

The Daily COVID-19 Literature Surveillance Summary

September 24, 2020



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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			
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

- Although the United States received an overall top [Global Health Security \(GHS\) Index](#) score, ability to curtail COVID-19 transmission was hindered by low scores on public confidence in the government, access to health care without barriers, and limitations of federal regulations, suggesting a need for greater emphasis on country leadership and public confidence in future GHS indices as well as a national review of the United States' pandemic approach to identify and address other problem areas.

Adjusting Practice During COVID-19

- A review of mask fit testing for N95/FFP2/N99/FFP3s identify inadequate mask fit testing as a risk factor for infection among healthcare workers, arguing that [well fitted N95/FFP2/N99/FFP3 masks are essential to protect healthcare workers](#) against respiratory viruses such as COVID19, particularly during aerosol generating procedures. Additionally, quantitative fit testing has been evidenced to detect facial leaks better than qualitative fit testing protocols.

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CLIMATE

GLOBAL

SUBOPTIMAL US RESPONSE TO COVID-19 DESPITE ROBUST CAPABILITIES AND RESOURCES

Nuzzo JB, Bell JA, Cameron EE.. JAMA. 2020 Sep 16. doi: 10.1001/jama.2020.17395. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

Public health experts discuss the Global Health Security (GHS) Index and its ability to identify strengths and weaknesses regarding pandemic preparedness in various countries. Although the United States received an overall top GHS score, ability to curtail COVID-19 transmission was hindered by low scores on public confidence in the government and access to health care without barriers, as well as limitations of federal regulations. Authors suggest a need for greater emphasis on country leadership and public confidence in future GHS indices, recommending a national review of the United States' pandemic approach to identify and address other problem areas.

DISPARITIES

OBESITY AND HYPERTENSION IN THE TIME OF COVID-19

Rodgers GP, Gibbons GH.. JAMA. 2020 Sep 9. doi: 10.1001/jama.2020.16753. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

In this editorial, directors of the National Institute of Diabetes and Digestive and Kidney diseases (NIDDK) and National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH) discuss how the obesity epidemic and poorly controlled hypertension as risk factors for COVID-19 morbidity and mortality affect racial/ethnic minority groups disproportionately. Authors suggest these findings represent the profound effects of systemic racism and social determinants of health as "complex drivers of health disparities", which calls for comprehensive and multilevel interventions aimed at achieving health equity nationwide.

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

COVID-19, NAUSEA AND VOMITING

Andrews PLR, Cai W, Rudd JA, Sanger GJ.. J Gastroenterol Hepatol. 2020 Sep 21. doi: 10.1111/jgh.15261. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A review conducted by biomedical and gastrointestinal researchers from London and Hong Kong found the overall incidence of nausea, vomiting, and diarrhea in COVID-19 infection can be as high as ~10% (Figure 1). Proposed potential mechanisms include SARS-CoV-2 modulation on vagal afferents causing anorexia from area postrema activation, SARS-CoV-2 receptor (angiotensin converting enzyme 2, ACE2) expression in upper GI enterocytes leading to peripheral and central emetic drives, and SARS-CoV-2-induced increase in angiotensin II which acts as a centrally acting emetic (Figure 2). Given these mechanisms potentially implicated in COVID-19, more attention is warranted for recognizing nausea and vomiting as early symptoms of infection.

ABSTRACT

Exclusion of nausea (N) and vomiting (V) from detailed consideration as symptoms of COVID-19 is surprising as N can be an early presenting symptom. We examined the incidence of NV during infection before defining potential mechanisms. We estimate that the overall incidence of nausea (median 10.5%), although variable, is comparable to diarrhoea. Poor definition of N, confusion with appetite loss, and reporting of N and/or V as a single entity may contribute to reporting variability and likely underestimation. We propose that emetic mechanisms are activated by mediators released from the intestinal epithelium by SARS-CoV-2 modulate vagal afferents projecting to the brainstem and after entry into the blood, activate the area postrema (AP) also implicated in anorexia. The receptor for spike protein of SARS-CoV-2, angiotensin 2 converting enzyme (ACE2), and transmembrane protease serine (for viral entry) are expressed in upper GI enterocytes, ACE2 is expressed on enteroendocrine cells (EECs), and SARS-CoV-2 infects enterocytes but not EECs (studies needed with native EECs). The resultant virus-induced release of epithelial mediators due to exocytosis, inflammation and apoptosis provides the peripheral and central emetic drives. Additionally, data from SARS-CoV-2 shows an increase in plasma angiotensin II (consequent on SARS-CoV-2/ACE2 interaction), a centrally (AP) acting emetic, providing a further potential mechanism in COVID-19. Viral invasion of the dorsal brainstem is also a possibility but more likely in delayed onset symptoms. Overall, greater attention must be given to nausea as an early symptom of COVID-19 and for the insights provided into the GI effects of SARS-CoV-2.

FIGURES

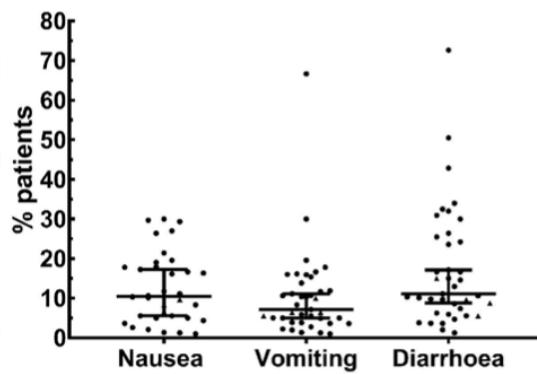


Figure 1. The incidence of nausea and/or vomiting and diarrhoea from 41 clinical studies 1, 2, 4, 5, 16, 22-28, 30, 31, 35, 36, 41, 42, 92, 113-134 :nausea, n=34; vomiting, n=39; diarrhoea, n=39. Values for individual studies are shown together with the median and 95% confidence intervals. No distinction was made between nausea and vomiting in 10 studies so the same incidence was used in both categories. The total number of patients in the studies was 12239. Five studies (data indicated by triangles) reported only data on children (1.5 months to 17 years) 28, 42, 114, 115, 128.

