COVID-19 Therapeutics

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@syctong

Hydroxychloroquine
Early data

Gautret IJAA 2020

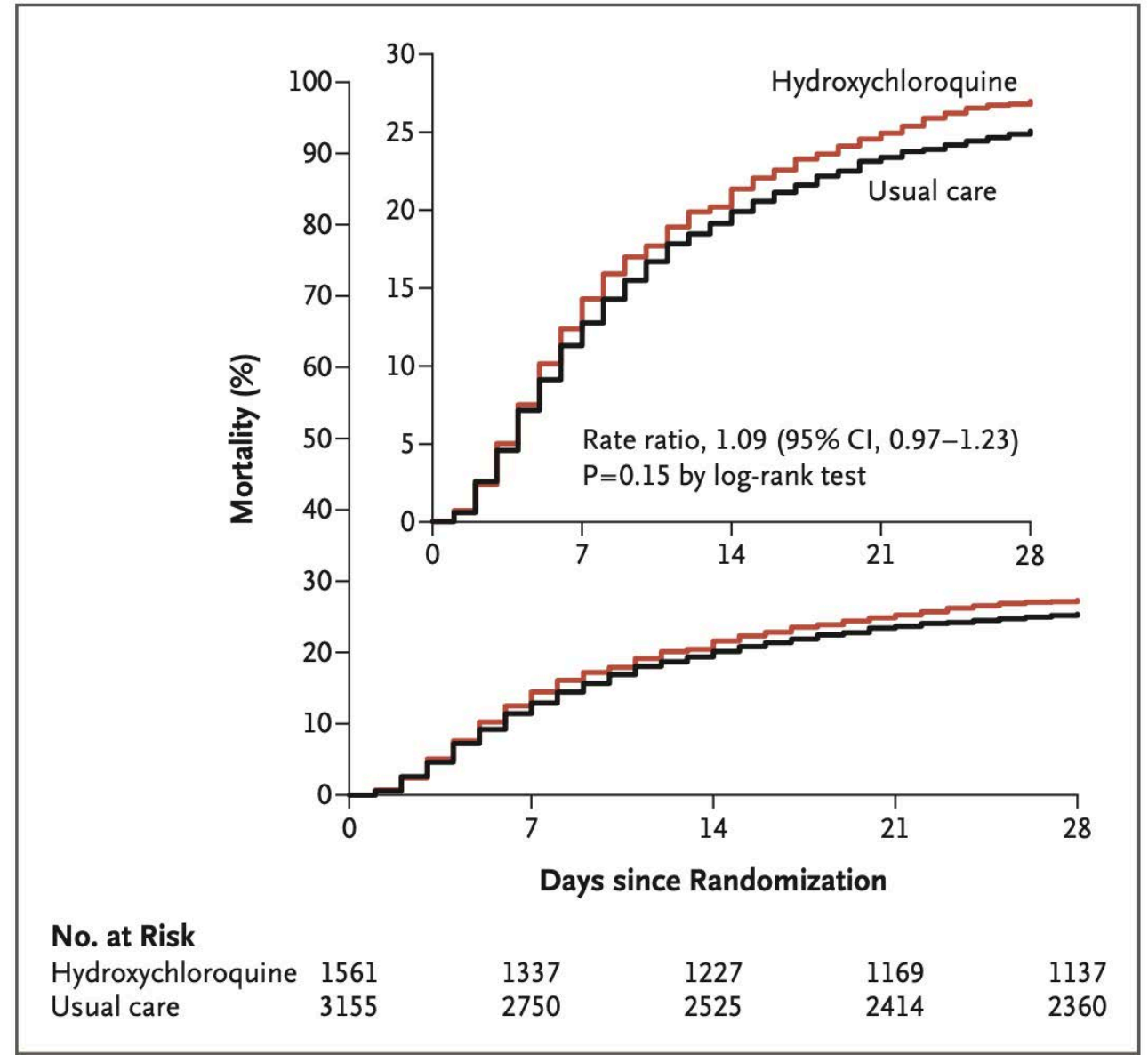# Hydroxychloroquine RECOVERY

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UK Trial

Large numbers: 4,716 total

28 day mortality:

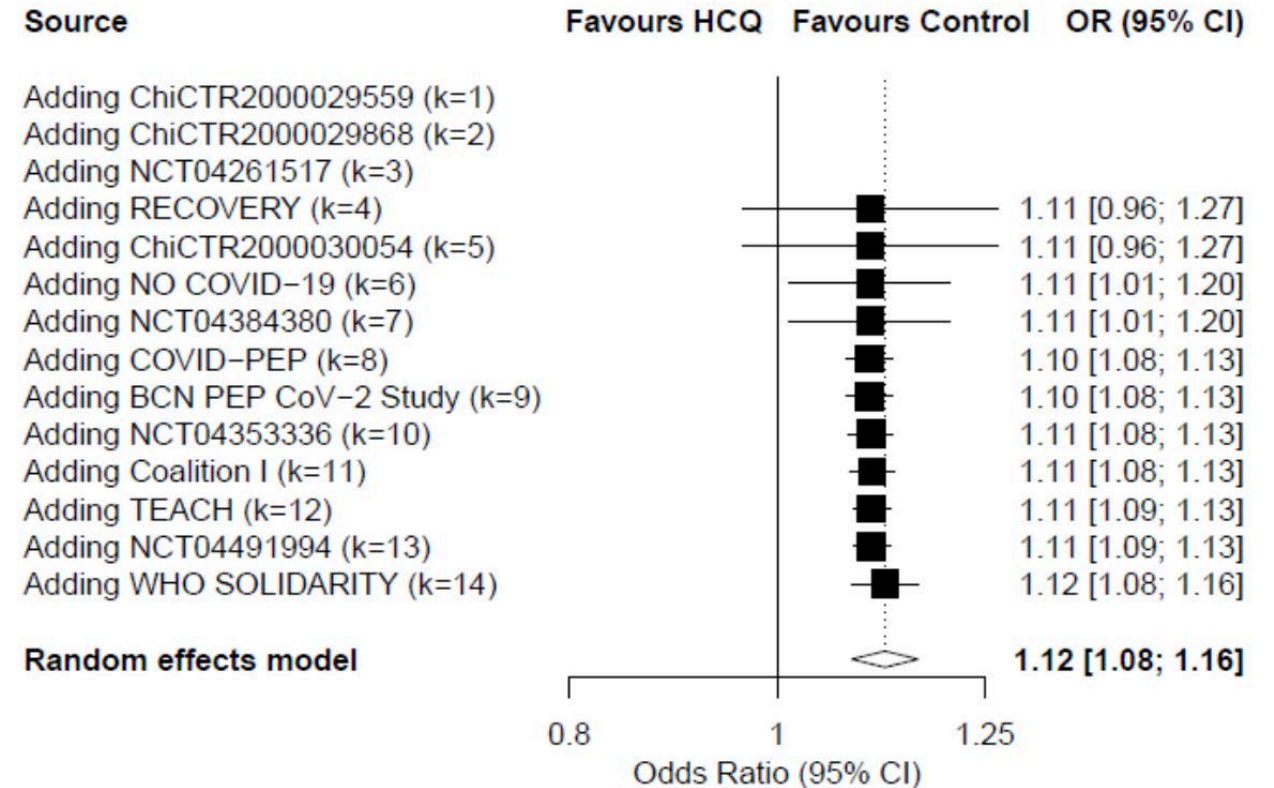|	
Control:	25.0%
HCQ:	27.0%

Horby NEJM 2020

Hydroxychloroquine Meta-analysis

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RECOVERY (47%) and SOLIDARITY (19%) dominated

Mortality ~15%

HCQ associated with increased mortality:

OR 1.12 (95% CI 1.08 to 1.16)

Figure 3B. Cumulative meta-analysis for mortality for treatment of COVID-19 with Hydroxychloroquine

(publications and preprints only)

Source	Favours HCQ Favours Control	OR (95% CI)
Adding ChiCTR2000029559 (k=1)		
Adding ChiCTR2000029868 (k=2)		
Adding NCT04261517 (k=3)		
Adding RECOVERY (k=4)		1.11 [0.96; 1.27]
Adding ChiCTR2000030054 (k=5)		1.11 [0.96; 1.27]
Adding NO COVID-19 (k=6)		1.11 [1.01; 1.20]
Adding NCT04384380 (k=7)		1.11 [1.01; 1.20]
Adding COVID-PEP (k=8)		1.10 [1.08; 1.13]
Adding BCN PEP CoV-2 Study (k=9)		1.10 [1.08; 1.13]
Adding NCT04353336 (k=10)		1.11 [1.08; 1.13]
Adding Coalition I (k=11)		1.11 [1.08; 1.13]
Adding TEACH (k=12)		1.11 [1.09; 1.13]
Adding NCT04491994 (k=13)		1.11 [1.09; 1.13]
Adding WHO SOLIDARITY (k=14)		1.12 [1.08; 1.16]
Random effects model		**1.12 [1.08; 1.16]**

Odds Ratio (95% CI)

Comment on this paper

Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19: an international collaborative meta-analysis of randomized trials

The pointlessness of observational data

Prof Darrel Francis 😋 **Mk CardioFellows Great Again** @... · May 2 ⌄
We decide if treatments are beneficial by doing scientific experiments, I.e. RCTs.

