# COVID-19 Update

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# Dynamic interventions to control COVID-19 pandemic: a multivariate prediction modelling study comparing 16 worldwide countries

- Non-pharmacological interventions (NPI) have been the mainstay for controlling the COVID-19 pandemic.
  - While NPIs are effective in preventing health systems overload, these long-term measures are likely to have significant adverse economic consequences
- Many countries are currently considering to lift the NPIs
- Dynamic NPIs, with intervals of relaxed social distancing, may provide a more suitable alternative,
  - But the ideal frequency and duration of intermittent NPIs, and the ideal “break” when interventions can be temporarily relaxed, remain uncertain

**Chowdhury R, Heng K, Shawon SR et al. European Journal of Epidemiology (2020) 35:389–399**
**https://doi.org/10.1007/s10654-020-00649-w**

# Dynamic interventions to control COVID-19 pandemic: a multivariate prediction modelling study comparing 16 worldwide countries

- Multivariate prediction model
  - Based on up-to-date transmission and clinical parameters
  - 16 countries, from diverse regions and economic categories.
- Modeling evaluated the impacts on intensive care unit (ICU) admissions and deaths over an 18-month period for following scenarios:
  1. No intervention
  2. Consecutive cycles of **mitigation** measures followed by a relaxation period
  3. Consecutive cycles of **suppression** measures followed by a relaxation period.

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# Dynamic interventions to control COVID-19 pandemic: Definitions

1. **Mitigation cycle**: a combination of measures, such as general social distancing measures, hygiene rules, case-based isolation, shielding of vulnerable groups, school closures or restricting of large public events; target $R = 0.8$ followed by
    a) Relaxation period comprising of case-based home isolation of positive cases and shielding of vulnerable groups
2. **Suppression cycle:** Additional measures of strict physical distancing, including lockdowns; target $R = 0.5$ followed by
    a) Relaxation period (as defined above)
3. Continuous suppression measure with no relaxation.

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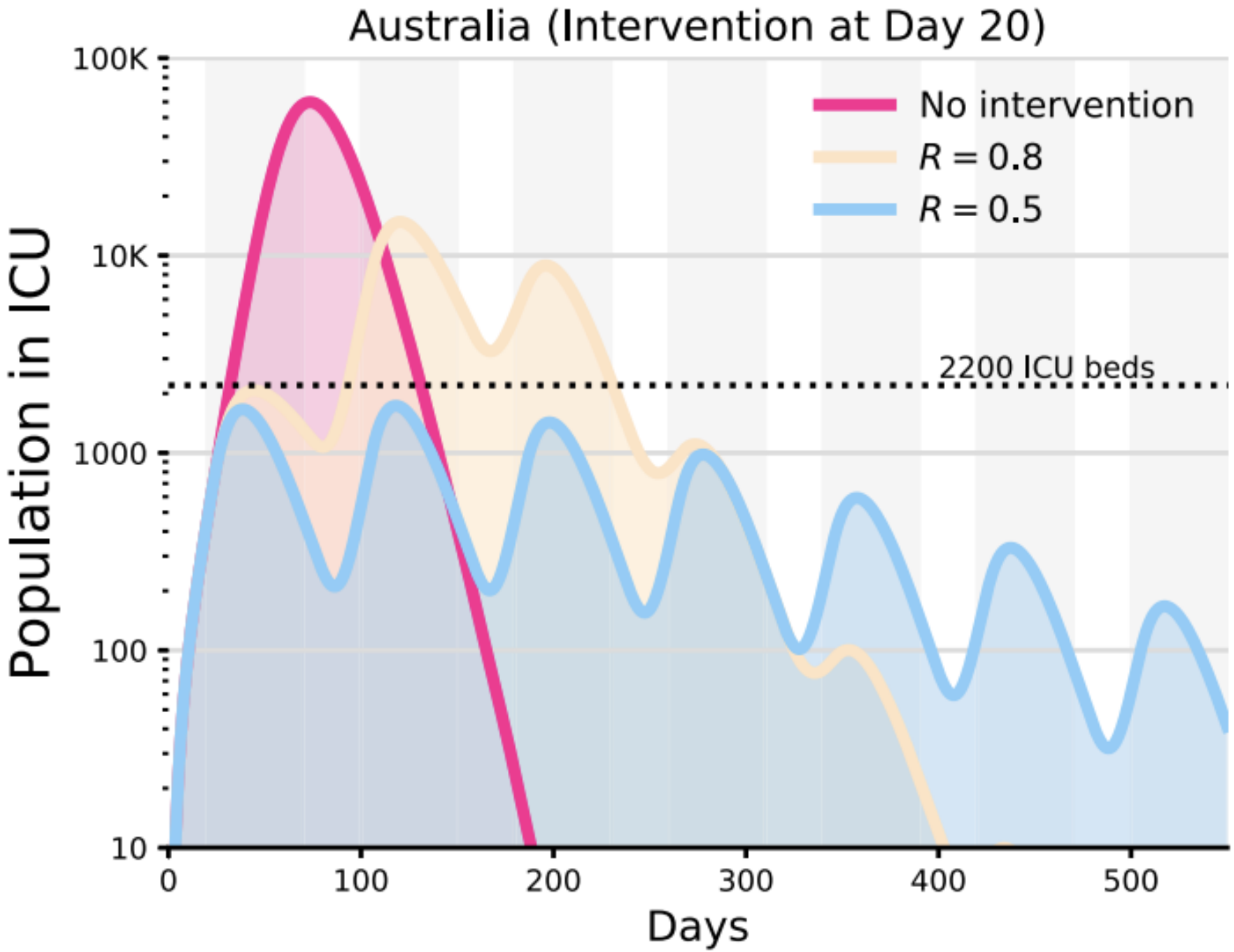
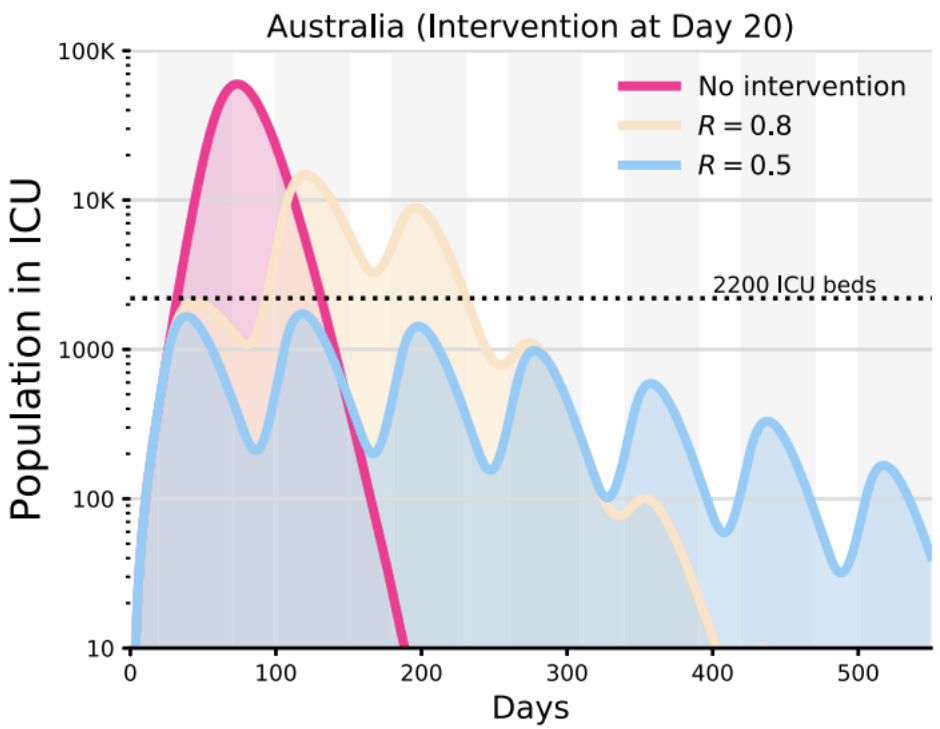