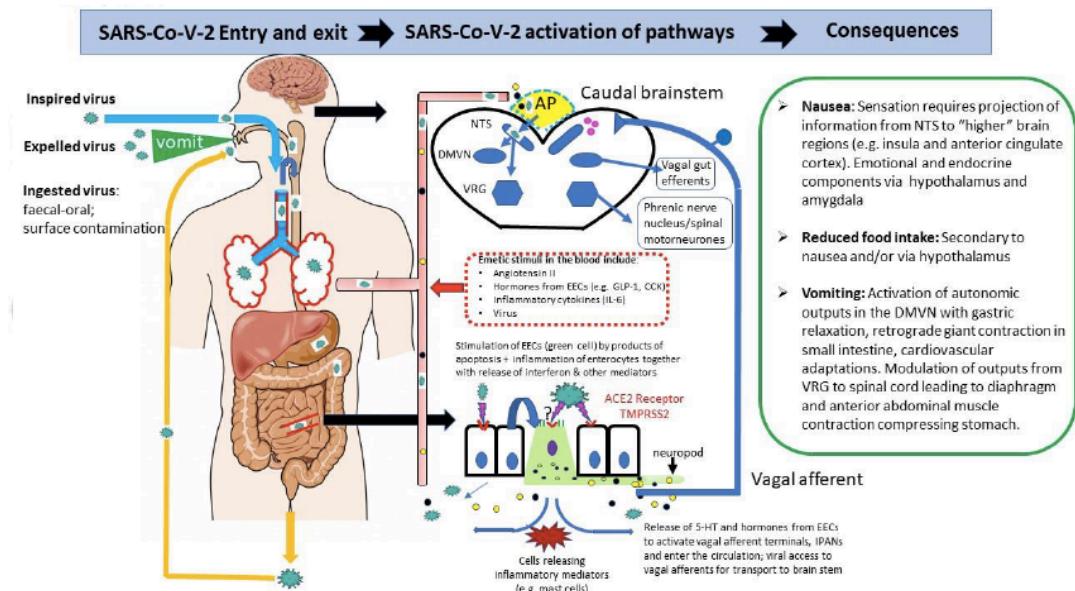


Figure 2. Diagram summarising the potential mechanisms by which SARS-Co-V-2 could induce nausea and vomiting. The left-hand panel shows the routes by which virus can enter the body to access the airways and digestive tract. Air can enter the digestive tract during swallowing. The presence of high levels of angiotensin converting enzyme 2 receptor in the airways and digestive tract is indicated by red lines. The middle panel shows the potential mechanisms (based on evidence discussed in the text) for the interaction of the virus with the digestive tract epithelium leading to release of neuroactive agents from enteroendocrine cells and inflammatory mediators which act either by stimulating/sensitising abdominal vagal afferent terminals and /or act on the area postrema in the dorsal medulla where the blood-brain and blood-cerebrospinal fluid barriers are relatively permeable. In addition, angiotensin II levels may increase and have central actions together with virus which may enter the circulation from damaged lungs and digestive tract epithelia. The right-hand panel summarises the consequences of vagal afferent and area postrema activation to induce nausea and vomiting by projection of information to higher brain regions (nausea and anorexia) and vomiting by motor pathways in the ventral brainstem and spinal cord.

Abbreviations: ACE 2: angiotensin converting enzyme receptor 2; AP: area postrema; NTS: nucleus tractus solitarius; DMVN: dorsal motor vagal nucleus; VRG: ventral respiratory group of neurones; EEC: enteroendocrine cells in the digestive tract; GLP-1: glucagon-like peptide-1; CCK: cholecystokinin; IL-6: interleukin-6; TMPRSS2: transmembrane protease serine 2; 5-HT: 5-hydroxytryptamine.

UNDERSTANDING THE PATHOLOGY

THE IMPACT OF AGING AND COVID-19 ON OUR IMMUNE SYSTEM: A HIGH-RESOLUTION MAP FROM SINGLE CELL ANALYSIS

Yang J, Li H.. Protein Cell. 2020 Sep 7. doi: 10.1007/s13238-020-00782-y. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

Investigators affiliated with University of Electronic Science and Technology of China and University of California review Zheng et al.'s study in which single cell RNA sequencing and mass cytometry were performed to analyze isolated peripheral blood mononuclear cells (PBMC) from both healthy and COVID-19-infected young and elderly humans. They found that the healthy, aging group had decreased T-cells and B-cells and increased natural killer cells and monocytes, illustrating that "aging shifts the immune cells towards more polarized and inflammatory populations." Additionally, they noted that the COVID-19 group showed depletion of T cells and increased pro-inflammatory monocytes. Based on these findings, Zheng at el. suggests that aging and COVID-19 act "synergistically" to deplete the adaptive immune system, which may contribute to the severity of COVID-19 symptoms in older patients.

IN VITRO

RAPID DECAY OF ANTI-SARS-COV-2 ANTIBODIES IN PERSONS WITH MILD COVID-19

Ibarrondo FJ, Fulcher JA, Goodman-Meza D, Elliott J, Hofmann C, Hausner MA, Ferbas KG, Tobin NH, Aldrovandi GM, Yang OO.. N Engl J Med. 2020 Sep 10;383(11):1085-1087. doi: 10.1056/NEJMc2025179. Epub 2020 Jul 21.

Level of Evidence: Other - Mechanism-based reasoning

BLUF

Physicians at the David Geffen School of Medicine at the University of California in Los Angeles analyzed antibody decay rate of the anti-SARS-CoV-2 spike receptor-binding domain of serum immunoglobulin G (IgG) using enzyme-linked immunosorbent assay (ELISA) on samples from 34 patients, which showed an antibody half-life of 36 days and overall faster antibody loss than the rate reported for SARS-CoV-1 (Figure 1). Authors highlight concerns regarding length of humoral immunity against SARS-CoV-2, emphasizing the need for better understanding of antibody decay and durability as vaccine development is underway.