Prof Darrel Francis 😋 **Mk CardioFellows Great Again** @... · May 2 ⌄
I don't read it.

Just like I don't count the blades of grass I walk past on the way to work every day.

I could do, but it would be like a broken pencil.

Pointless.

Prof Darrel Francis 😋 **Mk CardioFellows Great Again** @... · May 2 ⌄
Note that this does not mean I don't myself look at non randomized data I want to know things.

Like what proportion of people are men.

Or what proportion of Covid patients get ventilated.

💬 1   🔁   ♡ 7   ↥

Prof Darrel Francis 😋 **Mk CardioFellows Great Again** @... · May 2 ⌄
But never to see if a treatment is good.

💬 1   🔁   ♡ 7   ↥

Ivermectin

February 4, 2021 11:45 am EST

KENILWORTH, N.J., Feb. 4, 2021 – Merck (NYSE: MRK), known as MSD outside the United States and Canada, today affirmed its position regarding use of ivermectin during the COVID-19 pandemic. Company scientists continue to carefully examine the findings of all available and emerging studies of ivermectin for the treatment of COVID-19 for evidence of efficacy and safety. It is important to note that, to-date, our analysis has identified:

— No scientific basis for a potential therapeutic effect against COVID-19 from pre-clinical studies;
— No meaningful evidence for clinical activity or clinical efficacy in patients with COVID-19 disease, and;
— A concerning lack of safety data in the majority of studies.

We do not believe that the data available support the safety and efficacy of ivermectin beyond the doses and populations indicated in the regulatory agency-approved prescribing information.

Overview

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Observational vs randomized

Disease stages

A game of numbers

Therapeutics: antibody, antivirals, immunomodulation

Disease stages
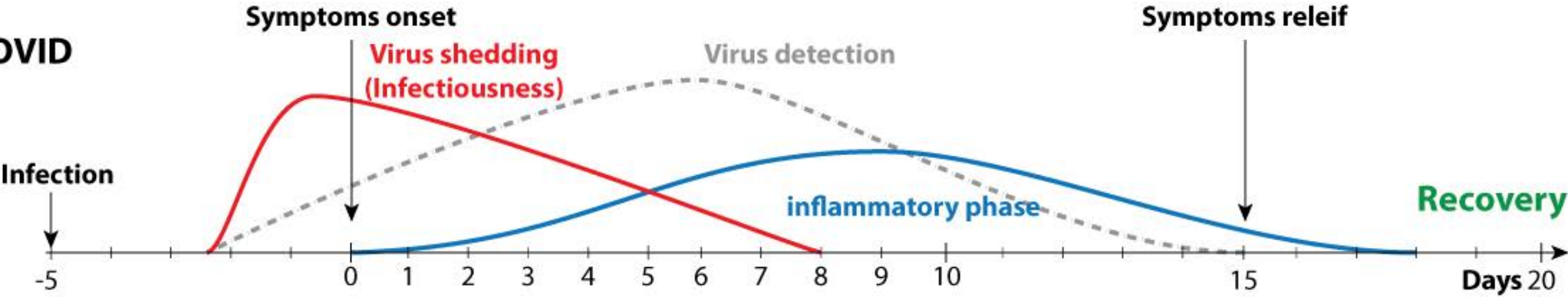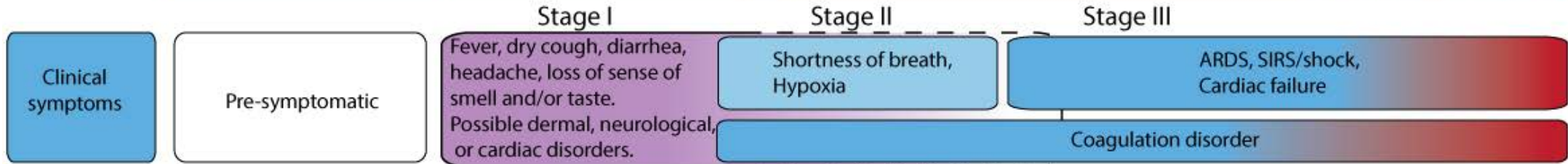
Mild COVID

Infection

Symptoms onset

Virus shedding (Infectiousness)

