

The Daily COVID-19 Literature Surveillance Summary

November 12, 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

Epidemiology

- A retrospective cohort study by physicians in Wuhan, China found [no significant difference in levels of testosterone, follicle-stimulating hormone, or luteinizing hormone](#) between 39 male patients with SARS-CoV-2 and 22 control patients without SARS-CoV-2 ($p<0.05$) nor between cases with severe versus moderate disease severity; however, 20 patients with >50 days of viral shedding had elevated estradiol levels compared to those with shorter shedding duration ($p<0.05$), suggesting that SARS-CoV-2 is unlikely to cause sterility or hypogonadism.

Transmission & Prevention

- An international group of vaccine development experts from the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Working Group conducted a review of available literature regarding vaccine-associated enhanced disease (VAED) and determined that the [risk of COVID-19 VAED is similar to the risk associated with any other viral vaccine](#) and acknowledge that the human experience of COVID-19 may differ from animal or in-vitro studies, recommending rigorous surveillance and phase 3 trials to evaluate safety and efficacy of any COVID-19 vaccine.

Management

- A retrospective cohort study by pediatricians in Florence, Italy of central precocious puberty (CPP) in girls presenting to their clinic during and after the Italian COVID-19 lockdown (March-July 2020) compared to the same period in 2015-2019 found [more new cases of CPP in 2020 compared to previous years](#) (37 vs. 16-19, $p<0.0005$) with accelerated progression in girls with previously diagnosed CPP ($p<0.0005$), more advanced Tanner stage in newly diagnosed CPP ($p<0.005$), and higher levels of luteinizing hormone (LH) and estradiol (E2) ($p<0.005$). These changes are attributed to the psychological stresses, increased BMI, and increased electronic device use during lockdown and suggest environmental factors strongly influence pubertal development.

Adjusting Practice During COVID-19

- A letter to the editor by The Netherlands Comprehensive Cancer Organization discusses derailed oncological care due to COVID-19 and subsequent reprioritization of health care services and determined that healthcare changes resulting from COVID-19 contributed to [fewer breast and colorectal cancer diagnoses](#) among age groups eligible for cancer screening, with slow return to expected rates following gradual restarts of cancer screenings. More information is needed to determine the long term clinical outcomes of decreased cancer screening and diagnoses, particularly whether these findings may represent decreased "overdiagnosis of particular early-stage cancers," but believe the trend warrants further investigation.

R&D: Diagnosis & Treatments

- Spanish immunologists investigated immunogenicity of cysteine-like protease (Mpro, a non-structural SARS-CoV-2 protein) by comparing samples from 36 COVID-19 patients diagnosed via RT-PCR versus 33 negative controls and, using ELISA (Mpro sensitivity 97% and specificity 100%), found [high titers of IgG, IgM, and IgA against Mpro in serum and detected Mpro antibodies in all saliva samples](#) collected from patients with the highest serum antibody titers ($n=12$), suggesting that detection of Mpro antibodies could be used to distinguish infected from non-infected individuals and that saliva tests could be used as a reliable, non-invasive test for seropositivity.
- An in vitro study by researchers in Ecuador proposed development of [amino-ester magnetic nanoparticles \(Poly-NH₂-MNP\) as a cost-efficient and rapid method for COVID-19 diagnostics](#), in an effort to improve and expand testing across Latin America, and predict that utilizing magnetic nanoparticles (MNPs) will allow for production of ~50,000 COVID-19 tests in two days. Their efficacy was confirmed via RT-PCR analysis detecting presence of SARS-CoV-2 and correct RNA extraction by Poly-NH₂-MNP in 38 minutes.

Mental Health & Resilience Needs

- Public health experts at the University of Nevada, Las Vegas conducted a cross-sectional survey of 194 undergraduate and graduate students assessing demographic factors, exercise minutes, and PHQ-9 scores before and after the issuance of a stay-at-home order (May 7-28, 2020) and found [mean PHQ-9 score increased from 5.58 pre-order to 9.61 after \(\$p<0.01\$ \) and mean physical activity minutes decreased](#) from 409 to 330 minutes ($p=0.01$), suggesting that because the stay-at-home order correlated with increased levels of depression and decreased levels of physical activity among college students, colleges should consider targeted interventions teaching coping skills and resiliency for students.

Resources

- A study by anesthesiologists at University Medical Centre Maribor, Slovenia and Bern University Hospital, Switzerland [compared quality of 155 COVID-19 related publications versus 130 non-COVID-19 publications](#) in the New England Journal of Medicine, Journal of the American Medical Association, and The Lancet from and found non-COVID-19 publications were more likely to have higher levels of evidence (95% CI for OR, 7.0-47; p<0.001) and had favorable quantitative quality scores (mean difference, 11.1; 95% CI, 8.5-13.7; p<0.001) compared to COVID-19 publications, indicating that initial COVID-19 research published in these major scientific journals was not up to their typical standards, but further analysis on progression of COVID-19 research is warranted.
- Swedish emergency physicians and a data scientist [assessed trends in published scientific literature on COVID-19](#) by analyzing 16,670 articles published between February 14 and June 1, 2020 with a PubMed title or abstract including the phrase "covid" or "covid-19" and, using Latent Dirichlet Allocation, identified 14 main topics and assessed their frequency as the pandemic progressed, finding that the proportion of papers on epidemiology, modeling, healthcare response, and radiology decreased throughout their study period while those on clinical manifestations and protective measures increased.

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EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

ADULTS

EFFECTS OF SARS-COV-2 INFECTION ON MALE SEX-RELATED HORMONES IN RECOVERING PATIENTS

Xu H, Wang Z, Feng C, Yu W, Chen Y, Zeng X, Liu C.. Andrology. 2020 Nov 5. doi: 10.1111/andr.12942. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

In this retrospective cohort study, physicians at Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology in Wuhan, China found no significant difference in levels of testosterone, follicle-stimulating hormone, or luteinizing hormone between male patients with SARS-CoV-2 ($n=39$) and control patients without SARS-CoV-2 ($n=22$) ($p<0.05$) nor between cases with severe versus moderate disease severity (Tables 1,3). However, patients with >50 days of viral shedding ($n=20$) had elevated estradiol levels compared to those with shorter shedding duration ($p<0.05$) (Table 2). Based on this, these authors believe SARS-CoV-2 is unlikely to cause sterility or hypogonadism, but do urge further study of the virus' potential effects on male fertility.

ABSTRACT

BACKGROUND: A novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causing the pandemic of coronavirus disease 2019 (COVID-19), may attack testes by angiotensin-converting enzyme 2. **OBJECTIVE:** To assess whether SARS-CoV-2 infection can affect sex-related hormones and testicular function in recovering patients. **MATERIALS AND METHODS:** The patients were separately classified according to the duration of viral shedding (long-term positive vs normal-term group, with the former cases having a duration >50 days) and disease severity (moderate vs severe group). Differences in sex-related hormone levels were compared between groups and linear regression analysis was used to compare the associations of testosterone (T) and estradiol with various clinical and laboratory factors. **RESULTS:** A total of 39 COVID-19 patients were included in this study. The mean T level was in the normal reference range while the mean estradiol level was above the normal limit. There were no significant differences between the long-term positive and normal-term groups in T ($p=0.964$), follicle-stimulating hormone (FSH; $p=0.694$), luteinizing hormone (LH; $p=0.171$), prolactin (PRL; $p=0.836$) or T/LH ($p=0.512$). However, estradiol was higher in the normal-term group than the long-term positive group ($p<0.001$). Moreover, there were also no significant differences between the moderate and severe groups in sex-related hormones, duration of viral shedding, or serum biochemical or inflammation indicators. Additionally, regression analyses showed that there were no associations between the T level and the clinical and laboratory factors, while estradiol was negatively associated with the duration of viral shedding. **CONCLUSION:** In males infected with SARS-CoV-2, most sex-related hormones (T, FSH and LH levels) remain within the normal reference ranges after recovery from COVID-19, and no significant associations were observed between T level and disease duration or severity. At present, there is insufficient evidence to show that SARS-CoV-2 causes hypogonadism and sterility, but the potential risk should not be ignored.

FIGURES

Table 1. Clinical characteristics of 39 male patients with COVID-19

	Patients with COVID-19 (N=39)	Patients without COVID-19 (N=22)	Normal range ^a
Age (yrs)	60.0 (46.5, 65.5)	62 (52, 68.75)	N/A
Body mass index (BMI)	25.1 (2.8)	26.9 (3.6)	N/A
Severity			
Mild type	0	N/A	N/A
Moderate type	20 (51.3%)	N/A	N/A
Severe type	17 (43.6%)	N/A	N/A
Critical type	2 (5.1%)	N/A	N/A
Duration of viral shedding (days)			
Normal term group (≤ 50 days)	19 (48.7%)	N/A	N/A
Long-term positive group (> 50 days)	20 (51.3%)	N/A	N/A
Symptoms			
Fever	34 (87.2%)	N/A	N/A
Cough	22 (56.4%)	N/A	N/A
Chest distress	9 (23.1%)	N/A	N/A
Headache	4 (10.3%)	N/A	N/A
Myalgia	7 (17.9%)	N/A	N/A
Diarrhea	8 (20.5%)	N/A	N/A
Comorbidity			
Hypertension	16 (41.0%)	N/A	N/A
Diabetes	6 (15.4%)	N/A	N/A
Others	14 (35.9%)	N/A	N/A
Serum biochemical indicator			
Alanine transaminase (ALT, U/L)	26.2 (12.6)	21.3 (14.5)	≤ 41
Aspartate transaminase (AST, U/L)	21.5 (8.0)	19.7 (8.4)	≤ 40
Total cholesterol (TC, mmol/L)	4.229 (0.938)	3.843 (0.751)	< 5.18
Creatinine (Cre, mmol/L)	86.1 (52.4)	81.6 (25.5)	59~104
Inflammation indicator			
White blood cell count (WBC, $\times 10^9$ /L)	6.367 (2.323)	6.034 (1.754)	3.50~9.50
Lymphocytes Count ($\times 10^9$ /L)	1.782 (0.652)	1.861 (0.591)	1.10~3.20
C-reactive protein (CRP, mg/L)	9.55 (15.56)*	1.31 (1.63)	$\leq 10.0^b$
Interleukin 2 receptor (IL2R, U/mL)	434.6 (204.2)	-	223~710
Interleukin 6 (IL6, pg/mL)	5.14 (4.75)	-	< 7.0
Tumor necrosis factor alpha (TNF α , pg/mL)	10.95 (8.88)	-	< 8.1
Sex-related hormone			
Testosterone (T, ng/mL)	3.932 (1.081)	3.838 (0.966)	1.75~7.81
Free testosterone (FT, nmol/L) ^c	0.374 (0.148)	0.274 (0.125)	0.11~0.66
Bioavailable testosterone (BioT, nmol/L) ^c	8.062 (3.007)	6.335 (2.993)	0.28~15.50
Follicle-stimulating hormone (FSH, mIU/mL)	8.763 (4.952)*	14.407 (12.918)	1.27~19.26

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Luteinizing hormone (LH, mIU/mL)	5.519 (2.705)*	8.051 (6.048)	1.24~8.62
Prolactin (PRL, ng/mL)	14.594 (5.154)	13.196 (4.955)	2.64~13.13
Estradiol (E2, pg/mL)	50.9 (18.8)*	34.9 (18.5)	≤ 47

Data are presented as means (standard deviation) for distributed continuous data, median (interquartile range) for non-normally distributed continuous data, and n (%) for categorical variables.

* $p<0.05$, means significance compared with patients without COVID-19.

^b Only 14 out of 39 COVID-19 patients were tested for FT and BioT.

^c All the normal range were derived from our clinical laboratory system.

* CRP >10 suggested the possibility of inflammatory infection in our clinical laboratory system.