FIGURES

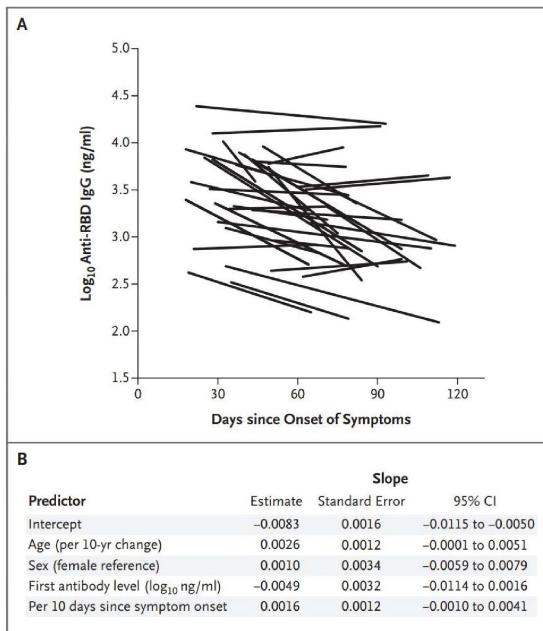


Figure 1. Longitudinal Assessment of Anti-SARS-CoV-2 Receptor-Binding Domain IgG in Persons Who Recovered from Covid-19.

Approximately 80 persons who recovered from Covid-19 referred themselves to our institution to inquire about observational research. Of 68 persons who volunteered to provide initial blood samples, 41 returned to provide repeat samples. Of those persons, 3 were excluded from this analysis because of unclear timing of infection and 4 were excluded because of initial and repeat serum antibody measurements below the limit of reliable quantitative detection. For the 34 participants in our analysis, anti-SARS-CoV-2 receptor-binding domain (RBD) serum IgG concentrations were quantified by enzyme-linked immunosorbent assay as equivalent binding activity to a concentration of a control monoclonal IgG for at least two time points (31 of the 34 participants had two measurements, and the remaining 3 participants had three measurements). Panel A shows log-transformed IgG concentrations plotted against the time since the onset of symptoms in each participant. Panel B shows a linear regression model that was created to estimate the effects of the participants' age and sex, the days from symptom onset to the first measurement, and the first measured \log_{10} antibody level on the slope reflecting the change in anti-RBD antibody levels (in \log_{10} ng per milliliters per day). The values for age and antibody level were centered at the mean.

The time since symptom onset was centered at day 18 and adjusted per 100 days. Thus, the intercept of the model can be interpreted as the average slope adjusted for age, sex, and time and value of the first measurement. CI denotes confidence interval.

TRANSMISSION & PREVENTION

PREVENTION IN THE HOSPITAL

DECONTAMINATION OF SARS-COV-2 AND OTHER RNA VIRUSES FROM N95 LEVEL MELTBLOWN POLYPROPYLENE FABRIC USING HEAT UNDER DIFFERENT HUMIDITIES

Campos RK, Jin J, Rafael GH, Zhao M, Liao L, Simmons G, Chu S, Weaver SC, Chiu W, Cui Y.. ACS Nano. 2020 Sep 21. doi: 10.1021/acsnano.0c06565. Online ahead of print.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A study by members from the University of Texas, Stanford University, and various biomedical research institutions across Texas and California investigated efficacy of heat inactivation of SARS-CoV-2 and two similar viruses dried on meltblown polypropylene fabric used to make some N95 masks. They found that temperatures of 75°C for 30 min or 85°C for 20 min using 100% relative humidity (Figure 3) resulted in efficient decontamination of SARS-CoV-2 without comprising the filtration efficiency of the fabric over at least 20 treatments. The authors concluded that this could be a promising decontamination method during mask shortages, in addition to the discovery that humidity enhances the decontamination process, which may be helpful in the formation of certain public policies.

ABSTRACT

In March of 2020, the World Health Organization declared a pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pandemic led to a shortage of N95-grade filtering facepiece respirators (FFRs), especially surgical-grade N95 FFRs for protection of healthcare professionals against airborne transmission of SARS-CoV-2. We and others have previously reported promising decontamination methods that may be applied to the recycling and reuse of FFRs. In this study we tested disinfection of three viruses including SARS-CoV-2, dried on a piece of meltblown fabric, the principal component responsible for filtering of fine particles in N95-level FFRs, under a range of temperatures (60–95 °C) at ambient or 100% relative humidity (RH) in conjunction with filtration efficiency testing. We found that heat treatments of 75 °C for 30 min or 85 °C for 20 min at 100% RH resulted in efficient decontamination from the fabric of SARS-CoV-2, human coronavirus NL63 (HCoV-NL63), and another enveloped RNA virus, chikungunya virus vaccine strain 181/25 (CHIKV-181/25), without lowering the meltblown fabric's filtration efficiency.

FIGURES

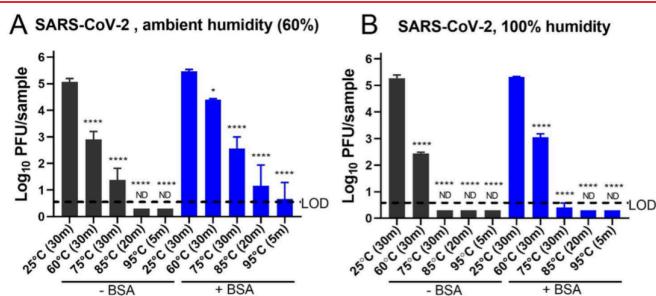


Figure 3. Heat inactivation of SARS-CoV-2 dried on a piece of meltblown fabric is more efficiently inactivated by 100% humidity. A. Heat treatment of SARS-CoV-2 dried on meltblown fabric at ambient humidity (approximately 60%). B. Heat treatment of SARS-CoV-2 dried on meltblown fabric at 100% humidity. Error bars represent SD. ND (not detected) are conditions in which each of the triplicates were below the LOD. Statistical significance was assessed by one-way ANOVA using Sidak's multiple correction test. * p < 0.05, **** p < 0.0001.

* BSA: bovine serine albumin; used in this study to mimic bodily fluids such as sputum, which is known to stabilizes viruses.

MANAGEMENT

ACUTE CARE

SPONTANEOUS PNEUMOTHORAX AND SUBPLEURAL BULLAE IN A PATIENT WITH COVID-19: A 92-DAY OBSERVATION

Fan Q, Pan F, Yang L.. Eur J Cardiothorac Surg. 2020 Sep 20:ezaa305. doi: 10.1093/ejcts/ezaa305. Online ahead of print.
Level of Evidence: Other - Case Report

BLUF

This case report from the Department of Radiology at Union Hospital in Wuhan, China describes a previously healthy 32 year old male who was treated for COVID-19 and viral pneumonia with good recovery aside from a cough. Three days after initial recovery, the patient developed respiratory distress and was found to have spontaneous pneumothorax and subpleural bullae on chest CT imaging (Figure 1, 2). This case suggests that subpleural consolidation with persistent cough in the setting of COVID-19 may increase the risk for non-traumatic pneumothorax and subpleural bullae.