Virus detection

Symptoms releif

inflammatory phase

Recovery

-5   0 1 2 3 4 5 6 7 8 9 10   15   Days 20

Severe COVID

Infection

Symptoms onset

Virus detection

Admission to ICU

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

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes

Proposed Disease Pathogenesis

Viral replication

Inflammation

Potential Treatment

Antiviral therapy

Antibody therapy

Antiinflammatory therapy

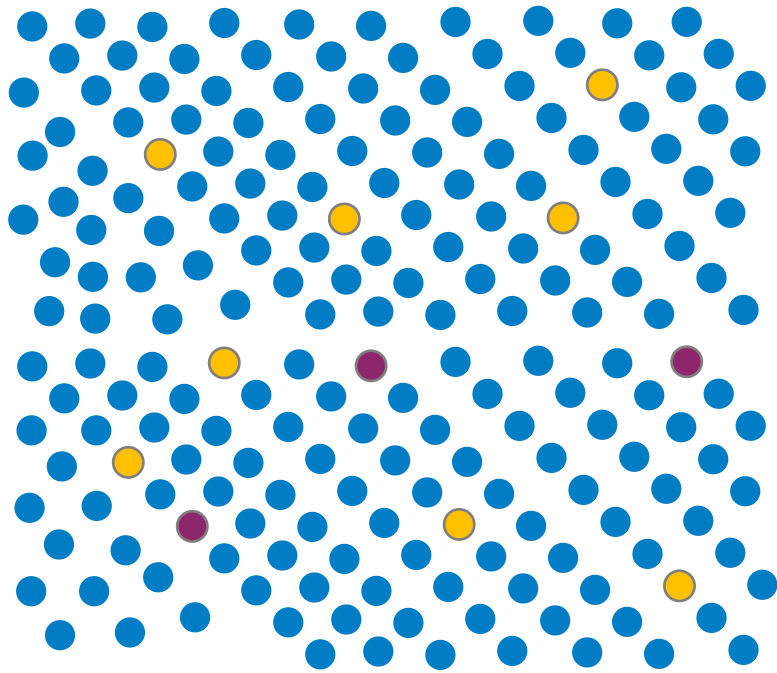|	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Numbers and timing
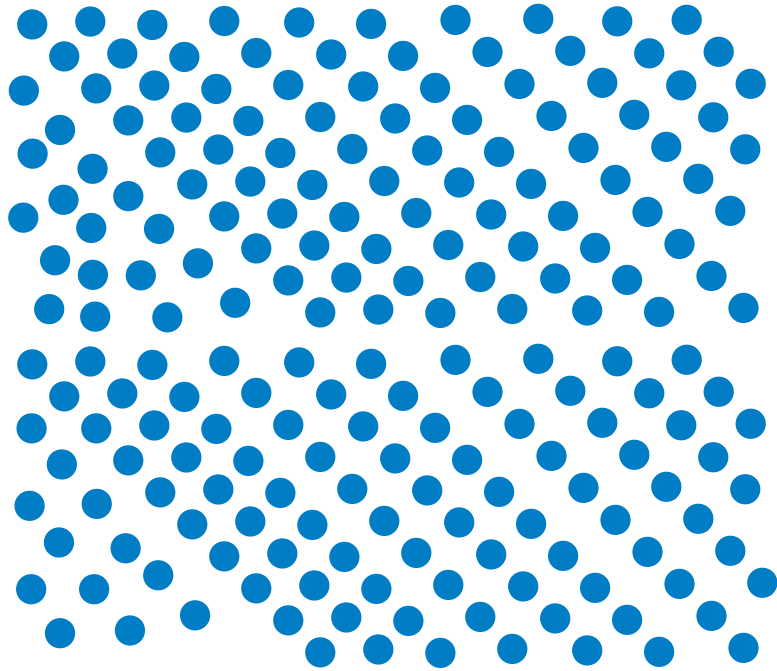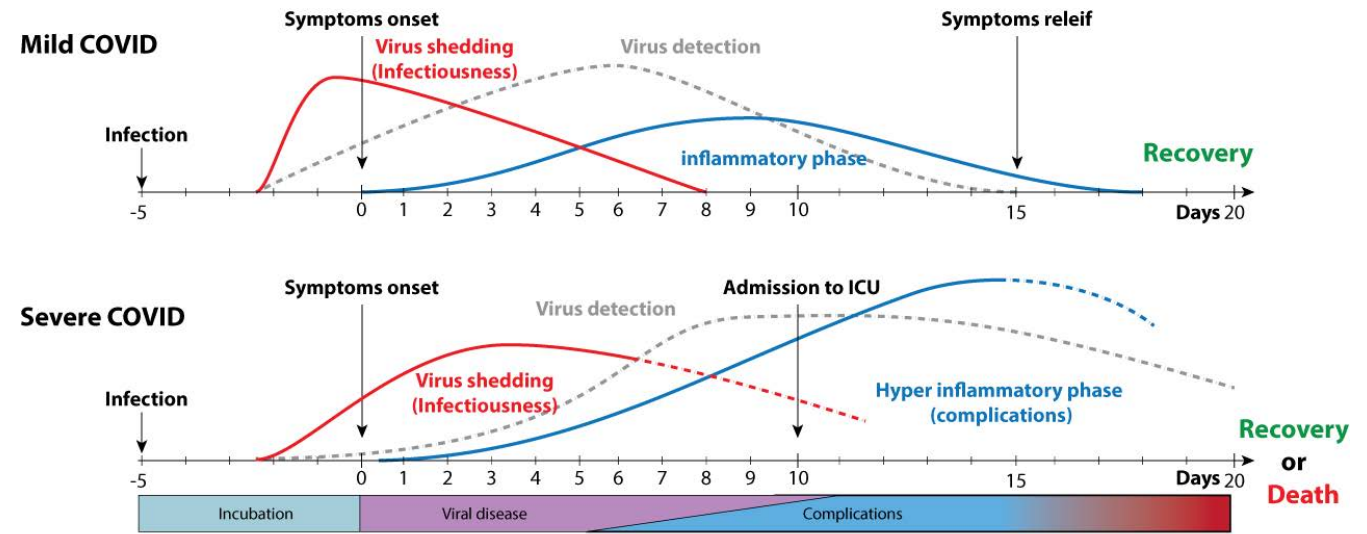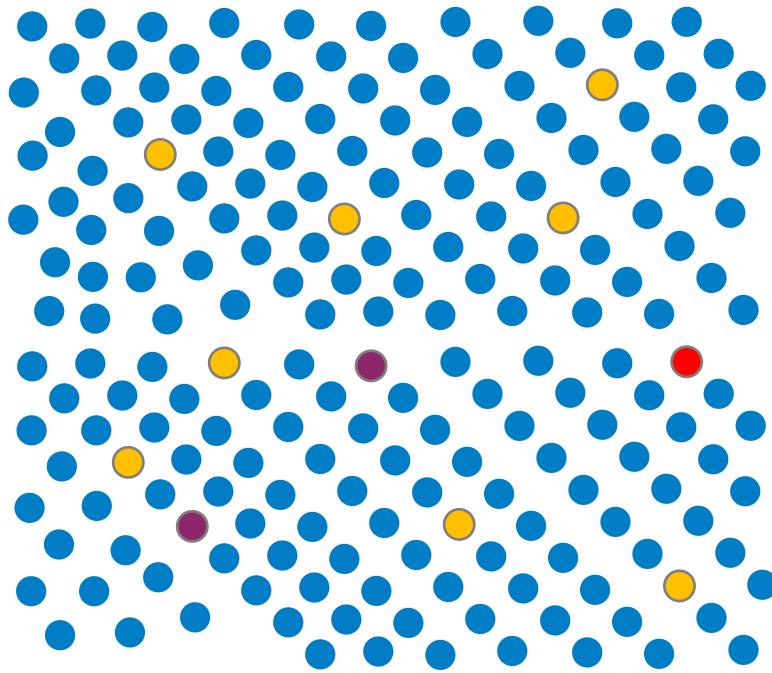
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Numbers and timing

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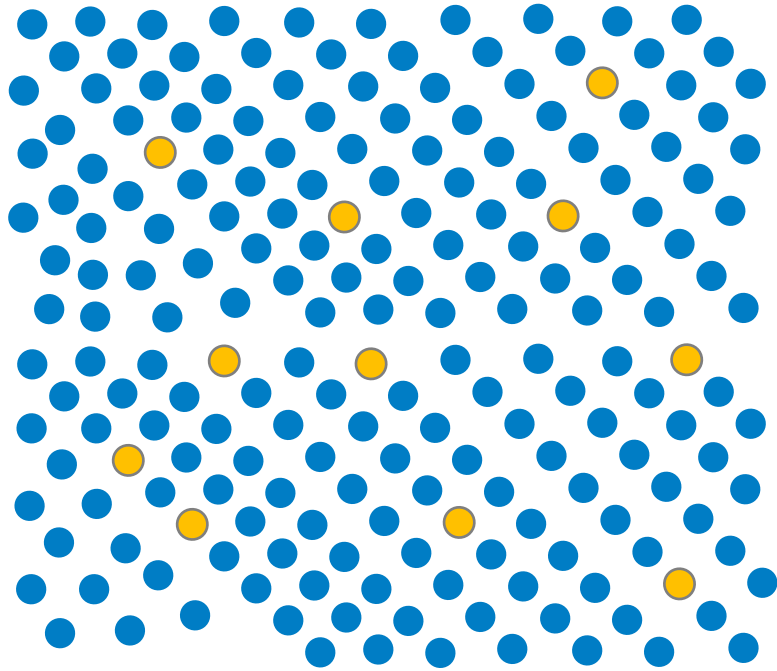
Numbers and timing