- not measured

Table 2. Clinical characteristics, laboratory characteristics and sex-related hormone profiles in COVID-19 long-term positive group and normal term group

	Long-term positive group (N=20)	Normal term group (N=19)	p value
Age (yrs)	61.5 (55.0, 66.0)	60.0 (46.5, 63.0)	0.533
Body mass index (BMI)	25.2 (2.7)	25.0 (3.0)	0.880
Duration of viral shedding (days)	79.0 (73.5, 82.3)	27.0 (18.0, 30.5)	<0.001*
Severity group, severe group	9 (45.0%)	10 (52.6%)	0.876
Serum biochemical indicator			
Alanine transaminase (ALT, U/L)	26.6 (14.5)	25.8 (10.7)	0.864
Aspartate transaminase (AST, U/L)	21.7 (9.0)	21.3 (7.0)	0.898
Total cholesterol (TC, mmol/L)	4.151 (0.801)	4.311 (0.79)	0.602
Creatinine (mmol/L)	85.0 (27.3.0)	87.3 (70.8)	0.893
Inflammation indicator			
White blood cell count (WBC, x 10 ⁹ /L)	5.731 (1.413)	7.037 (2.892)	0.087
Lymphocytes Count (x 10 ⁹ /L)	1.826 (0.572)	1.736 (0.741)	0.672
C-reactive protein (CRP, mg/L)	11.60 (17.83)	7.12 (12.47)	0.404
Interleukin 2 receptor (IL2R, U/mL)	396.9 (222.5)	526.7 (156.9)	0.057
Interleukin 6 (IL6, pg/mL)	5.08 (5.33)	5.20 (4.12)	0.941
Tumor necrosis factor alpha (TNF α , pg/mL)	10.38 (10.85)	11.67 (5.8)	0.672
Sex-related hormone			
Testosterone (T, ng/mL)	3.925 (1.152)	3.941 (1.035)	0.964
Follicle-stimulating hormone (FSH, mIU/mL)	8.453 (5.23)	9.089 (4.760)	0.694
Luteinizing hormone (LH, mIU/mL)	4.938 (2.028)	6.132 (3.213)	0.171
Prolactin (PRL, ng/mL)	14.425 (4.821)	14.772 (5.612)	0.836
Estradiol (pg/mL)	40.2 (17.4)	62.1 (33.0)	<0.001*
T/LH	0.894 (0.372)	0.810 (0.417)	0.512

Data are presented as means (standard deviation) for distributed continuous data, median (interquartile range) for non-normally distributed continuous data, and n (%) for categorical variables.

*statistically significant

Table 3. Clinical characteristics, laboratory characteristics and sex-related hormone profiles in COVID-19 moderate group and severe group

	Severe group (N=19)	Moderate group (N=20)	p value
Age (yrs)	62.0 (60.0, 66.0)	56.5 (46.0, 62.5)	0.220
Body mass index (BMI)	25.1 (3.3)	25.1 (2.3)	0.989
Duration of viral shedding (days)	43.0 (23.5, 74.5)	62.5 (29.5, 82.0)	0.309
Serum biochemical indicator			
Alanine transaminase (ALT, U/L)	24.2 (13.2)	28.2 (12.0)	0.331
Aspartate transaminase (AST, U/L)	20.0 (6.8)	22.9 (8.9)	0.263
Total cholesterol (TC, mmol/L)	4.167 (0.918)	4.288 (0.976)	0.694
Creatinine (mmol/L)	96.4 (74.0)	76.4 (10.7)	0.259
Inflammation indicator			
White blood cell count (WBC, x 10 ⁹ /L)	6.302 (2.391)	6.430 (2.317)	0.866
Lymphocytes Count (x 10 ⁹ /L)	1.603 (0.488)	1.953 (0.751)	0.092
C-reactive protein (CRP, mg/L)	11.42 (18.76)	8.16 (12.99)	0.549
Interleukin 2 receptor (IL2R, U/mL)	451.3 (157.5)	457.2 (239.3)	0.932
Interleukin 6 (IL6, pg/mL)	5.66 (4.18)	4.75 (5.20)	0.583
Tumor necrosis factor alpha (TNF α , pg/mL)	13.57 (12.48)	8.86 (3.457)	0.161
Sex-related hormone			
Testosterone (T, ng/mL)	3.630 (0.783)	4.220 (1.257)	0.089
Follicle-stimulating hormone (FSH, mIU/mL)	9.800 (5.568)	7.778 (4.194)	0.207
Luteinizing hormone (LH, mIU/mL)	6.103 (3.282)	4.965 (1.938)	0.200
Prolactin (PRL, ng/mL)	14.929 (5.653)	14.275 (4.758)	0.697
Estradiol (pg/mL)	46.6 (19.9)	54.9 (17.3)	0.174
T/LH	0.731	0.969	0.057

Data are presented as means (standard deviation) for distributed continuous data, median (interquartile range) for non-normally distributed continuous data.

INFECTIOUS ENDOCARDITIS OF THE PROSTHETIC MITRAL VALVE AFTER COVID-19 INFECTION

Alizadeh Asl A, Salehi P, Roudbari S, Peighambari MM.. Eur Heart J. 2020 Nov 7:eaha852. doi: 10.1093/eurheartj/eaha852. Online ahead of print.

Level of Evidence: Other - Case Report

BLUF

Cardiologists from Tehran, Iran present the case of a 24-year-old male with a history of mechanical mitral valve replacement experiencing fever, chills, and anorexia 3 weeks after being discharged from a COVID-19 hospitalization where he received azithromycin, hydroxychloroquine and corticosteroids. Further studies revealed several vegetations on the posterior prosthetic mitral valve leaflet (Figure 1) and blood cultures grew *Staphylococcus aureus*. The authors call for future studies to investigate the relationship between the COVID-19 systemic inflammatory response and the development of bacterial endocarditis.

FIGURES

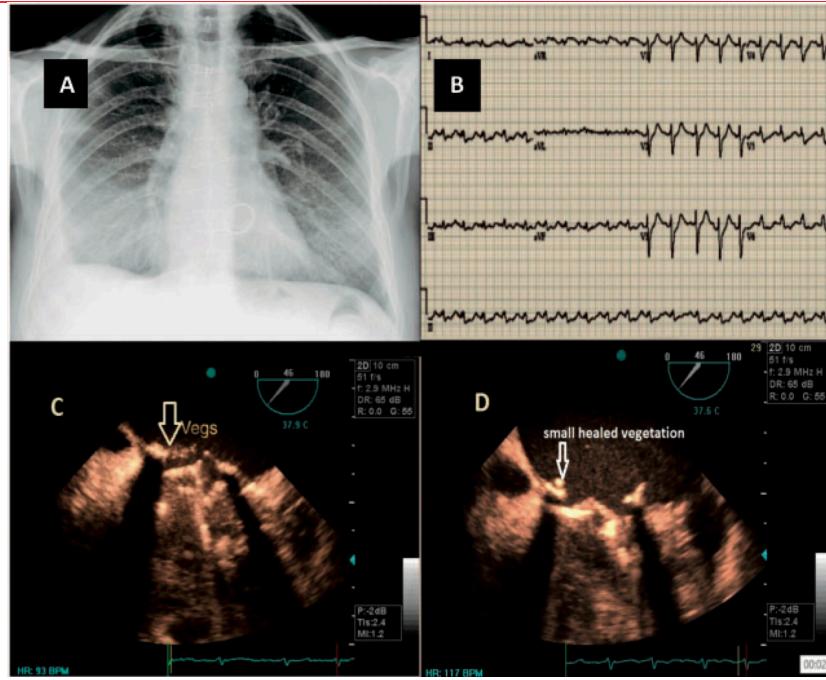


Figure 1.

A: "chest X-ray suggest[ing] viral pneumonia"

B: "electrocardiogram display[ing] sinus tachycardia"

C: transoesophageal echocardiogram revealing "several typical vegetations on the posterior prosthetic mitral valve leaflet"

D: "repeated trans-thoracic oesophageal echocardiogram (TEE) display[ing] healing of the vegetative lesions"

PROSPECTS FOR A SAFE COVID-19 VACCINE

Haynes BF, Corey L, Fernandes P, Gilbert PB, Hotez PJ, Rao S, Santos MR, Schuitemaker H, Watson M, Arvin A.. Sci Transl Med. 2020 Nov 4;12(568):eabe0948. doi: 10.1126/scitranslmed.abe0948. Epub 2020 Oct 19.

Level of Evidence: Other - Review / Literature Review

BLUF

An international group of vaccine development experts from the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Working Group conducted a review of available literature regarding vaccine-associated enhanced disease (VAED) and determined that the risk of COVID-19 VAED is similar to the risk associated with any other viral vaccine (Figure 1, Table 1). They acknowledge that the human experience of COVID-19 may differ from animal or in-vitro studies, recommending rigorous surveillance and phase 3 trials to evaluate safety and efficacy of any COVID-19 vaccine (Table 2).

ABSTRACT

Rapid development of an efficacious vaccine against the viral pathogen SARS-CoV-2, the cause of the coronavirus disease-2019 (COVID-19) pandemic, is essential, but rigorous studies are required to determine the safety of candidate vaccines. Here, on behalf of the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) Working Group, we evaluate research on the potential risk of immune enhancement of disease by vaccines and viral infections, including coronavirus infections, together with emerging data about COVID-19 disease. Vaccine-associated enhanced disease has been rarely encountered with existing vaccines or viral infections. Although animal models of SARS-CoV-2 infection may elucidate mechanisms of immune protection, we need observations of enhanced disease in people receiving candidate COVID-19 vaccines to understand the risk of immune enhancement of disease. Neither principles of immunity nor preclinical studies provide a basis for prioritizing among the COVID-19 vaccine candidates with respect to safety at this time. Rigorous clinical trial design and post-licensure surveillance should provide a reliable strategy to identify adverse events, including the potential for enhanced severity of COVID-19 disease, following vaccination.

FIGURES

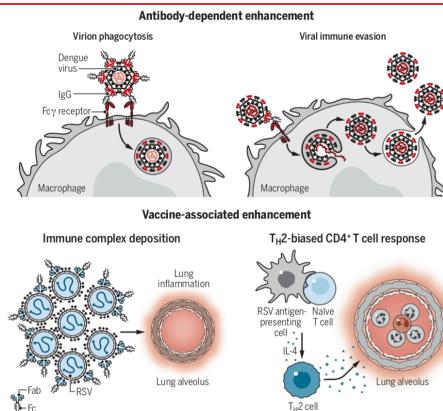


Fig. 1: Immune enhancement of human viral disease. Immune enhancement of human viral disease through viral reinfection or vaccination has been documented in (top) natural dengue virus infection and (bottom) vaccination with a formalin-inactivated vaccine for RSV. (Top) During natural dengue virus infection, IgG antibodies protect against dengue virus of one serotype by causing uptake of virus particles and their degradation when the Fab fragment of IgG binds to a surface viral protein and the

Fc portion of IgG binds to Fc α receptors expressed by macrophages and other immune cells. A second infection with a different dengue virus serotype creates a risk of ADE of disease because cross-reactive antibodies against the first serotype that have limited neutralizing capacity can mediate internalization of the virus by Fc α receptor-bearing cells. Viral immune evasion mechanisms then allow the production and release of new virions. (Bottom) Vaccine-associated enhancement of disease (VAED) occurred in some children given a formalin-inactivated RSV vaccine in the 1960s. Although the immunological mechanisms of VAED remain undefined, fatal RSV infection occurred in two children after vaccination and was associated with complement activation. This was attributed to the formation of immune complexes and their deposition in the lungs, and peribronchiolitis and alveolitis associated with pulmonary infiltration by neutrophils and eosinophils, which is consistent with a TH2-biased CD4+ T cell response. To date, none of these mechanisms are known to apply to SARS-CoV-2 infection.

