

The Daily COVID-19 Literature Surveillance Summary

February 16, 2021



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COVID-19 Daily Literature Surveillance

COVID19LST



Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard"**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)*	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non-randomized controlled cohort/follow-up study**	Case-series, case-control or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. <http://www.cebm.net/index.aspx?o=5653>

* OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson

EXECUTIVE SUMMARY

Climate

- [Infectious Disease Society of America \(IDSA\) made 4 strong recommendations for preventing COVID-19 infection in health care personnel.](#) A pulmonologist and interventional cardiologist from the Cleveland Clinic and Emory University critique recently published IDSA guidelines for preventing COVID-19 infection in healthcare workers. They argue the recommendation to use either respirators or surgical masks conflicts with Centers for Disease Control guidance to use respirators, and believe the guidelines are missing recommendations on proper gloving strategies, which are crucial to avoid self-contamination. The authors suggest the IDSA must clarify these points to alleviate confusion for healthcare workers who are inundated with recommendations from multiple organizations.

Transmission & Prevention

- A retrospective observational study conducted by physicians at the Military Instruction Hospital during April 2020 found that among 1,739 crew members aboard a French [aircraft carrier](#) in April 2020, 64% tested positive for COVID-19 via real-time polymerase chain reaction (RT-PCR), with there being significant variations in symptomatic presentation and antibody development. This article suggests viral circulation in local outbreaks requires further testing and analysis.
- [Can COVID-19 be detected by dogs?](#) Physicians from the Lebanese American University in Beirut, Lebanon review current literature regarding the potential role of dogs as a more mobile and cost-efficient community detection system for COVID-19 screening. They review dogs' olfactory capabilities, evidence that diseases create distinct odor profiles and a recent study showing dogs identified COVID-19 specific sweat odor with a positive detection rate of 83-100%. Authors suggest that while these results are promising, real-life operational settings may diminish dogs' performance due to confounding factors and sensory associations.
- [Mask wearing continues to show improvement in community spread of SARS-CoV-2.](#) In this review article, physicians from the Centers for Disease Control and Prevention (CDC), detail the current known benefits of community mask wearing as an effective non-pharmacological intervention during the COVID-19 pandemic, citing several recent studies. They suggest mask wearing is beneficial for both infected and uninfected people, and when combined with additional mitigation measures, compliance will protect the greater community especially in the setting of emerging SARS-CoV-2 variants.

Management

- [Remdesivir for adults with COVID-19 may decrease time on mechanical ventilation.](#) A multi-specialty team from Minnesota and Oregon conducted a systematic review of 5 randomized-controlled trials evaluating remdesivir as a treatment for adults with COVID-19. They found that a 10-day course of remdesivir may reduce the proportion of patients receiving mechanical ventilation (RR: 0.71 [CI, 0.56 to 0.90]; 3 RCTs), but was associated with a statistically insignificant decrease in mortality (RR: 0.93 [95% CI, 0.82 to 1.06]; 4 RCTs) compared to control groups. Authors suggest that remdesivir use probably confers little to no mortality benefit but may improve recovery by reducing time on mechanical ventilation.
- [Allergy testing can help maintain safety with SARS-CoV-2 vaccines.](#) In this letter to the editor, Italian researchers at the University of Turin and Mauriziano Hospital discuss SARS-CoV-2 vaccine safety, highlighting data showing a similar rate of anaphylaxis with the Pfizer-BioNTech vaccine (1 in 100,000) compared to quadrivalent human papilloma virus (HPV) vaccine (Gardasil) (1 in 190,000). They note that the excipient polysorbate 80 was identified as the culprit in one case of anaphylaxis to the Gardasil vaccine, and since this molecule and other polyethylene glycol (PEG) derivatives are also utilized in current SARS-CoV-2 vaccines, they recommend potential use of skin allergy testing for at-risk populations to ensure safe vaccine administration.
- [American Society of Hematology \(ASH\) 2021 released guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19.](#) The ASH conditionally recommended both critically and acutely ill COVID-19 patients without suspected or diagnosed venous thromboembolism (VTE) receive prophylactic rather than intermediate or therapeutic intensity anticoagulation. The panel recognized potential benefit in these therapy recommendations, but noted evidence is low certainty, and therefore encourage clinicians to exercise their own clinical judgment.

Adjusting Practice During COVID-19

- [Methodological quality has been lower in some COVID-19 clinical research.](#) As part of a systemic review of COVID-19 research quality, a team of molecular biologists, physicians, and statisticians from the University of Ottawa compared the

quality of 686 research articles published during the COVID-19 pandemic to 593 historical controls matched for journal and study design published pre-pandemic. COVID-19 publications had a shorter time to acceptance (13.0 vs. 110 days, $p<0.0001$) and lower methodological quality scores compared to historical controls. Authors suggest the push for rapid research during the pandemic may result in lower quality research, and highlight the need for higher quality evidence.

R&D: Diagnosis & Treatments

- **SARS-CoV-2 lethal infected with K18-hACE2 transgenic mice may offer post-exposure protection.** Researchers from the Israel Institute for Biological Research in Ness-Ziona, Israel analyzed the efficacy of monoclonal MD65 antibodies in K18-hACE2 transgenic mice with SARS-CoV-2 infection, finding a greater survival rate compared to mice without MD65 antibodies, in the setting of both prophylactic and post-exposure administration, as well as decreased viral load in lung tissue. 100% of mice treated with MD65 antibodies within 3 days of exposure survived infection, while only 20% without antibodies survived. The authors suggest these results demonstrate promising outcomes that may translate to human prophylaxis and treatment of COVID-19.
- **SARS-CoV-2 infection may be treated and prevented by EIDD-2801.** Translational scientists, molecular biologists, and drug development experts from the University of North Carolina, Chapel Hill created human lung-only mice (LoM) models to evaluate the replication of the three human coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) and test a newly emerging antiviral treatment (EIDD-2801). They found SARS-CoV-2 successfully replicated in LoM models (Figure 1) and that EIDD-2801 reduced the number of infectious particles by 4.4 logs within as quickly as two days of treatment. Authors suggest their results indicate the potential strength of a new therapy (EIDD-2801) and further supports the use of LoM models as a means for viral research.
- **Remdesivir Metabolite GS-441524 was shown to inhibit SARS-CoV-2 infection in mouse models.** Drug discovery and synthesis experts from Shenzhen, China compared the anti-SARS-CoV-2 activity of remdesivir and its metabolite GS-441524 in an in-vitro and in-vivo laboratory study. They found GS-441524 more effectively inhibited SARS-CoV-2 replication in Vero E6 than remdesivir (IC_{50} 0.70 vs 1.35 μM). In vivo, GS-441524 significantly decreased viral titers by qRT-PCR in both AAV-hACE2 and MHV infected mouse models. Authors suggest GS-441524, which has a longer half-life than remdesivir, is a valuable potential therapeutic option for COVID-19.

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CLIMATE

AFFECTING THE HEALTHCARE WORKFORCE

IDSA MADE 4 STRONG RECOMMENDATIONS FOR PREVENTING COVID-19 INFECTION IN HEALTH CARE PERSONNEL

Dugar SP, Vallabhajosyula S.. Ann Intern Med. 2021 Feb 2. doi: 10.7326/ACPJ202102160-014. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

A pulmonologist and interventional cardiologist from the Cleveland Clinic and Emory University critique recently published Infectious Diseases Society of America (IDSA) guidelines for preventing COVID-19 infection in healthcare workers (see Results table). They argue the recommendation to use either respirators or surgical masks conflicts with Centers for Disease Control guidance to use respirators, and believe the guidelines are missing recommendations on proper gloving strategies, which are crucial to avoid self-contamination. The authors suggest the IDSA must clarify these points to alleviate confusion for healthcare workers who are inundated with recommendations from multiple organizations.

ABSTRACT

SOURCE CITATION: Lynch JB, Davitkov P, Anderson DJ, et al. Infectious Diseases Society of America guidelines on infection prevention for health care personnel caring for patients with suspected or known COVID-19. Clin Infect Dis. 2020. [Epub ahead of print.] 32716496.

FIGURES

 **Results:** IDSA recommendations for preventing infection in HCP caring for patients with known or suspected COVID-19

Setting*	Recommendations† for HCP (strength)	Evidence
Routine care (moderate-certainty evidence based on GRADE)		
Conventional	Use surgical mask or respirator (N95, N99, or PAPR) vs. no mask (strong)	Indirect evidence: Mask (OR, 0.13 [95% CI, 0.03 to 0.62]) or N95 (OR, 0.12 [CI, 0.06 to 0.26]) reduced SARS-CoV-1 infection vs. inconsistent or no mask use (5 OS). N95 and mask did not differ for SARS-CoV-1 infection, 2.8% vs. 5.3% (3 OS; n = 593), or viral respiratory illness, 16% vs. 21% (4 RCI; n = 4453)
Contingency or crisis capacity	Use surgical mask or reprocessed respirator vs. no mask (strong)	Same as above
Aerosol-generating procedures (very-low-certainty evidence based on GRADE)		
Conventional	Use respirator (N95, N99, or PAPR) vs. surgical mask (strong)	Indirect evidence: Exposure to aerosol generating procedures increased SARS-CoV-1 risk (OR 2.8 for preintubation manual ventilation to OR 6.6 for tracheal intubation)
Contingency or crisis capacity	Use reprocessed N95 respirator for reuse vs. surgical mask (conditional)	Indirect evidence from laboratory studies of decontamination and anecdotal reports
	Add face shield or surgical mask to cover the N95 respirator to extend its use (strong)	Indirect evidence from laboratory studies, mathematical models, and anecdotal reports
	Add face shield or surgical mask to cover the N95 respirator to allow for its reuse (conditional)	Same as above

Insufficient evidence exists for recommendations on use of double vs. single gloves or shoe covers vs. no shoe covers as part of appropriate PPE for routine care in conventional, contingency, or crisis capacity settings.

COVID-19 = coronavirus disease 2019; GRADE = Grading of Recommendations Assessment, Development and Evaluation; HCP = health care personnel; IDSA = Infectious Diseases Society of America; OR = odds ratio; OS = observational studies; PAPR = powered air-purifying respirator; PPE = personal protective equipment; RCI = randomized controlled trial; SARS-CoV-1 = severe acute respiratory syndrome coronavirus 1; CI defined in Glossary.

*Conventional = usual supplies available and used; contingency = supplies need to be conserved, adapted, substituted, or reused; crisis = lack of critical supplies.

†In addition to appropriate PPE (use of gowns, gloves, and eye protection) and adherence to donning and doffing standards.

‡Strong = most people should receive the recommended action; conditional = appropriate action may differ depending on a person's values.

Bottom line:
IDSA made 4 strong
and 2 conditional
recommendations for
preventing infection in
HCP caring for patients
with COVID-19.

EPIDEMIOLOGY

SARS-COV-2 SETTING-SPECIFIC TRANSMISSION RATES: A SYSTEMATIC REVIEW AND META-ANALYSIS

Thompson HA, Mousa A, Dighe A, Fu H, Arnedo-Pena A, Barrett P, Bellido-Blasco J, Bi Q, Caputi A, Chaw L, De Maria L, Hoffmann M, Mahapure K, Ng K, Raghuram J, Singh G, Soman B, Soriano V, Valent F, Vimercati L, Wee LE, Wong J, Ghani AC, Ferguson NM.. Clin Infect Dis. 2021 Feb 9:ciab100. doi: 10.1093/cid/ciab100. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A systematic review and meta-analysis by a group of global infectious disease specialists from multiple institutions explored epidemiological studies on the transmission of SARS-CoV-2 in different settings through examining secondary attack rates (SAR) and observed reproduction numbers (R). 97 studies were analyzed to identify the types of contacts and locations that constitute higher transmission potential and the differences in these parameters by age of index cases and their contacts, duration of household exposure to the index case, household size, and symptom status of index cases. The results suggest an increase in SARS-CoV-2 transmission potential in settings with familiar contacts such as households and other residential locations (Table 1), highlighting the need for efficient testing, tracing, and strategies for rapid isolation.

SUMMARY

The results of this study indicated highest transmission rates in households with pooled SAR of 21.1% (95% CI: 0.67-1.32). Rates were significantly higher where the duration of household exposure exceeded 5 days as opposed to durations less than 5 days. Furthermore, SARs were highest among contacts at social events with family and friends as compared to casual contacts at 5.9% and 1.2% respectively. There was some evidence indicating a reduction in transmission potential both to and from individuals under 20 years of age in the household context. However, the authors note the need for further research on transmission in different social setting including schools and workplaces to continue to inform transmission reduction strategies.

ABSTRACT

BACKGROUND: Understanding the drivers of SARS-CoV-2 transmission is crucial for control policies but evidence of transmission rates in different settings remains limited. **METHODS:** We conducted a systematic review to estimate secondary attack rates (SAR) and observed reproduction numbers (Rob) in different settings exploring differences by age, symptom status, and duration of exposure. To account for additional study heterogeneity, we employed a Beta-Binomial model to pool SARs across studies and a Negative-binomial model to estimate Robs. **RESULTS:** Households showed the highest transmission rates, with a pooled SAR of 21.1% (95%CI:17.4%-24.8%). SARs were significantly higher where the duration of household exposure exceeded 5 days compared with exposure of <=5 days. SARs related to contacts at social events with family and friends were higher than those for low-risk casual contacts (5.9% vs. 1.2%). Estimates of SAR and Robs for asymptomatic index cases were approximately a seventh, and for pre-symptomatic two thirds of those for symptomatic index cases. We found some evidence for reduced transmission potential both from and to individuals under 20 years of age in the household context, which is more limited when examining all settings. **CONCLUSIONS:** Our results suggest that exposure in settings with familiar contacts increases SARS-CoV-2 transmission potential. Additionally, the differences observed in transmissibility by index case symptom status and duration of exposure have important implications for control strategies such as contact tracing, testing and rapid isolation of cases. There was limited data to explore transmission patterns in workplaces, schools, and care-homes, highlighting the need for further research in such settings.

FIGURES

Setting	Pooled SAR (%)	95% Confidence Interval (%)	Pooled R _{obs}	95% Confidence Interval
Households	21.1	17.4 - 24.8	0.96	0.67 - 1.32
Social gatherings with family and friends	5.9	3.8 - 8.1	0.38	0.18 - 0.64
Travel	5.0	0.3 - 9.8	-	-
Healthcare	3.6	1.0 - 6.9	1.18	0.65 - 2.04
Workplace	1.9	0.0 - 3.9	-	-
Casual close contacts	1.2	0.3 - 2.1	-	-

Table 1. Summary of the pooled SAR and R for the exposure locations considered in this study. Where values are missing there was not enough data available to estimate a pooled value. SAR: Secondary Attack Rate; R: Observed Reproduction Number.

GONORRHOEA DURING COVID-19 IN LONDON, UK

Whitlock GG, McOwan A, Nugent D; Dean Street Collaborative Group.. Sex Transm Infect. 2021 Feb 11:sextrans-2020-054943. doi: 10.1136/sextrans-2020-054943. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Infectious disease physicians from London reviewed cases of *Neisseria gonorrhoeae* (NG) infection diagnosed at a single sexual health clinic to evaluate how the COVID-19 pandemic has affected sexual behavior and incidence of sexually transmitted infections. Compared to the same week in 2019, fewer cases were diagnosed in known contacts (6 vs 44) and asymptomatic individuals (14 vs 144) with a similar number of symptomatic cases (42 vs 46) and the proportion of clinic attendees testing positive for NG increased (Figure 1). The authors suggest there was little change in the number of symptomatic cases, though cannot comment on changes in sexual activity since their results may be confounded by how many symptomatic individuals attended the clinic during lockdown.

FIGURES

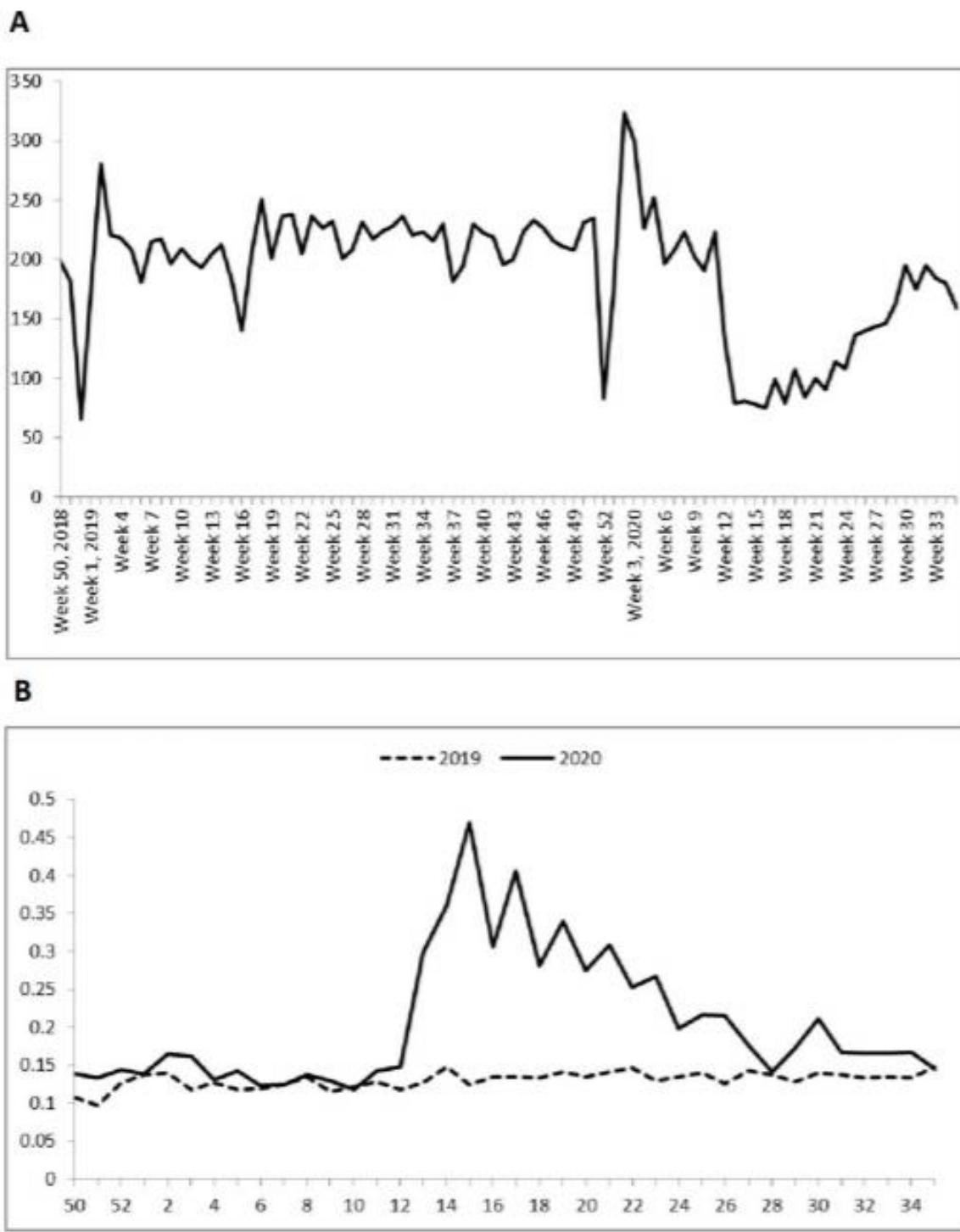


Figure 1 (A) Weekly number of individuals diagnosed with *Neisseria gonorrhoeae* at 56 Dean Street, London, UK from week 50 (2018) to week 35 (2020). (B) Proportion of individuals that underwent testing and were positive for *Neisseria gonorrhoeae* at 56 Dean Street, London, UK from week 50 of the preceding year to week 35 for 2019 (broken line) and 2020 (solid line).