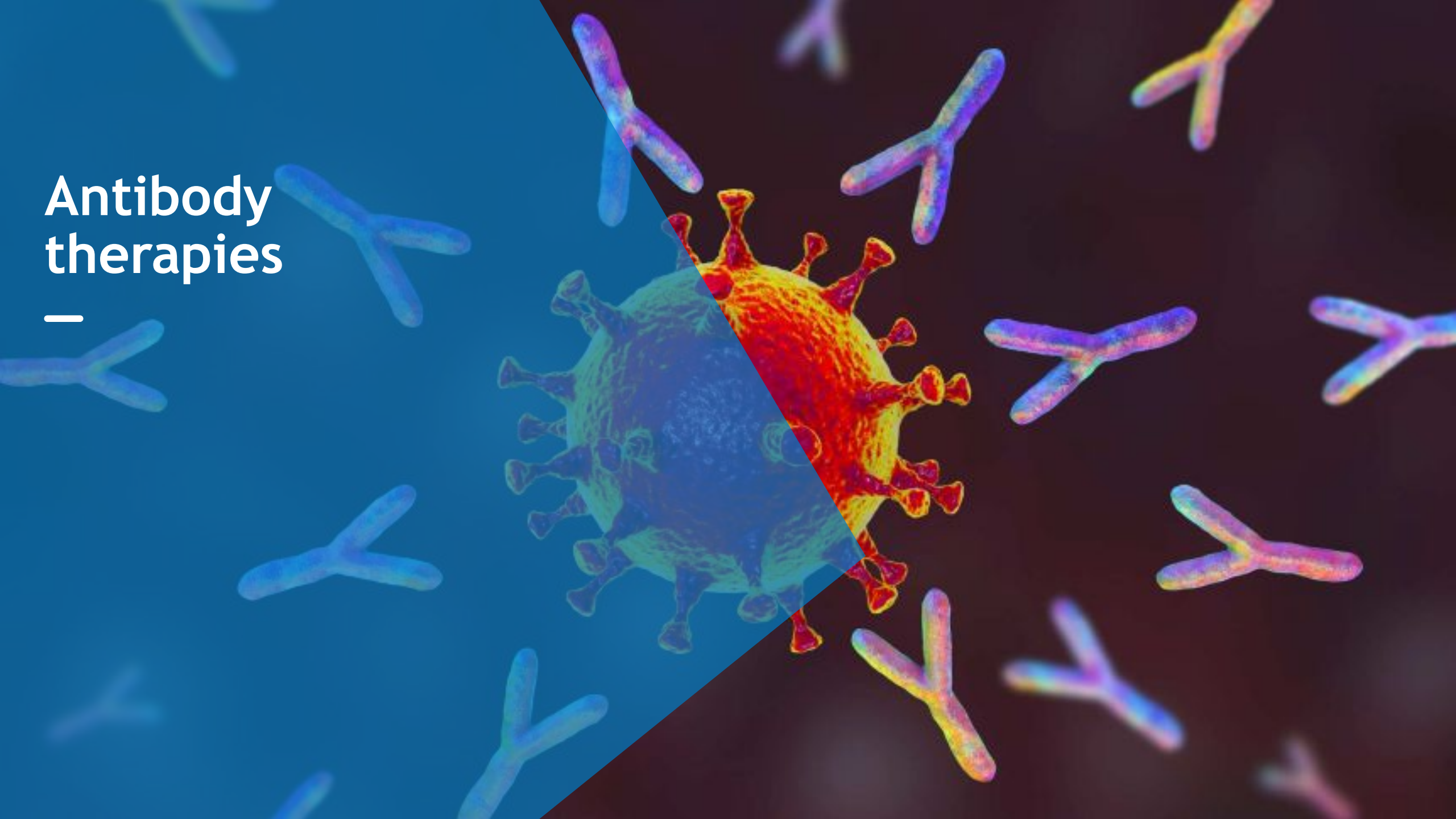# Numbers and timing

Antibody therapies

	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
Features	Positive SARS-CoV-2 test; no symptoms	Mild symptoms (e.g., fever, cough, or change in taste or smell); no dyspnea	Clinical or radiographic evidence of lower respiratory tract disease; oxygen saturation ≥94%	Oxygen saturation <94%; respiratory rate ≥30 breaths/min; lung infiltrates >50%	Respiratory failure, shock, and multiorgan dysfunction or failure
Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis	Viral replication	Viral replication	Viral replication / Inflammation	Inflammation	Inflammation
Potential Treatment	Antiviral therapy	Antiviral therapy / Antibody therapy	Antiviral therapy / Antibody therapy	Antiinflammatory therapy	Antiinflammatory therapy
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Convalescent plasma

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US Expanded Access program: >100,000 hospitalized patients received CP[1]

RECOVERY: Press release Jan 15 2021

10,406 randomized patients

No difference in 28d mortality: 18% vs 18%

Other RCTs: no benefit[2]

Overall, no benefit in reducing mortality

Possible benefit if high titre, given early
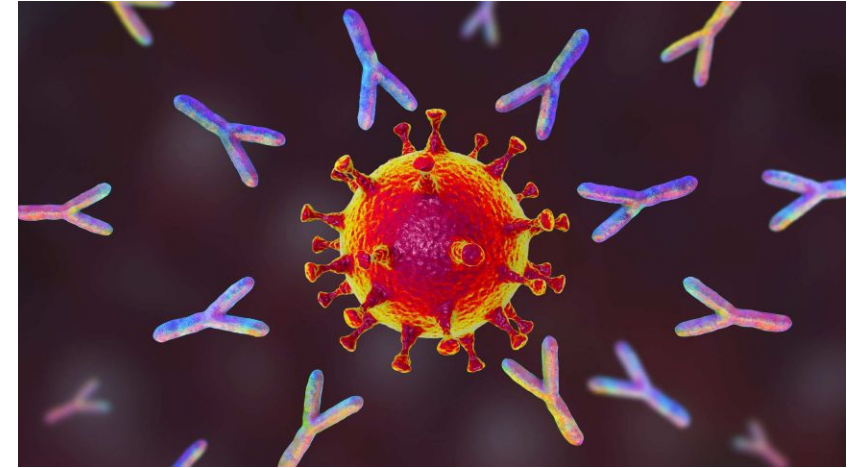
1. Joyner NEJM 2021
2. Agarwal BMJ 2020

Monoclonal antibodies

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Bamlanivimab (Eli Lily)[1,2,3]

- 452 outpatient trial.
  - Hospital / ED presentation: 9/143 (6%) with placebo vs 5/309 (1.6%) with bamlanivimab
- 314 inpatient trial.
  - NO benefit.

Casirivimab Plus Imdevimab (Regeneron)[3]

- 799 outpatient trial.
  - Hospital / ED presentation: 10/231 (4%) with placebo vs 8/434 (2%) with REGN

Likely benefit in reducing hospitalization

Didn't work for already hospitalized

More effective if given before antibody response has developed

Logistically difficult

1. Chen NEJM 2021
2. Gottlieb JAMA 2021
3. ACTIV-3 NEJM 2021
4. Weinreich NEJM 2021

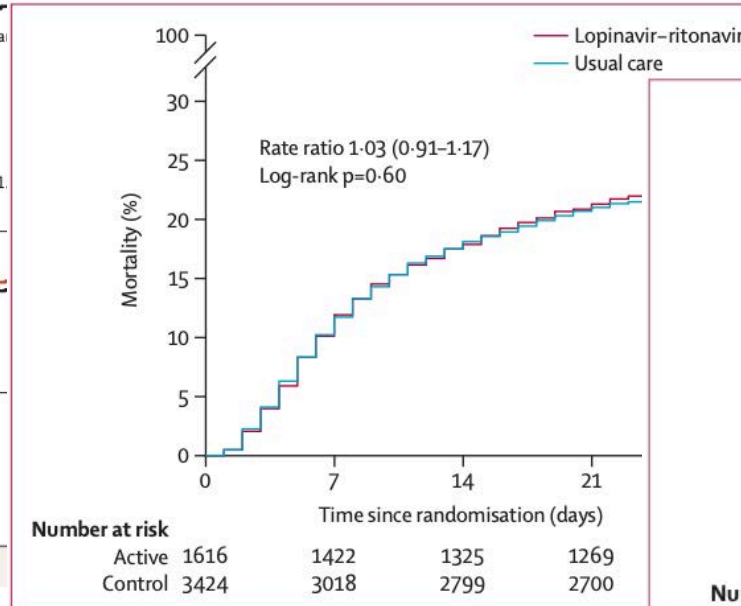|	Asymptomatic or Presymptomatic	Mild Illness	Moderate Illness	Severe Illness	Critical Illness
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Testing	Screening testing; if patient has known exposure, diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing	Diagnostic testing
Isolation	Yes	Yes	Yes	Yes	Yes
Proposed Disease Pathogenesis	Viral replication				
			Inflammation		
Potential Treatment	Antiviral therapy				
		Antibody therapy		Antiinflammatory therapy	
Management Considerations	Monitoring for symptoms	Clinical monitoring and supportive care	Clinical monitoring; if patient is hospitalized and at high risk for deterioration, possibly remdesivir	Hospitalization, oxygen therapy, and specific therapy (remdesivir, dexamethasone)	Critical care and specific therapy (dexamethasone, possibly remdesivir)

