay on SARS-COV2 isolates from patients

Imai et al, NEJM 2023



Imai et al, NEJM 2023

Retained efficacy of antivirals *versus* circulating VOCs



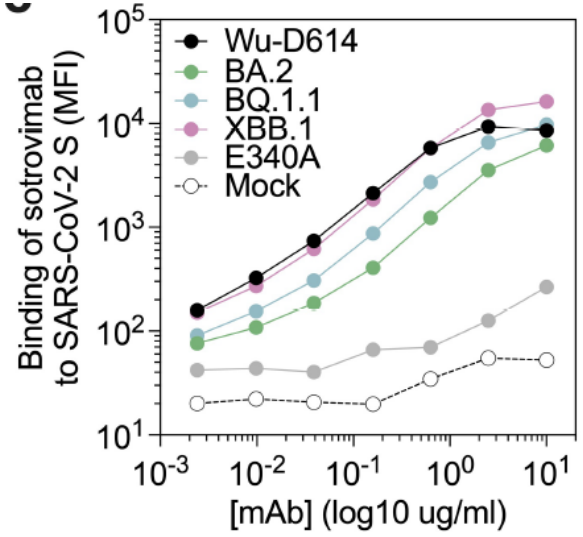
Imai et al, NEJM 2023

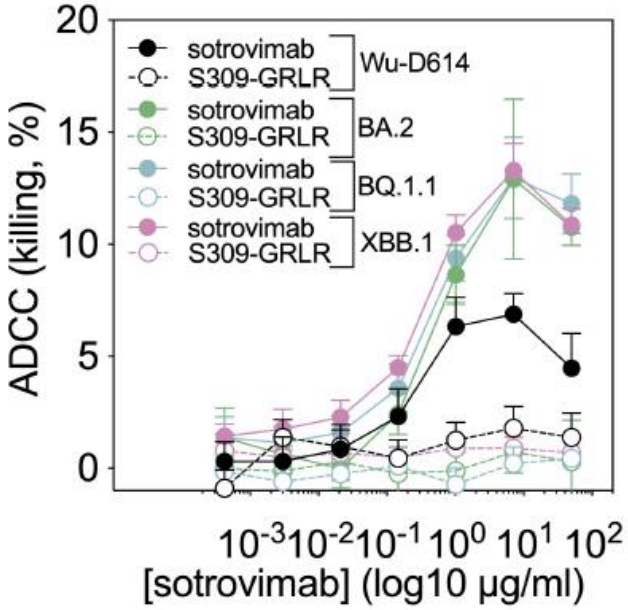
mAb: the fall (?)

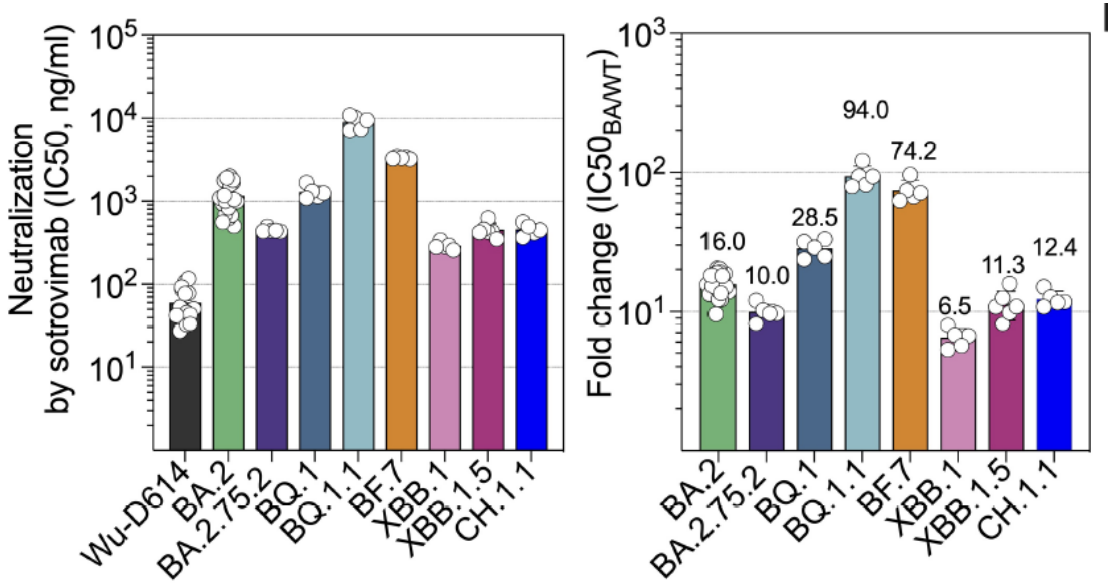
And yet…..preclinical and clinical data to suggest that this might not be fully true

mAb: the fall (?)

And yet.....**preclinical** and clinical data to suggest that this might not be fully true

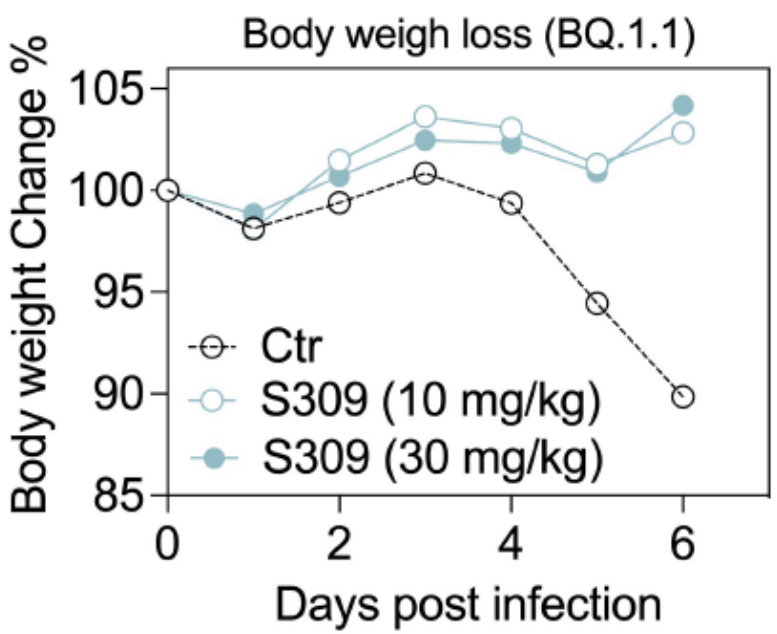


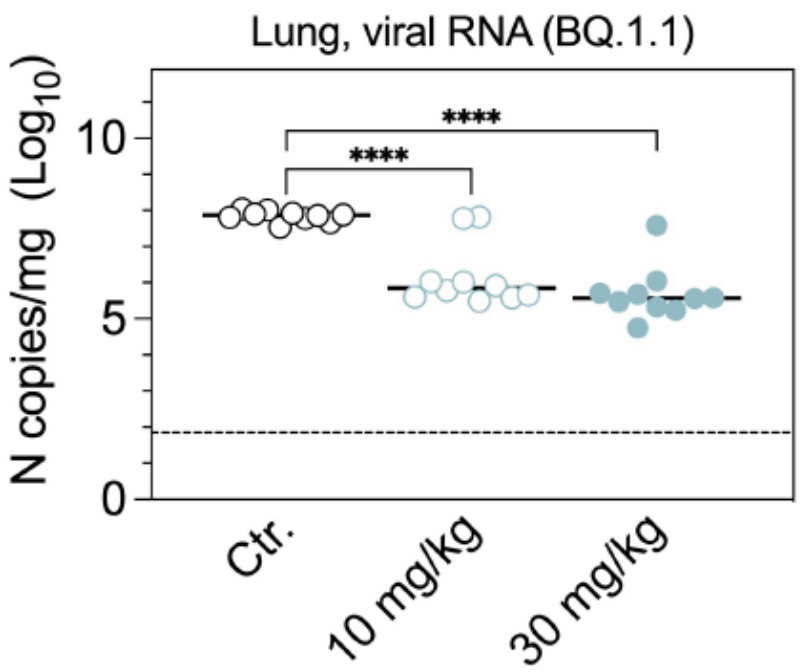


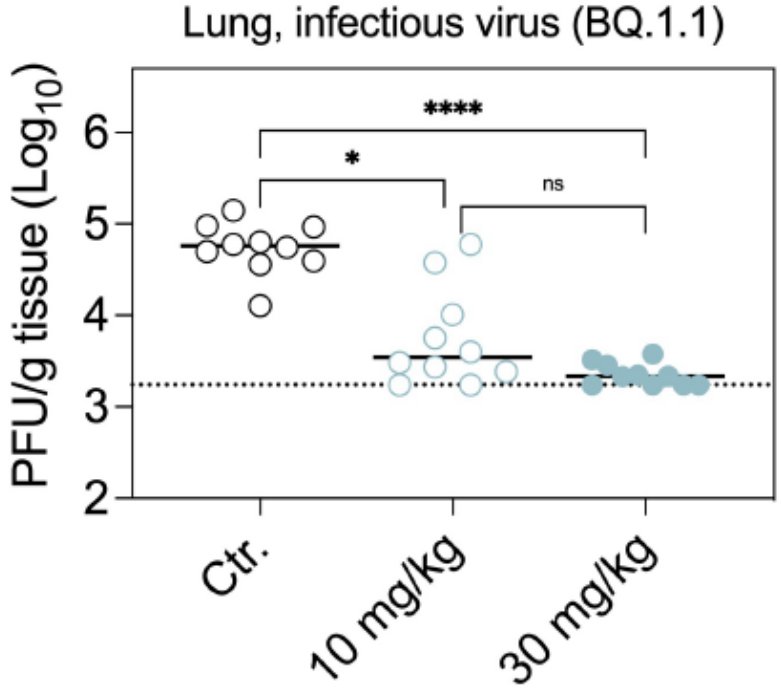


Sotrovimab binds avidly to all Omicron variants, promotes Fc51 dependent effector functions

Addetia et al, https://doi.org/10.1101/2023.01.17.523798







Addetia et al, https://doi.org/10.1101/2023.01.17.523798

mAb: the fall (?)

