The Daily COVID-19 Literature Surveillance Summary

March 18, 2021

DISCLAIMER

This free and open source document represents a good faith effort to provide real time, distilled information for guiding best practices during the COVID-19 pandemic. This document is not intended to and cannot replace the original source documents and clinical decision making. These sources are explicitly cited for purposes of reference but do not imply endorsement, approval or validation.

This is not an official product or endorsement from the institutions affiliated with the authors, nor do the ideas and opinions described within this document represent the authors' or their affiliated institutions' values, opinions, ideas or beliefs. This is a good faith effort to share and disseminate accurate summaries of the current literature.

NOW LIVE!

Daily audio summaries of the literature in 10 minutes or less.
https://www.covid19lst.org/podcast/

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

Transmission & Prevention

- Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US: Center for Disease Control and Prevention (CDC) reviewed Vaccine Adverse Event Reporting System (VAERS) data for anaphylaxis after receiving the Pfizer-BioTech (n= 9,943,247) or Moderna (n= 7,581,429) COVID-19 vaccine and found rates of 4.7 cases/million for Pfizer-Biotech and 2.5 cases/million for Moderna. There were no deaths reported after receiving Pfizer-BioTech or Moderna vaccinations and with rare anaphylaxis rates, the benefits of vaccination far outweigh the risks of anaphylaxis, especially compared to the context of morbidity and mortality from COVID-19 infection.

Adjusting Practice During COVID-19

- Involving Pregnant Individuals in Clinical Research on COVID-19 Vaccines: Physician and doctorate researchers associated with the National Institutes of Health (NIH) describe the risks of pregnant and lactating people getting COVID-19. These include an increased risk of hospitalization, cesarean delivery (RR=1.57), postpartum hemorrhage (RR=2.04), hypertensive disorders (RR=1.64), and preterm birth (RR=3.53). The authors express concern over the lack of inclusion of pregnant and lactating people in SARS-CoV-2 vaccine clinical trials.

TABLE OF CONTENTS

Right-click to update field.

EVIDENCE OF FOODBORNE TRANSMISSION OF THE CORONAVIRUS (COVID-19) THROUGH THE ANIMAL PRODUCTS FOOD SUPPLY CHAIN

Hu L, Gao J, Yao L, Zeng L, Liu Q, Zhou Q, Zhang H, Lu D, Fu J, Liu QS, Li M, Zhao X, Hou X, Shi J, Liu L, Guo Y, Wang Y, Ying GG, Cai Y, Yao M, Cai Z, Wu Y, Qu G, Jiang G.. Environ Sci Technol. 2021 Mar 2;55(5):2713-2716. doi: 10.1021/acs.est.0c06822. Epub 2021 Feb 16.
Level of Evidence: 5 - Review / Literature Review

BLUF

Food safety experts from China review literature regarding SARS-CoV-2 infection in domestic animals and animal products. They suggest the persistence of low doses of SARS-CoV-2 variants in meat and seafood products presents a risk for global dissemination via cold food supply chain (Figure 1) and emphasize the importance of new packaging methods, UV disinfection, and surveillance systems in meat and seafood industries to combat disease transmission globally.

FIGURES

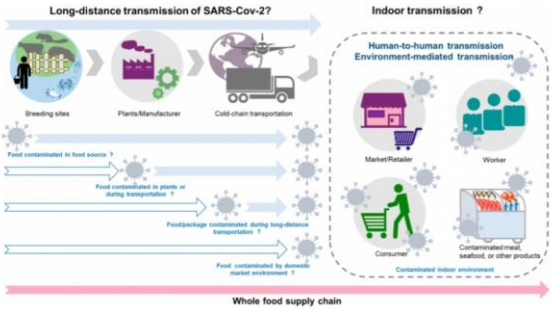


Figure 1: "Possible food-associated transmission routes of COVID-19".

ADULTS

ELEVATED FREQUENCIES OF CD14(+)HLA-DR(LO/NEG) MDSCS IN COVID-19 PATIENTS

Xue G, Jiang M, Zhao R, Le A, Li J.. Aging (Albany NY). 2021 Feb 26;13. doi: 10.18632/aging.202571. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers of Nanchang University, Jiangxi, China in a case series of 27 patients, evaluated the relationship between severity of disease in COVID-19 patients and level of HLA-DRlo/neg myeloid-derived suppressor cells (MDSCs). They found that levels of HLA-DR lo/neg MDSCs were higher in ICU admitted patients (P<0.001)(Figure 1) and those with decreased T-cell populations. This study has shown that high levels of HLA-DRlo/neg MDSCs could be a prognostic factor of COVID-19 infection severity and survival (summary).

SUMMARY

MDSCs have been previously shown to suppress the effects of T-cells, NK cells, dendritic cells, and macrophages in an phenomenon called "immunoparalysis." Decreased expression of HLA-DR on MDSCs in critically ill patients as well as anti-inflammatory mediators like IL-4 and IL-10 have been reported to be the cause of decreased lymphocyte count in COVID-19 patients and thus a poorer prognosis.

ABSTRACT

BACKGROUND: The immune responses, hyper-inflammation or immunosuppression, may be closely related to COVID-19 progression. We aimed to evaluate the changes of frequency of CD14+HLA-DRlo/neg MDSCs, a population of cells with potent immunosuppressive capacity, in COVID-19 patients. METHODS: The levels of CD14+HLA-DRlo/neg MDSCs were determined by flow cytometry in 27 COVID-19 patients, and their association with clinical characteristics and laboratory data were analyzed. RESULTS: The frequency of CD14+HLA-DRlo/neg MDSCs was elevated in COVID-19 patients, particularly severe patients. A follow-up comparison revealed a decline of CD14+HLA-DRlo/neg MDSCs percentages in most patients 1 day after testing negative for SARS-CoV-2 nucleic acid, but the levels of CD14+HLA-DRlo/neg MDSCs were still greater than 50.0% in 3 ICU patients 4-10 days after negative SARS-CoV-2 results. Elevated frequency of CD14+HLA-DRlo/neg MDSCs was positively correlated with oropharyngeal viral loads and length of hospital stay, while negatively correlated with lymphocyte counts and serum albumin. Moreover, strong correlations were observed between the frequency of CD14+HLA-DRlo/neg MDSCs and T cell subsets, NK cell counts, and B cell percentages. The frequency of CD14+HLA-DRlo/neg MDSCs could be used as a predictor of COVID-19 severity. CONCLUSIONS: A high frequency of CD14+HLA-DRlo/neg MDSCs, especially in severe patients, may indicate an immunoparalysis status and could be a predictor of disease severity and prognosis.

