COVID-19 Therapeutics

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@syctong

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

Overview

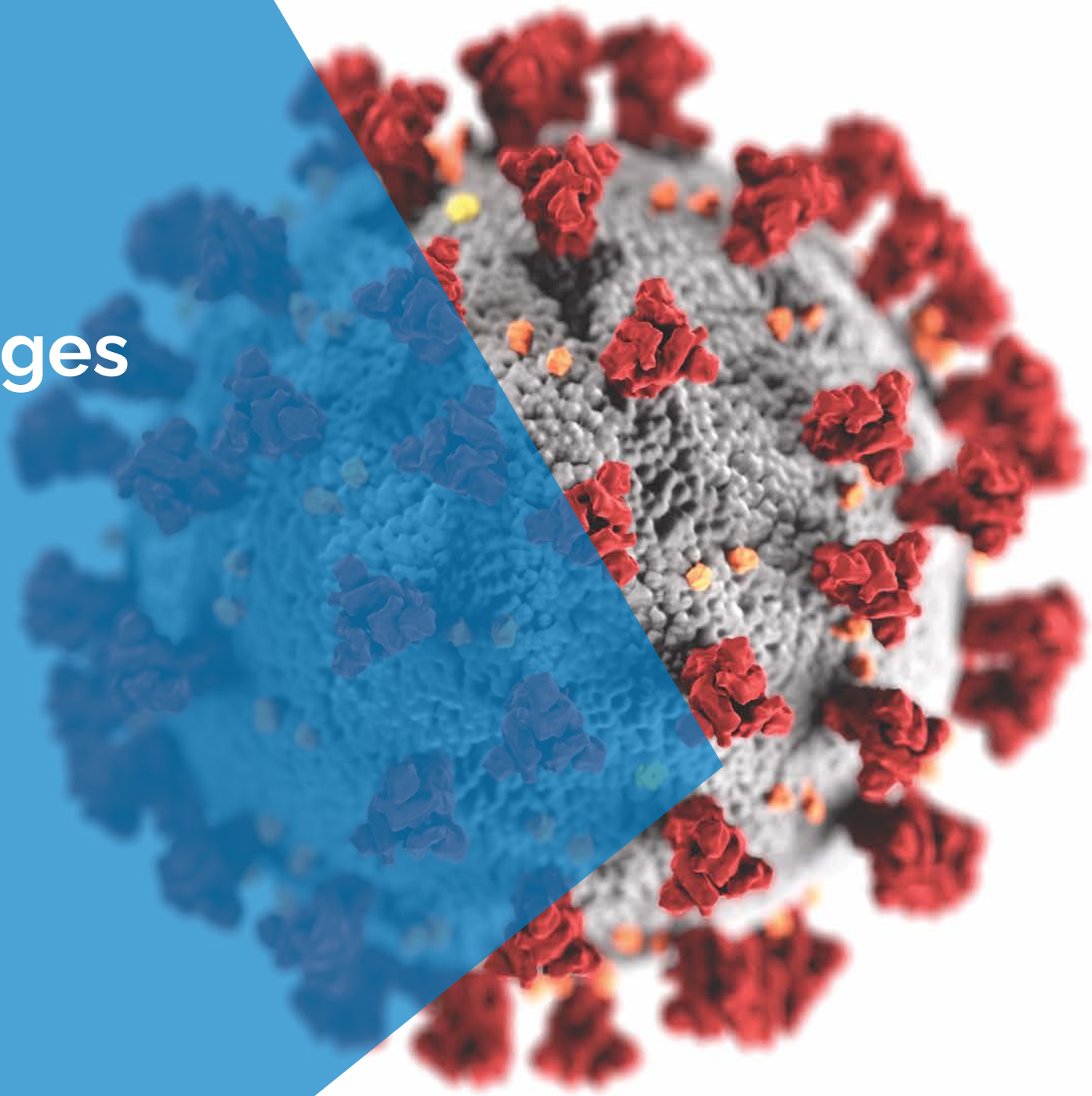
Disease stages

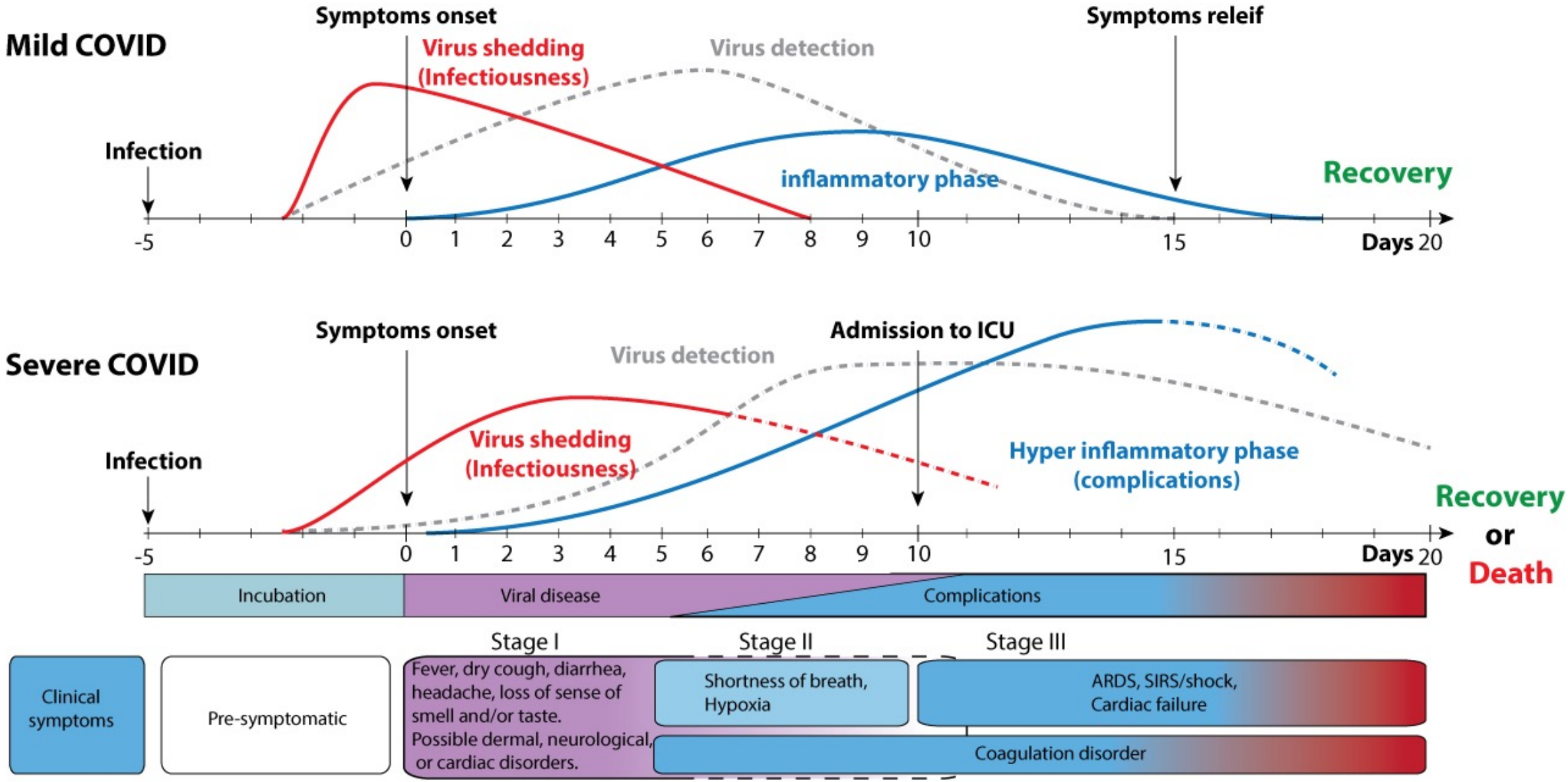
Moderate / critical

Mild / early

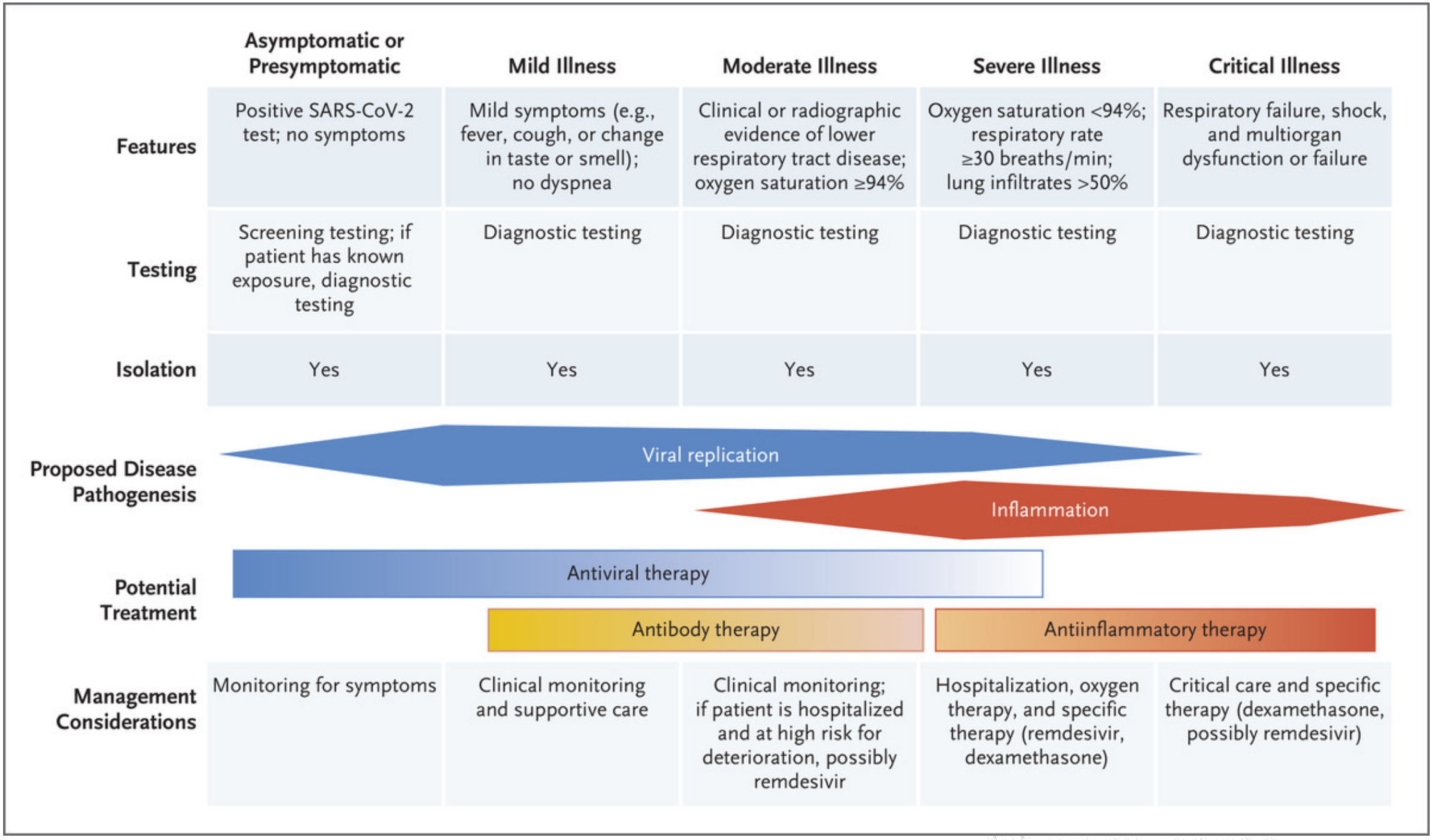
Ongoing needs

Disease stages



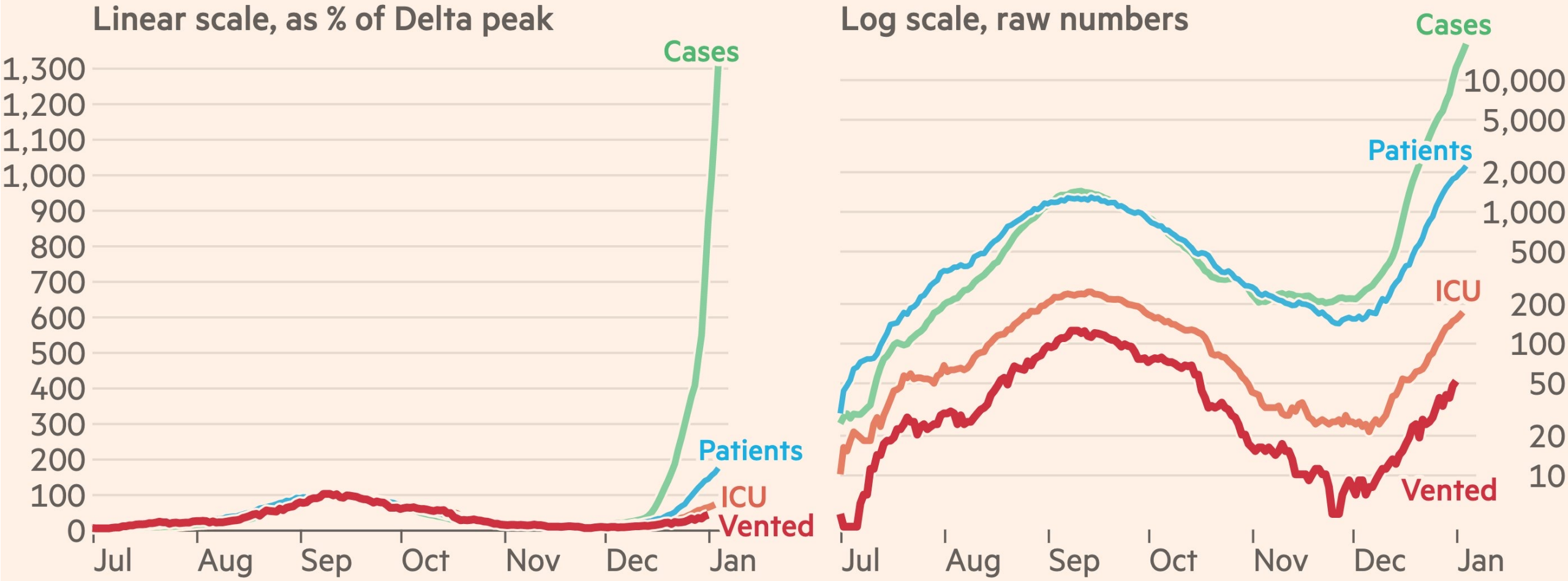

Mild COVID
Symptoms onset
Symptoms releif
Virus shedding
(Infectiousness)
Virus detection
Infection
inflammatory phase
Recovery
-5
0
1
2
3
4
5
6
7
8
9
10
15
Days 20
Severe COVID
Symptoms onset
Admission to ICU
Virus detection
Infection
Virus shedding
(Infectiousness)
Hyper inflammatory phase
(complications)
Recovery
or
Death
-5
0
1
2
3
4
5
6
7
8
9
10
15
Days 20