And yet…..preclinical and **clinical** data to suggest that this might not be fully true

Characteristic	Patients, No. (%)	
	Nontreated (n = 141 942)	Treated (n = 25 241)
Age, mean (SD), y	45.4 (18.3)	56.0 (16.9)
Sex		
Female	82 279 (58.0)	13 390 (53.0)
Male	59 658 (42.0)	11 851 (47.0)
Not specified	5 (<0.1)	0
Race		
American Indian or Alaska Native	1206 (0.8)	185 (0.7)
Asian	3769 (2.7)	521 (2.1)
Black or African American	9593 (6.8)	1153 (4.6)
Native Hawaiian or other Pacific Islander	1607 (1.1)	193 (0.8)
White	117 286 (82.6)	22 093 (87.5)
Other[a]	5659 (4.0)	743 (2.9)
Not specified	2822 (2.0)	353 (1.4)
Ethnicity		
Hispanic or Latino	21 154 (14.9)	2461 (9.8)
Non-Hispanic or non-Latino	116 714 (82.2)	22 186 (87.9)
Not specified	4074 (2.9)	594 (2.4)
COVID-19 vaccination status		
No record of vaccination	89 983 (63.4)	14 971 (59.3)
Partially vaccinated	3693 (2.6)	710 (2.8)
Fully vaccinated	35 828 (25.2)	8456 (33.5)
Fully vaccinated and boosted	12 418 (8.7)	1095 (4.3)

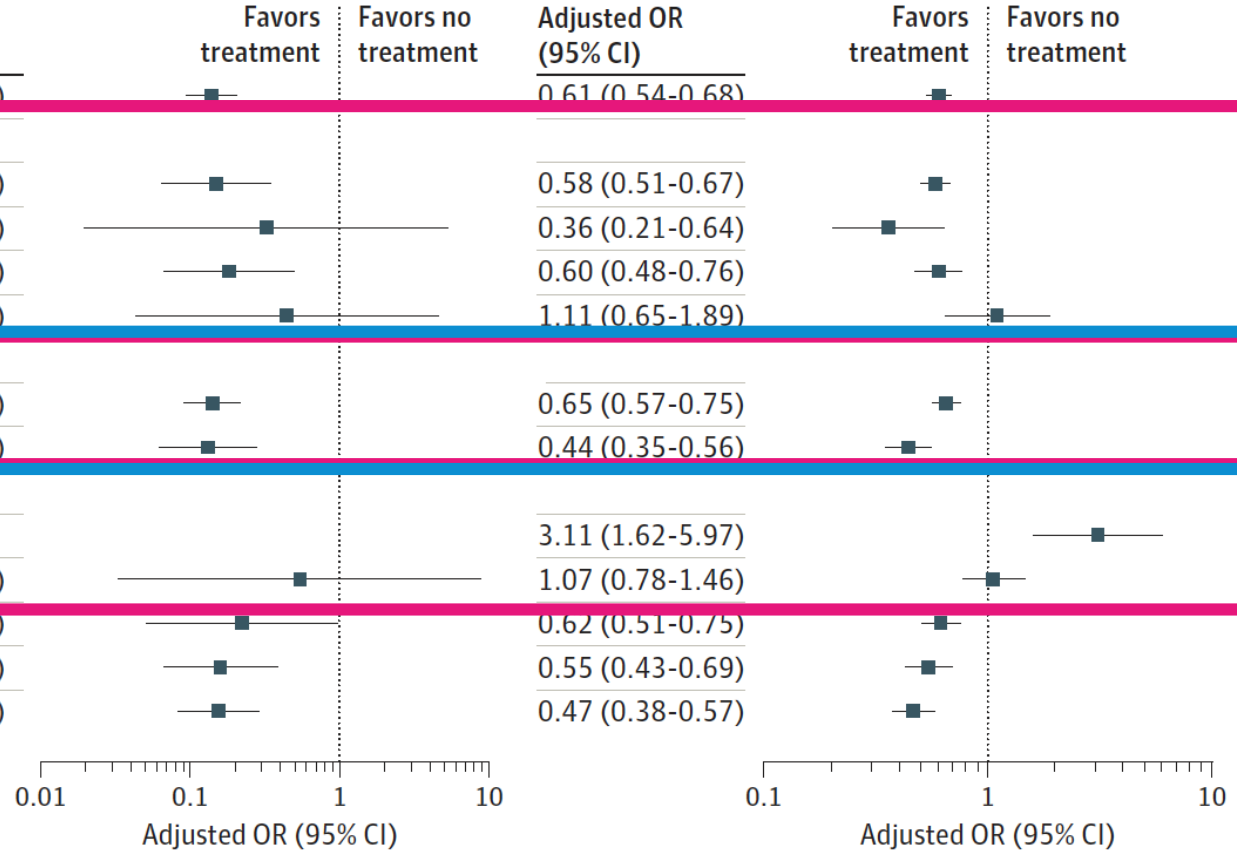
November 9, 2020, and January 31, 2022

bamlanivimab, bamlanivimab-etesevimab, casirivimab imdevimab, and sotrovimab

Ambrose et al. JAMA open 2023

B Mortality and composite

	No. of patients (No. treated)	30-d Mortality Adjusted OR (95% CI)	30-d Composite Adjusted OR (95% CI)
Overall nMAb outcome	167 183 (25 241)	0.14 (0.10-0.20)	0.61 (0.54-0.68)
By COVID-19 immunization status			
No vaccine record	104 954 (14 971)	0.15 (0.07-0.34)	0.58 (0.51-0.67)
Partial	4403 (710)	0.33 (0.02-5.30)	0.36 (0.21-0.64)
Full	44 284 (8456)	0.18 (0.07-0.49)	0.60 (0.48-0.76)
Full plus boosted	13 513 (1095)	0.45 (0.04-4.55)	1.11 (0.65-1.89)
By immunocompromised status			
Not immunocompromised	152 164 (21 321)	0.14 (0.09-0.22)	0.65 (0.57-0.75)
Immunocompromised	15 019 (3920)	0.13 (0.06-0.27)	0.44 (0.35-0.56)
By risk of severe COVID-19			
Stratum (lowest risk)	42 318 (1692)	NA	3.11 (1.62-5.97)
Stratum 2	50 242 (5531)	0.54 (0.03-8.82)	1.07 (0.78-1.46)
Stratum 3	38 340 (7654)	0.22 (0.05-0.96)	0.62 (0.51-0.75)
Stratum 4	24 132 (6761)	0.16 (0.07-0.38)	0.55 (0.43-0.69)
Stratum 5 (highest risk)	12 152 (3604)	0.15 (0.08-0.28)	0.47 (0.38-0.57)



Ambrose et al. JAMA open 2023

247 patients (109 vaccinated) ASST Santi Paolo e Carlo, 03/2021-05/2022

Higher proportion of recovery and more rapid viral clearance in vaccinated patients

Characteristics	Study population N 247	Unvaccinated patients N 109 (44.2%)	Vaccinated patients N 138 (55.8%)	p values
Adverse events, n (%):				**<0.001**
No	226 (91.5%)	91 (83.5%)	135 (97.8%)	
Yes	21 (8.5%)	18 (16.5%)	3 (2.2%)	
Virological clearance at T7, n (%):				0.557
No	153 (61.9%)	71 (65.1%)	82 (59.4%)	
Yes	86 (34.8%)	34 (31.2%)	52 (37.7%)	
Days from symptom onset to virological clearance,* median (IQR)	16 (12-21)	18 (13-24)	15 (11-21)	**0.011**
Outcome, n (%):				**<0.001**
Recovery	205 (83%)	78 (71.6%)	127 (93.4%)	
Hospitalization	19 (7.7%)	18 (16.5%)	1 (0.7%)	
Death	9 (3.6%)	4 (3.7%)	5 (3.7%)	
Lost to follow up	12 (4.9%)	9 (8.3%)	3 (2.2%)	