Virus	Infection or vaccine	Animal model	Immune enhancement of disease after virus exposure	Virus neutralizing antibody (VNA) titers	Reference	Notes
SARS-CoV-2	Infection with live virus	Rhesus macaques	No	83–197 by the pseudovirus neutralization assay; 35–326 by the live virus neutralization assay	(31, 32)	After virus reinfection
	DNA vaccine	Rhesus macaques	No	Median titer, 74	(35)	
	Inactivated virus vaccine with alum	Rhesus macaques	No	145–400	(5, 34)	
	Adenovirus vector vaccine	Rhesus macaques	No	5–40	(33)	
SARS-CoV-1	Infection with live virus	Ferrets	No	720–800 U	(43)	After virus reinfection
	Infection with live virus	African green monkeys	Yes	10^3 – 10^4	(44)	After virus reinfection
	Modified virus vaccinia Ankara (MVA) vector vaccine	Ferrets	Yes	20–40 before challenge, up to 1280 after challenge	(46, 125)	No neutralizing antibody in rMVA expressing N protein
	MVA vector vaccine	Chinese rhesus macaques	Yes	10^3 – 10^4	(45)	Immunopathology associated with IL-8
	Recombinant vaccinia vaccine	Mice	Yes	Not reported	(47)	Immunopathology associated with IL-6
	Dendritic cell peptide immunization with or without a recombinant vaccinia virus booster	Mice	No	Not reported	(52, 54)	Protection associated with CD8 ⁺ T cell responses
	Venezuelan equine encephalitis replicon	Mice	Yes/no	PRNT ₈₀ 100–1600	(48, 82)	Conflicting results implicating viral nucleoprotein
MERS-CoV	Inactivated virus vaccine	Mice	Yes	Geometric mean neutralizing antibody log ₂ 7–10	(50, 53)	Immunopathology with unadjuvanted whole-virus vaccine, despite protection; reduced immunopathology with alum
				VNA detected after challenge only		
			Yes (spike protein)	Geometric mean neutralizing antibody log ₂ 5–10		
	Spike protein and spike protein receptor binding domain subunit vaccines	Mice	No (spike protein receptor binding domain)	Geometric mean neutralizing antibody log ₂ 4–6	(50, 51, 53)	Conflicting results with spike protein (both reduced and enhanced with alum)
				VNA detected after challenge only		
			DNA vaccine	Rhesus macaques		
	Spike protein (Ribi) and receptor binding domain subunit vaccines with alum	Rhesus macaques	No	About 10 ²	(55)	Spike protein formulated with Ribi; receptor binding domain formulated with alum
	Adenovirus vector vaccine	Rhesus macaques	No	Pseudovirus inhibition (PI) ₅₀ = 400–1200	(56, 57)	
Infection with live virus	New Zealand white rabbits	Yes	Neutralizing antibodies associated with protection from viral infection and associated pathology	(63)	Immunopathology after virus reinfection associated with non-neutralizing antibodies, complement activation, and CD8 ⁺ T cells, but no clinically discernable disease	
Inactivated virus vaccine	Mice	Yes	Geometric mean titer log ₂ 4–6	(64)	Eosinophilic pathology with both unadjuvanted vaccine or vaccine with alum or MF59	

Table 1: Immune enhancement of coronavirus disease in animal models.

Annual incidence in placebo arm [†]	HR (vaccine/placebo) of severe COVID-19				Results reported if an elevated rate of severe COVID-19 disease was just detected [‡]			
	1.25	1.5	2.0	3.0	Expected # of placebo cases	# of vaccine cases	Est. HR	95% CI
^a 0.0010	0.083	0.183	0.537	0.959	10	40	2.00	1.01–4.00
^b 0.0020	0.141	0.367	0.851	>0.999	20	66	1.65	1.01–2.72
^c 0.0040	0.233	0.629	0.991	>0.999	40	115	1.44	1.00–2.06
^d 0.0050	0.264	0.732	0.997	>0.999	50	139	1.39	1.01–1.92
^e 0.01	0.479	0.949	>0.999	>0.999	99	251	1.27	1.01–1.60

^{*}Power calculated on the basis of a one-sided 0.025-level log-rank test comparing the rate of severe COVID-19 disease in vaccine versus placebo groups; participants were followed for an average of 12 months with 2% annual dropout; all events after enrollment were counted; calculations assume a constant rate of the severe COVID-19 endpoint over time. [†]The five placebo arm incidence scenarios correspond to (a) 2% annual COVID-19 incidence and 5% severe cases, (b) 4% annual COVID-19 incidence and 5% severe cases, (c) 4% annual COVID-19 incidence and 10% severe cases, (d) 2% annual COVID-19 incidence and 25% severe cases, and (e) 4% annual COVID-19 incidence and 25% severe cases. [‡]Expected numbers of observed placebo group cases of severe COVID-19 disease (expected # of placebo cases) are calculated on the basis of the incidence assumed in the first column, with 2% annual dropout. Estimated HR is the smallest estimated HR of severe COVID-19 disease (vaccine/placebo) such that the Wald two-sided 95% CI in a Cox proportional hazards model just lies above 1.0, where # of vaccine cases and 95% CI correspond to this estimate.

Table 2: Power calculation to detect an elevated rate of severe COVID-19 disease in vaccine versus placebo recipients over 12 months, with 20,000 enrolled vaccine recipients and 10,000 enrolled placebo recipients*. Est., estimated; HR, hazard ratio; CI, confidence interval.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

EXPLORING THE OUT OF SIGHT ANTIGENS OF SARS-COV-2 TO DESIGN A CANDIDATE MULTI-EPITOPE VACCINE BY UTILIZING IMMUNOINFORMATICS APPROACHES

Safavi A, Kefayat A, Mahdevar E, Abiri A, Ghahremani F.. Vaccine. 2020 Nov 10;38(48):7612-7628. doi: 10.1016/j.vaccine.2020.10.016. Epub 2020 Oct 9.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An in silico study conducted in Iran proposes a novel multi-epitope vaccine against SARS-CoV-2 by incorporating non-structural proteins (i.e., nsp7, nsp8, nsp9, nsp10, nsp12 and nsp14) and S Protein of SARS-CoV-2 to induce T cell and B cell responses, respectively (Figure 2). Analyses showed that the proposed vaccine should be immunogenic, non-allergenic, and able to form stable interactions with TLR-4/MD (Table 4 and Figure 3). While the authors report that the designed vaccine showed high efficacy in the in silico analyses, future studies are necessary to further examine efficacy and safety in vitro and in vivo.

ABSTRACT

SARS-CoV-2 causes a severe respiratory disease called COVID-19. Currently, global health is facing its devastating outbreak. However, there is no vaccine available against this virus up to now. In this study, a novel multi-epitope vaccine against SARS-CoV-2 was designed to provoke both innate and adaptive immune responses. The immunodominant regions of six non-structural proteins (nsp7, nsp8, nsp9, nsp10, nsp12 and nsp14) of SARS-CoV-2 were selected by multiple immunoinformatic tools to provoke T cell immune response. Also, immunodominant fragment of the functional region of SARS-CoV-2 spike (400-510 residues) protein was selected for inducing neutralizing antibodies production. The selected regions' sequences were connected to each other by furin-sensitive linker (RVRR). Moreover, the functional region of beta-defensin as a well-known agonist for the TLR-4/MD complex was added at the N-terminus of the vaccine using (EAAAK)3 linker. Also, a CD4 + T-helper epitope, PADRE, was used at the C-terminal of the vaccine by GPGPG and A(EAAAK)2A linkers to form the final vaccine construct. The physicochemical properties, allergenicity, antigenicity, functionality and population coverage of the final vaccine construct were analyzed. The final vaccine construct was an immunogenic, non-allergen and unfunctional protein which contained multiple CD8 + and CD4 + overlapping epitopes, IFN-gamma inducing epitopes, linear and conformational B cell epitopes. It could form stable and significant interactions with TLR-4/MD according to molecular docking and dynamics simulations. Global population coverage of the vaccine for HLA-I and II were estimated 96.2% and 97.1%, respectively. At last, the final vaccine construct was reverse translated to design the DNA vaccine. Although the designed vaccine exhibited high efficacy in silico, further experimental validation is necessary.

FIGURES

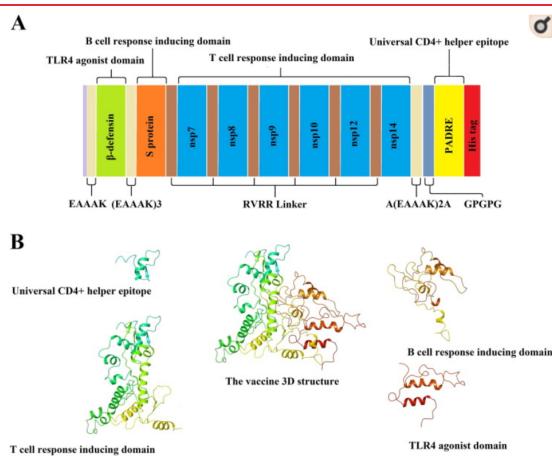


Figure 2. (A) Schematic diagram of the final vaccine construct. (B) 3D model of the final vaccine construct and its main consisting domains.

Properties	Parameters/Tools	Value/Score/Probability			
		C1	C2	C3	Candidate vaccine
Physicochemical	Molecular weight	2.44 kDa	5.05 kDa	6.38 kDa	51.64 kDa
	Isoelectric point (pI)	6.24	8.67	9.61	10
	Instability index (II)	28	22.78	33.38	27.09
	GRAVY	-0.88	-0.32	-1.127	-0.354
	Aliphatic index	65.94	-	53.53	79
	ANTIGENpro	0.67	0.94	0.62	0.74
	Secret-AAR	42.6	27.59	35.4	39.8
Antigenicity	VaxiJen	0.65	0.67	0.61	0.59

Table 4. Comparative investigation of the physicochemical and antigenicity properties of the positive vaccine controls (C1, C2, C3) and SARS-CoV-2 candidate vaccine.

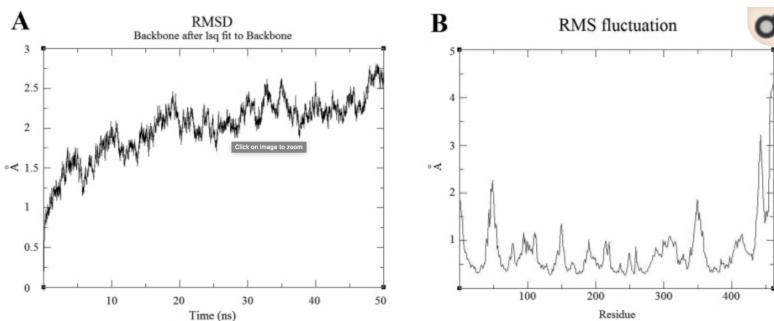


Figure. 3 (A) The root-mean-square deviation (RMSD) and (B) root-mean-square fluctuation (RMSF) of atomic positions in the "last" molecular dynamics simulation of the vaccine construct, depicting stable conformations during the simulation.

VACCINATION AGAINST SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

Plotkin SA.. J Pediatric Infect Dis Soc. 2020 Nov 10;9(5):517-518. doi: 10.1093/jpids/piaa093.

Level of Evidence: Other - Expert Opinion

BLUF

A pediatrician from the University of Pennsylvania with 60 years of experience as a vaccine consultant reviews the current SARS-CoV-2 vaccine developments. They outline current approaches including a killed virus, live attenuated virus, spike protein particles, spike protein vectors (Human or chimp Adenovirus, Measles, Vesicular Stomatitis Virus), DNA coding for spike RNA, and RNA Coding for spike (Table 1). The author anticipates many vaccines will reach the clinical trial stage, but the complex process will likely lead to unexpected findings and additional questions to investigate.

FIGURES

Table 1. Approaches to Vaccines Against Covid-19

Killed Virus
Live Virus genetically attenuated
Spike protein or parts of it
Vectors for spike protein
Adenovirus (human or chimp)
Measles
Vesicular Stomatitis Virus
DNA coding for spike RNA
RNA Coding for spike

MANAGEMENT

MEDICAL SUBSPECIALTIES

CARDIOLOGY

RETURN-TO-PLAY GUIDELINES FOR ATHLETES AFTER COVID-19 INFECTION-REPLY

Phelan D, Kim JH, Chung EH.. JAMA Cardiol. 2020 Nov 4. doi: 10.1001/jamacardio.2020.5351. Online ahead of print.
Level of Evidence: Other - Guidelines and Recommendations

BLUF

In this commentary, cardiologists elaborate on their prior return-to-play guidelines for athletes following COVID-19 infection (Figure 1, link to original paper in summary). In response to Santos-Ferreira and colleagues recommending emphasis on retesting and symptom burden, these authors advise pulmonary testing be deferred until the end of the quarantine period in the interest of public health. In response to Greene and colleagues, they agree more research is needed for establishing normal high sensitivity cardiac troponin (hs-cTn) ranges in athletes and interpreting serial hs-cTn values. However, the authors still endorse use of their guidelines despite the questions/commentary presented by Greene et al and Santos-Ferreira et al.