ABSTRACT

This report describes a patient with COVID-19 who developed spontaneous pneumothorax and subpleural bullae during the course of the infection. Consecutive chest computed tomography images indicated that COVID-19-associated pneumonia had damaged the subpleural alveoli and distal bronchus. Coughing might have induced a sudden increase in intra-alveolar pressure, leading to the rupture of the subpleural alveoli and distal bronchus and resulting in spontaneous pneumothorax and subpleural bullae. At the 92-day follow-up, the pneumothorax and subpleural bullae had completely resolved, which indicated that these complications had self-limiting features.

FIGURES

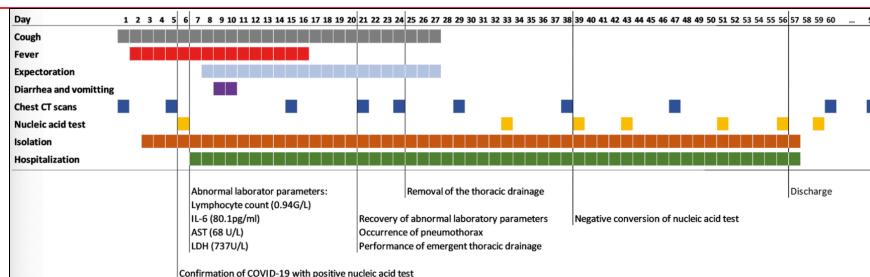


Figure 1: Timeline of the clinical course. AST: aspartate aminotransferase; COVID-19: coronavirus disease-2019; CT: computed tomography; IL: interleukin; LDH: lactate dehydrogenase.

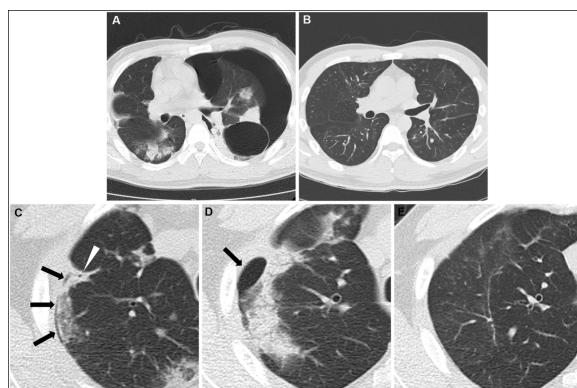


Figure 2: Typical chest computed tomography manifestations at different time points. Day 21, pneumothorax was found on the left side with a subpleural giant bulla (A), which was completely absorbed on day 92 (B). Day 21, a subpleural hypodense line (B, black arrows) was noticed in the right upper lung attaching to a branch of a peripheral bronchus (C, white arrowhead) surrounded with consolidation; day 24, the previous subpleural hypodense line became a localized pneumothorax (D, black arrow); day 92, the localized pneumothorax was completely absorbed (E). All images have the same window level of -600 and window width of 1600.

IMPORTANT PHARMACOGENETIC INFORMATION FOR DRUGS PRESCRIBED DURING THE SARS-COV-2 INFECTION (COVID-19)

Zubiaur P, Koller D, Saiz-Rodríguez M, Navares-Gómez M, Abad-Santos F.. Clin Transl Sci. 2020 Sep 16. doi: 10.1111/cts.12866. Online ahead of print.

Level of Evidence: Other - Review / Literature Review

BLUF

A review by authors affiliated with the Clinical Pharmacology Department at Universidad Autónoma de Madrid (UAM) in Spain summarize pharmacogenetic biomarkers of drugs used for COVID-19 patient management during the pandemic, while providing an easily accessible list of drug characteristics (Table 1). Authors acknowledge a need for further research to elaborate on pharmacogenetic properties of these drugs and others in the setting of COVID-19, suggesting that further knowledge in this area could improve clinical guidelines and establish more efficient and cost-effective treatment.

ABSTRACT

In December 2019, the severe acute respiratory syndrome virus-2 pandemic began, causing the coronavirus disease 2019. A vast variety of drugs is being used off-label as potential therapies. Many of the repurposed drugs have clinical pharmacogenetic guidelines available with therapeutic recommendations when prescribed as indicated on the drug label. The aim of this review is to provide a comprehensive summary of pharmacogenetic biomarkers available for these drugs, which may help to prescribe them more safely.

FIGURES

Drug	Biomarker	Level of evidence
Chloroquine and hydroxychloroquine	G6PD	2
	CYP2C8, CYP3A4, and CYP2D6	4
Remdesivir	CYP2C8, CYP2D6, and CYP3A4	4
Losartan	CYP2C9	3
Captopril, enalapril, and lisinopril	ACE rs1799752	3
Spironolactone	ADD1 rs4961	3
Ribavirin and peg-interferon alfa 2a/2b	IFNL3 (IL28B) rs12979860	1
Lopinavir/ritonavir	CYP3A4	4
Atazanavir/ritonavir	UGT1A1	1
Corticosteroids	ABCB1	3
Progesterone	CYP2C19	3
Nonsteroidal anti-inflammatory drugs	CYP2C9	1
Tocilizumab	IL-6R rs4329505, rs12083537, and rs11265618	3
	CYP3A4	4
Sarilumab	CYP3A4	4
	IL-6R rs4329505, rs12083537, and rs11265618	4
Siltuximab	CYP3A4	4
	IL-6R rs4329505, rs12083537, and rs11265618	4
Sirolimus	CYP3A5	3
Nicotine	CYP1A1 and CYP1A2	3
Fluvoxamine	CYP2D6	1
Ruxolitinib	CYP3A4 and CYP2C9	4
Baricitinib	CYP3A4 and ABCB1	4
Anakinra	IL-1 rs17651	3
Colchicine	CYP2D6	3

Table 1. Summary of Used During COVID-19 Pandemic with Corresponding Pharmacogenetic Information. Levels of evidence - 1: Biomarkers with clinical pharmacogenetic guidelines; 2: Biomarkers with clinical pharmacogenetic guidelines applied to other drugs; 3: Candidate pharmacogenetic biomarkers as published in peer-review journals without clinical pharmacogenetic guidelines; 4: Speculative biomarkers. Abbreviations - ABCB1, ATP binding cassette subfamily B member 1; ACE, angiotensin-converting enzyme; ADD1, adducin 1 (alpha); COVID-19, coronavirus disease 2019; CYP, cytochrome P450; G6PD, glucose-6-phosphate dehydrogenase; IFNL3, interferon lambda 3; IL-1, interleukin-1; IL-6R, interleukin-6 receptor; UGT1A1, UDP glucuronosyltransferase family 1 member A1.