FIGURES

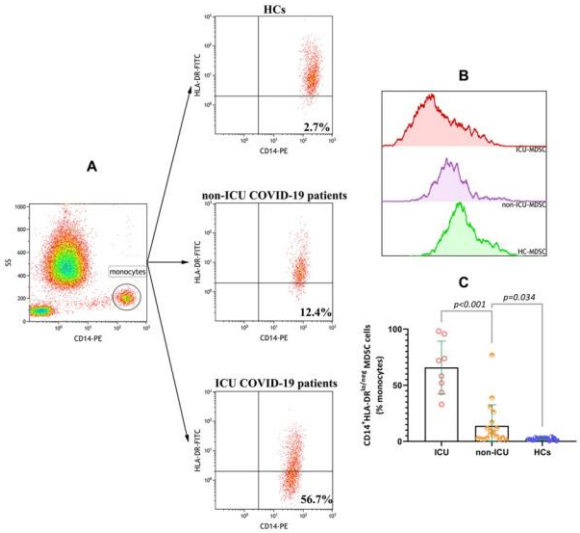


Figure 1. Increased %CD14+HLA-DRlo/neg MDSCs in COVID-19 patients. (A) Representative gating strategy used to identify CD14+HLADRlo/neg MDSCs in whole blood. (B) Flow cytometry overlay histograms for HLA-DR expressions on monocytes in HC, non-ICU COVID-19patient and ICU COVID-19 patient. (C) Comparisons of CD14+HLA-DRlo/neg MDSC(%) in HCs group, non-ICU group and ICU group. Abbreviations: ICU, intensive care unit; HCs, healthy controls; MDSC, myeloid-derived suppressor cells.

PRESENCE OF ANTIBODY-DEPENDENT CELLULAR CYTOTOXICITY (ADCC) AGAINST SARS-COV-2 IN COVID-19 PLASMA

Tso FY, Lidenge SJ, Poppe LK, Peña PB, Privatt SR, Bennett SJ, Ngowi JR, Mwaiselage J, Belshan M, Siedlik JA, Raine MA, Ochoa JB, Garcia-Diaz J, Nossaman B, Buckner L, Roberts WM, Dean MJ, Ochoa AC, West JT, Wood C.. PLoS One. 2021 Mar 4;16(3):e0247640. doi: 10.1371/journal.pone.0247640. eCollection 2021.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A study conducted by microbiologists and virologists investigated plasma from 3 uninfected controls and 20 subjects exposed to or recovering from SARS-CoV-2 to measure antibody-dependent cellular cytotoxicity (ADCC). They used immunofluorescence to detect IgG antibodies (Figure 1), which were present in all subjects. All but 3 plasma samples showed >80% neutralizing capacity to a SARS-CoV-2 pseudo-typed virus (Figure 2) and strong ADCC was demonstrated in 19/20 SARS-CoV-2 subjects (Figure 3). These findings suggest efficacy of COVID-19 vaccination should be evaluated by the total SARS-CoV-2 specific humoral response and durability of ADCC and other non-neutralizing antibody effector mechanisms for a more complete analysis.

ABSTRACT

BACKGROUND: Neutralizing-antibody (nAb) is the major focus of most ongoing COVID-19 vaccine trials. However, nAb response against SARS-CoV-2, when present, decays rapidly. Given the myriad roles of antibodies in immune responses, it is possible that antibodies could also mediate protection against SARS-CoV-2 via effector mechanisms such as antibody-dependent cellular cytotoxicity (ADCC), which we sought to explore here. METHODS: Plasma of 3 uninfected controls and 20 subjects exposed to, or recovering from, SARS-CoV-2 infection were collected from U.S. and sub-Saharan Africa. Immunofluorescence assay was used to detect the presence of SARS-CoV-2 specific IgG antibodies in the plasma samples. SARS-CoV-2 specific neutralizing capability of these plasmas was assessed with SARS-CoV-2 spike pseudotyped virus. ADCC activity was assessed with a calcein release assay. RESULTS: SARS-CoV-2 specific IgG antibodies were detected in all COVID-19 subjects studied. All but three COVID-19 subjects contained nAb at high potency (>80% neutralization). Plasma from 19/20 of COVID-19 subjects also demonstrated strong ADCC activity against SARS-CoV-2 spike glycoprotein, including two individuals without nAb against SARS-CoV-2. CONCLUSION: Both neutralizing and non-neutralizing COVID-19 plasmas can mediate ADCC. Our findings argue that evaluation of potential vaccines against SARS-CoV-2 should include investigation of the magnitude and durability of ADCC, in addition to nAb.

FIGURES

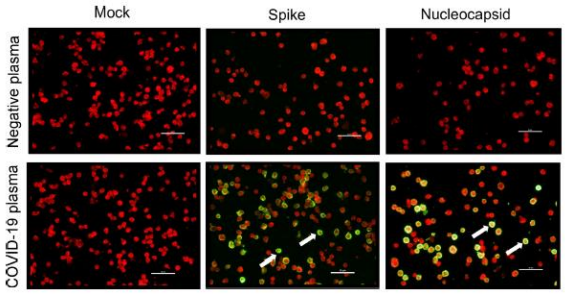


Fig 1. Immunofluorescence assay (IFA) against SARS-CoV-2 proteins. Representative pictures of IFA against either the mock, SARS-CoV-2 spike or
nucleocapsid expressing HEK-293T cells. The upper row shows IFA with negative control plasma collected before the COVID-19 pandemic. The lower row
shows IFA with COVID-19 plasma, where strong green color positive cells (indicated by white arrows) were only observed in cells expressing either
SARS-CoV-2 spike or nucleocapsid proteins. The lack of green color positive cells with negative control plasma and mock cells demonstrated the specificity of

the IFA. All pictures were taken at 20X magnification with Nikon Eclipse 50i fluorescence microscope. The white scale bars indicate 50 μm.

