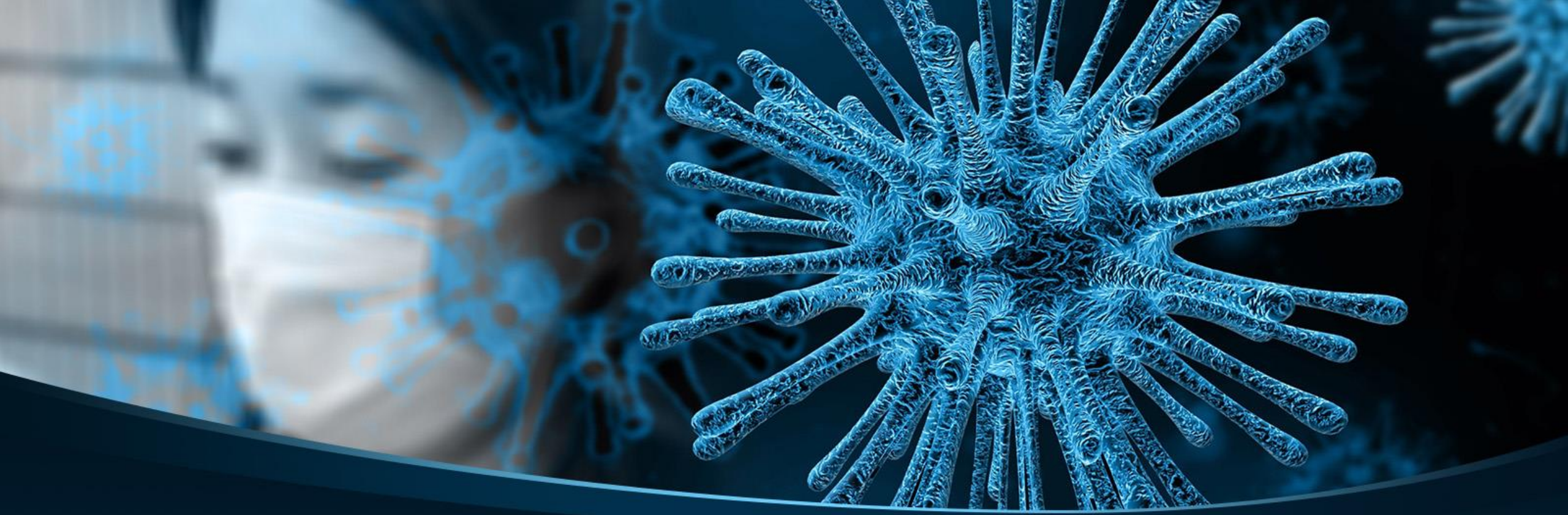
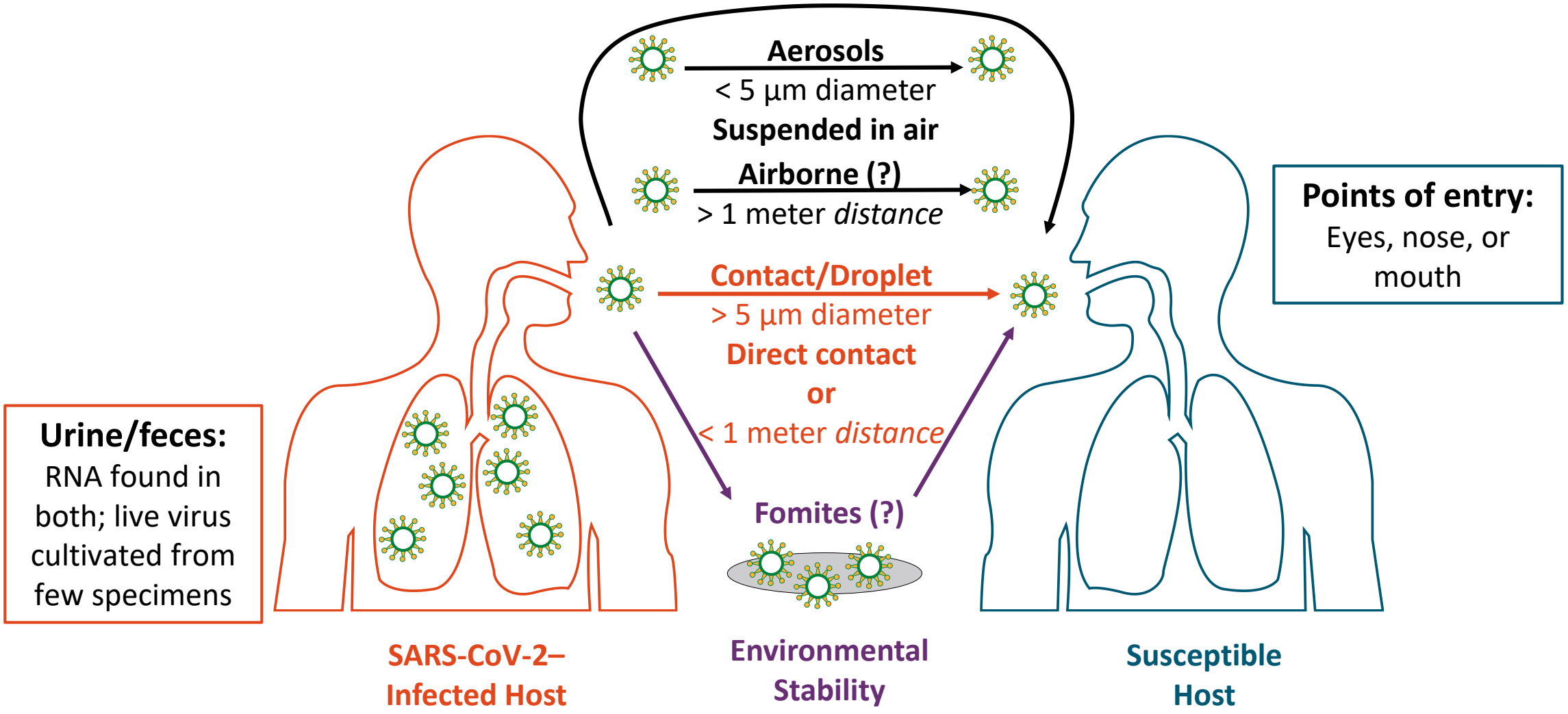


Coronavirus Disease 2019 (COVID-19) Treatment Guidelines

COVID-19 Treatment Guidelines

M.Moghadami MD. Infectious disease subspecialty

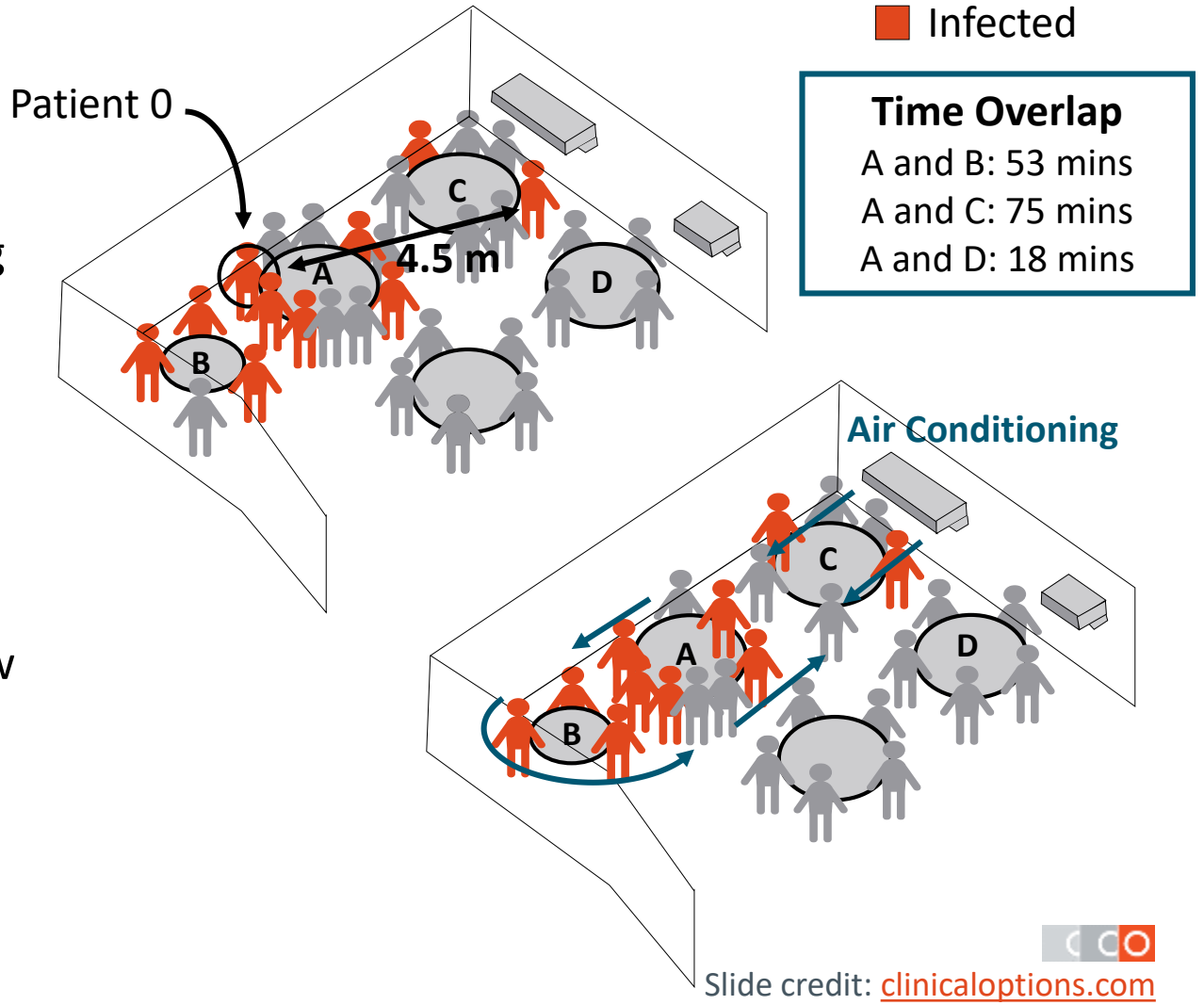
Proposed Routes of SARS-CoV-2 Transmission



Galbadage. Front Public Health. 2020;8:163. WHO. Scientific Brief. July 9, 2020.

SARS-CoV-2 Transmission: Recirculated Air and Poor Ventilation

- 3 families (A, B, and C) ate lunch at a restaurant on January 24, 2020 at 3 neighboring tables
  - 10 of those sitting at these tables (including the index case) were later found to have been infected with sARS-CoV-2 at the restaurant
  - None of the waiters or 68 patrons at the remaining 15 tables became infected
  - Authors note that these results do not show that long-range aerosol transmission can occur in *any* indoor space, but that transmission may occur in crowded/poorly ventilated spaces



Li. medRxiv;[Preprint]. Note: this study has not been peer reviewed.