Incubation
Viral disease
Complications
Stage I
Stage II
Stage III
Clinical symptoms
Pre-symptomatic
Fever, dry cough, diarrhea, headache, loss of sense of smell and/or taste.
Possible dermal, neurological, or cardiac disorders.
Shortness of breath, Hypoxia
ARDS, SIRS/shock, Cardiac failure
Coagulation disorder

ViralZone



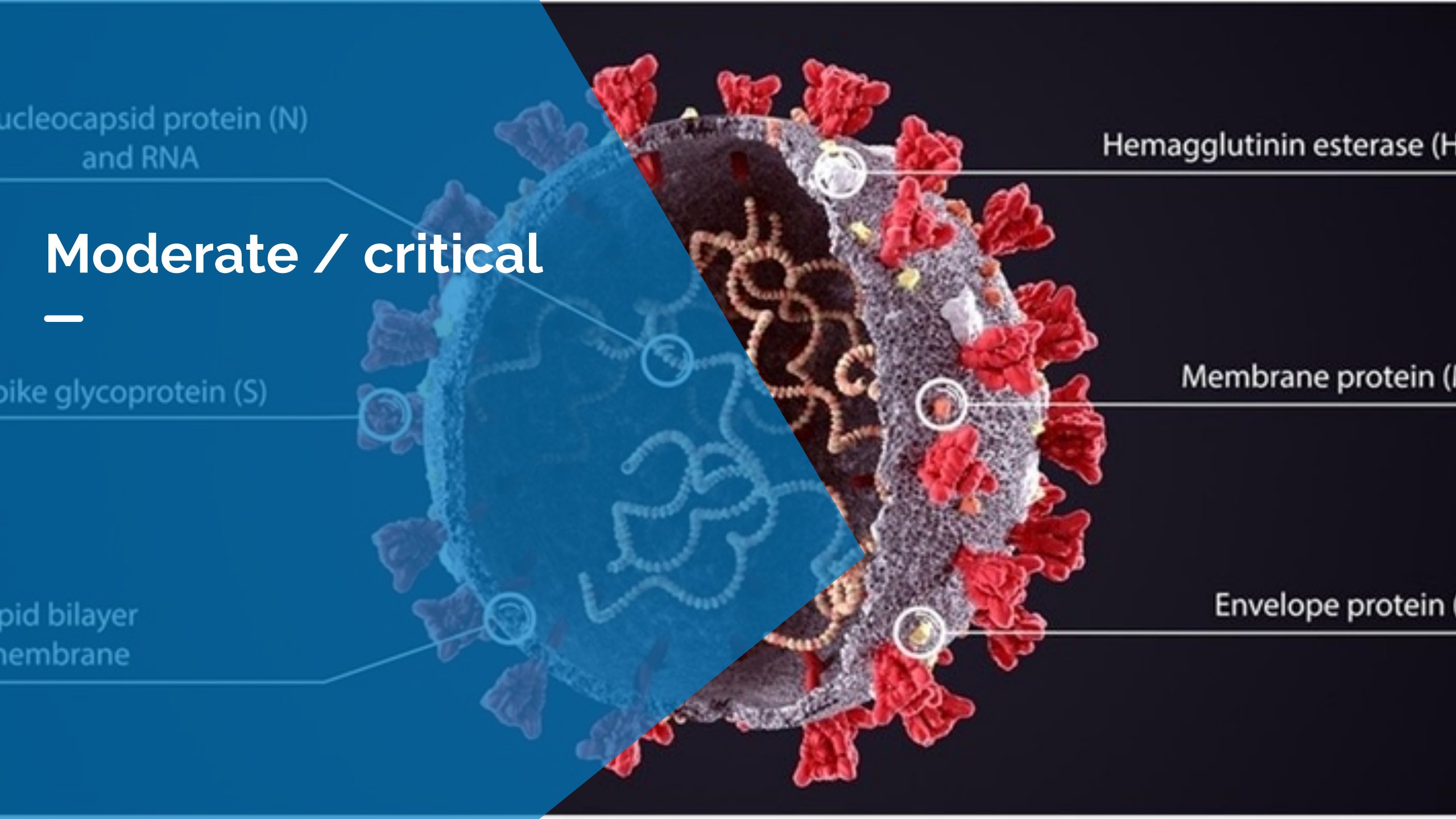
RT Gandhi et al. N Engl J Med 2020;383:1757-1766.

The number of patients with severe disease in New South Wales is rising, but the ratio of severe disease to cases has weakened considerably

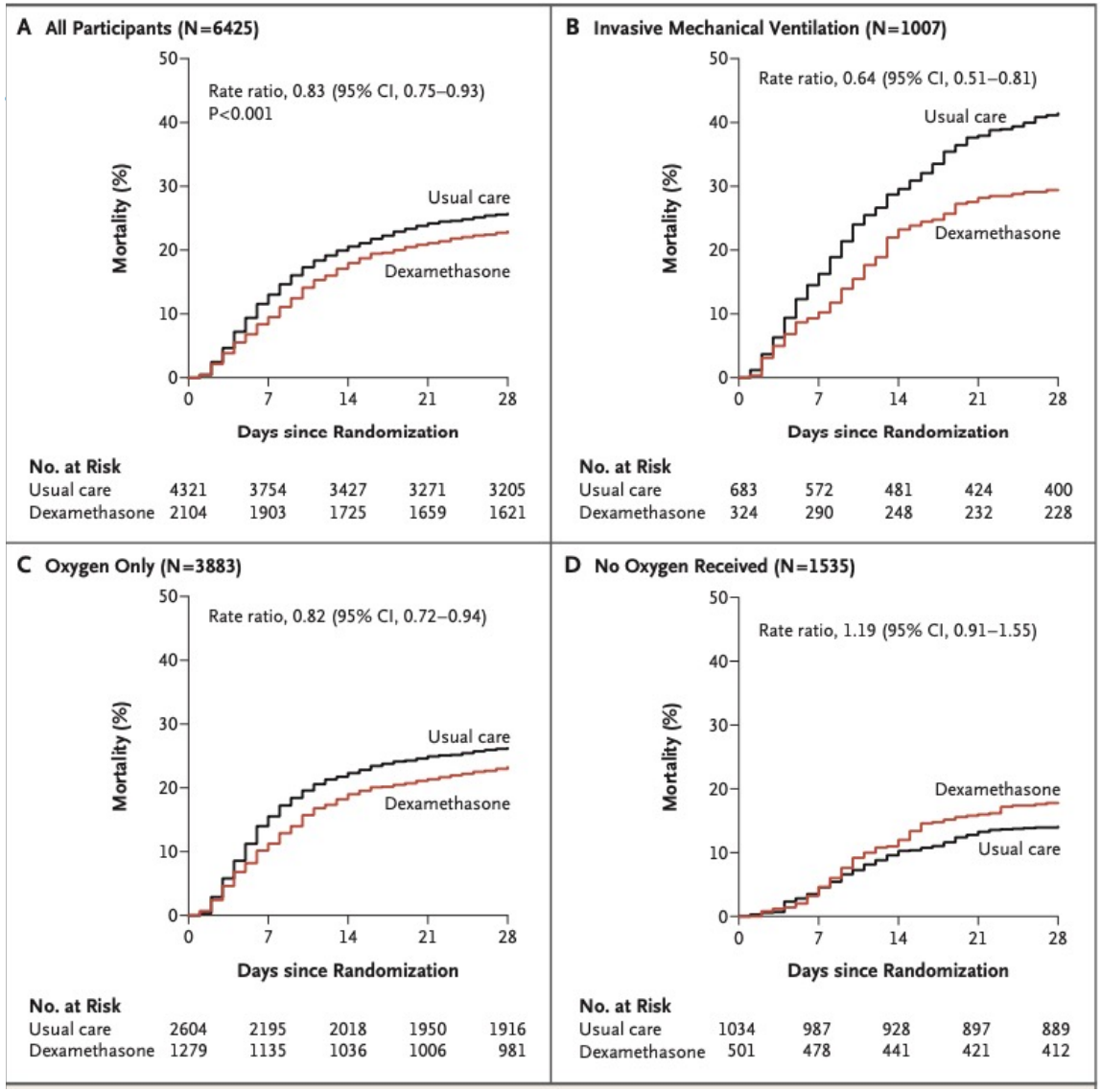


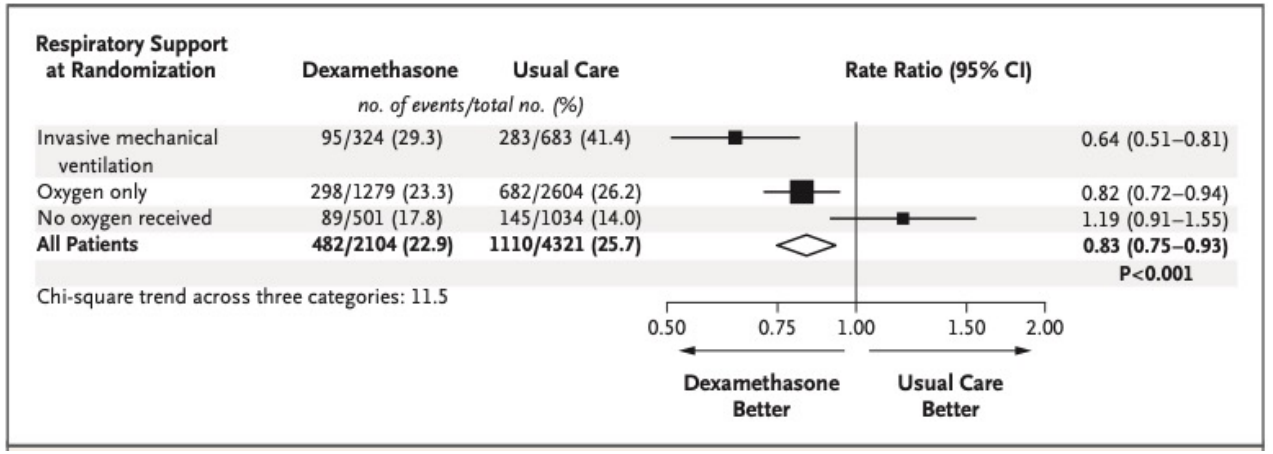
Source: covidlive.com.au. Hospital series shifted backward to adjust for lag
FT graphic by John Burn-Murdoch / @jburnmurdoch
© FT