OCCUPATIONAL RISK FACTORS FOR SARS-COV-2 INFECTION AMONG HEALTHCARE PERSONNEL: A CROSS-SECTIONAL ANALYSIS OF SUBJECTS ENROLLED IN THE COPE STUDY

Howard-Anderson J, Adams C, Sherman AC, Dube WC, Smith TC, Edupuganti N, Chea N, Magill SS, Espinoza DO, Zhu Y, Phadke VK, Edupuganti S, Steinberg JP, Lopman BA, Jacob JT, Collins MH, Fridkin SK.. Infect Control Hosp Epidemiol. 2021 Feb 9:1-20. doi: 10.1017/ice.2021.54. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Infectious disease experts from the Emory University School of Medicine investigated seropositivity rates of health care personnel (HCP) working in close proximity with COVID-19 infected patients between May and June 2020. Using data from four Atlanta hospitals (353 HCPs), authors found HCPs had an increased 6.5% seropositivity rate compared to the estimated community seroprevalence of 2.5% (Table 1). African Americans HCPs were eight times more likely to have SARS-CoV-2 antibody compared to white HCPs (OR 8.4, 95% CI: 2.7-27.4) (Table 2). Authors suggest HCPs are at greater risk for SARS-CoV-2 infection than the general public, though they recommend longitudinal assessment given possible confounding biases in the study methodology.

ABSTRACT

Among 353 healthcare personnel in a longitudinal cohort in four hospitals in Atlanta, GA (May-June 2020), 23 (6.5%) had SARS-CoV-2 antibodies. Spending >50% of a typical shift at bedside (OR 3.4, 95% CI: 1.2-10.5) and Black race (OR 8.4, 95% CI: 2.7-27.4) were associated with SARS-CoV-2 seropositivity.

FIGURES

Variable ^a	Healthcare personnel occupation						Total (n = 353)	
	Nurse (n = 144)	Physician/ APP (n = 92)	Other HCP (n = 53)	Radiology technician (n = 16)	Respiratory therapist (n = 14)	Administrator (n = 34)		
Demographics and community exposures								
Age, median years (IQR)	33 (27–49)	37 (32–47)	39 (32–52)	40 (36–50)	50 (39–58)	40 (32–52)	37 (30–49)	
Female – no. (%)	126 (88)	54 (59)	44 (83)	13 (81)	12 (86)	20 (59)	269 (76)	
Race ^b – no. (%)	Asian Black White Other	11 (8) 23 (16) 98 (70) 8 (6)	18 (20) 5 (5) 64 (70) 5 (5)	4 (8) 10 (19) 34 (65) 4 (8)	0 (0) 1 (6) 13 (81) 2 (12)	0 (0) 2 (14) 11 (79) 1 (7)	2 (6) 6 (18) 25 (74) 1 (3)	35 (10) 47 (13) 245 (69) 20 (6)
Hispanic or Latinx ethnicity ^b – no. (%)	10 (7)	1 (1)	4 (8)	1 (7)	1 (8)	0 (0)	17 (5)	
BMI, median (IQR)	26 (23–30)	24 (22–26)	25 (24–30)	27 (24–31)	30 (26–34)	28 (26–32)	26 (23–30)	
Immunocompromised ^c – no. (%)	16 (11)	6 (7)	5 (9)	1 (6)	0 (0)	2 (6)	30 (8)	
Activities outside of work – no. (%)								
Using public transportation	3 (2)	1 (1)	1 (2)	0 (0)	0 (0)	4 (12)	9 (3)	
Shopping outside the home	134 (93)	72 (78)	51 (96)	11 (69)	12 (86)	31 (91)	311 (88)	
Attending gathering of > 10 people	7 (5)	1 (1)	3 (6)	0 (0)	1 (7)	3 (9)	15 (4)	
Healthcare occupational activities^d								
Primary hospital of work – no. (%)								

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Variable ^a	Healthcare personnel occupation						Total (n = 319)
	Nurse (n = 144)	Physician/ APP (n = 92)	Other HCP (n = 53)	Radiology technician (n = 16)	Respiratory therapist (n = 14)	Administrator (n = 34)	
Referral							
Referral	58 (40)	44 (48)	22 (42)	6 (38)	9 (64)	--	139 (44)
Academic-community							
Academic-community	26 (18)	19 (21)	16 (30)	5 (31)	3 (21)	--	69 (22)
Community							
Community	39 (27)	8 (9)	9 (17)	5 (31)	2 (14)	--	63 (20)
Safety-net							
Safety-net	21 (15)	21 (23)	6 (11)	0 (0)	0 (0)	--	48 (15)
Primary work setting (n=296)^e – no. (%)							
Emergency department	28 (20)	13 (15)	2 (4)	2 (12)	0 (0)	--	45 (15)
Inpatient medical/surgical floor	69 (49)	45 (52)	20 (43)	6 (38)	3 (23)	--	143 (48)
ICU	40 (28)	18 (21)	3 (7)	1 (6)	10 (77)	--	72 (24)
Outpatient/other	4 (3)	10 (12)	21 (46)	1 (6)	0 (0)	--	36 (12)
Number of shifts in the 2 weeks prior to survey completion, median (IQR)							
6 (6–7)	7 (4–10)	10 (6–10)	10 (8–10)	8 (6–8)	--		6 (6–9)
Proportion of shifts in COVID-19 units – no. (%)							
None or nearly none	56 (39)	38 (41)	36 (68)	5 (31)	3 (21)	--	138 (43)
At least some	87 (60)	52 (57)	17 (32)	11 (69)	11 (79)	--	178 (56)
Average proportion of shift spent directly at bedside – no. (%)							
≤ 50%	28 (19)	58 (63)	48 (91)	7 (44)	4 (29)	--	145 (45)
> 50%	115 (80)	32 (35)	5 (9)	9 (56)	10 (71)	--	171 (54)
Performed or present during ≥ 1 AGP in a COVID-19 unit^{f,g} – no. (%)							
56 (39)	18 (20)	2 (4)	0 (0)	9 (64)	--		85 (27)
Had concerns about PPE (e.g., fit, adequacy, comfort) while in a COVID-19 unit^f – no. (%)							
25 (17)	9 (10)	2 (4)	3 (19)	3 (21)	--		42 (13)
Able to consistently social							
39 (27)	38 (41)	23 (43)	9 (56)	5 (36)	--		114 (36)

Table 1: Description of demographics and healthcare occupational activities stratified by job title in healthcare personnel in four hospitals in Atlanta, GA

Variable ^a	Healthcare personnel occupation						Total	
	Nurse (n = 144)	Physician/ APP (n = 92)	Other HCP (n = 53)	Radiology technician (n = 16)	Respiratory therapist (n = 14)	Administrator (n = 34)		
distance from coworkers – no.								
(%)								
Practiced universal masking nearly all the time at work – no.	112 (78)	74 (80)	34 (64)	13 (81)	9 (64)	--	242 (76)	
(%)								
Had a CDC-defined high-risk exposure to SARS-CoV-2 ^b – no.	18 (12)	9 (10)	1 (2)	2 (12)	2 (14)	--	32 (10)	
(%)								

Abbreviations: APP, advanced practice provider; HCP, healthcare personnel; IQR, interquartile range; BMI, body mass index; ICU, intensive care unit; AGP, aerosol generating procedure; PPE, personal protective equipment; CDC, Centers for Disease Control and Prevention

- a) All questions about occupational activities refer to the two weeks prior to the survey completion date
- b) Survey options for race included: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Other race or Prefer not to answer. Due to small numbers, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander and Other were collapsed into one category. We excluded participants who preferred not to answer. Ethnicity was examined separately from race.
- c) HCP were considered immunocompromised if they had an autoimmune or rheumatologic disorder, active malignancy, solid organ or hematologic stem cell transplant, or other self-reported immunosuppressive condition or medication.
- d) These questions were not asked for the HCP classified as an administrator, so they were excluded from the new denominator (n = 319)
- e) Excludes HCP where primary location was not able to be determined due to multiple locations being written in
- f) Only asked for participants who worked at least some shifts in COVID-19 units; percentages calculated with denominators equal to only participants who were asked the question
- g) The following procedures were specifically asked about as AGPs: airway suctioning, non-invasive positive pressure ventilation, manual (bag) ventilation, nebulizer treatments, intubation, cardiopulmonary resuscitation, chest physiotherapy, mini-bronchoalveolar lavage, breaking ventilation circuit, sputum induction, bronchoscopy, high-flow oxygen delivery
- h) A high-risk occupational exposure to SARS-CoV-2 was defined according to the CDC guidelines as having prolonged close contact with a patient(s) on a non-COVID-19 unit that later was found to have SARS-CoV-2 while: 1) the HCP was not wearing a respirator or facemask 2) the HCP was not wearing eye protection while the patient was not wearing a facemask or

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intubated, or 3) the HCP was not wearing all recommended PPE (gown, gloves, eye protection and respirator) while performing an AGP¹⁰

Table 1 continued

Table 2: Factors associated with SARS-CoV-2 seropositivity in healthcare personnel

Variable^a	Seropositive (n = 23)	Seronegative (n = 330)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Age < 40 years	9 (39)	191 (58)	0.5 (0.2–1.1)	0.4 (0.2–1.1)
Female	18 (78)	251 (76)	1.1 (0.4–3.5)	0.6 (0.2–2.1)
Race^b				
Asian	2 (9)	33 (10)	1.8 (0.3–7.5)	2.4 (0.3–10.9)
Black	9 (41)	38 (12)	7.0 (2.5–19.8)	8.4 (2.7–27.4)
Other	3 (14)	17 (5)	5.2 (1.1–20.0)	4.5 (0.8–19.4)
White	8 (36)	237 (73)	Ref	Ref
Hispanic or Latinx ethnicity^b	3 (13)	14 (4)	3.5 (0.8–11.9)	3.5 (0.6–15.1)
Immunocompromised^c	3 (13)	27 (8)	1.7 (0.4–5.3)	
Occupation				
Nursing	10 (43)	134 (41)	0.9 (0.3–3.5)	
Physician/APP	4 (17)	88 (27)	0.6 (0.1–2.4)	
Respiratory therapist	2 (9)	12 (4)	2.0 (0.3–11.8)	
Radiology technician	2 (9)	14 (4)	1.8 (0.2–10.0)	
Other HCP	4 (17)	49 (15)	Ref	
Administrator	1 (4)	33 (10)	0.4 (0.02–2.6)	
Primary hospital of work				
Referral	8 (35)	131 (40)	Ref	
Academic-community	6 (26)	63 (19)	1.6 (0.5–4.7)	
Community	6 (26)	57 (17)	1.7 (0.5–5.2)	
Safety-net	2 (9)	46 (14)	0.7 (0.1–3.0)	
Administrator (no healthcare location)	1 (4)	33 (10)	0.5 (0.03–2.8)	
Primary work setting (n = 296)^d				
Emergency department	3 (13)	42 (14)	0.8 (0.1–4.5)	
Inpatient medical/surgical floor	12 (52)	131 (43)	1.0 (0.3–4.6)	

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Variable^a	Seropositive (n = 23)	Seronegative (n = 330)	Univariable OR (95% CI)	Multivariable OR (95% CI)
ICU	4 (17)	68 (22)	0.6 (0.1–3.4)	
Outpatient/other	3 (13)	33 (11)	Ref	
Administrator (no healthcare location)	1 (4)	33 (11)	0.3 (0.02–2.8)	
Proportion of shifts in COVID-19 units (n = 350)^d				
At least some ^f	14 (61)	164 (50)	1.5 (0.7–3.8)	1.6 (0.6–4.7)
None or nearly none	9 (39)	163 (50)	Ref	Ref
Average proportion of shift spent directly at bedside (n = 350)^e				
> 50%	16 (70)	155 (47)	2.5 (1.1–6.7)	3.4 (1.2–10.5)
≤ 50%	7 (30)	172 (53)	Ref	Ref
Performed or present during at least one AGP in a COVID-19 unit (n = 350)^{e,g,h}				
Yes	5 (22)	80 (24)	0.9 (0.3–2.2)	0.4 (0.1–1.3)
No	18 (78)	247 (76)	Ref	Ref
Able to consistently social distance from co-workers (n = 330)				
No	12 (55)	170 (55)	0.8 (0.3–2.1)	
Yes	9 (41)	105 (34)	Ref	
Administrator	1 (5)	33 (11)	0.4 (0.02–2.0)	
Practiced universal masking nearly all the time at work (n = 350)				
No	3 (13)	71 (22)	0.5 (0.1–1.5)	
Yes	19 (83)	223 (68)	Ref	
Administrator	1 (4)	33 (10)	0.4 (0.02–1.8)	
Had a CDC-defined high-risk exposure to SARS-CoV-2 (n = 349)^{i,j}				
Yes	4	28	2.2 (0.6–6.5)	
No	19	298	Ref	
Cumulative incidence of COVID-19 by zip code/10,000 population (median (IQR))^j	317 (177–836)	466 (177–1645)	0.7 (0.3–1.5)	1.4 (0.5–3.5)

Table 2: Factors associated with SARS-CoV-2 seropositivity in healthcare personnel

SYMPTOMS AND CLINICAL PRESENTATION

PEDIATRICS

COVID-19 AND MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Yasuhara J, Watanabe K, Takagi H, Sumitomo N, Kuno T.. Pediatr Pulmonol. 2021 Jan 11. doi: 10.1002/ppul.25245. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A meta analysis and systematic review of 27 studies from PubMed and EMBASE through August 30, 2020 by physicians (including pediatric cardiologists) from the US and the Japan found that of 917 COVID-19-related multisystem inflammatory syndrome in children (MIS-C) patients, 87.3% had GI symptoms (95% CI: 82.9-91.6), 65.8% had shock (95% CI: 51.1-80.4), 55.3% had cardiovascular involvement (95% CI: 42.4-68.2), and the mortality rate was 1.9% (95% CI: 1.0-2.8; Table 1), suggesting MIS-C can lead to severe multiple organ failure and has distinct features from Kawasaki disease.

ABSTRACT

BACKGROUND: Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 has been increasingly recognized. However, the clinical features of MIS-C and the differences from Kawasaki disease remain unknown. The study aims to investigate the epidemiology and clinical course of MIS-C. **METHODS:** PubMed and EMBASE were searched through August 30, 2020. Observational studies describing MIS-C were included. Data regarding demographic features, clinical symptoms, laboratory, echocardiography and radiology findings, treatments, and outcomes were extracted. Study-specific estimates were combined using one-group meta-analysis in a random-effects model. **RESULTS:** A total of 27 studies were identified including 917 MIS-C patients. The mean age was 9.3 (95% confidence interval [CI], 8.4-10.1). The pooled proportions of Hispanic and Black cases were 34.6% (95% CI, 28.3-40.9) and 31.5% (95% CI, 24.8-38.1), respectively. The common manifestations were gastrointestinal symptoms (87.3%; 95% CI, 82.9-91.6) and cardiovascular involvement such as myocardial dysfunction (55.3%; 95% CI, 42.4-68.2), coronary artery aneurysms (21.7%; 95% CI, 12.8-30.1) and shock (65.8%; 95% CI, 51.1-80.4), with marked elevated inflammatory and cardiac markers. The majority of patients received intravenous immunoglobulin (81.0%; 95% CI, 75.0-86.9), aspirin (67.3%; 95% CI, 48.8-85.7), and corticosteroids (63.6%; 95% CI, 53.4-73.8) with a variety of anti-inflammatory agents. Although myocardial dysfunction improved in 55.1% (95% CI, 33.4-76.8) at discharge, the rate of extracorporeal membrane oxygenation use was 6.3% (95% CI, 2.8-9.8) and the mortality was 1.9% (95% CI, 1.0-2.8). **CONCLUSION:** Our findings suggest that MIS-C leads to multiple organ failure, including gastrointestinal manifestations, myocardial dysfunction and coronary abnormalities, and has distinct features from Kawasaki disease.