Slide credit: clinicaloptions.com

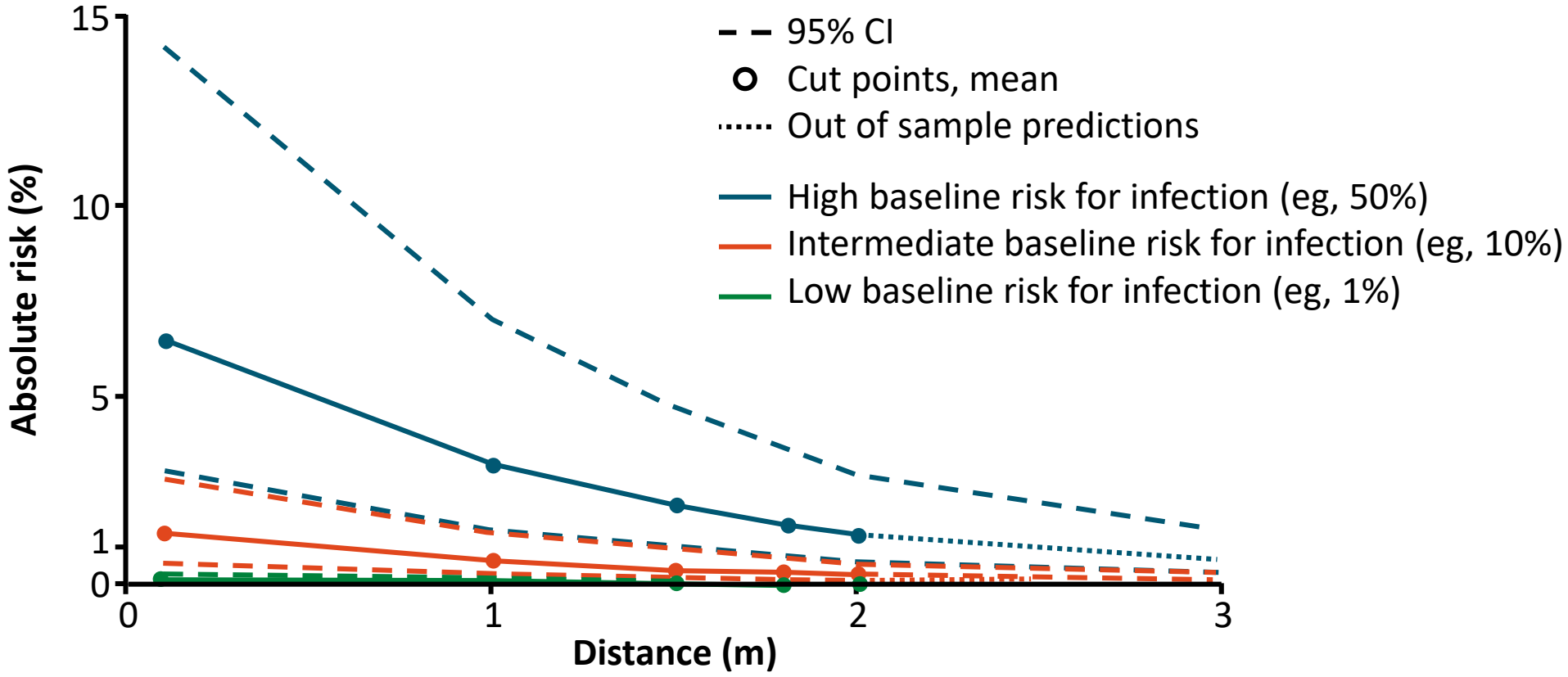
SARS-CoV-2 Transmission in Enclosed vs Outdoor Settings

- Study in Japan traced contacts of 110 people with COVID-19 in ten indoor clusters and assessed the environment in which transmission between contacts occurred[1]
  - 27 primary cases generated secondary cases (24.6%)
- Odds that a primary case transmitted SARS-CoV-2 in an enclosed environment **18.7 x higher** compared with odds of estimated transmission rates in an open-air environment (95% CI: 6.0-57.9)[1]
- **6 of 7 superspreading events** (to 3 or more people) occurred in enclosed environments (OR vs open-air environments: 32.6; 95% CI: 3.7-289.5)[1]
- Consistent with cluster in Germany from indoor work meeting, cluster from a ski chalet France, cluster from choir practice in the US, and church- and hospital-associated clusters in South Korea[2-5]

1. Nishiura. medRxiv;[Preprint]. Note: this study has not been peer reviewed. 2. Hijnen. Emerg Infect Dis. 2020;26:1935.
3. Danis. Clin Infect Dis. 2020;71:825. 4. Hamner. MMWR. 2020;69:606. 5. Shim. Int J Infect Dis. 2020;93:339.

Physical Distance and Transmission

- Systematic review and meta-analysis of data from 172 studies investigating the spread of SARS-CoV-2, SARS, and MERS (n = 10,736)



Chu. Lancet. 2020;395:1973.

Efficacy of Face Coverings in Prevention of SARS-CoV-2 Transmission

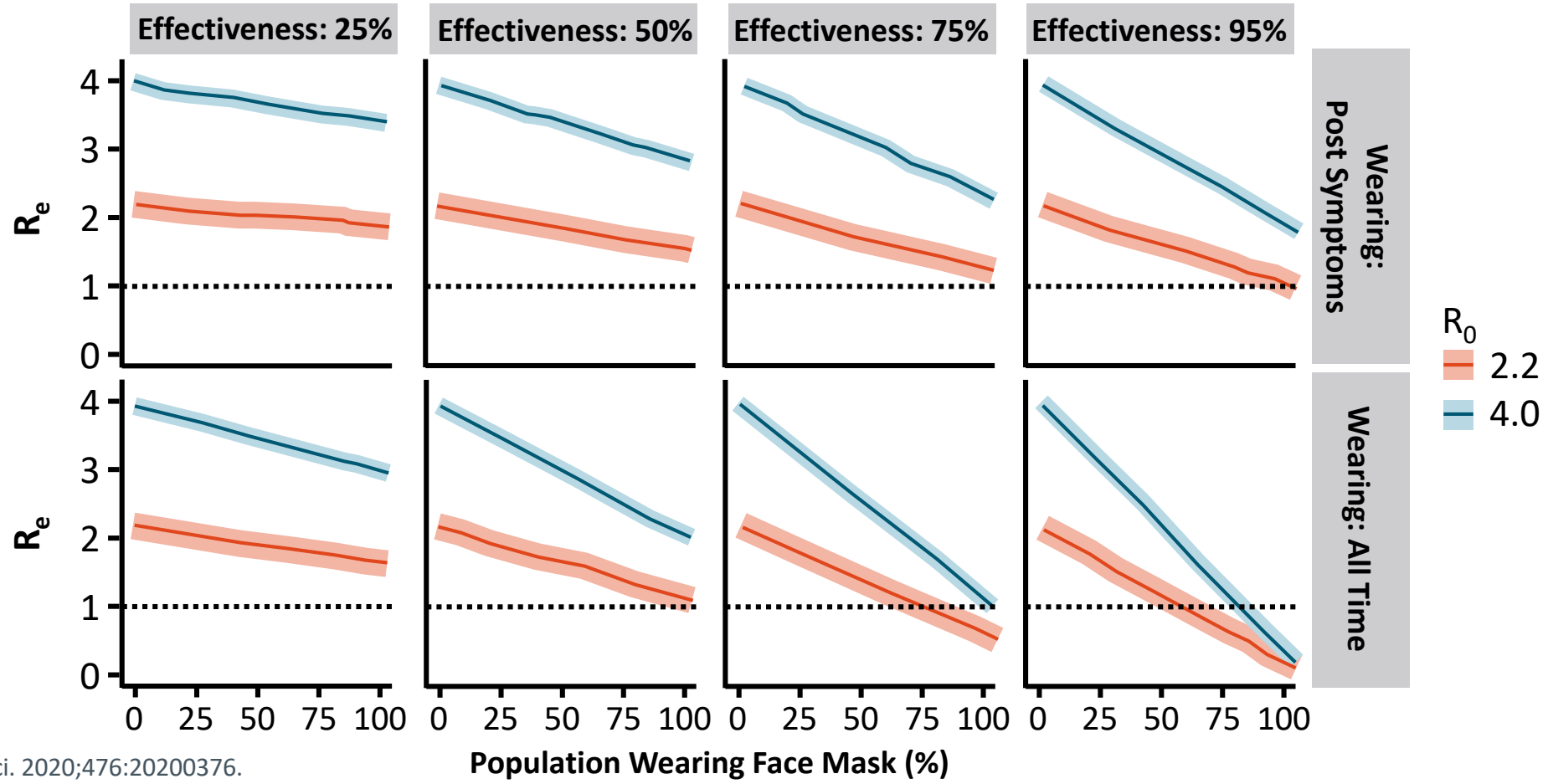
- Systematic review and meta-analysis of data from 172 studies investigating the spread of SARS-CoV-2, SARS, and MERS (n = 2647)[1]
  - Face mask use (surgical, N95, or cotton mask) resulted **in large reduction in infection (OR: 0.15; 95% CI: 0.07-0.34)**
  - Association was stronger for N95 or respirators vs disposable or 12-16 layer cotton masks ($P_{interaction}$ = .090)
- Study of human coronaviruses in exhaled breath of children and adults with acute respiratory illnesses wearing surgical face masks vs no mask (N = 246)[2]
  - Virus detected in **respiratory droplets** in 3 of 10 samples collected without face masks vs **0 of 11 samples with a mask (*P* = .07)**
  - Virus detected in **aerosols** in 4 of 10 samples collected without face masks vs **0 of 11 samples with a mask (*P* = .02)**

1. Chu. Lancet. 2020;395:1973. 2. Leung. Nat Med. 2020;26:676.

Predicted Efficacy of Face Masks on SARS-CoV-2 Transmission Dynamics

Updated

- Simulations with branching process model to investigate the reduction in transmission by wearing face masks on the R_e (expected number of new cases caused by a single infectious person at any given point)



Stutt. Proc Math Phys Eng Sci. 2020;476:20200376.

Fatality

- probability of fatal disease is highest in people aged ≥65 years and those living in a nursing home or long-term care facility.
- Hypertension
- Cardiovascular disease
- Diabetes
- Chronic respiratory disease
- Cancer
- Renal disease
- Obesity

WHO: Suspect Case Definition

Acute onset of fever and cough OR ≥ 3 of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status

And 1 of the following within 14 days of symptom onset:

- Residing or working in an area with high risk of transmission*
- Residing or travel to an area with community transmission
- Working in a healthcare setting

OR:

Patient with severe acute respiratory illness (acute respiratory infection with history of fever or measured fever ≥ 38°C and a cough; onset within last 20 days; requires hospitalization)

*Closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons.