Australia (Intervention at Day 20)
100K
10K
1000
100
10
Population in ICU
No intervention
$R = 0.8$
$R = 0.5$
2200 ICU beds
0
100
200
300
400
500
Days

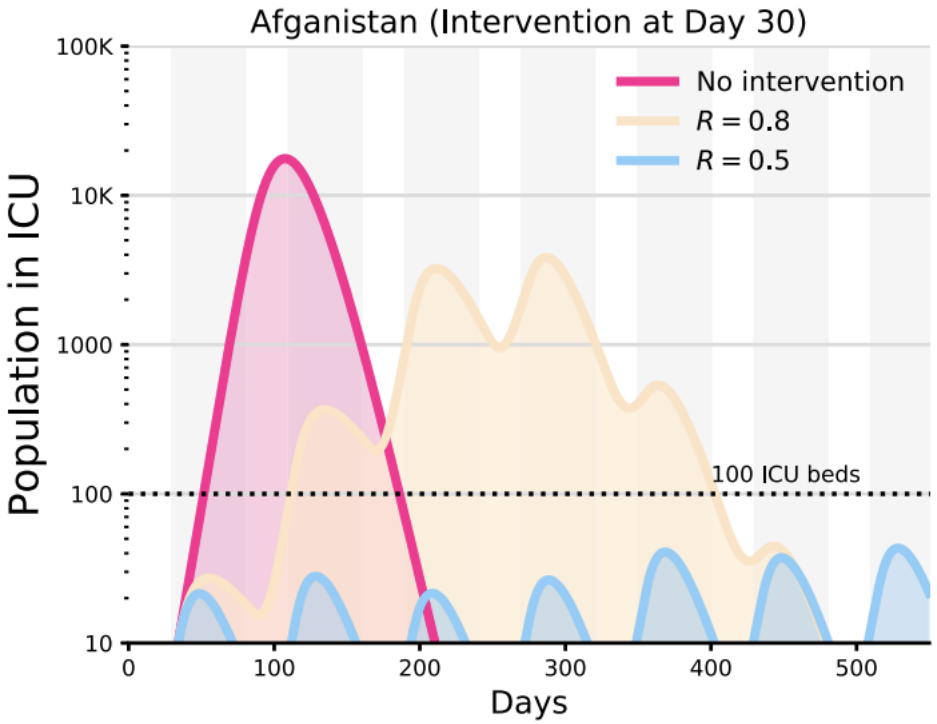
# Dynamic interventions to control COVID-19 pandemic: a multivariate prediction modelling study comparing 16 worldwide countries

European Journal of Epidemiology (2020) 35:389–399 https://doi.org/10.1007/s10654-020-00649-w

