The Daily COVID-19 Literature Surveillance Summary

June 12, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

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

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

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

- Association of Facial Paralysis With mRNA COVID-19 Vaccines: A Disproportionality Analysis Using the World Health Organization Pharmacovigilance Database: A analysis study conducted by doctorate researchers affiliated with Grenoble Alpes University Hospital investigated the World Health Organization pharmacovigilance database on March 9, 2021 which included 133,883 cases of adverse drug reactions. This data included 844 (0.6%) facial paralysis-related events, 749 cases following the Pfizer-BioNTech vaccine and 95 cases following the Moderna vaccine (Table). There was no detected signal of disproportionality of facial paralysis for broad and narrow definitions and no increased incidence of facial paralysis in the mRNA COVID-19 vaccine compared to other viral vaccines (Figure), suggesting that the risk of facial paralysis is likely very low for recipients of the vaccine.

Transmission & Prevention

- Safety Monitoring of the Janssen (Johnson & Johnson) COVID-19 Vaccine - United States, March-April 2021: Researchers on the CDC COVID-19 Response Team discuss the adverse effects of the Janssen COVID-19 vaccine reported to the Vaccine Adverse Events Reporting System (VAERS) and v-safe system. VAERS received 13,725 adverse event reports, including 17 reports of thrombosis with thrombocytopenia syndrome (TTS), 3 of which were due to non-cerebral venous sinus thrombosis (non-CVST) etiology (Table 2). V-safe data reviewed 338,765 people who received the Janssen vaccine, 76% of whom reported at least 1 systemic reaction and 61% had at least 1 injection site reaction (Table 3). These findings describe the safety profile of the Janssen COVID-19 vaccine, with a rare adverse effect of TTS.

- BNT162b2 mRNA Covid-19 Vaccine Effectiveness among Health Care Workers: A letter to the editor from researchers affiliated with Hadassah Hebrew University Medical Center (HHUMC) in Jerusalem investigated efficacy of the BNT162b2 vaccine among HHUMC health care workers. They discusses how 689 out of 6680 (10.3%) workers had been infected with COVID-19 through January 31, 2021, similar to the overall rates in Jerusalem which has the highest COVID-19 incidence in Israel. The trend in weekly incidence of COVID-19 decreased dramatically and remained low after 4 weeks (Table 1) despite the B.1.1.7 variant surge in up to 80% of cases. These findings suggest the effectiveness of the BNT162b2 vaccine among high-incidence areas and against variants.

Adjusting Practice During COVID-19

- Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients: In a research letter, surgery and pathology specialists associated with Johns Hopkins University School of Medicine discuss their study on antibody responses by 2-dose SARS-CoV-2 mRNA vaccination in 658 transplant recipients. At a median of 21 days after dose 1, antibody was detected in 98 participants (15%) with median antibody levels of > 250 U/mL (Roche Elecsys anti–SARS-CoV-2 S enzyme immunoassay) and 9.23 arbitrary units (EUROIMMUN enzyme immunoassay) (Figure). Antibodies were detected in 357 participants (54%) after a median of 29 days after dose 2, with a median antibody level of 142.1 U/mL (Roche) and 6.48 arbitrary units (EUROIMMUN). These results suggest that although a higher antibody response was noted after dose 2, transplant recipients still have a substantial risk of acquiring COVID-19.

R&D: Diagnosis & Treatments

- SARS-CoV-2 RNAemia predicts clinical deterioration and extrapulmonary complications from COVID-19: A prospective cohort study conducted by researchers from Stanford University School of Medicine collected plasma and analyzed quantitative (qPCR) and digital PCR (dPCR) to quantify SARS-CoV-2 RNA from 191 patients who presented to the ED with COVID-19 infection. Twenty-three percent (44/191) of SARS-CoV-2 positive patients had viral RNA detected in plasma by dPCR compared to 1.4% (2/147) by qPCR, indicating than dPCR is more sensitive than qPCR for detection of SARS-CoV-2 RNAemia. Compared with non-RNAemic patients, those with RNAemia were more likely to develop severe disease (odds ratio 6.72 [95% CI, 2.45 – 19.79]) (Figure 2), and require hospital admission (90.9% vs 70.1%, difference = 20.8% [95% CI, 8.1%-33.6%]), and tended toward higher rates of all EPC categories ($p < 0.05$) (Figure 4). These findings demonstrate how RNAemia on presentation could serve as an indicator for early therapies to be administered for the patients at highest risk for severe COVID-19 infection and deterioration.

- Remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials: Researchers from University of Manitoba, Canada conducted a systematic review and meta-analysis on 5 studies examining remdesivir use in COVID-19 treatment (Table 1). Results indicated that a 10-day course of 100 mg remdesivir did not reduce all-cause mortality (RR 0.94, 95% CI 0.82-1.07; I^2=0%) or clinical progression of COVID-19 (RR 0.82, 95% CI 0.40-1.66; I^2=0%) (Figure 3). A 5-day course improved clinical progression (RR 1.05, 95% CI 1.01–1.10), but trial sequential analysis was inconclusive (Figure 4). This suggests that despite use of remdesivir for COVID-19 patients, no significant benefits are seen after 10 days of use in comparison to no treatment/placebo.

TABLE OF CONTENTS

ASSOCIATION OF FACIAL PARALYSIS WITH MRNA COVID-19 VACCINES: A DISPROPORTIONALITY ANALYSIS USING THE WORLD HEALTH ORGANIZATION PHARMACOVIGILANCE DATABASE

Renoud L, Khouri C, Revol B, Lepelley M, Perez J, Roustit M, Cracowski JL.. JAMA Intern Med. 2021 Apr 27. doi: 10.1001/jamainternmed.2021.2219. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

A analysis study conducted by doctorate researchers affiliated with Grenoble Alpes University Hospital investigated the World Health Organization pharmacovigilance database on March 9, 2021 which included 133,883 cases of adverse drug reactions. This data included 844 (0.6%) facial paralysis-related events, 749 cases following the Pfizer-BioNTech vaccine and 95 cases following the Moderna vaccine (Table). There was no detected signal of disproportionality of facial paralysis for broad and narrow definitions and no increased incidence of facial paralysis in the mRNA COVID-19 vaccine compared to other viral vaccines (Figure), suggesting that the risk of facial paralysis is likely very low for recipients of the vaccine.

FIGURES

Table. Characteristics of mRNA COVID-19 Vaccine-Related Facial Paralysis Cases Reported In the WHO Pharmacovigilance Database

Characteristic	No. (%)
Sex	
Female	572 (67.8)
Male	260 (30.8)
Missing data	12 (1.4)
Age, y	
≤11	4 (0.5)
12-17	0
18-44	308 (36.5)
45-64	295 (35.0)
65-74	67 (7.9)
≥75	117 (13.9)
Missing data	53 (6.3)
Most reporting countries	
US	312 (37.0)
United Kingdom	196 (23.2)
Italy	73 (8.6)
France	52 (6.2)
Spain	32 (3.8)
Germany	31 (3.7)
Drug (WHO drug trade name)	
Pfizer BioNTech COVID-19 Vaccine	749 (88.7)
Moderna COVID-19 vaccine	95 (11.3)
Seriousness*	
Yes	473 (56.0)
No	371 (44.0)
Reported facial symptoms (MedDRA preferred terms)	
Paralysis	698 (80.9)
Paresis	168 (19.9)
Spasm	25 (3.0)
Nerve disorder	13 (1.5)
Most associated symptoms (coreported MedDRA preferred terms)	
Headache	113 (13.4)
Hypoesthesia	107 (12.7)
Paresthesia	93 (11.0)
Fatigue	63 (7.5)
Hypoesthesia, oral	40 (4.7)
Evolution	
Recovered	179 (19.8)
Recovered with sequelae	3 (0.3)
Recovering	120 (13.3)
Not recovered	216 (23.9)
Death	1 (0.1)
Unknown	386 (42.7)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; WHO, World Health Organization.

* Fatal, life-threatening, requiring hospitalization, resulting in significant disability/incapacity, and other medically important conditions.

Table. Characteristics of mRNA COVID-19 Vaccine–Related Facial Paralysis Cases Reported in the WHO Pharmacovigilance Database

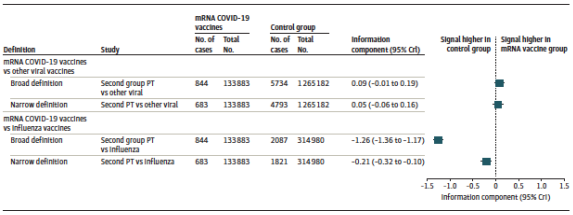


Figure. Forest Plot of the Information Component Values of mRNA COVID-19 Vaccine–Related Facial Paralysis vs All Other Viral Vaccines and Influenza Vaccines Alone

Number of facial paralysis cases (No. of cases) and total number of adverse drug reaction cases (Total No.) reported in theWorld Health Organization pharmacovigilance database are described. Broad definitions of facial paralysis correspond to the following Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs): facial nerve disorder, facial paralysis, facial paresis, facial spasm, oculofacial paralysis, VIIth nerve injury; narrow definition, only to the facial paralysis PT. CrI indicates credible interval.