SUMMARY

Original Viewpoint Paper: <https://jamanetwork.com/journals/jamacardiology/fullarticle/2766124>

FIGURES

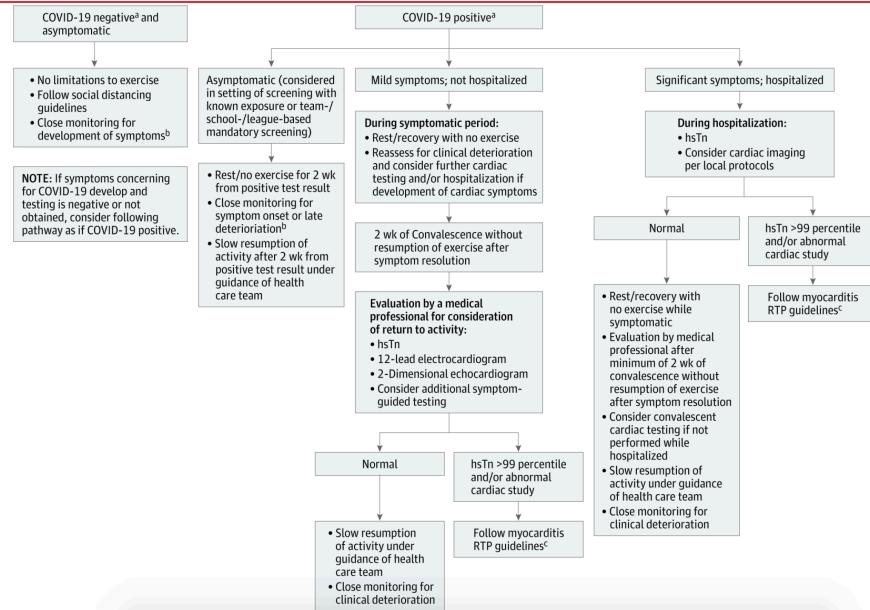


Figure 1: COVID-19 Return-to-Play Algorithm for Competitive Athletes and Highly Active People.

COVID-19 indicates coronavirus disease 2019; hsTn, high-sensitivity troponin I; RTP, return to play.

(a) Typical testing obtained via a nasopharyngeal swab. All athletes with positive testing should be isolated for 2 weeks regardless of symptoms.

(b) If clinical and/or cardiac symptoms develop, follow appropriate clinical pathway.

(c) Given lack of clear pathophysiology, we recommend American College of Cardiology/American Heart Association athlete myocarditis guidelines.

INCREASED INCIDENCE OF PRECOCIOUS AND ACCELERATED PUBERTY IN FEMALES DURING AND AFTER THE ITALIAN LOCKDOWN FOR THE CORONAVIRUS 2019 (COVID-19) PANDEMIC

Stagi S, De Masi S, Bencini E, Losi S, Paci S, Parpagnoli M, Ricci F, Ciofi D, Azzari C.. Ital J Pediatr. 2020 Nov 4;46(1):165. doi: 10.1186/s13052-020-00931-3.

Level of Evidence: 3 - Local non-random sample

BLUF

Pediatricians from Anna Meyer Children's University Hospital in Florence, Italy conducted a retrospective cohort study examining central precocious puberty (CPP) in girls presenting to their clinic during and after the Italian COVID-19 lockdown (March-July 2020) compared to the same period in 2015-2019. They found more new cases of CPP in 2020 compared to previous years (37 vs. 16-19, $p<0.0005$) with accelerated progression in girls with previously diagnosed CPP ($p<0.0005$), more advanced Tanner stage in newly diagnosed CPP ($p<0.005$), and higher levels of luteinizing hormone (LH) and estradiol (E2) ($p<0.005$)(Tables 1,2). Authors attribute these changes to the psychological stresses, increased BMI, and increased electronic device use during lockdown and suggest environmental factors strongly influence pubertal development.

ABSTRACT

BACKGROUND: The timing of puberty in girls is occurring at an increasingly early age. While a positive family history is recognised as a predisposing factor for early or precocious puberty, the role of environmental factors is not fully understood.

AIMS OF THE STUDY: To make a retrospective evaluation of the incidence of newly diagnosed central precocious puberty (CPP) and the rate of pubertal progression in previously diagnosed patients during and after the Italian lockdown for COVID-19, comparing data with corresponding data from the previous 5 years. To determine whether body mass index (BMI) and the use of electronic devices increased during lockdown in these patients.

PATIENTS AND METHODS: The study included 49 females with CPP. We divided the patients into two groups: group 1, patients presenting a newly diagnosed CPP and group 2, patients with previously diagnosed slow progression CPP whose pubertal progression accelerated during or after lockdown.

We collected auxological, clinical, endocrinological and radiological data which were compared with data from two corresponding control groups (patients followed by our Unit, March to July 2015-2019). Patients' families completed a questionnaire to assess differences in the use of electronic devices before and during lockdown.

RESULTS: Thirty-seven patients presented newly diagnosed CPP (group 1) and 12, with previously diagnosed but untreated slow progression CPP presented an acceleration in the rate of pubertal progression (group 2). The number of new CPP diagnoses was significantly higher than the mean for the same period of the previous 5 years ($p < 0.0005$). There were no significant differences between patients in group 1 and control group 1 regarding time between appearance of B2 and CPP diagnosis, although group 1 patients had a significantly earlier chronological age at B2, a more advanced Tanner stage at diagnosis ($p < 0.005$), higher basal LH and E2 levels, higher LH peak after LHRH test ($p < 0.05$) and increased uterine length ($p < 0.005$) and ovarian volume ($p < 0.0005$).

The number of patients with previously diagnosed CPP whose pubertal development accelerated was also statistically higher compared to controls ($p < 0.0005$). In this group, patients' basal LH ($p < 0.05$) and E2 levels ($p < 0.0005$) became more markedly elevated as did the LH peak after LHRH test ($p < 0.05$). These patients also showed a significantly accelerated progression rate as measured by the Tanner scale ($p < 0.0005$), uterine length ($p < 0.005$), and ovarian volume ($p < 0.0005$). In both group 1 and group 2, BMI increased significantly ($p < 0.05$) and patients' families reported an increased use of electronic devices ($p < 0.0005$).

CONCLUSION: Our data show an increased incidence of newly diagnosed CPP and a faster rate of pubertal progression in patients with a previous diagnosis, during and after lockdown compared to previous years. We hypothesize that triggering environmental factors, such as the BMI and the use of electronic devices, were enhanced during lockdown, stressing their possible role in triggering/influencing puberty and its progression. However, more studies are needed to determine which factors were involved and how they interacted.

FIGURES

Table 1 Clinical data and laboratory results in the patients of group 1 and controls

Variable	Group 1	Previous 5 years ^a	P
Population number	37	89	–
Chronological age at B2 (as referred by parents or family pediatrician)	6.86 ± 0.61	7.22 ± 0.48	p < 0.005
Chronological age at diagnosis (yr)	7.11 ± 0.72	7.53 ± 0.50	p < 0.0005
Time from B2 to diagnosis (months)	3.1 ± 0.9	3.0 ± 0.8	P = NS
Height, SDS	0.84 ± 1.32	0.79 ± 1.44	P = NS
BMI, SDS	0.83 ± 0.91	0.68 ± 0.88	P = NS
Tanner stage at diagnosis (percentage)			
II	43.8	55.5	
III	53.1	38.8	p < 0.05
IV	3.1	5.4	
V	–	–	
Bone age (yr)	9.40 ± 1.10	9.60 ± 1.20	p = NS
Bone age minus chronological age (yr)	2.29 ± 0.38	2.07 ± 0.70	P = NS
Basal LH, IU/L	1.2 ± 0.7	0.8 ± 0.6	p < 0.005
Basal FHS, IU/L	1.9 ± 1.7	2.2 ± 1.3	p = NS
Peak LH at GnRH stimulation, IU/L	11.9 ± 4.2	9.4 ± 4.0	p < 0.005
Basal estradiol (females only), pmol/L	129.9 ± 18.7	117.6 ± 19.2	p < 0.005
Uterine length, cm	4.42 ± 0.43	3.99 ± 0.47	p < 0.0005
Ovarian volume, cm ³	3.32 ± 0.42	2.83 ± 0.46	p < 0.0005
Electronic device use (h)	3.9 ± 1.5	–	–

^a= mean/yr. BA bone age, CA chronological age, SDS standard deviation score, BMI body mass index, LH luteinizing hormone, FSH follicle-stimulating hormone, GnRH gonadotropin releasing hormone test

Table 2 Clinical data and laboratory results of group 2 and controls (two evaluations after the same time of follow-up)

Variable	Group 2		Controls	
	before lockdown	after lockdown	visit 1	visit 2
Population number	12	12	11	11
Chronological age at diagnosis (yr)	7.47 ± 0.53	–	7.41 ± 0.61	–
Chronological age at follow-up (yr)	7.95 ± 0.49	8.26 ± 0.47	7.93 ± 0.51	8.31 ± 0.53
Time between the two visits (yr)	–	0.31 ± 0.02	–	0.38 ± 0.02
Height, SDS	0.87 ± 1.22	0.89 ± 1.25	0.86 ± 1.13	0.90 ± 1.16
BMI, SDS	0.61 ± 0.85	0.92 ± 0.87	0.60 ± 0.93	0.69 ± 0.94
Δ BMI, SDS	–	0.32 ± 0.02***	–	0.09 ± 0.01***
Tanner stage, percentage				
II	47.6	–***	63.6	54.5
III	52.4	71.4***	36.4	45.5
IV	–	28.6***	–	–
V	–	–	–	–
Basal LH (IU/L)	0.8 ± 0.6*	1.4 ± 0.6*	0.9 ± 0.7	1.1 ± 0.7
Basal FHS (IU/L)	1.9 ± 1.5	1.5 ± 1.3	1.6 ± 1.4	1.5 ± 1.2
Peak LH at GnRH stimulation (IU/L)	9.6 ± 3.4*	12.5 ± 3.1*	9.0 ± 3.1	11.7 ± 3.3
Basal estradiol (females only)	111.3 ± 15.2**	133.4 ± 18.3**	113.8 ± 13.9	119.1 ± 15.4
Uterine length, cm	4.10 ± 0.49*	4.59 ± 0.47*	4.00 ± 0.35	4.35 ± 0.37
Ovarian volume, cm ³	2.94 ± 0.52*	3.43 ± 0.48*	2.86 ± 0.46	3.18 ± 0.46
Electronic device use (h)	1.6 ± 0.9***	3.9 ± 1.5***	–	–

* = p < 0.05; ** P = 0.005; *** = p < 0.0005. BA bone age, CA chronological age, SDS standard deviation score, BMI body mass index, LH luteinizing hormone, FSH follicle-stimulating hormone, GnRH gonadotropin releasing hormone test

ADJUSTING PRACTICE DURING COVID-19

FOR HEALTHCARE PROFESSIONALS

THE COVID-19 PANDEMIC THROUGH EYES OF A NYC FERTILITY CENTER: A UNIQUE LEARNING EXPERIENCE WITH OFTEN UNEXPECTED RESULTS

Gleicher N.. Reprod Biol Endocrinol. 2020 Nov 4;18(1):105. doi: 10.1186/s12958-020-00663-3.

Level of Evidence: Other - Guidelines and Recommendations

BLUF

This correspondence from The Center for Human Reproduction in New York City details efforts by one fertility center to remain functional during the COVID-19 pandemic, attributing current low rates of infection to herd immunity rather than preventative public health policies alone, and suggesting that a new less infectious strain of SARS-CoV-2 is responsible for the "second wave" of infections primarily on the western coast of the US. The author details several procedural policies (see summary) the fertility center followed to minimize infection risk to remain operational amid the initial COVID-19 wave that struck New York City (Table 1).

SUMMARY

Mitigation policies are as follows:

1. Only patients were allowed inside the facility – no guests.
2. Staff who were able to work from home were advised to.
3. Two shifts were created for essential workers so that if one shift was infected, the other could take over.
4. Staff was instructed to avoid public transportation, and the facility helped cover the cost of private parking.
5. Plexiglass barriers were used in the reception area.
6. All consultations were done virtually.
7. All visitors were subjected to temperature checks.