## High Income Country




## Low Income Country




Mitigation: R=0.8

Suppression: R=0.5

# Dynamic interventions to control COVID-19 pandemic: a multivariate prediction modelling study comparing 16 worldwide countries

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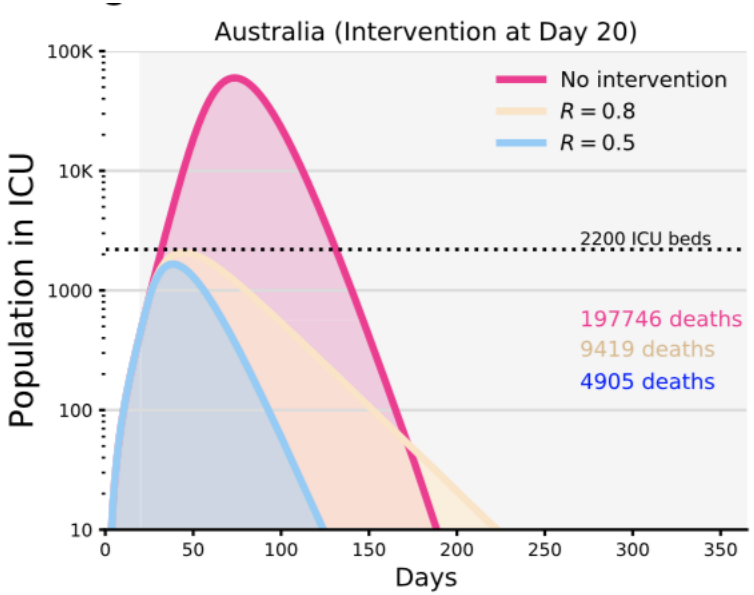


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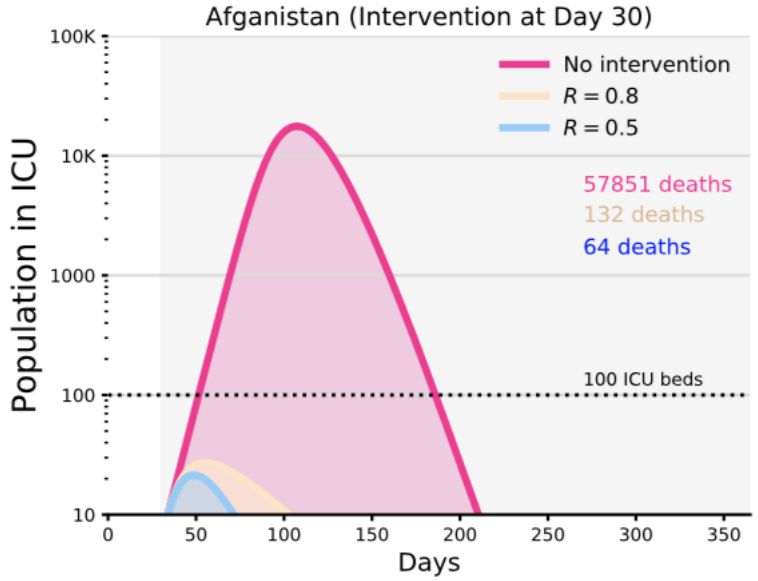


Mitigation: R=0.8

Suppression: R=0.5

# Dynamic interventions to control COVID-19 pandemic: Conclusions

- Dynamic cycles of 50-day **mitigation** followed by a 30-day relaxation reduced transmission
  - However, were unsuccessful in lowering ICU hospitalizations below manageable limits.
- Dynamic cycles of 50-day **suppression** followed by a 30-day relaxation kept the ICU demands below capacity
  - Significant number of new infections and deaths, especially in resource-poor countries, would be averted if these dynamic suppression measures were kept in place over an 18-month period.
- Intermittent reductions of *R* below 1 through combination of suppression interventions and relaxation can be an effective strategy for COVID-19 pandemic control.
  - Such a “schedule” of social distancing might be particularly relevant to low-income countries, where a single, prolonged suppression intervention is unsustainable.
- Efficient implementation of dynamic suppression interventions, therefore, confers a pragmatic option to:
  - Prevent critical care overload and deaths
  - Ggain time to develop preventive and clinical measures
  - Reduce economic hardship globally.

**Chowdhury R, Heng K, Shawon SR et al. European Journal of Epidemiology (2020) 35:389–399**
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# Treatment with Hydroxychloroquine, Azithromycin, and Combination in Patients Hospitalized with COVID-19

**Limitations**

- Retrospective, non-randomized, non-blinded study design.
- Information on duration of symptoms prior to hospitalization was not available
- Inclusion bias
  - "The combination of hydroxychloroquine + azithromycin was reserved for selected patients with severe COVID-19 and with minimal cardiac risk factors"
  - More patients in the control group were older, hypoxic and had comorbidities
  - Our results also require further confirmation in prospective, randomized controlled trials that rigorously evaluate the safety, and efficacy of hydroxychloroquine therapy for COVID-19 in hospitalized patients.