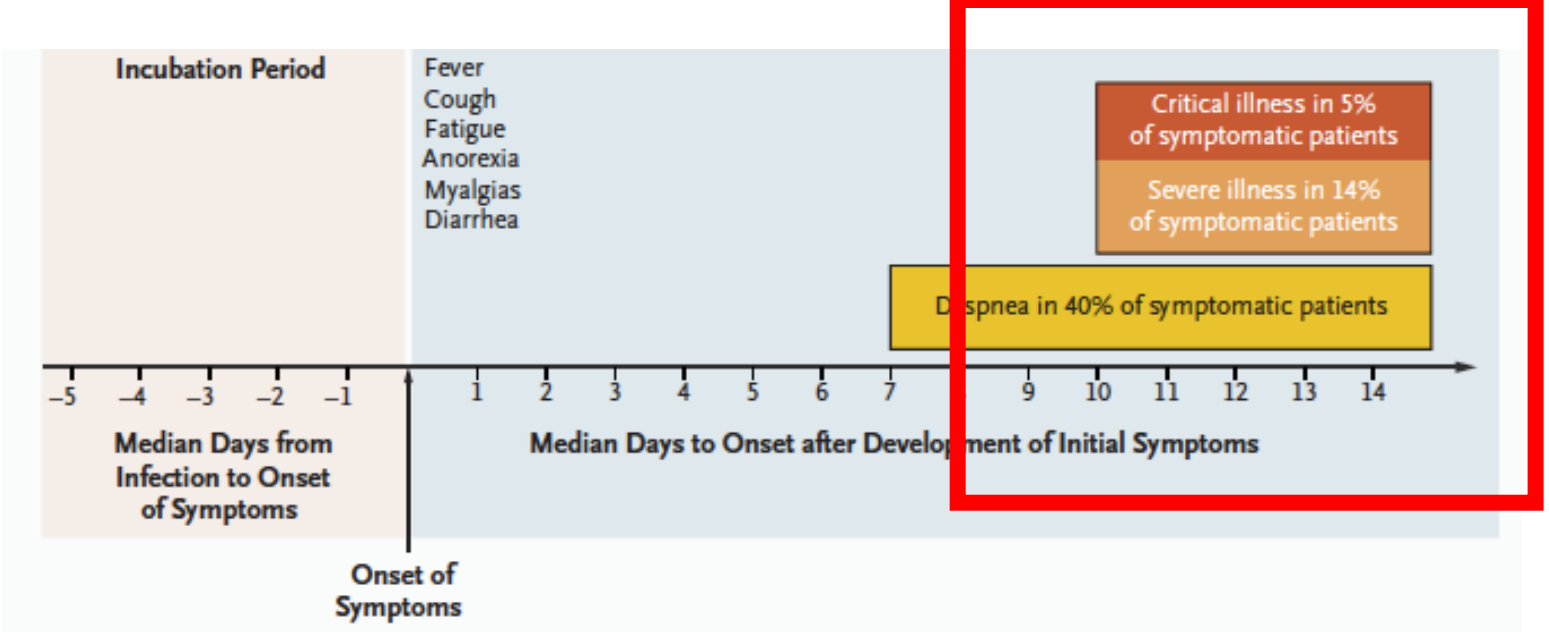
Bai F et al. Submitted ICAR 2023

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

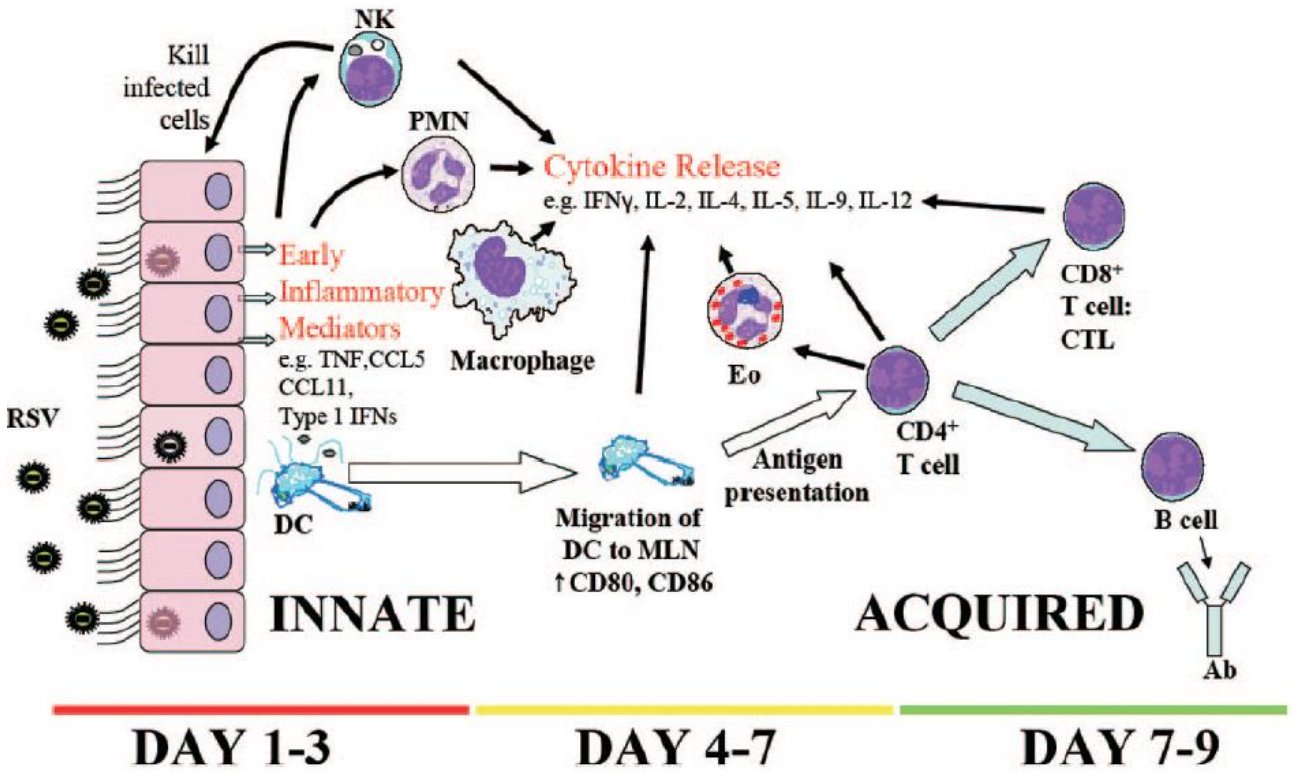
Final draft guidance

Therapeutics for people with COVID-19

The committee noted that in vitro evidence on sotrovimab's neutralisation activity was inconsistent between the studies with some evidence suggesting partial reduction in neutralisation activity. The clinical experts explained that partial reductions in neutralisation are difficult to interpret without additional clinical evidence such as in vivo (in animals) or pharmacodynamic and pharmacokinetic data. They explained that in such cases the in vitro data are only pieces of the puzzle rather than an individual indication of the potential clinical efficacy. The committee considered additional evidence (Addetia et al. 2023) on sotrovimab. The company explained that, unlike the other neutralising monoclonal antibodies, sotrovimab's effectiveness against the virus depends on the expression levels of ACE2 to which the SARS-CoV-2 receptor binds. If the cell line used in the in vitro study over-expresses ACE2 then sotrovimab may appear not to neutralise the virus in laboratory studies. The results from these in vitro studies may underestimate sotrovimab's neutralising ability against the real virus. The committee considered this added uncertainty to the interpretations of the in vitro evidence for sotrovimab.



