

# The Daily COVID-19 Literature Surveillance Summary

April 02, 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)
<b>How common is the problem?</b>	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
<b>Is this diagnostic or monitoring test accurate? (Diagnosis)</b>	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
<b>What will happen if we do not add a therapy? (Prognosis)</b>	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
<b>Does this intervention help? (Treatment Benefits)</b>	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
<b>What are the COMMON harms? (Treatment Harms)</b>	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
<b>What are the RARE harms? (Treatment Harms)</b>	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
<b>Is this (early detection) test worthwhile? (Screening)</b>	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

## Understanding the Pathology

- 80% of SARS-CoV-2 positive patients will have IgM antibodies by 7 days (decline at 27 days), and 95% will have IgM antibodies by 12 days (decline at 120 days). A team of internists from the Portland VA Research Foundation in Oregon conducted a sequential systematic review of 66 observational studies (n=16525) regarding antibody responses after SARS-CoV-2 infections and found 80% of SARS-CoV-2 positive patients developed detectable IgM antibody at a mean of 7 days with a decline after day 27. Measurable IgG was detectable in 95% of patients by day 12, plateaued at day 25, and declined after 120 days. Although limited by the quality of included studies, authors suggest their review provides a basis for understanding humoral immune responses to SARS-CoV-2 and recommend further studies evaluating both humoral and cell-mediated responses.

## Transmission & Prevention

- Moist heat, microwave-generated steam processing, and ultraviolet germicidal irradiation are favorable to vaporized hydrogen peroxide and ethylene oxide decontamination processes. A systematic review conducted by researchers from the School of Medicine at UCLA in Los Angeles, California involved 42 articles from PubMed and EMBASE published through January 31, 2021 regarding 5 types of respirator-decontaminating processes. Moist heat, microwave-generated steam processing, and ultraviolet germicidal irradiation provide the most effective pathogen removal with preserved filtration and are easily implementable due to readily available equipment and lesser treatment times. These options are more favorable than vaporized hydrogen peroxide which has longer treatment times and higher cost and ethylene oxide which has toxic residues. Decision making strategies for choosing the most effective means of decontamination are suggested. Many of these studies didn't specifically involve SARS-CoV-2 decontamination, so additional research is needed for further investigation of these methods.

## Adjusting Practice During COVID-19

- Children and teenagers in China were found to have accelerated reversible myopic progression during different rounds of the lockdown. Researchers from the Eye Hospital and School of Ophthalmology and Optometry at Wenzhou Medical University and the National Clinical Research Center for Ocular Diseases in Wenzhou, Zhejiang, China conducted an analysis of 29,719 junior high students in Hangzhou, China participating in the cohort study, Myopia Screening Survey Of Children and Teenagers In Schools (MYOSOTIS), examining their corrected and non-corrected visual acuity (VA) and change in spherical equivalent refraction (SER) during the COVID-19 lockdown. They found an accelerated reversible myopic progression during different rounds of the lockdown, which they speculate is from accumulative spasms, and suggest further consideration and management for this condition in children and teenagers in the setting of future lockdowns.

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## FORECASTING THE SPREAD OF SARS-COV-2 IS INHERENTLY AMBIGUOUS GIVEN THE CURRENT STATE OF VIRUS RESEARCH

Koenen M, Balvert M, Brekelmans R, Fleuren H, Stienen V, Wagenaar J.. PLoS One. 2021 Mar 3;16(3):e0245519. doi: 10.1371/journal.pone.0245519. eCollection 2021.

Level of Evidence: 5 - Modeling

### BLUF

Researchers at the Department of Econometrics and Operations Research, Tilburg School of Economics and Management in the Netherlands, developed and evaluated a model for predicting SARS-CoV-2 spread based on community and individual characteristics (age, working status, location of residency, etc). Based on existing epidemiological data they found 18 different sets of parameters that were able to accurately predict local ICU case loads; however, their models were highly variable when predicting number of infections and total number of immune individuals. They concluded that though ICU case loads can be accurately assessed by epidemiological models, policymakers should be careful when making decisions based on model-derived total infection and immunity statistics.

### ABSTRACT

Since the onset of the COVID-19 pandemic many researchers and health advisory institutions have focused on virus spread prediction through epidemiological models. Such models rely on virus- and disease characteristics of which most are uncertain or even unknown for SARS-CoV-2. This study addresses the validity of various assumptions using an epidemiological simulation model. The contributions of this work are twofold. First, we show that multiple scenarios all lead to realistic numbers of deaths and ICU admissions, two observable and verifiable metrics. Second, we test the sensitivity of estimates for the number of infected and immune individuals, and show that these vary strongly between scenarios. Note that the amount of variation measured in this study is merely a lower bound: epidemiological modeling contains uncertainty on more parameters than the four in this study, and including those as well would lead to an even larger set of possible scenarios. As the level of infection and immunity among the population are particularly important for policy makers, further research on virus and disease progression characteristics is essential. Until that time, epidemiological modeling studies cannot give conclusive results and should come with a careful analysis of several scenarios on virus- and disease characteristics.

### FIGURES

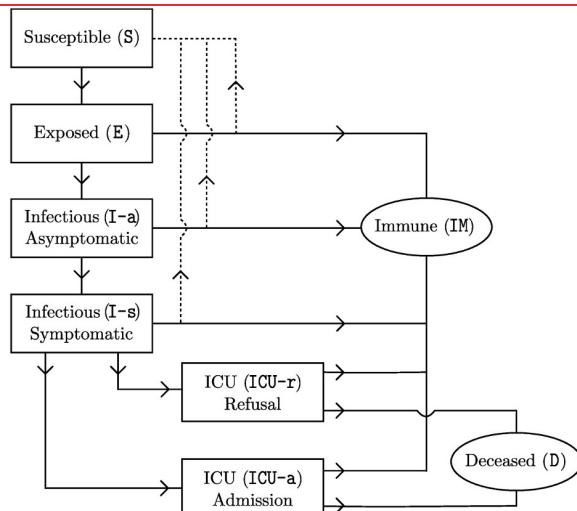


Figure 1. Progression of disease stages in our simulation model.

## SYMPTOMS AND CLINICAL PRESENTATION

### **COVID-19 CASE PROFILE IS CHANGING WITH THE VACCINE**

Flahault A.. Anaesth Crit Care Pain Med. 2021 Mar 23;100851. doi: 10.1016/j.accpm.2021.100851. Online ahead of print.  
Level of Evidence: 5 - Expert Opinion

#### **BLUF**

A physician researcher from the Institute of Global Health at University of Geneva in Switzerland discusses how there has been a significant shift in the profile of COVID-19 infection from predominantly severe infection in elderly patients, who are now the emphasis for COVID-19 vaccination efforts, to severe disease in younger patients, who often require more aggressive management and longer hospitalizations for full recovery. These characteristics emphasize the need for integrated global strategies involving mass immunization and aggressive suppression efforts to minimize the transmission of COVID-19 infection.

# UNDERSTANDING THE PATHOLOGY

## ANTIBODY RESPONSE AFTER SARS-COV-2 INFECTION AND IMPLICATIONS FOR IMMUNITY : A RAPID LIVING REVIEW

Arkhipova-Jenkins I, Helfand M, Armstrong C, Gean E, Anderson J, Paynter RA, Mackey K.. Ann Intern Med. 2021 Mar 16. doi: 10.7326/M20-7547. Online ahead of print.

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

### BLUF

A team of internists from the Portland VA Research Foundation in Oregon conducted a sequential systematic review of 66 observational studies (n=16525) regarding antibody responses after SARS-CoV-2 infections. They found 80% of SARS-CoV-2 positive patients developed detectable IgM antibody at a mean of 7 days; IgM levels declined after day 27 (Figure 2). Measurable IgG was detectable in 95% of patients by day 12, plateaued at day 25, and declined after 120 days (Figure 3). Although limited by the quality of included studies, authors suggest their review provides a basis for understanding humoral immune responses to SARS-CoV-2 and recommend further studies evaluating both humoral and cell-mediated responses.

### ABSTRACT

**BACKGROUND:** The clinical significance of the antibody response after SARS-CoV-2 infection remains unclear. **PURPOSE:** To synthesize evidence on the prevalence, levels, and durability of detectable antibodies after SARS-CoV-2 infection and whether antibodies to SARS-CoV-2 confer natural immunity. **DATA SOURCES:** MEDLINE (Ovid), Embase, CINAHL, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, World Health Organization global literature database, and Covid19reviews.org from 1 January through 15 December 2020, limited to peer-reviewed publications available in English. **STUDY SELECTION:** Primary studies characterizing the prevalence, levels, and duration of antibodies in adults with SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction (RT-PCR); reinfection incidence; and unintended consequences of antibody testing. **DATA EXTRACTION:** Two investigators sequentially extracted study data and rated quality. **DATA SYNTHESIS:** Moderate-strength evidence suggests that most adults develop detectable levels of IgM and IgG antibodies after infection with SARS-CoV-2 and that IgG levels peak approximately 25 days after symptom onset and may remain detectable for at least 120 days. Moderate-strength evidence suggests that IgM levels peak at approximately 20 days and then decline. Low-strength evidence suggests that most adults generate neutralizing antibodies, which may persist for several months like IgG. Low-strength evidence also suggests that older age, greater disease severity, and presence of symptoms may be associated with higher antibody levels. Some adults do not develop antibodies after SARS-CoV-2 infection for reasons that are unclear. **LIMITATION:** Most studies were small and had methodological limitations; studies used immunoassays of variable accuracy. **CONCLUSION:** Most adults with SARS-CoV-2 infection confirmed by RT-PCR develop antibodies. Levels of IgM peak early in the disease course and then decline, whereas IgG peaks later and may remain detectable for at least 120 days. **PRIMARY FUNDING SOURCE:** Agency for Healthcare Research and Quality. (PROSPERO: CRD42020207098).