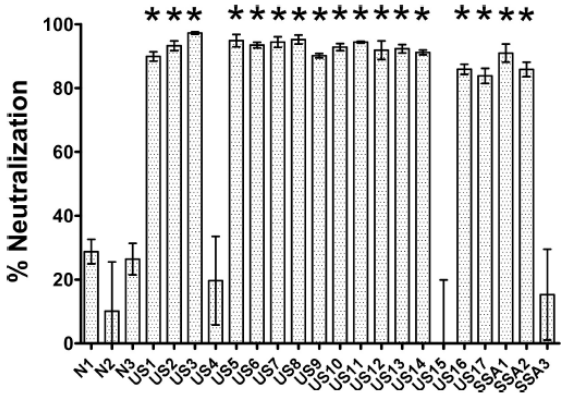


Fig 2. SARS-CoV-2 spike pseudotyped virus neutralization assay. SARS-CoV-2 spike pseudotyped lentivirus virus encoding EGFP were
tested against negative control pre-pandemic plasmas (N1, N2 and N3) and COVID-19 plasmas (US1 to US17 and SSA1 to SSA3) at 1:40
plasma dilution. At 72-hours post-infection, percentage of GFP positive cells were quantified with BD Accuri C6 Plus flow cytometer. The
mean of triplicate wells was shown with error bars representing SEM. P-values were calculated via one-way ANOVA and "*" denotes
$p < 0.05$ relative to negative control plasmas.

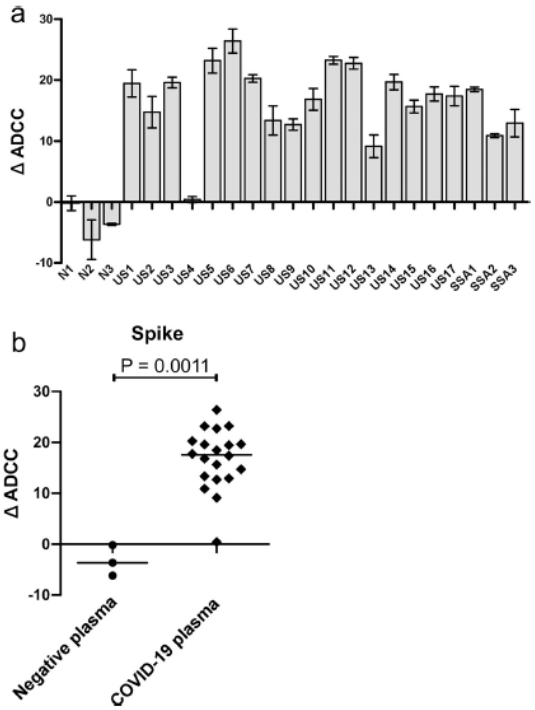


Fig 3. Antibody-dependent cellular cytotoxicity (ADCC) assay. The ADCC activity of COVID-19 plasmas were tested against HEK-293T cells expressing SARS-CoV-2 spike protein, which served as the target cells. After incubation with plasma, Calcein-AM labeled target cells were incubated with NK cells (NK92.05-CD16-176V) which served as the effector cells. The amount of fluorescent calcein released into the medium was then measured with Victor3V plate reader. A) changes in ADCC (ΔADCC) activity against the spike protein, relative to their respective activity against mock cells. N denotes pre-pandemic negative control plasmas. US and SSA denotes COVID-19 samples from USA and sub-Saharan Africa, respectively. B) Comparison of ΔADCC against the spike protein between COVID-19 and negative control plasmas. P-values were calculated via Mann Whitney test.

IN VITRO

SARS-COV-2 HIJACKS FOLATE AND ONE-CARBON METABOLISM FOR VIRAL REPLICATION

Zhang Y, Guo R, Kim SH, Shah H, Zhang S, Liang JH, Fang Y, Gentili M, Leary CNO, Elledge SJ, Hung DT, Mootha VK, Gewurz BE.. Nat Commun. 2021 Mar 15;12(1):1676. doi: 10.1038/s41467-021-21903-z.
Level of Evidence: 5 - Mechanism-based reasoning

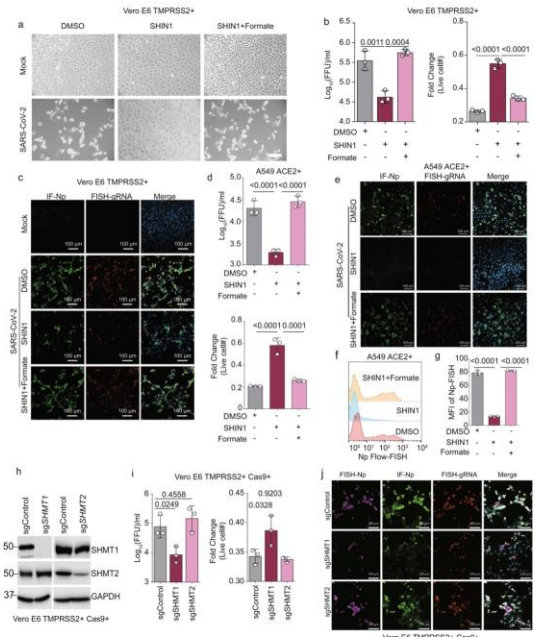
BLUF

Researchers from various institutions in Boston, Illinois, and China investigated the transcriptional and metabolic changes SARS-CoV-2 induces in host cells using Vero E6 TMPRSS2 + infected cells (Figure 3). Analysis 8 hours post infection revealed increased induction of transcriptional genes and stress response including upregulation of purine metabolism and increased lactate levels, suggestive of viral induced glycolysis and one-carbon metabolism used for viral genomic RNA and protein production within the host cell (Figure 4). This study suggests additional targeted antiviral therapies for host cell metabolism are needed given the potential for future zoonotic coronavirus pandemics.

ABSTRACT

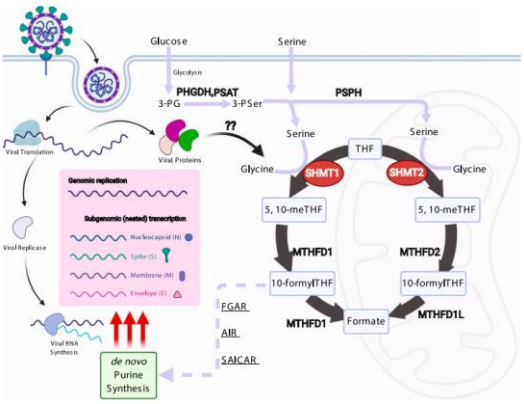
The recently identified Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of the COVID-19 pandemic. How this novel beta-coronavirus virus, and coronaviruses more generally, alter cellular metabolism to support massive production of ~30 kB viral genomes and subgenomic viral RNAs remains largely unknown. To gain insights, transcriptional and metabolomic analyses are performed 8 hours after SARS-CoV-2 infection, an early timepoint where the viral lifecycle is completed but prior to overt effects on host cell growth or survival. Here, we show that SARS-CoV-2 remodels host folate and one-carbon metabolism at the post-transcriptional level to support de novo purine synthesis, bypassing viral shutoff of host translation. Intracellular glucose and folate are depleted in SARS-CoV-2-infected cells, and viral replication is exquisitely sensitive to inhibitors of folate and one-carbon metabolism, notably methotrexate. Host metabolism targeted therapy could add to the armamentarium against future coronavirus outbreaks.