FIGURES

TABLE 1 Random-effects estimate (95% confidence interval [CI]) of the demographics, clinical characteristics, treatment, outcomes, laboratory, echocardiogram, and imaging findings of the patients with MIS-C

	Random-effects estimate (95% CI)
Demographics	
Age, years	9.3 (8.4–10.1)
BMI, kg/m ²	19.2 (17.7–20.6)
Male, %	56.8 (52.1–61.5)
Race/ethnicity	
Hispanic, %	34.6 (28.3–40.9)
Black, %	31.5 (24.8–38.1)
White, %	18.9 (14.3–23.6)
Asian, %	18.7 (8.6–28.9)
Other, %	19.0 (10.0–28.0)
Comorbidity	
Total, %	30.7 (24.7–36.7)
Obesity, %	18.0 (11.0–24.9)
Asthma/CLD, %	14.4 (11.2–17.5)
Symptoms	
Fever, %	99.3 (98.8–99.9)
Any respiratory symptoms, %	40.7 (23.1–58.4)
Cough, %	35.2 (22.2–48.1)
Dyspnea, %	37.6 (22.2–53.0)
Sore throat, %	18.5 (10.6–26.3)
Any neurologic symptoms, %	36.0 (22.8–49.2)
Headache, %	25.3 (19.6–31.0)
Meningeal signs, %	14.8 (5.8–23.8)
Any gastrointestinal symptoms, %	87.3 (82.9–91.6)
Diarrhea, %	57.0 (49.3–64.7)
Vomiting, %	60.0 (52.6–67.4)
Abdominal pain, %	70.1 (58.4–81.7)
Conjunctivitis, %	57.0 (47.3–66.6)
Rash, %	59.0 (52.8–65.2)
Peripheral extremity changes, %	32.9 (20.6–45.1)
Cervical lymphadenopathy, %	25.2 (15.0–35.3)
Oral mucosal changes, %	42.3 (31.7–53.0)
Myalgia, %	14.2 (8.3–20.0)
Laboratory values	
Hematology	
White blood cell, × 10 ⁹ /L	11.8 (10.5–13.2)
Neutrophil count, × 10 ⁹ /L	10.8 (9.3–12.4)
Lymphocyte count, × 10 ⁹ /L	0.8 (0.7–1.0)
Platelet count, × 10 ⁹ /L	155.1 (143.2–167.1)
Hemoglobin, g/dL	10.7 (9.9–11.5)
Inflammatory markers	
C-reactive protein, mg/L	235.5 (215.8–255.5)
Procalcitonin, ng/ml	8.5 (5.3–11.7)
Ferritin, ng/ml	711.0 (599.5–822.4)

TABLE 1 (Continued)

	Random-effects estimate (95% CI)
ESR, mm/h	62.8 (58.9–66.6)
Interleukin-6, pg/ml	172.2 (137.9–206.5)
Biochemistry	
Albumin, g/dL	2.7 (2.4–2.9)
Serum sodium, mEq/L	131.7 (129.6–133.8)
Serum creatinine, mg/dL	0.8 (0.7–1.0)
AST, U/L	49.1 (35.5–62.7)
ALT, U/L	44.6 (32.9–60.4)
Lactate dehydrogenase, U/L	347.7 (292.5–403.0)
Coagulation	
o-Dimer, µg/ml	3.5 (2.9–4.1)
Fibrinogen, mg/dL	643.0 (598.6–687.5)
Cardiac markers	
Troponin, ng/L	100.8 (55.2–146.3)
BNP, pg/ml	2191.5 (1334.2–3048.7)
NT-proBNP, pg/ml	14072.0 (7975.1–20168.9)
Echocardiography findings	
LV systolic dysfunction or myocarditis, %	55.3 (42.4–68.2)
LVEF, %	41.7 (36.1–47.4)
LVEF < 30%, %	7.9 (2.6–13.2)
LVEF 30–50%, %	53.8 (37.0–70.5)
Coronary artery dilation or aneurysm, %	21.4 (12.8–30.1)
Pericardial effusion, %	31.7 (23.5–40.0)
Chest X-ray findings	
Infiltrates or Opacities, %	38.3 (29.7–46.9)
Treatment	
Intravenous immunoglobulin, %	81.0 (75.0–86.9)
Corticosteroids, %	63.6 (53.4–73.8)
Tocilizumab (IL-6 receptor antagonist), %	27.7 (15.2–40.3)
Anakinra (IL-1 receptor antagonist), %	10.8 (8.2–13.4)
Infliximab (TNF-α antagonist), %	8.0 (2.9–13.1)
Remdesivir, %	8.3 (0.0–16.7)
Aspirin, %	67.3 (48.8–85.7)
Anticoagulation, %	56.5 (41.8–71.1)
Inotropes, %	62.9 (53.2–72.6)
High-flow nasal cannula, %	16.8 (10.4–23.3)
Noninvasive ventilation, %	24.6 (14.4–34.7)
Mechanical ventilation, %	33.0 (24.5–41.5)
ECMO, %	6.3 (2.8–9.8)
Outcomes	
ICU admission, %	79.1 (71.6–86.7)
Kawasaki Disease, %	44.3 (34.7–53.9)
Shock, %	65.8 (51.1–80.4)

TABLE 1 (Continued)

	Random-effects estimate (95% CI)
Recovery of LV systolic dysfunction at discharge, %	55.1 (33.4–76.8)
Death, %	1.9 (1.0–2.8)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BNP, B-type natriuretic peptide; CLD, chronic lung disease; ECMO, extracorporeal membrane oxygenation; ESR, erythrocyte sedimentation rate; ICU, intensive care unit; IL, interleukin; LV left ventricular; LVEF, left ventricular ejection fraction; MIS-C, multisystem inflammatory syndrome in children; NA, not available, NT-proBNP, N-terminal proBNP; TNF-α, tumor necrosis factor-α.

Table 1. Random-effects estimate (95% confidence interval [CI]) of the demographics, clinical characteristics, treatment, outcomes, laboratory, echocardiogram, and imaging findings of the patients with MIS-C.

UNDERSTANDING THE PATHOLOGY

IN VITRO

LACK OF CROSS-REACTIVITY BETWEEN ANTI-A IgG ISOAGGLUTININS AND ANTI-SARS-COV-2 IgG ANTIBODIES

Franchini M, Moi P, Cortellazzi M, Danese N, Caruso S, Pasolini P, Ferrazzo S, Piccinini S, Dall'Oglio A, Zovetti P, Negri N, Braga D, Pasquali C, Zuliani E, Glingani C.. Clin Chem Lab Med. 2021 Feb 9. doi: 10.1515/cclm-2021-0025. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Investigators from the Department of Hematology and Transfusion Medicine at the Carlo Poma Hospital in Mantova, Italy, analyzed and compared 12 convalescent plasma donors with blood group O who recovered from COVID-19 (group I) versus 12 plasma donor serums that were adsorbed on O blood type RBCs for the measurement of post-RBC adsorption anti-SARS-CoV-2 IgG antibodies (group II), in order to evaluate cross-reactivity between anti-A IgG isoagglutinins and anti-SARS-CoV-2 IgG antibodies. The results revealed no statistically significant difference between the two groups (Table 1), suggesting a lack of cross-reactivity between anti-A IgG isoagglutinins and anti-SARS-CoV-2 IgG antibodies.

FIGURES

Convalescent plasma donors	Progressive no.	Sex	Age, years	Anti-A IgG isoagglutinin titer	Anti-SARS-CoV-2 neutralizing titer	Anti-SARS-CoV-2 IgG antibody titer		
						Basal	Post-RBC adsorption ^a	p-Value ^b
O blood type (Group I, cases)	1	Male	60	32	320	221	201	NS
	2	Female	44	32	160	81	73	
	3	Male	30	32	20	40	34	
	4	Male	47	32	160	83	73	
	5	Male	29	128	80	20	16	
	6	Male	46	128	40	130	123	
	7	Male	56	256	80	171	152	
	8	Male	44	64	160	249	240	
	9	Male	64	128	160	132	117	
	10	Male	37	64	20	8	7	
	11	Female	57	256	40	63	54	
	12	Male	50	128	20	30	26	
O blood type (Group II, controls)	1	Male	30	32	160	74	50	NS
	2	Male	45	64	20	33	22	
	3	Female	44	128	20	69	54	
	4	Male	54	64	80	110	90	
	5	Male	57	64	160	80	72	
	6	Female	30	256	160	240	220	
	7	Female	32	32	320	265	254	
	8	Male	61	256	160	223	201	
	9	Male	63	128	80	174	152	
	10	Male	47	128	160	228	221	
	11	Male	54	128	40	65	55	
	12	Male	28	128	80	35	23	

Table 1. Relationship between anti-A IgG isoagglutinins and anti-SARS-CoV-2 IgG antibodies in cases and controls.

TRANSMISSION & PREVENTION

AN OUTBREAK OF COVID-19 ON AN AIRCRAFT CARRIER

Bylicki O, Paleiron N, Janvier F.. N Engl J Med. 2021 Feb 10;384(10):10.1056/NEJMc2034424#sa1. doi: 10.1056/NEJMc2034424. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective observational study conducted by physicians at the Military Instruction Hospital during April 2020 found that, among 1739 crew members aboard a French aircraft carrier in April 2020, 64% tested positive for COVID-19 via real-time polymerase chain reaction (RT-PCR), with there being significant variations in symptomatic presentation (Figure 1) and antibody development. This article suggests viral circulation in local outbreaks requires further testing and analysis.

SUMMARY

- Of the 64% who tested positive, 24% were asymptomatic.
- The observed disparity in symptomatic presentation could be related to older infections, as well as the level of infection.
- Only 60% of those who underwent serologic testing were antibody positive after quarantining
- The rate of antibody positivity varied between those who were hospitalized (91%), symptomatic (64%), and asymptomatic (84%)

FIGURES

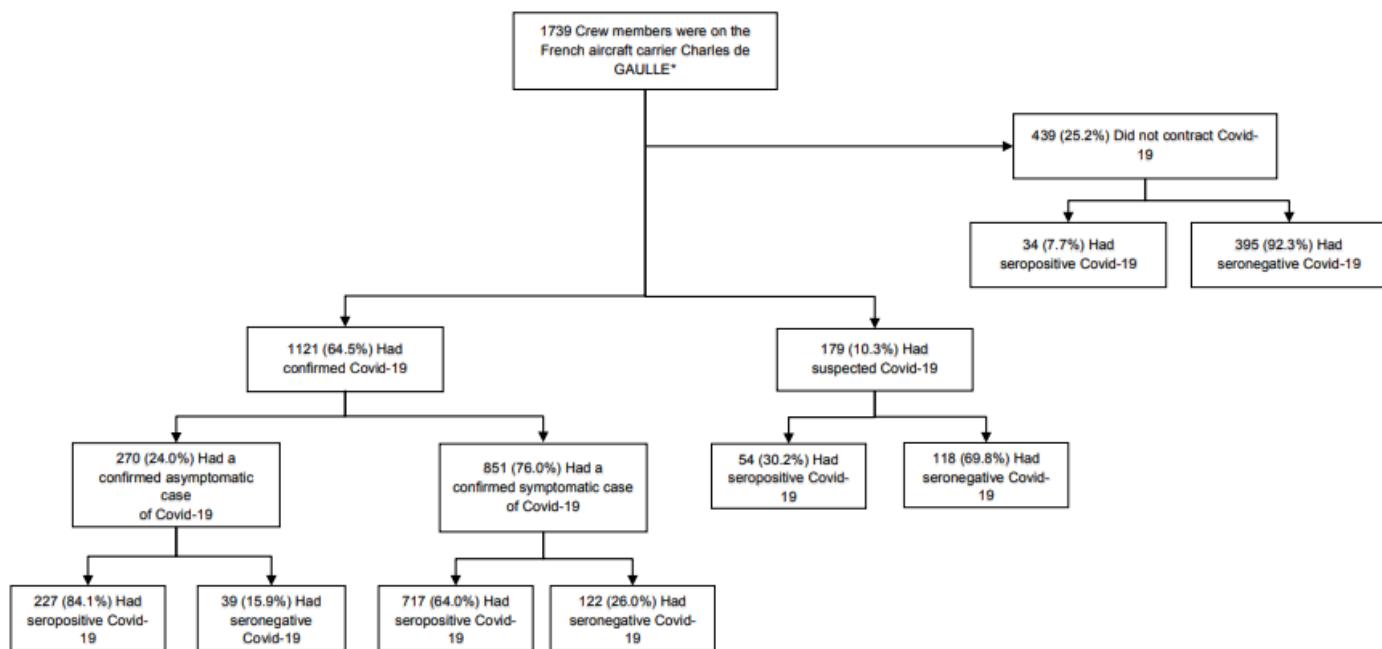


Figure 1. Distribution of Personnel According to case status

AEROSOL EMISSION OF ADOLESCENTS VOICES DURING SPEAKING, SINGING AND SHOUTING

Mürbe D, Kriegel M, Lange J, Schumann L, Hartmann A, Fleischer M.. PLoS One. 2021 Feb 10;16(2):e0246819. doi: 10.1371/journal.pone.0246819. eCollection 2021.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Audiologists from the Universitätsmedizin Berlin and the Hermann-Rietzel-Institut in Germany assessed emission of aerosolized droplets from speaking, singing and shouting adolescents. They found emission rates (PM, in particles per second [P/s]) for singing were between 141-1240 P/s, shouting 683-4332 P/s and speaking 16-267 P/s ($p<0.00001$) (Fig. 3) and increasing sound pressure level by one unit correlated with a PM increase of .05 units of \log_{10} (Fig. 4). Authors suggest activities involving singing and shouting spread more respiratory droplets that may harbor SARS-CoV-2 and adolescents engaging in such activities should take precautions to limit exposure.

ABSTRACT

Since the outbreak of the COVID-19 pandemic, singing activities for children and young people have been strictly regulated with far-reaching consequences for music education in schools and ensemble and choir singing in some places. This is also due to the fact, that there has been no reliable data available on aerosol emissions from adolescents speaking, singing, and shouting. By utilizing a laser particle counter in cleanroom conditions we show, that adolescents emit fewer aerosol particles during singing than what has been known so far for adults. In our data, the emission rates ranged from 16 P/s to 267 P/s for speaking, 141 P/s to 1240 P/s for singing, and 683 P/s to 4332 P/s for shouting. The data advocate an adaptation of existing risk management strategies and rules of conduct for groups of singing adolescents, like gatherings in an educational context, e.g. singing lessons or choir rehearsals.

FIGURES

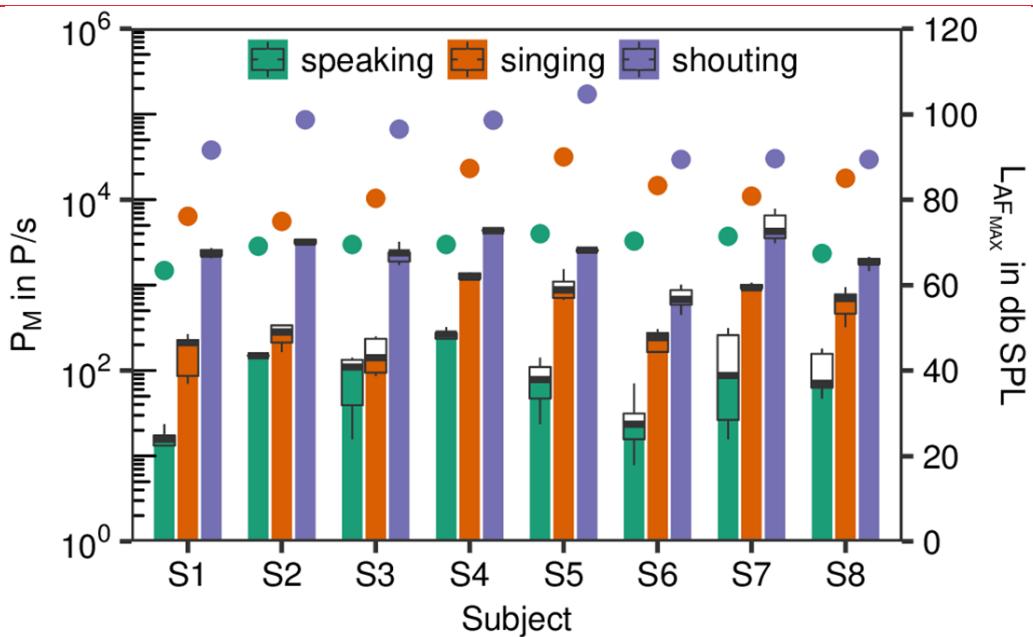


Fig 3. Emission rates.

Boxplots of the emission rates (P_M in P/s , left y-axis) for the test conditions speaking, singing and shouting for subjects S1-S4 (girls) and S5-S8 (boys). The maximum sound pressure levels ($L_{AF_{MAX}}$ in $db\ SPL$) are also shown (right y-axis) with different colored full circles for the test conditions.

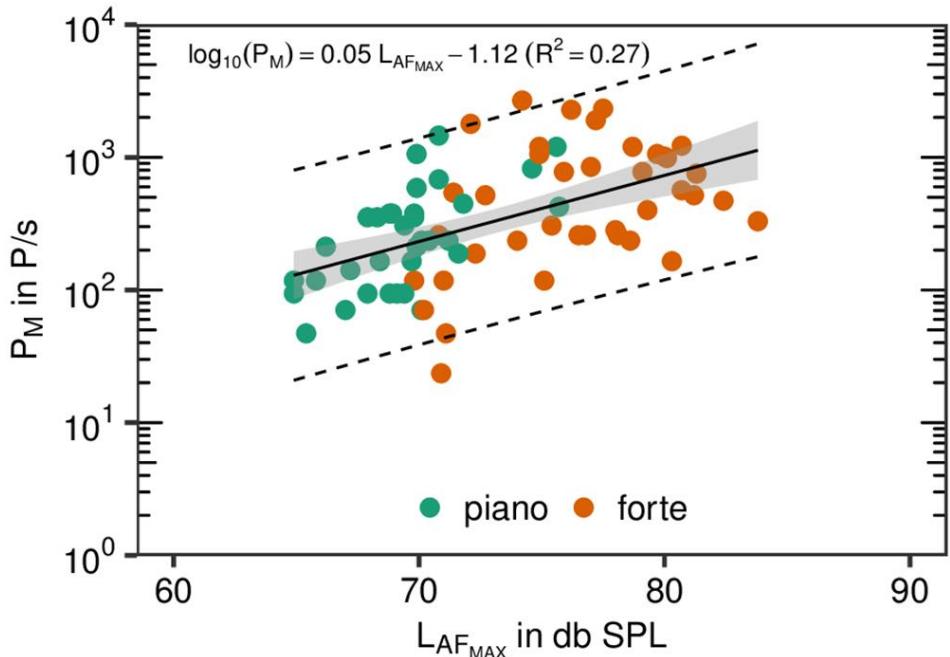


Fig 4. Emission rates vs. sound pressure level.

Emission rate PM plotted over maximum sound pressure level LAFMAX for sustained syllable /la/. All five repetitions for the two loudness conditions are represented by colored points as denoted in the legend. The black solid line represents the linear regression (see inset for details), the gray colored area represents the 95% confidence region, whereas the black dashed lines restrict the 95% prediction band.

A MINIMAL MODEL FOR HOUSEHOLD-BASED TESTING AND TRACING IN EPIDEMICS

Huber G, Kamb M, Kawagoe K, Li LM, McGeever A, Miller J, Veytsman BA, Zigmond D.. Phys Biol. 2021 Jan 12. doi: 10.1088/1478-3975/abdacd. Online ahead of print.

Level of Evidence: 5 - Modeling

BLUF

A follow-up manuscript to the previous paper by an international group of biologists and physicists discussing the transmission dynamics of SARS-CoV-2 due to a uniform clustering of contacts in the population. In this present text, the authors propose a minimal testing and tracing strategy for COVID-19 in the stratified population described in their previous paper through mathematical modeling and understanding epidemic dynamics. The strategy proposed includes tracing only the most frequent contacts of an infected person to mitigate and suppress the spread of the disease.

SUMMARY

The proposed strategy is effective as long as there are high rates of testing and the time between tests for a randomly selected individual is smaller than the average rate of infection during inter-household contacts. As for real-world application of this strategy, testing rates should be increased for tests with low-sensitivity in order to keep discovery rates high.

Furthermore, the authors note the limitations of this strategy due to socioeconomic factors that might impact people's ability to quarantine, leading to many symptomatic people being unable to isolate even with a positive test. In this sense, the calculations shown in this manuscript provide lower estimates for the required levels of testing.

ABSTRACT

In a previous work [Huber et al. A minimal model for household effects in epidemics. Physical Biology, 17(6):065010], we discussed virus transmission dynamics modified by a uniform clustering of contacts in the population: close contacts within households and more distant contacts between households. In this paper, we discuss testing and tracing in such a stratified population. We propose a minimal tracing strategy consisting of random testing of the entire population plus full testing of the households of those persons found positive. We provide estimates of testing frequency for this strategy to work.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

SARS-COV-2 DETECTION IN HUMAN MILK: A SYSTEMATIC REVIEW

Kumar J, Meena J, Yadav A, Kumar P.. J Matern Fetal Neonatal Med. 2021 Feb 8:1-8. doi: 10.1080/14767058.2021.1882984.
Online ahead of print.