WHO COVID-19 Case Definition. Updated August 7, 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1

WHO: Probable Case Definition

Acute onset of fever and cough OR ≥ 3 of the following: fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhea, altered mental status

AND:

Contact of probable or confirmed case or epidemiologically linked to a cluster with at least 1 confirmed case

OR:

Suspect case with chest imaging showing findings suggestive of COVID-19 disease*

OR:

Recent onset of loss of smell or taste in the absence of any other identified cause

OR:

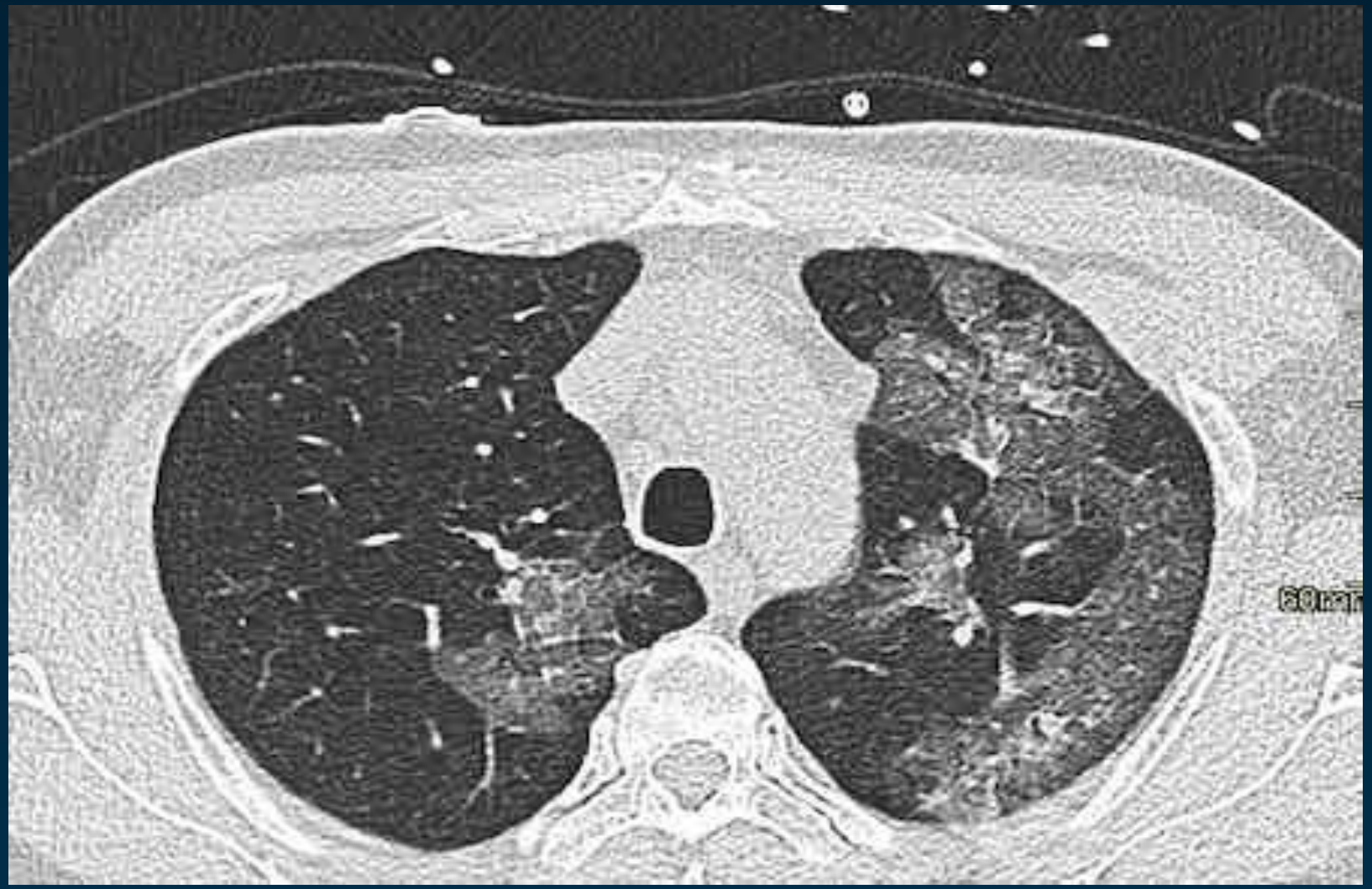
Unexplained death in an adult with respiratory distress who was a contact of a probable or confirmed case or epidemiologically linked to a cluster with at least 1 confirmed case

*Hazy opacities with peripheral and lower lung distribution on chest radiography; multiple bilateral ground glass opacities with peripheral and lower lung distribution on chest CT; or thickened pleural lines, B lines, or consolidative patterns on lung ultrasound.

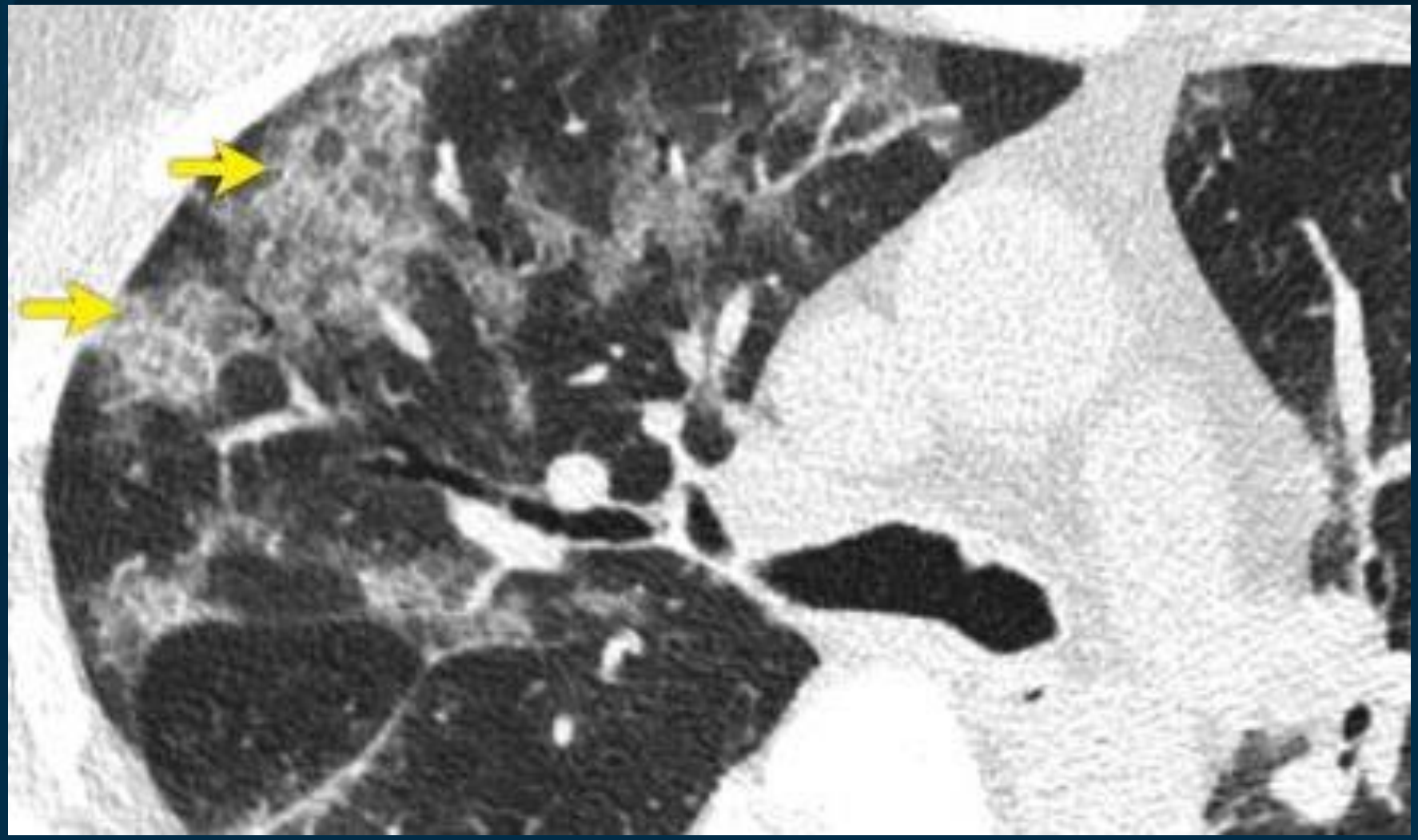
WHO COVID-19 Case Definition. Updated August 7, 2020. https://www.who.int/publications/i/item/WHO-2019-nCoV-Surveillance_Case_Definition-2020.1