**Pros**

- Large cohort (n= 2541)
- High rate of comorbidities
  - Overall mortality 18 %
- Multivariate analysis performed using Cox regression modeling and propensity score matching to control for potential

*International Journal of Infectious Diseases*
S1201-9712(20)30534-8
https://doi.org/10.1016/j.ijid.2020.06.099

Media Advisory Saturday, June 20, 2020

# NIH halts clinical trial of hydroxychloroquine

*Study shows treatment does no harm, but provides no benefit*

## What

A clinical trial to evaluate the safety and effectiveness of hydroxychloroquine for the treatment of adults hospitalized with coronavirus disease 2019 (COVID-19) has been stopped by the National Institutes of Health. A data and safety monitoring board (DSMB) met late Friday and determined that while there was no harm, the study drug was very unlikely to be beneficial to hospitalized patients with COVID-19. After its fourth interim analysis the DSMB, which regularly monitors the trial, recommended to the National Heart, Lung, and Blood Institute (NHLBI), part of NIH, to stop the study. NHLBI halted the trial immediately.

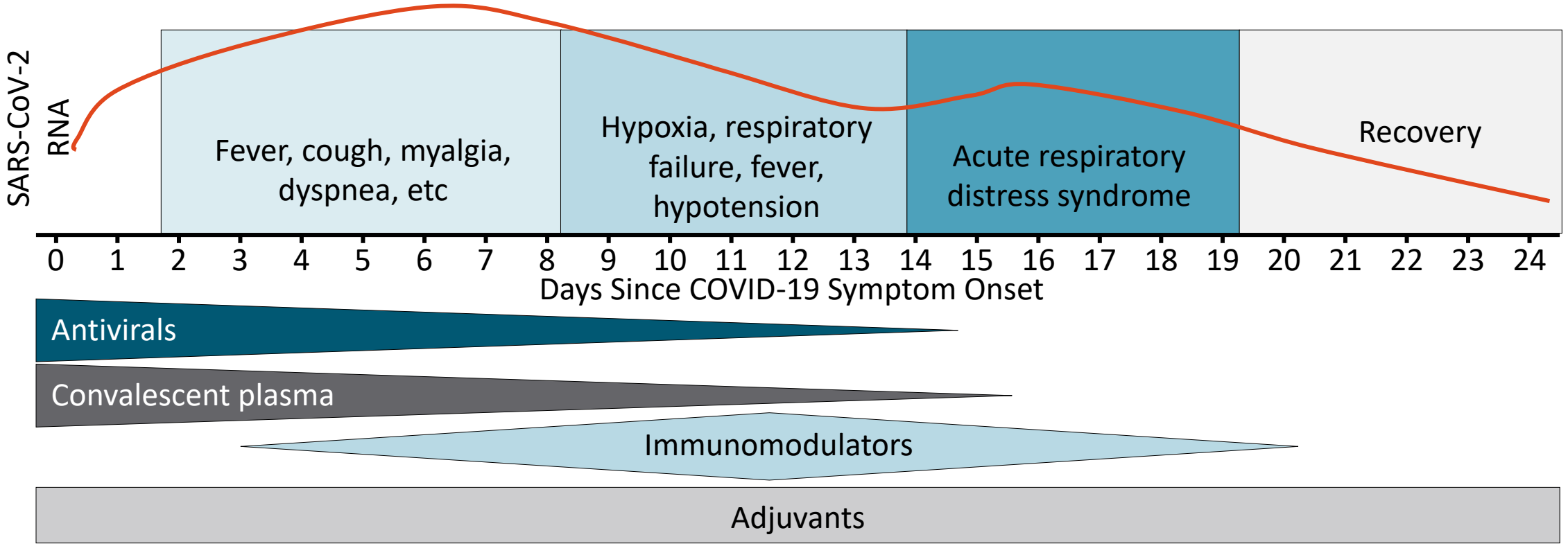
**Table 2. Outcomes of Hydroxychloroquine Therapy for Postexposure Prophylaxis against Covid-19.***

| Outcome | Hydroxychloroquine (N=414) | Placebo (N=407) | P Value |
|---|---|---|---|
| | *number (percent)* | | |
| Confirmed or probable Covid-19 | 49 (11.8) | 58 (14.3) | 0.35 |
| Laboratory-confirmed diagnosis | 11 (2.7) | 9 (2.2) | 0.82 |
| Symptoms compatible with Covid-19 | 48 (11.6) | 55 (13.5) | 0.46 |
| All new symptoms | 57 (13.8) | 59 (14.5) | 0.84 |
| Any hospitalization | 1 (0.2) | 1 (0.2) | 0.99 |
| Death | 0 | 0 | — |

* Symptoms were adjudicated by four infectious disease physicians, who were unaware of the trial-group assignments, in accordance with U.S. Council of State and Territorial Epidemiologists case definition of probable Covid-19 after an epidemiologic link with a close contact.[15] (Descriptions of the symptom complex are provided in the Supplementary Appendix.) The median number of new symptoms reported in the hydroxychloroquine group was 4 (interquartile range, 2 to 6), as compared with 3 (interquartile range, 2 to 5) in the placebo group.

# Effectiveness of Hydroxychloroquine for SARS-COV-2

# Timing of Treatment in Relation to Onset of Symptoms




Optimal timing of therapeutic use unknown; proposed schematic based on medication type, potential for direct antiviral effect, mitigation of cytokine storm, or nonspecific adjuvant effect

JHMI Clinical Recommendations for Available Pharmacologic Therapies for COVID-19. Last updated May 19, 2020.