ABSTRACT

Affecting basic tenets of human existence such as health, economic as well as personal security and, of course, reproduction, the COVID-19 pandemic transcended medical specialties and professional disciplines. Yet, six months into the pandemic, there still exists no consensus on how to combat the virus in absence of a vaccine. Facing unprecedented circumstances, and in absence of real evidence on how to proceed, our organization early in the pandemic decided to act independently from often seemingly irrational guidance and, instead, to carefully follow a quickly evolving COVID-19 literature. Here described is the, likely, unique journey of a fertility center that maintained services during peaks of COVID-19 and political unrest that followed. Closely following publicly available data, we recognized relatively early that New York City and other East Coast regions, which during the initial COVID-19 wave between March and May represented the hardest-hit areas in the country, during the second wave, beginning in June and still in progress, remained almost completely unaffected. In contrast, south western regions, almost completely unaffected by the initial wave, were severely affected in the second wave. These two distinctively different infectious phenotypes suggested two likely explanations: The country was witnessing infections with two different SARS-CoV-2 viruses and NYC (along with the East Coast) acquired during the first wave much better immunity to the virus than south western regions. Both hypotheses since have been confirmed: East and West Coasts, indeed, were initially infected by two distinctively different lineages of the virus, with the East Coast lineage being 10-times more infectious. In addition, immunologists discovered an up to this point unknown long-term anti-viral innate (cellular) immune response which offers additional and much broader anti-viral immunity than the classical adaptive immunity via immobilizing antibodies that has been known for decades. Consequently, we predict that in the U.S., even in absence of an available vaccine, COVID-19, by September-October, will be at similarly low levels as are currently seen in NYC and other East Coast regions (generally < 1% test-positivity). We, furthermore, predict that, if current mitigation measures are maintained and no newly aggressive mutation of the virus enters the country, a significant fall-wave of COVID-19, in combination with the usual fall wave of influenza, appears unlikely. To continue serving patients uninterrupted throughout the pandemic, turned for all of our center's staff into a highly rewarding experience, garnered respect and appreciation from patients, and turned into an absolutely unique learning experience.

FIGURES

Date in 2020	Event	Cases (n) in NY-state	Deaths (n) in NY-state
Sometimes in December	First COVID-19 cases in Wuhan, China		
1/17	1st U.S. cases on West Coast		
3/1	1st case in NYC	1	0
3/7	State of emergency in New York state	76	0
3/10	1st regional quarantine in New Rochelle	173	0
3/12	Prohibition of gatherings >500 people	325	0
	Broadway closes		
3/14	First deaths	613	2
3/16	Governor issues work from home order for non-essential workers; schools and movie theaters closed	950	7
3/17	1st ASRM GUIDANCE		
3/18	Non-essential retail stores closed	2382	16
3/20	All non-essential businesses closed NY state "on pause"	7102	46
4/1		83,712	1,957
4/6		139,689	4,774
4/12		188,694	9,401
6/1	Riots in NYC		
By July			
NY state		~390,000	~31,000
NYC		~ 214,500	~21,000

^aApproximately two-third of all cases occurred in NYC

Table 1. A brief timeline of COVID-19 in New York state

MEDICAL SUBSPECIALTIES

HEMATOLOGY AND ONCOLOGY

THE IMPACT OF THE TEMPORARY SUSPENSION OF NATIONAL CANCER SCREENING PROGRAMMES DUE TO THE COVID-19 EPIDEMIC ON THE DIAGNOSIS OF BREAST AND COLORECTAL CANCER IN THE NETHERLANDS

Dinmohamed AG, Cellamare M, Visser O, de Munck L, Elferink MAG, Westenend PJ, Wesseling J, Broeders MJM, Kuipers EJ, Merkx MAW, Nagtegaal ID, Siesling S.. J Hematol Oncol. 2020 Nov 4;13(1):147. doi: 10.1186/s13045-020-00984-1.
Level of Evidence: 3 - Local non-random sample

BLUF

A letter to the editor conducted by The Netherlands Comprehensive Cancer Organization in Utrecht, The Netherlands discusses derailed oncological care due to COVID-19 and subsequent reprioritization of health care services, while investigating and analyzing the impact of halting population screening for breast and colorectal cancer. They determined that healthcare changes resulting from COVID-19 contributed to fewer breast and colorectal cancer diagnoses among age groups eligible for cancer screening, with slow return to expected rates following gradual restarts of cancer screenings (Figure 1). They note that more information is needed to determine the long term clinical outcomes of decreased cancer screening and diagnoses, particularly whether these findings may represent decreased "overdiagnosis of particular early-stage cancers," but believe the trend warrants further investigation.

ABSTRACT

Oncological care was largely derailed due to the reprioritisation of health care services to handle the initial surge of COVID-19 patients adequately. Cancer screening programmes were no exception in this reprioritisation. They were temporarily halted in the Netherlands (1) to alleviate the pressure on health care services overwhelmed by the upsurge of COVID-19 patients, (2) to reallocate staff and personal protective equipment to support critical COVID-19 care, and (3) to mitigate the spread of COVID-19. Utilising data from the Netherlands Cancer Registry on provisional cancer diagnoses between 6 January 2020 and 4 October 2020, we assessed the impact of the temporary halt of national population screening programmes on the diagnosis of breast and colorectal cancer in the Netherlands. A dynamic harmonic regression model with ARIMA error components was applied to assess the observed versus expected number of cancer diagnoses per calendar week. Fewer diagnoses of breast and colorectal cancer were objectified amid the early stages of the initial COVID-19 outbreak in the Netherlands. This effect was most pronounced among the age groups eligible for cancer screening programmes, especially in breast cancer (age group 50–74 years). Encouragingly enough, the observed number of diagnoses ultimately reached and virtually remained at the level of the expected values. This finding, which emerged earlier in age groups not invited for cancer screening programmes, comes on account of the decreased demand for critical COVID-19 care since early April 2020, which, in turn, paved the way forward to resume screening programmes and a broad range of non-critical health care services, albeit with limited operating and workforce capacity. Collectively, transient changes in health-seeking behaviour, referral practices, and cancer screening programmes amid the early stages of the initial COVID-19 epidemic in the Netherlands conjointly acted as an accelerant for fewer breast and colorectal cancer diagnoses in age groups eligible for cancer screening programmes. Forthcoming research is warranted to assess whether the decreased diagnostic scrutiny of cancer during the COVID-19 pandemic resulted in stage migration and altered clinical management, as well as poorer outcomes.

FIGURES

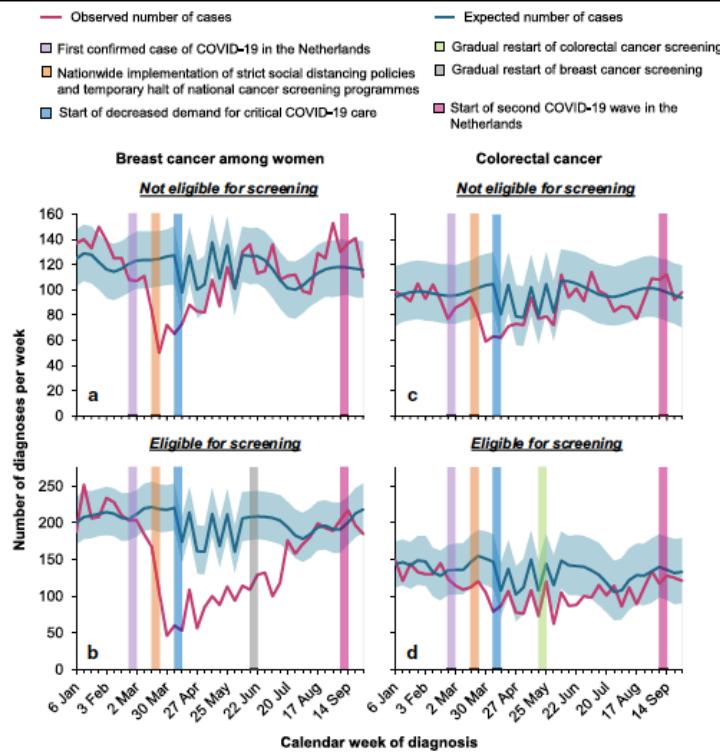


Fig. 1 The weekly number of breast and colorectal cancer diagnoses in the Netherlands between 6 January 2020 and 4 October 2020. The difference between the observed (pink line) and expected number of cancer diagnoses (blue line) is considered statistically significant when the observed number of cancer diagnoses does not fall within the range of the 95% confidence intervals of the expected number of cancer diagnoses (blue shaded area). a, b The observed and expected number of breast cancer diagnoses among women age < 50 or > 74 years (i.e. those not invited for biennial mammography screening) and women aged 50–74 years (i.e. those invited for biennial mammography screening), respectively. c, d The observed and expected number of colorectal cancer diagnoses among individuals age < 55 or > 75 years (i.e. those not invited for biennial faecal immunochemical testing) and individuals aged 55–75 years (i.e. those invited for biennial faecal immunochemical testing), respectively. The current statistics do not yet include cases diagnosed in one of the 74 hospitals in the Netherlands. Of note, the 'sawtooth effect' for both the expected and observed number of cancer diagnoses between early-mid-April 2020 and early June 2020 can be explained, in part, by four official national holidays spanning that period. On these holidays, a broad range of non-essential services, such as routine diagnostic practices, are closed.

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN DIAGNOSTICS

SARS-COV-2 CYSTEINE-LIKE PROTEASE ANTIBODIES CAN BE DETECTED IN SERUM AND SALIVA OF COVID-19-SEROPOSITIVE INDIVIDUALS

Martínez-Fleta P, Alfranca A, González-Álvaro I, Casasnovas JM, Fernández-Soto D, Esteso G, Cáceres-Martell Y, Gardeta S, López-Sanz C, Prat S, Mateu-Albero T, Gabrie L, López-Granados E, Sánchez-Madrid F, Reyburn HT, Rodríguez Frade JM, Valés-Gómez M.. J Immunol. 2020 Nov 4:ji2000842. doi: 10.4049/jimmunol.2000842. Online ahead of print.

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

BLUF

Spanish immunologists investigated immunogenicity of cysteine-like protease (Mpro; a non-structural SARS-CoV-2 protein) by comparing samples from COVID-19 patients diagnosed via RT-PCR (n=36) versus negative controls (n=33). Using ELISA (Mpro sensitivity 97% and specificity 100%), they found high titers of IgG, IgM, and IgA against Mpro in serum (Figures 1,2) and detected Mpro antibodies in all saliva samples collected from patients with the highest serum antibody titers (n=12; Figure 6). Authors suggest detection of Mpro antibodies can distinguish infected from non-infected individuals, and saliva tests could be used as a reliable, non-invasive test for seropositivity.

ABSTRACT

Currently, there is a need for reliable tests that allow identification of individuals that have been infected with SARS-CoV-2 even if the infection was asymptomatic. To date, the vast majority of the serological tests for SARS-CoV-2-specific Abs are based on serum detection of Abs to either the viral spike glycoprotein (the major target for neutralizing Abs) or the viral nucleocapsid protein that is known to be highly immunogenic in other coronaviruses. Conceivably, exposure of Ags released from infected cells could stimulate Ab responses that might correlate with tissue damage and, hence, they may have some value as a prognostic indicator. We addressed whether other nonstructural viral proteins, not incorporated into the infectious viral particle, specifically the viral cysteine-like protease, might also be potent immunogens. Using ELISA tests, coating several SARS-CoV-2 proteins produced in vitro, we describe that COVID-19 patients make high titer IgG, IgM, and IgA Ab responses to the Cys-like protease from SARS-CoV-2, also known as 3CLpro or Mpro, and it can be used to identify individuals with positive serology against the coronavirus. Higher Ab titers in these assays associated with more-severe disease, and no cross-reactive Abs against prior betacoronavirus were found. Remarkably, IgG Abs specific for Mpro and other SARS-CoV-2 Ags can also be detected in saliva. In conclusion, Mpro is a potent Ag in infected patients that can be used in serological tests, and its detection in saliva could be the basis for a rapid, noninvasive test for COVID-19 seropositivity.