CT FINDING

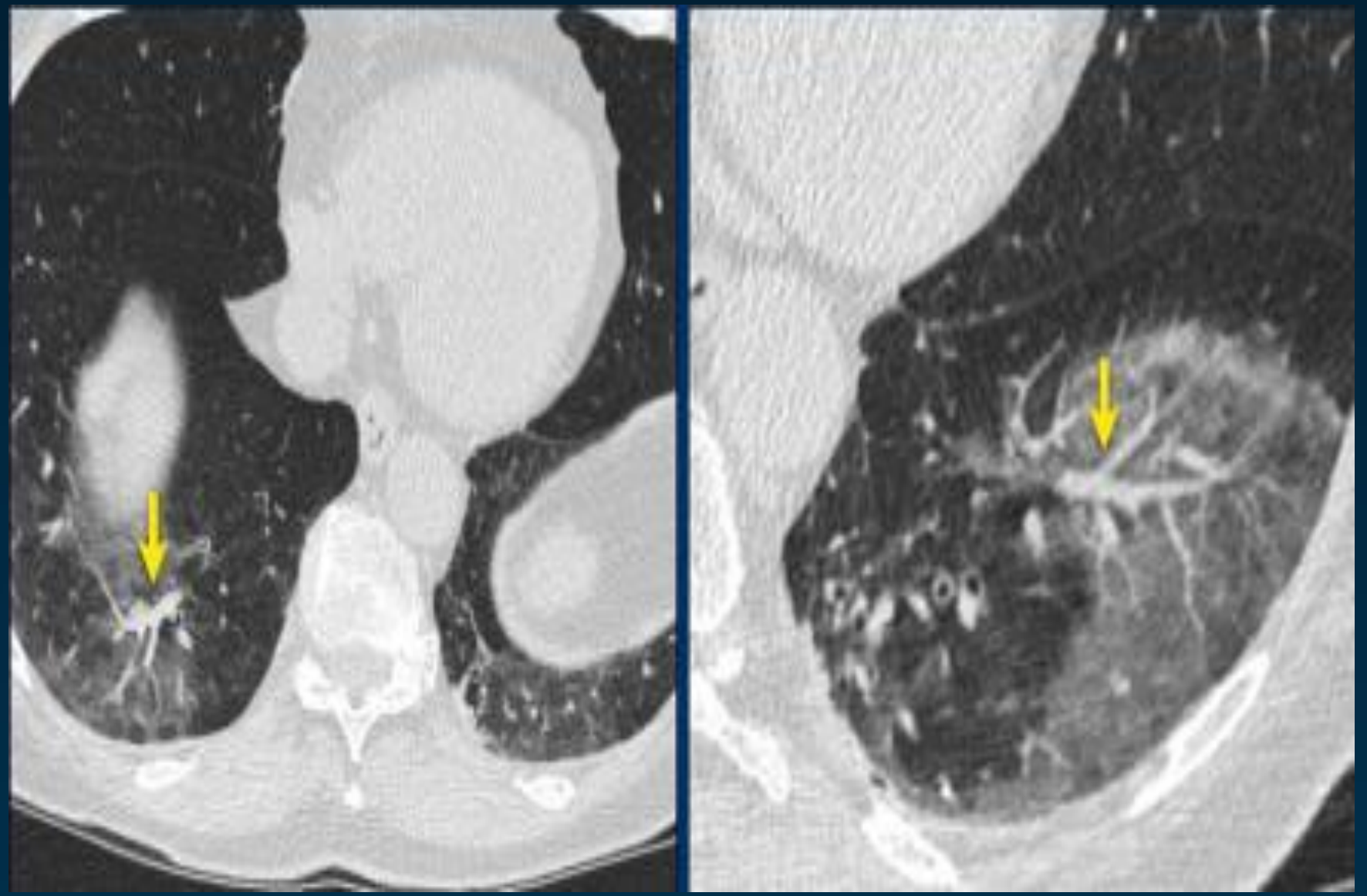
Ground glass



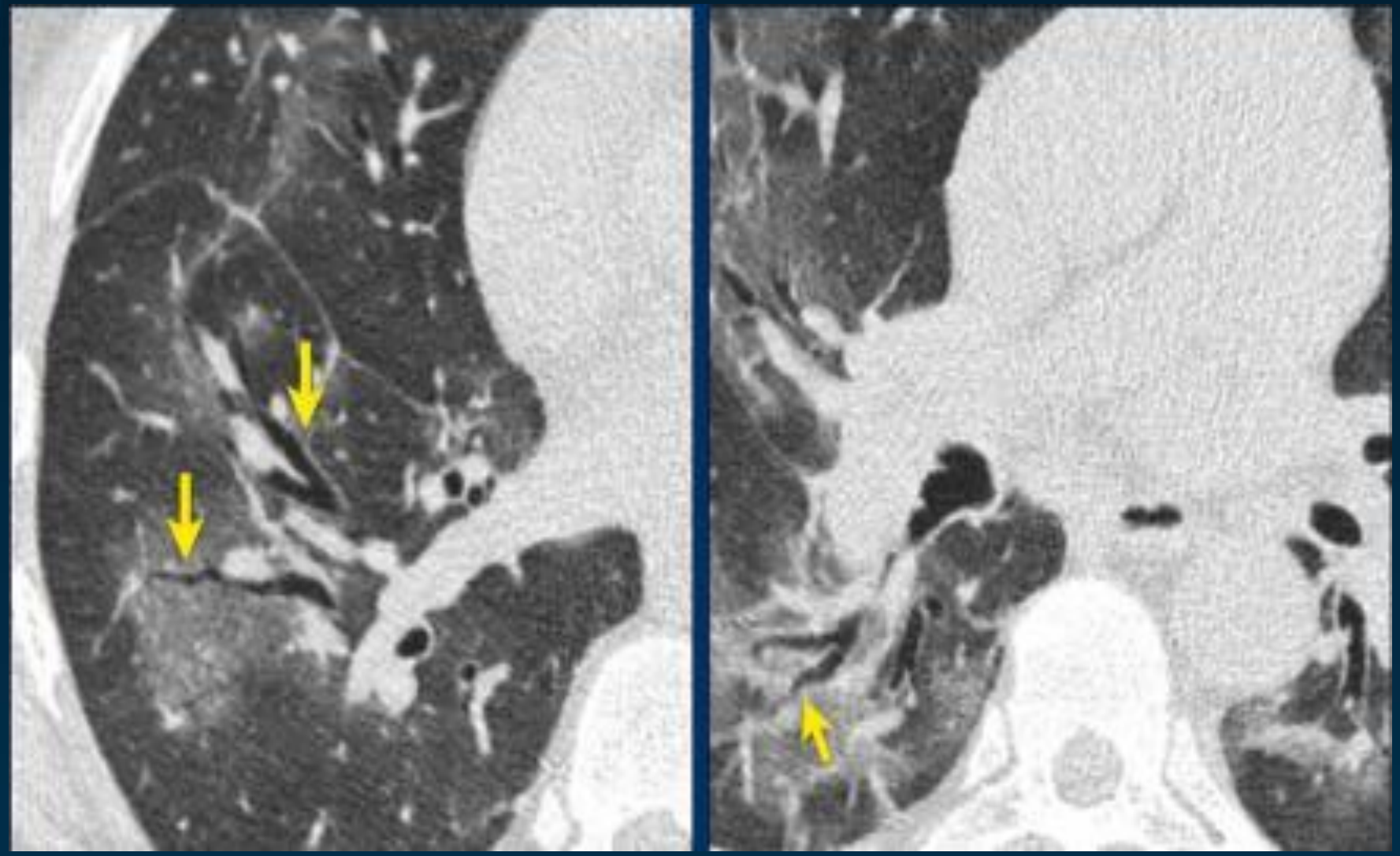
Crazy paving



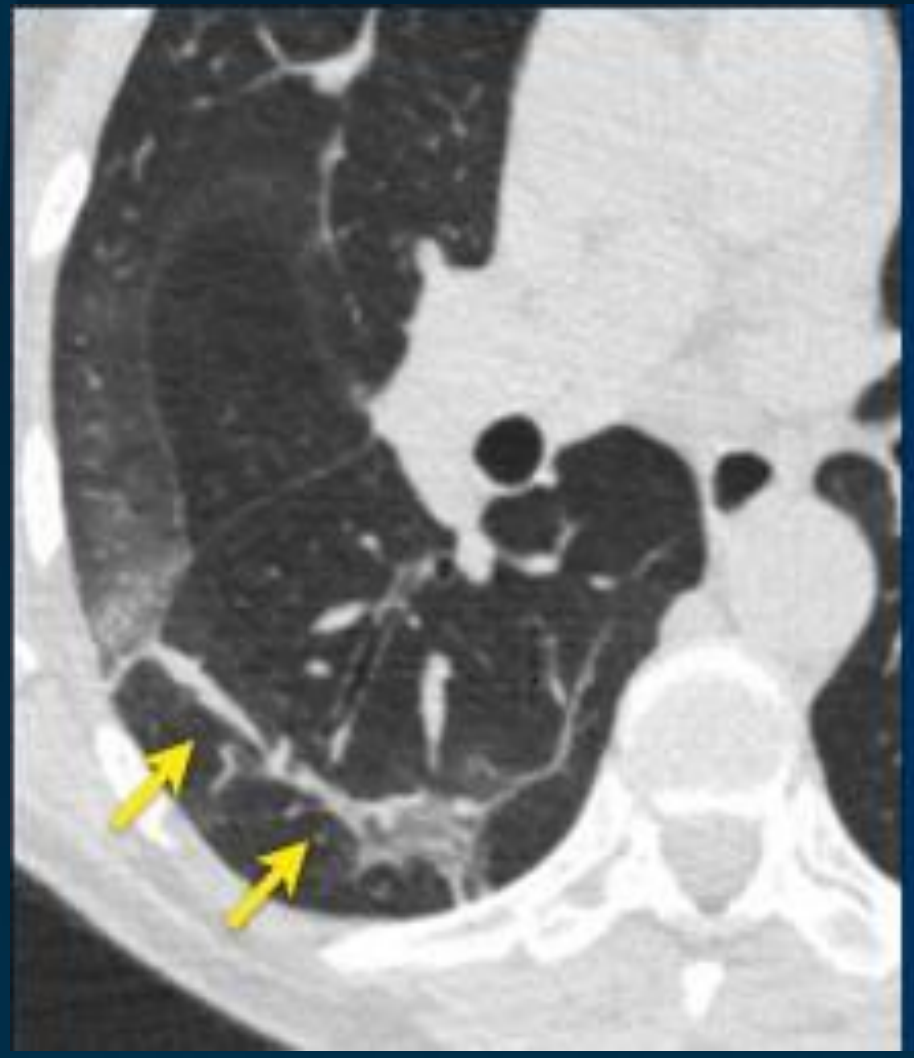
Vascular dilatation

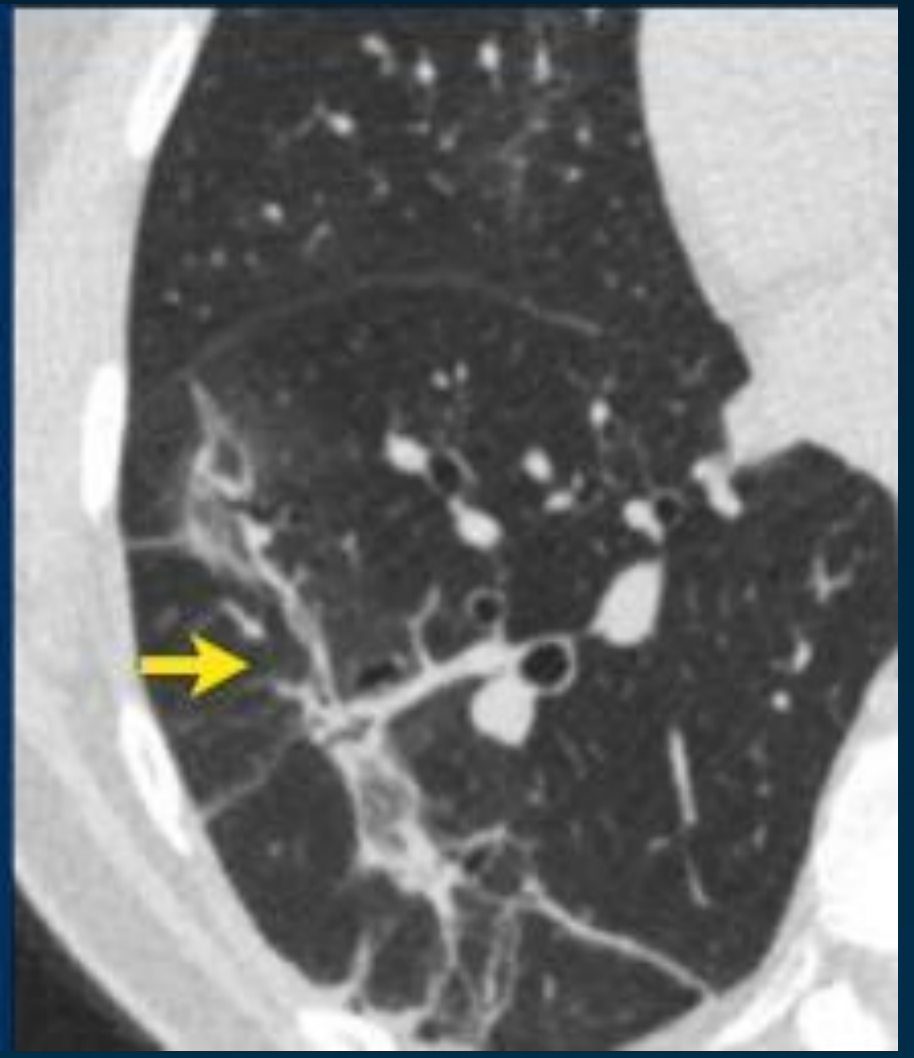


Traction Bronchiectasis



Subpleural bands and Architectural distortion





CT-changes over time

Early stage	0-4 days	GGO, partial crazy paving, lower number of involved lobes
Progressive stage	5-8 days	Progressive (5-8 days): Extension of GGO, increased crazy paving pattern
Peak stage	10-13 days	Consolidation
Absorption stage	≥14 days	Gradual resolution

Diagnosis of SARS-CoV-2 Infection

would be conducted for

- all patients with a syndrome consistent with COVID-19
- people with known high-risk exposures
- people likely to be at repeated risk of exposure, such as health care workers and first responders

Pre- and post Exposure Prophylaxis

- **At present, no agent given before an exposure (i.e., as PrEP) and after an exposure (i.e., as PEP) is known to be effective in preventing SARS-CoV-2 infection**

Management of Persons with COVID-19

Classification of presentation

- *Asymptomatic or Presymptomatic Infection:* Individuals who test positive for SARS-CoV-2 but have no symptoms
- *Mild Illness:* Individuals who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain) without shortness of breath, dyspnea, or abnormal imaging

- *Moderate Illness:* Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) >93% on room air at sea level
- *Severe Illness:* Individuals who have respiratory frequency >30 breaths per minute, SpO2 ≤93% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300, or lung infiltrates >50%
- *Critical Illness:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

Asymptomatic or Presymptomatic Infection

- Persons who test positive for SARS-CoV-2 and who are asymptomatic should self-isolate.
- **no additional laboratory testing and no specific treatment.**
- If they remain asymptomatic, they can discontinue isolation 7 days after the date of their first positive SARS-CoV-2 test.