Moderate / critical



Steroids – RECOVERY



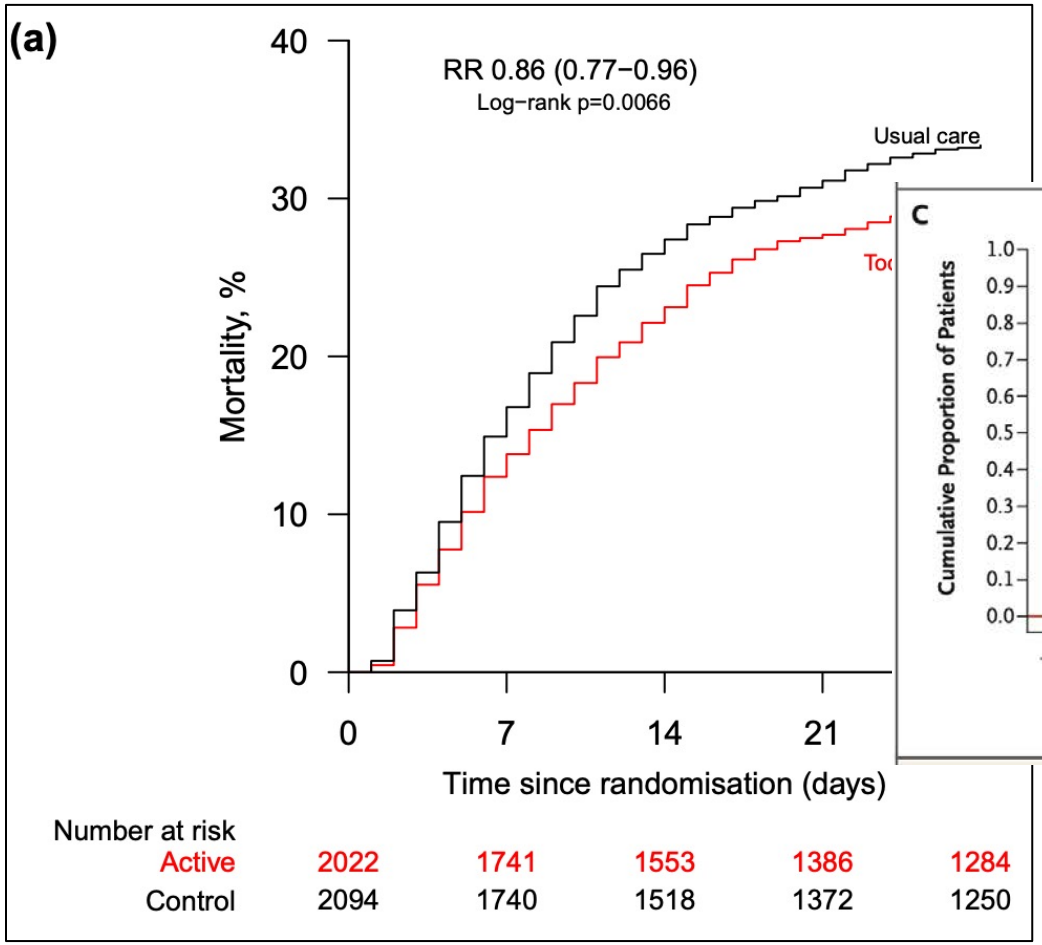


Clear benefit of dexamethasone

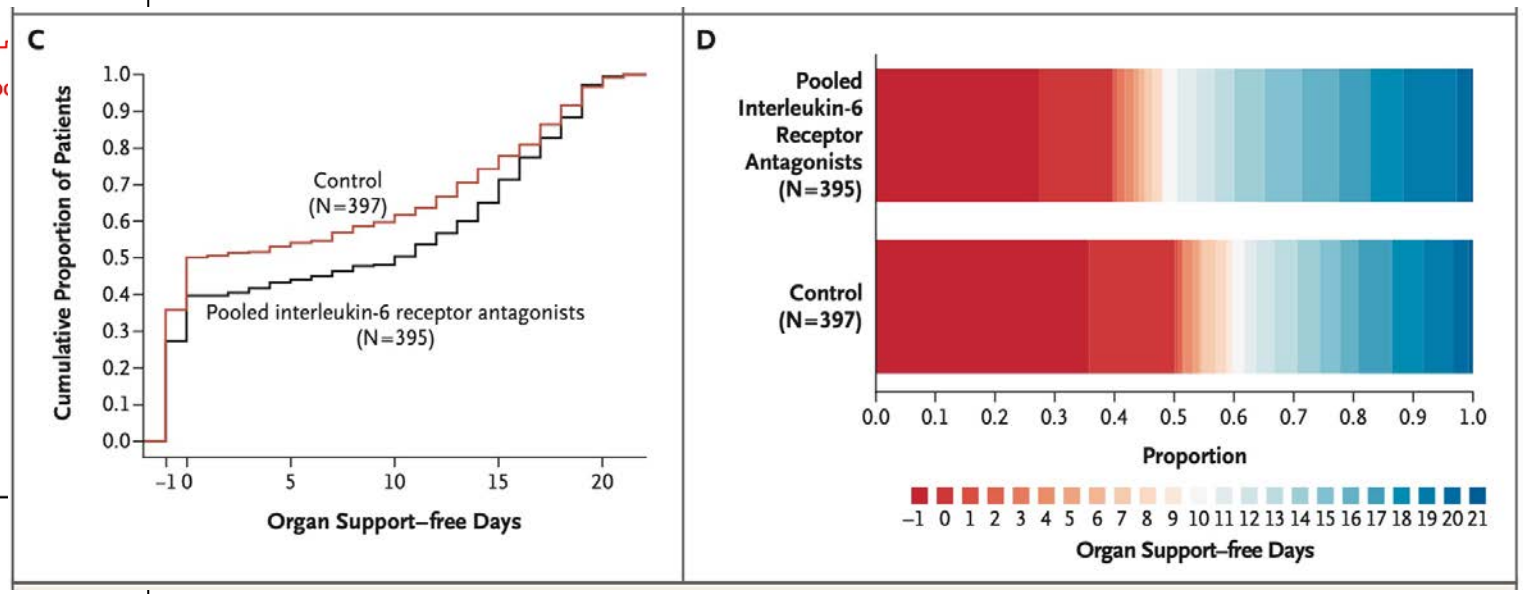
Standard of care

RECOVERY NEJM 2020

Il-6 antagonists

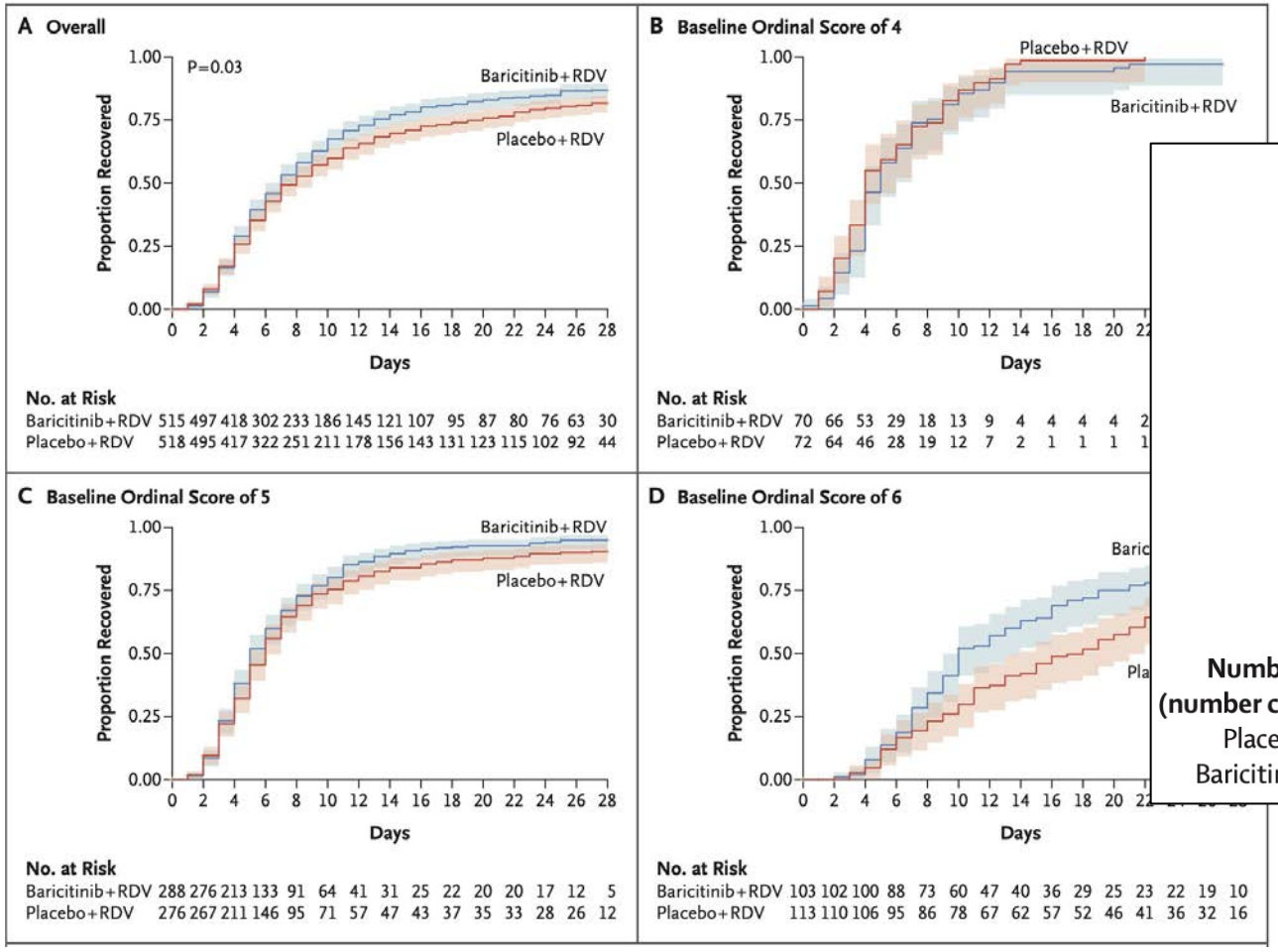


RECOVERY Lancet 2021

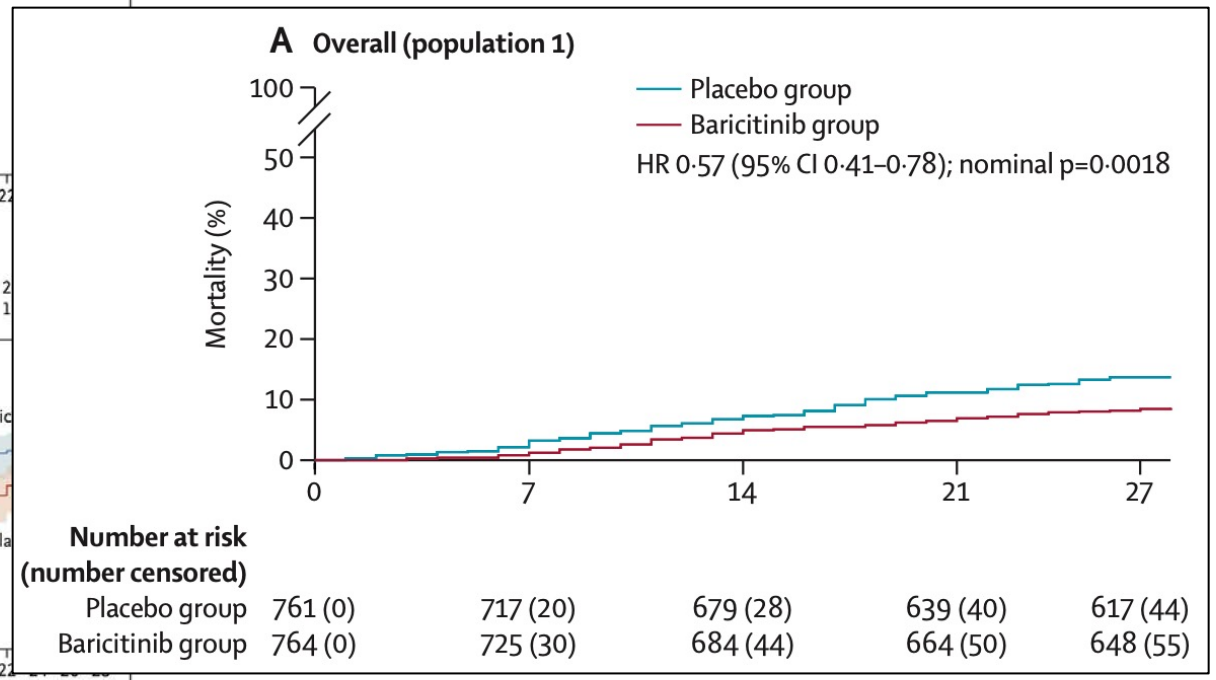


REMAP-CAP NEJM 2021

Baricitinib – JAK inhibitor