### FIGURES

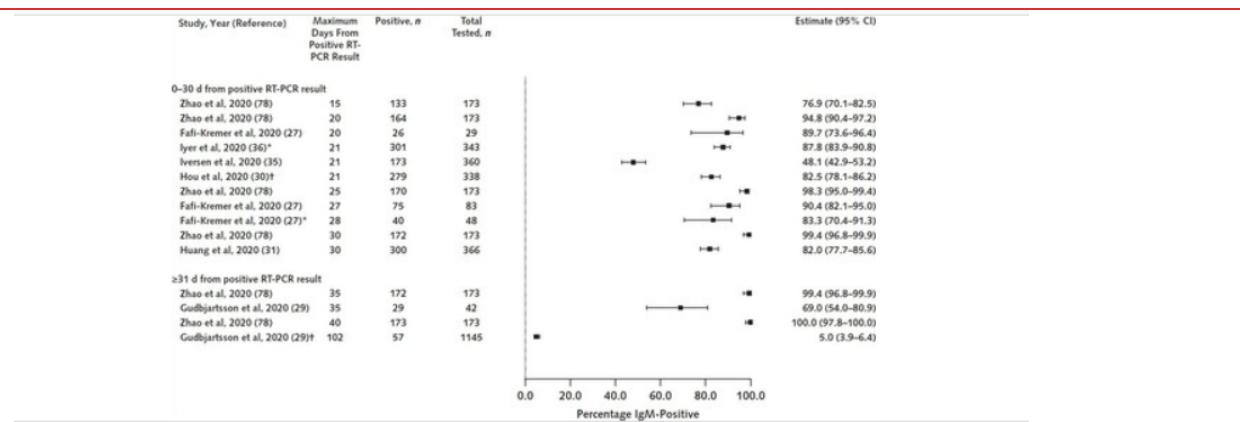


Figure 2. IgM prevalence at 0-30 d and after 30 d.

Studies represented had well-characterized patient populations and settings, measured antibodies using validated immunoassays, and lacked serious methodological problems. RT-PCR = reverse transcriptase polymerase chain reaction.

\* Number of days from positive result on RT-PCR is minimum of unbounded range (e.g., >20 d).

† Study provided mean or median number of days from positive result on RT-PCR.

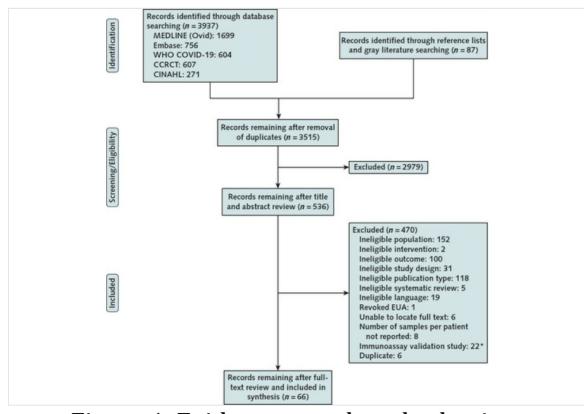


Figure 1. Evidence search and selection.

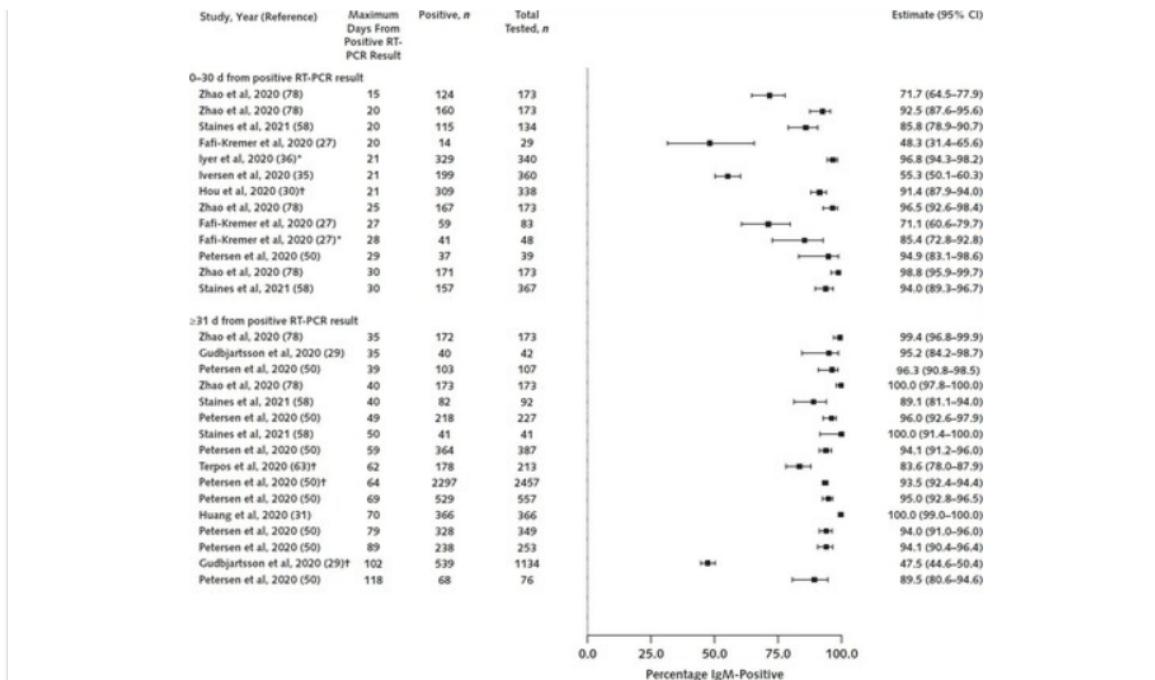


Figure 3. IgG prevalence at 0–30 d and after 30 d.

Studies represented had well-characterized patient populations and settings, measured antibodies using validated immunoassays, and lacked serious methodological problems. RT-PCR = reverse transcriptase-polymerase chain reaction.

\* Number of days from positive result on RT-PCR is minimum of unbounded range (e.g., >20 d).

† Study provided mean or median number of days from positive result on RT-PCR.

99% developed neutralizing antibodies (Table 1) developed immediately and declined, others plateaued and remained detectable for several months , low confidence

# SUSTAINABILITY OF SARS-COV-2 INDUCED HUMORAL IMMUNE RESPONSES IN COVID-19 PATIENTS FROM HOSPITALIZATION TO CONVALESCENCE OVER SIX MONTHS

Zheng Y, Zhang Q, Ali A, Li K, Shao N, Zhou X, Ye Z, Chen X, Cao S, Cui J, Zhou J, Wang D, Hou B, Li M, Cui M, Deng L, Sun X, Zhang Q, Yang Q, Li Y, Wang H, Lei Y, Yu B, Cheng Y, Tong X, Men D, Zhang XE.. Virol Sin. 2021 Mar 4. doi: 10.1007/s12250-021-00360-4. Online ahead of print.

Level of Evidence: 4 - Case-series or case-control studies, or poor quality prognostic cohort study

## BLUF

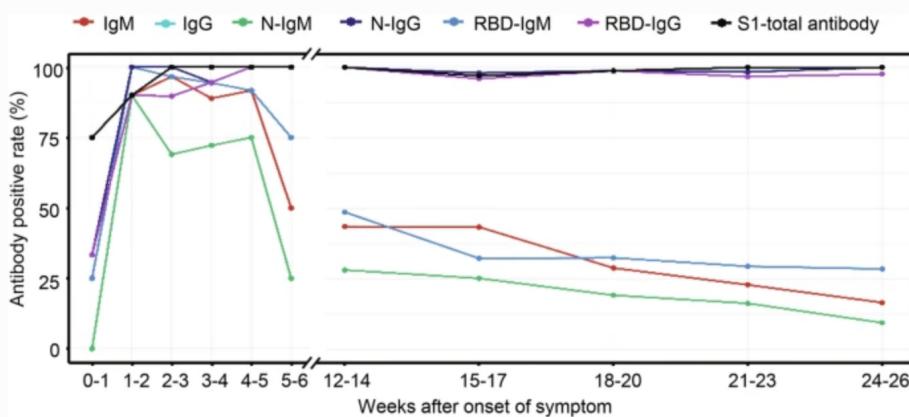
In a retrospective cohort study in Wuhan, China on 404 serum samples of 172 COVID-19 patients who were admitted to Wuhan hospital, the sustainability of different types of antibody (IgG, IgM) titers were analyzed over 6 months by looking at the rate of positivity among patients (Figure 1) and the trend in antibody titers across all patients (Figure 2). At the 6 month time-point, they found that IgM was present in only 25% of patients, and titer levels dropped to 16.7% of peak, but IgG continued to be present in all patients with titers dropping to 85.9% of the peak seen at 4-5 weeks. These findings suggest that the humoral immunity that develops in response to SARS-CoV-2 is relatively sustained.

## ABSTRACT

Understanding the persistence of antibody in convalescent COVID-19 patients may help to answer the current major concerns such as the risk of reinfection, the protection period of vaccination and the possibility of building an active herd immunity. This retrospective cohort study included 172 COVID-19 patients who were hospitalized in Wuhan. A total of 404 serum samples were obtained over six months from hospitalization to convalescence. Antibodies in the specimens were quantitatively analyzed by the capture chemiluminescence immunoassays (CLIA). All patients were positive for the anti-SARS-CoV-2 IgM/IgG at the onset of COVID-19 symptoms, and the IgG antibody persisted in all the patients during the convalescence. However, only approximately 25% of patients can detect the IgM antibodies, IgM against N protein (N-IgM) and receptor binding domain of S protein (RBD-IgM) at the 27th week. The titers of IgM, N-IgM and RBD-IgM reduced to 16.7%, 17.6% and 15.2% of their peak values respectively. In contrast, the titers of IgG, N-IgG and RBD-IgG peaked at 4-5th week and reduced to 85.9%, 62.6% and 87.2% of their peak values respectively at the end of observation. Dynamic behavior of antibodies and their correlation in age, gender and severity groups were investigated. In general, the COVID-19 antibody was sustained at high levels for over six months in most of the convalescent patients. Only a few patients with antibody reducing to an undetectable level which needs further attention. The humoral immune response against SARS-CoV-2 infection in COVID-19 patients exhibits a typical dynamic of acquired immunity.

## FIGURES

Fig. 1



The positive rate of antibodies from the onset of symptoms to convalesces. Demonstrating the positive rate of different antibody appearances, peak point, intensities and durability from the onset of the symptoms (on hospitalization) to the convalescent phase till 26th week. Note: IgG line is overlapped by N-IgG.