Mild Illness

- **There are insufficient data to recommend either for or against any antiviral or immunomodulatory therapy in patients COVID-19 with mild illness.**

- managed in an ambulatory setting
- For people who are at high risk for complications to have a pulse oximeter to self-monitor the oxygen saturation

Moderate Illness

- evidence of lower respiratory disease by clinical assessment or imaging with SpO2 >93% on room air at sea level.

- Given that pulmonary disease can rapidly progress in patients with COVID-19, patients with moderate COVID-19 should be admitted to a health care facility for close observation.

Population

This recommendation applies only to people with these characteristics:

Patients with confirmed covid-19

Disease severity

Non-severe	Severe	Critical
Absence of signs of severe or critical disease	Oxygen saturation <90% on room air	Requires life sustaining treatment
	Signs of pneumonia	Acute respiratory distress syndrome
	Signs of severe respiratory distress	Sepsis
		Septic shock

Interventions

Casirivimab and imdevimab

Neutralising monoclonal antibodies

Non-severe	Severe	Critical
Recommendation in favour (conditional)	Recommendation in favour (conditional)	
For those with highest risk of hospitalisation	For those with seronegative status	
	Assessed by accurate and rapid testing	

Laboratory testing

- complete blood count (CBC) with differential metabolic profile, including liver and renal function tests.
- inflammatory markers such as C-reactive protein (CRP), D-dimer, and ferritin, while not part of standard care, may have prognostic value

- **There are insufficient data for the Panel to recommend either for or against any antiviral or immunomodulatory therapy in patients with COVID-19 with moderate illness (AIII).**

Severe Illness

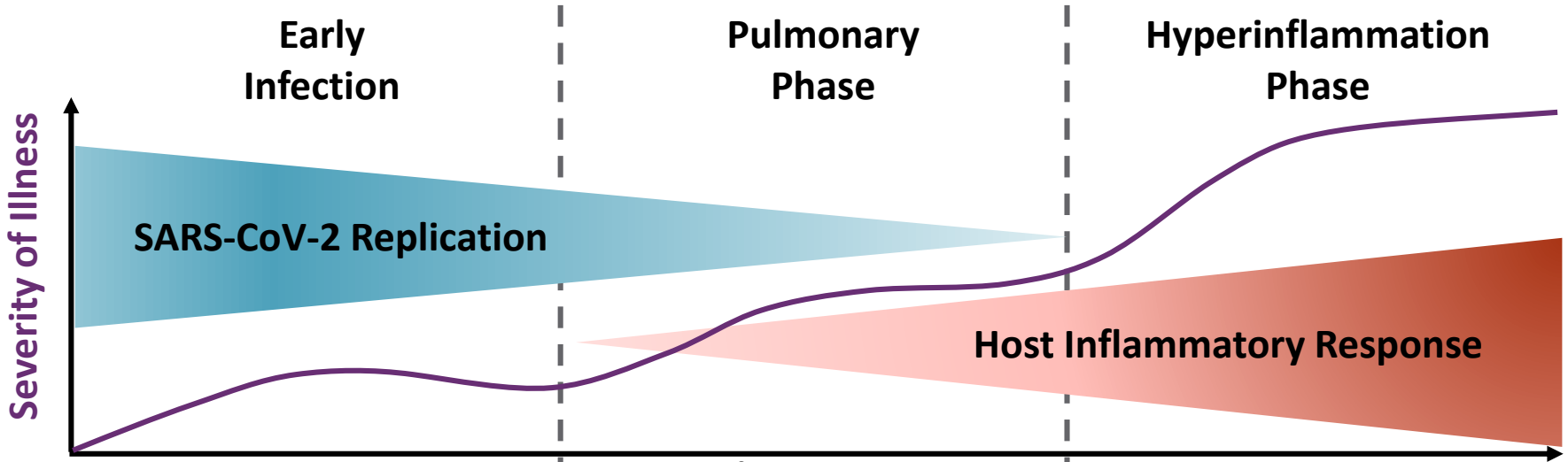
- SpO2 ≤93% on room air at sea level, respiratory rate >30, PaO2/FiO2 <300, or lung infiltrates >50%.

- Administer oxygen therapy immediately using nasal cannula or high-flow oxygen.
- secondary bacterial pneumonia or sepsis is suspected, administer empiric antibiotics, re-evaluate daily, and if no evidence of bacterial infection, de-escalate or stop antibiotics.

Critical Illness

- acute respiratory distress syndrome (ARDS), septic shock that may represent virus-induced distributive shock, cardiac dysfunction, elevations in multiple inflammatory cytokines that provoke a cytokine storm, and/or exacerbation of underlying comorbidities

Benefit of Therapeutic Classes Dictated by SARS-CoV-2 Pathogenesis



Clinical Signs/ Symptoms	Lymphopenia, mild constitutional symptoms, fever >99.6°F, dry cough	Shortness of breath ± hypoxia, abnormal chest imaging, transaminitis, low-normal procalcitonin	ARDS, SIRS/shock, cardiac failure; elevated inflammatory markers, troponin, and NT-proBNP
Treatment Goals	Reduce onward transmission	Reduce progression/ hospitalization	Reduce morbidity/ mortality
	Enhance immunity; use antivirals		Dampen immunopathogenesis, coagulation

NIH COVID-19 Treatment Guidelines. Clinical management summary. Last updated July 8, 2021. Siddiqi. J Heart Lung Transplant. 2020;39:405.

Slide credit: clinicaloptions.com

Bacterial Superinfection of COVID-19-Associated Pneumonia

- For the treatment of shock, however, broad-spectrum empiric antimicrobial therapy is standard of care. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

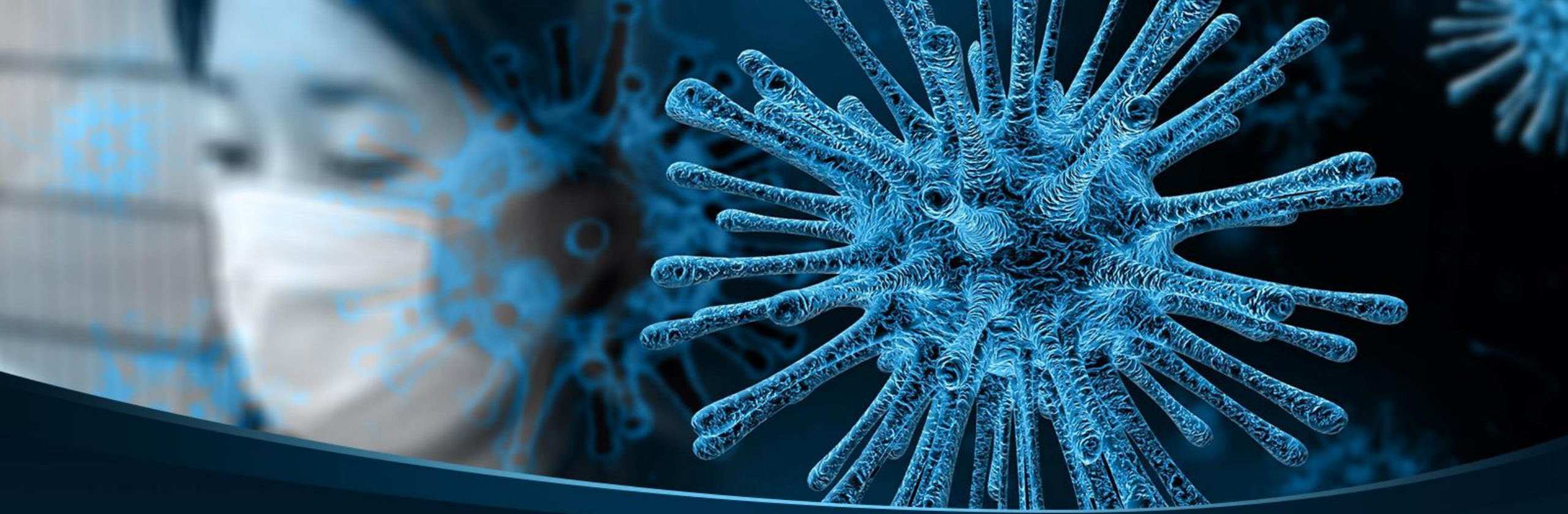
Oxygenation and Ventilation

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV)

- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure for whom HFNC is not available

- low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predictedbody weight) over higher tidal volumes (Vt >8 mL/kg) **(AI)**.
- targeting plateau pressures of <30 cm H2O **(AII)**.
- a conservative fluid strategy over a liberal fluid strategy **(BII)**.
- **against** the routine use of inhaled nitric oxide **(AI)**.

- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over alower PEEP strategy **(BII)**.
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation **(BII)**.



Pharmacologic Interventions

Key Therapeutic Agents Approved or Under Evaluation for Treatment of COVID-19

Antivirals

(Hydroxy)chloroquine
Ivermectin
Lopinavir/ritonavir
Nitazoxanide
Remdesivir

Anti–SARS-CoV-2 mAbs

Bamlanivimab plus etesevimab
Casirivimab plus imdevimab
Sotrovimab

Immunomodulators

Colchicine
Corticosteroids
Fluvoxamine
GM-CSF inhibitors
IL-1 and IL-6 inhibitors
Interferons
Kinase inhibitors
Non–SARS-CoV-2 IVIG

NIH COVID-19 Treatment Guidelines. Accessed August 18, 2021.

- There are insufficient data for the Panel to recommend either for or against the use of interleukin 6 (IL-6) antagonists (e.g., sarilumab, siltuximab, tocilizumab) for the treatment of COVID-19
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia

Remdesivir

- investigational nucleotide prodrug of an adenosine analog.

Remdesivir

- **does not recommend** using **remdesivir** for the treatment of mild or moderate COVID-19.

- for the treatment of COVID-19 in hospitalized patients with severe disease (defined as having SpO2 ≤94% on ambient air [at sea level], requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation [ECMO])

- Those who require supplemental oxygen **but not** high-flow oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO); *and*
- Those who require high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO.