Slide credit: clinicaloptions.com

# IDSA Recommendations on Treatment and Management of Patients With COVID-19

- Overarching goal: recruit patients into ongoing trials to provide needed evidence regarding efficacy and safety of potential therapies

| Treatment of Patients Admitted to the Hospital With COVID-19 | |
|---|---|
| Recommended for hospitalized patients with severe disease* | ▪ Remdesivir†<br>▪ Glucocorticoids |
| Recommended in the context of a clinical trial | ▪ (Hydroxy)chloroquine<br>▪ Convalescent plasma |
| Recommended only‡ in the context of a clinical trial | ▪ (Hydroxy)chloroquine + azithromycin<br>▪ Lopinavir/ritonavir<br>▪ Tocilizumab |
| Suggests against outside the context of a clinical trial | ▪ Famotidine |

Note: Among patients admitted to the hospital, corticosteroids recommended in the context of a clinical trial for ARDS due to COVID-19 but suggested against for COVID-19 pneumonia.

*Severe illness defined as SpO2 ≤ 94% on room air, and those who require supplemental oxygen, mechanical ventilation or ECMO. †For patients on supplemental oxygen but not on mechanical ventilation or ECMO, the panel suggests 5 days of remdesivir (vs 10 days). ‡Addition of "only" indicates increased uncertainty and/or potential for harm.

IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 2.0.0.

Slide credit: clinicaloptions.com

# NIH Guidelines: Investigational COVID-19 Treatments

## Antivirals

| Guidance | Treatment |
|---|---|
| Recommends for hospitalized patients with severe* COVID-19 | ▪ Remdesivir |
| Insufficient data to recommend for or against for patients with mild to moderate COVID-19 | ▪ Remdesivir |
| Recommends against | ▪ High-dose chloroquine (600 mg BID for 10 days) |
| Recommends against except in context of clinical trials | ▪ (Hydroxy)chloroquine<br>▪ Hydroxychloroquine + azithromycin<br>▪ Lopinavir/ritonavir or other HIV protease inhibitors |

## Immune-Based Therapies

| Guidance | Treatment |
|---|---|
| Recommended in patients with COVID-19 who require supplemental oxygen or who are mechanically ventilated | ▪ Dexamethasone |
| Insufficient data to recommend for or against | ▪ Convalescent plasma<br>▪ SARS-CoV-2 immune globulins<br>▪ IL-1 inhibitors<br>▪ IL-6 inhibitors |
| Recommends against except in the context of clinical trials | ▪ Non-SARS-CoV-2–specific IVIG<br>▪ Immunomodulators (eg, IFNs or JAK inhibitors) |

*Severe defined as $SpO_2 \leq 94\%$ on ambient air at sea level, requiring supplemental oxygen, mechanical ventilation, or ECMO.

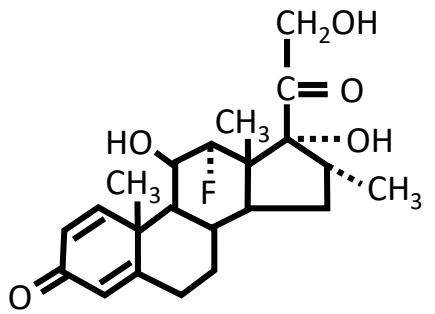
NIH COVID-19 Treatment Guidelines. Last updated June 25, 2020.

Slide credit: clinicaloptions.com

# Dexamethasone

- Dexamethasone is a corticosteroid with anti-inflammatory effects that has been used to treat allergies, asthma, dermatitis, rheumatic disorders, MS, other autoimmune disorders, etc
- Can be administered IV or orally
- Contraindicated by FDA in patients with systemic fungal infections
- Pregnancy category C

- **Warnings:** can cause elevation in blood pressure, left ventricular free wall rupture in patients with recent MI, adrenocortical insufficiency, increased susceptibility to infection, and cataracts/glaucoma with possible damage to the optic nerve




Dexamethasone PI. Dexamethasone sodium phosphate PI.

Slide credit: clinicaloptions.com

# Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial Among Hospitalised Patients