ADULTS

SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2 P.2 LINEAGE ASSOCIATED WITH REINFECTION CASE, BRAZIL, JUNE-OCTOBER 2020

Resende PC, Bezerra JF, Teixeira Vasconcelos RH, Arantes I, Appolinario L, Mendonça AC, Paixao AC, Duarte AC, Silva T, Rocha AS, Lima ABM, Pauvolid-Corrêa A, Motta FC, Teixeira DLF, de Oliveira Carneiro TF, Neto FPF, Herbster ID, Leite AB, Riediger IN, do Carmo Debur M, Naveca FG, Almeida W, Livorati M, Bello G, Siqueira MM.. Emerg Infect Dis. 2021 Apr 22;27(7). doi: 10.3201/eid2707.210401. Online ahead of print.
Level of Evidence: 5 - Case report

BLUF

A case report conducted by researchers affiliated with multiple medical institutions in Texas and Brazil studied a 37 year old female physician in Rio Grande do Norte who was diagnosed with mild COVID-19 infection on June 17th, 2020 and diagnosed with a second mild COVID-19 infection on October 13th, 2020, confirmed via nasopharyngeal swab and rRT-PCR (Table). The primary infection was determined to be caused by the B.1.1.33 variant, which has been commonly transmitted in Brazil and the second infection was attributed to P.2, a newly emerging variant lineage (Figure 2) that is associated with mutation E484K, allowing it to escape from neutralizing antibodies from previous strains of infection. These findings suggest that since neutralizing antibodies post-COVID-19 infection may not last past 2 months, there is no guarantee that previous exposure to COVID-19 will result in immunity against recurrent infection, thus individuals must stay vigilant in non-pharmacologic protective measures. More studies regarding the immune response and viral and host factors in cases of SARS-CoV-2 reinfection with this emerging variant are needed.

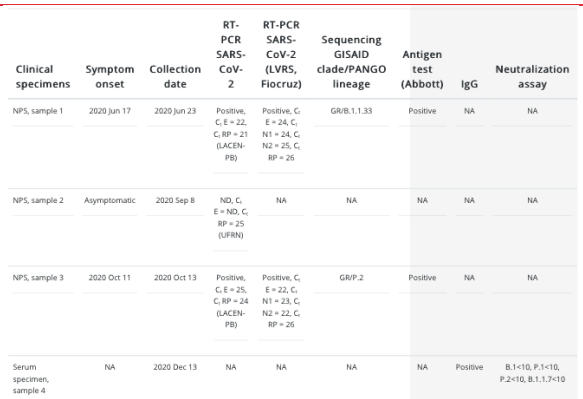
SUMMARY

37 y/o female physician with no past medical history in Rio Grande do Norte, Brazil presented on June 17th with headache, runny nose, diarrhea, and myalgia and was subsequently diagnosed with mild COVID-19. She presented again on October 11 with intense headache, ageusia, anosmia, and fatigue, and two days later a nasopharyngeal swab specimen was collected and confirmed a second mild COVID-19 infection via rRT-PCR.

ABSTRACT

A 37-year-old healthcare worker from the northeastern region of Brazil experienced 2 clinical episodes of coronavirus disease. Infection with severe acute respiratory syndrome coronavirus 2 was confirmed by reverse transcription PCR in samples collected 116 days apart. Whole-genome sequencing revealed that the 2 infections were caused by the most prevalent lineage in Brazil, B.1.1.33, and the emerging lineage P.2. The first infection occurred in June 2020; Bayesian analysis suggests reinfection at some point during September 14-October 11, 2020, a few days before the second episode of coronavirus disease. Of note, P.2 corresponds to an emergent viral lineage in Brazil that contains the mutation E484K in the spike protein. The P.2 lineage was initially detected in the state of Rio de Janeiro, and since then it has been found throughout the country. Our findings suggest not only a reinfection case but also geographic dissemination of the emerging Brazil clade P.2.