- **Because remdesivir supplies are limited, the Panel recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO (BI).**

- The Panel recommends using **remdesivir** for 5 days or until hospital discharge, whichever comes first **(AI)**.
- If a patient who is on supplemental oxygen while receiving remdesivir progresses to requiring high-flow oxygen, noninvasive or invasive mechanical ventilation, or ECMO, the course of remdesivir should be completed.

Dose

- 200 mg IV first dose and then 100 mg IV QD for 10 days.

contraindications

- pregnancy or breast feeding
- hepatic cirrhosis
- alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal
- known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis

- The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension

Chloroquine or Hydroxychloroquine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19

Joshua Geleris, M.D., Yifei Sun, Ph.D., Jonathan Platt, Ph.D., Jason Zucker, M.D., Matthew Baldwin, M.D., George Hripcsak, M.D., Angelena Labella, M.D., Daniel K. Manson, M.D., Christine Kubin, Pharm.D., R. Graham Barr, M.D., Dr.P.H., Magdalena E. Sobieszczyk, M.D., M.P.H., and Neil W. Schluger, M.D.

ABSTRACT

BACKGROUND

Hydroxychloroquine has been widely administered to patients with Covid-19 without robust evidence supporting its use.

METHODS

We examined the association between hydroxychloroquine use and intubation or death at a large medical center in New York City. Data were obtained regarding consecutive patients hospitalized with Covid-19, excluding those who were intubated, died, or discharged within 24 hours after presentation to the emergency department (study baseline). The primary end point was a composite of intubation or death in a time-to-event analysis. We compared outcomes in patients who received hydroxychloroquine with those in patients who did not, using a multivariable Cox model with inverse probability weighting according to the propensity score.

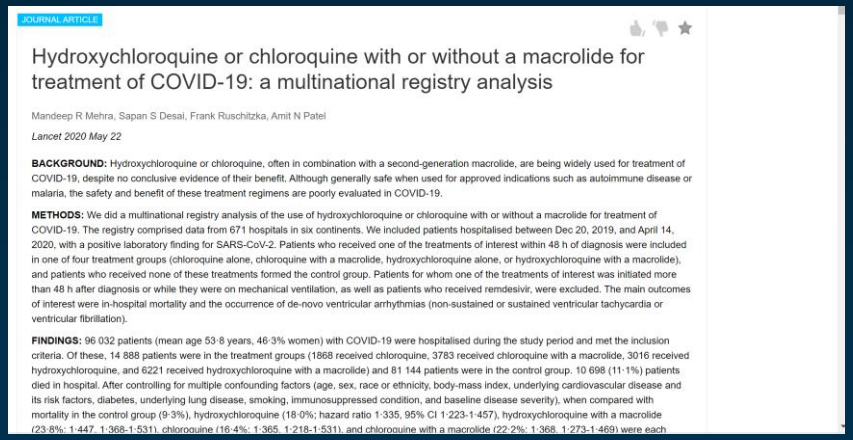
RESULTS

Of 1446 consecutive patients, 70 patients were intubated, died, or discharged within 24 hours after presentation and were excluded from the analysis. Of the remaining 1376 patients, during a median follow-up of 22.5 days, 811 (58.9%) received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of 5 days); 45.8% of the patients were treated within 24 hours after presentation to the emergency department, and 85.9% within 48 hours. Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine (median ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen, 223 vs. 360). Overall, 346 patients (25.1%) had a primary end-point event

From the Divisions of General Medicine, Infectious Diseases, and Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine (J.G., J.Z., M.B., A.L., D.K.M., C.K., R.G.B., M.E.S., N.W.S.), the Departments of Biostatistics (Y.S.) and Epidemiology (J.P., R.G.B., N.W.S.), Mailman School of Public Health, and the Department of Biomedical Informatics (G.H.), Vagelos College of Physicians and Surgeons, Columbia University, and New York–Presbyterian Hospital–Columbia University Irving Medical Center (J.G., J.Z., M.B., A.L., D.K.M., C.K., R.G.B., M.E.S., N.W.S.) — all in New York. Address reprint requests to Dr. Schluger at the Division of Pulmonary, Allergy, and Critical Care Medicine, Columbia University Irving Medical Center, PH-8 E., Rm. 101, 622 W. 168th St., New York, NY 10032, or at ns31@cumc.columbia.edu.

This article was published on May 7, 2020, and updated on May 14, 2020, at NEJM.org.

DOI: 10.1056/NEJMoa2012410



JOURNAL ARTICLE

Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis

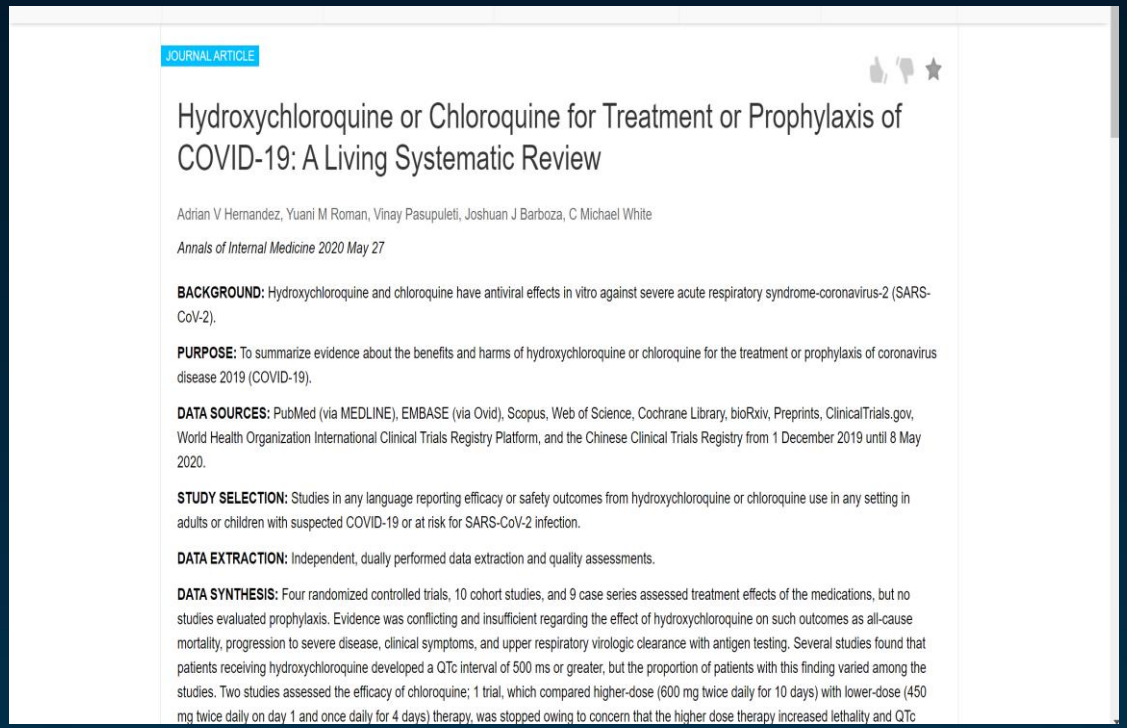
Mandeep R Mehra, Sapan S Desai, Frank Ruschitzka, Amit N Patel

Lancet 2020 May 22

BACKGROUND: Hydroxychloroquine or chloroquine, often in combination with a second-generation macrolide, are being widely used for treatment of COVID-19, despite no conclusive evidence of their benefit. Although generally safe when used for approved indications such as autoimmune disease or malaria, the safety and benefit of these treatment regimens are poorly evaluated in COVID-19.

METHODS: We did a multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents. We included patients hospitalised between Dec 20, 2019, and April 14, 2020, with a positive laboratory finding for SARS-CoV-2. Patients who received one of the treatments of interest within 48 h of diagnosis were included in one of four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide), and patients who received none of these treatments formed the control group. Patients for whom one of the treatments of interest was initiated more than 48 h after diagnosis or while they were on mechanical ventilation, as well as patients who received remdesivir, were excluded. The main outcomes of interest were in-hospital mortality and the occurrence of de-novo ventricular arrhythmias (non-sustained or sustained ventricular tachycardia or ventricular fibrillation).

FINDINGS: 96 032 patients (mean age 53·8 years, 46·3% women) with COVID-19 were hospitalised during the study period and met the inclusion criteria. Of these, 14 888 patients were in the treatment groups (1868 received chloroquine, 3783 received chloroquine with a macrolide, 3016 received hydroxychloroquine, and 6221 received hydroxychloroquine with a macrolide) and 81 144 patients were in the control group. 10 698 (11·1%) patients died in hospital. After controlling for multiple confounding factors (age, sex, race or ethnicity, body-mass index, underlying cardiovascular disease and its risk factors, diabetes, underlying lung disease, smoking, immunosuppressed condition, and baseline disease severity), when compared with mortality in the control group (9·3%), hydroxychloroquine (18·0%; hazard ratio 1·335, 95% CI 1·223–1·457), hydroxychloroquine with a macrolide (23·8%; 1·447, 1·368–1·531), chloroquine (16·4%; 1·365, 1·218–1·531), and chloroquine with a macrolide (22·2%; 1·368, 1·273–1·469) were each



JOURNAL ARTICLE

Hydroxychloroquine or Chloroquine for Treatment or Prophylaxis of COVID-19: A Living Systematic Review

Adrian V Hernandez, Yuani M Roman, Vinay Pasupuleti, Joshuan J Barboza, C Michael White

Annals of Internal Medicine 2020 May 27

BACKGROUND: Hydroxychloroquine and chloroquine have antiviral effects in vitro against severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2).

PURPOSE: To summarize evidence about the benefits and harms of hydroxychloroquine or chloroquine for the treatment or prophylaxis of coronavirus disease 2019 (COVID-19).

DATA SOURCES: PubMed (via MEDLINE), EMBASE (via Ovid), Scopus, Web of Science, Cochrane Library, bioRxiv, Preprints, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform, and the Chinese Clinical Trials Registry from 1 December 2019 until 8 May 2020.

STUDY SELECTION: Studies in any language reporting efficacy or safety outcomes from hydroxychloroquine or chloroquine use in any setting in adults or children with suspected COVID-19 or at risk for SARS-CoV-2 infection.

DATA EXTRACTION: Independent, dually performed data extraction and quality assessments.