FIGURES



'Fig. 3: SARS-CoV-2 induced serine one-carbon metabolism supports viral RNA and protein expression, replication, and cytopathic effect.' a. Phase microscopic images of SARS-CoV-2 versus mock infected Vero E6 TMPRSS2 + cells cultured with DMSO, 10 μM of the dual SHMT1/2 inhibitor SHIN1 or 10 μM SHIN1 + 1 μM formate, as indicated. White scale bar indicates 100 μm. The experiment was reproduced in at least six independent experiments. b Mean ± SD fold change TCID50 (left) and live cell (right) from n = 3 biologically independent replicates, as in a. c IF of Np, FISH for +strand gRNA, and merge with Hoechst stained nuclei in mock-infected or SARS-CoV-2-infected Vero E6 TMPRSS2 + cells treated with DMSO, SHIN1, or SHIN1 + formate. d Mean ± SD fold change TCID50 (top) and live cell (bottom) values in SARS-CoV-2-infected A549 ACE2 + cells, treated with the indicated conditions, from n = 3 biologically independent replicates. e IF of Np, FISH for +strand gRNA, and merge with Hoechst stained nuclei in mock-infected or SARS-CoV-2-infected A549 ACE2 + cells treated with DMSO,

SHIN1, or SHIN1 + formate. f Flow-FISH analysis of Np subgenomic RNA in SARS-CoV-2-infected A549 ACE2 + cells treated with the indicated conditions. g Mean ± SD values from n = 3 biologically independent replicates of viral subgenomic RNA Flow-FISH MFI values, as in f. h Immunoblot analysis of whole cell lysates from Cas9 + TMPRSS2 + Vero E6 expressing control, SHMT1 or SHMT2 sgRNAs. i Mean ± SD fold change TCID50 (left) and live cell (right) values from Vero E6 TMPRSS2 + with control, SHMT1 or SHMT2 targeting sgRNAs infected by SARS-CoV-2 from n = 3 biologically independent replicates are shown. j FISH of subgenomic Np RNA, IF of Np, FISH for +strand gRNA, and merge with Hoechst stained nuclei in cells with control, SHMT1 or SHMT2 targeting sgRNAs infected by SARS-CoV-2. In all panels, cells were infected at MOI = 0.1 for 48 h. Microscopy images are representative of at least n = 3 biologically independent values. P-values in this figure were calculated by one-way ANOVA with multiple comparisons using Sidak method. Source data are provided as a Source Data file.



'Fig. 4 Schematic of SARS-CoV-2 induced one-carbon metabolism in support of viral replication.' SARS-CoV-2 induces glycolysis and one-carbon metabolism at the post-transcriptional level in newly infected cells. Serine metabolism, particularly by cytosolic SHMT1 produces carbon units for de novo purine synthesis in support of massive viral subgenomic RNA synthesis, non-structural protein expression, and viral replication.

TRANSMISSION & PREVENTION

BORDER CONTROL AND SARS-COV-2: AN OPPORTUNITY FOR GENERATING HIGHLY POLICY-RELEVANT, REAL-WORLD EVIDENCE

Burns J, Movsisyan A, Rehfuess EA, Stratil JM.. J Travel Med. 2021 Mar 12:taab037. doi: 10.1093/jtm/taab037. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

Based on findings from their previous systematic review, public health researchers from Munich, Germany propose a study regarding border control measures that they believe can limit SARS-CoV-2 transmission internationally. Their proposal includes understanding the time period of infectiousness through repeated RT-PCR testing and monitoring of cycle threshold of COVID-19 positive patients. Genome sequencing can be used to investigate whether the transmission occurs before, during, or after travel and how border control measures can decrease the risk of importing mutant SARS-CoV-2 strains from abroad. Researchers suggest that such a study can provide insight on the optimal strategy of border control measures and international travel during the current COVID-19 pandemic.

'BLUE TOES' FOLLOWING VACCINATION WITH THE BNT162B2 MRNA COVID-19 VACCINE

Davido B, Mascitti H, Fortier-Beaulieu M, Jaffal K, de Truchis P.. J Travel Med. 2021 Feb 23:taab024. doi: 10.1093/jtm/taab024. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

Infectious disease specialists from Hôpital Universitaire Raymond-Poincaré in Garches, France present the case of a 41-year-old female with a history of bipolar disorder who presented with blue toes on her left foot 10 days after BNT162b2 mRNA COVID-19 vaccine (Figure). Labs, doppler ultrasound of lower limb arteries, manifold capillaroscopy and echocardiogram were normal; low level of anti-spike antibodies (0.642UI/ml) were detected (see summary). Authors suggest this presentation is consistent with "COVID toes" associated with vaccination rather than SARS-CoV-2 infection.

SUMMARY

The patient developed toe pain and nighttime itching 4 days post-vaccination and presented for care 10 days after vaccination with blue toes. She has a history of bipolar disorder under valproate treatment for past 10 years.

Labs included:
- Normal white blood cells
- Normal lipid profile
- Serum creatinine 70 mmol/L
- CRP <1 mg/L
- Antinuclear antibody titer of 1:160 without anti-DNA or anti-ENA
- Negative ANCA, cryoglobulin, cold agglutinin or antiphospholipid antibodies

Patient was treated with apixaban and low dose aspirin until demonstrated to have low levels of circulating immune complexes (<3 µg Eq/mL) after 14 days of treatment. Her second vaccine dose was deferred.

All but one lesion resolved by 4 weeks; the unresolved lesion remained for 150 days.

FIGURES

Figure legend: Non-painful violaceous lesions on the big toe, the 3th toe and the left-side of the 4th toe, compatible with the so-called "COVID toes"

DEVELOPMENTS IN TRANSMISSION & PREVENTION

REPORTS OF ANAPHYLAXIS AFTER RECEIPT OF MRNA COVID-19 VACCINES IN THE US-DECEMBER 14, 2020-JANUARY 18, 2021

Shimabukuro TT, Cole M, Su JR.. JAMA. 2021 Mar 16;325(11):1101-1102. doi: 10.1001/jama.2021.1967.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

Researchers from the Center for Disease Control and Prevention (CDC) reviewed submissions to the Vaccine Adverse Event Reporting System (VAERS) of anaphylaxis episodes after receiving the Pfizer-BioTech (n= 9,943,247) or Moderna (n= 7,581,429) COVID-19 vaccine between December 14, 2020 and January 18, 2021 and found the anaphylaxis reporting rate was 4.7 cases/million for Pfizer-Biotech and 2.5 cases/million for Moderna. Sixty-six case reports in VAERS met the Brighton Collaboration case definition criteria for anaphylaxis (Table), including 21 with prior reported episodes of anaphylaxis and all 66 patients receiving treatment in a healthcare setting (n= 32 in hospital, n= 34 in emergency department). There were no deaths reported after receiving Pfizer-BioTech or Moderna vaccinations and with rare anaphylaxis rates, the benefits of vaccination far outweigh the risks of anaphylaxis, especially compared to the context of morbidity and mortality from COVID-19 infection.