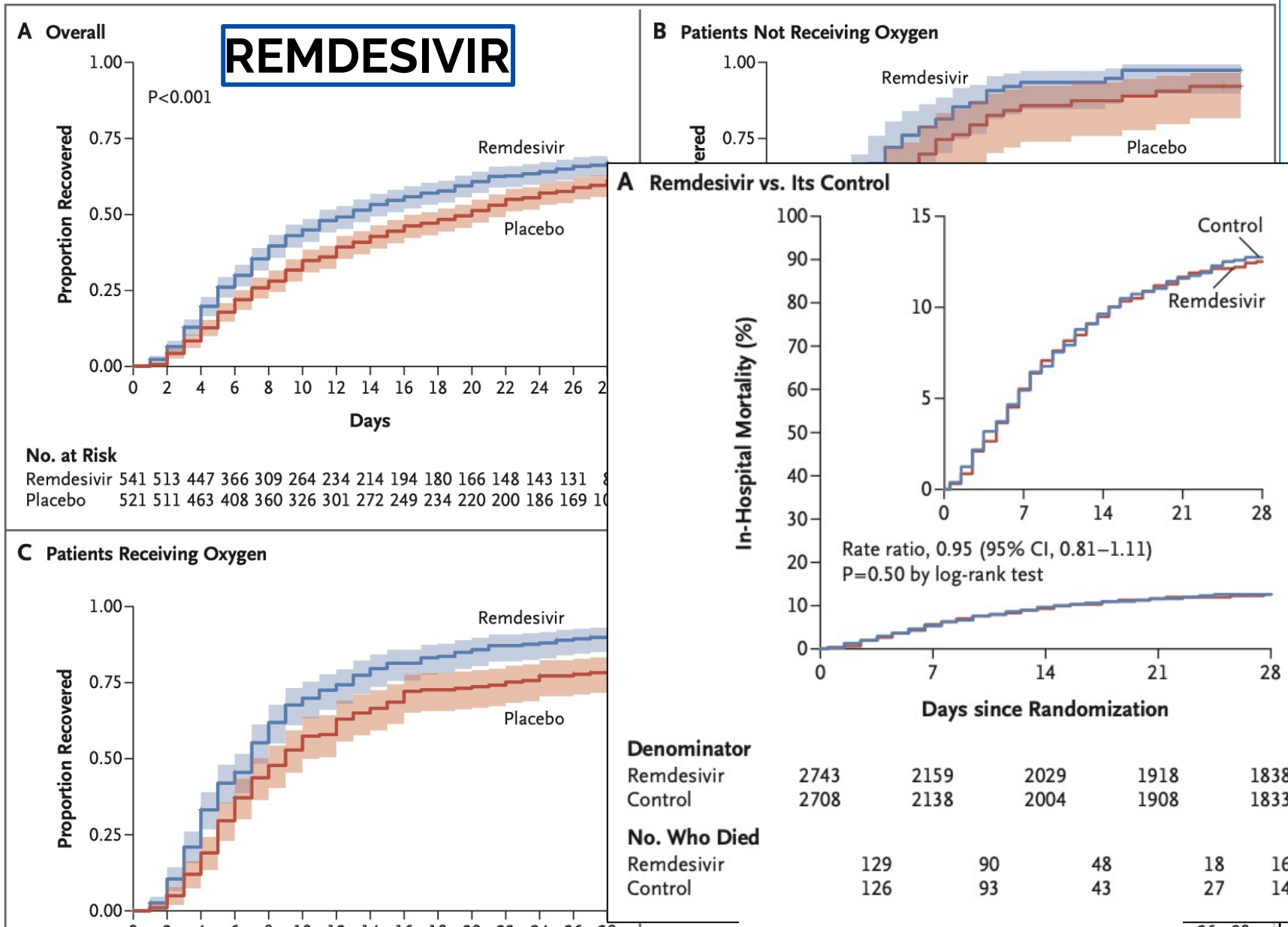


Kalil ACTT-2 NEJM 2021

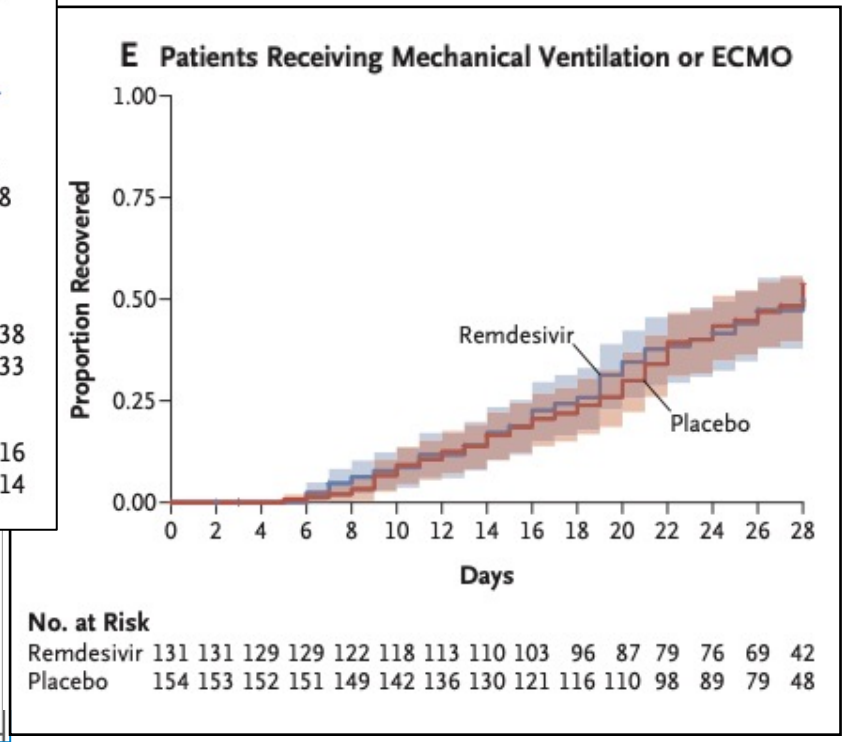


Marconi COV-Barrier Lancet RM 2021

REMDESIVIR



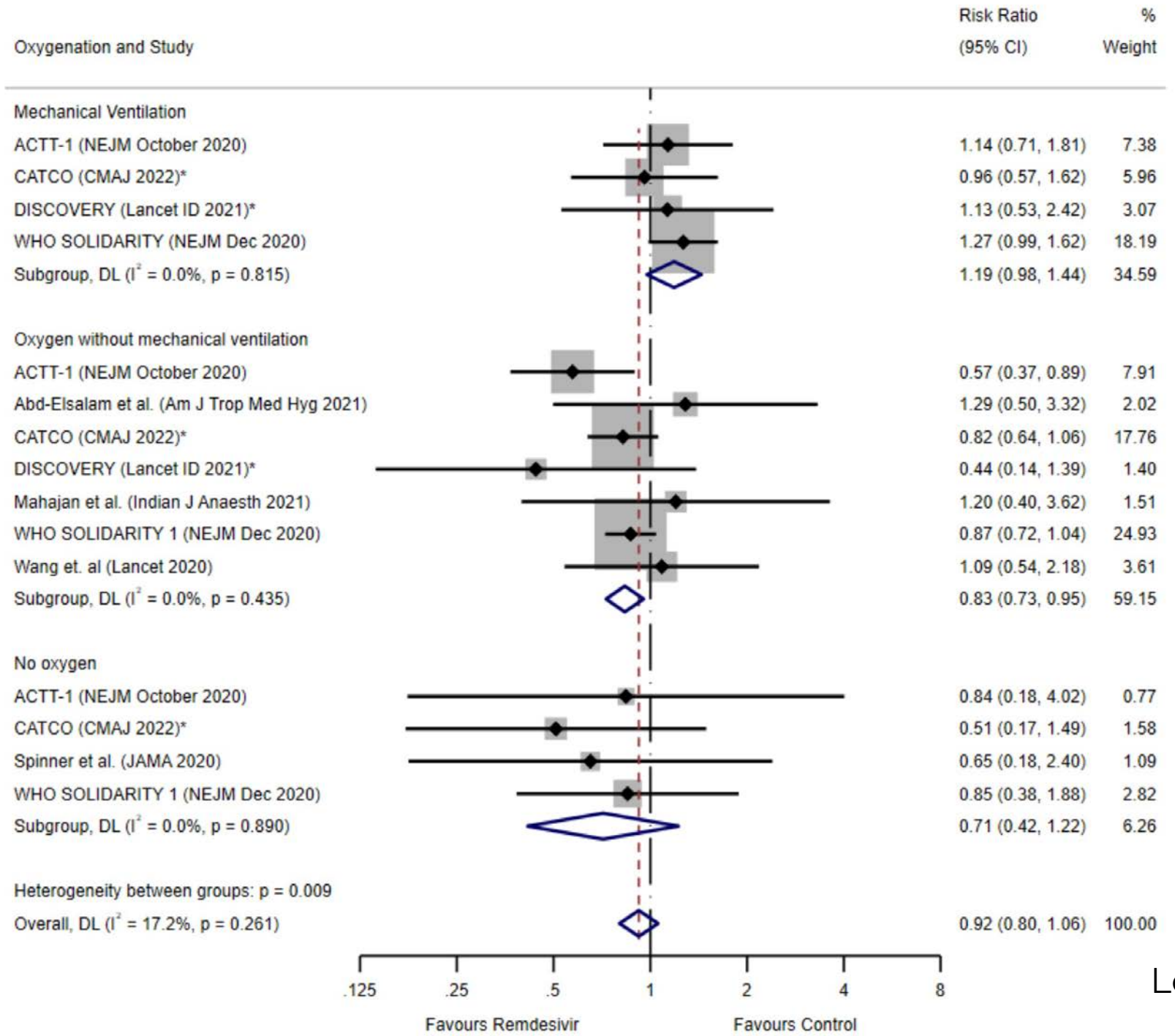
SOLIDARITY NEJM 2021



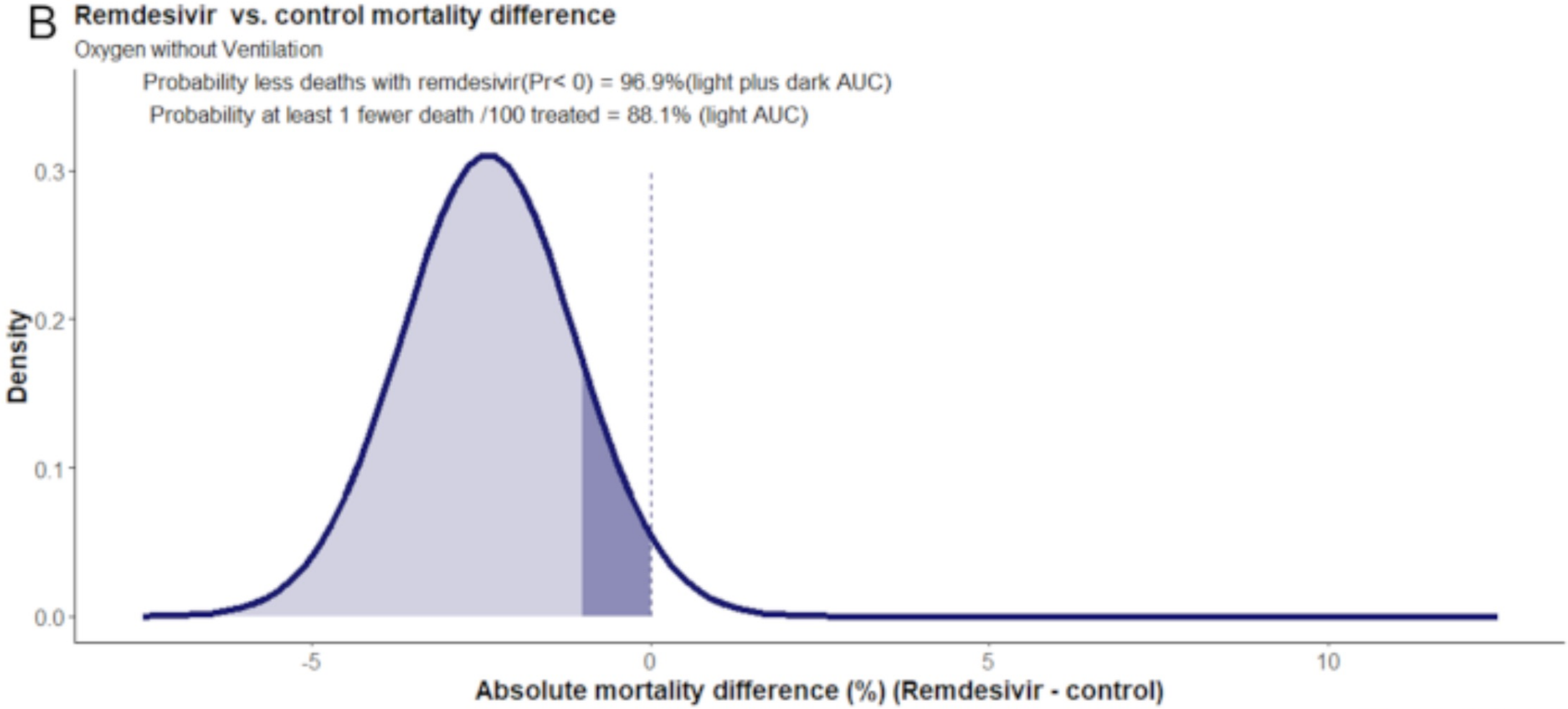
Time to clinical improvement
(median)
Remdesivir 10 days; control 15 days
P<0.001