WHICH ARE THE MAIN ASSESSMENT TOOLS OF FUNCTIONAL CAPACITY IN POST-ACUTE COVID-19 PATIENTS ADMITTED TO REHABILITATION UNITS?

Curci C, Pisano F, Negrini F, De Sire A.. Eur J Phys Rehabil Med. 2020 Sep 16. doi: 10.23736/S1973-9087.20.06579-X. Online ahead of print.

Level of Evidence: Other - Expert Opinion

BLUF

In this letter to the editor, specialists in rehabilitative medicine across Italy respond to uncertainties raised by Rivera-Lillo et al. 2020 regarding assessment of functional capacity in post-COVID-19 patients. Authors affirm that functional capacity assessment is crucial in these patients as they may be susceptible to serious disabilities, and they suggest use of various methods including the six-minute-walking test (6-MWT), one-minute sit-to-stand (1-min STS), and the Chelsea Critical Care Physical Assessment Tool (CPAx). Authors argue that larger scale studies are needed to compare these different methods and learn more about their usefulness in COVID-19 patient populations.

ADJUSTING PRACTICE DURING COVID-19

COUNTRY-LEVEL FACTORS ASSOCIATED WITH THE EARLY SPREAD OF COVID-19 CASES AT 5, 10 AND 15 DAYS SINCE THE ONSET

Allel K, Tapia-Muñoz T, Morris W.. Glob Public Health. 2020 Sep 7;1:1-14. doi: 10.1080/17441692.2020.1814835. Online ahead of print.

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

BLUF

This epidemiological study using cross-sectional data generated a database containing information on the number of COVID-19 cases at 5, 10, and 15 days since the first confirmed case in 134 countries in order to assess country level factors associated with the spread of COVID-19 (Summary, Table 1, Figure 1, Figure 3). They found that establishment of government measures within the first five days was a strong predictor of the spread of COVID-19 during the next 10 days (IRR 0.95, SE 0.02), suggesting that stringent government practices help limit the spread of COVID-19.

SUMMARY

Six country-level factors were analyzed to study the early spread of COVID-19. They include socioeconomic factors, sociodemographic factors, risk factors for non-communicable diseases, healthcare resources and expenditures, government measures in response to outbreak, other. Results showed all of the factors help determine spread within first five days but country differences are driven by healthcare resources and expenditures after day 10 (IRR ($t=15$) 0.81, SE 0.07; IRR ($t=5$) 0.88, SE 0.06). "Government measures within the first five days was found to be a strong predictor of the spread of COVID-19 during the next 10 days (IRR 0.95, SE 0.02)."

ABSTRACT

The COVID-19 pandemic is causing a significant global health crisis. As the disease continues to spread worldwide, little is known about the country-level factors affecting the transmission in the early weeks. The present study objective was to explore the country-level factors, including government actions that explain the variation in the cumulative cases of COVID-19 within the first 15 days since the first case reported. Using publicly available sources, country socioeconomic, demographic and health-related risk factors, together with government measures to contain COVID-19 spread, were analysed as predictors of the cumulative number of COVID-19 cases at three time points ($t = 5, 10$ and 15) since the first case reported ($n = 134$ countries). Drawing on negative binomial multivariate regression models, HDI, healthcare expenditure and resources, and the variation in the measures taken by the governments, significantly predicted the incidence risk ratios of COVID-19 cases at the three time points. The estimates were robust to different modelling techniques and specifications. Although wealthier countries have elevated human development and healthcare capacity in respect to their counterparts (low- and middle-income countries) the early implementation of effective and incremental measures taken by the governments are crucial to controlling the spread of COVID-19 in the early weeks.

FIGURES

Variables	Mean	SD	IQR (75%-25%)
COVID-19 testing at $t = 5, 10, 15$ days after the first case appeared			
Number of cases at $t = 5$	11.31	14.40	12.00
Number of cases at $t = 10$	50.97	117.23	51.00
Number of cases at $t = 15$	179.39	555.27	168.00
Socioeconomic factors			
Human Development Index (HDI)	74.84	14.49	19.02

Table 1. Descriptive statistics (N = 134 countries).

See entire table <https://www.tandfonline.com/doi/full/10.1080/17441692.2020.1814835>

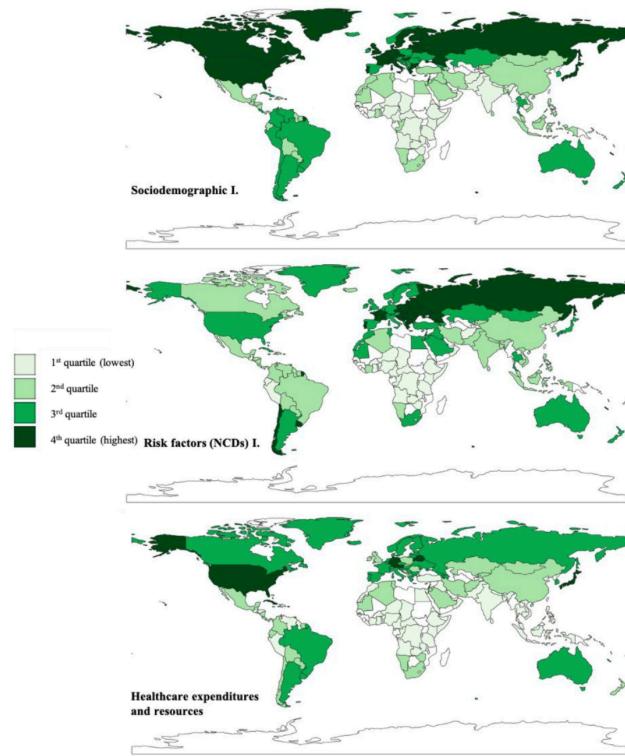


Figure 3. Map of the distribution of the sociodemographic indexes constructed ($N = 134$).