FIGURES

Characteristics	No. (%) of cases	
	Pfizer-BioNTech (n = 47)	Moderna (n = 19)
Age, median (range), y	39 (27-63)[a]	41 (24-63)
Female sex	44 (94)	19 (100)
Minutes to symptom onset, median (range)	10 (<1-1140 [19 h])[b]	10 (1-45)
Symptom onset, min		
≤15	34 (76)[b]	16 (84)
≤30	40 (89)[b]	17 (89)
Reported history[c]		
Allergies or allergic reactions	36 (77)	16 (84)
Prior anaphylaxis	16 (34)	5 (26)
Vaccine dose		
First	37	17
Second	4	1
Unknown	6	1
Brighton Collaboration case definition level[d]		
1	21 (45)	10 (52)
2	23 (49)	8 (43)
3	3 (6)	1 (5)
Anaphylaxis reporting rate (cases per million doses administered)	4.7	2.5

Table. Characteristics of Reported Cases of Anaphylaxis Following Receipt of Pfizer-BioNTech (9 943 247 Doses) and Moderna (7 581 429 Doses) COVID-19 Vaccines—Vaccine Adverse Events Reporting System (VAERS), US, December 14, 2020-January 18, 2021

Abbreviation: COVID-19, coronavirus disease 2019.
a Age missing in 1 Pfizer-BioNTech report.
b Time to symptom onset missing in 2 BioNTech reports.
c To rabies vaccine, influenza A(H1N1) vaccine, seasonal influenza vaccine, unspecified vaccines, gadolinium- and iodine-based contrast media, unspecified intravenous contrast media, unspecified infusions, sulfa drugs, penicillin, prochlorperazine, latex,walnuts, unspecified tree nuts, jellyfish stings, unspecified multiple environmental and food allergens, unspecified exposure.
d The Brighton Collaboration case definition uses combinations of symptoms to define levels of diagnostic certainty. Brighton level 1 represents the highest level of diagnostic certainty that a reported case represents anaphylaxis; levels 2 and 3 are successively lower levels of diagnostic certainty. Level 4 is a case reported as anaphylaxis but that does not meet the Brighton Collaboration case definition, and level 5 is a case that was neither reported as anaphylaxis nor meets the case definition.

ADJUSTING PRACTICE DURING COVID-19

OBGYN

INVOLVING PREGNANT INDIVIDUALS IN CLINICAL RESEARCH ON COVID-19 VACCINES

Bianchi DW, Kaeser L, Cernich AN.. JAMA. 2021 Mar 16;325(11):1041-1042. doi: 10.1001/jama.2021.1865.
Level of Evidence: 5 - Expert Opinion

BLUF

Physician and doctorate researchers associated with the National Institutes of Health (NIH) describe the dangerous risks of pregnant and lactating people getting COVID-19. These include an increased risk of hospitalization, cesarean delivery (RR=1.57), postpartum hemorrhage (RR=2.04), hypertensive disorders (RR=1.64), and preterm birth (RR=3.53). The lack of inclusion of pregnant and lactating people in SARS-CoV-2 vaccine clinical trials produces several gaps in knowledge. Authors suggest that pregnant and lactating people should have access to the same scientific evidence that all other individuals get when receiving a vaccine or medication and should be included in clinical research.

PSYCHIATRY

EVIDENCE SYNTHESIS OF DIGITAL INTERVENTIONS TO MITIGATE THE NEGATIVE IMPACT OF THE COVID-19 PANDEMIC ON PUBLIC MENTAL HEALTH: RAPID META-REVIEW

Rauschenberg C, Schick A, Hirjak D, Seidler A, Paetzold I, Apfelbacher C, Riedel-Heller SG, Reininghaus U.. J Med Internet Res. 2021 Mar 10;23(3):e23365. doi: 10.2196/23365.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

This rapid meta-review of 83 peer-reviewed systematic reviews and meta-analyses led by the Central Institute of Mental Health and other public health professionals in Germany investigates the theoretical and empirical base, user perspective, safety, effectiveness, and cost-effectiveness of digital interventions directed towards mental health promotion, prevention, and treatment. Studies published through April 2020 were collected from CENTRAL, MEDLINE, and PsycINFO databases. It was found that internet and app based mobile health interventions have played a key role in alleviating the negative effects of the COVID-19 pandemic on public mental health, suggesting the need for more efforts in developing and improving digital strategies aimed toward mental health care.

ABSTRACT

BACKGROUND: Accumulating evidence suggests negative effects of the COVID-19 pandemic on public mental health. Digital interventions that have been developed and evaluated in recent years may be used to mitigate negative consequences of the COVID-19 pandemic. However, evidence-based recommendations on the use of existing telemedicine and internet-based (eHealth) and app-based mobile Health (mHealth) interventions are lacking. OBJECTIVE: The aim was to investigate the theoretical and empirical base, user perspective, safety, effectiveness, and cost-effectiveness of digital interventions in public mental health provision (i.e. mental health promotion, prevention and treatment of mental disorders) that may help to reduce the consequences of the current COVID-19 pandemic. METHODS: A rapid meta-review was conducted. MEDLINE, PsycINFO, and CENTRAL databases were searched on May 11, 2020. Study inclusion criteria were broad and considered systematic reviews and meta-analyses that investigated digital tools for health promotion, prevention, or treatment of mental health conditions and determinants likely affected by the COVID-19 pandemic. RESULTS: Overall, 815 peer-reviewed systematic reviews and meta-analyses were identified of which 83 met inclusion criteria. The present findings suggest that there is good evidence on the usability, safety, acceptance/satisfaction, and effectiveness of eHealth interventions while evidence on mHealth apps is promising, especially if social components (e.g. blended care) and strategies to promote adherence are incorporated. Although most digital interventions focus on the prevention or treatment of mental disorders, there is some evidence on mental health promotion. However, evidence on process quality, cost-effectiveness, and long-term effects is very limited. CONCLUSIONS: There is evidence that digital interventions are particularly suited to mitigating psychosocial consequences at the population level. In times of physical distancing, quarantine, and restrictions on social contacts, decision-

makers should develop digital strategies for continued mental health care and invest time and efforts in the development and implementation of mental health promotion and prevention programs.