Mortality
28 days:
Remdesivir 11.4%; control 15.2%
Not statistically significant**

Beigel NEJM 2020

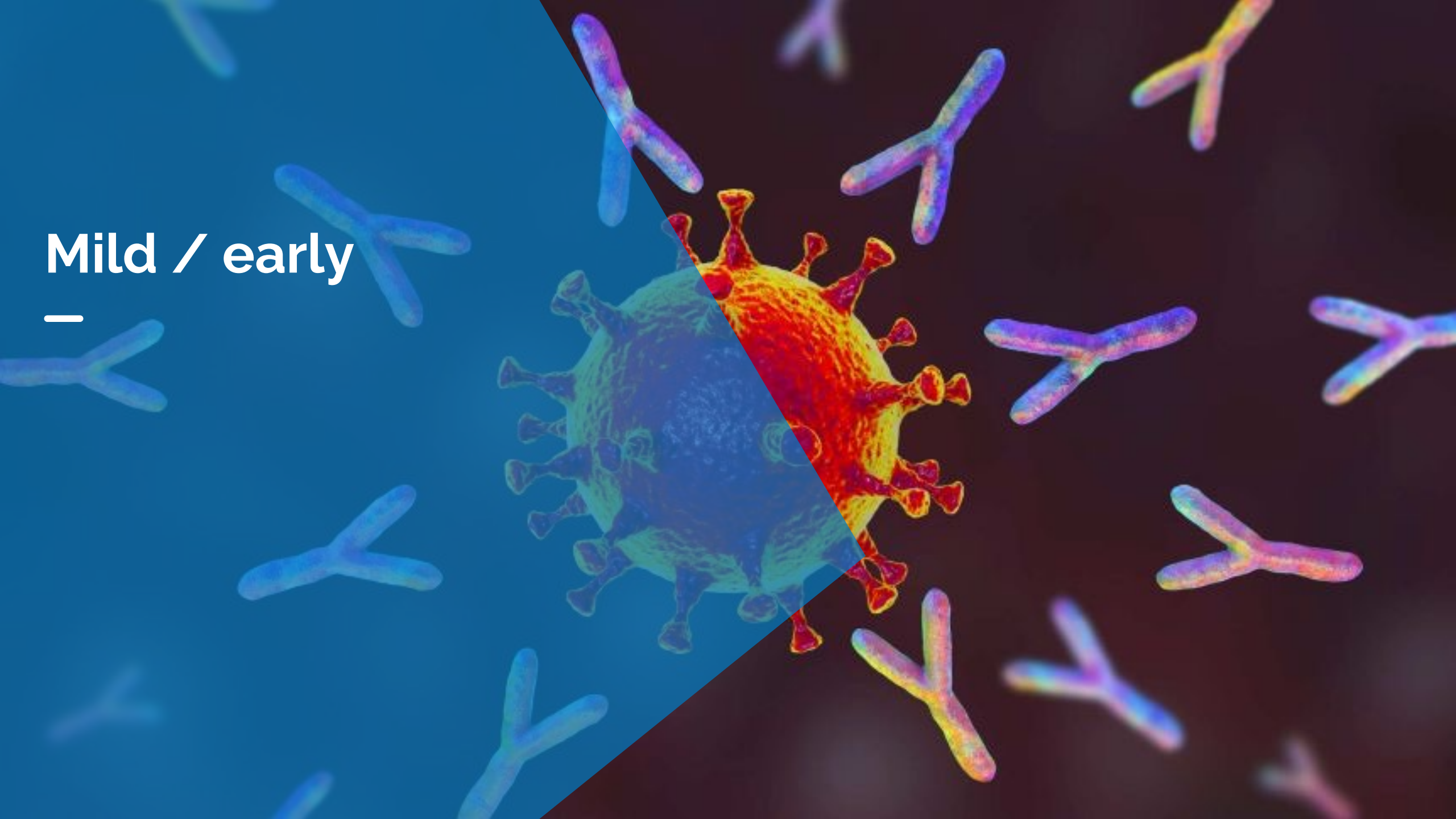


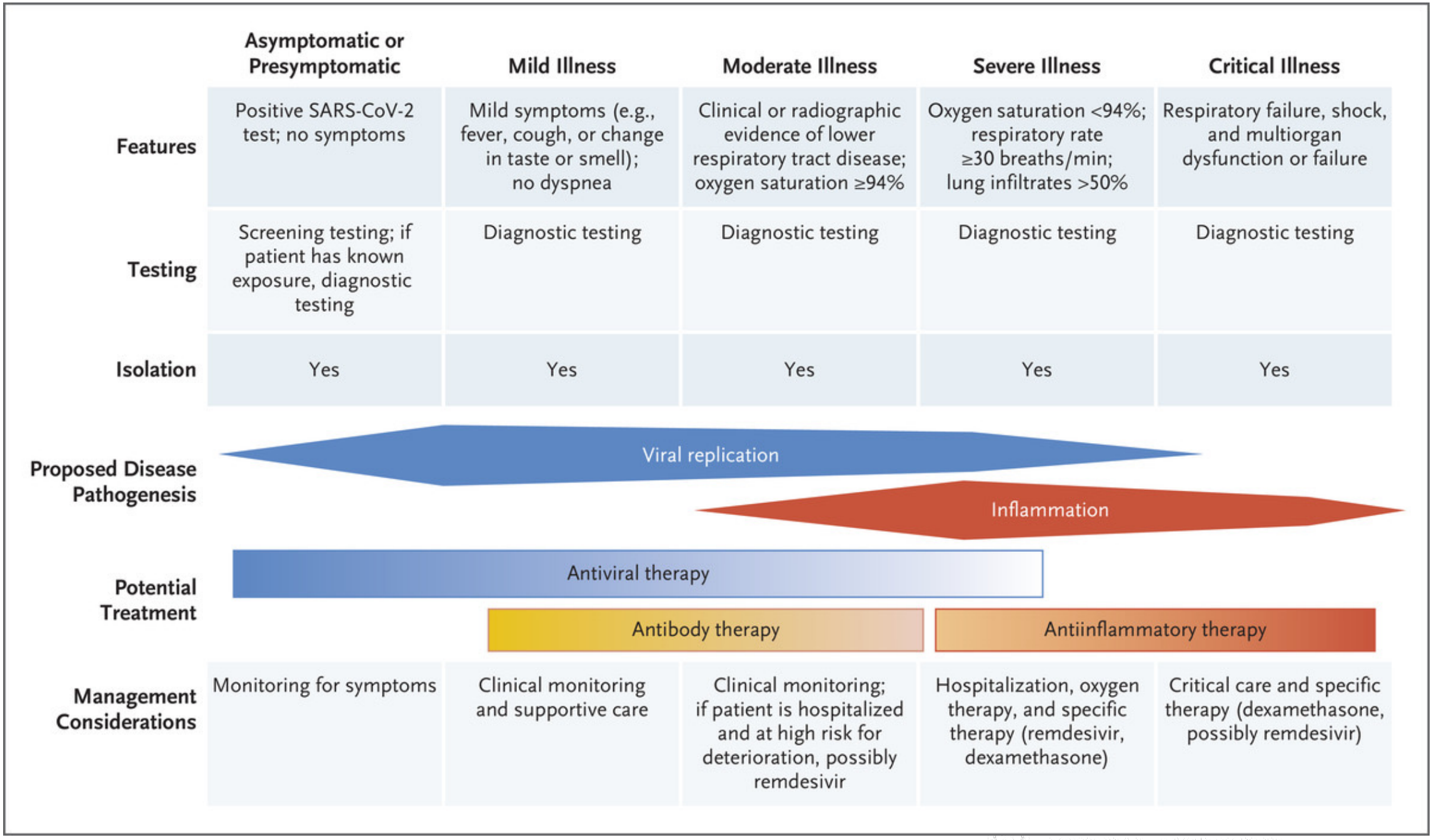
Lee medRxiv 2022



Lee medRxiv 2022

Mild / early



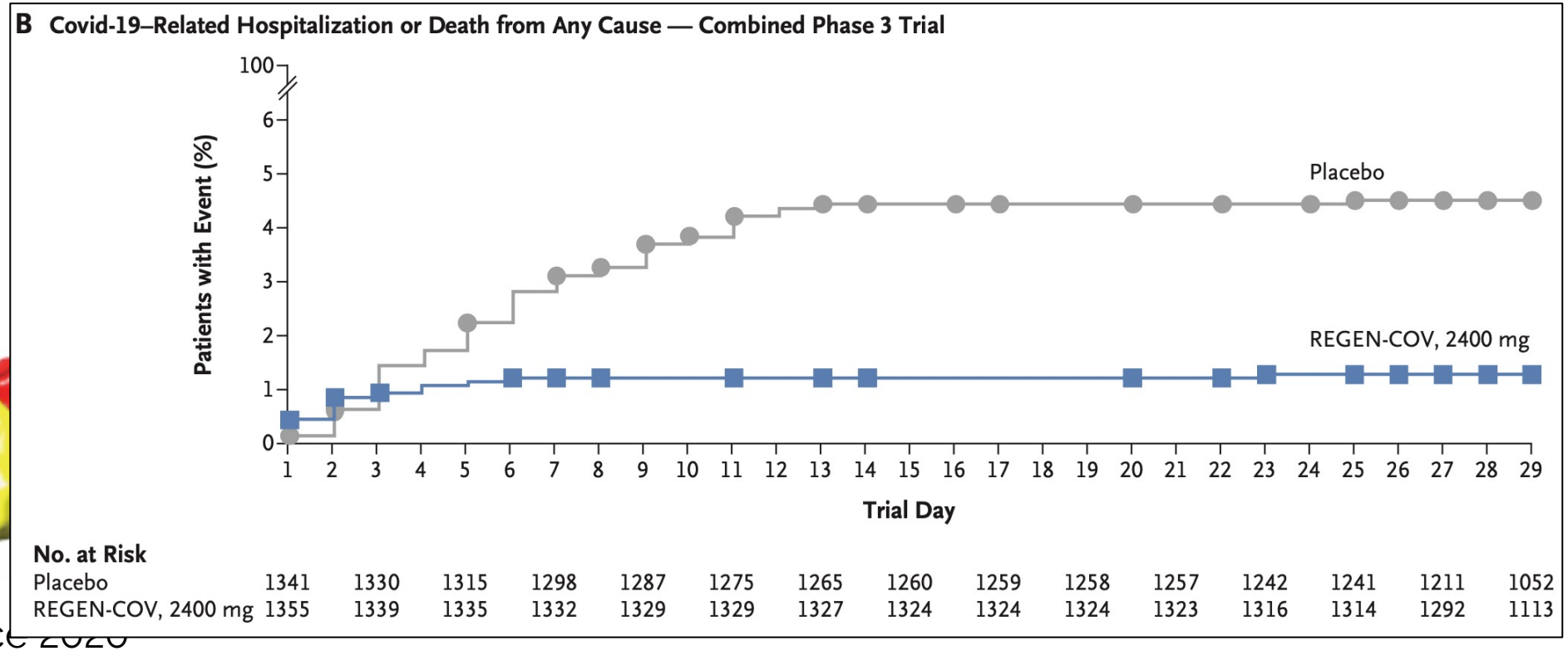


RT Gandhi et al. N Engl J Med 2020;383:1757-1766.