Antivirals – RECOVERY

1. RECOVERY NEJM 2020
2. RECOVERY Lancet 2020
3. RECOVERY Lancet 2021
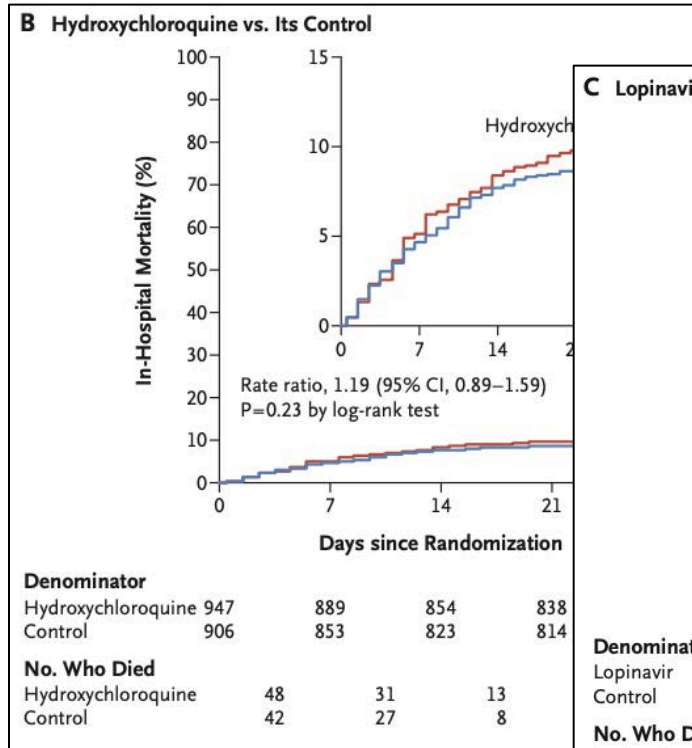
Hydroxychloroquine[1]
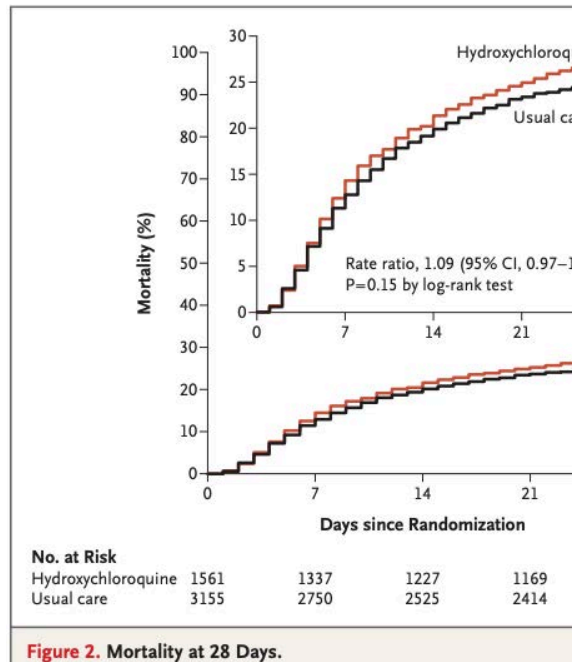
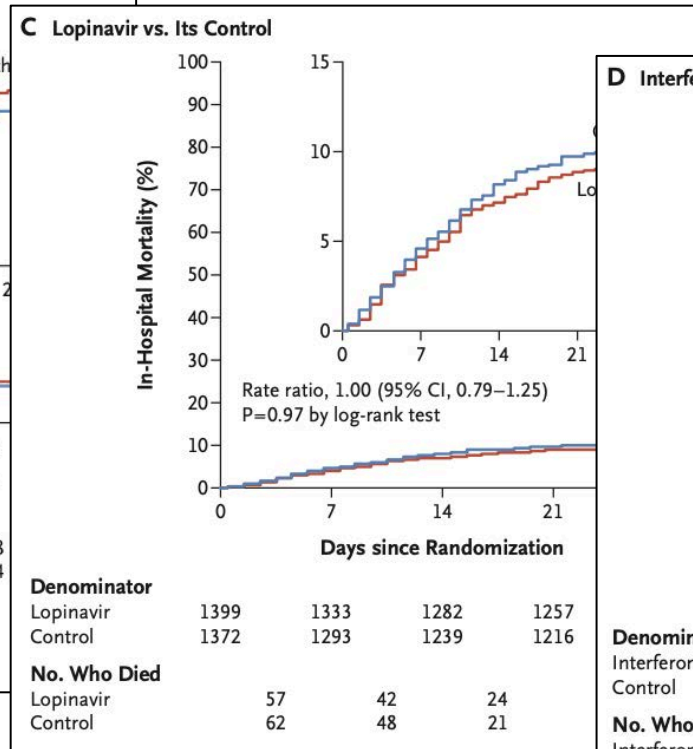## Lopinavir-ritonavir[2]

Azithromycin[3]

Figure 2. Mortality at 28 Days.

Figure 2: Effect of allocation to lopinavir–ritonavir on 28-day mortality

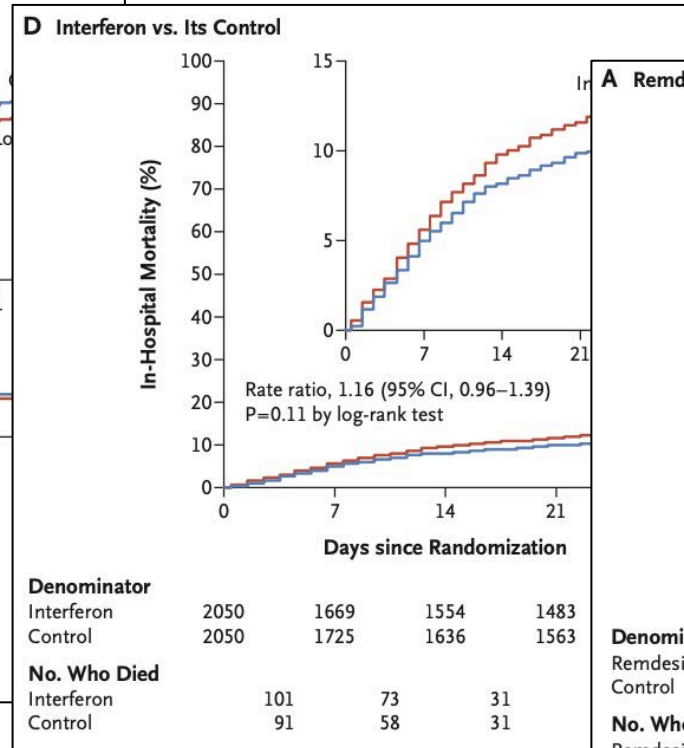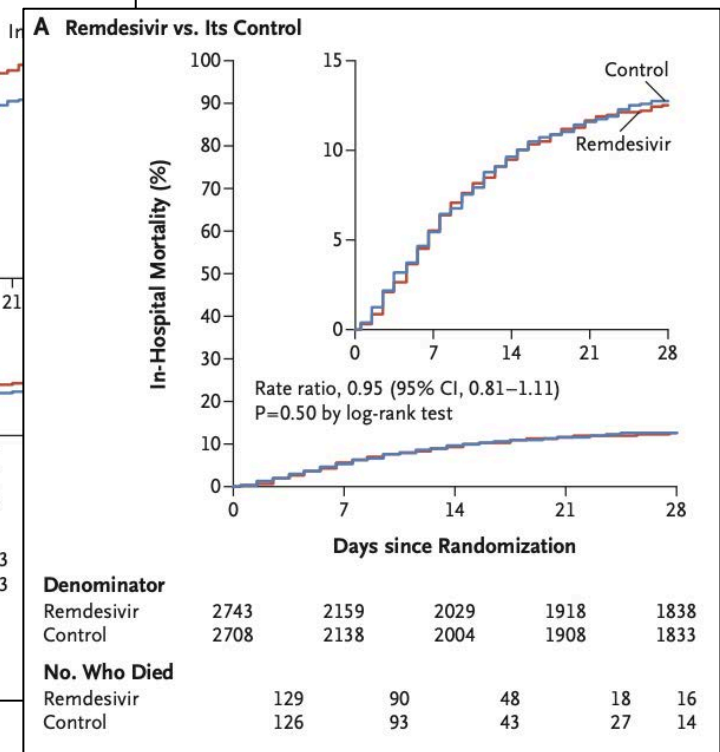Figure 2: Effect of allocation to azithromycin on 28-day mortality
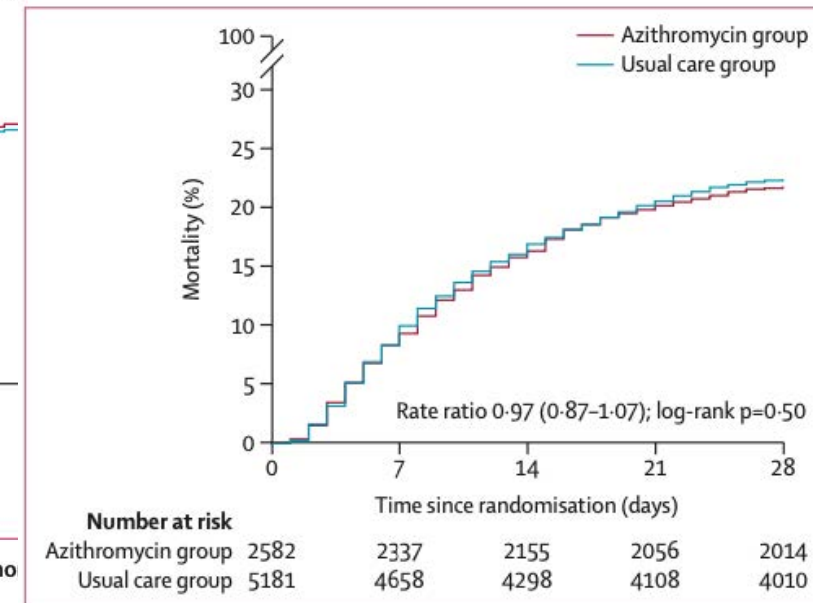
Antivirals – WHO SOLIDARITY Trial NEJM 2020