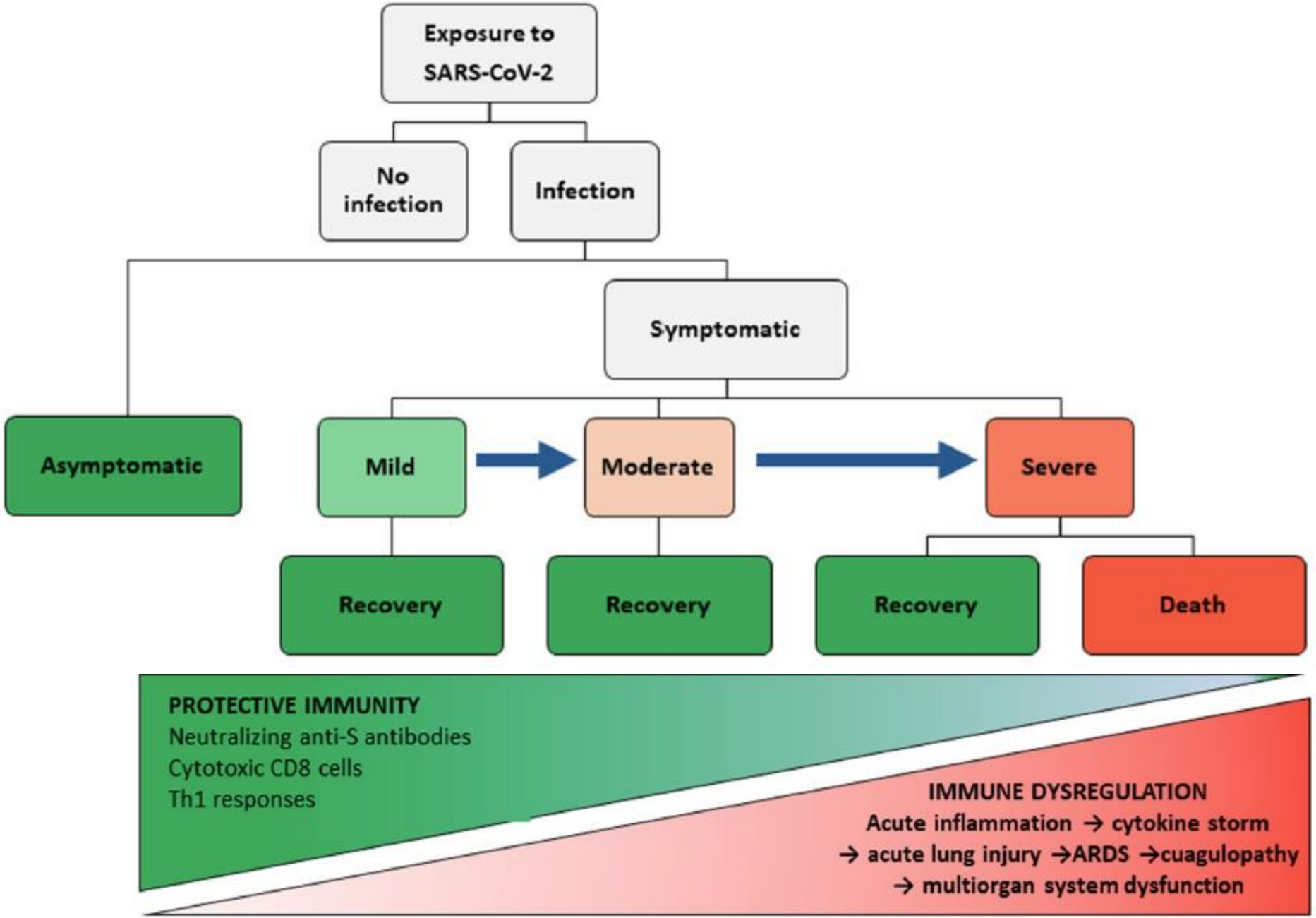
Berlin NEJM 2020



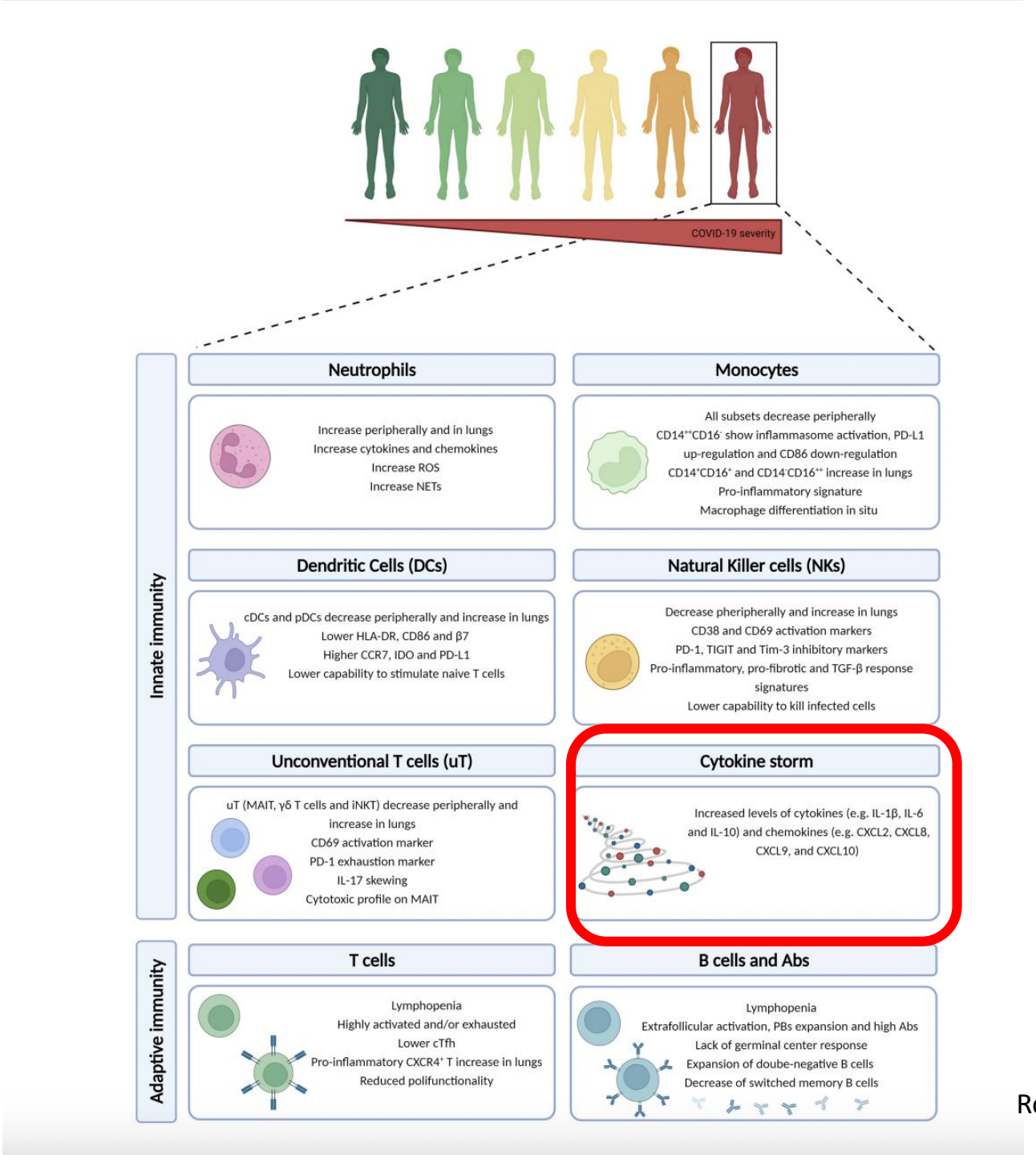
Phase 2. immune dysfunction

Immune-mediators

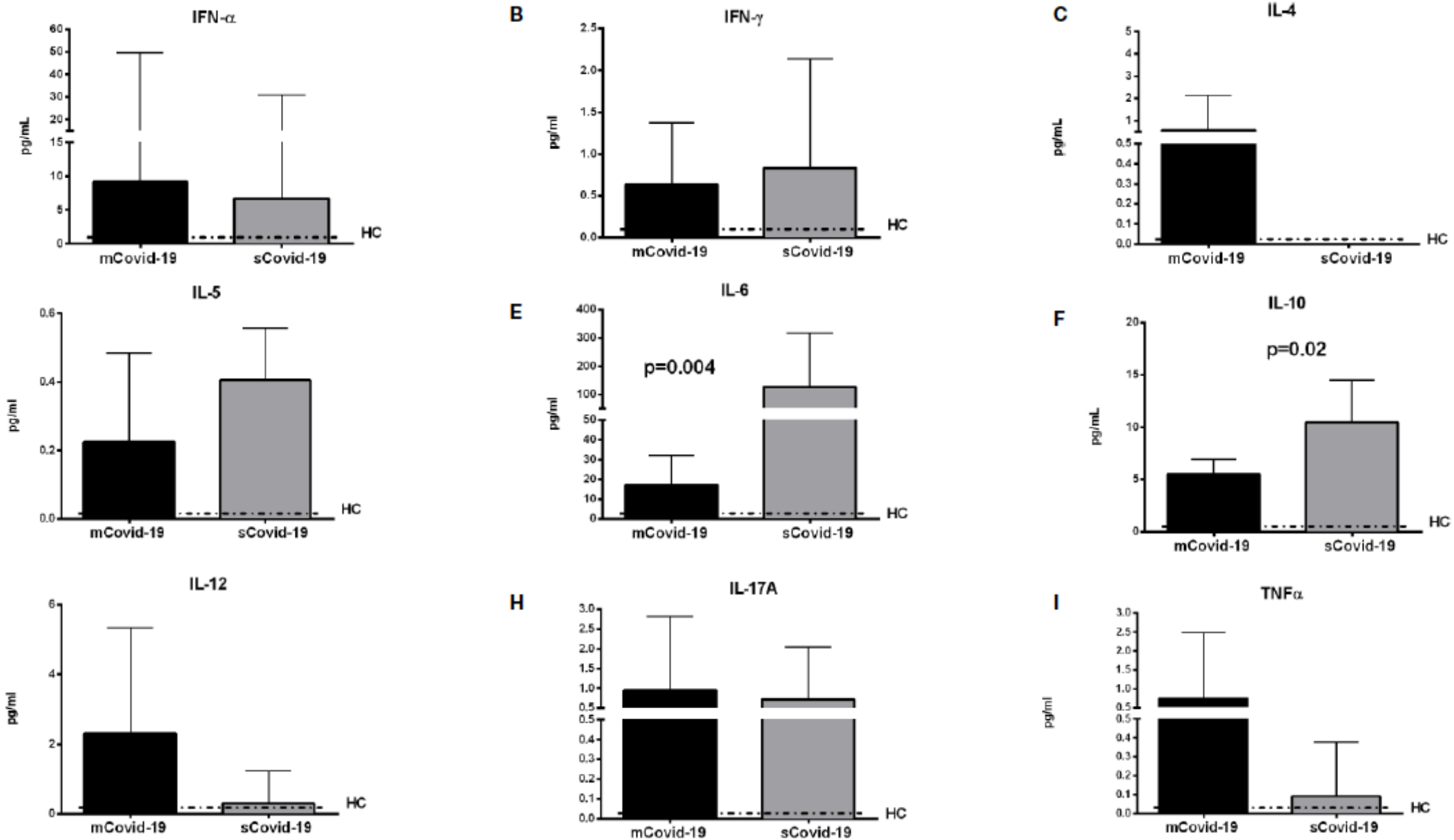
Openshaw et al. Clinical Microbiolgy Reviews 2005