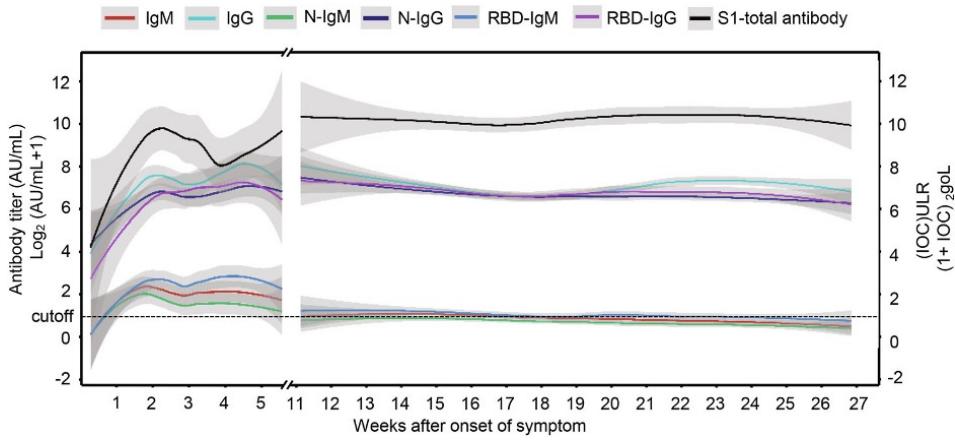


Figure. 2 The titer of different antibodies from the onset of symptoms to the convalescent phase. The titer of different antibodies starts rising from the onset of symptoms to their peak value during the infection with notable disparities in their intensities, and the most sustainable antibodies can maintain up to 6 months. The dotted line is the cutoff value, and the gray shading is the 95% confidence interval.

## A NETWORK-INFORMED ANALYSIS OF SARS-COV-2 AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS GENES' INTERACTIONS POINTS TO NEUTROPHIL EXTRACELLULAR TRAPS AS MEDIATORS OF THROMBOSIS IN COVID-19

Ding J, Hostallero DE, El Khili MR, Fonseca GJ, Milette S, Noorah N, Guay-Belzile M, Spicer J, Daneshtalab N, Sirois M, Tremblay K, Emad A, Rousseau S.. PLoS Comput Biol. 2021 Mar 8;17(3):e1008810. doi: 10.1371/journal.pcbi.1008810. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

### BLUF

A network-informed analysis by biotechnologist researchers of the United States and Canada, explored the interaction between different hemophagocytic lymphohistiocytosis (HLH) (summary) genes and SARS-CoV-2, and the role these genes play in the coagulopathy seen in many COVID-19 patients. They found that expression of the HLH gene subtype AP3B1 is correlated with neutrophil degranulation and release of Neutrophil Extracellular Traps (NETs). These findings support their hypothesis that NET activation in the presence of SARS-CoV-2 endothelial damage leads to platelet activation and venous thromboembolism and suggests that genetic factors favoring NET release could predispose individuals to severe COVID-19.

### SUMMARY

The relationship between HLH proteins and inflammatory response, endothelial damage, and thrombosis have been observed before in conditions such as H1N1, lung cancer, and Kawasaki Disease.

### ABSTRACT

Abnormal coagulation and an increased risk of thrombosis are features of severe COVID-19, with parallels proposed with hemophagocytic lymphohistiocytosis (HLH), a life-threatening condition associated with hyperinflammation. The presence of HLH was described in severely ill patients during the H1N1 influenza epidemic, presenting with pulmonary vascular thrombosis. We tested the hypothesis that genes causing primary HLH regulate pathways linking pulmonary thromboembolism to the presence of SARS-CoV-2 using novel network-informed computational algorithms. This approach led to the identification of Neutrophils Extracellular Traps (NETs) as plausible mediators of vascular thrombosis in severe COVID-19 in children and adults. Taken together, the network-informed analysis led us to propose the following model: the release of NETs in response to inflammatory signals acting in concert with SARS-CoV-2 damage the endothelium and direct platelet-activation promoting abnormal coagulation leading to serious complications of COVID-19. The underlying hypothesis is that genetic and/or environmental conditions that favor the release of NETs may predispose individuals to thrombotic complications of COVID-19 due to an increase risk of abnormal coagulation. This would be a common pathogenic mechanism in conditions including autoimmune/infectious diseases, hematologic and metabolic disorders.

## FIGURES

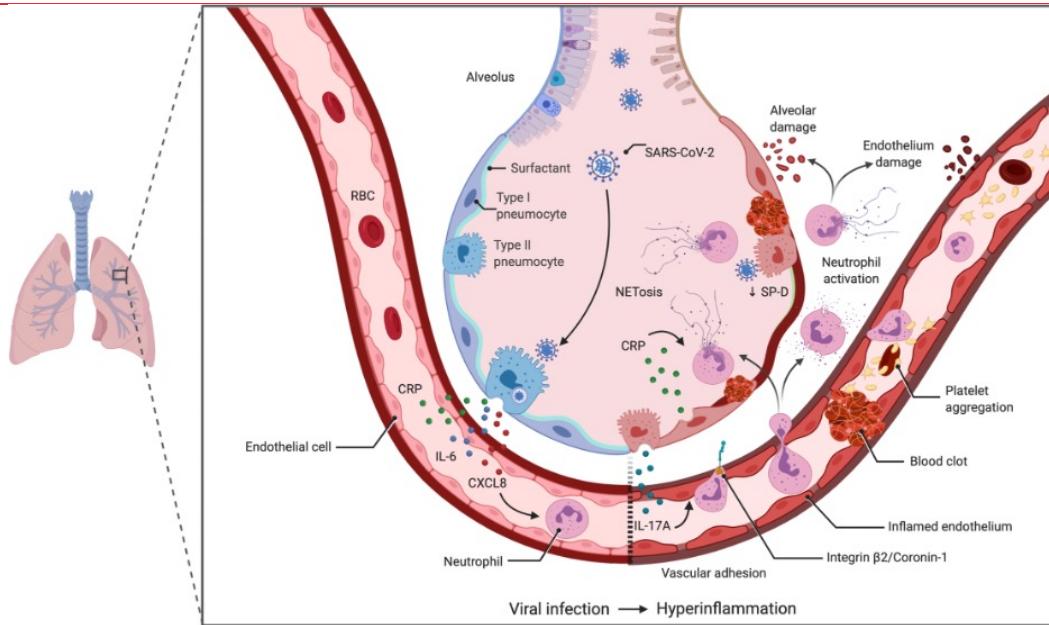


Fig 5. Model of NET-mediated endothelial damage contributing to pulmonary vascular thrombosis in severe COVID-19. Infection by SARS-CoV-2 in vulnerable population will lead to hyperinflammation either from underlying genetic mutations, specific epigenetic landscapes or external factors, that will result in the increase circulation of acute phase reactants such as CRP and pro-inflammatory cytokines associated with neutrophilia like IL-6, IL-17A/F and CXCL8 (IL-8). IL-17A activates the endothelium to induce neutrophil adhesion [105], where the increase in CRP can trigger the release of NETs, resulting in damage to the endothelium as well as aggregation and activation of platelets. Additionally, the presence of SARS-CoV-2 E protein in type II pneumocytes could disturb the surfactant cargo via its interaction with AP3B1, leading to impaired secretion of SP-D and greater NET formation by septal and intra-alveolar neutrophils increasing the risk of thrombosis in the pulmonary microvasculature. In some predisposed patients the combinations of these mechanisms will lead to severe COVID-19 complications. The identification of mediators of this pro-coagulation cascade is essential in achieving the two-fold task of identifying vulnerable populations and developing a personalized medicine approach.

## TRANSMISSION & PREVENTION

### THE RISK OF TRANSMISSION OF THE NOVEL CORONAVIRUS (SARS-COV-2) WITH HUMAN HEART VALVE TRANSPLANTATION: EVALUATION OF CARDIO-VASCULAR TISSUES FROM TWO CONSECUTIVE HEART DONORS WITH ASYMPTOMATIC COVID-19

Jashari R, Van Esbroeck M, Vanhaebost J, Micalessi I, Kerschen A, Mastrobuoni S.. Cell Tissue Bank. 2021 Mar 9. doi: 10.1007/s10561-021-09913-z. Online ahead of print.

Level of Evidence: 5 - Case-series

#### BLUF

Researchers of European Homograft Bank and the Department of pathology at the University of Brussels, Belgium studied the explanted hearts (for valve donation) from 2 living donors with asymptomatic SARS-CoV-2-PCR-positive infection. The hearts were being explanted due to ischemic cardiomyopathy in the first patient and hypertrophic obstructive cardiomyopathy in the second. Histologic analysis of the first explanted heart revealed a moderate eosinophilic infiltrate with diffuse ACE2 in immunostaining, the second heart exhibited no inflammatory infiltrate with discrete presence of the ACE2 in immunostaining (Figure 2,3), and neither heart exhibited any trace of SARS-CoV-2 (via RT-PCR) in the myocardium or valves suggesting that clinical use of the valves from explanted hearts of SARS-CoV-2 positive patients presents minimal risk of disease transmission.

#### ABSTRACT

We report on two living donors of explanted hearts while receiving heart transplantation that tested positive for SARS-CoV-2 on the day of donation, although clinically asymptomatic. They underwent heart transplantation for ischaemic and hypertrophic obstructive cardiomyopathy, respectively. After evaluation of donor hearts, we cryopreserved and stored two pulmonary valves for clinical application and one aortic valve for research. Light microscopy of myocardium, mitral valve and aortic and pulmonary arterial wall and RT-PCR SARS-CoV-2 test of myocardium, mitral and tricuspid valve and aortic wall for detection of SARS-CoV-2 were performed. Presence of ACE2 in tissues was assessed with immunostaining. Light microscopy revealed a mild eosinophilic myocarditis in the ischemic cardiomyopathy heart, whereas enlarged cardiomyocytes with irregular nucleus and some with cytoplasmic vacuoles in the hypertrophic obstructive cardiomyopathy heart. Aortic and pulmonary wall were histologically normal. Immunostaining revealed diffuse presence of ACE2 in the myocardium of the heart with eosinophilic myocarditis, but only discrete presence in the hypertrophic cardiomyopathy heart. The RT-PCR SARS-CoV-2 test showed no presence of the virus in tested tissues. Despite eosinophilic myocarditis in the ischemic cardiomyopathy heart, no viral traces were found in the myocardium and valve tissues. However, ACE2 was present diffusely in the ischemic cardiomyopathy heart. SARS-CoV-2 could not be detected in the cardiac tissues of these COVID-19 asymptomatic heart donors. In our opinion, clinical application of the valves from these donors presents negligible risk for coronavirus transmission. Nonetheless, considering the uncertainty regarding the risk of virus transmission with the human tissue transplantation, we would not release in any case the pulmonary valve recovered from the eosinophilic myocarditis heart. In contrast, we may consider the release of the pulmonary valve from the dilated cardiomyopathy heart only for a life-threatening situation when no other similar allograft were available.