Hydroxychloroquine

Lopinavir

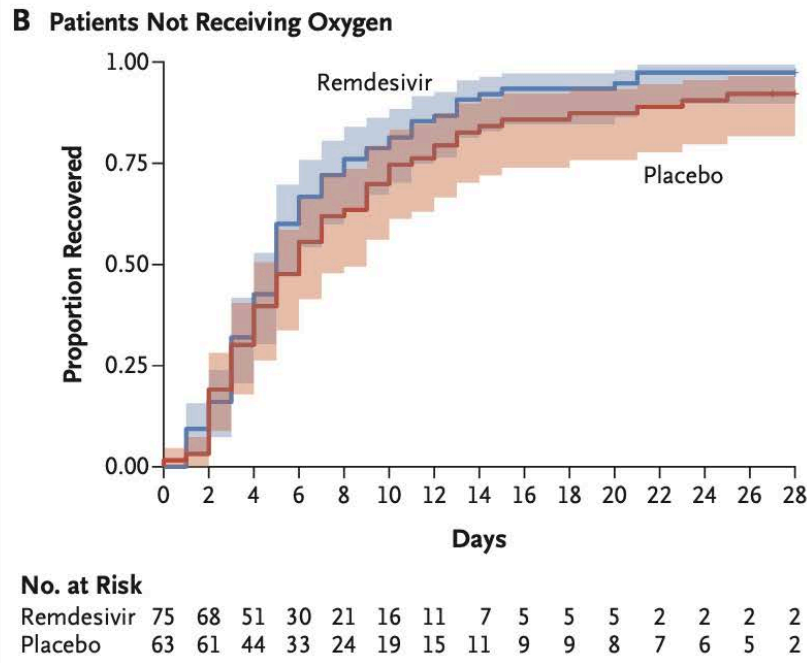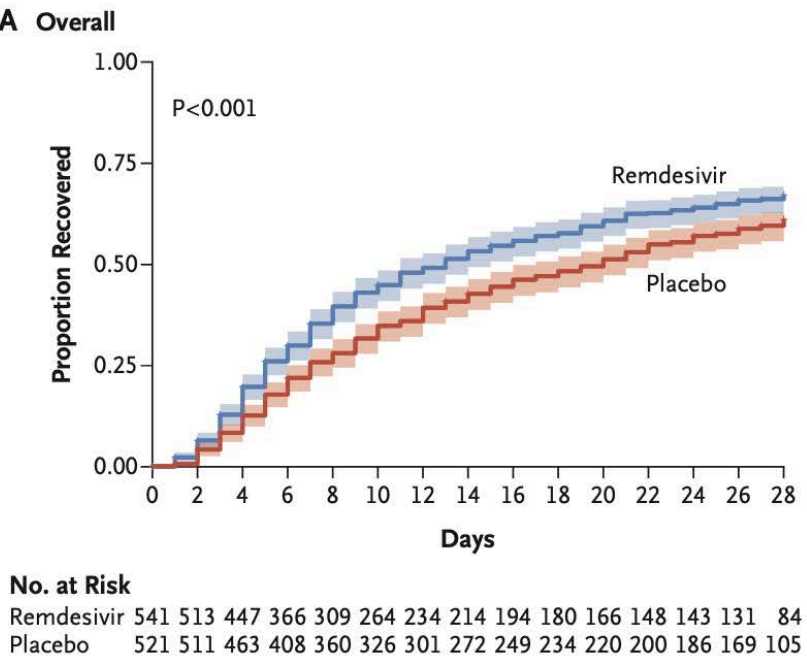Interferon

Remdesivir

A Overall

No. at Risk
Remdesivir 541 513 447 366 309 264 234 214 194 180 166 148 143 131 84
Placebo 521 511 463 408 360 326 301 272 249 234 220 200 186 169 105

B Patients Not Receiving Oxygen

No. at Risk
Remdesivir 75 68 51 30 21 16 11 7 5 5 5 2 2 2 2
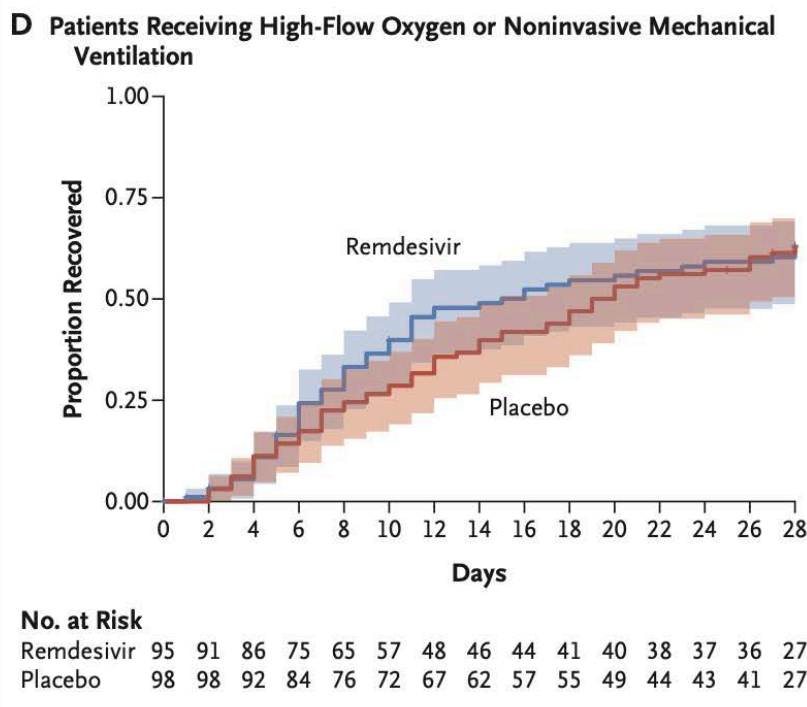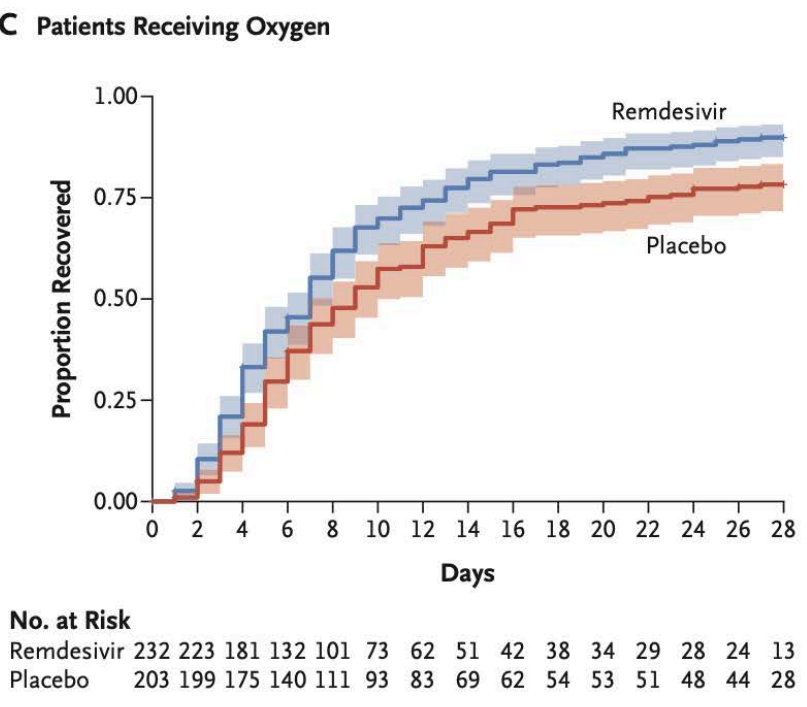Placebo 63 61 44 33 24 19 15 11 9 9 8 7 6 5 2