DATA SYNTHESIS: Four randomized controlled trials, 10 cohort studies, and 9 case series assessed treatment effects of the medications, but no studies evaluated prophylaxis. Evidence was conflicting and insufficient regarding the effect of hydroxychloroquine on such outcomes as all-cause mortality, progression to severe disease, clinical symptoms, and upper respiratory virologic clearance with antigen testing. Several studies found that patients receiving hydroxychloroquine developed a QTc interval of 500 ms or greater, but the proportion of patients with this finding varied among the studies. Two studies assessed the efficacy of chloroquine; 1 trial, which compared higher-dose (600 mg twice daily for 10 days) with lower-dose (450 mg twice daily on day 1 and once daily for 4 days) therapy, was stopped owing to concern that the higher dose therapy increased lethality and QTc

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** using **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19

Immune-Based Therapy Under Evaluation for Treatment of COVID-19

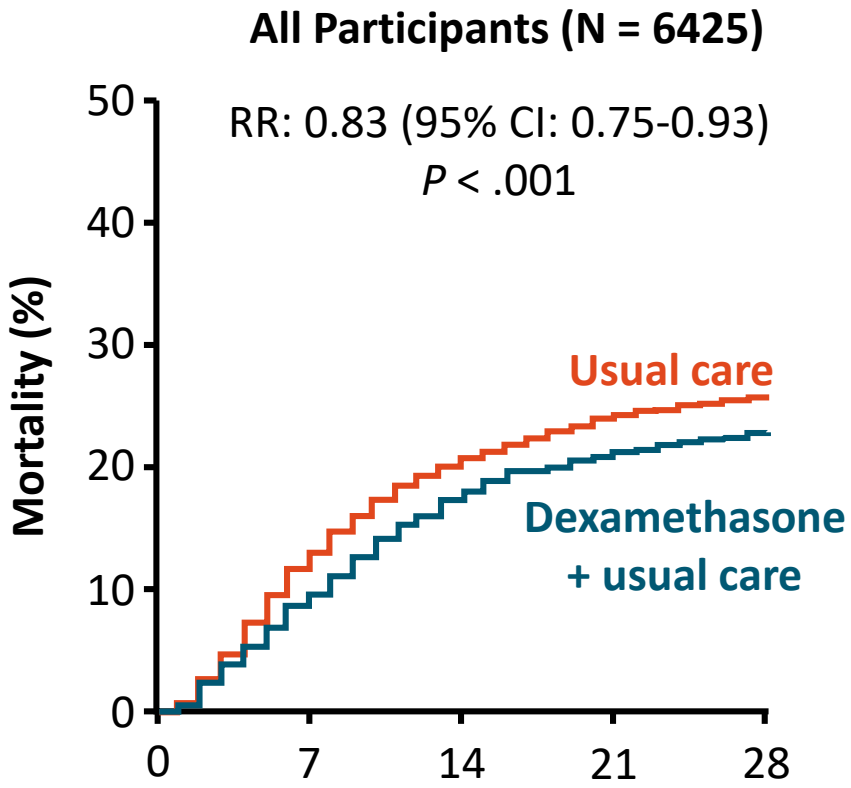
Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial Among Hospitalized Patients

- 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, 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 hospital organizations in the UK

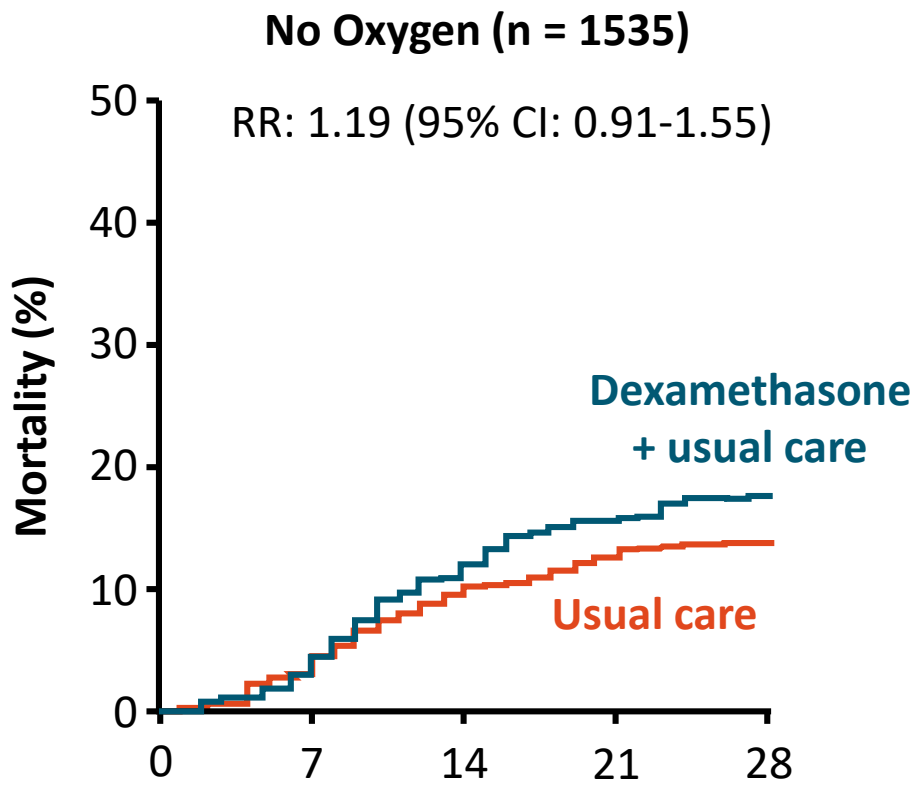
6/8/2020: recruitment to dexamethasone arm halted because sufficient patient numbers enrolled to establish potential benefit

https://www.recoverytrial.net. RECOVERY Collaborative Group. NEJM. 2020;[Epub]. NCT04381936.

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



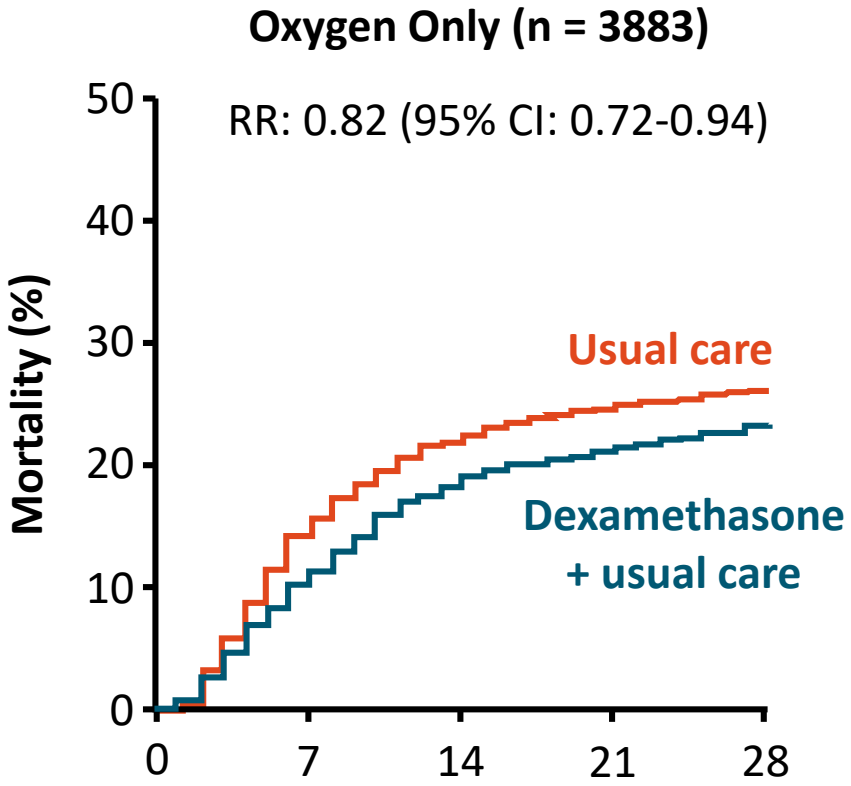
Patients at Risk, n					
Dexamethasone	2104	1903	1725	1659	1621
Usual care	4321	3754	3427	3271	3205



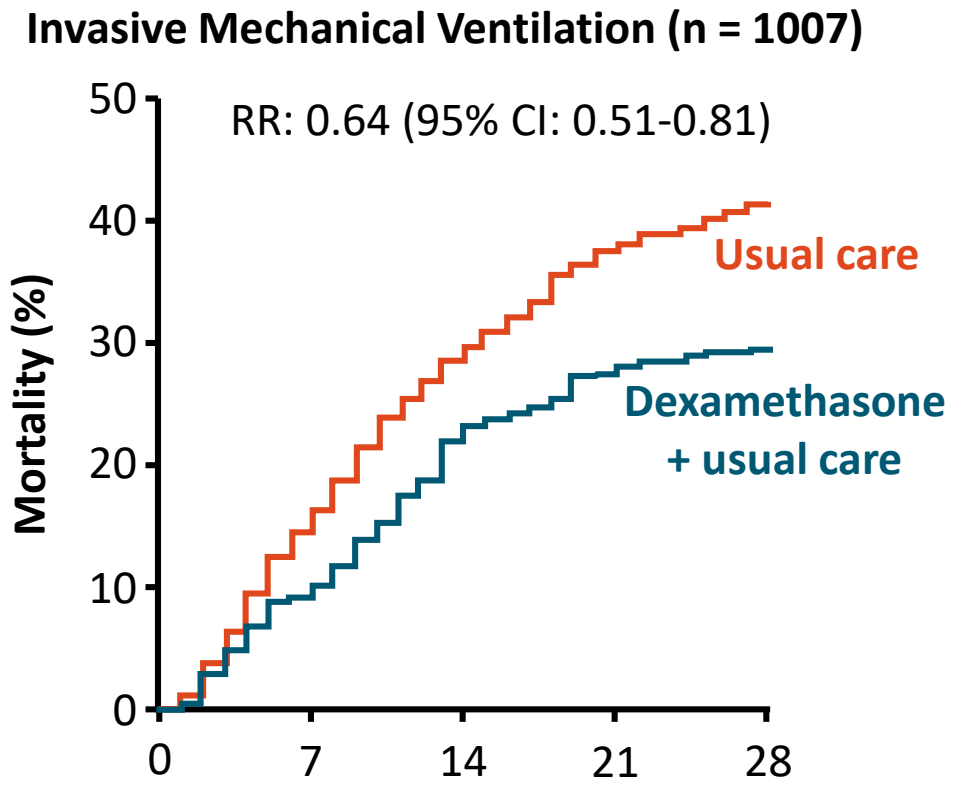
Patients at Risk, n					
Dexamethasone	501	478	441	421	412
Usual care	1034	987	928	897	889

RECOVERY Collaborative Group. NEJM. 2020;[Epub].

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



Patients at Risk, n					
Dexamethasone	1279	1135	1036	1006	981
Usual care	2604	2195	2018	1950	1916



Patients at Risk, n					
Dexamethasone	324	290	248	232	228
Usual care	683	572	481	424	400

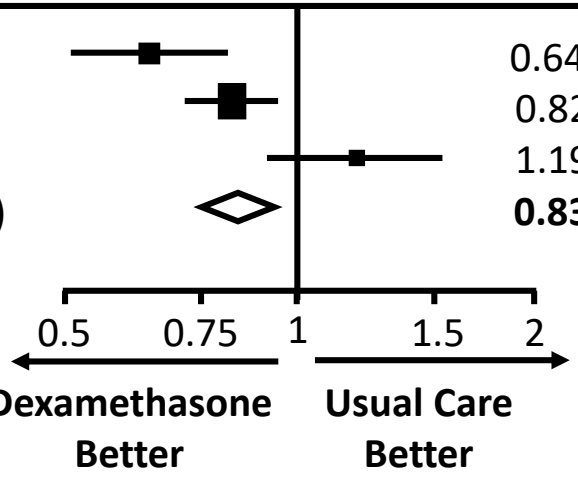
RECOVERY Collaborative Group. NEJM. 2020;[Epub].