## FIGURES

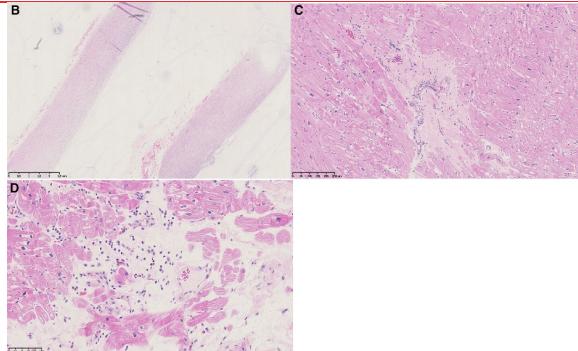


Figure 2.

Light microscopy of cardiac tissue examination, H&E staining (hypertrophic cardiomyopathy): b: Low magnification of aorta and pulmonary artery ( $\times 12.5$ ); c: Mild perivascular fibrosis, few irregular nuclei in large cardiomyocytes, with several cytoplasmic vacuoles, coherent with hypertrophic cardiomyopathy ( $\times 100$ ); d: Aspecific mixed inflammatory infiltrate in the interstitium with neutrophils and monocytes ( $\times 200$ )

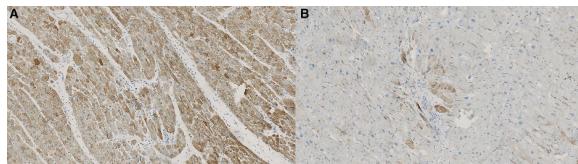


Figure 3.

ACE2 Immunostaining of both specimens ( $\times 100$ ). a: diffuse cytoplasmic ACE2 immunostaining in the ischemic cardiomyopathy heart; b: discrete ACE2 immunostaining, marking some scattered cardiomyocytes in the hypertrophic cardiomyopathy heart

## DEVELOPMENTS IN TRANSMISSION & PREVENTION

### PERSISTENT MACULOPAPULAR RASH AFTER THE FIRST DOSE OF PFIZER-BIONTECH COVID-19 VACCINE

Ackerman M, Henry D, Finon A, Binois R, Esteve E.. J Eur Acad Dermatol Venereol. 2021 Mar 30. doi: 10.1111/jdv.17248. Online ahead of print.

Level of Evidence: 5 - Case Report

#### BLUF

A letter to the editor conducted by researchers from the Centre Hospitalier Regional d' Orleans in France discusses the case of a 53 year old male who developed a pruritic maculopapular rash (Figure 1 A-D) beginning 3 hours after receiving the first dose of the PfizerBioNtech COVID-19 vaccine. The rash persisted for over 1 month before improving with corticosteroids and was also associated with elevated liver enzymes. This case highlights the importance of healthcare providers being vigilant in recognizing and reporting adverse events associated with the COVID-19 vaccines and describing the mechanisms to assist in understanding them.

#### SUMMARY

A 53 year old male with no past medical history or history of drug allergies received the first dose of the Pfizer-BioNTech COVID-19 vaccine and 3 hours later, developed a localized pruritic eruption spreading to his face, trunk, arms, and thighs, without fever, arthralgia, or other systemic symptoms. Lab studies revealed evidence of elevated liver enzymes and hepatic cytosis but negative HIV, HBV, HCV, CMV, EBV and measles serology. Dermatologist consult revealed maculopapular exanthema with 30% body involvement, comparable with maculopapular taxiderma. The rash improved after 1 month with corticosteroid treatment and the liver enzymes improved over the same course.

## **ABSTRACT**

The ongoing global pandemic COVID-19 led regulatory agencies to recently issue an emergency authorization for two effective Covid-19 vaccines from Pfizer-BioNTech and Moderna. Both vaccines use a novel technology of administering vaccination, namely a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the spike glycoprotein of SARS-CoV-2 for subsequent antigen presentation and immune system activation (1).

## **FIGURES**



Figure 1.

## **PREVENTION IN THE COMMUNITY**

### **REOPENING BUSINESSES AND RISK OF COVID-19 TRANSMISSION**

O'Donoghue A, Dechen T, Pavlova W, Boals M, Moussa G, Madan M, Thakkar A, DeFalco FJ, Stevens JP.. NPJ Digit Med. 2021 Mar 16;4(1):51. doi: 10.1038/s41746-021-00420-9.

Level of Evidence: 1 - Local and current random sample surveys (or censuses)

## **BLUF**

Economists from the Center for Healthcare Delivery Science at Beth Israel Deaconess Medical Center in Boston analyzed traffic at 1,272,260 businesses via cell phone data across eight states between January and June 2020. They created a transmission risk metric based on visits per square foot and the average length of visits and determined based on this metric that predicted risk increased as states reopened (Figure 3) and correlated with county-level increases in positive COVID-19 cases. Authors suggest their risk index could provide a means to guide policies for re-opening.

## **ABSTRACT**

The true risk of a COVID-19 resurgence as states reopen businesses is unknown. In this paper, we used anonymized cell-phone data to quantify the potential risk of COVID-19 transmission in business establishments by building a Business Risk Index that measures transmission risk over time. The index was built using two metrics, visits per square foot and the average duration of visits, to account for both density of visits and length of time visitors linger in the business. We analyzed trends in traffic patterns to 1,272,260 businesses across eight states from January 2020 to June 2020. We found that potentially risky traffic behaviors at businesses decreased by 30% by April. Since the end of April, the risk index has been increasing as states reopen. There are some notable differences in trends across states and industries. Finally, we showed that the time series of the

average Business Risk Index is useful for forecasting future COVID-19 cases at the county-level ( $P < 0.001$ ). We found that an increase in a county's average Business Risk Index is associated with an increase in positive COVID-19 cases in 1 week (IRR: 1.16, 95% CI: (1.1-1.26)). Our risk index provides a way for policymakers and hospital decision-makers to monitor the potential risk of COVID-19 transmission from businesses based on the frequency and density of visits to businesses. This can serve as an important metric as states monitor and evaluate their reopening strategies.

## FIGURES

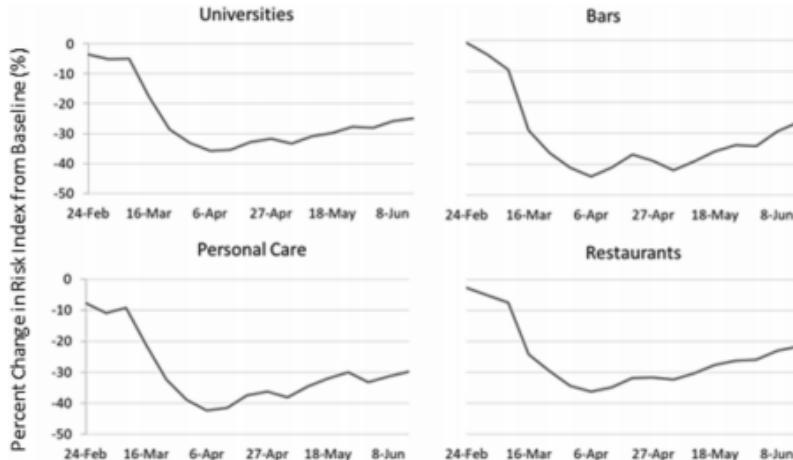


Figure 3. Percent change in Business Risk Index by industry. Percent change in Business Risk Index by types of potential high-risk industries over time from January 2020 to June 2020.

## PREVENTION IN THE HOSPITAL

### FILTERING FACEPIECE RESPIRATOR (N95 RESPIRATOR) REPROCESSING: A SYSTEMATIC REVIEW

Schumm MA, Hadaya JE, Mody N, Myers BA, Maggard-Gibbons M.. JAMA. 2021 Mar 3. doi: 10.1001/jama.2021.2531. Online ahead of print.

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

#### BLUF

A systematic review conducted by researchers from the School of Medicine at UCLA in Los Angeles, California involved 42 articles from PubMed and EMBASE published through January 31, 2021 regarding 5 types of respirator-decontaminating processes. Moist heat, microwave-generated steam processing, and ultraviolet germicidal irradiation provide the most effective pathogen removal with preserved filtration and are easily implementable due to readily available equipment and lesser treatment times. These options are more favorable than vaporized hydrogen peroxide which has longer treatment times and higher cost and ethylene oxide which has toxic residues. Decision making strategies for choosing the most effective means of decontamination are suggested (Figure 1). Many of these studies didn't specifically involve SARS-CoV-2 decontamination, so additional research is needed for further investigation of these methods.