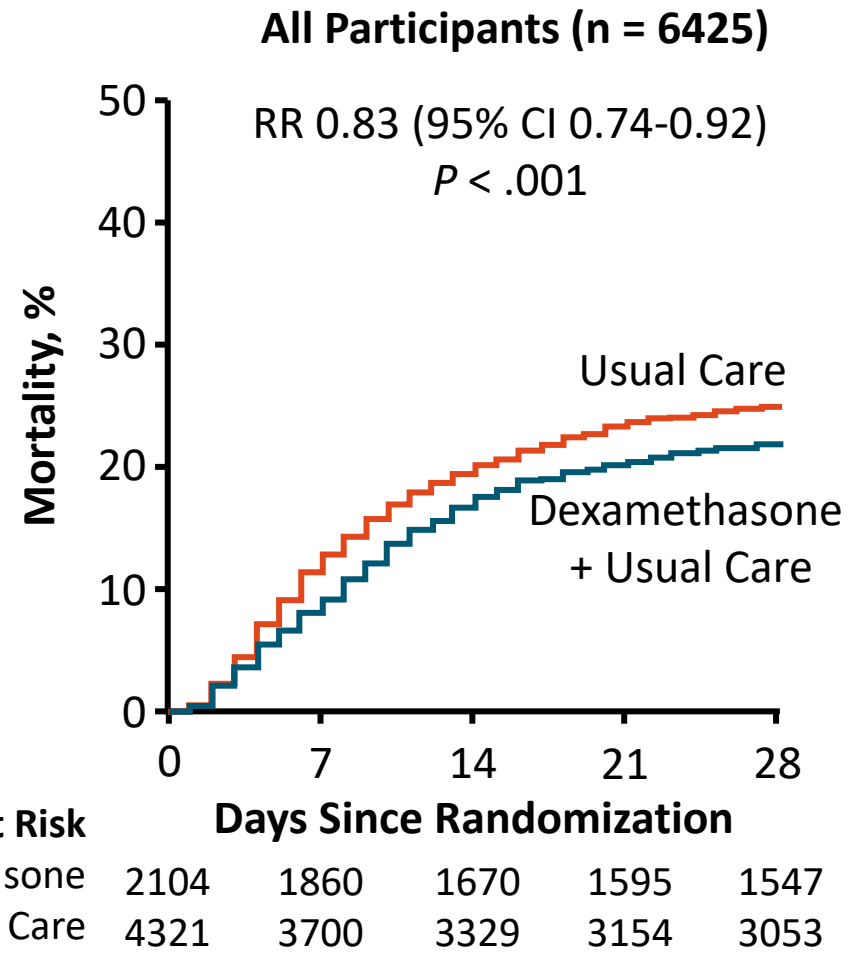
- Hospitalized patients with clinically suspected or laboratory confirmed SARS-CoV-2
  - Initial recruitment was in patients ≥ 18 yrs of age but age limit was removed on 5/9/2020
- Patients randomized to usual care plus: no additional treatment, **lopinavir/ritonavir, dexamethasone, hydroxychloroquine (HCQ), or azithromycin**
  - Factorial design with simultaneous allocation to no additional tx vs **convalescent plasma**
  - If progressive disease (hyper-inflammatory state), subsequent randomization to no additional treatment vs **tocilizumab**
- > 11,500 patients enrolled from > 175 NHS hospitals in UK

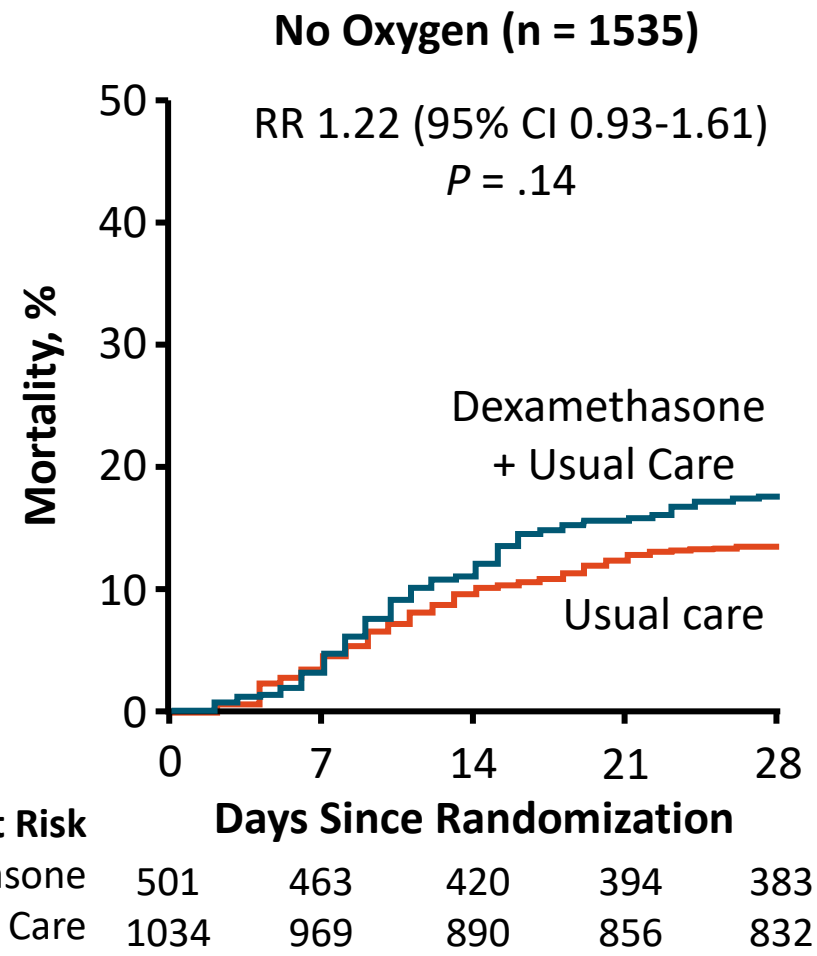
**6/8/2020:** recruitment to dexamethasone arm halted because sufficient patient numbers enrolled to establish potential benefit

https://www.recoverytrial.net. https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf. https://www.recoverytrial.net/files/recovery_dexamethasone_statement_160620_final.pdf. Horby. medRxiv. 2020;[Preprint].
Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