Level of Evidence: 1 - Systematic review of randomized trials

BLUF

A systematic review conducted in Chandigarh, India, during early 2021 by the Department of Pediatrics, Post Graduate Institute of Medical Education and Research that included 34 studies with 116 COVID-19 confirmed women, found that 10 (2.16%) COVID-19 confirmed women had SARS-CoV-2 RNA in low quantities in breast milk (95% CI: 0.0-8.81). Based upon the limited, poor evidence, no conclusion can be drawn about infectivity and women should continue to exclusively breastfeed unless otherwise contraindicated.

SUMMARY

- The group utilized 34 studies for the systematic review, of which 24 were case-reports, and 10 were cohort studies. This resulted in 116 confirmed COVID-19 lactating women.
- Out of the 34 studies, 10 women with confirmed COVID-19 infections had positive SARS-CoV-2 RNA in milk
- Only 2.16% were found to have the virus in the milk (95% CI: 0.0-8.81; Figure 2), and only four studies reported detection of antibodies in milk at low proportions.
- 6 patients had SARS-CoV-2 antibodies in milk samples

ABSTRACT

PURPOSE: To synthesize the current evidence for the presence of SARS-CoV-2 RNA in the human milk of mothers with confirmed COVID-19 and its potential role in neonatal SARS-CoV-2 infection. **MATERIALS AND METHODS:** Using terms related to novel coronavirus 2019 and human milk, a systematic search was performed in three electronic databases (PubMed, EMBASE, and Web of Science) for studies published between December 2019 and 15 October 2020. Published peer-reviewed studies reporting the results of RT-PCR for SARS-CoV-2 RNA in human milk in mothers with confirmed COVID-19 were included. Proportion meta-analysis of case series and prospective cohort studies was performed using STATA version 14.2 (StataCorp, College Station, TX) and pooled estimate (with 95% confidence interval) of overall incidence of SARS-CoV-2 transmission was calculated. **RESULTS:** We identified 936 records, of which 34 studies (24 case-reports, 10 cohort studies) were eligible for this systematic review. A total of 116 confirmed COVID-19 lactating women (88 in cohort and 28 in case-reports) underwent RT-PCR testing in human milk, and 10 (six in case reports) were detected to have SARS-CoV-2 RNA. The overall pooled proportion (from cohort studies) for SARS-CoV-2 RNA detection in human milk was 2.16% (95% CI: 0.0-8.81%, I²: 0%). Four studies (six patients) also reported the presence of SARS-CoV-2 specific antibodies (along with RT-PCR) in human milk. **CONCLUSIONS:** The limited low-quality evidence suggests that SARS-CoV-2 RNA is detected in human milk in an extremely low proportion, however, based on current evidence no conclusion can be drawn about its infectivity and impact on the infants. In concordance with World Health Organization recommendations, exclusive breastfeeding should be considered in all cases unless any other contraindication exists.

FIGURES

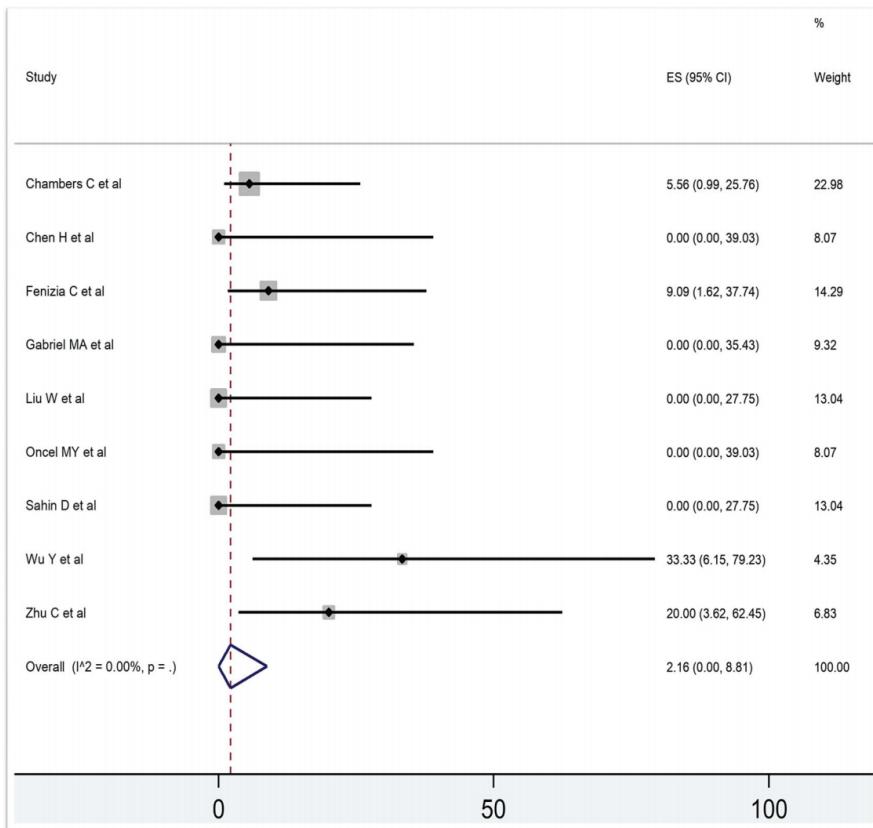


Figure 2. Forest plot showing pooled prevalence of SARS-CoV-2 detection in human milk of mothers with COVID-19.

PREVENTION IN THE COMMUNITY

COVID-19 DETECTION BY DOGS: FROM PHYSIOLOGY TO FIELD APPLICATION-A REVIEW ARTICLE

Sakr R, Ghsoub C, Rbeiz C, Lattouf V, Riachi R, Haddad C, Zoghbi M.. Postgrad Med J. 2021 Feb 11:postgradmedj-2020-139410. doi: 10.1136/postgradmedj-2020-139410. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

BLUF

Physicians from the Lebanese American University in Beirut, Lebanon review current literature regarding the potential role of dogs as a more mobile and cost-efficient community detection system for COVID-19 screening. They review dogs' olfactory capabilities, evidence that diseases create distinct odor profiles and a recent study showing dogs identified COVID-19 specific sweat odor with a positive detection rate of 83-100%. Authors suggest that while these results are promising, real-life operational settings may diminish dogs' performance due to confounding factors and sensory associations.

ABSTRACT

For years, the dog, man's best friend, was the most widely employed scent-detector tool for civilian and military purposes. Recently, many studies highlighted the role of canine olfactory ability in the medical field, specifically in detecting different infectious, metabolic and neoplastic conditions. The objective of this literature review is to clarify the rationale behind dog's ability to detect diseases, to assess the possible application for COVID-19 detection and to discuss the evidence available on the matter. Available evidence shows that properly trained disease-detector dogs are an efficient tool for identification of specific disease-associated volatile organic compounds marker profiles for a particular disease. And since COVID-19 positive persons have a specific volatilome different from non-infected persons, they can be recognised by the dogs, by sniffing different body fluids consequently aiding in the diagnosis of COVID-19. Possible applications of dogs as COVID-19 detectors will be an easy real-time mobile diagnostic aid with low cost and good performance. More evidence is needed to be able to

describe standardised measures concerning the best fluid to test, testing procedure, time of possible detection according to disease evolution, risks associated with the dog exposure and to translate the good results in study setting into the real-life operational one.

EFFECTIVENESS OF MASK WEARING TO CONTROL COMMUNITY SPREAD OF SARS-COV-2

Brooks JT, Butler JC.. JAMA. 2021 Feb 10. doi: 10.1001/jama.2021.1505. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

BLUF

In this review article, physicians from the Centers for Disease Control and Prevention (CDC), detail the current known benefits of community mask wearing as an effective non-pharmacological intervention during the COVID-19 pandemic, citing several recent studies (Table). They suggest mask wearing is beneficial for both infected and uninfected people, and when combined with additional mitigation measures, compliance will protect the greater community especially in the setting of emerging SARS-CoV-2 variants.

FIGURES

Table. Studies of the Effect of Mask Wearing on SARS-CoV-2 Infection Risk^a

Source	Location	Population studied	Intervention	Outcome
Hendrix et al	Hair salon in Springfield, Missouri	139 Patrons at a salon with 2 infected and symptomatic stylists	Universal mask wearing in salon (by local ordinance and company policy)	No COVID-19 infections among 67 patrons who were available for follow-up
Payne et al	USS Theodore Roosevelt, Guam	382 US Navy service members	Self-reported mask wearing	Mask wearing reduced risk of infection by 70% (unadjusted odds ratio, 0.30 [95% CI, 0.17-0.52])
Wang Y et al	Households in Beijing, China	124 Households of diagnosed cases comprising 335 people	Self-reported mask wearing by index cases or ≥1 household member prior to index case's diagnosis	Mask wearing reduced risk of secondary infection by 79% (adjusted odds ratio, 0.21 [95% CI, 0.06-0.79])
Doung-ngern et al	Bangkok, Thailand	839 Close contacts of 211 index cases	Self-reported mask wearing by contact at time of high-risk exposure to case	Always having used a mask reduced infection risk by 77% (adjusted odds ratio, 0.23 [95% CI, 0.09-0.60])
Gallaway et al	Arizona	State population	Mandatory mask wearing in public	Temporal association between institution of mask wearing policy and subsequent decline in new diagnoses
Rader et al	US	374 021 Persons who completed web-based surveys	Self-reported mask wearing in grocery stores and in the homes of family or friends	A 10% increase in mask wearing tripled the likelihood of stopping community transmission (adjusted odds ratio, 3.53 [95% CI, 2.03-6.43])
Wang X et al	Boston, Massachusetts	9850 Health care workers (HCWs)	Universal masking of HCWs and patients in the Mass General Brigham health care system	Estimated weekly decline in new diagnoses among HCWs of 3.4% after full implementation of the mask wearing policy
Mitze et al	Jena (Thuringia), Germany	City population aged ≥15 y	Mandatory mask wearing in public spaces (eg, public transport, shops)	Estimated daily decline in new diagnoses of 1.32% after implementation of the mask mandate
Van Dyke et al	Kansas	State population	Mandatory mask wearing in public spaces	Estimated case rate per 100 000 persons decreased by 0.08 in counties with mask mandates but increased by 0.11 in those without
Lyu and Wehby	15 US states and Washington, DC	State populations	Mandatory mask wearing in public	Estimated overall initial daily decline in new diagnoses of 0.9% grew to 2.0% at 21 days following mandates
Karaivanov et al	Canada	Country population	Mandatory mask wearing indoors	Estimated weekly 25%-40% decline in new diagnoses following mask mandates

^a See the Supplement for the complete table.

Table. Studies of the Effect of Mask Wearing on SARS-CoV-2 Infection Risk.

MAJOR UPDATE: REMDESIVIR FOR ADULTS WITH COVID-19 : A LIVING SYSTEMATIC REVIEW AND META-ANALYSIS FOR THE AMERICAN COLLEGE OF PHYSICIANS PRACTICE POINTS

Kaka AS, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, Wilt TJ.. Ann Intern Med. 2021 Feb 9. doi: 10.7326/M20-8148. Online ahead of print.

Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

A multi-specialty team from Minnesota and Oregon conducted a systematic review of 5 randomized-controlled trials evaluating remdesivir as a treatment for adults with COVID-19. They found that a 10-day course of remdesivir may reduce the proportion of patients receiving mechanical ventilation (RR: 0.71 [CI, 0.56 to 0.90]; 3 RCTs), but was associated with a statistically insignificant decrease in mortality (RR: 0.93 [95% CI, 0.82 to 1.06]; 4 RCTs) compared to control groups (Figure 1, Figure 2). Authors suggest that remdesivir use probably confers little to no mortality benefit, but may improve recovery by reducing time on mechanical ventilation.

ABSTRACT

BACKGROUND: Remdesivir is being studied and used for treatment of coronavirus disease 2019 (COVID-19). **PURPOSE:** To update a previous review of remdesivir for adults with COVID-19, including new meta-analyses of patients with COVID-19 of any severity compared with control. **DATA SOURCES:** Several sources from 1 January 2020 through 7 December 2020. **STUDY SELECTION:** English-language, randomized controlled trials (RCTs) of remdesivir for COVID-19. New evidence is incorporated by using living review methods. **DATA EXTRACTION:** 1 reviewer abstracted data; a second reviewer verified the data. The Cochrane Risk of Bias Tool and GRADE (Grading of Recommendations Assessment, Development and Evaluation) method were used. **DATA SYNTHESIS:** The update includes 5 RCTs, incorporating data from a new large RCT and the final results of a previous RCT. Compared with control, a 10-day course of remdesivir probably results in little to no reduction in mortality (risk ratio [RR], 0.93 [95% CI, 0.82 to 1.06]; 4 RCTs) but may result in a small reduction in the proportion of patients receiving mechanical ventilation (RR, 0.71 [CI, 0.56 to 0.90]; 3 RCTs). Remdesivir probably results in a moderate increase in the percentage of patients who recovered and a moderate decrease in serious adverse events and may result in a large reduction in time to recovery. Effect on hospital length of stay or percentage remaining hospitalized is mixed. Compared with a 10-day course for those not requiring ventilation at baseline, a 5-day course may reduce mortality, the need for ventilation, and serious adverse events while increasing the percentage of patients who recovered or clinically improved. **LIMITATION:** Summarizing findings was challenging because of varying disease severity definitions and outcomes. **CONCLUSION:** In hospitalized adults with COVID-19, remdesivir probably results in little to no mortality difference but probably improves the percentage recovered and reduces serious harms and may result in a small reduction in the proportion receiving ventilation. For patients not receiving ventilation, a 5-day course may provide greater benefits and fewer harms with lower drug costs than a 10-day course. **PRIMARY FUNDING SOURCE:** U.S. Department of Veterans Affairs.

FIGURES

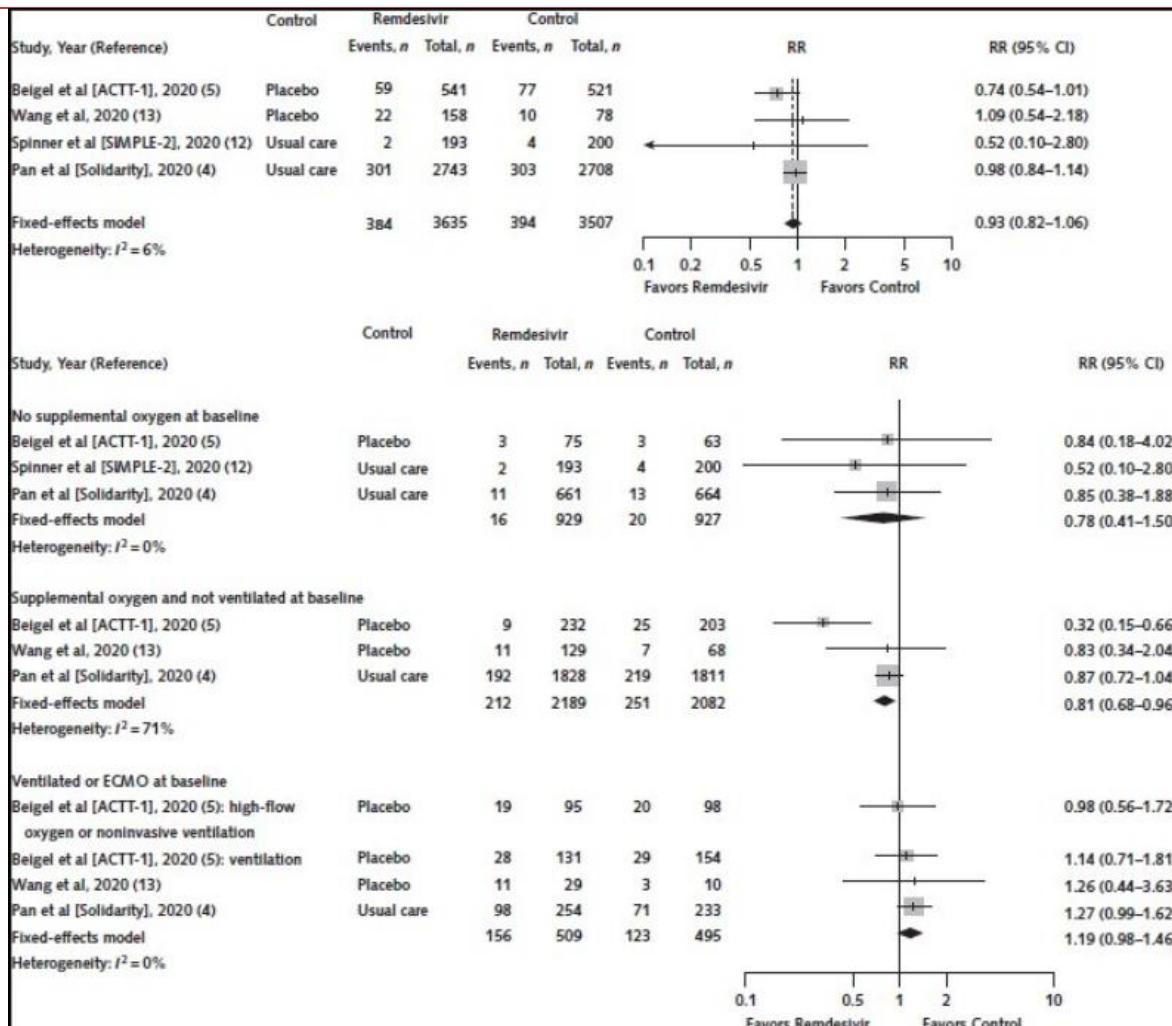


Figure 1. Mortality for remdesivir 10-d course vs. control (placebo or standard care).

The black diamonds reflect pooled results from randomized controlled trials (listed above) that enrolled patients in the corresponding respiratory support subgroups. ACTT-1 = Adaptive COVID-19 Treatment Trial; ECMO = extracorporeal membrane oxygenation; RR = risk ratio; SIMPLE-2 = Study to Evaluate the Safety and Antiviral Activity of Remdesivir [GS-5734] in Participants With Moderate Coronavirus Disease [COVID-19] Compared to Standard of Care Treatment. Top. Overall. Bottom. Results by initial respiratory status.