#### ABSTRACT

**Importance:** The COVID-19 pandemic has resulted in a persistent shortage of personal protective equipment; therefore, a need exists for hospitals to reprocess filtering facepiece respirators (FFRs), such as N95 respirators. **Objective:** To perform a systematic review to evaluate the evidence on effectiveness and feasibility of different processes used for decontaminating N95 respirators. **Evidence Review:** A search of PubMed and EMBASE (through January 31, 2021) was completed for 5 types of respirator-decontaminating processes including UV irradiation, vaporized hydrogen peroxide, moist-heat incubation, microwave-generated steam, and ethylene oxide. Data were abstracted on process method, pathogen removal, mask filtration efficiency, facial fit, user safety, and processing capability. **Findings:** Forty-two studies were included that examined 65 total types of masks. All were laboratory studies (no clinical trials), and 2 evaluated respirator performance and fit with actual clinical use of N95 respirators. Twenty-seven evaluated UV germicidal irradiation, 19 vaporized hydrogen peroxide, 9 moist-heat incubation, 10 microwave-generated steam, and 7 ethylene oxide. Forty-three types of N95 respirators were treated with

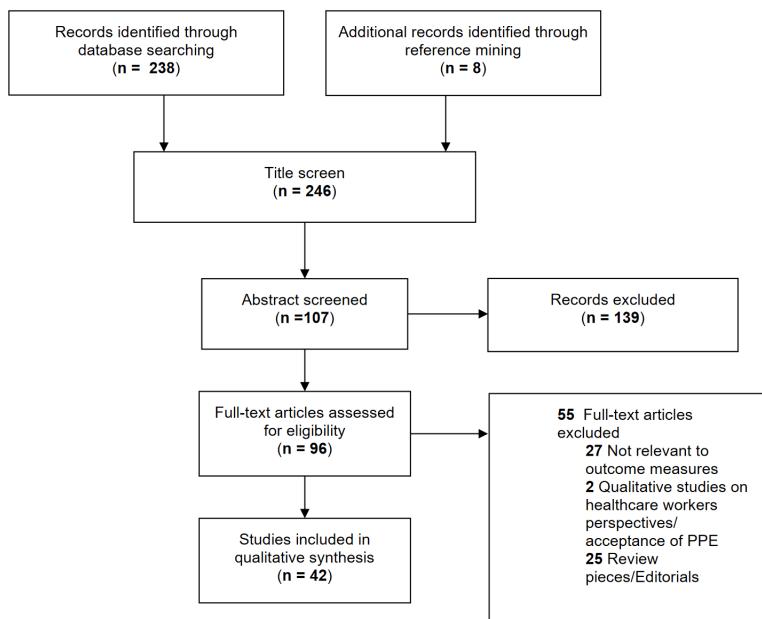
UV irradiation. Doses of 1 to 2 J/cm<sup>2</sup> effectively sterilized most pathogens on N95 respirators (>103 reduction in influenza virus [4 studies], MS2 bacteriophage [3 studies], Bacillus spores [2 studies], Escherichia virus MS2 [1 study], vesicular stomatitis virus [1 study], and Middle East respiratory syndrome virus/SARS-CoV-1 [1 study]) without degrading respirator components. Doses higher than 1.5 to 2 J/cm<sup>2</sup> may be needed based on 2 studies demonstrating greater than 103 reduction in SARS-CoV-2. Vaporized hydrogen peroxide eradicated the pathogen in all 7 efficacy studies (>104 reduction in SARS-CoV-2 [3 studies] and >106 reduction of Bacillus and Geobacillus stearothermophilus spores [4 studies]). Pressurized chamber systems with higher concentrations of hydrogen peroxide caused FFR damage (6 studies), while open-room systems did not degrade respirator components. Moist heat effectively reduced SARS-CoV-2 (2 studies), influenza virus by greater than 104 (2 studies), vesicular stomatitis virus (1 study), and Escherichia coli (1 study) and preserved filtration efficiency and facial fit for 11 N95 respirators using preheated containers/chambers at 60 °C to 85 °C (5 studies); however, diminished filtration performance was seen for the Caron incubator. Microwave-generated steam (1100-W to 1800-W devices; 40 seconds to 3 minutes) effectively reduced pathogens by greater than 103 (influenza virus [2 studies], MS2 bacteriophage [3 studies], and Staphylococcus aureus [1 study]) and maintained filtration performance in 10 N95 respirators; however, damage was noted in least 1 respirator type in 4 studies. In 6 studies, ethylene oxide preserved respirator components in 16 N95 respirator types but left residual carcinogenic by-product (1 study). Conclusions and Relevance: Ultraviolet germicidal irradiation, vaporized hydrogen peroxide, moist heat, and microwave-generated steam processing effectively sterilized N95 respirators and retained filtration performance. Ultraviolet irradiation and vaporized hydrogen peroxide damaged respirators the least. More research is needed on decontamination effectiveness for SARS-CoV-2 because few studies specifically examined this pathogen.

## FIGURES

Box. How to Choose a Filtering Facepiece Respirator (FFR) Decontamination Method During Critical Shortages	
<b>What Are the Best Large-Scale Decontamination Methods?</b> Ultraviolet germicidal irradiation (UVGI) is cost-effective and should be considered when equipment (UV lamps or bulbs, biosafety cabinets/laboratory hoods, or whole-room decontamination systems) are available. Vaporized hydrogen peroxide (VHP) is a comparable method and its equipment is often available because it is used for sterilizing other medical equipment (but cost is higher).	<b>How Should FFRs Be Evaluated After Reprocessing?</b> Systematic evaluation of reprocessed FFRs should occur after decontamination methods are implemented. The FFR should be visually inspected for damage, filtration performance and facial fit assessed, and a proper seal ensured. Reprocessed FFRs should not be used for aerosol-generating procedures, such as intubation or bronchoscopy.
<b>What Is the Evidence Supporting High-Volume FFR Reprocessing In a Large Room With UV lights?</b> Filtration performance of FFRs is maintained with up to 9 to 10 cycles of whole-room UVGI decontamination (3 studies). The efficacy of pathogen decontamination has been demonstrated in 1 study.	<b>Visual Inspection</b> Decontaminated FFRs should be examined for visible signs of deterioration/damage such as changes in texture (softness, pliability, coarseness) and separation of inner foam nose cushion from FFR body.
<b>What Are the Best Small-Scale Decontamination Methods?</b> Consider UVGI box reprocessing, as it appears to damage FFRs the least. If UVGI is unavailable, moist-heat incubation (MHI) using preheated containers/chambers and microwave-generated steam (MGS) are comparable options. With MHI, the Caron incubator should be avoided because of the greatest risk of mask damage. With MGS, efficacy is dependent on volume of water used in the reservoir to produce adequate amount of steam (50-100 mL).	<b>Mask Filtration Performance and Facial Fit</b> The integrity of FFRs should be assessed (elastic function and breathing resistance) and qualitative fit testing performed. Filtering facepiece respirators donned more than 5 times should undergo qualitative FFR fit performance evaluation. Fit testing should be performed for new FFR models or change in decontamination protocol.
<b>Is FFR Reprocessing Using Ethylene Oxide Safe?</b> No reduction in FFR filtration performance with ethylene oxide has been reported. However, ethylene oxide is a human carcinogen and its chemical residue is an unresolved concern; this method has not been proven safe.	<b>User Seal Check</b> A user seal check should be performed by the wearer to ensure an adequate seal is achieved. If air leaks around the nose, the user should readjust the nose piece and straps. If air leaks between the facial seal, the FFR should be discarded.
	<b>When Should Reprocessed Respirators Be Discarded?</b> Reprocessed FFRs should be discarded when soiled or damaged, if the mask creates more difficulty breathing through it, or if there is failure to achieve a proper fit/seal during user seal check. The Centers for Disease Control and Prevention limits donnings to 5, then disposing of the reused FFRs, unless the manufacturer states otherwise.
	<b>When Should Reprocessing Be Discontinued?</b> Normal operations should resume when supplies meet projected FFR demand.

Figure 1. How to Choose a Filtering Facepiece Respirator (FFR) Decontamination Method During Critical Shortages

eFigure. PRISMA Flow Chart of Article Selection



## ADJUSTING PRACTICE DURING COVID-19

### SURGICAL SUBSPECIALTIES

#### COLORECTAL SURGERY

##### DELAY TO ELECTIVE COLORECTAL CANCER SURGERY AND IMPLICATIONS ON SURVIVAL: A SYSTEMATIC REVIEW AND META-ANALYSIS

Whittaker TM, Abdelrazek M, Fitzpatrick AJ, Froud J, Kelly JR, Williamson JS, Williams GL.. Colorectal Dis. 2021 Mar 13. doi: 10.1111/codi.15625. Online ahead of print.

Level of Evidence: 1 - Systematic review of inception cohort studies

#### BLUF

Medical students and colorectal surgeons from Cardiff University Medical School and Royal Gwent Hospital in the United Kingdom conducted a systematic review and meta-analysis of 7 articles (Figure 2) investigating how delays in elective colorectal cancer (CRC) surgery affected overall survival (OS) and disease-free survival (DFS). They found 3/7 studies showed surgical delay is associated with worse OS or DFS, with a hazard ratio (HR) of 1.13 at one-month delay (6 datasets; 95%CI 1.02-1.26, p=0.020) and 1.57 at 3 months (3 datasets; 95%CI 1.16-2.12, p=0.004)(Figure 4, Figure 6). The authors suggest delaying CRC elective surgery by more than 4 weeks is associated with worse outcomes and should be avoided whenever possible.

#### ABSTRACT

**AIM:** Covid-19 has delayed elective colorectal cancer (CRC) surgery. The aim of this study was to see whether or not this may affect overall survival (OS) and disease-free survival (DFS). **METHODS:** A systematic review was carried out in according to PRISMA guidelines (PROSPERO ID: CRD42020189158). Medline, EMBASE and Scopus were interrogated. Patients aged over 18 with a diagnosis of colon or rectal cancer who received elective surgery as their primary treatment were included. Delay to elective surgery was defined as the period between CRC diagnosis and the day of surgery. Meta-analysis of the outcomes OS and DFS were conducted. Forest plots, funnel plots, and tests of heterogeneity were produced. An estimated Number Needed to Harm (NNH) was calculated for statistically significant pooled Hazard Ratios (HRs). **RESULTS:** Of 3753 articles identified, seven met the inclusion criteria. Encompassing 314560 patients, three of the seven studies showed that a delay to elective resection is associated with poorer OS or DFS. OS was assessed at a one-month delay, the HR for six datasets was 1.13 (95%CI 1.02-1.26, p = 0.020) and at three months the pooled HR for three datasets was 1.57 (95%CI 1.16-2.12, p = 0.004). Estimated NNH for a delay at one month and three months were 35 and 10 respectively. Delay was non-significantly negatively associated with DFS on metanalysis. **CONCLUSION:** This study suggests that postponing elective CRC surgery by more than four weeks, after diagnosis is associated with a poorer outcome. Future research should try and identify those patients most at risk so that they can be prioritized in the event of any future pandemic.