CONVALESCENT PLASMA THERAPY FOR THE TREATMENT OF PATIENTS WITH COVID-19: ASSESSMENT OF METHODS AVAILABLE FOR ANTIBODY DETECTION AND THEIR CORRELATION WITH NEUTRALISING ANTIBODY LEVELS

Harvala H, Robb ML, Watkins N, Ijaz S, Dicks S, Patel M, Supasa P, Wanwisa D, Liu C, Mongkolsapaya J, Bown A, Bailey D, Vipond R, Grayson N, Temperton N, Gupta S, Ploeg RJ, Bolton J, Fyfe A, Gopal R, Simmonds P, Screaton G, Thompson C, Brooks T, Zambon M, Miflin G, Roberts DJ.. Transfus Med. 2020 Dec 17. doi: 10.1111/tme.12746. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Researchers from various institution in the UK assayed for SARS-CoV-2 neutralizing antibodies (nAbs) in blood samples from 52 SARS-CoV-2-positive patients using four ELISA tests. They found that nAb titers >1:20 were detected in 83% of samples, nAb titers >1:100 were detected in 42%, and the most robust association was seen with the EUROimmun IgG reactivity ELISA test (Spearman Rho correlation coefficient: 0.88; $p < 0.001$) (Figure 3, Figure 2). Convalescent plasma therapy is being explored as a possible therapy for COVID-19 and likely requires high titers of nAbs to be effective, and this assay may be a useful tool in producing convalescent plasma with potentially therapeutic levels of anti-SARS-CoV-2 nAbs.

ABSTRACT

INTRODUCTION: The lack of approved specific therapeutic agents to treat coronavirus disease (COVID-19) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has led to the rapid implementation of convalescent plasma therapy (CPT) trials in many countries, including the United Kingdom. Effective CPT is likely to require high titres of neutralising antibody (nAb) in convalescent donations. Understanding the relationship between functional neutralising antibodies and antibody levels to specific SARS-CoV-2 proteins in scalable assays will be crucial for the success of a large-scale collection. We assessed whether neutralising antibody titres correlated with reactivity in a range of enzyme-linked immunosorbent assays (ELISA) targeting the spike (S) protein, the main target for human immune response. METHODS: Blood samples were collected from 52 individuals with a previous laboratory-confirmed SARS-CoV-2 infection. These were assayed for SARS-CoV-2 nAbs by microneutralisation and pseudo-type assays and for antibodies by four different ELISAs. Receiver operating characteristic (ROC) analysis was used to further identify sensitivity and specificity of selected assays to identify samples containing high nAb levels. RESULTS: All samples contained SARS-CoV-2 antibodies, whereas neutralising antibody titres of greater than 1:20 were detected in 43 samples (83% of those tested) and >1:100 in 22 samples (42%). The best correlations were observed with EUROimmun immunoglobulin G (IgG) reactivity (Spearman Rho correlation coefficient 0.88; $p < 0.001$). Based on ROC analysis, EUROimmun would detect 60% of samples with titres of >1:100 with 100% specificity using a reactivity index of 9.1 (13/22). DISCUSSION: Robust associations between nAb titres and reactivity in several ELISA-based antibody tests demonstrate their possible utility for scaled-up production of convalescent plasma containing potentially therapeutic levels of anti-SARS-CoV-2 nAbs.

FIGURES

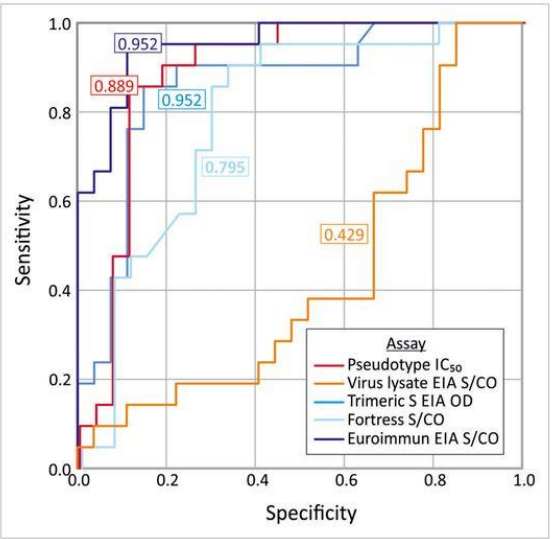


Figure 3. ROC analysis of serology assays predicting virus-neutralising antibody titres of ≥1/100. OC curves for the pseudo-type, virus lysate and three EIAs to correctly identify samples with neutralising antibody titres of 1:100 and over in the virus neutralisation assay. A total of 48 samples were included in these calculations (22 with neutralising antibody levels of or over 1:100 and the remaining 26 below 1:100). Areas under the curve for each assay are shown in colour-coded boxes.

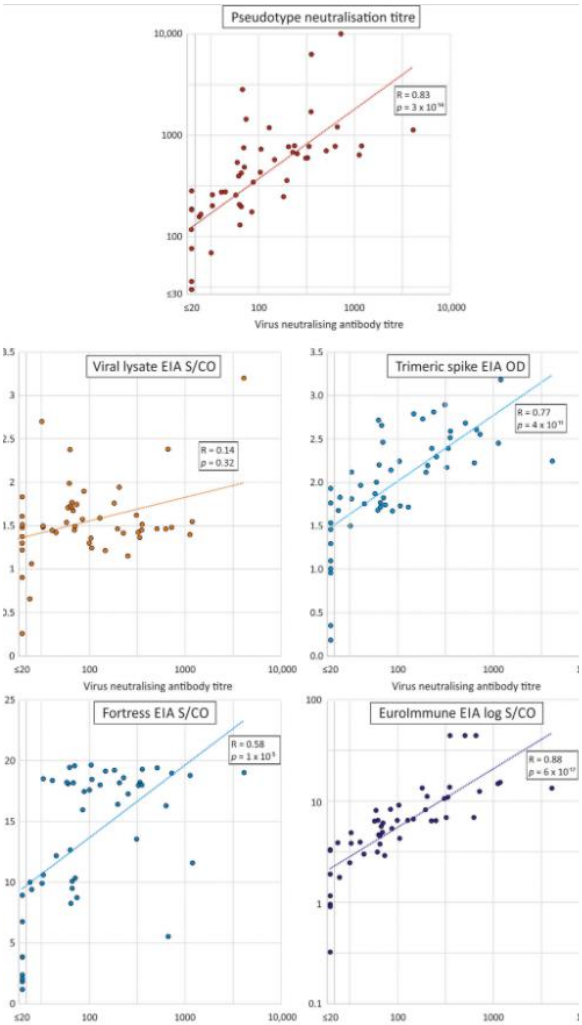


Figure 2. Correlations between neutralising and pseudo-type antibody titres and reactivities in EIAs. Scatter plots of neutralising antibody titres of test samples in the virus neutralisation assay with those of the pseudo-type assay and reactivities in EIAs. A line of best fit was estimated by linear regression using log-transformed values for the virus and pseudo-