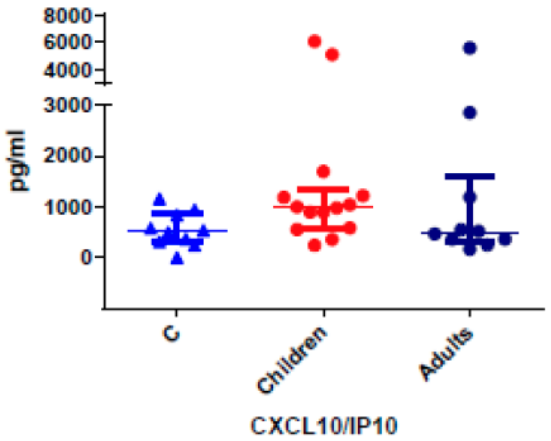
Garcia Frontiers Immunology 2020



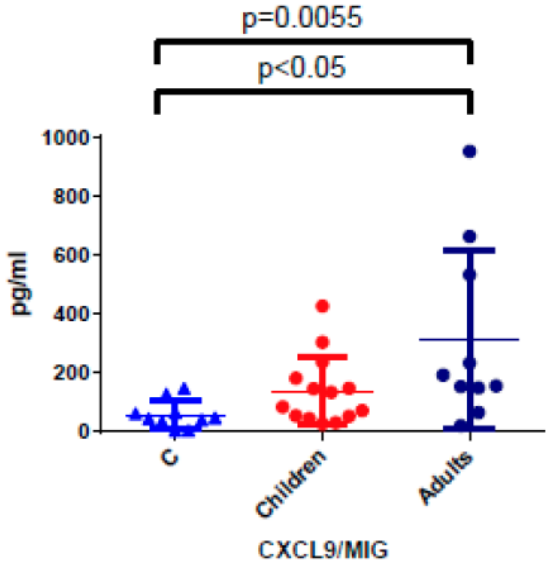
Rovito et al. Front Immunol 2022



Tincati, Cannizzo et al. Frontiers Immunol 2020



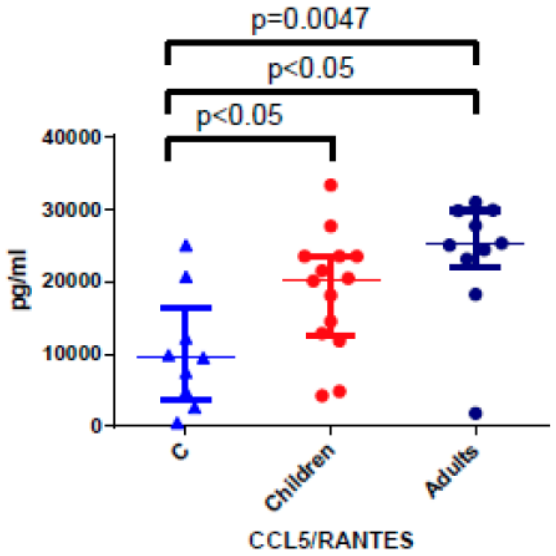
CXCL10/IP10



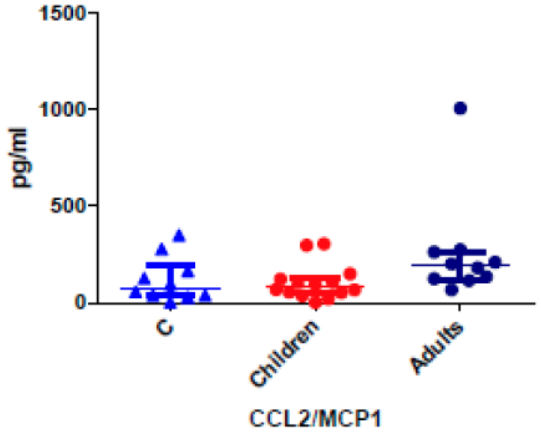
CXCL9/MIG

14 children versus 10 adults

Lower pro-inflammatory chemokines in children



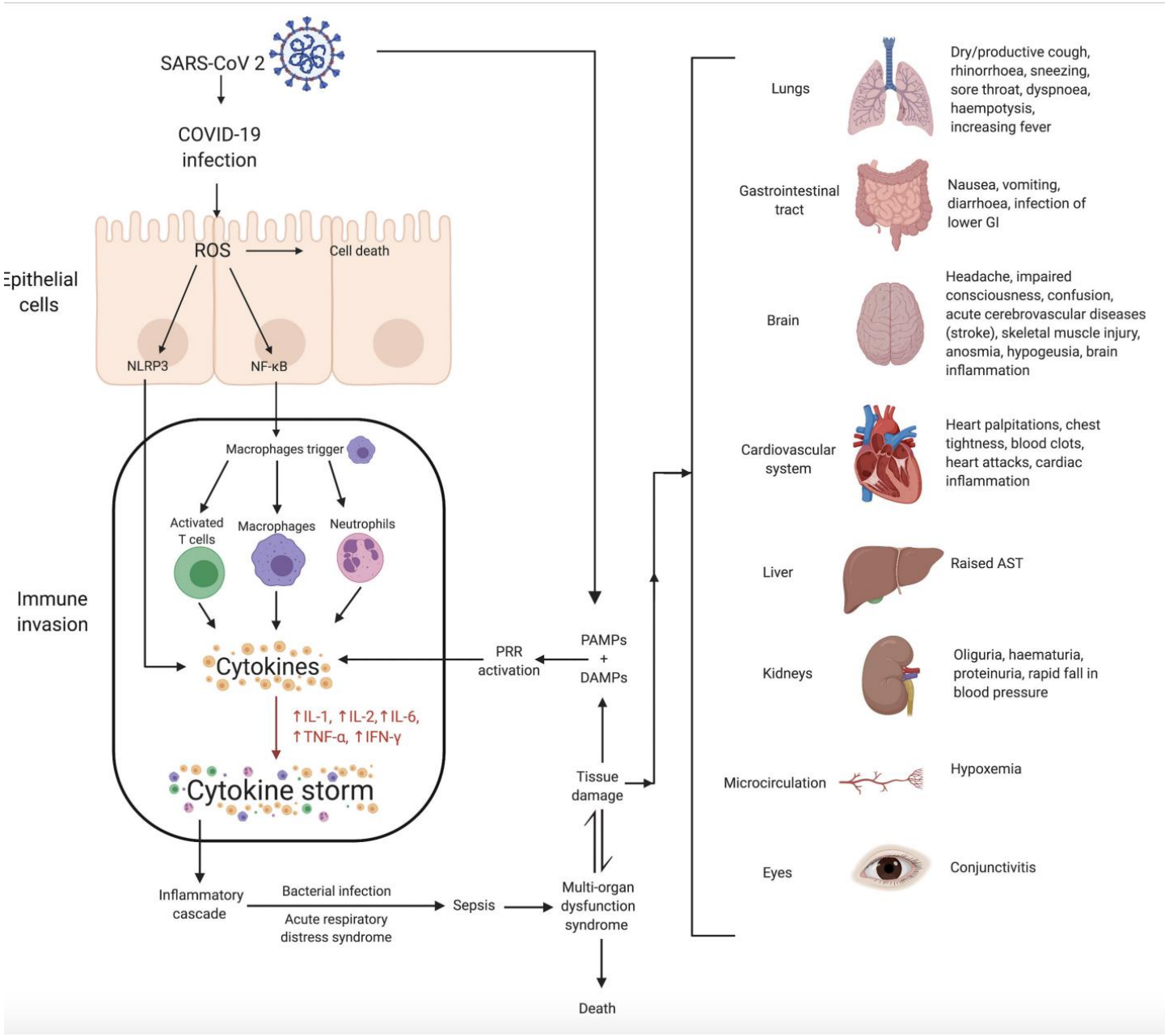
CCL5/RANTES



CCL2/MCP1

Moratto et al. *Eur J immunol* 2020 10.1002/eji.202048724.