## FIGURES

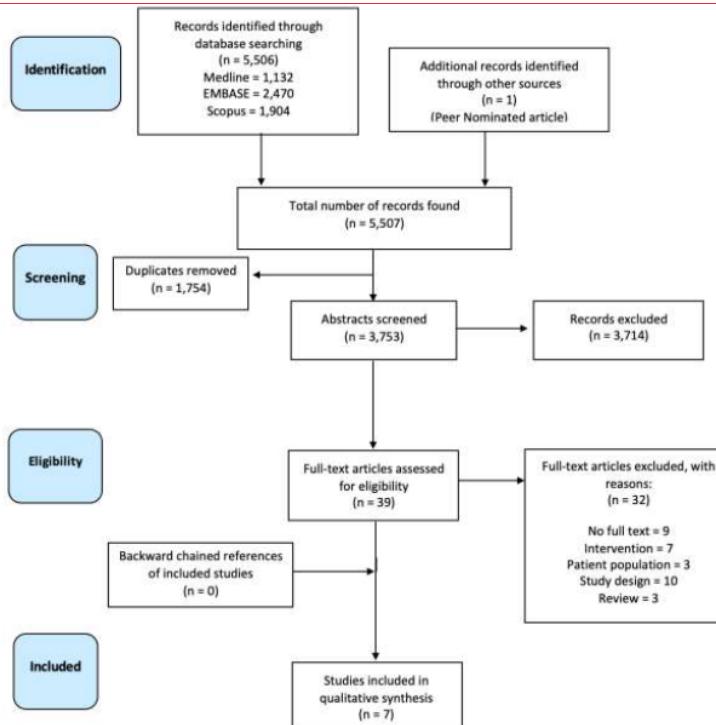


Figure 2. PRISMA Flow Diagram to show how search was conducted.

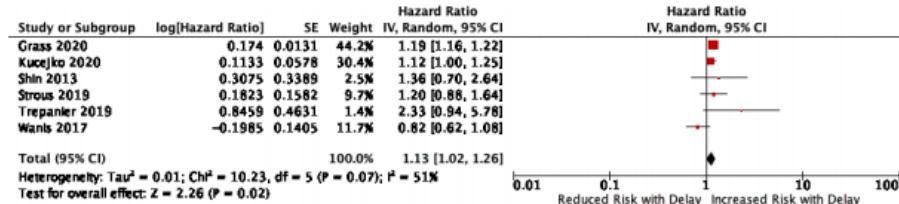


Figure 4. A random effects generic inverse variance forest plot and calculated pooled hazard ratio for the effects of a month's delay to curative colorectal cancer surgery on overall survival.

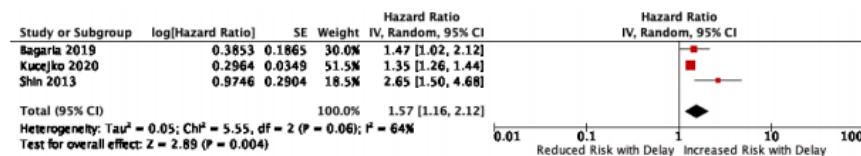


Figure 6. A random effects generic inverse variance forest plot and calculated pooled hazard ratio for the effects of a 12-week delay to curative colorectal cancer surgery on overall survival.

## COMPARISON OF THE MYOPIC PROGRESSION BEFORE, DURING AND AFTER COVID-19 LOCKDOWN

Chang P, Zhang B, Lin L, Chen R, Chen S, Zhao Y, Qu J.. Ophthalmology. 2021 Mar 23:S0161-6420(21)00234-7. doi: 10.1016/j.ophtha.2021.03.029. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

### BLUF

Researchers from the Eye Hospital and School of Ophthalmology and Optometry at Wenzhou Medical University and the National Clinical Research Center for Ocular Diseases in Wenzhou, Zhejiang, China conducted an analysis of 29,719 junior high students in Hangzhou, China participating in the cohort study, Myopia Screening Survey Of Children and Teenagers In Schools (MYOSOTIS), examining their corrected and non-corrected visual acuity (VA) and change in spherical equivalent refraction (SER) during the COVID-19 lockdown. They found an accelerated reversible myopic progression during different rounds of the lockdown (Figure 1), which they speculate is from accumulative spasms, and suggest further consideration and management for this condition in children and teenagers in the setting of future lockdowns.

### FIGURES

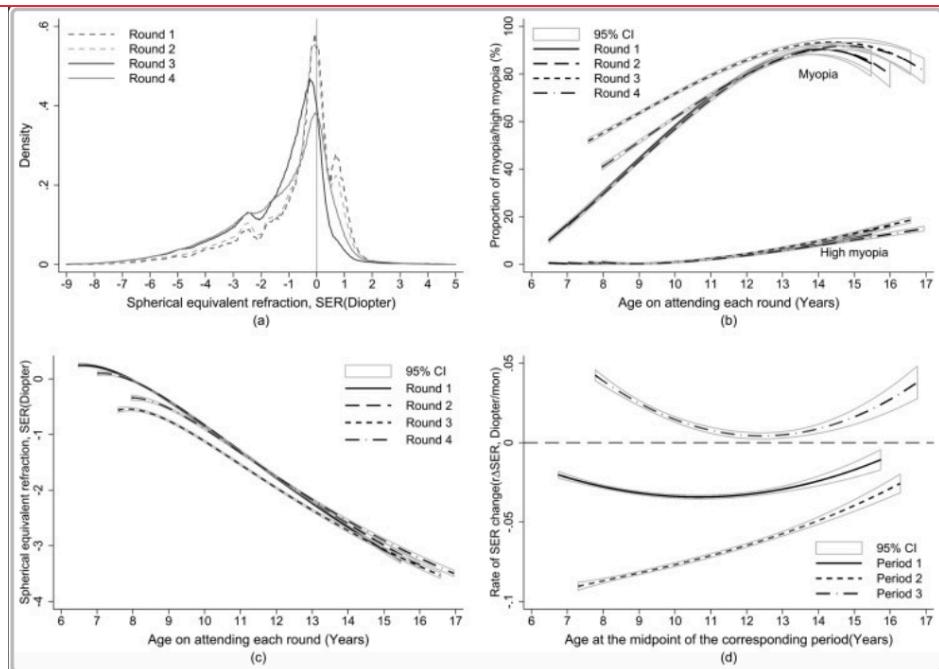


Figure 1. Curves of the cross-sectional distribution of (a) refractive state at each survey round; (b) proportions of myopia and high myopia by age at each survey round; (c) spherical equivalent refraction (SER) by age at each survey round. (d) Age curves of the rate of SER change ( $r\Delta SER$ ) during each survey period. (The curves in (a) are smoothed with kernel density estimates and the curves in (b)~(d) are smoothed with fractional-polynomial prediction).

## R&D: DIAGNOSIS & TREATMENTS

### DEVELOPMENTS IN DIAGNOSTICS

#### EARLY DETECTION OF SARS-COV-2 AND OTHER INFECTIONS IN SOLID ORGAN TRANSPLANT RECIPIENTS AND HOUSEHOLD MEMBERS USING WEARABLE DEVICES

Keating BJ, Mukhtar EH, Elftmann ED, Eweje FR, Gao H, Ibrahim LI, Kathawate RG, Lee AC, Li EH, Moore KA, Nair N, Chaluvadi V, Reason J, Zanoni F, Honkala AT, Al-Ali AK, Alrubaish FA, Ahmad Al-Mozaini M, Al-Muhanna FA, Al-Romaih K, Goldfarb SB, Kellogg R, Kiryluk K, Kizilbash SJ, Kohut TJ, Kumar J, O'Connor MJ, Rand EB, Redfield RR, Rolnik B, Rossano J, Sanchez PG, Alavi A, Bahmani A, Bogu GK, Brooks AW, Metwally AA, Mishra T, Marks SD, Montgomery RA, Fishman JA, Amaral S, Jacobson PA, Wang M, Snyder MP.. Transpl Int. 2021 Mar 18. doi: 10.1111/tri.13860. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

#### BLUF

A review article conducted by researchers from medical institutions throughout the US and UK proposes the role of wearable devices in the clinical management of solid organ transplant recipients by measuring biometric changes (summary) and providing a source of early infection detection before the clinical onset of symptoms. Recent algorithms have shown greater than 80% success of SARS-CoV-2 detection compared to using symptoms alone (AUC 0.8 vs. 0.71, p < 0.01). Confounding factors (Table 1), specifically for kidney transplant patients (Table 2), need to be considered in these algorithms due to the effect on COVID-19 physiological biometrics especially among transplant recipients, however these results can be implemented into clinical decision support to allow for timely detection and isolation of potentially infected household members (Figure 2). Focus on utility and practical challenges to implementation of wearable devices must be further investigated in future studies.

#### SUMMARY

-Biometrics included monitoring for changes in heart rate, heart rate variability, body temperature, respiratory status, activity, sleep patterns, and oxygen saturation

#### ABSTRACT

The increasing global prevalence of SARS-CoV-2 and the resulting COVID-19 disease pandemic pose significant concerns for clinical management of solid organ transplant recipients (SOTR). Wearable devices that can measure physiologic changes in biometrics including heart rate, heart rate variability, body temperature, respiratory, activity (such as steps taken per day) and sleep patterns and blood oxygen saturation, show utility for the early detection of infection before clinical presentation of symptoms. Recent algorithms developed using preliminary wearable datasets show that SARS-CoV-2 is detectable before clinical symptoms in >80% of adults. Early detection of SARS-CoV-2, influenza, and other pathogens in SOTR, and their household members, could facilitate early interventions such as self-isolation and early clinical management of relevant infection(s). Ongoing studies testing the utility of wearable devices such as smartwatches for early detection of SARS-CoV-2 and other infections in the general population are reviewed here, along with the practical challenges to implementing these processes at scale in pediatric and adult SOTR, and their household members. The resources and logistics, including transplant specific analyses pipelines to account for confounders such as polypharmacy and comorbidities, required in studies of pediatric and adult SOTR for the robust early detection of SARS-CoV-2 and other infections are also reviewed.