Monoclonals – 80-90% ⬇

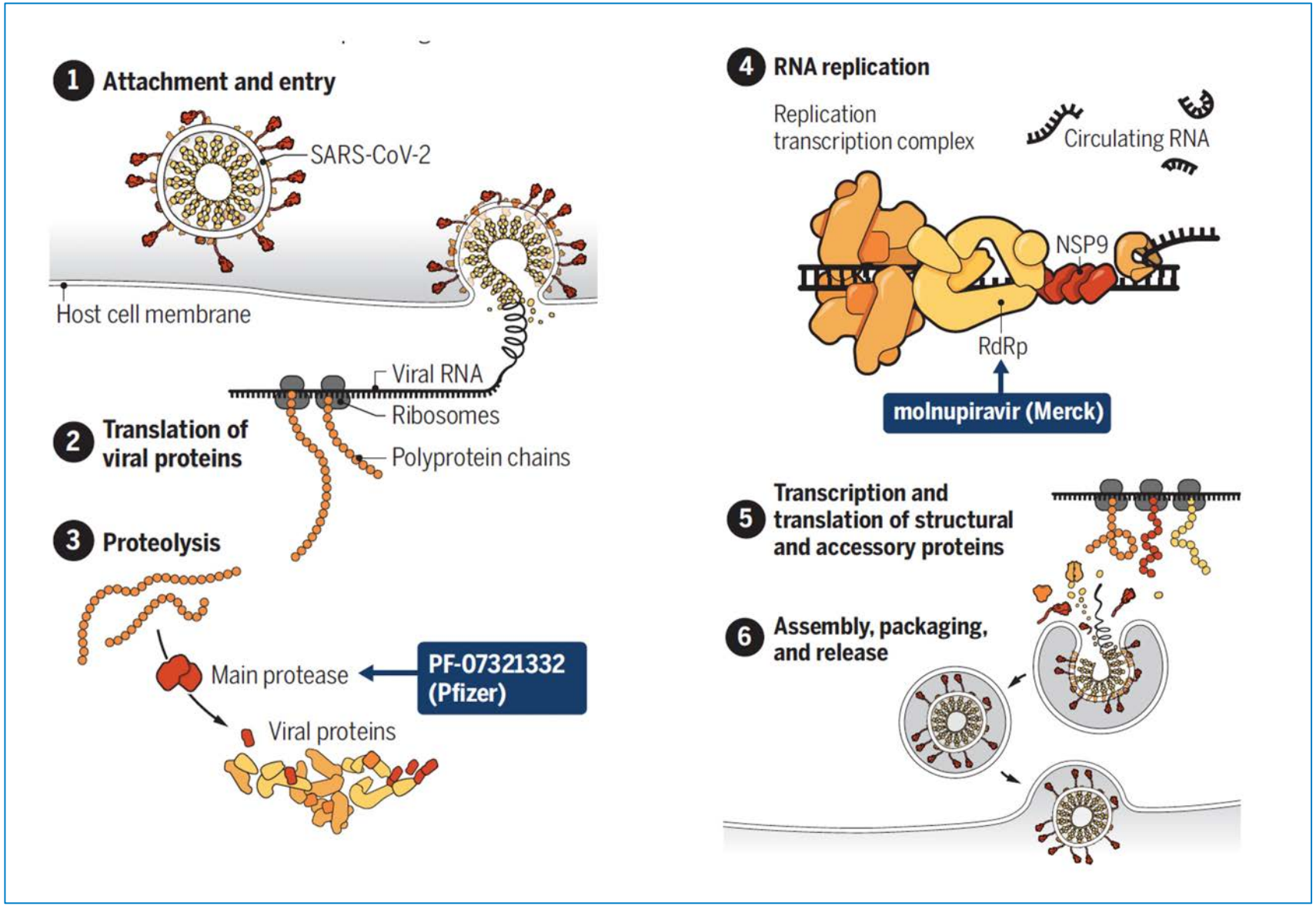
Hansen Science 2020
Baum Science 2020

OUTPATIENTS



Weinreich NEJM 2021
Gupta NEJM 2021

Antivirals



Couzin-Frankel Science 2021

Paxlovid: Nirmatrelvir / ritonavir

EPIC-HR trial: 80-90% reduction in hospitalization / death **

Australia: 500,000 courses

Three tablets twice daily for 5 days

Ritonavir: interactions - cytochrome P450 (CYP) 3A inhibitor

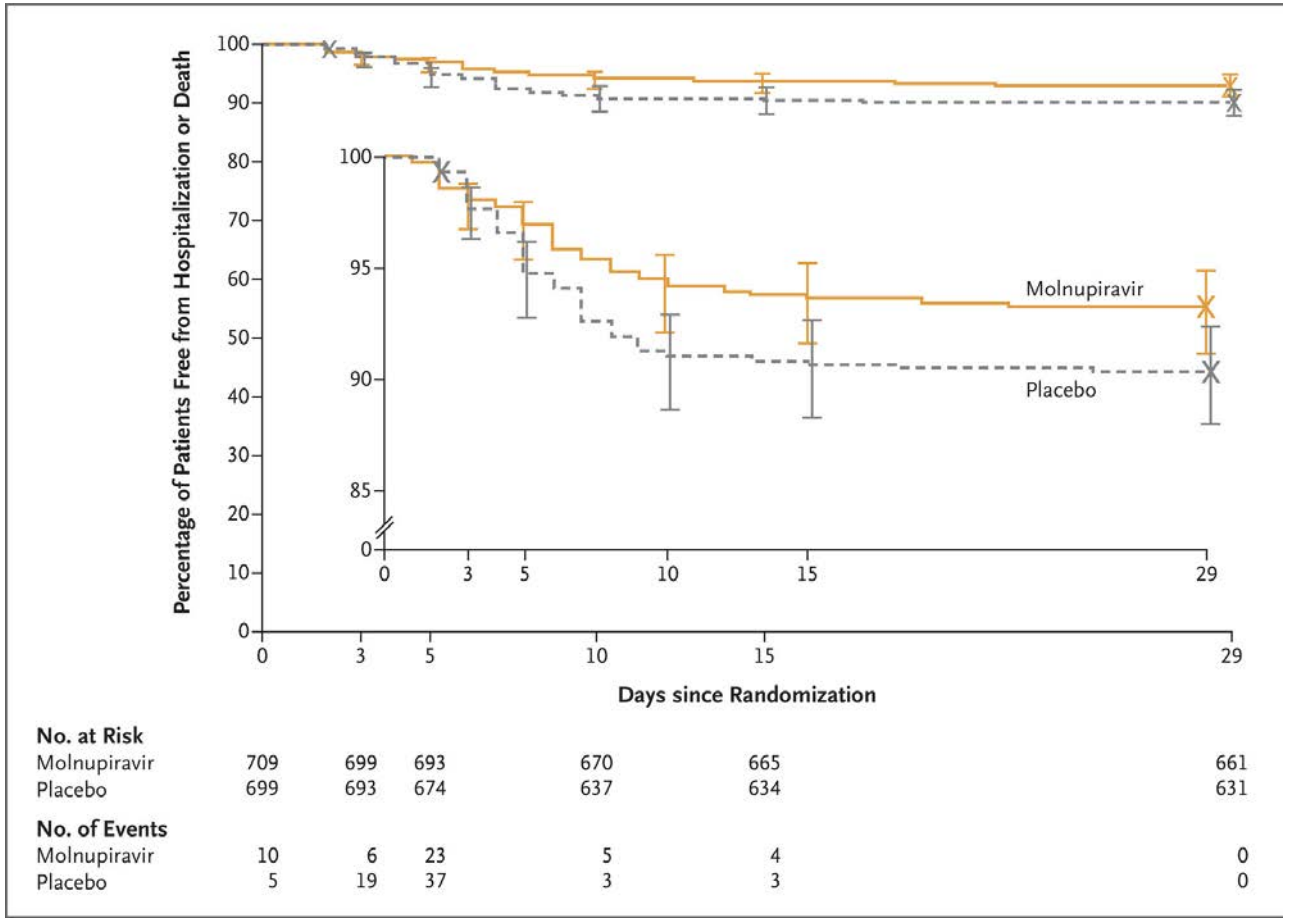
See https://www.covid19-druginteractions.org/

Monulpiravir

Less reduction in hospitalization (30%)