FIGURES



Clinical specimens	Symptom onset	Collection date	RT-PCR SARS-CoV-2	RT-PCR SARS-CoV-2 (LVRS, Fiocruz)	Sequencing GISAID clade/PANGO lineage	Antigen test (Abbott)	IgG	Neutralization assay
NPS, sample 1	2020 Jun 17	2020 Jun 23	Positive, C, E = 22, C, RP = 21 (LACEN-PB)	Positive, C, E = 24, C, N1 = 24, C, N2 = 25, C, RP = 26	GR/B.1.1.33	Positive	NA	NA
NPS, sample 2	Asymptomatic	2020 Sep 8	ND, C, E = ND, C, RP = 25 (UFRN)	NA	NA	NA	NA	NA
NPS, sample 3	2020 Oct 11	2020 Oct 13	Positive, C, E = 25, C, RP = 24 (LACEN-PB)	Positive, C, E = 22, C, N1 = 23, C, N2 = 22, C, RP = 26	GR/P.2	Positive	NA	NA
Serum specimen, sample 4	NA	2020 Dec 13	NA	NA	NA	NA	Positive	B.1<10, P.1<10, P.2<10, B.1.1.7<10

Table: Laboratory test results of severe acute respiratory syndrome coronavirus 2 reinfection case-patient, Brazil, June–October 2020*

*CPE, cytopathic effect; Ct, cycle threshold; E, envelope protein; LACEN-PB, Laboratório Central do Estado da Paraíba; LVRS, Respiratory Virus and Measles Laboratory; N1 and N2, portion of nucleoprotein; NA, not applicable; ND, not detected; NPS, nasopharyngeal swab specimen; PANGO, Phylogenetic Assignment of Named Global Outbreak Lineages; RP, human RNase P gene; RT-PCR, reverse transcription PCR; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UFRN, Federal University of Rio Grande do Norte.

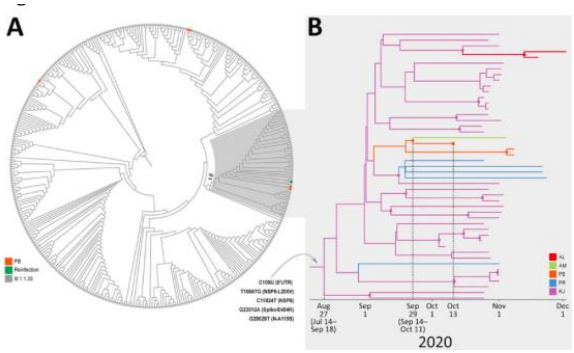


Figure 2. Emergence of the P.2 clade in study of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reinfection case, Brazil. A) Maximum-likelihood phylogenetic tree of B.1.1.28 SARS-CoV-2 whole-genome sequences (29,779-nt) from Brazil (n = 376). Shaded box highlights the P.2 clade (n = 47), and its statistical support (approximate-likelihood ratio test = 1.0) is indicated in the cladogram. Sequences from Paraíba are indicated in orange and sequences from the reinfection case are indicated by green. B) Time-scaled Bayesian maximum clade credibility tree of SARS-CoV-2 whole-genome sequences from the P.2 clade (n = 47). Branches are colored according to the most probable location state of their descendent nodes as indicated. The 5 lineage-defining single-nucleotide polymorphisms are indicated at the maximum clade credibility tree root node. Circular shapes mark nodes with high statistical support (posterior probability>9.0), and a square tip shape indicates the sequence from reinfection case. AL, Alagoas; AM, Amazonas; PB, Paraíba; PR, Parana; RJ, Rio de Janeiro; UTR, untranslated region.

ACE2, TMPRSS2 AND L-SIGN EXPRESSION IN PLACENTAE FROM HIV-POSITIVE PREGNANCIES EXPOSED TO ANTIRETROVIRAL THERAPY-IMPLICATIONS FOR SARS-COV-2 PLACENTAL INFECTION