## FIGURES

Medications			
Specific confounder	Baseline vs response	Impacted readout	Clinical factors possibly impacting biometric measurements
Immunosuppression Regimes	Baseline	BP	Most stay immunosuppression regimens include prednisone and tacrolimus which may cause PTDM, hypertension and hyperglycemia. Mycophenolate may cause nausea, vomiting, diarrhea and anemia. Multiple drug-drug interactions.
Beta blocker	Baseline & response	BP, HR, HRV	Beta blockers to treat hypertension can lower BP & HR, increased HRV and fatigue. Calcium channel antagonists to treat post-Tx hypertension can also cause low BP and reflex tachycardia.
Erythropoiesis stimulating agents	Baseline & response	HR, HRV	Post-transplant anemia can cause elevated HR, irregular HR, fatigue and shortness of breath which may resolve with erythropoiesis stimulating drugs.
Antiretroviral	Baseline & response	Multiple	Didanosine, a common antiretroviral for CMV prophylaxis, is associated with multiple GI symptoms, anemia, leukopenia, and thrombocytopenia.
Antibacterials/ Antifungals	Baseline & response	Multiple	Betamethasone can cause nausea, vomiting, anemia and rash. Nystatin can cause diarrhea, nausea and stomach pain. Antibiotics used to treat post-transplant bacterial infections are associated with GI symptoms such as diarrhea, nausea, stomach pain and rash.
Antidepressants	Baseline	HR, BP	Sedatives can cause nausea, vomiting, diarrhea, appetite change, headache, fatigue & possibly QT prolongation. SNRIs are associated with nausea, constipation, fatigue, urination difficulties, sweating & hypertension with serotonin syndrome. Multiple drug-drug interactions.
Over-the-Counter	Baseline & response	Multiple	Anaerogics may reduce fever, cough & cold products may increase HR, antihistamines may cause GI
Products			
<b>Underlying infection(s)</b>			
EBV	Baseline & response	Multiple	Can cause fever, changes in HRV that mimic SARS-CoV-2 infection. May cause PTLD which presents with fever, weight loss, fatigue.
CMV	Baseline & response	Multiple	Can cause fever, changes in HRV that mimic SARS-CoV-2. Prophylaxis may result in hypertension/hypotension and fever.
<b>Comorbidities</b>			
PTLD	Baseline & response	Multiple	Fever, weight loss, diarrhea, fatigue.
Hypertension	Baseline	BP	Post-transplant hypertension is very common.
Anemia	Baseline & response	HR, HRV	Anemia results in increased heart rate and reduced heart rate variability.
PTDM	Baseline & response	Multiple	PTDM is associated with hypertension as well as an increased risk for infection and sepsis, including UTIs, pneumonia, CMV.
CKD	Baseline & response	BP, HR, HRV	CKD effects physiology, including anemia, dehydration, and electrolyte imbalances, resulting in effects on BP, HR and HRV.

Table 1. Confounders impacting COVID-19 related physiological biometrics signatures

Table 1 Abbreviations: Blood Pressure (BP); Cytomegalovirus (CMV); Epstein-Barr virus (EBV), Heart Rate (HR); Heart Rate Variability (HR); proton pump inhibitors (PPI); Post-transplant diabetes mellitus (PTDM); Post-transplant lymphoproliferative disorders (PTLD); Selective serotonin reuptake; inhibitors (SSRIs), Serotonin and norepinephrine reuptake inhibitors (SNRIs); Updated information was taken from McDonald 2020

Indication for Kidney Transplant			
Specific confounder	Baseline vs response	Impacted readout	Clinical factors possibly impacting biometric measurements
Congenital anomalies of kidney & ureters (CAKUT)	Response	BP	Congenital anomalies of the kidney and ureters are common. Posterior urethral valves are associated with recurrent UTIs.
Glomerulonephritis	Baseline	Blood pressure	Glomerulonephritides recur post-transplant & provoke increased risk for post-Tx hypertension.
FSGS	Baseline	Proteinuria, BP	FSGS recipients present with nephrotic syndrome (peripheral edema, hypoalbuminemia, high-grade proteinuria, & hypertension).
<b>Underlying infection(s)</b>			
BK Virus	Baseline & response	Multiple	Reactivation can cause asymptomatic viraemia and viremia which may progress to nephropathy & lead to graft failure. <sup>17</sup>
Urinary tract infection	Baseline & response	Multiple	Infections can cause fever, changes in HRV that mimic SARS-CoV-2 infection.
<b>Comorbidities</b>			
FSGS recurrence	Baseline	BP	FSGS recipients present with nephrotic syndrome (peripheral edema, hypoalbuminemia, high-grade proteinuria, & hypertension).
CKD	Baseline & response	BP, HR, HRV	CKD effects physiology, including anemia, dehydration, and electrolyte imbalances, resulting in effects on BP, HR and HRV.
Reno-vascular disease	Baseline	BP	Reno-vascular disease is a common complication, causing persistent hypertension.

Table 2: Kidney Transplant Specific Confounders

Table 2 Abbreviations: Blood Pressure (BP); Focal segmental glomerulosclerosis (FSGS); Heart Rate (HR); Heart Rate Variability (HRV); Urinary tract infection (UTI). Updated information was taken from McDonald 2020

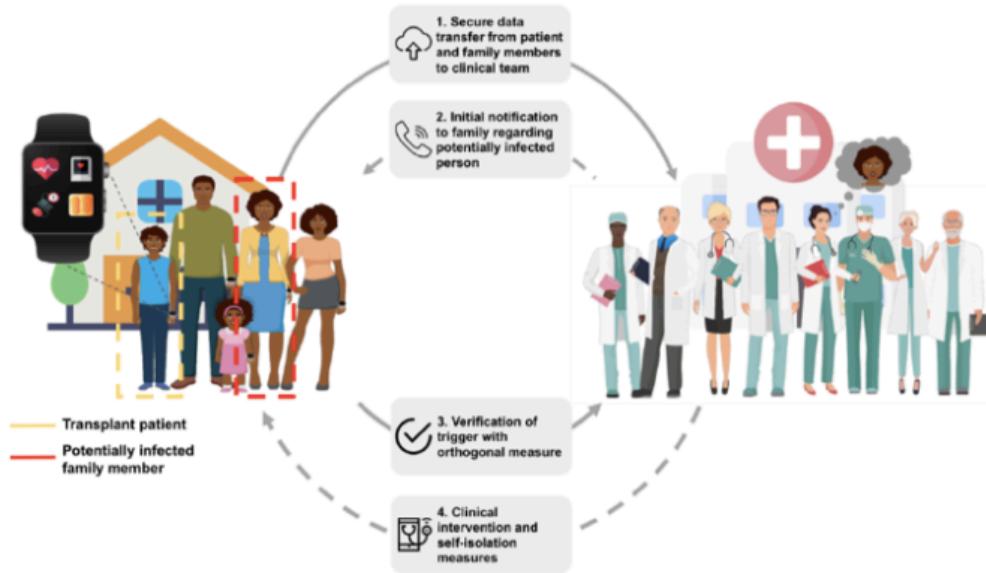


Figure 2: Monitoring of transplant recipients and their family members for early detection of infection

The data collected from wearables on transplant recipients and their families are monitored by a clinical team. Robust abnormal deviations of key physiological biometric baseline signals may indicate potential infection which can be verified through clinical/telehealth consults or measured using orthogonal devices. The algorithms sensitivities can be adjusted to reduce false negatives for confounding factors such as medications impacting HR and ambulatory BP.

Confirmed sustained biometric abnormalities can instigate preventative self-isolation of potentially infected household members and instigation of formal diagnoses of the infection(s). Anticipated triggering of recipients, and any telemedicine/other investigative care such as at home SARS-CoV-2 clinical testing, can be performed through defined protocols from the local clinical care team. Data protection includes no personal health information (PHI) transfer and limiting the activity data so that no geolocation data is recorded.

## DEVELOPMENTS IN TREATMENTS

### THE PRECLINICAL INHIBITOR GS441524 IN COMBINATION WITH GC376 EFFICACIOUSLY INHIBITED THE PROLIFERATION OF SARS-COV-2 IN THE MOUSE RESPIRATORY TRACT

Shi Y, Shuai L, Wen Z, Wang C, Yuanyuan Y, Jiao Z, Guo F, Fu ZF, Huanchun C, Bu Z, Peng G.. Emerg Microbes Infect. 2021 Mar 11:1-43. doi: 10.1080/22221751.2021.1899770. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

#### BLUF

An animal model study conducted by veterinary researchers in China investigated the antiviral activity of the remdesivir parent nucleotide analog, GS441542 and feline coronavirus prodrug, GC376 (Figure 1) with a mouse viral infection model. GS441542 prevented SARS-CoV-2 proliferation in upper and lower respiratory tracts in mice with better pharmacokinetics than GC376 and intramuscular administration was associated with protection in the lower respiratory tract but not upper respiratory tract (Figure 3). Additionally, combined application of intranasal and intramuscular GS441524 and GC376 produced a synergistic effect (Figure 4), suggesting that combined application intranasally and intramuscularly could protect the upper and lower respiratory tracts in mice from SARS-CoV-2 infection.

#### ABSTRACT

The unprecedented coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a serious threat to global public health. Development of effective therapies against SARS-CoV-2 is urgently needed. Here, we evaluated the antiviral activity of a remdesivir parent nucleotide analog, GS441524, which targets the coronavirus RNA-dependent RNA polymerase enzyme, and a feline coronavirus prodrug, GC376, which targets its main

protease, using a mouse-adapted SARS-CoV-2 infected mouse model. Our results showed that GS441524 effectively blocked the proliferation of SARS-CoV-2 in the mouse upper and lower respiratory tracts via combined intranasal (i.n.) and intramuscular (i.m.) treatment. However, the ability of high-dose GC376 (i.m. or i.n. and i.m.) was weaker than GS441524. Notably, low-dose combined application of GS441524 with GC376 could effectively protect mice against SARS-CoV-2 infection via i.n. or i.n. and i.m. treatment. Moreover, we found that the pharmacokinetic properties of GS441524 is better than GC376, and combined application of GC376 and GS441524 had a synergistic effect. Our findings support the further evaluation of the combined application of GC376 and GS441524 in future clinical studies.