Cytokine storm as cause of multiorgan impairment



Bhaskar et al, Frontiers Immunol 2020

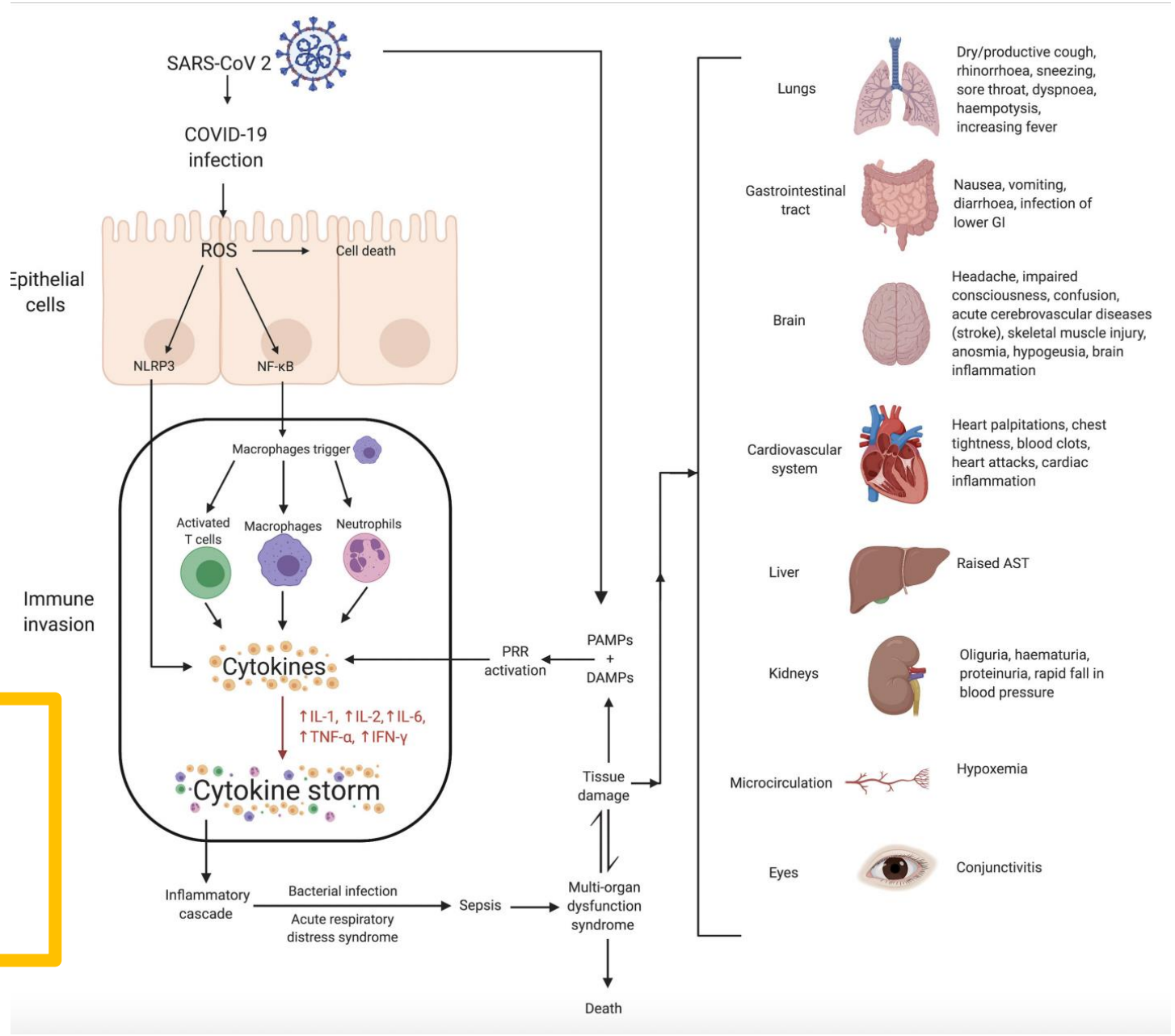
Treatment in hospitalised patients

Table 2b. Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

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

Cytokine storm as cause of multiorgan impairment

Pathogenetic correlates?

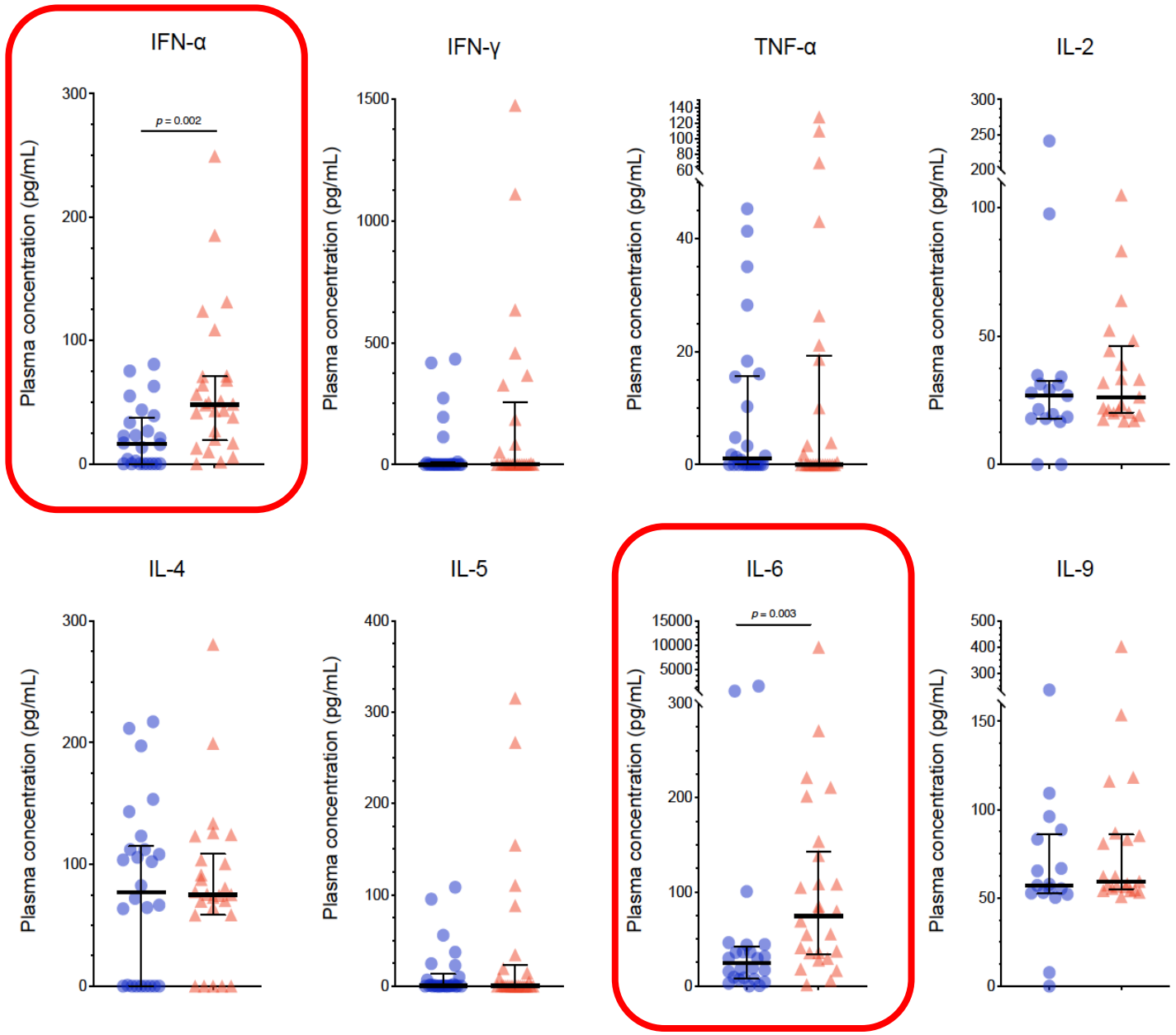


Bhaskar et al, Frontiers Immunol 2020

Any role of SARS-COV2 replication in peripheral blood?

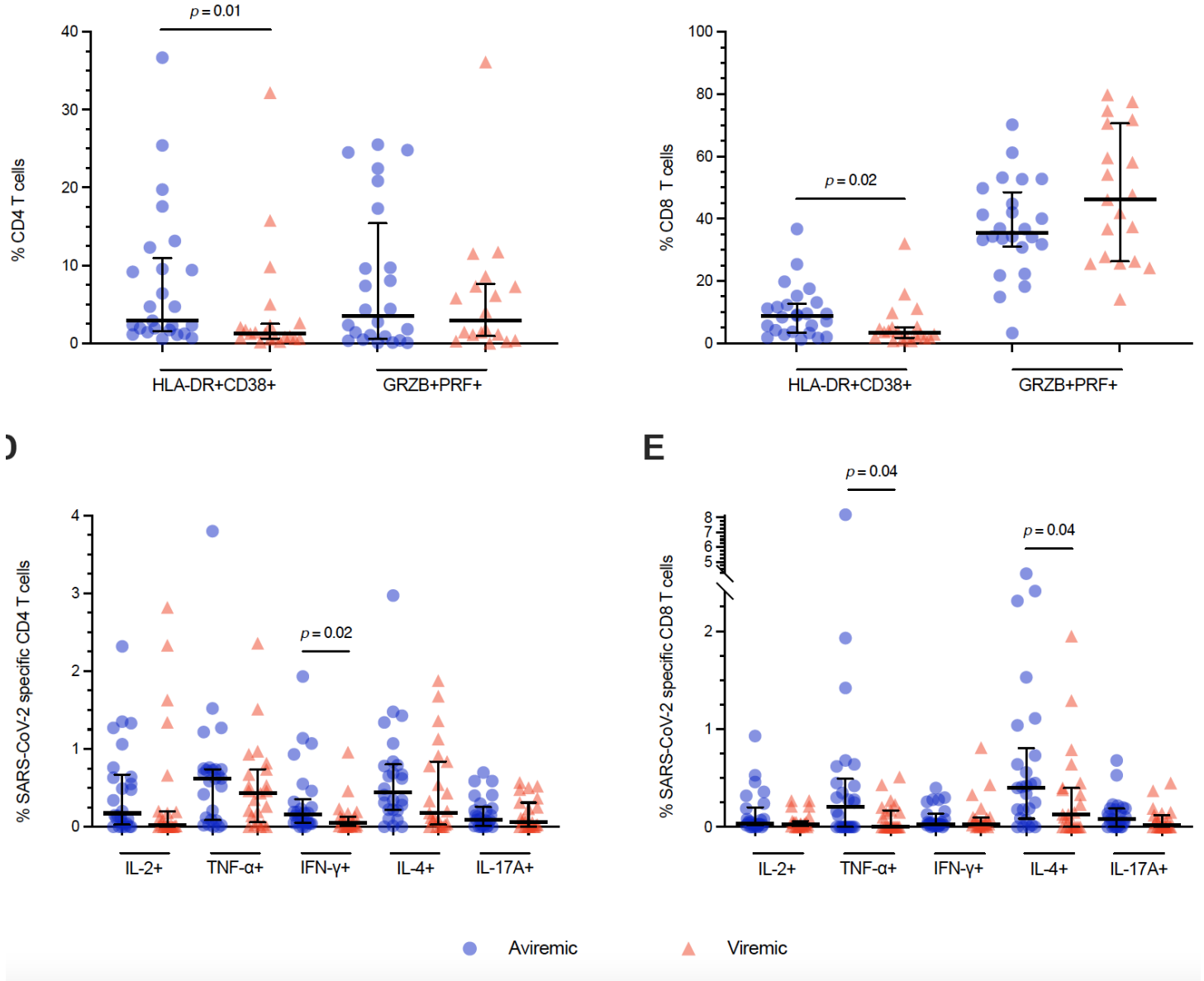
54 unvaccinated patients, 50% SARS-COV2 viremic