# RECOVERY Trial: Mortality With Dexamethasone + Usual Care vs Usual Care Alone

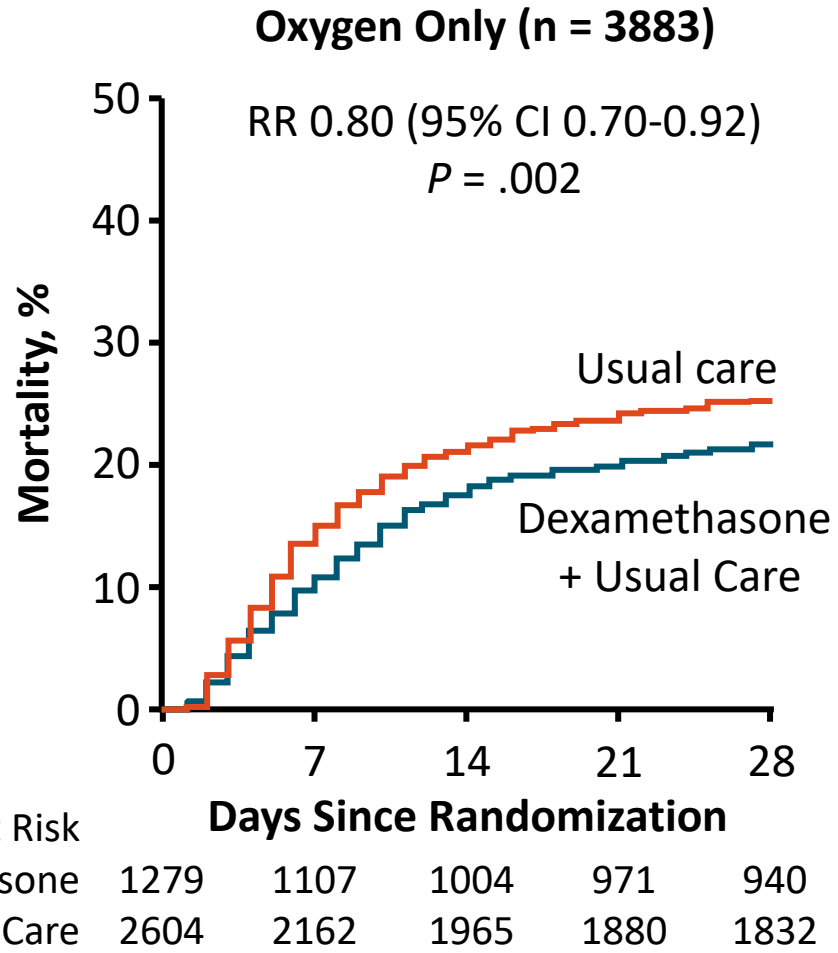


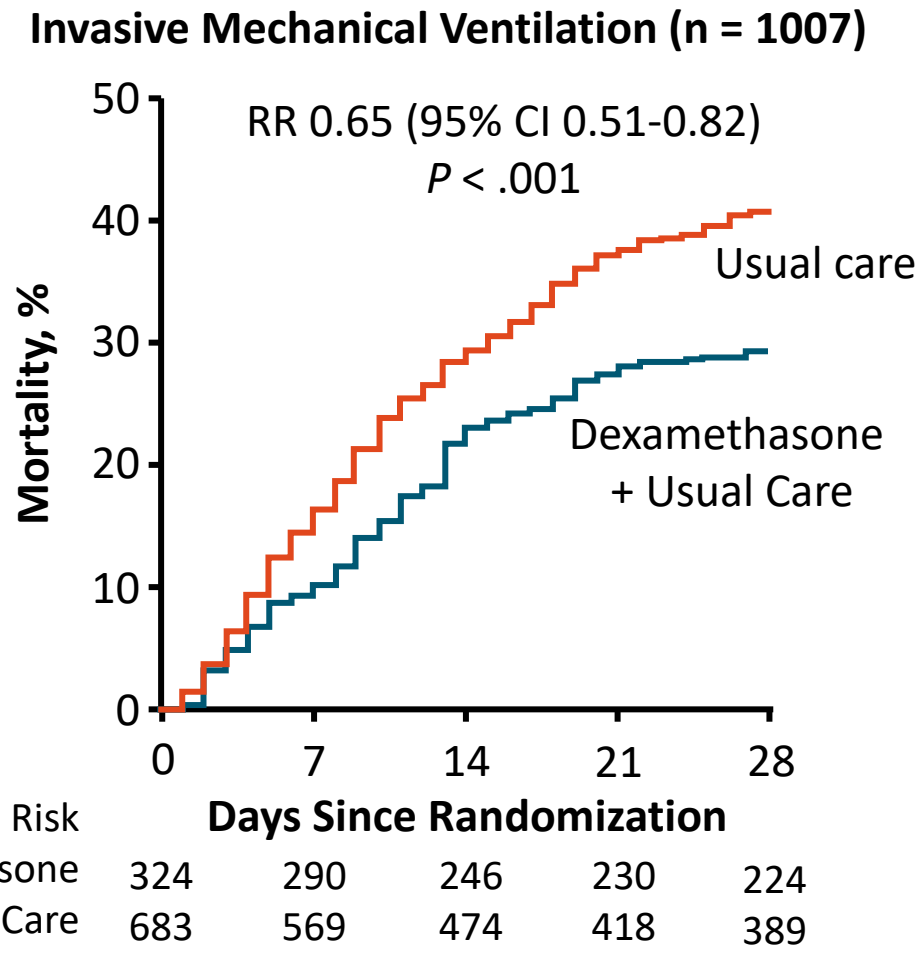

Horby. medRxiv. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

# RECOVERY Trial: Mortality in Patients On Oxygen or Mechanical Ventilation ± Dexamethasone




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Dexamethasone | 1279 | 1107 | 1004 | 971 | 940 |
| Usual Care | 2604 | 2162 | 1965 | 1880 | 1832 |




| No. at Risk | | | | | |
|---|---|---|---|---|---|
| Dexamethasone | 324 | 290 | 246 | 230 | 224 |
| Usual Care | 683 | 569 | 474 | 418 | 389 |

Horby. medRxiv. 2020;[Preprint]. Note: This study has not been peer reviewed.