type neutralising antibody assays and the EUROimmun EIA. Correlation coefficients and (two-tailed) p values were calculated by Spearman non-parametric test

DEVELOPMENTS IN TREATMENTS

THERMOVACCINATION: THERMOHELIOX AS AN IMMUNE RESPONSE STIMULANT. KINETICS OF ANTIBODIES AND C-REACTIVE PROTEIN SYNTHESIS IN CORONAVIRAL INFECTION

Varfolomeev SD, Zhuravel SV, Panin AA, Shogenova LV, Bykov VI, Tsybenova SB, Ryabokon AM, Utkina II, Gavrilov PV, Chuchalin AG.. Dokl Biochem Biophys. 2021 May;496(1):44-47. doi: 10.1134/S1607672921010129. Epub 2021 Mar 10.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A non-randomized controlled study conducted by medical and chemical researchers associated with Moscow State University and Sklifosovsky Federal Research Institute of Emergency Medicine between April 21-June 2020 assessed the efficacy of a novel COVID-19 therapy called thermoheliox, a technique using inhalation of high-temperature helium and oxygen to stimulate antibody response. The treatment group showed significant decline in positive COVID-19 PCR tests post-therapy($p \leq 0.05$) (Fig. 1), stimulated IgG and IgM antibody production compared to the control group (Fig. 2,3) and an average hospital stay 2 to 2.5 days less compared to control group. The clinical findings of this novel treatment are promising, suggesting that this therapy should be further researched.

ABSTRACT

The high efficiency of using thermoheliox (inhalation with a high-temperature mixture of helium and oxygen) in the treatment of patients affected by COVID-19 was shown. The dynamics of accumulation of IgG, IgM, and C-reactive protein (CRP) in patients with coronavirus infection in the "working" and control groups was studied experimentally. It was shown that thermoheliox intensifies the synthesis of IgG, IgM, and CRP antibodies, while eliminating the induction period on the kinetic curves of the synthesis of specific antibodies in the IgG form and transfers the synthesis of CRP to a fast phase. The results of experiments confirm the previously obtained data based on the analysis of the kinetic model of the development of coronaviral infection in the human body.

FIGURES

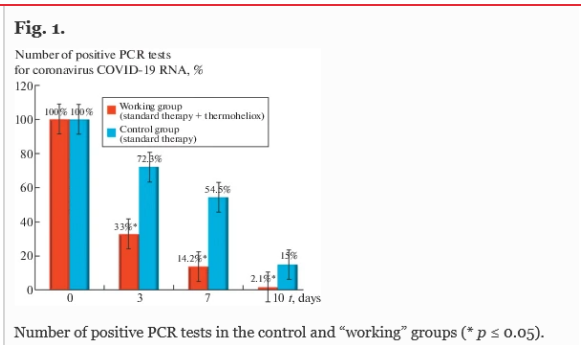


Fig. 1 Number of positive PCR tests in the control and “working” groups (* p ≤ 0.05).

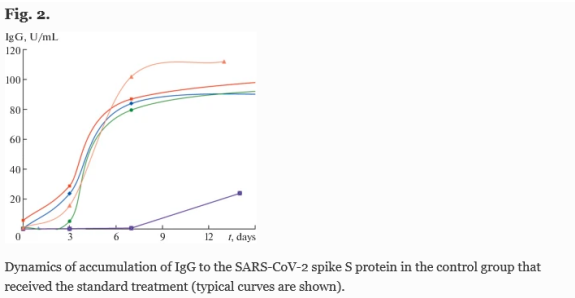


Fig. 2 Dynamics of accumulation of IgG to the SARS-CoV-2 spike S protein in the control group that received the standard treatment (typical curves are shown).

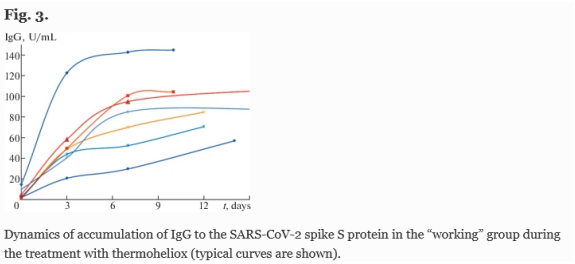


Fig. 3 Dynamics of accumulation of IgG to the SARS-CoV-2 spike S protein in the "working" group during the treatment with thermoheliox (typical curves are shown).

THE SEROTONIN REUPTAKE INHIBITOR FLUOXETINE INHIBITS SARS-COV-2 IN HUMAN LUNG TISSUE

Zimniak M, Kirschner L, Hilpert H, Geiger N, Danov O, Oberwinkler H, Steinke M, Sewald K, Seibel J, Bodem J.. Sci Rep. 2021 Mar 15;11(1):5890. doi: 10.1038/s41598-021-85049-0.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

A cross-sectional study conducted by researchers from multiple medical and research institutions in Hannover and Wurzberg, Germany tested the efficacy of selective serotonin reuptake inhibitors (SSRIs) as off-label treatments for COVID-19 and found fluoxetine inhibited SARS-CoV-2 at a similar concentration to the dose used for treatment of depression (0.8 ug/mL, EC50 = 387 ng/mL) (Figure 1), presumably by directly targeting viral replication, given that no inhibition was seen with paroxetine or escitalopram. Fluoxetine reduced viral loads by two orders of magnitude and reduced cytokine release (Figure 2) in human precision-cut lung slices infected with SARS-CoV-2. These findings suggest that the unique R-stereoisomer in Fluoxetine compared to S-stereoisomer of most other SSRIs can play a role in repressing SARS-CoV-2 and indicates need for clinical trials to acknowledge the role of fluoxetine as a potential treatment for SARS-CoV-2 infected patients.