Increased pro-inflammatory milieu in patients with SARS-COV2 RNA in plasma



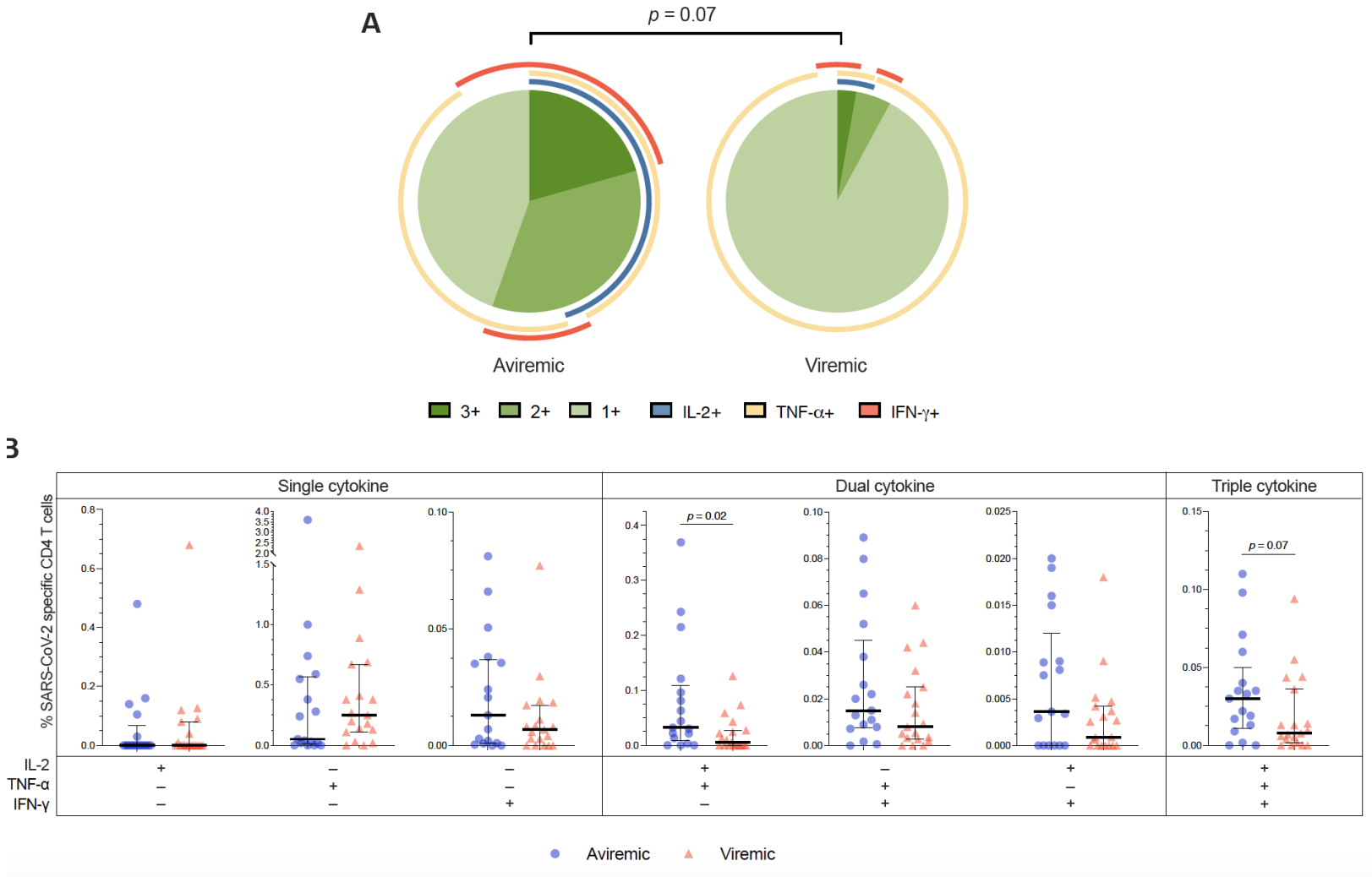
Rovito et al, Scientific Reports 2022

Lower SARS-COV2-specific T-cells in patients with SARS-COV2 RNA in plasma



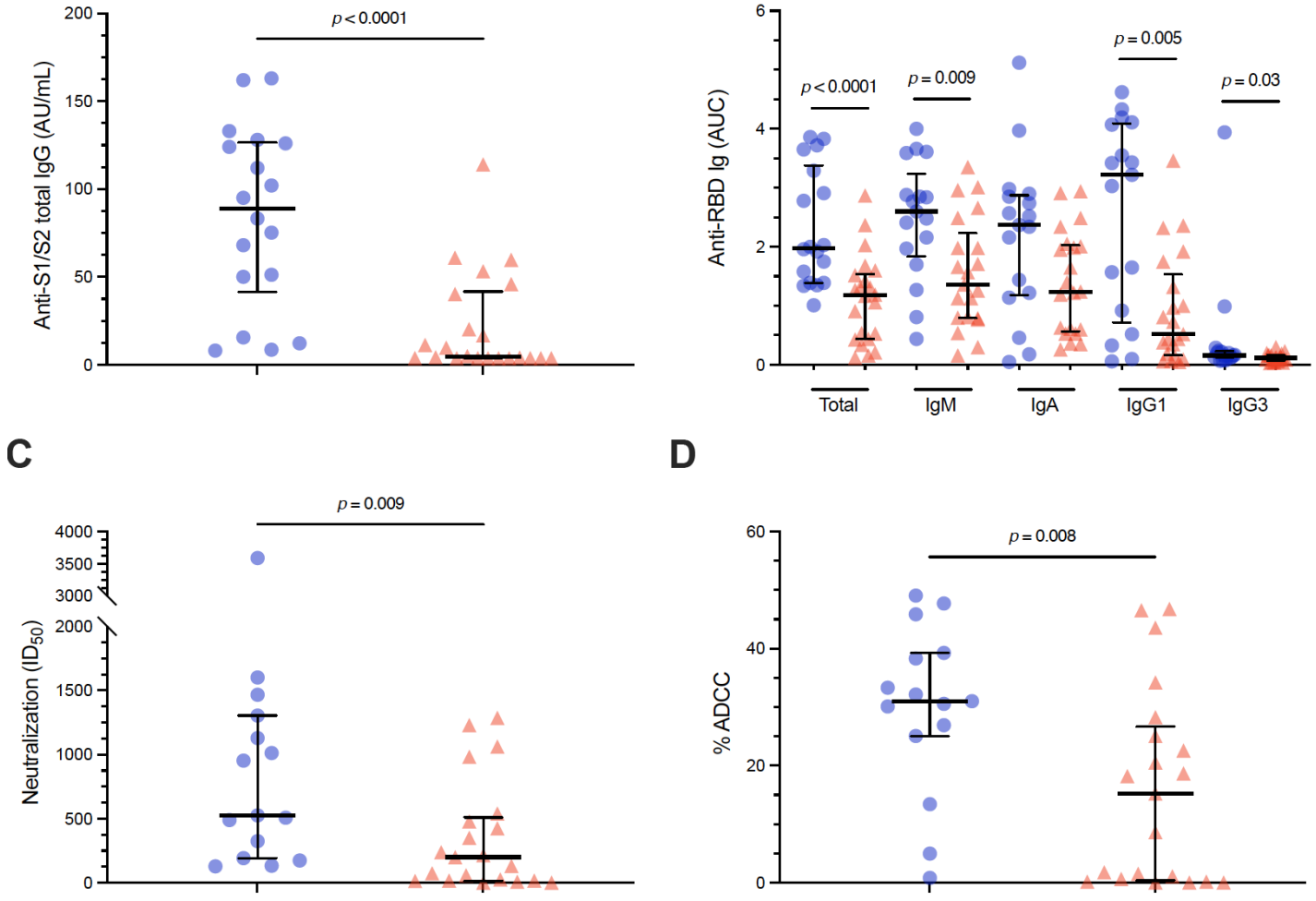
Rovito et al, Scientific Reports 2022

Lower polyfunctional SARS-COV2-specific T-cells in patients with SARS-COV2 RNA in plasma