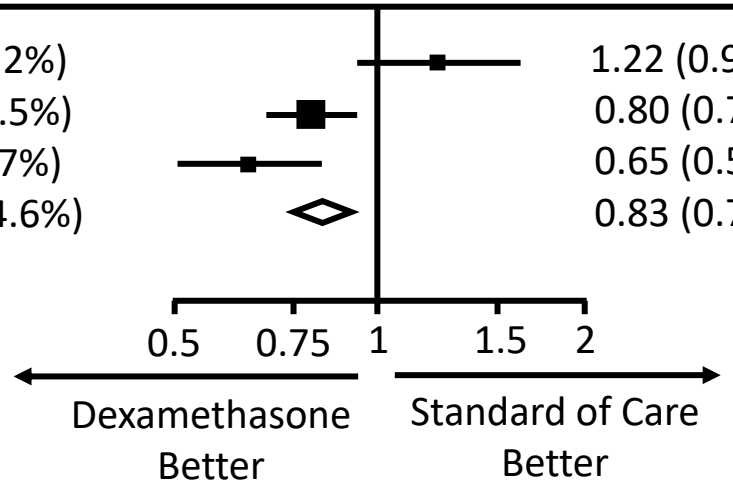
Slide credit: clinicaloptions.com

# RECOVERY Trial: Preliminary Primary Outcome Results With Dexamethasone

- Patients who received dexamethasone plus usual care (n = 2104) vs patients who usual care alone (n = 4321)
- Data suggest 1 death prevented by treatment of ~ 8 ventilated patients or ~ 25 patients requiring oxygen alone

| Respiratory Support at Randomization | Dexamethasone + Usual Care | Usual Care | 28-Day Mortality RR (95%CI) | *P* Value |
|---|---|---|---|---|
| No oxygen received | 85/501 (17.0%) | 137/1034 (13.2%) | 1.22 (0.93-1.61) | .14 |
| Oxygen only | 275/1279 (21.5%) | 650/2604 (21.5%) | 0.80 (0.70-0.92) | .002 |
| Invasive mechanical ventilation | 94/324 (29.0%) | 278/683 (40.7%) | 0.65 (0.51-0.82) | < .001 |
| All participants | 454/2104 (21.6%) | 1065/4321 (24.6%) | 0.83 (0.74-0.92) | < .001 |

Trend across three categories: $\chi^2_1$=11.49; *P* < .001




Horby. medRxiv. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

# RECOVERY Trial: Secondary Outcomes

| Outcome, n/N (%) | Dexamethasone + Usual Care | Usual Care Only | RR* (95% CI) | *P* Value |
|---|---|---|---|---|
| Discharged from hospital within 28 days | 1360/2104 (64.6) | 2639/4321 (61.1) | 1.11 (1.04-1.19) | .002 |
| Receipt of invasive mechanical ventilation or death† | 425/1780 (23.9) | 939/3638 (25.8) | 0.91 (0.82-1.00) | .049 |
| ▪ Invasive mechanical ventilation | 92/1780 (5.2) | 258/3638 (7.1) | 0.76 (0.61-0.96) | .021 |
| ▪ Death | 360/1780 (20.2) | 787/3638 (21.6) | 0.91 (0.82-1.01) | .07 |

*RR = rate ratio for outcomes of 28-day mortality and hospital discharge and risk ratio for outcome of receipt of invasive mechanical ventilation or death. RR estimates and 95% CI adjusted for age. †Analyses exclude those on invasive mechanical ventilation at the time of randomization.

Horby. medRxiv. 2020;[Preprint]. Note: This study has not been peer reviewed.

Slide credit: clinicaloptions.com

# NIH and IDSA COVID-19 Guidelines Updated to Include Dexamethasone for Severe Disease

New Slide

## NIH*

- The Panel recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (BI)
- The Panel recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI)

## IDSA

- For hospitalized patients with severe† COVID-19, the panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)
  - Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg
- For hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

*Recommendation rating: A = Strong; B = Moderate; C = Optional. Evidence rating: I = ≥ 1 randomized trials with clinical outcomes and/or validated lab endpoints; II = ≥ 1 well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion. †Severe illness is defined as patients with $SpO_2$ ≤ 94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

NIH COVID-19 Treatment Guidelines. Last updated June 25, 2020. IDSA COVID-19 Treatment Guidelines. Last updated June 25, 2020.

Slide credit: clinicaloptions.com

# Key Therapeutic Classes Under Investigation for Treatment of COVID-19

## Antivirals

Baloxivir
Convalescent plasma
Favipiravir
(Hydroxy)chloroquine
Interferon
Lopinavir/ritonavir
Nitazoxanide
Oseltamivir
Remdesivir
Ribavirin

## Immunomodulators

Corticosteroids
IL-1 inhibitors (eg, anakinra)
IL-6 inhibitors (eg, tocilizumab)
Intravenous immunoglobulin
JAK inhibitors (eg, baricitinib)

*"Appropriate management strategies for patients with COVID-19 are a rapidly evolving therapeutic challenge, and the optimal agents (if any) to treat infection or prevent progression to critical illness remain ill-defined."*

Barlow. Pharmacotherapy. 2020;40:416. McCreary. Open Forum Infect Dis. 2020;7:ofaa105. Sanders. JAMA. 2020;323:1824.