Australia: 300,000 courses

Four tablets twice daily for 5 days

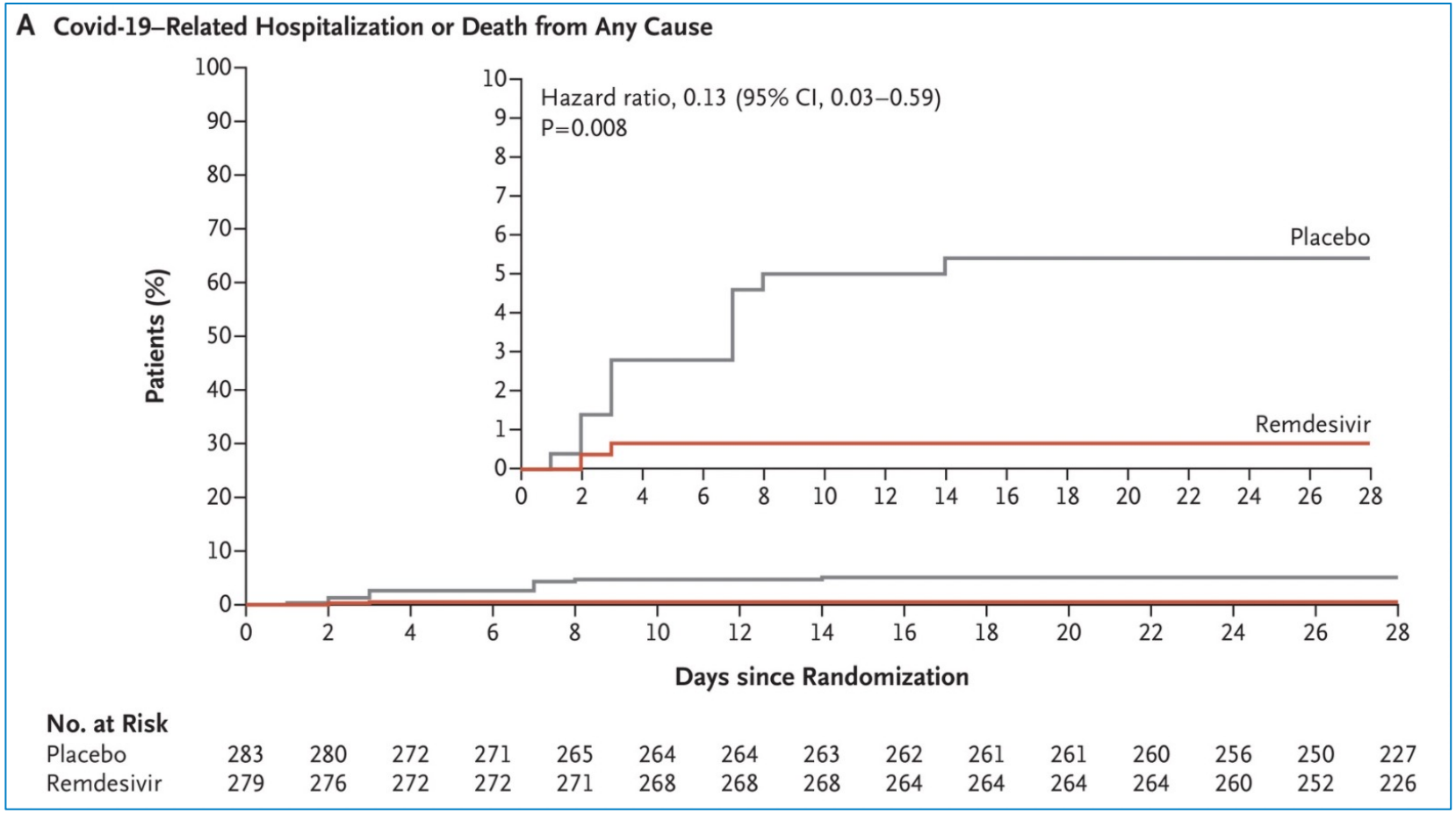


Bernal NEJM 2021

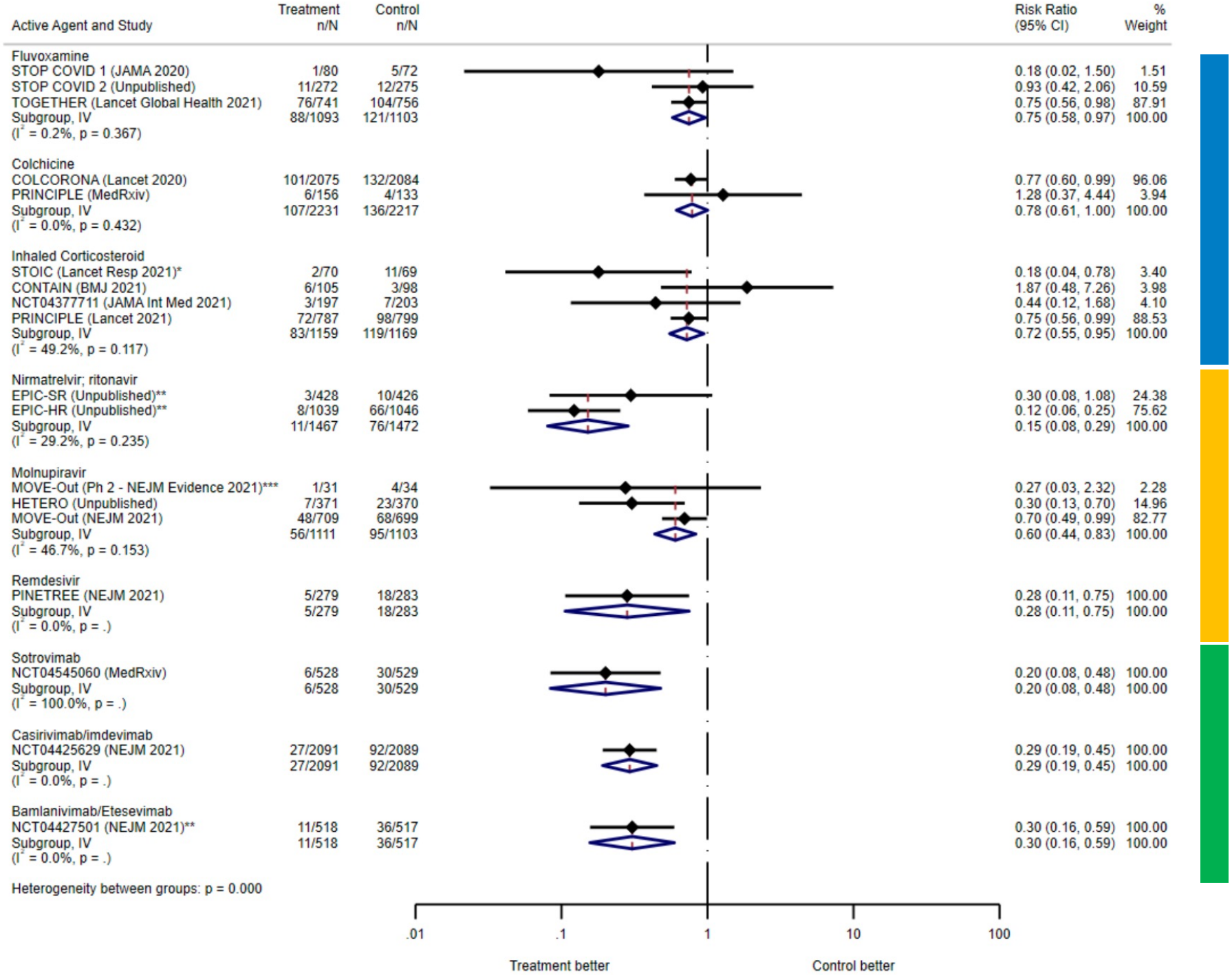
Remdesivir

83% reduction

IV infusion daily for 3 days



Gottlieb NEJM 2022

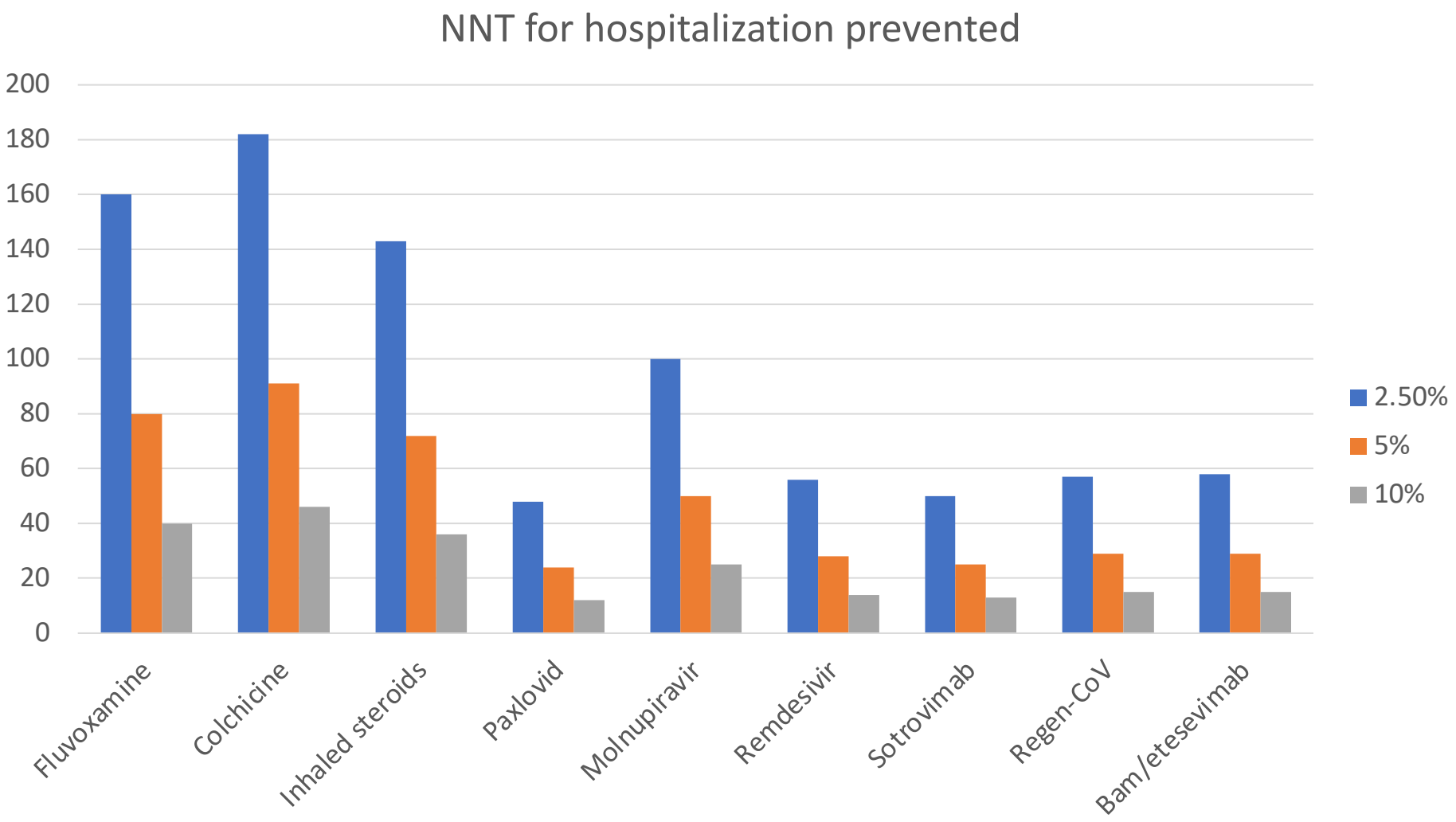


Non-specific

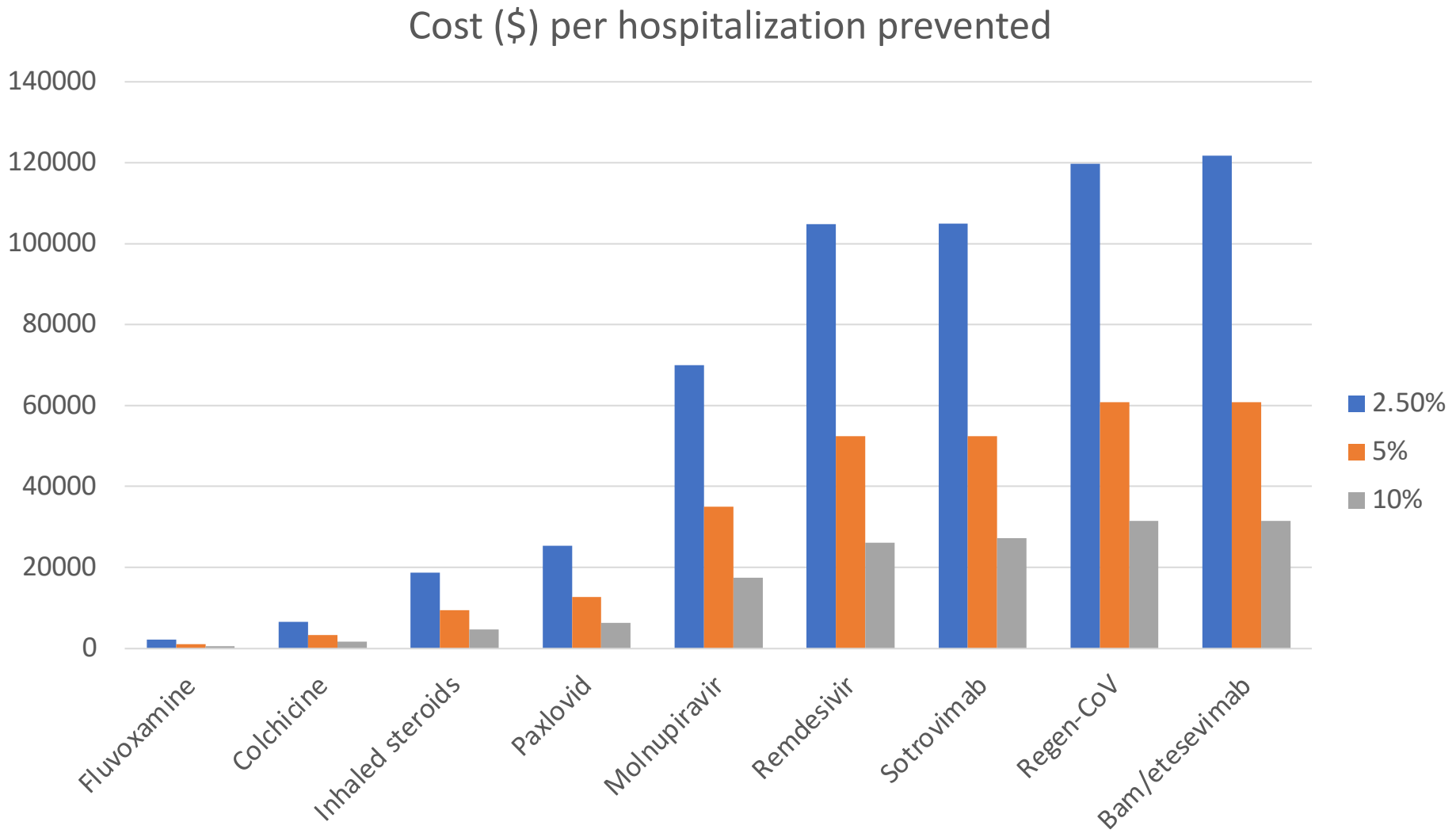
Antivirals

mAb

Lee OFID 2022



Lee OFID 2022

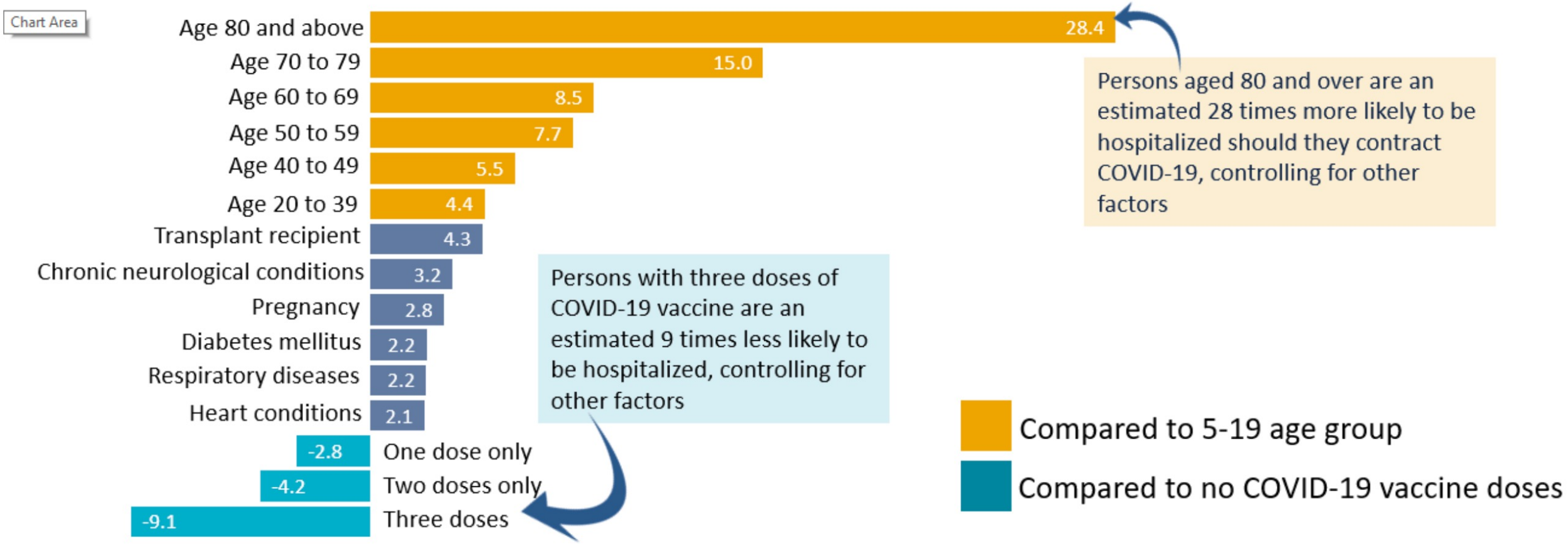


Lee OFID 2022

Study name	Intervention	Proportion vaccinated	Proportion with Omicron
Stop Covid 1	Fluvoxamine	0/152 (0%)	0/152 (0%)
Together	Fluvoxamine	0/1497 (0%)	0/1497 (0%)
Colcorona	Colchicine	0/4488 (0%)	0/4488 (0%)
Contain	Ciclesonide	0/203 (0%)	0/203 (0%)
Covis Pharma	Ciclesonide	Not reported	0/400 (0%)
Principle	Budesonide	14/1959 (0.7%)	0/1959 (0%)
STOIC	Budesonide	0/146 (0%)	0/146 (0%)
PINETREE	Remdesivir	0/562 (0%)	0/562 (0%)
MOVe-OUT	Molnupiravir	0/1408 (0%)	0/1408 (0%)
MOVe-OUT phase 2	Molnupiravir	Not reported	0/299 (0%)
COMET-ICE	Sotrovimab	0/583 (0%)	0/583 (0%)
REGEN-COV	Casirivimab and imdevimab	Not reported	0/4180 (0%)
BLAZE-1	Bamlanivimab and etesevimab	0/1035 (0%)	0/1035 (0%)

What puts a person at greater risk for COVID-19 hospitalization?

Age is the largest risk factor for COVID-19 hospitalization; each dose of vaccine provides added protection. Below are Times more likely (than a person under age 20) estimates.



https://news.gov.bc.ca/files/1.21.22_COVID_Hospitalizations.pdf

Risk of COVID-19 Hospitalization

Analysis from logistic regression on confirmed cases and hospitalizations Dec 14 – Jan 4.

# of at-risk conditions	Age group	Female				Male			
		0 Doses	1 Dose	2 Doses	3 Doses	0 Doses	1 Dose	2 Doses	3 Doses
0 at-risk conditions	<20	0.3%	0.1%	0.1%	0.0%	0.4%	0.2%	0.1%	0.0%
	20-39	1.5%	0.5%	0.4%	0.2%	1.8%	0.7%	0.4%	0.2%
	40-49	1.9%	0.7%	0.4%	0.2%	2.3%	0.8%	0.5%	0.3%
	50-59	2.7%	1.0%	0.6%	0.3%	3.2%	1.2%	0.8%	0.4%
	60-69	2.9%	1.1%	0.7%	0.3%	3.6%	1.3%	0.8%	0.4%
	70-79	5.2%	1.8%	1.2%	0.6%	6.3%	2.2%	1.5%	0.7%
	80+	9.5%	3.3%	2.2%	1.1%	11.8%	4.0%	2.7%	1.3%
1-2 at-risk conditions	<20	0.9%	0.3%	0.2%	0.1%	1.2%	0.4%	0.3%	0.1%
	20-39	4.5%	1.7%	1.1%	0.5%	4.7%	1.8%	1.1%	0.6%
	40-49	5.2%	1.9%	1.2%	0.6%	5.9%	2.2%	1.3%	0.7%
	50-59	6.8%	2.6%	1.6%	0.8%	8.3%	3.2%	1.9%	1.0%
	60-69	7.5%	3.0%	1.8%	0.9%	9.5%	3.6%	2.2%	1.1%
	70-79	13.9%	5.4%	3.3%	1.6%	17.2%	6.9%	4.2%	2.0%
	80+	26.2%	9.7%	6.2%	2.9%	33.9%	13.1%	8.1%	3.9%
3+ at-risk conditions	<20	5.5%	1.8%	1.3%	0.5%	7.3%	1.8%	1.4%	1.4%
	20-39	23.0%	10.6%	5.1%	2.9%	25.2%	11.0%	6.6%	3.6%
	40-49	26.2%	10.6%	5.8%	3.6%	35.6%	8.3%	6.5%	4.0%
	50-59	36.0%	13.2%	7.7%	4.3%	37.0%	12.3%	8.9%	5.1%