RECOVERY Trial: Mortality at Day 28 (Primary Outcome)

- Addition of dexamethasone to usual care associated with **lower mortality** among subsets receiving invasive mechanical ventilation or oxygen alone but not in those receiving no baseline respiratory support

Respiratory Support at Randomization	Dexamethasone + Usual Care	Usual Care Only	28-Day Mortality RR (95%CI)	*P* Value
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)**	**< .001**

Chi-square trend across 3 categories: 11.5



RECOVERY Collaborative Group. NEJM. 2020;[Epub].

Slide credit: clinicaloptions.com

NIH/ISDA: Dexamethasone for Severe COVID-19

NIH[1]*

- 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[2]*

- 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 (eg, methylprednisolone 32 mg, prednisone 40 mg) may be substituted if dexamethasone unavailable
- 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.
†Patients with SpO_2 ≤ 94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

1. NIH COVID-19 Treatment Guidelines. Immunomodulators under evaluation for the treatment of COVID-19. Last updated July 17, 2020.
2. IDSA. COVID-19 Guideline, Part 1: Treatment and Management. Version 2.1.0.

Convalescent Plasma and Immune Globulins

- There are insufficient data to recommend either for or against the use of **COVID-19 convalescent plasma** or **SARS-CoV-2 immune globulins** for the treatment of COVID-19 **(AIII)**.

Background: Passive Immunization

New

- Multiple ways to infuse neutralizing antibodies

Monoclonal Antibodies[1]	Hyperimmune Immunoglobulins[2]	Convalescent Plasma[1,2]
▪ Produced in laboratories ▪ Scalable ▪ Genetic modification of Fc domain can reduce the risk of ADE and extend half-life	▪ Derived from plasma ▪ Standardized product	▪ Plasma from recovered individuals ▪ Batch-to-batch variability ▪ Requires blood-type matching

1. Abraham. Nat Rev Immun. 2020;20:401. 2. Piechotta. Cochrane Database Syst Rev. 2020;7:CD013600.

Interleukin-6 (IL-6) Inhibitors

- The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab

NIH Guideline Panel's Statement on Tocilizumab for the Treatment of COVID-19

New

- **Recommends the use** of tocilizumab + dexamethasone:
  - Patients within 24 hrs of admission to ICU who require invasive or noninvasive mechanical ventilation or high-flow oxygen
  - Recently hospitalized patients with rapidly increasing oxygen needs and significantly increased markers of inflammation (eg, CRP ≥ 75 mg/L)
- **Insufficient data to identify subgroups likely to benefit** from addition of tocilizumab to remdesivir, dexamethasone ± remdesivir
  - Hospitalized patients with hypoxemia and need for conventional oxygen supplementation

NIH COVID-19 Treatment Guidelines. Statement on tocilizumab. Last updated March 5, 2021.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/ Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Tocilizumab	Cytokine release syndrome (induced by CAR T-cell therapy) Rheumatoid arthritis Giant cell arteritis Polyarticular juvenile idiopathic arthritis Systemic juvenile idiopathic arthritis[28]	Recombinant humanized monoclonal antibody IL-6 receptor antagonist	**For COVID-19** • *Press Release:* Early results from the CORIMUNO-TOCI trial (NCT04331808); open-label randomized trial of hospitalized patients with COVID-19 (n = 129; seven sites in France) at moderate or severe disease stage, who were randomized to receive tocilizumab (n = 65) or standard of care alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group compared with standard of care. Detailed results of the trial have not been reported.

Janus Kinase Inhibitors (e.g., Baricitinib)

- Baricitinib is approved by the Food and Drug Administration to treat rheumatoid arthritis and can ameliorate the chronic inflammation seen in interferonopathies

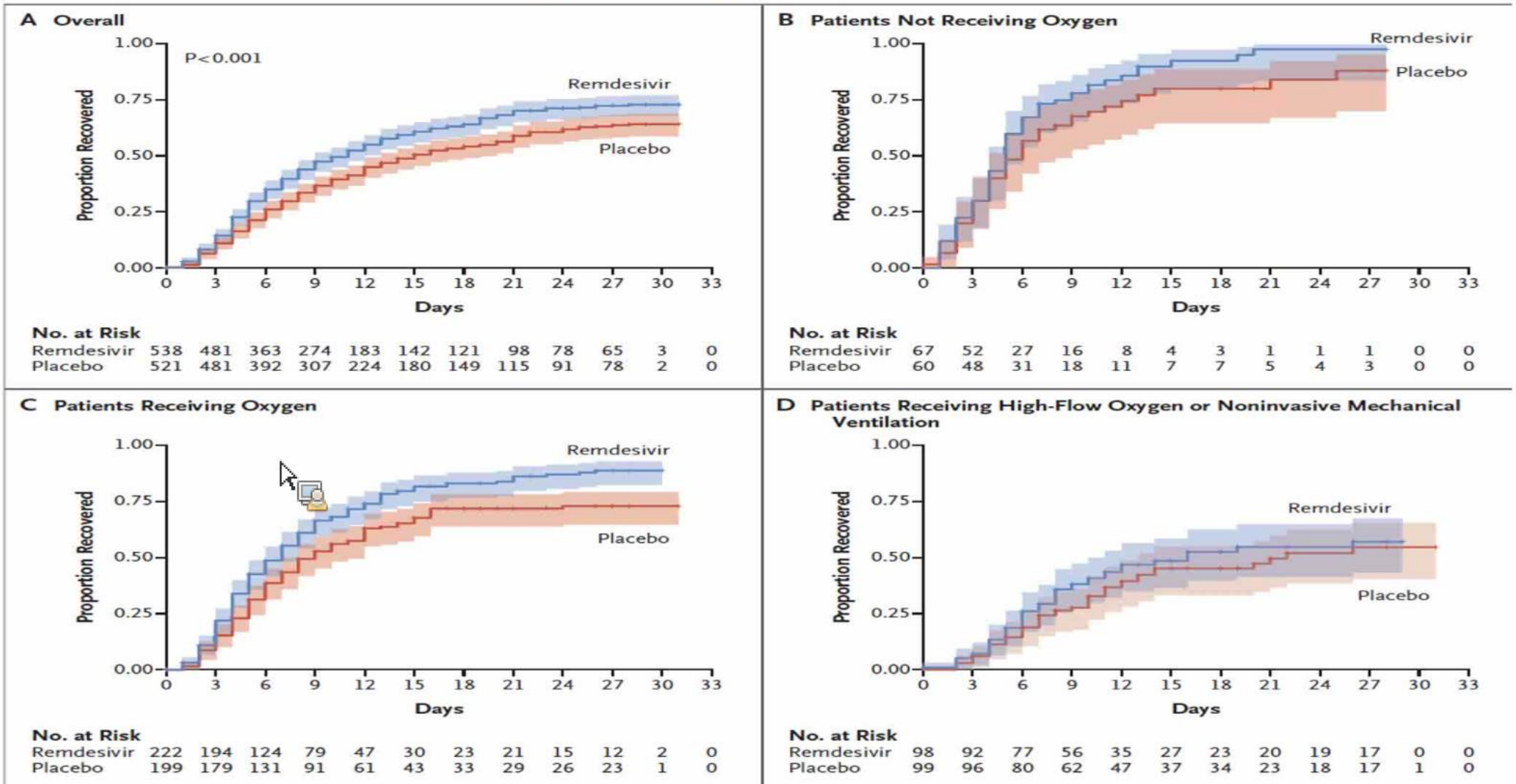
Antithrombotic Therapy in Patients with COVID-19

Laboratory Testing:

- In non-hospitalized patients with COVID-19, there are currently no data to support the measurement of coagulation markers (e.g., D-dimers, prothrombin time, platelet count, fibrinogen) **(AIII)**.
- In hospitalized patients with COVID-19, hematologic and coagulation parameters are commonly measured, although there are currently insufficient data to recommend for or against using this data to guide management decisions **(BIII)**.

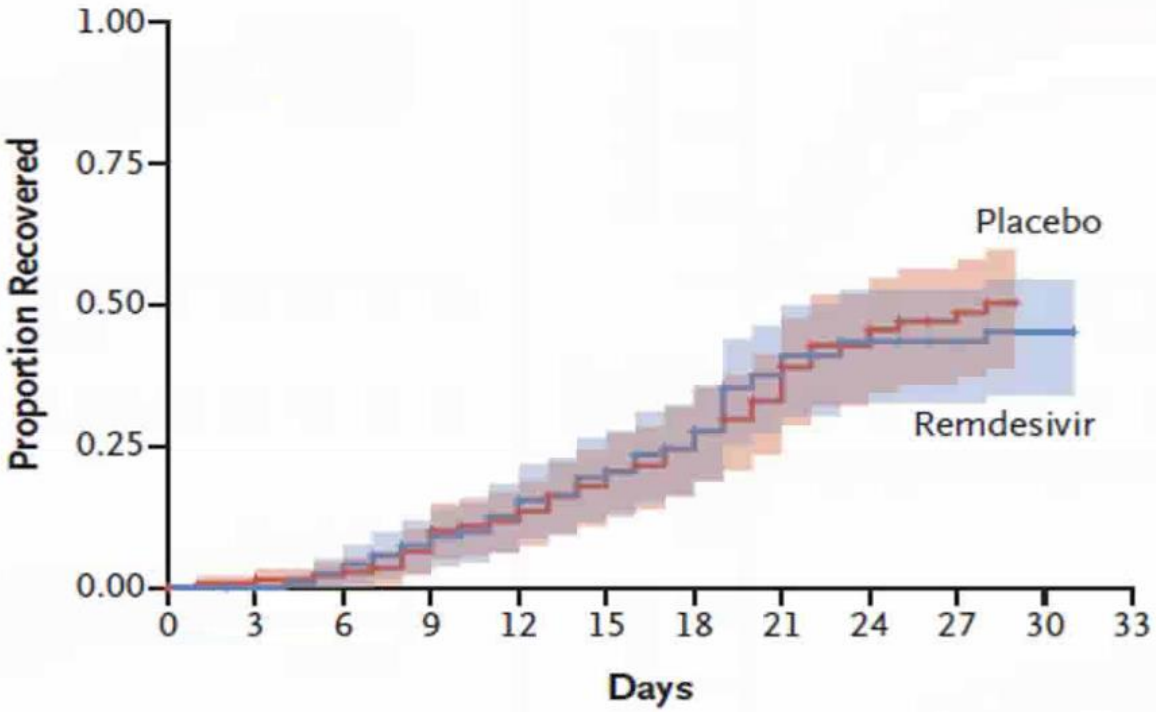
- Anticoagulant or antiplatelet therapy should not be used to prevent arterial thrombosis outside
- of the standard of care for those without COVID-19 **(AIII)**.

Kaplan–Meier Estimates of Cumulative Recoveries. Patients Receiving Oxygen



Kaplan–Meier Estimates of Cumulative Recoveries. Patients Receiving Mechanical VentilationorECMO

Patients Receiving Mechanical Ventilation or ECMO



No. at Risk

Remdesivir	125	124	120	111	91	80	71	55	42	34	1	0
Placebo	147	145	141	127	102	91	73	56	41	33	0	0


ANY
QUESTIONS?