Notes: The fourth quartile indicates the wealthier sociodemographic index and health system, while it also presents the higher accumulation of comorbidities as for risk factors (NCDs). Blank areas are missing data.

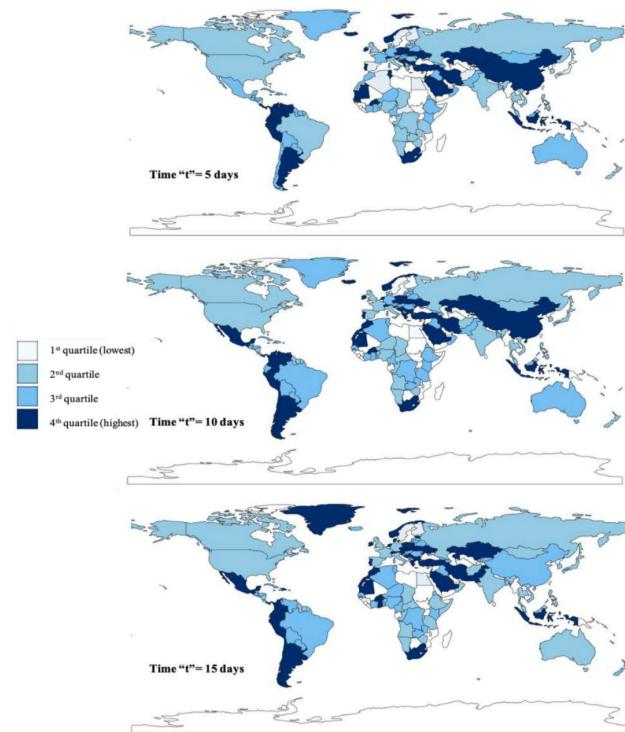


Figure 1. Map of the distribution of the number of cases by period ($N = 134$).

Notes: The fourth quartile indicates the higher number of cases accumulated at time ' t '. Blank areas are missing data.

RANDOMIZED ELIMINATION AND PROLONGATION OF ACE INHIBITORS AND ARBS IN CORONAVIRUS 2019 (REPLACE COVID) TRIAL PROTOCOL

Cohen JB, Hanff TC, Corrales-Medina V, William P, Renna N, Rosado-Santander NR, Rodriguez-Mori JE, Spaak J, Andrade-Villanueva J, Chang TI, Barbagelata A, Alfonso CE, Bernales-Salas E, Coacalla J, Castro-Callirgos CA, Tupayachi-Venero KE, Medina C, Valdivia R, Villavicencio M, Vasquez CR, Harhay MO, Chittams J, Sharkoski T, Byrd JB, Edmonston DL, Sweitzer N, Chirinos JA.. *J Clin Hypertens (Greenwich)*. 2020 Sep 16. doi: 10.1111/jch.14011. Online ahead of print.

Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Multidisciplinary investigators from various medical institutions describe the Randomized Elimination or ProLongation of ACEi and ARB in COronaVIrus Disease 2019 trial (REPLACE COVID NCT04338009; Figure 2), an international, randomized controlled study that began on March 31, 2020 and will continue to enroll up to a total 152 participants. In this trial, subjects with COVID-19 who are taking angiotensin-converting enzyme inhibitors (ACEis) and/or angiotensin receptor blockers (ARB) are randomized to either continue or discontinue these medications upon hospitalization. The primary outcome of this study is a hierarchical global rank score (Figure 4) that considers time to death from initial hospitalization, duration of mechanical ventilation and vasopressor therapy, duration of renal replacement, and multi-organ failure (assessed by Sequential Organ Failure Assessment score). The findings of this study will provide valuable information on the effect of ACEis and ARBs in COVID-19 patients.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), is associated with high incidence of multiorgan dysfunction and death. Angiotensin-converting enzyme 2 (ACE2), which facilitates SARS-CoV-2 host cell entry, may be impacted by angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), two commonly used antihypertensive classes. In a multicenter, international randomized controlled trial that began enrollment on March 31, 2020, participants are randomized to continuation vs withdrawal of their long-term outpatient ACEI or ARB upon hospitalization with COVID-19. The primary outcome is a hierarchical global rank score incorporating time to death, duration of mechanical ventilation, duration of renal replacement or vasopressor therapy, and multiorgan dysfunction severity. Approval for the study has been obtained from the Institutional Review Board of each participating institution, and all participants will provide informed consent. A data safety monitoring board has been assembled to provide independent oversight of the project.