ABSTRACT

To circumvent time-consuming clinical trials, testing whether existing drugs are effective inhibitors of SARS-CoV-2, has led to the discovery of Remdesivir. We decided to follow this path and screened approved medications "off-label" against SARS-CoV-2. Fluoxetine inhibited SARS-CoV-2 at a concentration of 0.8 microg/ml significantly in these screenings, and the EC50 was determined with 387 ng/ml. Furthermore, Fluoxetine reduced viral infectivity in precision-cut human lung slices showing its activity in relevant human tissue targeted in severe infections. Fluoxetine treatment resulted in a decrease in viral protein expression. Fluoxetine is a racemate consisting of both stereoisomers, while the S-form is the dominant serotonin reuptake inhibitor. We found that both isomers show similar activity on the virus, indicating that the R-form might specifically be used for SARS-CoV-2 treatment. Fluoxetine inhibited neither Rabies virus, human respiratory syncytial virus replication nor the Human Herpesvirus 8 or Herpes simplex virus type 1 gene expression, indicating that it acts virus-specific. Moreover, since it is known that Fluoxetine inhibits cytokine release, we see the role of Fluoxetine in the treatment of SARS-CoV-2 infected patients of risk groups.

FIGURES

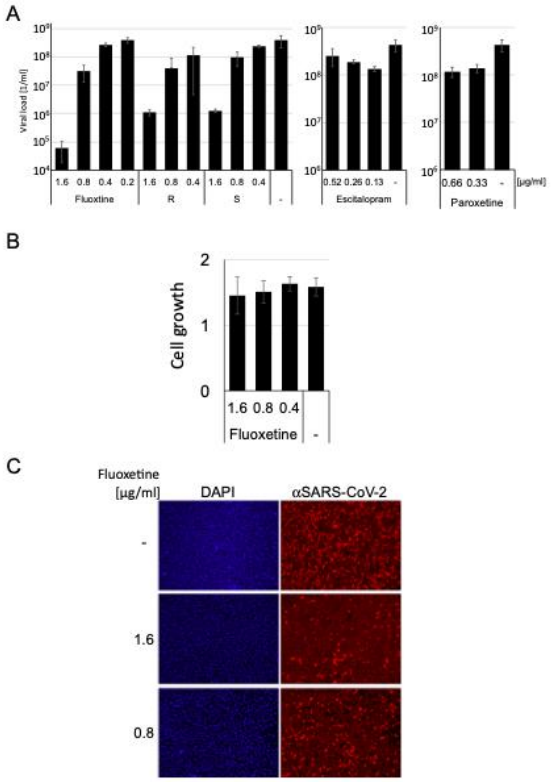


Figure 1. Fluoxetine inhibits SARS-CoV-2 replication. (A) Vero cells were incubated with the compounds and subsequently infected with SARS-CoV-2 (S S-stereoisomer, R R-stereoisomer). Cellular supernatants were collected 3 days after infection, and viral titers were determined with RTqPCR. (B) Fluoxetine is not toxic in Vero cells at concentrations used for the treatment of depression (0.8 µg/ml (= 2.58 µM)). Relative growth of Vero cells was determined. (C) Vero cells were infected with SARS-CoV-2 for 72 h, and viral proteins were detected with a SARS-CoV-2 specific antiserum (1:100) and a TexasRed-labeled donkey anti-human antibody (1:500, Dianova). The nuclei were stained with DAPI.

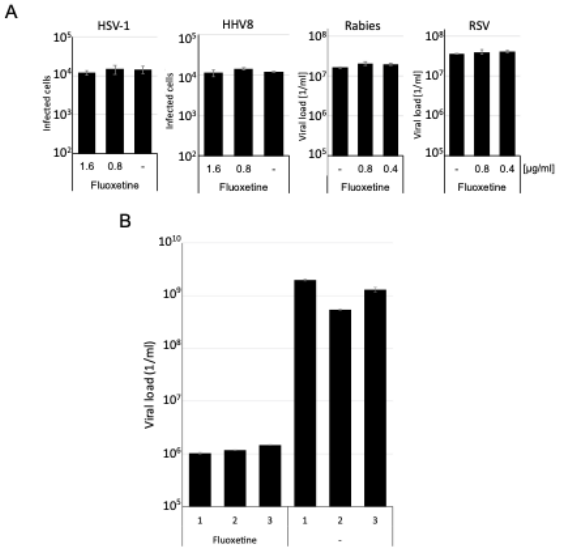


Figure 2. Fluoxetine inhibits virus replication specifically and SARS-CoV-2 in human lung tissue. (A) BHK21 and HepG2 cells were infected with either gfp-encoding HSV-1, HHV8, with a Rabies vaccine strain or with a patient-derived RSV. Viral titers were determined by RTqPCR (RSV, Rabies) or infected gfp-expressing cells were counted with an Ensight device (PerkinElmer). (B) Human precision-cut lung slices were treated with 1.6 µg/ml Fluoxetine infected with SARS-CoV-2. After 3 days virus, the supernatants were harvested, and viral infectivity was analysed by infecting Vero cells. The resulting viral load was determined by RTqPCR. Each bar represents the mean of 3 RTqPCR reactions from a single PCLS. The error bars represent the standard deviation.

MONOCLONAL ANTIBODY FOR PATIENTS WITH COVID-19

Jaworski JP.. N Engl J Med. 2021 Feb 3:10.1056/NEJMc2100221#sa1. doi: 10.1056/NEJMc2100221. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A virology and immunopathology researcher at the Consejo Nacional de Investigaciones Cientificas y Tecnicas in Buenos Aires, Argentina reports on a recent study which found that bamlanivimab was ineffective in treating COVID-19. The author cites his own research which found that, after subcutaneous injection of rhesus macaques, monoclonal antibodies against HIV-1 were found in higher concentrations in lung tissue than 26 other tissue types, suggesting that rapid selection of neutralization-resistant variants is responsible for the lack of benefit of bamlanivimab rather than bio-distribution of the medication.

ACKNOWLEDGEMENTS

CONTRIBUTORS

Ankita Dharmendran
Ashia Hackett
Brad Mott
Hamza Sultan
Kersti Bellardi
Krithika Kumarasan
Renate Meckl
Reza Aghaei
Veronica Graham

EDITORS

Jasmine Rah
John Michael Sherman
Julia Ghering
Maresa Woodfield

SENIOR EDITORS

Allison Hansen
Avery Forrow

CHIEF EDITOR

Jackson Schmidt

ADVISOR

Will Smith