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

C Patients Receiving Oxygen

No. at Risk
Remdesivir 232 223 181 132 101 73 62 51 42 38 34 29 28 24 13
Placebo 203 199 175 140 111 93 83 69 62 54 53 51 48 44 28

D Patients Receiving High-Flow Oxygen or Noninvasive Mechanical Ventilation

No. at Risk
Remdesivir 95 91 86 75 65 57 48 46 44 41 40 38 37 36 27
Placebo 98 98 92 84 76 72 67 62 57 55 49 44 43 41 27

E Patients Receiving Mechanical Ventilation or ECMO

No. at Risk
Remdesivir 131 131 129 129 122 118 113 110 103 96 87 79 76 69 42
Placebo 154 153 152 151 149 142 136 130 121 116 110 98 89 79 48

Remdesivir
SUMMARY
—

Clinical benefit in time to clinical improvement

Best in those requiring O2; no benefit if ventilated

No clear mortality benefit* (In ACTT-1, on supplemental O2, 12.7% [placebo] vs 4% [control])

5 days and 10 days similar

NATIONAL COVID-19 CLINICAL EVIDENCE TASKFORCE

6.2.1 Remdesivir for adults 2

Conditional recommendation

Consider using remdesivir for adults hospitalised with moderate to severe COVID-19 who do not require ventilation.

In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.
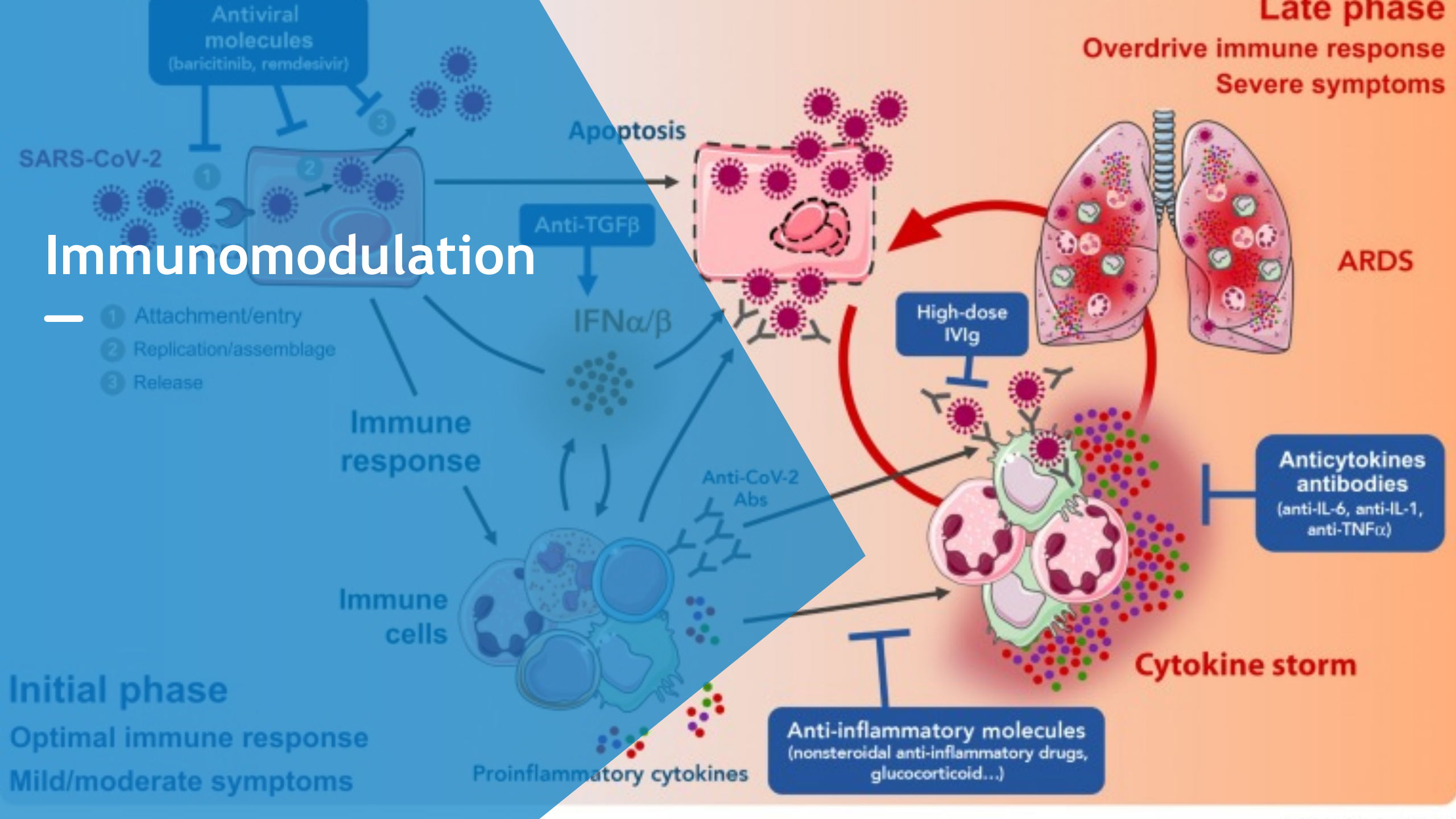
Steroids – RECOVERY
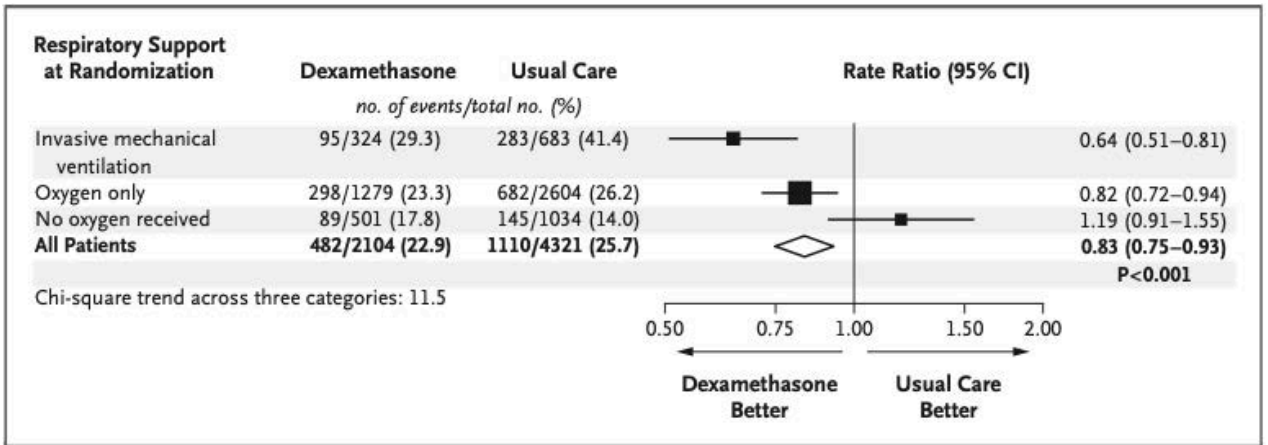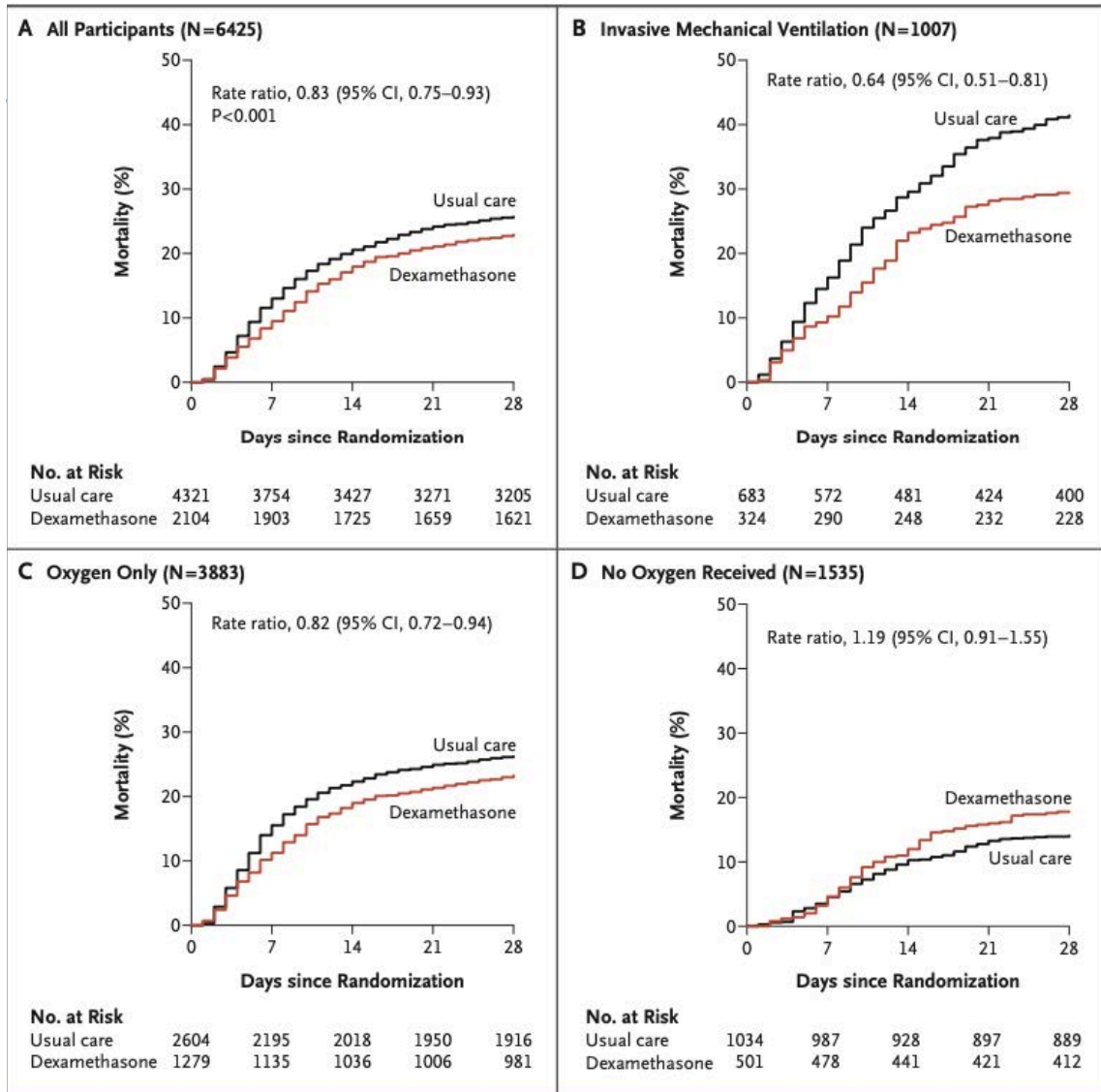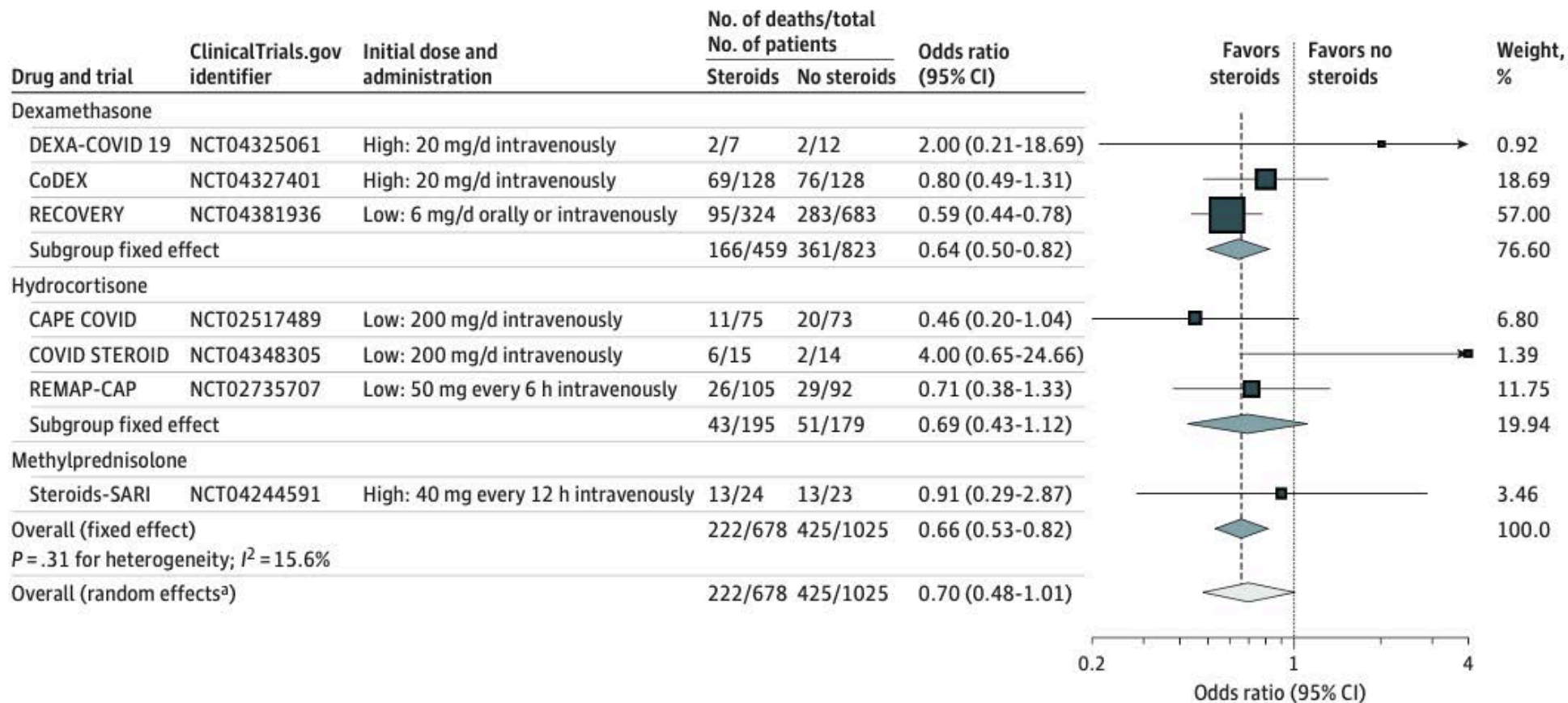