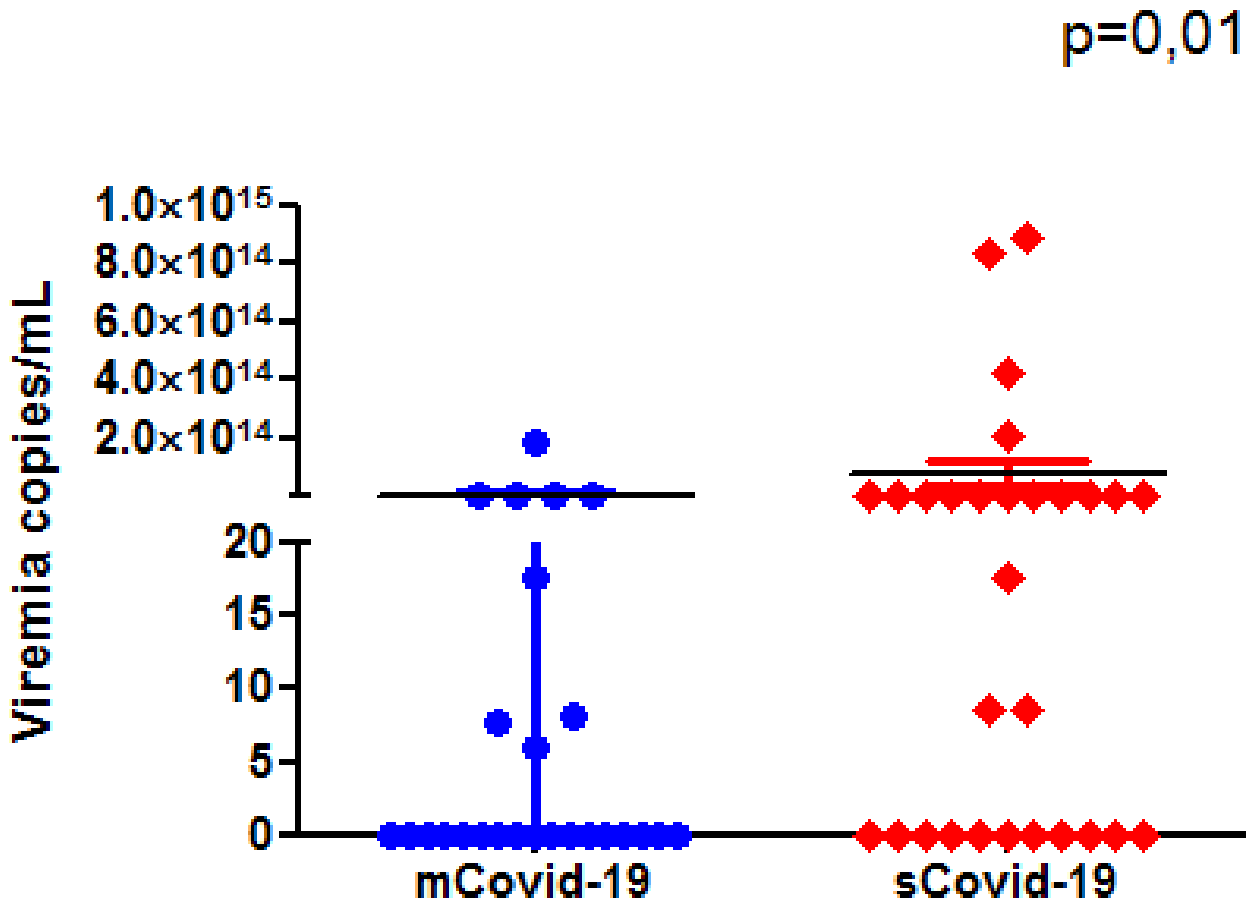
Rovito et al, Scientific Reports 2022

Lower SARS-COV2-specific Ab response in patients with SARS-COV2 RNA in plasma



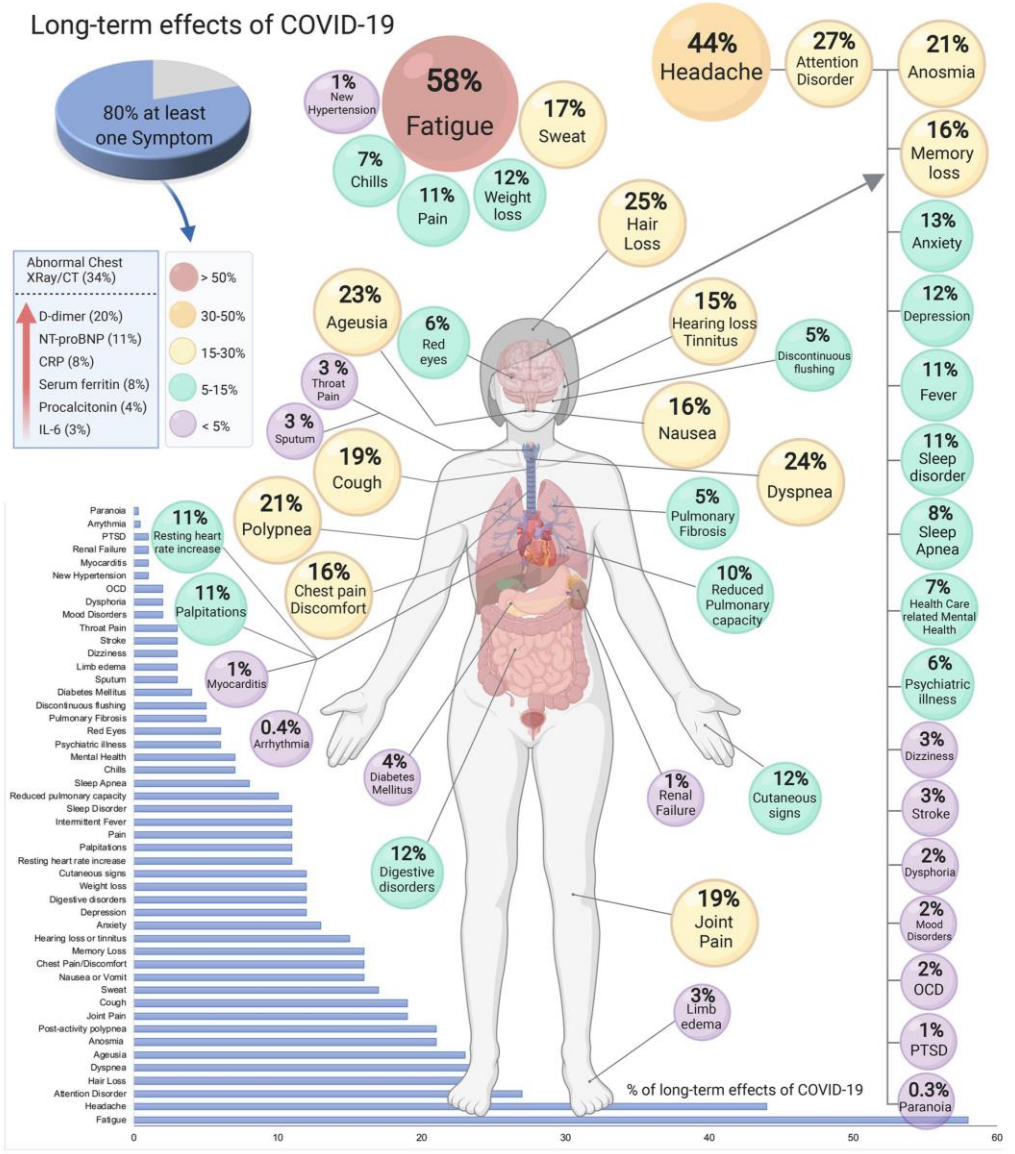
Rovito et al, Scientific Reports 2022

The detection of SARS-COV2 RNA in plasma correlates with disease severity



Adapted from Rovito et al, Scientific Reports 2022
Also, Chen et al. Emerg Microb and Infections 2020

Immune dysregulation in post acute COVID-19 sequelae (PASC)?



10-20% people develop some form of long term sequelae after COVID-19

Immune pathogenesis: heterogeneous data

- No differences in non-hospitalized COVID-19 patients at 2-11 months (Fang H. et al, Viruses, 2021; Galan M. et al, Front Immunol, 2022);
- Lower magnitude and functionality of SARS-CoV-2-specific humoral responses in hospitalized COVID-19 patients at 12 months (García-Abellán, J et al, Front Immunol, 2022);
- Lower funcitonality of humoral responses and higher cell activation when considering neurologic manifestation at 2-3 months (Spatola M. et al, Brain, 2023);
- Higher IFNs and activated circulating cells, lower lymphocytes functionality in a mixed cohort of hospitalized and non-hospitalized at 6-8 months (Santa-Cruz A. et al, Nat Commun, 2023; Phetsouphanh C. et al, Nat Commun, 2022).

Lopez-Leon S. et al, Sci Rep, 2021

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