FIGURES

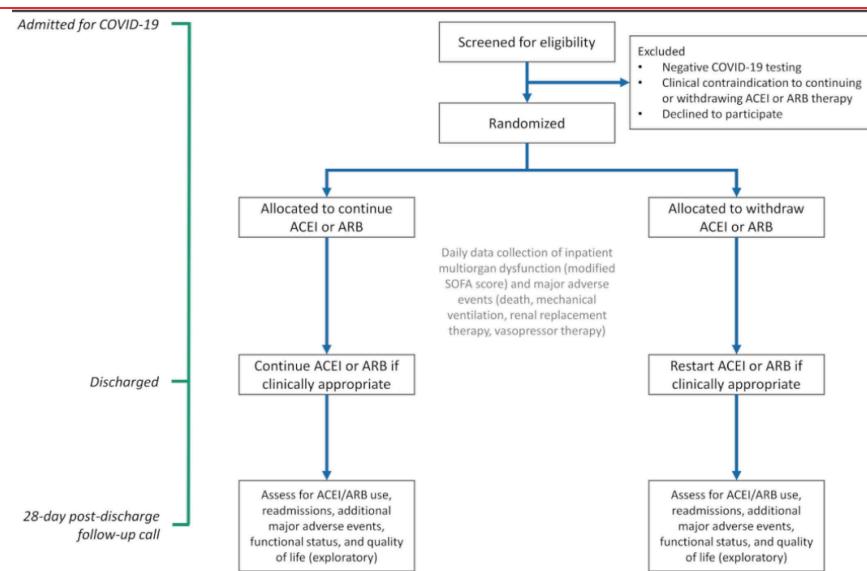


Figure 2. Study overview and design

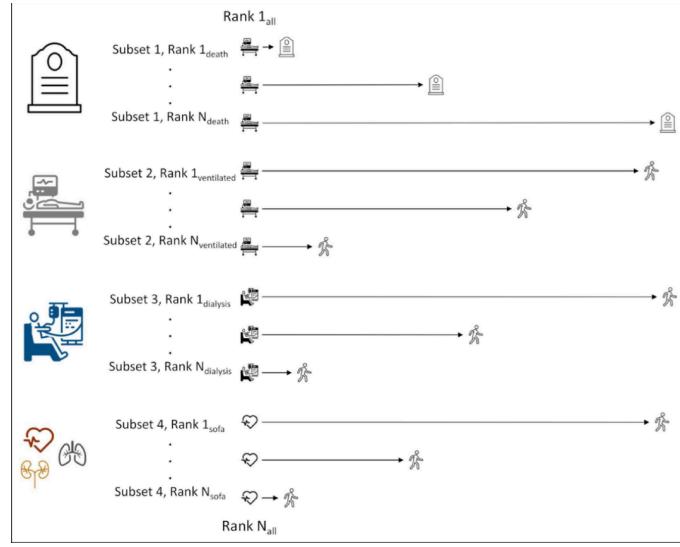


Figure 4. The REPLACE COVID global rank score. Participants are ranked from worst to best outcomes by (1) days in hospital to death; (2) days on invasive mechanical ventilation or extracorporeal membrane oxygenation; (3) days on renal replacement therapy or inotropic/vasopressor therapy; and (4) area under the curve of a modified SOFA score

THE ROLE OF FIT TESTING N95/FFP2/FFP3 MASKS: A NARRATIVE REVIEW

Regli A, Sommerfield A, von Ungern-Sternberg BS.. Anaesthesia. 2020 Sep 15. doi: 10.1111/anae.15261. Online ahead of print.
Level of Evidence: Other - Review / Literature Review

BLUF

Investigators affiliated with Fiona Stanley Hospital and Perth Children's Hospital in Australia review mask fit testing for N95/FFP2/N99/FFP3s and identify inadequate mask fit testing as a risk factor for infection among healthcare workers. They argue that well fitted N95/FFP2/N99/FFP3 masks are essential to protect healthcare workers against respiratory viruses such as COVID19, particularly during aerosol generating procedures (Table 1). Additionally, quantitative fit testing has been evidenced to detect facial leaks better than qualitative fit testing protocols (Table 2). For appropriate protection, the authors recommend mask fit testing, especially quantitative fit testing, for all healthcare workers.

ABSTRACT

For healthcare workers performing aerosol-generating procedures during the COVID-19 pandemic, well fitted filtering facepiece respirators, for example, N95/FFP2 or N99/FFP3 masks, are recommended as part of personal protective equipment. In this review, we evaluate the role of fit checking and fit testing of respirators, in addition to airborne protection provided by respirators. Filtering facepiece respirators are made of material with sufficient high filter capacity to protect against airborne respiratory viruses. Adequate viral protection can only be provided by respirators that properly fit the wearer's facial characteristics. Initial fit pass rates vary between 40% and 90% and are especially low in female and in Asian healthcare workers. Fit testing is recommended to ensure a proper fit of respirators for the individual healthcare worker so that alternative respirators can be selected if required. Although fit testing is required to comply with respirator standards, it is not performed consistently within all healthcare settings. Fit checking (a self-test) is recommended every time a healthcare worker dons a respirator, but is unreliable in detecting proper fit or leak. Additionally, fit testing has a high educational value and as such is best performed as part of a hospital respiratory protection programme. Whether fit checking alone, as opposed to fit tested and fit checked respirators, provides adequate airborne protection against aerosols containing the SARS-CoV-2 virus and other respiratory viruses remains unknown. While fit testing undoubtedly incurs additional costs, it is still recommended, not only to protect healthcare workers but also as it may reduce overall healthcare cost when considering the potential costs of sickness leave and the associated legal costs of compensation.

FIGURES

Table 1 Different types of respirators with fit test requirements and their protection factor.

Respirator class	Comments	Precaution	fit testing	Assigned protection factor	Measured protection factor
Surgical mask	Disposable masks designed to prevent wearer from contaminating surgical field ('sender reduction') Large leak of surgical masks limits the degree of airborne protection	Droplet precaution	n/a	n/a	1.2
N95/FFP2 mask – not fit-tested		n/a	n/a	n/a	3.3
N95/FFP2/N99/FFP3/N100 mask – fit tested	Disposable masks designed to protect wearer from airborne transmission if properly fitted ('receiver reduction') N95/FFP2/N99/FFP3/N100 mask (filtering facepiece respirators, particulate filter respirator) apply to different standards (FFP2 and FFP3: European Committee for Standardization:EN149:2001-A1:2009; N95:NIOSH 42 CFR Part 84; and P2: Standards Australia: AS/NZS ISO standard:1715:2009.)	Airborne precaution	Required	> 10	20.5
Elastomer half-mask respirator – not fit tested		n/a	n/a	n/a	7.3
Elastomer half-mask respirator – fit tested	Reusable masks with disposable N95/FFP2 side filters, mainly used outside the healthcare setting (e.g. mining, construction) are suitable alternative to N95/FFP2 masks Perceived restriction in communication and downward vision as well as the need to disinfect and store between shifts or carry around during shifts needs to be considered	Airborne precaution – alternative to disposable respirators	Required	> 10	13.0
Powered air purifying respirator	This consists of a hood that receives purified air via a pump (mostly carried on waist) and a high-efficiency particulate absorbing viral filter. Complex donning/doffing and disinfection procedure needs to be considered	Airborne precaution – alternative to disposable respirators especially if exposed to anticipated high/ prolonged viral load	Not required	> 25 (halfface) > 1000 (full face)	-

NIOSH, National Institute for Occupational Safety and Health.
The Occupational Safety and Health Administration (OSHA) defines an assigned protection factor (PF) for each respirator class that can be expected to protect 95% of the workplace if using a properly functioning and correctly fitted respirator [44]. It can be assumed that a properly fitted N95/P2 mask with an assigned PF of 10 reduces the number of inhaled particles by at least 10-fold. Assigned protection factors are mainly used to determine the 'maximum used concentration' of a hazardous atmospheric substance at a workplace and is of limited value when considering airborne protection. N95-masks are assigned a PF of 10 by OSHA while FFP2 and FFP3 masks are assigned PFs of 10 and 20 respectively in the UK [27]. Measured protection factor (5th percentile Simulated Work Force Protection) by Lawrence et al. [32].