Kala S, Meteleva K, Serghides L.. J Infect Dis. 2021 Apr 21:jiab166. doi: 10.1093/infdis/jiab166. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Immunology specialists associated with University Health Network, University of Toronto, and Women's College Hospital in Toronto, Ontario examined mRNA levels of 3 SARS-CoV-2 entry receptors: ACE2, TMPRSS2, and L-SIGN in placentae of 45 pregnant women with HIV (WHIV) who underwent protease inhibitor (PI)-based antiretroviral therapy (ART), 17 WHIV on non-PI-based ART, and 43 HIV-uninfected women. Results indicated that ACE2 levels were significantly lower in placentae in the PI-based ART group ($p<0.01$), while L-SIGN levels were higher ($p<0.01$) (Figure 1). Black women had a lower ACE2 expression and higher L-SIGN expression compared to White women ($p<0.01$) (Figure 3). ACE-2 levels were higher in placentae associated with a female fetus compared to male ($p=0.0036$) (Figure 4). These findings suggest that placental infection due to maternal COVID-19 may occur through L-SIGN receptors, since HIV is a potential risk-factor for death from COVID-19.

ABSTRACT

BACKGROUND: SARS-CoV-2 binding receptor ACE2 and the spike protein priming protease TMPRSS2 are co-expressed in human placentae. It is unknown whether their expression is altered in the context of HIV infection and antiretroviral therapy (ART). METHODS: We compared mRNA levels of SARS-CoV-2 cell-entry mediators ACE2, TMPRSS2 and L-SIGN (an alternative entry receptor) by qPCR in 105 placentae: 45 from pregnant women with HIV (WHIV) exposed to protease inhibitor (PI)-based ART, 17 from WHIV on non-PI-based ART, and 43 from HIV-uninfected women. RESULTS: ACE2 levels were lower, while L-SIGN levels were higher in placentae from WHIV on PI-based ART as compared to those on non-PI-based ART and to HIV-uninfected women. TMPRSS2 levels were similar between groups. Black race was significantly associated with lower expression of ACE2 and higher expression of L-SIGN. ACE2 levels were significantly higher in placentae of female fetuses. DISCUSSION: We have identified pregnant women of Black race and WHIV who are on PI-based ART to have relatively lower expression of placental ACE2 than those of White race and HIV-uninfected women. This effect may potentially contribute to altered susceptibility to COVID-19 in these women, either favorably; by reduced viral entry, or detrimentally; by loss of ACE2 protection against hyperinflammation.

FIGURES

Figure 1: Protease inhibitor exposure in pregnancy is associated with lower ACE2 and higher LSIGN expression levels in the placenta.

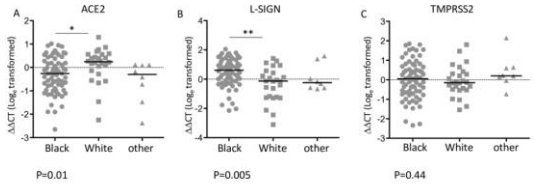


Figure 3: Placental expression levels of ACE2 and L-SIGN differ by race.

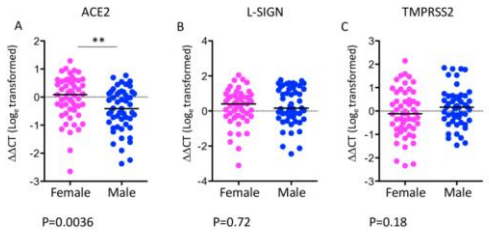


Figure 4: Placental expression levels of ACE2 differ by infant sex.

MULTIFACTORIAL TRAITS OF SARS-COV-2 CELL ENTRY RELATED TO DIVERSE HOST PROTEASES AND PROTEINS

You J, Seok JH, Joo M, Bae JY, Kim JI, Park MS, Kim K.. Biomol Ther (Seoul). 2021 Apr 20. doi: 10.4062/biomolther.2021.048. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A review study conducted by researchers affiliated with Korea University College of Medicine and Pusan National University investigates the biomolecular mechanisms of SARS-CoV-2 infection. They explore the viral entry process including the spike proteins and binding conformation (Figure 1), host proteins and cellular receptors of SARS-CoV-2 with proposed functional capabilities (Table 1), and a proposed mechanism of how viral cell entry occurs (Figure 3). This study suggests that gaining a better understanding of the biomolecular mechanism and viral entry process can provide insight into identifying preventative and therapeutic ways of disrupting virus propagation to control SARS-CoV-2 and other newly emerging viruses.