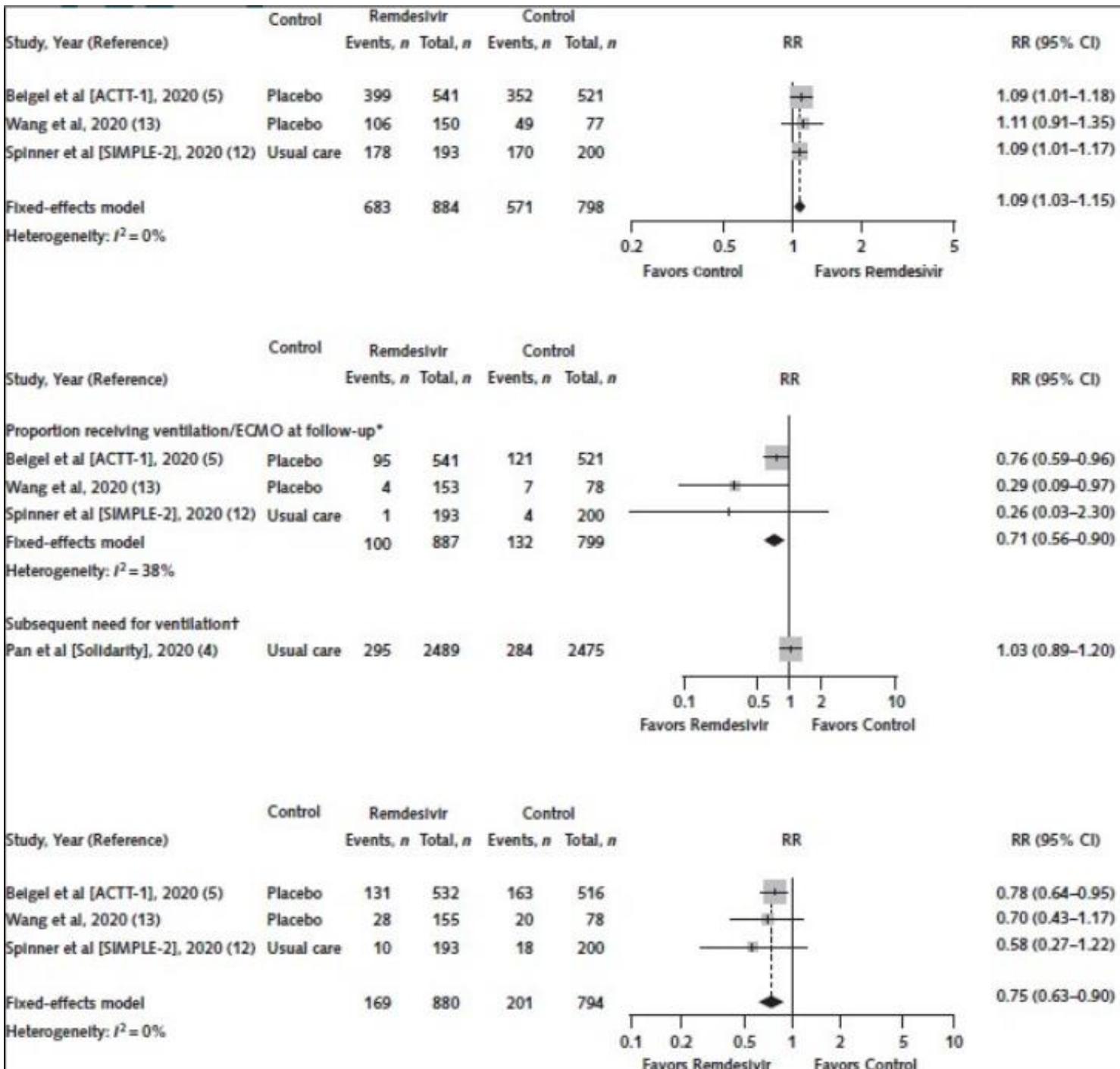


Figure 2. Nonmortality outcomes for remdesivir 10-d course vs. control (placebo or standard care).

ACTT-1 = Adaptive COVID-19 Treatment Trial; ECMO = extracorporeal membrane oxygenation; RR = risk ratio; SIMPLE-2 = Study to Evaluate the Safety and Antiviral Activity of Remdesivir [GS-5734] in Participants With Moderate Coronavirus Disease [COVID-19] Compared to Standard of Care Treatment. Top. Proportion of patients recovered. Middle. Need for invasive ventilation/ECMO. Bottom. Patients with ≥1 serious adverse event.

* For the pooled trials, defined as proportion receiving invasive ventilation/ECMO (new vs. continued from baseline) at follow-up (ACTT-1 on day 15, Wang et al on day 14, and SIMPLE-2 on day 11).

† Unpooled Solidarity trial, defined as subsequent need for ventilation in those not receiving ventilation at baseline (through day 28).

MEDICAL SUBSPECIALTIES

ALLERGY AND IMMUNOLOGY

MAINTAINING SAFETY WITH SARS-COV-2 VACCINES

Rolla G, Brussino L, Badiu I.. N Engl J Med. 2021 Feb 10:10.1056/NEJMc2100766#sa1. doi: 10.1056/NEJMc2100766. Online ahead of print.

Level of Evidence: 5 - Expert Opinion

BLUF

In this letter to the editor, Italian researchers at the University of Turin and Mauriziano Hospital discuss SARS-CoV-2 vaccine safety, highlighting data showing a similar rate of anaphylaxis with the Pfizer-BioNTech vaccine (1 in 100,000) compared to quadrivalent human papilloma virus (HPV) vaccine (Gardasil) (1 in 190,000). They note that the excipient polysorbate 80 was identified as the culprit in one case of anaphylaxis to the Gardasil vaccine, and since this molecule and other polyethylene glycol (PEG) derivatives are also utilized in current SARS-CoV-2 vaccines, they recommend potential use of skin allergy testing for at-risk populations to ensure safe vaccine administration.

HEMATOLOGY AND ONCOLOGY

AMERICAN SOCIETY OF HEMATOLOGY 2021 GUIDELINES ON THE USE OF ANTICOAGULATION FOR THROMBOPROPHYLAXIS IN PATIENTS WITH COVID-19

Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, Davila J, DeSancho MT, Diuguid D, Griffin DO, Kahn SR, Klok FA, Lee AI, Neumann I, Pai A, Pai M, Righini M, Sanfilippo KM, Siegal D, Skara M, Touri K, A Akle E, Bou Akle I, Boulos M, Brignardello-Petersen R, Charide R, Chan M, Dearness K, Darzi AJ, Kolb P, Colunga-Lozano LE, Mansour R, Morgano GP, Morsi RZ, Noori A, Piggott T, Qiu Y, Roldan Y, Schünemann F, Stevens A, Solo K, Ventresca M, Wiercioch W, Mustafa RA, Schünemann HJ.. Blood Adv. 2021 Feb 9;5(3):872-888. doi: 10.1182/bloodadvances.2020003763.

Level of Evidence: 5 - Guidelines and Recommendations

BLUF

The American Society of Hematology (ASH) released a set of 2021 guidelines for thromboprophylaxis in patients with COVID-19. The ASH conditionally recommended both critically and acutely ill (Table 2) COVID-19 patients without suspected or diagnosed venous thromboembolism (VTE) receive prophylactic rather than intermediate or therapeutic intensity anticoagulation (Table 1, 3). The panel recognized potential benefit in these therapy recommendations, but noted evidence is low certainty, and therefore encourage clinicians to exercise their own clinical judgment.

ABSTRACT

BACKGROUND: Coronavirus disease 2019 (COVID-19)-related critical illness and acute illness are associated with a risk of venous thromboembolism (VTE). **OBJECTIVE:** These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in decisions about the use of anticoagulation for thromboprophylaxis for patients with COVID-19-related critical illness and acute illness who do not have confirmed or suspected VTE. **METHODS:** ASH formed a multidisciplinary guideline panel and applied strict management strategies to minimize potential bias from conflicts of interest. The panel included 3 patient representatives. The McMaster University GRADE Centre supported the guideline-development process, including performing systematic evidence reviews (up to 19 August 2020). The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE Evidence-to-Decision frameworks, to assess evidence and make recommendations, which were subject to public comment. **RESULTS:** The panel agreed on 2 recommendations. The panel issued conditional recommendations in favor of prophylactic-intensity anticoagulation over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19-related critical illness or acute illness who do not have confirmed or suspected VTE. **CONCLUSIONS:** These recommendations were based on very low certainty in the evidence, underscoring the need for high-quality, randomized

controlled trials comparing different intensities of anticoagulation. They will be updated using a living recommendation approach as new evidence becomes available.

FIGURES

Table 1.

Recommendations

Recommendation	Remarks
Recommendation 1. The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19-related critical illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○)	<ul style="list-style-type: none"> Between the time this recommendation was published online (27 October 2020) and when it was published in <i>Blood Advances</i>, a press release (https://www.nih.gov/news-events/news-releases/nih-activ-trial-blood-thinners-pauses-enrollment-critically-ill-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for patients with COVID-19-related critical illness. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients. Patients with COVID-19-related critical illness are defined as those suffering from an immediately life-threatening condition who would typically be admitted to an intensive care unit. Examples include patients requiring hemodynamic support, ventilatory support, and renal replacement therapy. An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity; risk-assessment models to estimate thrombotic and bleeding risk are available, but they have not been validated for patients with COVID-19; the panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk At present, there is no direct high-certainty evidence comparing different types of anticoagulants; the selection of a specific agent (eg, low-molecular-weight heparin, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19-infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption) This recommendation does not apply to patients who require anticoagulation to prevent thrombosis of extracorporeal circuits such as those on ECMO or CRRT
Recommendation 2. The ASH guideline panel suggests using prophylactic-intensity over intermediate-intensity or therapeutic-intensity anticoagulation for patients with COVID-19-related acute illness who do not have suspected or confirmed VTE (conditional recommendation based on very low certainty in the evidence about effects ⊕○○○)	<ul style="list-style-type: none"> Between the time this recommendation was published online (27 October 2020) and when it was published in <i>Blood Advances</i>, a press release (https://www.nih.gov/news-events/news-releases/full-dose-blood-thinners-decreased-need-life-support-improved-outcome-hospitalized-covid-19-patients) describing the results of a planned interim analysis of 3 randomized controlled trials, REMAP-CAP, ACTIV-4, and ATTACC (NCT 02735707, 04505774, and 04372589, respectively), was issued. In these trials, therapeutic-intensity anticoagulation was compared with prophylactic-intensity anticoagulation for moderately ill hospitalized patients with COVID-19. The ASH guideline panel plans to update this recommendation when the full results of REMAP-CAP, ACTIV-4, and ATTACC become available. Clinicians should weigh the potential benefits and harms based on the most up-to-date available evidence in caring for their patients. Patients with COVID-19-related acute illness are defined as those with clinical features that would typically result in admission to a medicine inpatient ward without requirement for advanced clinical support. Examples include patients with dyspnea or mild to moderate hypoxia. An individualized assessment of the patient's risk of thrombosis and bleeding is important when deciding on anticoagulation intensity; risk-assessment models to estimate thrombotic and bleeding risk are available, but they have not been validated for patients with COVID-19; the panel acknowledges that higher-intensity anticoagulation may be preferred for patients judged to be at high thrombotic risk and low bleeding risk At present, there is no direct high-certainty evidence comparing different types of anticoagulants; the selection of a specific agent (eg, low-molecular-weight heparin, unfractionated heparin, etc) may be based on availability, resources required, familiarity, and the aim of minimizing PPE use or staff exposure to COVID-19-infected patients as well as patient-specific factors (eg, renal function, history of heparin-induced thrombocytopenia, concerns about gastrointestinal tract absorption)

Table 1.

Recommendations

Table 2.

Definitions of target populations

Target population	Definition
Critically ill	<ul style="list-style-type: none">Patients with COVID-19 who develop respiratory or cardiovascular failure normally requiring advanced clinical support in the ICU or CCU, but could include admission to another department if the ICU/CCU was over capacityICU/CCU capacity and admission criteria could vary according to the specific setting
Acutely ill	<ul style="list-style-type: none">Patients with COVID-19 who require hospital admission without advanced clinical support (ie, not to the ICU/CCU), but could include treatment in other settings if the hospital was over capacityHospital capacity and admission criteria could vary according to the specific setting

Table 2.

Definitions of target populations

Table 3.
Classification of anticoagulant regimens by intensity

Regimen
Prophylactic*
Ajolaban 2.5 mg, PO BID (with intent for VTE prophylaxis)
Bemiparin 3500 U, SC OD
Betrixaban 80 mg, PO OD
Betrixaban 160 mg, PO OD
Dabigatran 220 mg, PO OD
Dalteparin 8000 U, SC OD
Enoxaparin 30 mg (3000 U), SC OD (for GFR 15–30)
Enoxaparin 30 mg (3000 U), SC BID (for BMI ≥40 kg/m ²)
Enoxaparin 30 mg (3000 U), SC OD
Enoxaparin 40 mg (4000 U), SC BID (for BMI ≥40 kg/m ²)
Fondaparinux 2.5 mg, SC OD
Unfractionated heparin 6000 U, SC BID
Unfractionated heparin 5000 U, SC TID
Unfractionated heparin 7500 U, SC q24h (for BMI ≥40 kg/m ²)
Nadroparin 2850 U, SC q24h (post-op general surgery)
Nadroparin 5700 U, SC q24h (high-risk medical patients >70 kg)
Nadroparin 3800 U, SC q24h (high-risk medical patients <70 kg or post-op hip replacement surgery)
Rivaroxaban 10 mg, PO OD
Thinzaparin 3500 U, SC OD
Thinzaparin 4500 U, SC OD
Thinzaparin 75 U/kg, SC OD
Intermediate*
Enoxaparin 0.6 mg/kg (50 U/kg), SC BID (if CrCl >30 mL/min)
Enoxaparin 0.6 mg/kg (50 U/kg), SC OD (if CrCl <30 mL/min)
Enoxaparin 30 mg (3000 U), SC BID (for BMI >40 kg/m ²)
Enoxaparin 40 mg (4000 U), SC BID (for CrCl >30 mL/min and BMI <40 kg/m ²)
Enoxaparin 60 mg (6000 U), SC BID (for CrCl <30 mL/min and BMI >40 kg/m ²)
Unfractionated heparin 7500 U, SC TID
Dalteparin 6000 U, SC BID
Therapeutic*
Aenocoumarol, PO (target INR 2.0–3.0 or greater)
Ajolaban 1 mg, PO BID
Ajolaban 10 mg, PO BID
Argatroban, IV to target aPTT therapeutic range as per institutional guidelines
Bemiparin 6000 U, SC OD (if weight >60 kg and CrCl >30 mL/min)
Bemiparin 7500 U, SC OD (if weight 60–70 kg and CrCl >30 mL/min)
Bemiparin 10000 U, SC OD (if weight 70–100 kg and CrCl >30 mL/min)
Bemiparin 115 U/kg, SC OD (if weight >100 kg and CrCl >30 mL/min)
Bivalirudin, IV to target aPTT therapeutic range as per institutional guidelines
Dabigatran 75 mg, PO BID (if CrCl 15–30 mL/min)
Dabigatran 110 mg, PO BID (if age ≥80 y, or ≥76 y and 1 or more risk factors for bleeding)
Dabigatran 150 mg, PO BID (if CrCl >30 mL/min)
Dalteparin 100 U/kg, SC BID
Dalteparin 150 U/kg, SC OD
Dalteparin 200 U/kg, SC OD
Edoxaban 30 mg, PO OD (≥60 kg, CrCl 15–50 mL/min)
Edoxaban 60 mg, PO OD (weight ≥60 kg and CrCl >50 mL/min)
Enoxaparin 0.8 mg/kg, SC BID (for BMI >40 and CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 U/kg), SC BID (for CrCl >30 mL/min)
Enoxaparin 1.5 mg/kg (150 U/kg), SC OD (for CrCl >30 mL/min)
Enoxaparin 1 mg/kg (100 U/kg), SC OD (for CrCl <30 mL/min)
Thinzaparin 175 U/kg, SC OD
Fluindione, PO (target INR 2.0–3.0 or greater)
Fondaparinux 2 mg, SC OD (if weight <60 and CrCl >50 mL/min)
Fondaparinux 6 mg, SC OD (if weight 60–100 kg and CrCl 30–60 mL/min)
Fondaparinux 7.5 mg, SC OD (if weight 60–100 kg and CrCl >60 mL/min)
Fondaparinux 7.5 mg, SC OD (if weight >100 kg and CrCl 30–60 mL/min)
Fondaparinux 10 mg, SC OD (if weight >100 kg and CrCl >60 mL/min)
Unfractionated heparin, IV to target aPTT therapeutic range as per institutional guidelines or anti-Xa activity 0.3–0.7 IU/mL
Unfractionated heparin 250 U/kg, SC q24h
Nadroparin 88 U/kg, SC q24h (for acute coronary syndrome)
Nadroparin 171 U/kg, q24h (for DVT treatment)
Phenprocoumon, PO (target INR 2.0–3.0 or greater)
Rivaroxaban 15 mg, PO BID
Rivaroxaban 15 mg, PO OD (for GFR 15–50 in AF patients)
Rivaroxaban 20 mg, PO OD
Warfarin, PO (target INR 2.0–3.0 or greater)

All atrial fibrillation: aPTT, activated partial thromboplastin time; BID, twice daily; BMI, body mass index; CrCl, creatinine clearance; GFR, glomerular filtration rate; INR, international normalized ratio; OD, once a day; PO, oral; post-op, postoperative; q12h, every 12 hours; q24h, every 24 hours; SC, subcutaneous; TID, 3 times a day.

*Intensity of anticoagulation.

Table 3. Classification of anticoagulant regimens by intensity AF, atrial fibrillation; aPTT, activated partial thromboplastin time; BID, twice daily; BMI, body mass index; CrCl, creatinine clearance; GFR, glomerular filtration rate; INR, international normalized ratio; OD, once a day; PO, oral; post-op, postoperative; q12h, every 12 hours; q24h, every 24 hours; SC, subcutaneous; TID, 3 times a day. *Intensity of anticoagulation.

ADJUSTING PRACTICE DURING COVID-19

METHODOLOGICAL QUALITY OF COVID-19 CLINICAL RESEARCH

Jung RG, Di Santo P, Clifford C, Prosperi-Porta G, Skanes S, Hung A, Parlow S, Visintini S, Ramirez FD, Simard T, Hibbert B.. Nat Commun. 2021 Feb 11;12(1):943. doi: 10.1038/s41467-021-21220-5.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

As part of a systemic review of COVID-19 research quality, a team of molecular biologists, physicians, and statisticians from the University of Ottawa compared the quality of 686 research articles published during the COVID-19 pandemic (Figure 1) to 593 historical controls matched for journal and study design published pre-pandemic. COVID-19 publications had a shorter time to acceptance (13.0 vs. 110 days, $p < 0.0001$) and lower methodological quality scores (Figure 4) compared to historical controls. Authors suggest the push for rapid research during the pandemic may result in lower quality research, and highlight the need for higher quality evidence.

ABSTRACT

The COVID-19 pandemic began in early 2020 with major health consequences. While a need to disseminate information to the medical community and general public was paramount, concerns have been raised regarding the scientific rigor in published reports. We performed a systematic review to evaluate the methodological quality of currently available COVID-19 studies compared to historical controls. A total of 9895 titles and abstracts were screened and 686 COVID-19 articles were included in the final analysis. Comparative analysis of COVID-19 to historical articles reveals a shorter time to acceptance [13.0[IQR, 5.0-25.0] days vs. 110.0[IQR, 71.0-156.0] days in COVID-19 and control articles, respectively; $p < 0.0001$]. Furthermore, methodological quality scores are lower in COVID-19 articles across all study designs. COVID-19 clinical studies have a shorter time to publication and have lower methodological quality scores than control studies in the same journal. These studies should be revisited with the emergence of stronger evidence.