FIGURES

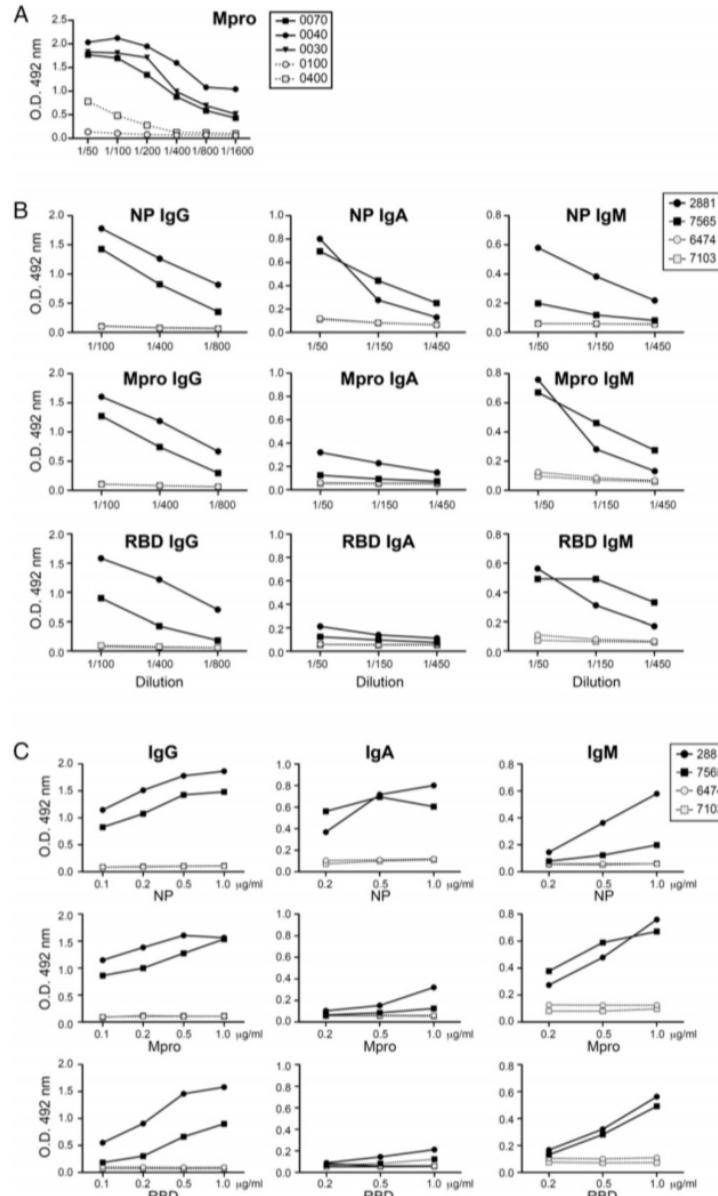


Figure 1: "Detection of SARS-CoV-2 Mpro-specific Abs by ELISA. (A) Sera titration on Mpro. Plates were coated with SARS-CoV-2 Mpro, and sera dilutions (1/50 to 1/1600) were tested. Detection was performed using anti-human F(ab)2' Ab. (B) Isotype recognition. Plates coated with SARS-CoV-2 Mpro, NP, and RBD were detected with Abs directed against human Ig of the three different subclasses: IgG, IgA, and IgM. Black symbols correspond to COVID-19 patients and gray symbols to donors pre-COVID-19. (C) Coating titration. Plates were coated with increasing amounts of SARS-CoV-2 Mpro, NP, and RBD, and sera diluted 1/100 for IgG detection and 1/50 for IgA and IgM were tested. Black symbols correspond to COVID-19 patients and gray symbols to donors pre-COVID-19. Experiments are representative of at least three replicates".

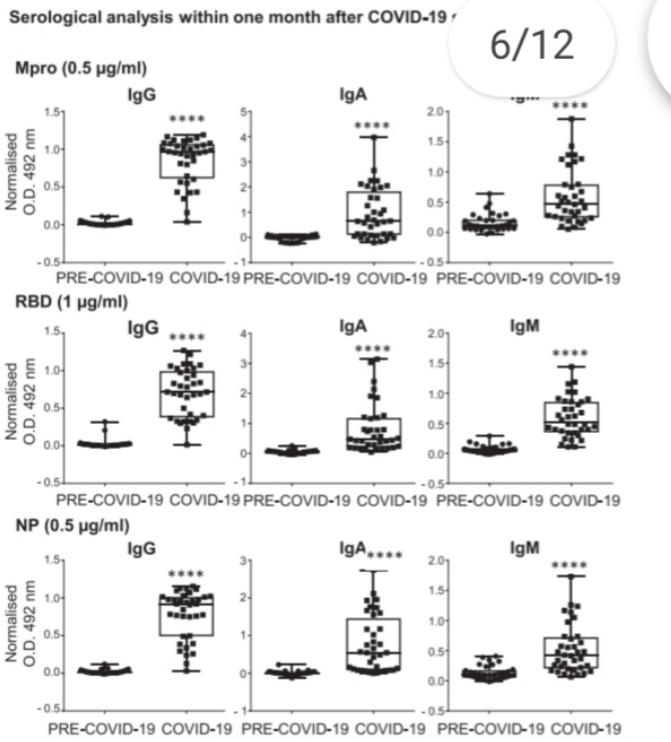


Figure 2: "Comparison of sera from 33 pre- COVID-19 versus 36 COVID-19 patients. Plates coated with either 0.5 or 1 mg/ml (as indicated) SARS-CoV-2 Mpro, NP, or RBD were used to perform ELISA tests on 36 COVID-19-positive and 33 -negative control sera (obtained before

the pandemic outbreak, pre-COVID-19). Detection was done using Abs directed against human Ig of the three different subclasses: IgG, IgA, and IgM. Sera dilutions from 1/50 to 1/3200 were carried out. Data were normalized for each Ag using the signal obtained against a pool of positive sera. Box and whisker plots of all the sera tested at the 1/200 dilution for IgG and 1/50 for IgA and IgM. Statistical significance was analyzed in Mann–Whitney tests. ***p , 0.0001".

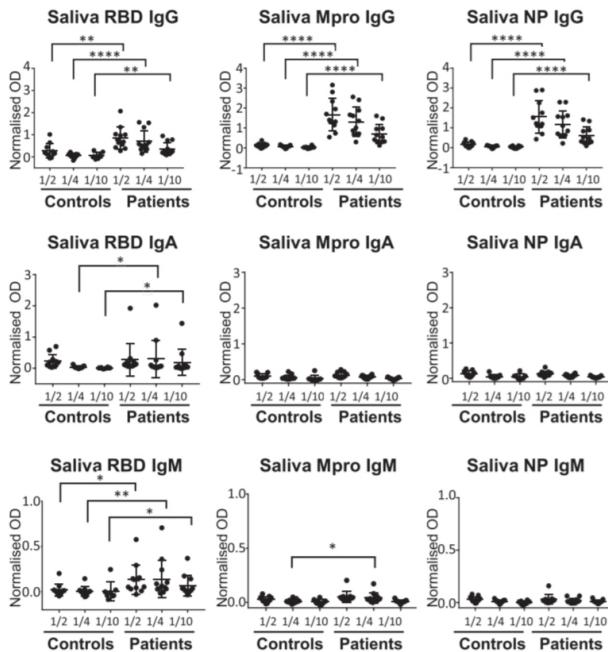


Figure 6: "Comparison of saliva from 11 healthy donors and 12 COVID-19 seropositive individuals. Plates coated with either 0.5 mg/ml SARS-CoV-2 Mpro and NP or 1 mg/ml RBD, and ELISA tests were carried out on saliva samples diluted 1/2 to 1/10. Detection was done using Abs directed against human IgG, IgM, or IgA. Data were normalized for each Ag using the signal obtained for the positive control histidine-tag. Mann–Whitney U test was performed to compare the values obtained for each dilution in healthy donors and patients. *p , 0.05, **p , 0.01, ****p , 0.0001".

OPTIMIZED AND SCALABLE SYNTHESIS OF MAGNETIC NANOPARTICLES FOR RNA EXTRACTION IN RESPONSE TO DEVELOPING COUNTRIES' NEEDS IN THE DETECTION AND CONTROL OF SARS-COV-2

Chacón-Torres JC, Reinoso C, Navas-León DG, Briceño S, González G.. Sci Rep. 2020 Nov 4;10(1):19004. doi: 10.1038/s41598-020-75798-9.

Level of Evidence: 5 - Mechanism-based reasoning

BLUF

An in vitro study by researchers associated with Yachay Tech University in Ecuador proposed development of amino-ester magnetic nanoparticles (Poly-NH₂-MNP; Figure 1) as a cost-efficient and rapid method for COVID-19 diagnostics, in an effort to improve and expand testing across Latin America. Authors predict that utilizing magnetic nanoparticles (MNPs) will allow for production of ~50,000 COVID-19 tests in two days, and their efficacy was confirmed via RT-PCR analysis detecting presence of SARS-CoV-2 and correct RNA extraction by Poly-NH₂-MNP in 38 minutes (Figure 5). The authors suggest utilizing MNPs could allow for crucial expansion of SARS-CoV-2 testing, especially in neglected areas.

ABSTRACT

Ecuador is one of the most affected countries, with the coronavirus disease 2019 (COVID-19) infection, in Latin America derived from an ongoing economic crisis. One of the most important methods for COVID-19 detection is the use of techniques such as real time RT-PCR based on a previous extraction/purification of RNA procedure from nasopharyngeal cells using functionalized magnetic nanoparticles (MNP). This technique allows the processing of ~ 10,000 tests per day in private companies and around hundreds per day at local Universities guaranteeing to reach a wide range of the population. However, the main drawback of this method is the need for specialized MNP with a strong negative charge for the viral RNA extraction to detect the existence of the SARS-CoV-2 virus. Here we present a simplified low cost method to produce 10 g of nanoparticles in 100 mL of solution that was scaled to one litter by parallelizing the process 10 times in just two days and allowing for the possibility of making ~ 50,000 COVID-19 tests. This communication helps in reducing the cost of acquiring MNP for diverse biomolecular applications supporting developing country budgets constraints and chemical availability specially during the COVID-19 International Health Emergency.

FIGURES

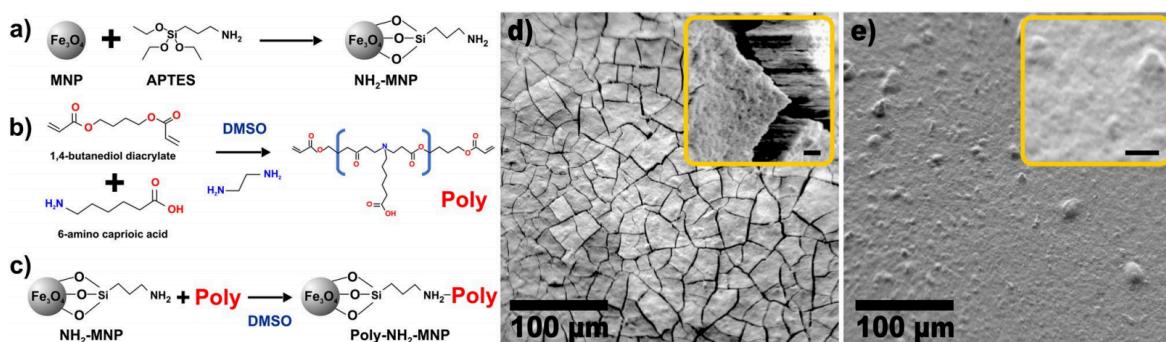


Figure 1. Schematic representation of the MNP synthesis and their resulting morphology. (a) Synthesis of amino-magnetic nanoparticles (NH₂-MNP). (b) Poly (amino-ester) is synthesized by the combination of 1,4-butanediol diacrylate + 6-aminocaproic acid at DMSO solution via diacrylate-amine polymerization. (c) The final amino-magnetic nanoparticles coated with the Poly (amino-ester) material are synthesized by following a Michael addition methodology⁸ as introduced by Zhao et al.⁵ and represented as Poly-NH₂-MNP in the following. (d) Magnetic nanoparticles dispersion dried on a SiO₂ wafer and placed in ultra high vacuum conditions (UHV, ~ 10⁻⁹ mbar). The observed morphology of this sample reveals a rough compact surface derived from the intrinsic magnetic interaction between the nanoparticles covered with APTES. (e) Final nanostructured magnetic nanoparticles dispersion dried on a SiO₂ wafer and placed in ultra high vacuum conditions (UHV, ~ 10⁻⁹ mbar). The observed morphology of this sample revealed a smooth continuous surface derived from the presence of the polymer on the MNP as active electronegative coating. Insets scale bar 10 μm.