Clear benefit of dexamethasone

Standard of care

1. RECOVERY NEJM 2020

Steroids for critically ill – WHO meta-analysis

—

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

1. WHO JAMA 2020
2. Angus JAMA 2020

Conclusions

—

Steroids for those requiring O2

Remdesivir for those requiring O2 NOT in critical care

Other antivirals no benefit

Possibly monoclonal antibodies very early

On the horizon

Tocilizumab – Il6 inhibitor

Colchicine

Anticoagulation

Ongoing treatments:

Aspirin

Colchicine

Baricitinib

Regeneron monoclonals

Tocilizumab

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Martin Landray @MartinLandray · Feb 2
RECOVERY Recruitment Update:

30 Dec: 23,000
5 Jan: 24,000
7 Jan: 25,000
10 Jan: 26,000
12 Jan: 27,000
14 Jan: 28,000
18 Jan: 29,000
20 Jan: 30,000
22 Jan: 31,000
26 Jan: 32,000
28 Jan: 33,000
2 Feb: 34,000

Remarkable & a tribute to wonderful NHS staff & patients

REMAP-CAP

10,214
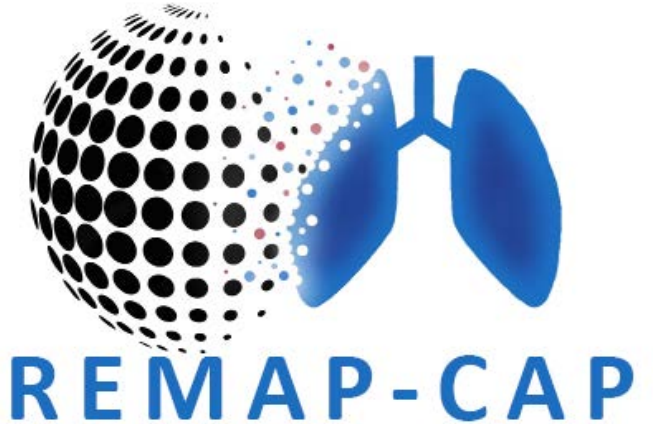Patient randomisations with suspected or proven COVID-19

31
Available interventions in 12 Domains

5,312
Patients with suspected or proven COVID-19

296
Active Sites