FIGURES

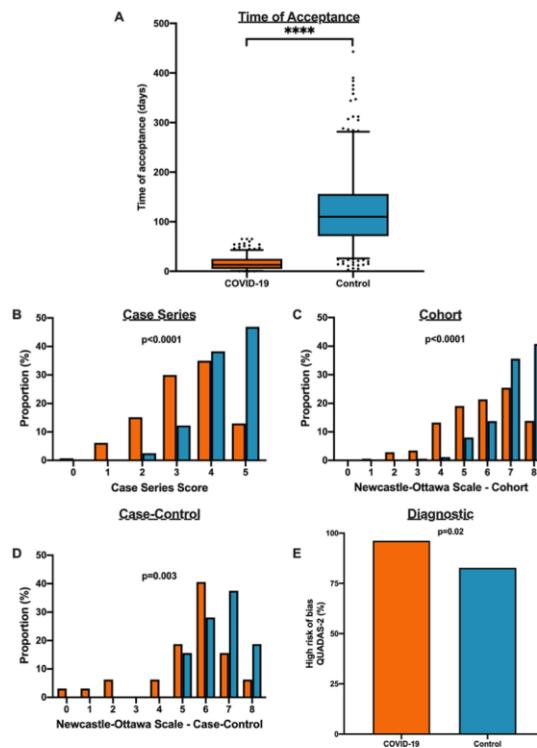
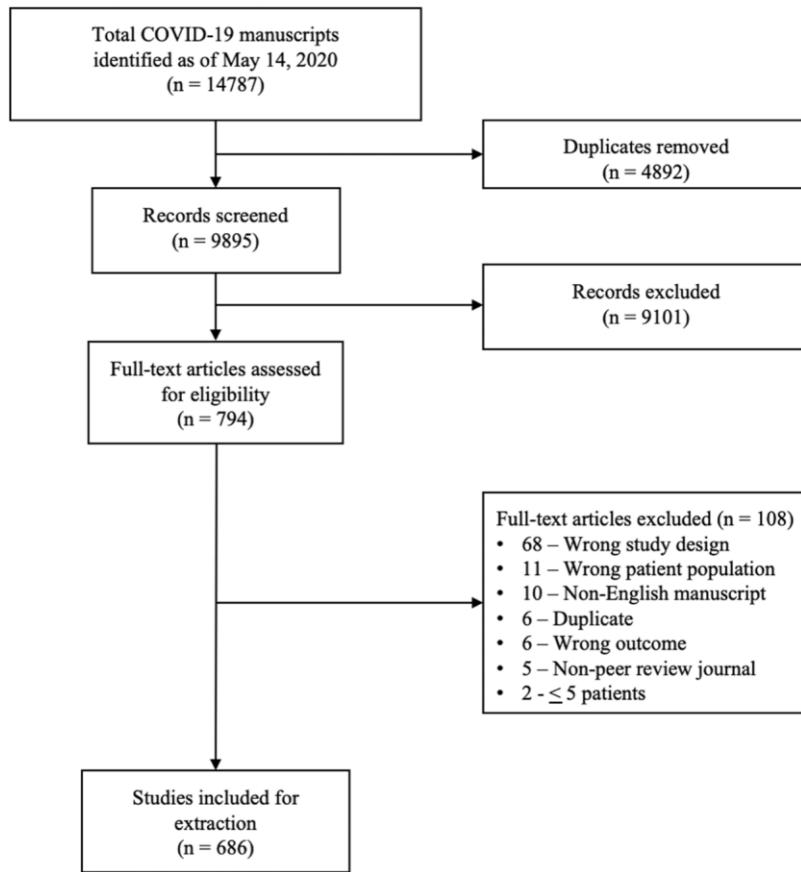


Fig. 4 Differences in methodological quality scores in COVID-19 compared to historical control articles. **A** Time to acceptance was reduced in COVID-19 articles compared to control articles (13.0 [IQR, 5.0-25.0] days vs. 110.0 [IQR, 71.0-156.0] days, $n = 347$ for COVID-19 and $n = 414$ for controls; $p < 0.0001$). **B** When compared to historical control articles, COVID-19 articles were associated with lower case series score ($n = 277$ for COVID-19 and $n = 277$ for controls; $p < 0.0001$). **C** COVID-19 articles were associated with lower NOS cohort score compared to historical control articles ($n = 174$ for COVID-19 and $n = 174$ for controls; $p < 0.0001$). **D** COVID-19 articles were associated with lower NOS case-control score compared to historical control articles ($n = 32$ for COVID-19 and $n = 32$ for controls; $p = 0.003$). **E** COVID-19 articles were associated with higher diagnostic risk of bias (QUADAS-2) compared to historical control articles ($n = 53$ for COVID-19 and $n = 53$ for controls; $p = 0.02$). For panel **A**, boxplot captures 5, 25, 50, 75 and 95% from the first to last whisker. Orange represents COVID-19 articles and blue represents control articles. Two-sided Mann-Whitney U-test was conducted to evaluate differences in time to acceptance between COVID-19 and control articles. Differences in study quality scores were evaluated by two-sided Kruskal-Wallis test. Differences in diagnostic risk of bias were quantified by Chi-squares test. $p < 0.05$ was considered statistically significant.

Fig. 1: Literature search and selection of COVID-19 articles.

From: Methodological quality of COVID-19 clinical research



MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

AN INVERSE STAGE-SHIFT MODEL TO ESTIMATE THE EXCESS MORTALITY AND HEALTH ECONOMIC IMPACT OF DELAYED ACCESS TO CANCER SERVICES DUE TO THE COVID-19 PANDEMIC

Degeling K, Baxter NN, Emery J, Jenkins MA, Franchini F, Gibbs P, Mann GB, McArthur G, Solomon BJ, IJzerman MJ.. Asia Pac J Clin Oncol. 2021 Feb 10. doi: 10.1111/ajco.13505. Online ahead of print.

Level of Evidence: 5 - Modeling

BLUF

Experts in cancer treatment and epidemiology from several Australian institutions modeled the impact of delayed diagnosis and treatment due to COVID-19 restrictions on the prognosis of breast, colon, and lung cancer patients. Using stage-shift scenarios outcomes from historical stage I/T1 to stage II/T2 progression of the disease (Table 1, Figure 1), the authors found a 3-month delay in time to treatment initiation (TTI) lead to 88 excess deaths and over \$12 million in excess healthcare costs over a 5 year period (Table 2) and a 6-month delay to 349 excess deaths and over \$46 million in expenses. Authors suggest the consequences of cancer treatment delays related to COVID-19 restrictions are of concern, though because their results focus

on stage I to stage II progression they recommend analyzing additional stage shifts for a more comprehensive understanding of restriction impacts.

ABSTRACT

AIM: Decreased cancer incidence and reported changes to clinical management indicate that the COVID-19 pandemic has delayed cancer diagnosis and treatment. This study aimed to develop and apply a flexible model to estimate the impact of delayed diagnosis and treatment on survival outcomes and healthcare costs based on a shift in the disease stage at treatment initiation. **METHODS:** A model was developed and made publicly available to estimate population-level health economic outcomes by extrapolating and weighing stage-specific outcomes by the distribution of stages at treatment initiation. It was applied to estimate the impact of 3- and 6-month delays based on Australian data for stage I breast cancer, colorectal cancer, and lung cancer patients, and for T1 melanoma. Two approaches were explored to estimate stage shifts following a delay: (a) based on the relation between time to treatment initiation and overall survival (breast, colorectal, and lung cancer), and (b) based on the tumor growth rate (melanoma). **RESULTS:** Using a conservative once-off 3-month delay and considering only shifts from stage I/T1 to stage II/T2, 88 excess deaths and \$12 million excess healthcare costs were predicted in Australia over 5 years for all patients diagnosed in 2020. For a 6-month delay, excess mortality and healthcare costs were 349 deaths and \$46 million over 5 years. **CONCLUSIONS:** The health and economic impacts of delays in treatment initiation cause an imminent policy concern. More accurate individual patient data on shifts in stage of disease during and after the COVID-19 pandemic are critical for further analyses.

FIGURES

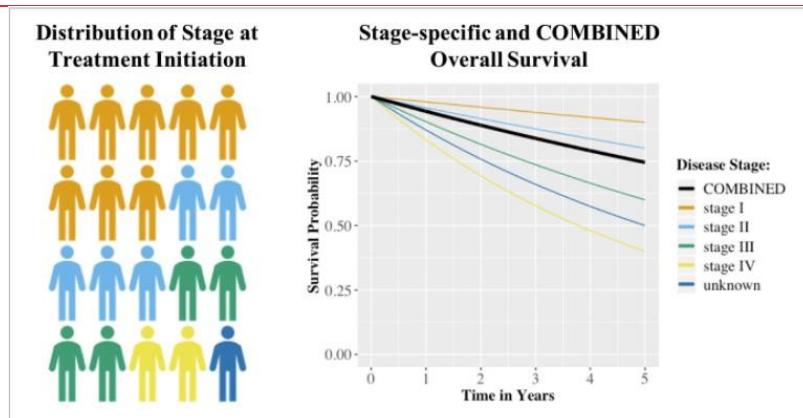


Figure 2. Graphical illustration of how the combined overall survival for a patient population is obtained by weighting stage-specific survival estimates by the stage distribution at treatment initiation

	Breast Cancer	Colorectal Cancer	Lung Cancer	Melanoma
Predicted incidence for 2020 (#)	19 998	16 634	13 092	15 691
Stage at Treatment Initiation (%)				
stage I / T1	43.0	22.1	11.7	61.8
stage II / T2	34.7	24.3	6.5	13.6
stage III / T3	12.1	23.6	11.2	10.2
stage IV / T4	4.6	17.7	42.2	6.6
stage unknown	5.5	12.3	28.5	7.8
1-year survival (%)				
stage I / T1	100.0	99.3	90.8	99.2
stage II / T2	99.9	96.4	69.8	98.0
stage III / T3	98.1	93.5	57.8	97.2
stage IV / T4	69.2	49.3	19.2	94.8
stage unknown	89.5	75.9	43.6	89.9

TABLE 1. Overview of the cancer type and stage-specific data used for estimating the impact in terms of survival and 5-year healthcare costs, with TNM classification and relative survival probabilities for breast, colorectal, and lung cancer, and T-stage classification and overall survival probabilities for melanoma

	Breast Cancer		Colorectal Cancer		Lung Cancer		Melanoma	
	3 Month Delay	6 Month Delay	3 Month Delay	6 Month Delay	3 Month Delay	6 Month Delay	3 Month Delay	6 Month Delay
Stage Progression								
Probability of progression from I to II or T1 to T2	5.6%	10.9%	3.0%	5.9%	8.3%	16.0%	32.0%	64.0%
% of patients who progressed	1.4%	5.5%	0.7%	2.9%	2.1%	8.0%	8.0%	32.0%
Health Outcomes								
Excess deaths after 5 years	7	25	3	11	11	43	67	270
Life years lost over a 5-year time horizon	20	64	7	29	44	170	195	791
Life years lost over a 10-year time horizon	77	239	24	96	98	373	626	2584

TABLE 2. Results of the exploratory analyses for the 2020 Australian incident populations, only considering shifts from stage I to stage II (breast cancer, colorectal cancer and lung cancer) and stage T1 to stage T2 (melanoma)

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN DIAGNOSTICS

HEAD-TO-HEAD COMPARISON OF SARS-COV-2 ANTIGEN-DETECTING RAPID TEST WITH PROFESSIONAL-COLLECTED NASAL VERSUS NASOPHARYNGEAL SWAB

Lindner AK, Nikolai O, Rohardt C, Burock S, Hülso C, Bölke A, Gertler M, Krüger LJ, Gaeddert M, Tobian F, Lainati F, Seybold J, Jones TC, Hofmann J, Sacks JA, Mockenhaupt FP, Denkinger CM.. Eur Respir J. 2021 Feb 11:2004430. doi: 10.1183/13993003.04430-2020. Online ahead of print.

Level of Evidence: 4 - Case-series, case-control, or historically controlled studies

BLUF

A diagnostic accuracy study conducted at Charité, Universitätsmedizin Berlin during late 2020 by authors from the Berlin Institute of Health found anterior nasal sampling for detection of COVID-19 had similar sensitivity and specificity to nasopharyngeal sampling (Table 1), suggesting that supervised self-sampling may provide similar accuracy to professional nasopharyngeal sampling.

SUMMARY

- The study utilized antigen-detecting rapid diagnostic tests.
- Due to discomfort from the Nasopharyngeal (NP) swab samples, researchers wanted to see if anterior nasal (AN) swabs would have similar sensitivity and specificity of sample detection.
- For 289 participants, almost all (97.6%) had symptoms consistent with COVID-19.
- For AN sampling: sensitivity was 74.4% and specificity was 99.2%. For NP sampling: sensitivity was 79.5% and specificity was 99.6%

FIGURES

No.	AN swab self-collected SD Q Ag-RDT	NP swab prof.-collected SD Q Ag-RDT	OP/NP swab RT-PCR		Symptom duration (days)
			CT value	Viral load ³	
1	pos (+++)	pos (+++)	17.33 ¹	9.59	2
2	pos (++)	pos (+++)	17.86 ¹	9.43	1
3	pos (+++)	pos (+++)	18.01 ¹	9.38	1
4	pos (++)	pos (+++)	18.31 ¹	9.29	3
5	pos (+++)	pos (+++)	18.40 ¹	9.27	3
6	pos (+++)	pos (+++)	18.76 ¹	9.16	4
7	pos (+++)	pos (+++)	18.77 ¹	9.16	5
8	pos (+++)	pos (+++)	18.78 ¹	9.16	5
9	pos (+++)	pos (+++)	19.05 ¹	9.08	3
10	pos. (+++)	pos. (+++)	19.40 ¹	8.97	2
11	neg.	pos (+++)	19.66 ¹	8.90	1
12	pos (+++)	pos (+++)	20.32 ¹	8.70	3
13	pos (+++)	pos (+++)	17.81 ²	8.68	4
14	pos (++)	pos (+++)	20.44 ¹	8.67	2
15	pos (++)	pos (++)	20.54 ¹	8.63	5
16	pos (+++)	pos (+++)	21.09 ¹	8.47	4
17	pos (+++)	pos (+)	18.62 ²	8.44	4
18	pos (+)	pos (++)	21.87 ¹	8.24	7
19	pos (++)	pos (+++)	19.34 ²	8.23	5
20	pos (++)	pos (+++)	22.05 ¹	8.19	2
21	pos (+++)	pos (+++)	19.47 ²	8.19	6
22	pos (+++)	pos (+++)	22.60 ¹	8.03	6
23	pos (+++)	pos (++)	23.66 ¹	7.71	6
24	pos (+)	pos (++)	26.42 ¹	6.90	5
25	pos (+++)	pos (+++)	26.77 ¹	6.79	5
26	neg.	neg.	24.25 ²	6.78	10
27	pos (++)	pos (+++)	24.77 ²	6.62	4
28	pos (+++)	pos (++)	25.29 ²	6.46	2
29	pos (+)	pos (++)	29.33 ¹	6.03	5
30	neg.	neg.	29.56 ¹	5.97	3
31	neg.	neg.	29.95 ¹	5.85	3
32	pos (+)	pos (+)	30.25 ¹	5.76	4
33	neg.	neg.	27.81 ²	5.72	8
34	pos (++)	pos (+)	31.20 ¹	5.48	8
35	neg.	pos (+)	31.61 ¹	5.36	10
36	neg.	neg.	32.58 ¹	5.07	10
37	neg.	neg.	32.86 ¹	4.99	2
38	neg.	neg.	34.62 ¹	4.47	7
39	neg.	neg.	35.53 ¹	4.20	14
Sensitivity 29/39 (74.4%)		Sensitivity 31/39 (79.5%)			
Positive percent agreement ⁴					

¹ Roche Cobas SARS-CoV-2 assay (E-gene, T2 target)

² Tib Molbiol assay, E-gene target.

³ log₁₀ RNA SARS-CoV2/swab

⁴ including 2 false positives on AN and 1 on NP

TABLE 1 Antigen-detecting RDT results with a supervised self-collected anterior nasal (AN) swab and with a professional-collected nasopharyngeal (NP) swab in RT-PCR positive patients from combined oro-/nasopharyngeal swab.

SENSITIVITY OF ANTI-SARS-COV-2 SEROLOGICAL ASSAYS IN A HIGH-PREVALENCE SETTING

Müller L, Ostermann PN, Walker A, Wienemann T, Mertens A, Adams O, Andree M, Hauka S, Lübke N, Keitel V, Drexler I, Di Cristanziano V, Hermsen DF, Kaiser R, Boege F, Klein F, Schaal H, Timm J, Senff T.. Eur J Clin Microbiol Infect Dis. 2021 Feb 3. doi: 10.1007/s10096-021-04169-7. Online ahead of print.

Level of Evidence: 4 - Case-control studies, or “poor or non-independent reference standard

BLUF

German virologists, lab scientists, and an infectious disease physician conducted neutralizing titer and immunofluorescence testing of serum from 42 contacts of an RT-PCR confirmed SARS-CoV-2 positive patient and compared the results to four commercially available antibody tests (see summary). They found all tests detected presence of antibodies with the two nucleocapsid based tests showing a slightly higher sensitivity (65.4% Roche, 61.54% Abbott) compared with the two spike protein based tests (EI IgG or IgA 46.2%, DiaSorin 61.54%) (Table 2), though spike protein based tests better correlated with functional antibody neutralization compared to nucleocapsid antigen based tests ($r=.7625$ and $r=.6886$ vs $r=.4579$ and $r=.3523$) (Figure 2). Authors suggest commercially available antibody testing can detect SARS-CoV-2 specific antibodies, though N-immunoassays appear to be more sensitive while spike assays better predict neutralization titers.

SUMMARY

"Our study included the (i) EUROIMMUN(EI)-anti-SARS-CoV-2 IgA and IgG ELISA test, which contains the S1 subunit of the spike protein (EI S1 IgG or EI S1 IgA); (ii) the LIAISON® SARS-CoV-2 S1/S2 IgG CLIA test, containing the S1 and S2 domain of the spike protein (DiaSorin S1/S2 IgG); (iii.)the SARS-CoV-2 IgG CMIA from Abbott detecting anti-nucleocapsid IgG antibodies (Abbott N IgG) and (iv) the Elecsys® anti-SARS-CoV-2 ECLIA test from Roche which uses biotinylated and ruthenylated nucleocapsid antigen for the determination of antibodies against SARS-CoV-2 (Roche N Ab)."