ABSTRACT

The most effective way to control newly emerging infectious disease, such as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, is to strengthen preventative or therapeutic public health strategies before the infection spreads worldwide. However, global health systems remain at the early stages in anticipating effective therapeutics or vaccines to combat the SARS-CoV-2 pandemic. While maintaining social distance is the most crucial metric to avoid spreading the virus, symptomatic therapy given to patients on the clinical manifestations helps save lives. The molecular properties of SARS-CoV-2 infection have been quickly elucidated, paving the way to therapeutics, vaccine development, and other medical interventions. Despite this progress, the detailed biomolecular mechanism of SARS-CoV-2 infection remains elusive. Given virus invasion of cells is a determining factor for virulence, understanding the viral entry process can be a mainstay in controlling newly emerged viruses. Since viral entry is mediated by selective cellular proteases or proteins associated with receptors, identification and functional analysis of these proteins could provide a way to disrupt virus propagation. This review comprehensively discusses cellular machinery necessary for SARS-CoV-2 infection. Understanding multifactorial traits of the virus entry will provide a substantial guide to facilitate antiviral drug development.

FIGURES

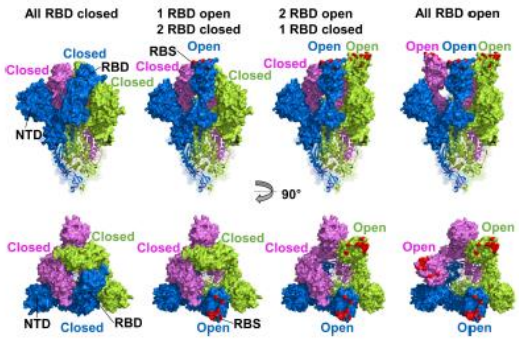


Fig. 1. RBD conformations of SARS-CoV-2 S protein. Cryo-EM structure of SARS-CoV-2 S protein trimer (PDB ID 6VXX and 6VYB) drawn by surface and ribbon diagrams, S1 and S2 domains, respectively. The three protomers are colored blue, pink, and green, and the human ACE2 receptor binding site (RBS) was highlighted by red color, respectively. Side (upper panel) and top (lower panel) views of the S protein structures are divided by open and closed configurations of the RBD. RBS is hidden

and buried in protomers' interspace (RBD closed) and not accessible to the receptor. When the RBD status has opened, RBS is exposed and ready to interact with the ACE2 receptor. The figures were created with PyMOL (https://www.pymol.org/).

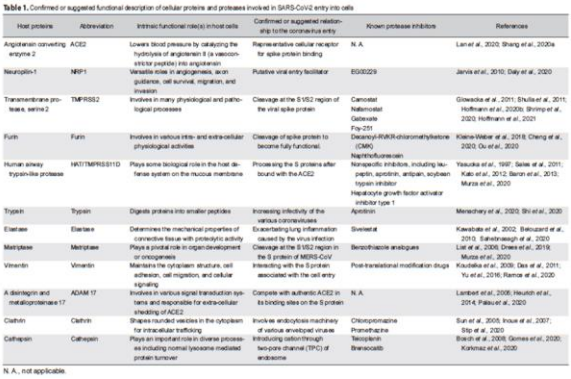


Table 1. Confirmed or suggested functional description of cellular proteins and proteases involved in SARS-CoV-2 entry into cells

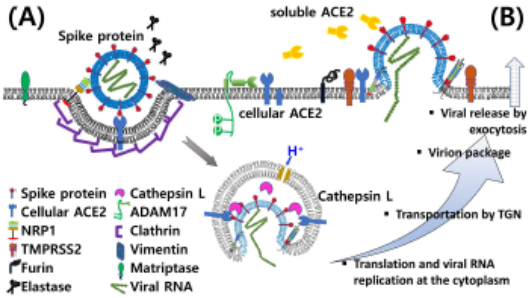


Fig. 3. Schematic diagram of postulated multifactorial SARS-CoV-2 cell entry through endocytosis (A) and direct membrane fusion (B). The SARS-CoV-2 preferentially utilizes ACE2 (angiotensin converting enzyme 2) as a cellular receptor to recognize susceptible cells. Another host factor, NRP1, may facilitate cellular receptors for the virus' cell entry; once the NRP1 interacts with trimerized viral spike proteins, entry machinery induces conformational alteration of spike proteins in the cell membrane. A variety of membranous proteins participate in the endocytic pathway and/or virus-to-cell fusion process is illustrated. Each cellular and viral factor described in the figure is not on a scale. ACE2, angiotensin converting enzyme 2; TMPRSS2, transmembrane protease serine subtype 2; NRP1, neuropilin-1; ADAM17, a disintegrin and metalloproteinase 17; TGN, trans-Golgi network.