## FIGURES

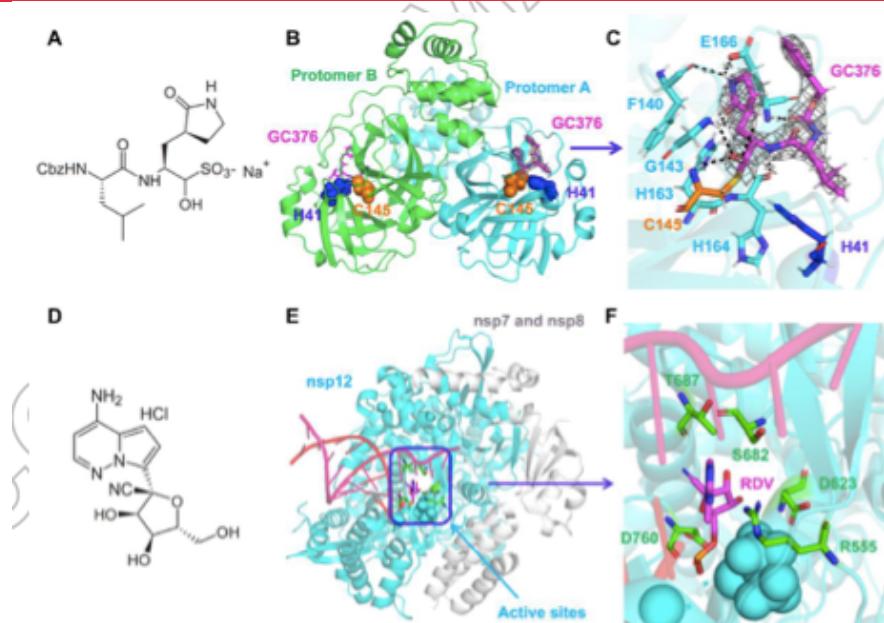


Figure 1. Structural analysis of GC-376 and GS441524 targeting SARS-CoV-2 Mpro and RdRp. (A) The dipeptidyl protease inhibitor, GC376. (B) Crystal structure of SARS-CoV-2 Mpro in complex with GC376. (C) GC376 interacts covalently with the active cysteine site of SARS-CoV-2 Mpro. Electron density at  $1.5 \sigma$  is shown in gray mesh. Hydrogen bonds are shown as red dashed lines. (D) The chemical structure of GS-441524. (E) Cryo-EM structure of the apo nsp12-nsp7-nsp8 RdRp complex (PDB ID: 7BV2). (F) Enlarged view of the active sites, depicting the interaction between RDV and surrounding amino acids.

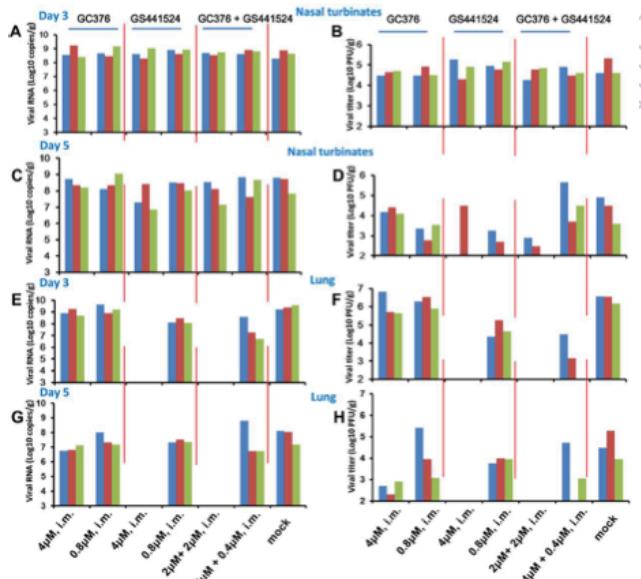


Figure 3. Evaluation of i.m. GC376, GS441524 and GC376+GS441524 against SARS-CoV-2 infection in mice. Four- to six-week-old female BALB/c mice were intramuscularly administered a loading dose of GC376 (4 or 0.8  $\mu$ M), GS441524 (4 or 0.8  $\mu$ M), GC376+GS441524 (2  $\mu$ M+2  $\mu$ M or 0.4  $\mu$ M+0.4  $\mu$ M), followed by a corresponding daily maintenance dose. Control mice were administered vehicle solution (12% sulfobutylether- $\beta$ -cyclodextrin, pH 3.5) daily, in parallel (0  $\mu$ M). One hour after administration of the loading dose of GC376, GS441524, GC376+GS441524 or vehicle solution, the mice were inoculated intranasally with 103.6 PFU of HRB26M in a volume of 50  $\mu$ l. On days 3 and 5 p.i., three mice in each group were euthanized and their nasal turbinates and lungs were collected. The viral RNA copies and infectious titers in the nasal turbinates (A-D) and lungs (E-H) were detected by qPCR and viral titration. The concentrations of the daily maintenance doses are shown.

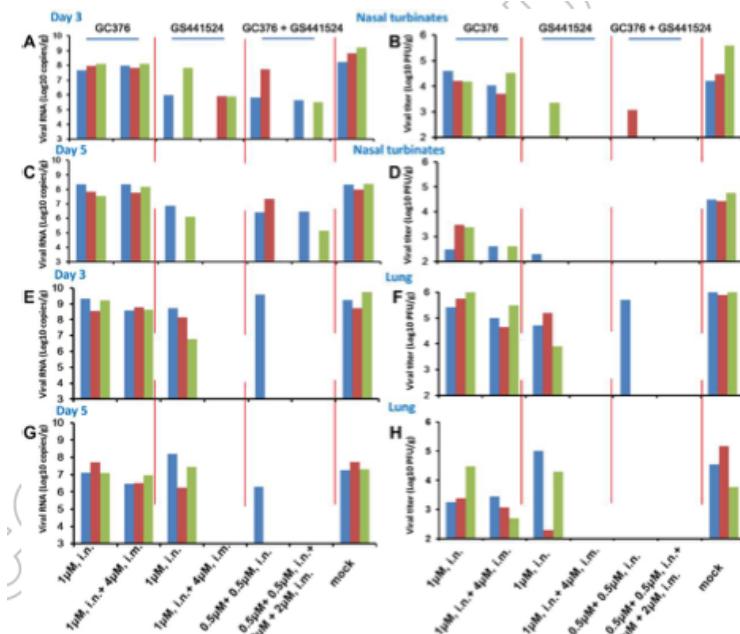


Figure 4. Evaluation of i.n. and i.m. GC376, GS441524 and GC376+GS441524 against SARS-CoV-2 infection in mice. Four- to six-week-old female BALB/c mice were administered a loading dose of GC376 (1  $\mu$ M, i.n. or 1  $\mu$ M, i.n.+4  $\mu$ M, i.m.), GS441524 (1  $\mu$ M, i.n. or 1  $\mu$ M, i.n.+4  $\mu$ M, i.m.), GC376 + GS441524 (0.5  $\mu$ M+0.5  $\mu$ M, i.n. or 0.5  $\mu$ M+0.5  $\mu$ M, i.n. and 2  $\mu$ M+2  $\mu$ M, i.m.), followed by a corresponding daily maintenance dose. Control mice were administered vehicle solution (12% sulfobutylether- $\beta$ -cyclodextrin, pH 3.5) daily in parallel (0  $\mu$ M). One hour after administration of the loading dose of GC376, GS441524, GC376 + GS441524 or vehicle solution, the mice were inoculated intranasally with 103.6 PFU of HRB26M in a volume of 50  $\mu$ l. On days 3 and 5 p.i., three mice in each group were euthanized and their nasal turbinates and lungs were collected. The viral RNA copies and infectious titers in the nasal turbinates (A-D) and lungs (E-H) were detected by qPCR and viral titration. The concentrations of the daily maintenance doses are shown.

# MENTAL HEALTH & RESILIENCE NEEDS

## IMPACT ON PUBLIC MENTAL HEALTH

### EXERCISE AND COVID-19: REASONS INDIVIDUALS SOUGHT COACHING SUPPORT TO ASSIST THEM TO INCREASE PHYSICAL ACTIVITY DURING COVID-19

Barrett S, Rodda K, Begg S, O'Halloran PD, Kingsley MI.. Aust N Z J Public Health. 2021 Mar 8. doi: 10.1111/1753-6405.13089. Online ahead of print.

Level of Evidence: 4 - Case-series

#### BLUF

Exercise scientists from La Trobe University in Australia conducted in-depth, semi-structured telephone interviews with eight individuals seeking coaching support to increase physical activity (PA) during the COVID-19 pandemic. They found all participants had decreased their PA during lockdowns (Table 2), and interviewees cited a need for listening support and issues with self-regulation as their primary motivations for seeking coaching. Because generalizability is limited due to use of a small convenience samples, authors suggest further research to understand if similar barriers to PA during the pandemic are present in the wider population.

#### ABSTRACT

**OBJECTIVE:** This paper explores the experiences of individuals who reported substantially decreasing physical activity (PA) as a result of COVID-19 and sought coaching support to increase PA. **METHODS:** A qualitative study using phenomenological analysis. Eight individuals participated in semi-structured interviews that focused on their experiences of decreasing PA as a result of physical distancing measures, and why they sought PA coaching to overcome these issues. Responses were analysed thematically. **RESULTS:** The participants reported markedly decreasing their PA following the enactment of physical distancing measures. The inability to subsequently engage in regular PA was a source of frustration for participants. Interview analysis revealed two themes that contributed to the understanding of why these individuals felt they needed PA coaching to increase PA; namely, a desire for both listening support and PA self-regulation support. **CONCLUSION:** The individuals who decreased PA due to COVID-19 desired an autonomy-supportive counselling style, centred on listening support and self-regulatory support. Online PA interventions were not highlighted as strategies to overcome PA barriers. Implications for public health: The effect of physical distancing measures on the determinants of overall PA is important, particularly if prolonged physical distancing is required.

#### FIGURES

Table 2: Overview of participants' pre COVID-19 physical activity.

Participant	Age	Gender	Pre COVID-19 physical activity
1	54	Female	Gym: 3-4 sessions/week - mixture of spin classes, body pump, body combat and yoga
2	44	Female	Boot-camp group training: 3 sessions a week
3	61	Male	Strength training: 2 days a week Walking group: 1 day a week
4	40	Male	Swimming: 2 sessions a week Basketball: 1 session a week
5	48	Female	Parkrun: 1 session a week Gym: 2 sessions a week – mixture of weights and cardio
6	57	Female	Walking: 4 x 5km walks a week
7	51	Female	Gym: 3 sessions a week – mixture of weights and cardio
8	50	Male	Mixed Martial Arts: 3 sessions a week

Table 2. Overview of participants' pre COVID-19 physical activity

# ACKNOWLEDGEMENTS

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