Table 2 Advantages and disadvantages of fit checking, qualitative and quantitative fit testing.

	Fit check	Qualitative fit test	Quantitative fit test
Recommendations	Minimum requirement every time before donning a respirator	Reasonable alternative on a departmental level should quantitative fit-testing not be available	Quantitative fit-testing is the gold standard and recommended to comply with international and national standards
Method	HCW uses both positive and negative pressure and self assesses for leak	Aerosolised test agent bitter/sweet is applied in test hood to assess leak	Quantitative fit testing provides a fit factor calculated as the ratio of substance concentration outside to inside a respirator. A fit factor value > 100 indicates adequate fit
Ease of performance	Easy to perform	Relatively easy to perform on a departmental level. Requires dedicated staff with training and time	Requires staff with specific training. Best forms part of a hospital respiratory protection program
Additional requirement	Best performed as part of the donning/doffing procedure and ideally together 'companion' or mirror	Relative inexpensive test equipment (\$300–\$1000 can test around 100–400 HCW). Cost mainly derives from time required to test HCW (around 20–40 min per HCW)	Relative expensive equipment (about \$15–30,000). Less time required than qualitative fit testing (around 10 min)
Educational value	Educational value can be enhanced if combined with appropriate training or as part of a hospital respiratory protection program	High educational value and may increase confidence in respirator protection when passing the fit-test	High educational value and may increase confidence in respirator protection when passing the fit test
Advantages	Minimal additional time and health care cost	Respirator can be reused for the HCW after being tested (e.g. in sealed bag)	Objective measure of fit and is considered the gold standard. Circumnavigates subjectiveness in anxious patients, more accurate assessment
Disadvantages	Poor ability to detect leak. Sensitivity and specificity to correctly detect leak is 26% and 79%, respectively	Subjective nature as test relies on the ability of HCW to taste bitter/sweet. Some HCW cannot be tested (claustrophobic, cannot taste sweet or bitter, anxiety). Qualitative fit testing is inferior to quantitative fit testing in detecting leak Sensitivity and specificity to correctly detect leak is 53 and 99% respectively	Higher equipment cost Disposable N95/FFP2 masks are punched and not reusable after test. EHMRs require specific test adaptors
Infection control	Recommended hospital donning/doffing procedure	Test hood requires disinfection that best follows local infection control guidelines. Of note many disinfectants produce bitter taste and require appropriate drying time Adhering to national and local guidelines during pandemic regarding quarantine and social distancing is advised	Minimal infection risk as adaptors and tubing are of disposable nature Adhering to national and local guidelines during pandemic regarding quarantine and social distancing is advised

HCW, healthcare worker; EHMR, elastomer half mask respirator.

SARS-COV-2 AND DENTISTRY-REVIEW

Melo Neto CLM, Bannwart LC, de Melo Moreno AL, Goiato MC.. Eur J Dent. 2020 Sep 15. doi: 10.1055/s-0040-1716438.
Online ahead of print.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

Authors from São Paulo State University (UNESP), School of Dentistry in Brazil reviewed current literature on emergence, transmission, and disease caused by SARS-CoV-2. Since close proximity to the oral cavity may pose a higher risk for dentists and associated employees during the COVID-19 pandemic, they make recommendations for reducing transmission in the setting of dental clinics.

SUMMARY

Precautions and guidelines the authors recommended include:

- Implementing dental triage to screen patients for recent travel, symptoms, and urgency of dental care needed.
- Adjusting waiting rooms by removing common items such as reading material, toys, beverages, as well as adding hand sanitizer and physical barriers to separate people.
- Ensuring adequate ventilation in waiting rooms and using high-volume evacuation (HVE) filters and high-efficiency particulate air (HEPA) filters when applicable with daily cleaning.
- Making sure employees have proper personal protective equipment (PPE), including N95 masks (if available), coats, caps, gloves, shoe covers, protective glasses, and/or face protectors.
- Encouraging adequate antimicrobial oral rinsing preoperatively to reduce the number of microbes in the oral cavity.
- Exercising caution when executing procedures that create bioaerosols.
- After procedures, cautiously sanitizing and/or discarding materials and instruments used immediately.
- Deferring all elective and non-emergent procedures until a later date.

ABSTRACT

SARS-CoV-2 (or 2019-nCoV) is the novel Coronavirus that affects humans. It originated in China at the end of 2019 due to the consumption of animals contaminated with this pathogen. SARS-CoV-2 causes the disease known as COVID-19 (coronavirus disease - 2019), and until May 21, 2020, approximately 213 countries and territories had been affected by SARS-CoV-2. The objective of this study was to review the origin and characteristics of this virus (SARS-CoV-2), symptoms and diagnosis of COVID-19, treatment of people with COVID-19, forms of transmission of the SARS-CoV-2, and precautions in dentistry. A literature search on PubMed/Medline was performed on the May 21, 2020, using the keywords (Mesh terms) "COVID-19" or "SARS-CoV-2" or "Coronavirus" associated with "dentistry" or "dental care" or "oral medicine." SARS-CoV-2 articles about the origin and characteristics of this virus (SARS-CoV-2), symptoms and diagnosis of COVID-19, treatment of people with COVID-19, forms of transmission of the SARS-CoV-2, and precautions in dentistry were included. The search was expanded according to necessity. Articles related to precautions in dentistry and SARS-CoV-1 or MERS-CoV were also selected, since precautions used in the dental clinic to avoid these viruses also apply to SARS-CoV-2. In addition, the references cited in the publications of articles included were also considered when appropriate. There was no limit in relation to the year of publication, and only articles written in English were included. In this study, suggestions for the safety of dental professionals were also included. Forty-seven articles and nine websites were included in this review.

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