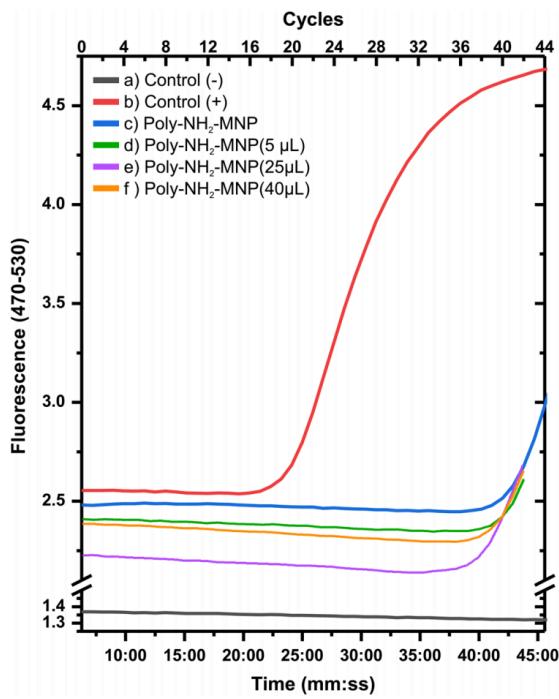


Figure 5. Real Time RT-PCR Amplification. After ~38 min (cycle 35 approx.) we observed an increase in the fluorescence when using Poly-NH₂-MNP magnetic nanoparticles, being. (a) Negative control, qRT-PCR mix was employed with just 8 µL of ultrapure. (b) Positive control, 8 µL of viral RNA from a commercial extraction kit were placed together with the qRT-PCR mixture. (c) Positive sample experiment implementing 10 µL of our Poly-NH₂-MNP magnetic nanoparticles instead of the ones from the qRT-PCR mixture coming in the commercial extraction kit. (d) The same extraction procedure was carried out as in (c) varying the amount of Poly-NH₂-MNP magnetic nanoparticles to 5 µL. Finally, the volume of magnetic nanoparticles (Poly-NH₂-MNP) employed in the qRT-PCR mixture was increased to 25 µL in (e) and 40 µL (f) accordingly. The observed amplification behavior remains relatively constant and independent of the Poly-NH₂-MNP magnetic nanoparticles concentration which highlights their performance.

MENTAL HEALTH & RESILIENCE NEEDS

IMPACT ON PUBLIC MENTAL HEALTH

CHANGES IN DEPRESSION AND PHYSICAL ACTIVITY AMONG COLLEGE STUDENTS ON A DIVERSE CAMPUS AFTER A COVID-19 STAY-AT-HOME ORDER

Coughenour C, Gakh M, Pharr JR, Bungum T, Jalene S.. J Community Health. 2020 Nov 9. doi: 10.1007/s10900-020-00918-5. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

Public health experts at the University of Nevada, Las Vegas conducted a cross-sectional survey of 194 undergraduate and graduate students (Table 1) assessing demographic factors, exercise minutes, and PHQ-9 scores before and after the issuance of a stay-at-home order (May 7-28, 2020). They found mean PHQ-9 score increased from 5.58 pre-order to 9.61 after ($p<0.01$) and mean physical activity minutes decreased from 409 to 330 minutes ($p=0.01$) (Tables 2, 3). Authors suggest because the stay-at-home order correlated with increased levels of depression and decreased levels of physical activity among college students, colleges should consider targeted interventions teaching coping skills and resiliency for students.

ABSTRACT

The numerous negative health impacts of COVID-19, which include expected changes to psychiatric illness and physical activity (PA), are disproportionately distributed in the United States. Mental illnesses and physical inactivity are prevalent among U.S. college students. This study examined whether there was a change in minutes of PA and depression scores after a stay-at-home order and examined predictors of these changes. An online survey was sent to all undergraduate and graduate students attending a large, diverse university via an electronic newsletter. The survey requested information about demographic and academic data, cardiorespiratory fitness, and depression symptoms. Paired t-tests and logistic regression were employed. Our sample ($n = 194$) was predominantly female (73%), young (mean age of 25), not a sexual minority (82%), and had a mean 3.4 GPA. Students reported worse depression scores ($p < 0.01$) and fewer minutes of PA ($p = 0.01$) after the stay-at-home order. There was a small but significant ($p = 0.04$) correlation between changes in total minutes of PA and depression scores. Senior ($p = 0.05$) and Hispanic ($p = 0.03$) students were less likely to report worsening depression scores than freshmen and white students, respectively. Asian students were significantly more likely than white students to report decreased PA. This study suggests that COVID-19 and its consequences may be contributing to reduced PA and greater depression symptoms in college students and that sub-groups have been affected differently. Targeted interventions to promote PA and support mental health may bolster the ability for resilience of college students.

FIGURES

Table 2 Univariate logistic regression results examining factors related to a change in patient health questionnaire (PHQ-9) score from a spring 2020 survey conducted at a diverse urban campus (n=194)

Continuous variables	B	S.E.	Wald	p-value	Exp(B)
Change in physical activity minutes	-0.001	0.00	1.978	0.160	0.999
Age	-0.02	0.02	0.78	0.38	0.98
GPA	0.47	0.32	2.08	0.15	1.60
eCRF	0.03	0.02	2.21	0.14	1.03
Categorical variables					
Class standing					
First-year	REF	REF	REF	REF	REF
Sophomore	-0.47	0.78	0.36	0.55	0.63
Junior	-0.96	0.69	1.91	0.17	0.39
Senior	-1.38	0.70	3.87	0.05	0.25
Graduate/other	-0.85	0.72	1.38	0.24	0.43
Race	-0.09	0.09	0.92	0.34	0.92
White	REF	REF	REF	REF	REF
Asian	-0.49	0.40	1.52	0.22	0.61
Black	-0.53	0.49	1.19	0.28	0.59
Hispanic	-0.94	0.43	4.68	0.03	0.39
Other	-0.24	0.57	0.19	0.67	0.78
SGM					
No	REF	REF	REF	REF	REF
Yes	0.44	0.41	1.17	0.28	1.56
Sex	0.10	0.33	0.10	0.75	1.11
Male	REF	REF	REF	REF	REF
Female	0.06	0.33	0.03	0.87	1.06
Transgender*					

REF reference group, GPA grade point average, Ecrf estimated cardiorespiratory fitness

*Cell size too small for analysis

Table 3 Univariate logistic regression results examining factors related to a change in physical activity minutes from a spring 2020 survey conducted at a diverse urban campus (n=194)

Continuous variables	B	S.E.	Wald	p-value	Exp (B)
Change in PHQ-9 score	0.036	0.024	2.174	0.140	1.036
Age	-0.02	0.02	0.49	0.48	0.99
GPA	0.51	0.36	2.04	0.15	1.67
Ecrf	0.03	0.02	2.55	0.11	1.03
Categorical variables					
Class standing					
Freshman	REF	REF	REF	REF	REF
Sophomore	-0.86	0.77	1.21	0.27	0.42
Junior	-1.130	0.71	2.52	0.11	0.32
Senior	-0.69	0.73	0.90	0.34	0.50
Graduate/other	-1.15	0.74	2.417	0.12	0.32
Race					
White	REF	REF	REF	REF	REF
Asian	0.84	0.40	4.35	0.04	2.32
Black	0.11	0.47	0.06	0.81	1.12
Hispanic	0.18	0.44	0.17	0.68	1.20
Other	0.57	0.54	1.10	0.29	1.76
SGM					
No	REF	REF	REF	REF	REF
Yes	-0.00	0.38	0.00	0.99	1.00
Sex					
Male	REF	REF	REF	REF	REF
Female	-0.282	0.34	0.70	0.40	0.75
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RESOURCES

SCIENTIFIC QUALITY OF COVID-19 AND SARS COV-2 PUBLICATIONS IN THE HIGHEST IMPACT MEDICAL JOURNALS DURING THE EARLY PHASE OF THE PANDEMIC: A CASE CONTROL STUDY

Zdravkovic M, Berger-Estilita J, Zdravkovic B, Berger D.. PLoS One. 2020 Nov 5;15(11):e0241826. doi: 10.1371/journal.pone.0241826. eCollection 2020.

Level of Evidence: 4 - Review / Literature Review

BLUF

A study conducted by anesthesiologists at University Medical Centre Maribor, Slovenia and Bern University Hospital, Switzerland compared quality of 155 COVID-19 related publications versus 130 non-COVID-19 publications in the New England Journal of Medicine, Journal of the American Medical Association, and The Lancet from March 12 to April 12, 2020 (Figure 1) and found non-COVID-19 publications were more likely to have higher levels of evidence (95% confidence interval [CI] for odds ratio, 7.0-47; p<0.001) and had favorable quantitative quality scores (mean difference, 11.1; 95% CI, 8.5-13.7; p<0.001) compared to COVID-19 publications (Table 2, Figure 2). Authors indicate that initial COVID-19 research published in these major scientific journals was not up to their typical standards, but further analysis on progression of COVID-19 research is warranted.

ABSTRACT

BACKGROUND: A debate about the scientific quality of COVID-19 themed research has emerged. We explored whether the quality of evidence of COVID-19 publications is lower when compared to nonCOVID-19 publications in the three highest ranked scientific medical journals. **METHODS:** We searched the PubMed Database from March 12 to April 12, 2020 and identified 559 publications in the New England Journal of Medicine, the Journal of the American Medical Association, and The Lancet which were divided into COVID-19 (cases, n = 204) and nonCOVID-19 (controls, n = 355) associated content. After exclusion of secondary, unauthored, response letters and non-matching article types, 155 COVID-19 publications (including 13 original articles) and 130 nonCOVID-19 publications (including 52 original articles) were included in the comparative analysis. The hierarchical level of evidence was determined for each publication included and compared between cases and controls as the main outcome. A quantitative scoring of quality was carried out for the subgroup of original articles. The numbers of authors and citation rates were also compared between groups. **RESULTS:** The 130 nonCOVID-19 publications were associated with higher levels of evidence on the level of evidence pyramid, with a strong association measure (Cramer's V: 0.452, P <0.001). The 155 COVID-19 publications were 186-fold more likely to be of lower evidence (95% confidence interval [CI] for odds ratio, 7.0-47; P <0.001). The quantitative quality score (maximum possible score, 28) was significantly different in favor of nonCOVID-19 (mean difference, 11.1; 95% CI, 8.5-13.7; P <0.001). There was a significant difference in the early citation rate of the original articles that favored the COVID-19 original articles (median [interquartile range], 45 [30-244] vs. 2 [1-4] citations; P <0.001). **CONCLUSIONS:** We conclude that the quality of COVID-19 publications in the three highest ranked scientific medical journals is below the quality average of these journals. These findings need to be verified at a later stage of the pandemic.

FIGURES

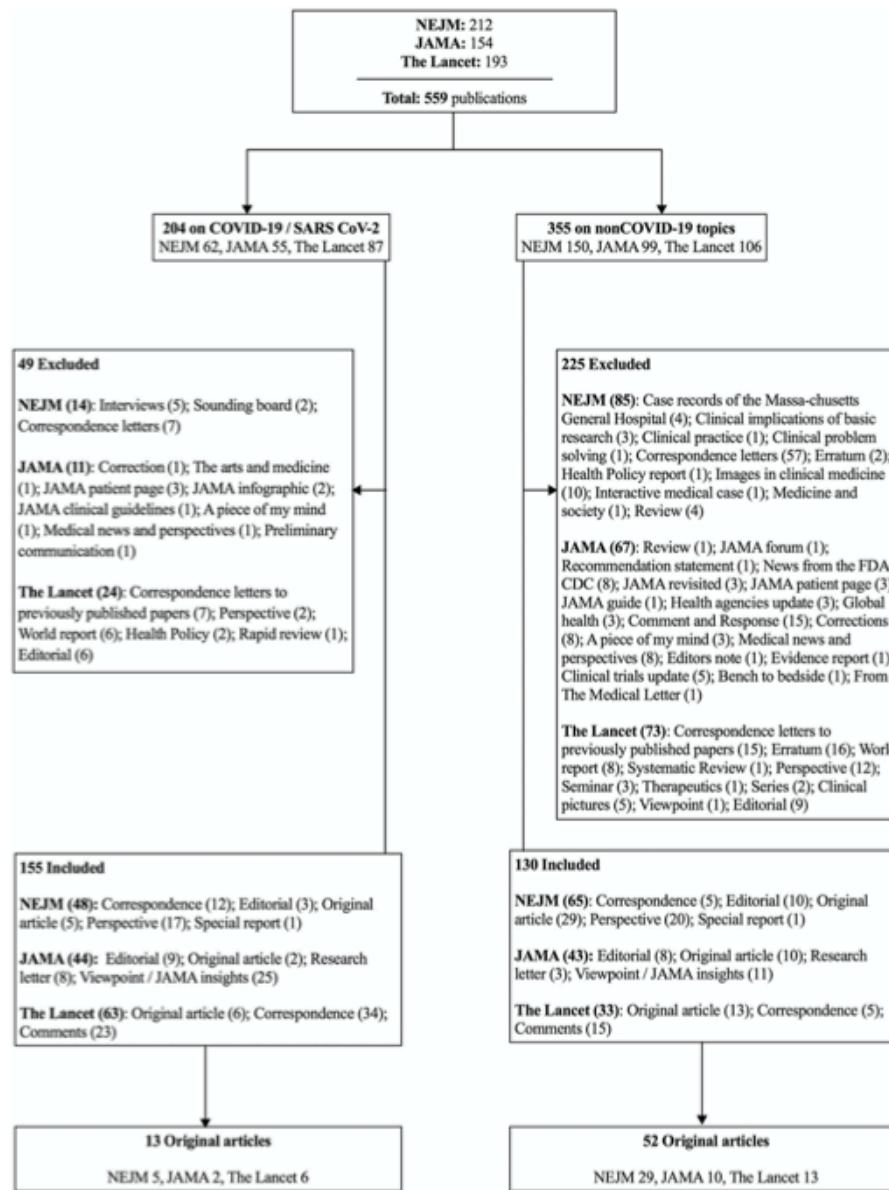


Fig 1. Flow chart of the processing of the publications included in this study. The article types in the NEJM are grouped (by the publisher) into *Original Research* (Research Articles and Special Articles for research on economics, ethics, law and health care systems), *Clinical Cases* (Brief Reports and Clinical Problem Solving), *Review Articles* (Clinical Practice Review or Other Reviews), *Commentaries* (Editorials, Perspectives, Clinical Implications of Basic Research, Letters to the Editor, Images and Videos in Clinical Medicine), and *other articles* (Special Reports, Policy Reports, Sounding Board, Medicine and Society and Case Records of the Massachusetts General Hospital). The JAMA articles are grouped by the publisher into *Research* (Original Investigation, Clinical Trials, Caring for the Critically Ill Patient, Meta-Analysis, Brief Reports and Research letters), *Clinical Review and Education* (Systematic Reviews, Advances in Diagnosis and Treatment, Narrative Reviews, Special Communications, Clinical Challenges,

Table 2. Frequency distribution of the original articles on the levels of evidence pyramid [23, 24].