	60-69	33.2%	14.8%	7.6%	3.9%	40.3%	16.2%	9.4%	5.0%
	70-79	50.1%	23.2%	12.8%	5.9%	59.6%	26.6%	15.9%	7.5%
	80+	71.9%	31.8%	20.7%	9.4%	83.7%	43.8%	26.3%	12.7%

Model estimates* of the proportion of cases that would result in hospitalization by demographic group and vaccine status

Hospitalization risk for younger people with two or more doses approaches zero

Even with 3 doses, substantial risk observed for those over 80+ (over 10%) when multiple risk conditions present

*Point estimates expected to change as more data becomes available. Differences between same-colored cells may not be statistically significant.

IMMUNISATION COALITION

RISK OF DYING FROM COVID-19

Estimated deaths per 10,000 COVID-19 cases by age, sex, and vaccination status
Australia, January 2022. Version 2.0.

(based on circulating variants = 90% omicron and 10% delta)

AZ=AstraZenca COVID-19 vaccine. Pfz = Pfizer COVID-19 vaccine. Mod = Moderna COVID-19 vaccine.

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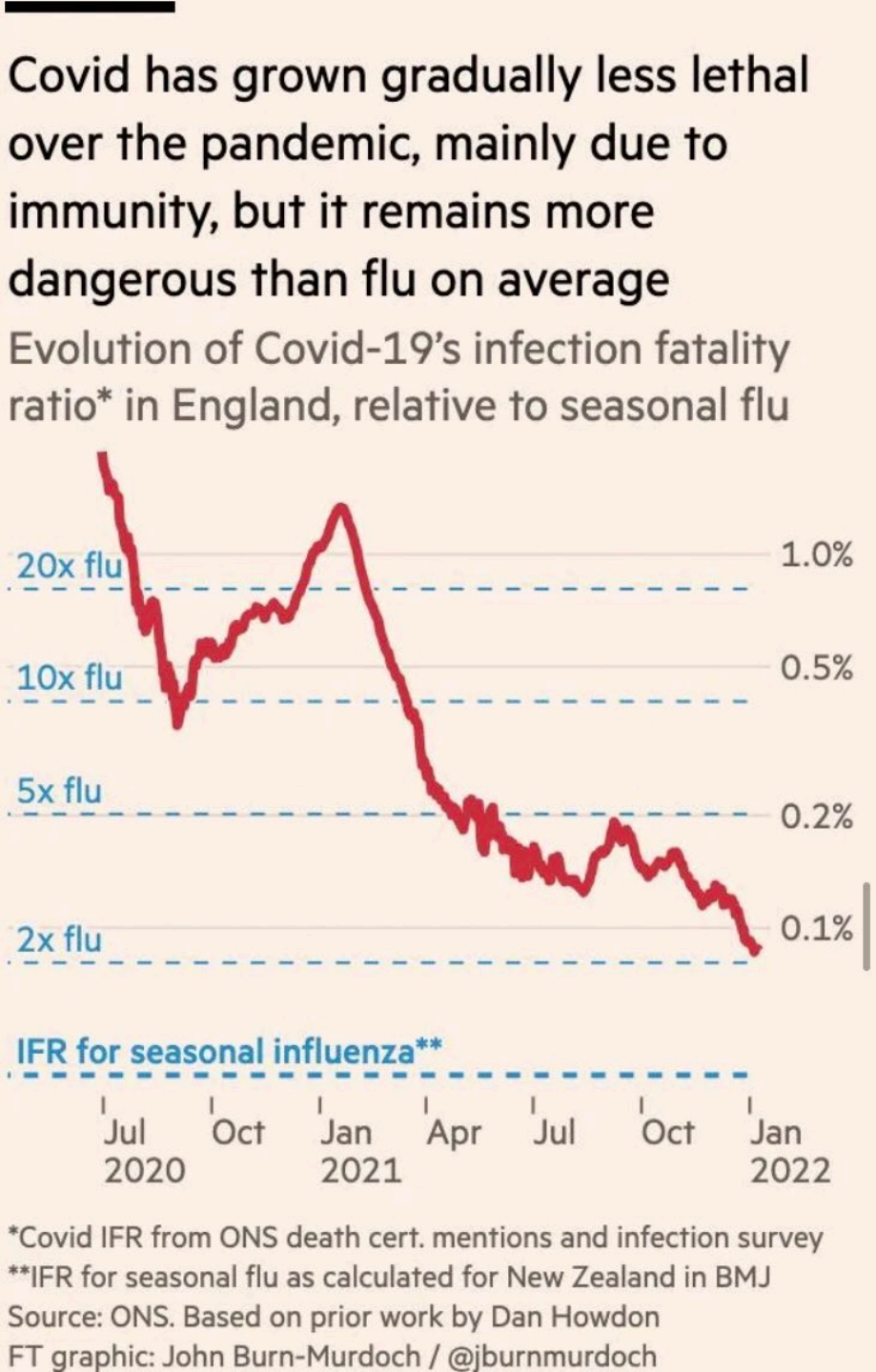
Flinders UNIVERSITY

Gender	Age group (years)	Not vaccinated	1 dose of AZ (3 weeks ago)	2 doses of AZ (2nd dose less than 2 mths ago)	2 doses of AZ (2nd dose 2 to 4 mths ago)	2 doses of AZ (2nd dose 4 to 6 mths ago)	2 doses of AZ + Pfz or Mod booster (2 mths ago)	1 dose of Pfz (3 weeks ago)	2 doses of Pfz (2nd dose less than 2 mths ago)	2 doses of Pfz (2nd dose 2 to 4 mths ago)	2 doses of Pfz (2nd dose 4 to 6 mths ago)	2 doses of Pfz + Pfz or Mod booster (2 mths ago)
Male	12-19	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	20-29	0.3	0.1	0.1	0.1	0.2	<0.1	0.1	0.1	0.1	0.1	<0.1
	30-39	1.4	0.4	0.4	0.4	0.6	0.1	0.3	0.2	0.2	0.4	0.1
	40-49	4	1.0	0.7	0.8	1.3	0.2	0.8	0.4	0.4	0.8	0.2
	50-59	11	3	2	2	4	0.4	2	1.0	1.0	2	0.4
	60-69	38	9	6	7	12	1.4	7	3	3	7	1.4
	70+	362	98	74	80	134	18	75	42	42	83	18
Female	12-19	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	20-29	0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1	<0.1
	30-39	0.4	<0.1	<0.1	<0.1	0.1	<0.1	0.1	<0.1	<0.1	<0.1	<0.1
	40-49	1.6	0.4	0.3	0.3	0.6	0.1	0.3	0.2	0.2	0.3	0.1
	50-59	7	2	1.5	1.6	3	0.4	1.4	0.8	0.8	1.6	0.4
	60-69	22	7	6	6	10	1.4	5	3	3	6	1.4
	70+	322	77	55	61	106	13	62	31	31	63	13

=3.2%

Estimated deaths per 10,000 cases

- Less than 0.1
- 0.11 to 1.0
- 1.1 to 10
- 10.1 to 50
- 50.1 to 150
- More than 150



Immunity and variants challenges the external validity of existing trial data

Need for accurate risk assessment:

- Up to date
- Local

Need for ongoing clinical trials (comparative effectiveness)

- Sotrovimab vs remdesivir vs paxlovid
- Baricitinib vs tocilizumab