ABSTRACT

Evaluation and power of seroprevalence studies depend on the performed serological assays. The aim of this study was to assess four commercial serological tests from EUROIMMUN, DiaSorin, Abbott, and Roche as well as an in-house immunofluorescence and neutralization test for their capability to identify SARS-CoV-2 seropositive individuals in a high-prevalence setting. Therefore, 42 social and working contacts of a German super-spreader were tested. Consistent with a high-prevalence setting, 26 of 42 were SARS-CoV-2 seropositive by neutralization test (NT), and immunofluorescence test (IFT) confirmed 23 of these 26 positive test results (NT 61.9% and IFT 54.8% seroprevalence). Four commercial assays detected anti-SARS-CoV-2 antibodies in 33.3-40.5% individuals. Besides an overall discrepancy between the NT and the commercial assays regarding their sensitivity, this study revealed that commercial SARS-CoV-2 spike-based assays are better to predict the neutralization titer than nucleoprotein-based assays are.

FIGURES

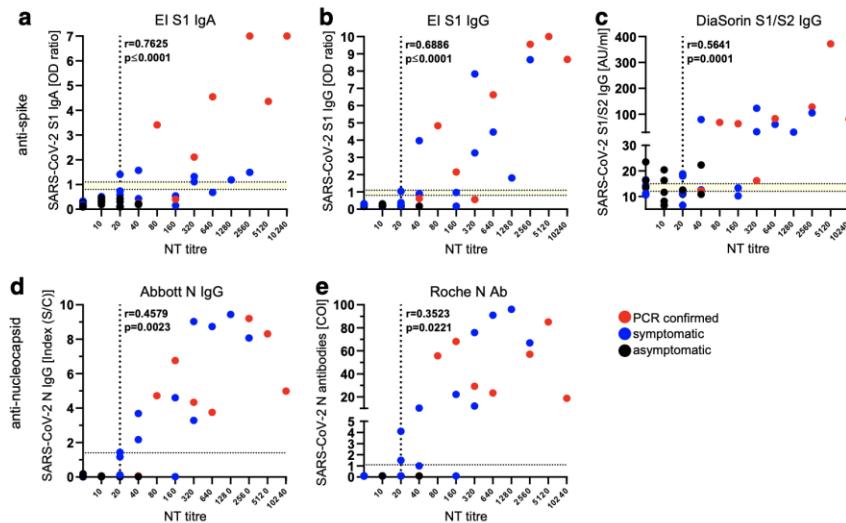


Fig. 2 Correlation between commercial SARS-CoV-2 antibody tests and the neutralization titer, Heinsberg District, Germany, April 2020 ($n = 42$). AU: arbitrary units; COI: cut-off index; EI: EUROIMMUN; N: nucleocapsid; NT: neutralization test; OD: optical density; r: correlation coefficient; S1: spike domain 1; S2: spike domain 2; S/C: sample/control; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. The reciprocal of the NT titre is depicted. RT-PCR-confirmed SARS-CoV-2 infections are depicted in red and symptomatic individuals in blue. All

asymptomatic individuals are displayed in black. **a** and **b** EUROIMMUN-anti-SARS-CoV-2 IgA and IgG ELISA (Euroimmun). **c** LIAISON® SARS-CoV-2 S1/S2 IgG (DiaSorin). **d** SARS-CoV-2 IgG CMIA (Abbott). **e** Elecsys® anti-SARS-CoV-2 ECLIA test (Roche). The dotted lines indicate the cut-off values recommended by the respective manufacturer to determine positive and negative test results. The borderline area if applicable is indicated in yellow and the vertical line represents the positive cut-off of an NT titre ≥ 20

Table 2

Performance characteristics of the EUROIMMUN, DiaSorin, Roche, and Abbott SARS-CoV-2 antibody platforms, Heinsberg District, Germany, April 2020 ($n = 26$)

		EUROIMMUN			DiaSorin	Roche	Abbott
		S1 IgA	S1 IgG	S1 IgA and/or IgG	S1/S2 IgG	N antibodies	N IgG
Overall NT positive	n/N	12/26	12/26	14/26	16/26	17/26	16/26
≥ 20	Value	0.462	0.462	0.538	0.615	0.654	0.615
	(95% CI)	0.288-0.645	0.288-0.645	0.355-0.712	0.425-0.776	0.462-0.806	0.425-0.776

For sensitivity calculations of the commercial assays, only the NT-positive samples (≥ 20) were used

CI confidence interval; N nucleocapsid; NT: neutralization test; S spike

DEVELOPMENTS IN TREATMENTS

POST-EXPOSURE PROTECTION OF SARS-COV-2 LETHAL INFECTED K18-HACE2 TRANSGENIC MICE BY NEUTRALIZING HUMAN MONOCLONAL ANTIBODY

Rosenfeld R, Noy-Porat T, Mechaly A, Makdasi E, Levy Y, Alcalay R, Falach R, Aftalion M, Epstein E, Gur D, Chitlari T, Vitner EB, Melamed S, Politi B, Zauberan A, Lazar S, Beth-Din A, Evgy Y, Yitzhaki S, Shapira SC, Israely T, Mazor O.. Nat Commun. 2021 Feb 11;12(1):944. doi: 10.1038/s41467-021-21239-8.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers from the Israel Institute for Biological Research in Ness-Ziona, Israel analyzed the efficacy of monoclonal MD65 antibodies in K18-hACE2 transgenic mice with SARS-CoV-2 infection, finding a greater survival rate compared to mice without MD65 antibodies, in the setting of both prophylactic and post-exposure administration (Figure 3), as well as decreased viral load in lung tissue (Figure 4). 100% of mice treated with MD65 antibodies within 3 days of exposure survived infection, while only 20% without antibodies survived. The authors suggest these results demonstrate promising outcomes that may translate to human prophylaxis and treatment of COVID-19.

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), exhibits high levels of mortality and morbidity and has dramatic consequences on human life, sociality and global economy. Neutralizing antibodies constitute a highly promising approach for treating and preventing infection by this novel pathogen. In the present study, we characterize and further evaluate the recently identified human monoclonal MD65 antibody for its ability to provide protection against a lethal SARS-CoV-2 infection of K18-hACE2 transgenic mice. Eighty percent of the untreated mice succumbed 6-9 days post-infection, while administration of the MD65 antibody as late as 3 days after exposure rescued all infected animals. In addition, the efficiency of the treatment is supported by prevention of morbidity and ablation of the load of infective virions in the lungs of treated animals. The data demonstrate the therapeutic value of human monoclonal antibodies as a life-saving treatment for severe COVID-19 infection.

FIGURES

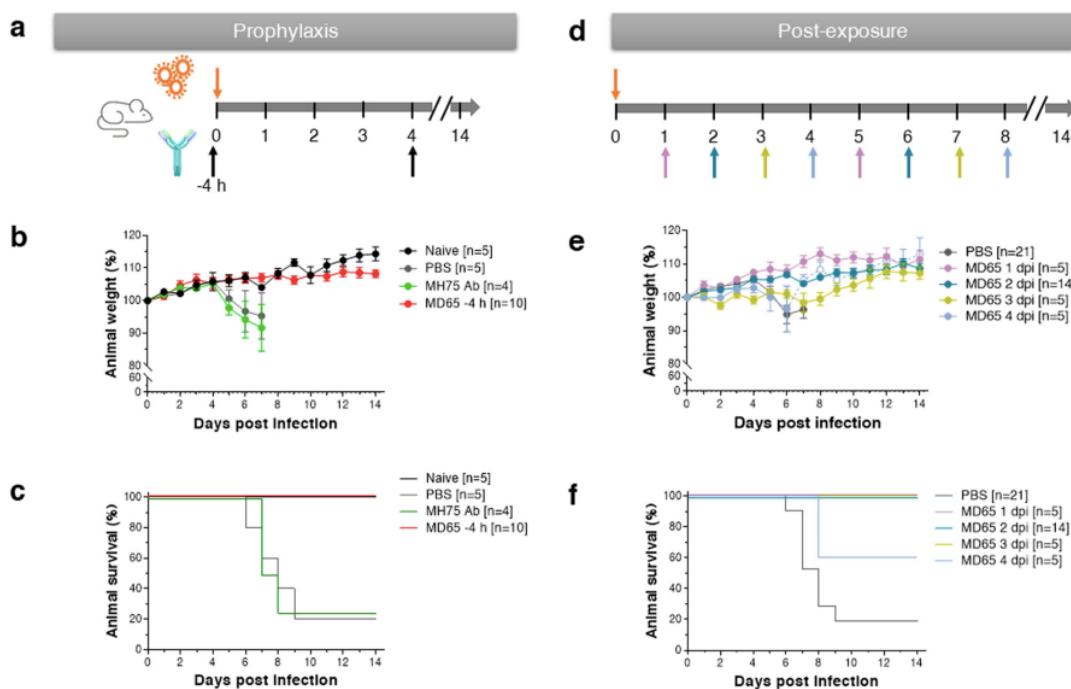


Figure 3 MD65 Ab-mediated prophylactic and post-exposure protection against SARS-CoV-2-infected K18-hACE2 mice. Prophylactic (a–c) or postexposure (d–f) in vivo protection experiments. Animals were intranasal infected with

200 PFU of SARS-CoV-2 BavPat1/2020 strain and IP administered with 1 mg/mouse of MD65 Ab at the indicated time points and 4 days later, for a second time. a Schematic description of the experimental design of the prophylactic treatment. b Body weight profiles. c Kaplan–Meyer surviving curves. Curves describe mice treated with the MD65 antibody (red line), naïve untreated and un-infected animals (black line), animals administered with PBS (gray line) or the isotype control irrelevant-Ab (anti-ricin MH75; green line) at the same time point as the MD65 treatment. d Schematic description of the experimental design of the post-exposure treatment. e Body weight profiles. f Kaplan–Meyer surviving curves. Curves describe mice treated with the MD65 antibody at various time points post-infection, as indicated by different colors in the legend within the panel and by the similarly colored arrows in panel d. Control animals (gray curves) were administered with PBS at day 2 and day 6 after infection. Body weight change is displayed as the percentage of initial weight. Only data of the first 7 days are presented in the control groups exhibiting significant mortality. In case of the mice treated 4 dpi (panel e), the weight of the surviving animals is indicated by hollow circles and dashed line. Data represent means ± SEM. The n numbers indicate the number of animals within each experimental group; when n > 5, the results were combined from several experiments in which each group included at least four animals.

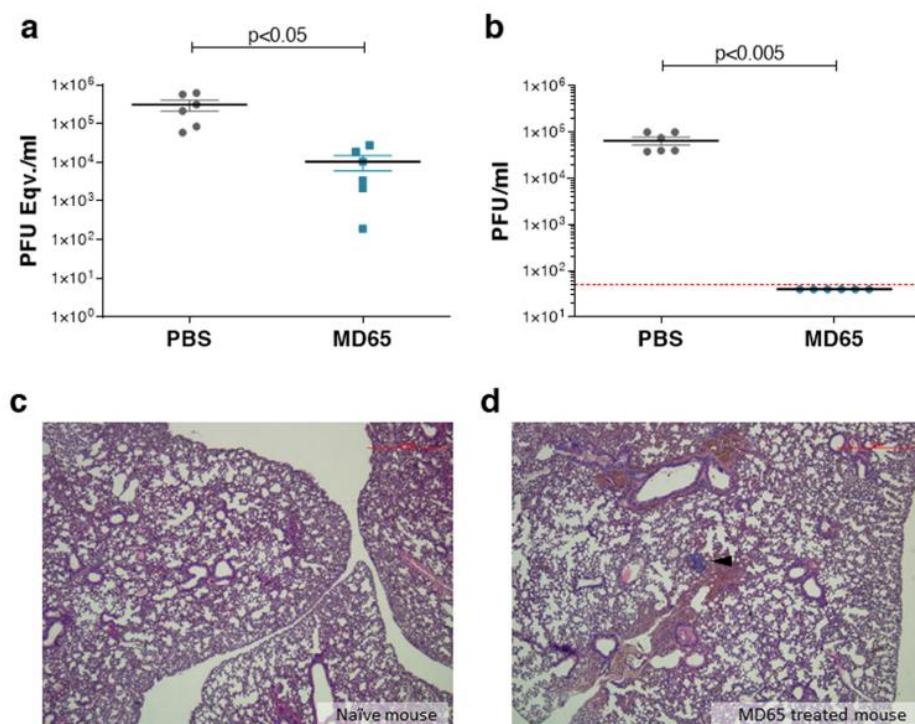


Figure 4. Viral load determination and histological analysis of lungs, collected from K18-hACE2 mice, infected with SARS-CoV-2, and treated 2 dpi with MD65 antibody. a, b Viral load in lung samples, collected 6 dpi from PBS-treated mice ($n = 6$, gray dots) and mice treated 2 dpi with 1 mg MD65 antibody ($n = 6$, turquoise dots). a Viral load was quantified by qRT-PCR and expressed as equivalents of PFU/ml. b Infectious viral load determined by plaque assay. Dotted red line indicates the assay limit of detection. Data in a, b represent individual values and mean ± SEM. Horizontal bars indicate statistical significance of paired values. P values calculated using two-tailed paired t-test were: in panel a—0.0295 and in panel b—0.0031. c, d Histological analysis of lung sections, collected 21 dpi from a naïve mouse (c) and a mouse that was infected with SARS-CoV-2 and treated 2 dpi with 1 mg MD65 antibody (d); black arrow indicates lymphoid aggregate. The panels include representative images ($n = 2$ for the naïve mice and $n = 6$ for the MD65-treated mice, which were independently infected and analyzed, yielding similar results; full images of the lungs are provided in Supplementary Fig. 3).

Magnification = ×40.

SARS-COV-2 INFECTION IS EFFECTIVELY TREATED AND PREVENTED BY EIDD-2801

Wahl A, Gralinski LE, Johnson CE, Yao W, Kovarova M, Dinnon KH 3rd, Liu H, Madden VJ, Krzystek HM, De C, White KK, Gully K, Schäfer A, Zaman T, Leist SR, Grant PO, Bluemling GR, Kolykhalov AA, Natchus MG, Askin FB, Painter G, Browne EP, Jones CD, Pickles RJ, Baric RS, Garcia JV.. Nature. 2021 Feb 9. doi: 10.1038/s41586-021-03312-w. Online ahead of print. Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Translational scientists, molecular biologists, and drug development experts from the University of North Carolina, Chapel Hill created human lung-only mice (LoM) models to evaluate the replication of the three human coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2) and test a newly emerging antiviral treatment (EIDD-2801). They found SARS-CoV-2 successfully replicated in LoM models (Figure 1) and that EIDD-2801 reduced the number of infectious particles by 4.4 logs within as quickly as two days of treatment (Figure 4). Authors suggest their results indicate the potential strength of a new therapy (EIDD-2801) and further supports the use of LoM models as a means for viral research.

ABSTRACT

All known recently emerged human coronaviruses probably originated in bats¹. Here we used a single experimental platform based on human lung-only mice (LoM) to demonstrate efficient *in vivo* replication of all recently emerged human coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2) and two highly relevant endogenous pre-pandemic SARS-like bat coronaviruses. Virus replication in this model occurs in bona fide human lung tissue and does not require any type of adaptation of the virus or the host. Our results indicate that bats harbour endogenous coronaviruses capable of direct transmission into humans. Further detailed analysis of pandemic SARS-CoV-2 *in vivo* infection of LoM human lung tissue showed predominant infection of human lung epithelial cells, including type II pneumocytes present in alveoli and ciliated airway cells. Acute SARS-CoV-2 infection was highly cytopathic and induced a robust and sustained type I interferon and inflammatory cytokine/chemokine response. Finally, we evaluated a therapeutic and pre-exposure prophylaxis strategy for coronavirus infection. Our results show that therapeutic and prophylactic administration of EIDD-2801, an oral broad spectrum antiviral currently in phase II-III clinical trials, dramatically inhibited SARS-CoV-2 replication *in vivo* and thus has significant potential for the prevention and treatment of COVID-19.

FIGURES

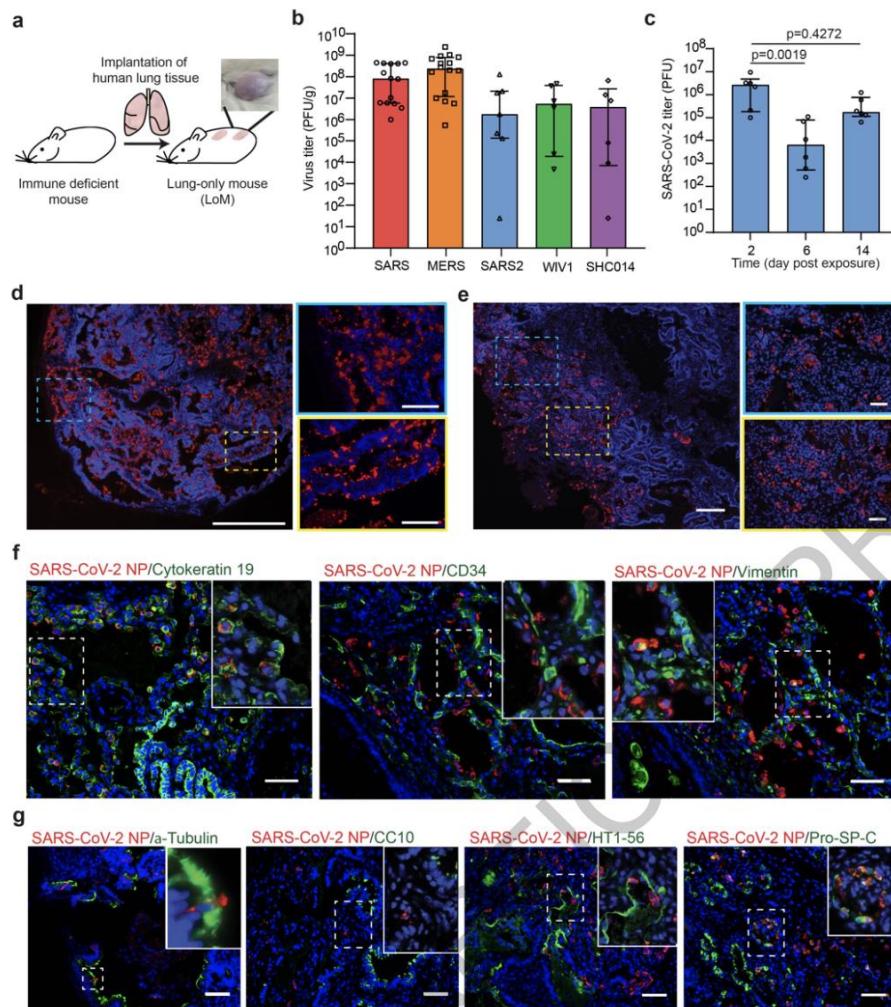


Fig. 1 | Robust replication of recently emerged human and bat coronaviruses in LoM demonstrate the potential of bat coronaviruses for direct transmission to humans and the predilection of SARS-CoV-2 for infection of human epithelial cells. **a**, LoM construction and image of a human lung implant. **b**, Viral titers in the human lung tissue of LoM injected with SARS-CoV (n=14, red), MERS-CoV (n=16, orange), SARS-CoV-2 (n=7, blue), WIV1-CoV (n=6, green), or SHC014 (n=6, purple) as determined by plaque assay (PFU, plaque forming units). **c**, SARS-CoV-2 titers in the human lung tissue of LoM at days 2 (n=6), 6 (n=6), and 14 (n=6) post-exposure were compared with a two-sided Kruskal-Wallis with Dunn's multiple comparisons test. **d**, SARS-CoV-2 RNA in LoM human lung tissue 2 days post-exposure (SARS-CoV-2 RNA+, red; nuclei, blue; scale bars, 750 μm [left image] and 250 μm [right images], n=3). **e**, Virus nucleoprotein in LoM human lung tissue two-days post-exposure

(positive cells, red; nuclei, blue; scale bars 200 μm [left image] and 50 μm [right images], n=6). **f**, Co-staining of LoM human lung tissue two days following SARS-CoV-2 exposure for virus nucleoprotein (red) and cytokeratin 19 (epithelial cells, green, n=6), CD34 (endothelial cells, green, n=4), or vimentin (mesenchymal cells, green, n=4). Nuclei, blue; scale bars 50 μm. **g**, Co-staining of LoM human lung tissue two days following SARS-CoV-2 exposure for virus nucleoprotein (red) and acetylated alpha-tubulin IV (ciliated cells, green, n=6), CC10 (club cells, green, n=6), HT1-56 (alveolar type 1 cells, green, n=6), or Pro-SP-C (alveolar type 2 cells, green, n=3). Nuclei, blue; scale bars 50 μm. In **b** and **c**, horizontal and vertical lines represent the median and interquartile range respectively. n= number of biologically independent lung tissues analyzed.