Study design	Level	Group	COVID-19 (n = 13) [n (%)]	nonCOVID-19 (n = 52) [n (%)]
Randomized controlled trial	Higher level of evidence		1 (7.7)	38 (73.1)
Well-designed controlled trial without randomization; prospective comparative cohort trial			0 (0)	1 (1.9)
Case-control study; retrospective cohort study			2 (15.4)	7 (13.5)
Case series without or with intervention; cross-sectional study	Lower level of evidence		9 (69.2)	6 (11.5)
Opinion papers; case reports			1 (7.7)	0 (0)
Animal or <i>in-vitro</i> research	6		0 (0)	0 (0)

<https://doi.org/10.1371/journal.pone.0241826.t002>

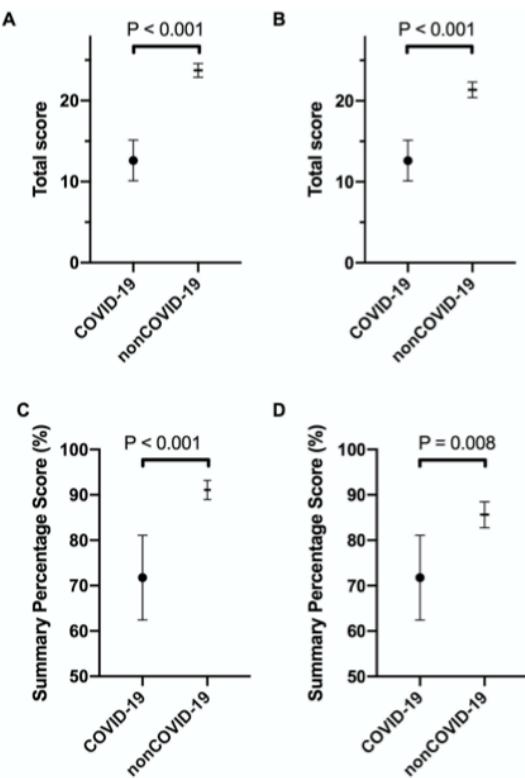


Fig 2. Quantitative appraisal of the quality of the COVID-19 versus nonCOVID-19 original articles. The "Standard quality assessment criteria for evaluating primary research papers from a variety of fields"25 was used, for a maximum total score of 28. (A, C) Primary analysis for mean total scores (A) and mean summary percentage scores (C) for all COVID-19 ($n = 13$) and nonCOVID-19 ($n = 52$) original articles. (B, D) Secondary analysis for mean total scores (B) and mean summary percentage scores (D) that included all of the COVID-19 original articles ($n = 13$) and the lower quality half of the nonCOVID-19 original articles ($n = 26$). Data are means with 95% CI. An adjusted threshold P value of 0.025 defines significance (adjusted for multiple testing, Welch's t-tests).

ANALYSIS OF SCIENTIFIC PUBLICATIONS DURING THE EARLY PHASE OF THE COVID-19 PANDEMIC: TOPIC MODELING STUDY

Algå A, Eriksson O, Nordberg M.. J Med Internet Res. 2020 Nov 10;22(11):e21559. doi: 10.2196/21559.

Level of Evidence: Other - Review / Literature Review

BLUF

Swedish emergency physicians and a data scientist assessed trends in published scientific literature on COVID-19 by analyzing 16,670 articles published between February 14 and June 1, 2020 with a PubMed title or abstract including the phrase "covid" or "covid-19." Using Latent Dirichlet Allocation, they identified 14 main topics (Table 1, Figure 3) and assessed their frequency as the pandemic progressed, finding the proportion of papers on epidemiology, modeling, healthcare response, and radiology decreased throughout their study period while those on clinical manifestations and protective measures increased (Figure 4). Authors suggest such analysis of research trends could help researchers and policy makers understand the current evidence base to better address gaps in knowledge.

ABSTRACT

BACKGROUND: The COVID-19 pandemic has spread with alarming speed and an effective treatment for the disease is still lacking. The body of evidence on COVID-19 increases at an impressive pace, calling for a method to rapidly assess the current knowledge and identify key information. Gold standard methods, such as systematic reviews and meta-analyses are unsuitable due to their narrow scope and high time-consumption. **OBJECTIVE:** To explore the published scientific literature on COVID-19 and map the research evolution during the early phase of the COVID-19 pandemic. **METHODS:** We analyzed the titles, keywords, and abstracts of articles on COVID-19 from PubMed. We used latent Dirichlet allocation modeling to extract topics and conducted trend analysis to explore the temporal changes of research for each topic, journal impact factor (JIF), and geographical origin. **RESULTS:** Our search identified 16 670 relevant articles dated between February 14, 2020, and June 1, 2020. Of these articles, six were reports from peer-reviewed randomized trials on COVID-19 patients. We identified 14 main research topics. The most common topics were healthcare response, and clinical manifestations with 2 812/16 670 (16.9%) and 1 828/16 670 (11.0%) publications, respectively. We found a growing trend of publications on clinical manifestations, and protective measures, and a decrease in research on disease transmission, epidemiology, healthcare response, and radiology. Publications on protective measures, immunology, and clinical manifestations were associated with the highest JIF. We calculated an overall median JIF of 3.7 (IQR 2.6-5.9) and found that the publications' JIF declined over time. The top countries of research origin were the USA, China, Italy, and the UK. **CONCLUSIONS:** In less than six months since the detection of the novel coronavirus, a remarkably high number of articles on COVID-19 have been published. We present the temporal changes of the available COVID-19 research during the early phase of the pandemic. Our findings may aid researchers and policy makers to form a structured view of the current COVID-19 evidence base and provide further research directions.

CLINICALTRIAL:

FIGURES

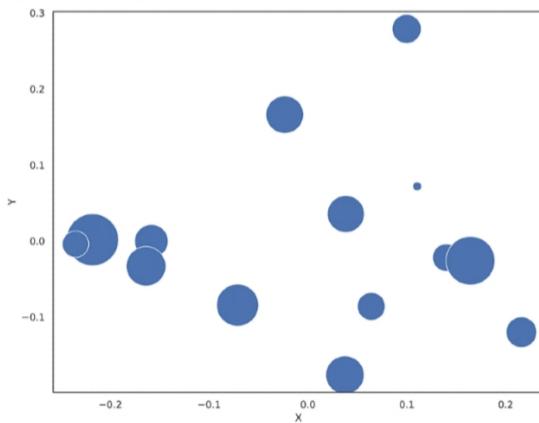


Figure 3: "Principal component analysis plot for the chosen latent Dirichlet allocation model with 14 topics. Overlaps are seen for three topic clusters; however, these topics were found to be separated by clinical relevance".

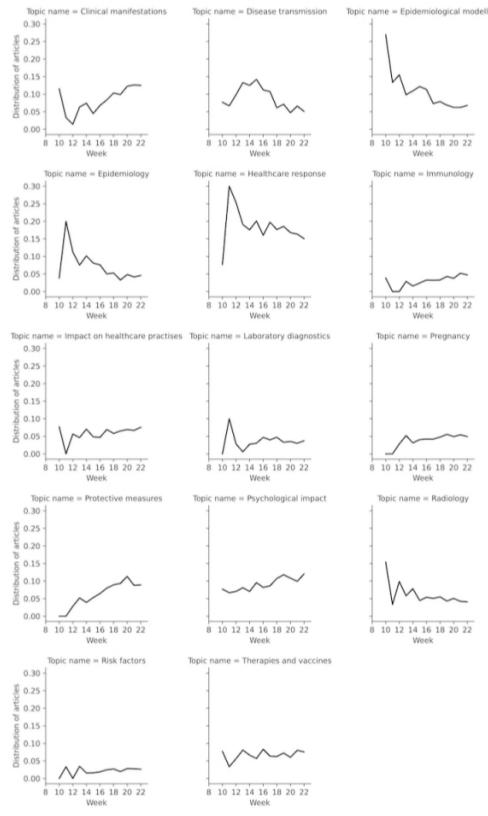


Figure 4: "Proportion of topics in relation to all COVID-19 articles published per week".

Topic No.	Label	Five most-frequent terms based on latent Dirichlet allocation	Five most-frequent PubMed keywords	Journal impact factor, median (IQR)	Articles published, n (%) (N=16,670)
1	Laboratory diagnostics	antibody, time, laboratory, diagnostic, assay	pcr, rt, testing, disease, test	3.36 (2.0-6.1)	599 (3.59)
2	Therapies and vaccines	chloroquine, anti, hydroxychloroquine, pandemic, potential	hydroxychloroquine, chloroquine, drug, disease, antiviral	4.10 (2.9-6.6)	1193 (7.15)
3	Risk factors	ecmo, renin, respiratory, clinical, risk	diabetes, angiotensin, ace, disease, enzyme	4.13 (2.9-6.5)	420 (2.51)
4	Health care response	worker, response, practice, service, recommendation	health, pandemic, public, infection, disease	3.39 (2.4-5.1)	2812 (16.86)
5	Epidemiology	risk, control, datum, period, rate	disease, respiratory, epidemiology, novel, infection	4.09 (2.8-6.3)	819 (4.91)
6	Disease transmission	cause, spread, health, transmission, outbreak	respiratory, disease, syndrome, acute, virus	3.36 (2.5-6.2)	1141 (6.84)
7	Impact on health care practices	change, resident, time, virtual, visit	education, telemedicine, pandemic, health, medical	3.86 (2.5-5.7)	1115 (6.68)
8	Radiology	imaging, tomography, lesion, diagnosis, feature	pneumonia, tomography, computed, disease, ct	3.69 (2.7-5.5)	774 (4.64)
9	Epidemiological modeling	control, spread, measure, public, italy	health, pandemic, model, disease, public	3.48 (2.5-5.2)	1219 (7.31)
10	Clinical manifestations	increase, associate, infection, cardiovascular, injury	disease, acute, syndrome, respiratory, severe	4.99 (3.3-7.8)	1828 (10.96)
11	Protective measures	equipment, high, practice, perform, protective	surgery, cancer, pandemic, management, personal	4.50 (2.6-5.5)	1466 (8.79)
12	Immunology	expression, target, inhibitor, enzyme, viral	ace, angiotensin, protein, molecular, converting	4.56 (3.1-8.1)	694 (4.16)
13	Pregnancy	systematic, datum, include, disease, search	pregnancy, infection, respiratory, transmission, disease	3.52 (2.3-5.1)	819 (4.91)
14	Psychological impact	increase, stress, old, physical, public	health, pandemic, mental, social, anxiety	3.35 (2.4-5.0)	1771 (10.62)

Table 1: "COVID-19 topics from latent Dirichlet allocation modeling".

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CONTRIBUTORS

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