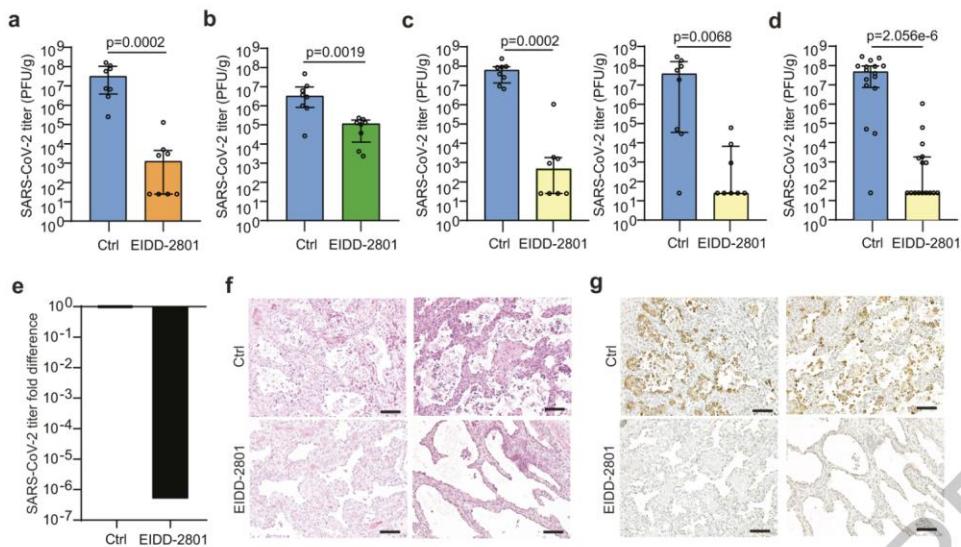


Fig. 4 | Treatment and pre-exposure prophylaxis with EIDD-2801, a broad-spectrum anti-coronavirus drug, potently inhibit SARS-CoV-2 infection in vivo. **a**, SARS-CoV-2 titers in the human lung tissue of LoM administered EIDD-2801 (n=8) or vehicle (n=8) 24 h post virus exposure. **b**, SARS-CoV-2 titers in the human lung tissue of LoM administered EIDD-2801 (n=8) or vehicle (n=8) 48 h post virus exposure. **c** and **d**, SARS-CoV-2 titers in the human lung tissue of LoM administered EIDD-2801 (n=8 per experiment, yellow) or control vehicle (Ctrl, n=8 per experiment, blue) at 2 days post-exposure in two independent experiments shown **c**, separately and **d**,

combined. **e**, Fold difference in SARS-CoV-2 titers in the human lung tissue of LoM relative to vehicle controls. **f**, H&E staining and **g**, immunohistochemical staining for virus nucleoprotein (positive cells, brown) of human lung tissue of LoM administered EIDD-2801 (n=8) or control vehicle (Ctrl, n=8) at 2 days post-exposure (scale bars, 100 μ m). **a-d**, Titors were compared with a two-tailed Mann-Whitney U test. Horizontal and vertical lines represent the median and interquartile range respectively. n = number of biologically independent lung tissues analyzed.

REMDESIVIR METABOLITE GS-441524 EFFECTIVELY INHIBITS SARS-COV-2 INFECTION IN MOUSE MODELS

Li Y, Cao L, Li G, Cong F, Li Y, Sun J, Luo Y, Chen G, Li G, Wang P, Xing F, Ji Y, Zhao J, Zhang Y, Guo D, Zhang X.. J Med Chem. 2021 Feb 1. doi: 10.1021/acs.jmedchem.0c01929. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Drug discovery and synthesis experts from Shenzhen, China compared the anti-SARS-CoV-2 activity of remdesivir and its metabolite GS-441524 in an in-vitro and in-vivo laboratory study. They found GS-441524 more effectively inhibited SARS-CoV-2 replication in Vero E6 than remdesivir (IC_{50} 0.70 vs 1.35 μ M, Figure 2). In vivo, GS-441524 significantly decreased viral titers by qRT-PCR in both AAV-hACE2 and MHV infected mouse models (Figures 4, 5). Authors suggest GS-441524, which has a longer half-life than remdesivir, is a valuable potential therapeutic option for COVID-19.

ABSTRACT

The outbreak of coronavirus disease 2019 (COVID-19) has resulted in a global pandemic due to the rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the time of this manuscript's publication, remdesivir is the only COVID-19 treatment approved by the United States Food and Drug Administration. However, its effectiveness is still under question due to the results of the large Solidarity Trial conducted by the World Health Organization. Herein, we report that the parent nucleoside of remdesivir, GS-441524, potently inhibits the replication of SARS-CoV-2 in Vero E6 and other cell lines. Challenge studies in both an AAV-hACE2 mouse model of SARS-CoV-2 and in mice infected with murine hepatitis virus, a closely related coronavirus, showed that GS-441524 was highly efficacious in reducing the viral titers in CoV-infected organs without notable toxicity. Our results support that GS-441524 is a promising and inexpensive drug candidate for treating of COVID-19 and other CoV diseases.

FIGURES

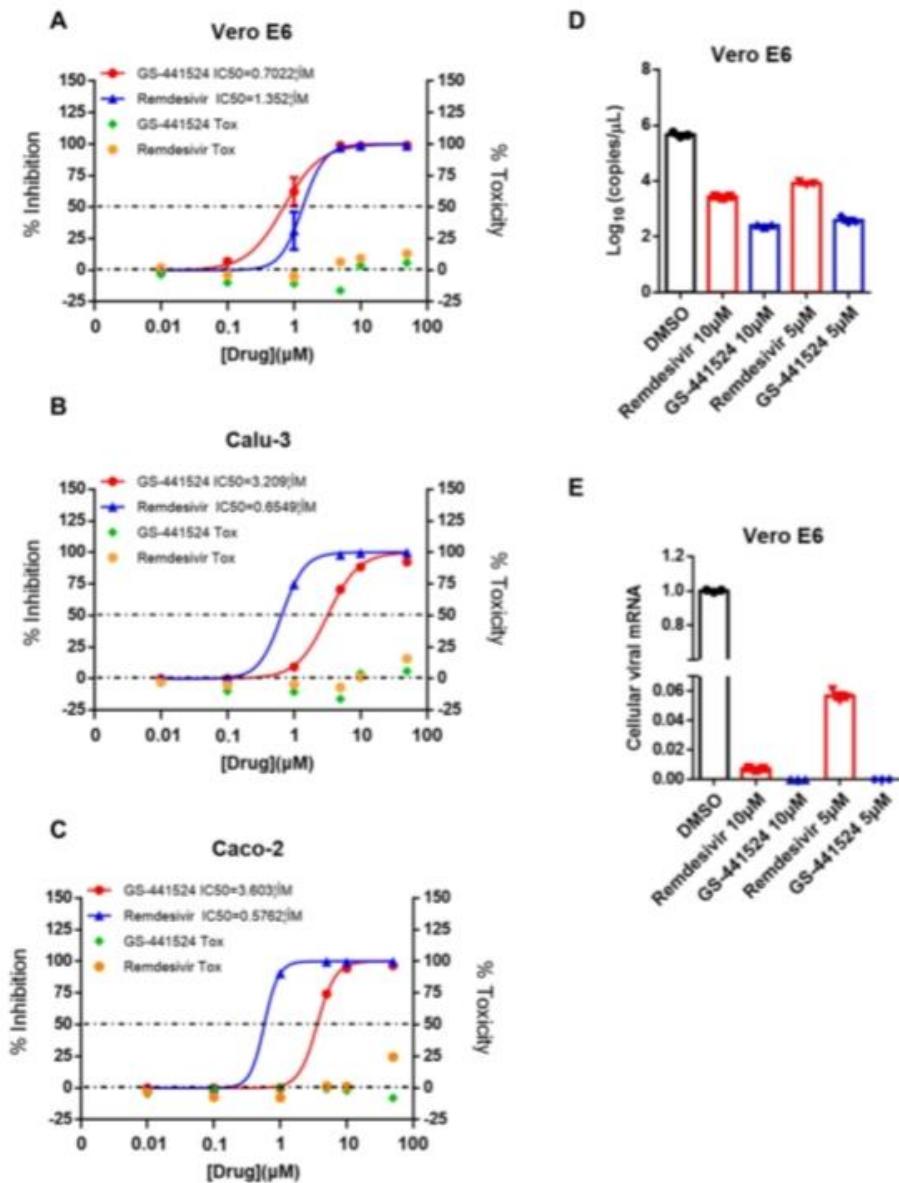


Figure 2: "Remdesivir and GS-441524 potently inhibit SARS-CoV-2 replication in vitro. Vero E6 (A), Calu-3 (B), and Caco-2 (C) were infected with SARS-CoV-2 at an MOI of 0.05 and treated with dilutions of either GS-441524 or remdesivir (0, 0.01, 0.1, 1, 5, 10, 50 μM) for 48 h. Viral yield in the cell supernatant was then quantified by qRT-PCR. Data represented are the mean value of % inhibition of SARS-CoV-2 in cells. Cytotoxicity of GS-441524 (green dots) and remdesivir (orange dots) was determined using a CCK-8 test. Vero E6 cells were infected with SARS-CoV-2 at an MOI of 0.05 and treated with dilutions of the indicated compounds for 48 h. Viral RNA in the cell supernatant (D) and pellet (E) was then quantified by qRT-PCR".

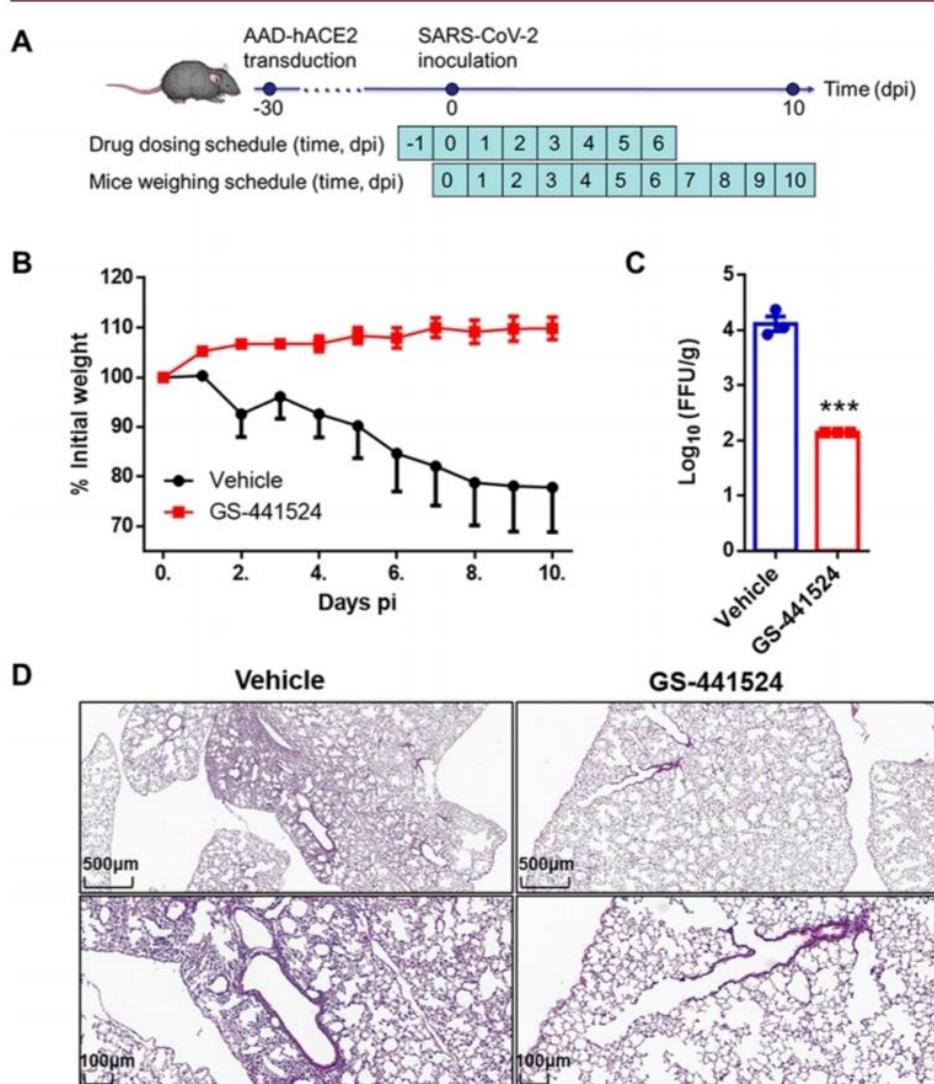


Figure 4: "Anti-SARS-CoV-2 efficacy of GS-441524 in an AAV-hACE2 mouse model. AAV-hACE2 transduced mice were infected with SARS-CoV-2. Mice were administrated either vehicle or GS-441524 (25 mg/kg/day) at 1 dpi and were treated for a total of 8 d. (A) Changes in body weight for either vehicle (black) or GS-441524 treated (red) mice. (B) Viral titers from lung tissue of three mice per group were harvested at 2 dpi and analyzed by FFA. ***p-value < 0.0005. (C) Representative H&E staining of lungs from hACE2 transduced mice. (D) Scale bars, 500 μm (top) and 100 μm (bottom)".

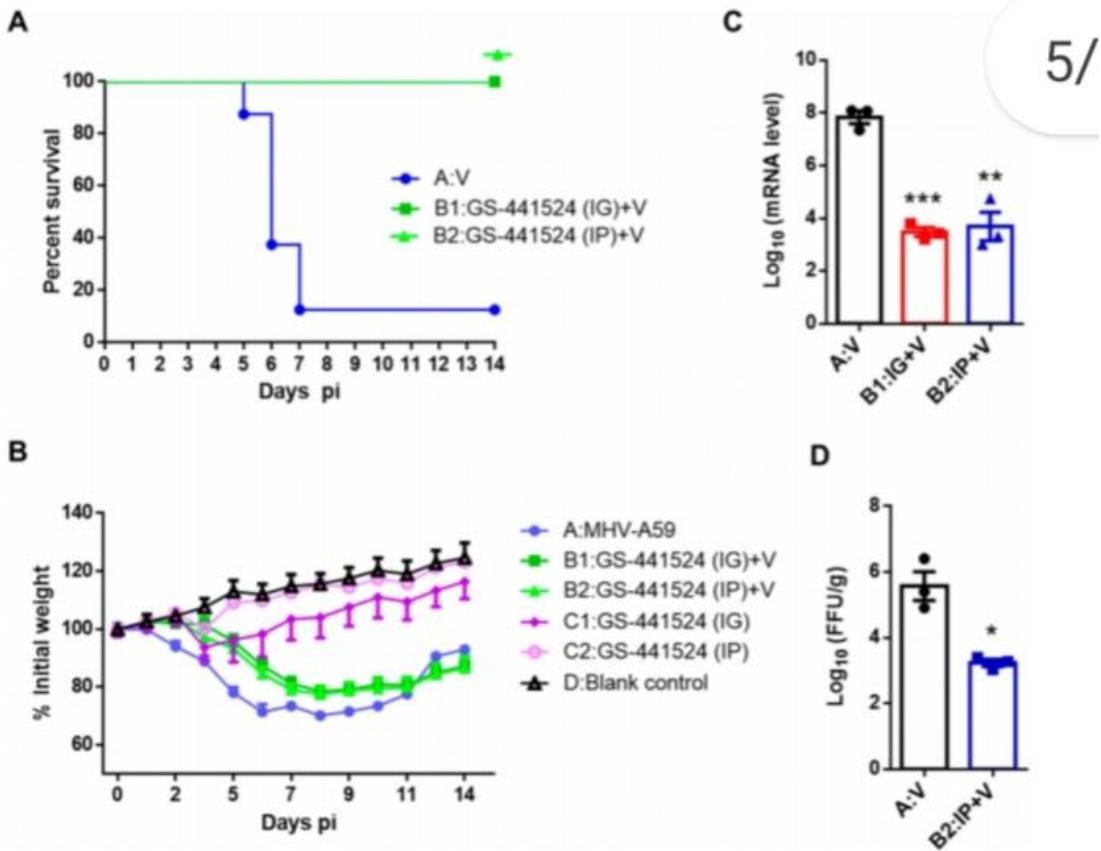


Figure 5: "Antiviral efficacy of GS-441524 in mice infected with MHV-A59: Mice were randomly divided into six groups: Group A: MHV-A59 infected, untreated control; Group B1: 100 mg/kg GS-441524 IG 0.5 hpi, then 50 mg/kg daily in infected mice; Group B2: 100 mg/kg GS-441524 IP 0.5 hpi, then 50 mg/kg daily in infected mice; Group C1: B2 matched control in uninfected mice; Group C2: B2 matched control in uninfected mice; Group D: uninfected control. Note: V = virus. (A) Survival curves of mice in Groups A (blue), B1 (dark green), and B2 (light green). Note: N = 8 per group. (B) Body weights of animals in the six groups; Note: N = 8 per group. (C) Viral titers in the liver of mice from Group A (black), Group B1 (red), and Group B2 (blue) quantified by qRT-PCR (N = 3 per group) at 3 dpi. (D) Viral titers in the liver of mice from Group A (black) and Group B2 (blue) were quantified by focus forming assay (FFU; N = 3 per group) at 3 dpi. *p-value < 0.05; **p-value < 0.005; ***p-value < 0.0005".

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