TRANSMISSION & PREVENTION

ONE IN EVERY THREE COVID-19 REINFECTIONS RESULT IN HOSPITALIZATION IN THE US

Bastos RH, Blos PK, Rodrigues VD, da S Miranda B, Pasqualotto AC.. Clin Infect Dis. 2021 Apr 26:ciab363. doi: 10.1093/cid/ciab363. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A letter to the editor written by physicians affiliated with the Universidade Federal de Ciencias da Saude de Porto Alegra in Brazil addresses how a recently published article by Sheehan et al. concluded the reinfection rate of COVID-19 was 4.9%, favoring post-COVID-19 "herd immunity" as a mechanism of protecting the public. This letter states that due to the retrospective and multicenter nature of the Sheehan et al. study, protection rates cannot be determined especially since the study arms were not properly balanced. Inclusion of a comparison of clinical findings of reinfection compared to the first COVID-19 episodes would also contribute to the relevance of this study. This letter suggests that while many COVID-19 reinfections were mild, a large proportion of episodes required admission to the hospital (29%), thus large-scale vaccination continues to be the leading effort at gaining herd immunity and protecting the world population against COVID-19.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

SAFETY MONITORING OF THE JANSSEN (JOHNSON & JOHNSON) COVID-19 VACCINE - UNITED STATES, MARCH-APRIL 2021

Shay DK, Gee J, Su JR, Myers TR, Marquez P, Liu R, Zhang B, Licata C, Clark TA, Shimabukuro TT.. MMWR Morb Mortal Wkly Rep. 2021 May 7;70(18):680-684. doi: 10.15585/mmwr.mm7018e2.
Level of Evidence: 3 - 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.)

BLUF

Researchers on the CDC COVID-19 Response Team discuss the adverse effects of the Janssen COVID-19 vaccine reported to the Vaccine Adverse Events Reporting System (VAERS) and v-safe system. VAERS received 13,725 adverse event reports, including 17 reports of thrombosis with thrombocytopenia syndrome (TTS), 3 of which were due to non-cerebral venous sinus thrombosis (non-CVST) etiology (Table 2). V-safe data reviewed 338,765 people who received the Janssen vaccine, 76% of whom reported at least 1 systemic reaction and 61% had at least 1 injection site reaction (Table 3). These findings describe the safety profile of the Janssen COVID-19 vaccine, with a rare adverse effect of TTS.

SUMMARY

- VAERS is a passive surveillance program used to monitor adverse effects after vaccinations. Used by CDC and FDA.
- V-safe is an active surveillance program which works through voluntary, text-based survey reports.
- CDC and FDA received 88 reports of death in people after receiving the Janssen vaccine. Vaccination to death was a median of 2 days (range = 0-23).

ABSTRACT

On February 27, 2021, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for Janssen (Ad.26.COV2.S) COVID-19 vaccine (Janssen Biotech, Inc., a Janssen Pharmaceutical company, Johnson & Johnson) (1). The Janssen COVID-19 vaccine, the third COVID-19 vaccine authorized for use in the United States, uses a replication-incompetent human adenoviral type 26 vector platform* (2) and is administered as a single intramuscular dose, whereas the first two authorized vaccines use an mRNA platform and require 2 doses. On February 28, 2021, the Advisory Committee on Immunization Practices (ACIP) issued interim recommendations for use of Janssen COVID-19 vaccine among persons aged >=18 years (3). During April 13-23, CDC and FDA recommended a pause in use of Janssen vaccine after reports of six cases of cerebral venous sinus thrombosis (CVST) with thrombocytopenia (platelet count <150,000/muL of blood) among Janssen vaccine recipients (4). Similar thrombotic events, primarily among women aged <60 years, have been described in Europe after receipt of the AstraZeneca COVID-19 vaccine, which uses a replication-incompetent chimpanzee adenoviral vector (5-7). The U.S. CVST cases that prompted the pause in Janssen vaccination, as well as subsequently detected CVST cases, are

described elsewhere (8). This report summarizes adverse events among Janssen vaccine recipients, including non-CVST cases of thrombosis with thrombocytopenia syndrome (TTS), reported to the Vaccine Adverse Events Reporting System (VAERS), a passive surveillance system, and through v-safe, an active monitoring system. As of April 21, 2021, 7.98 million doses of the Janssen COVID-19 vaccine had been administered. Among 13,725 VAERS reports reviewed, 97% were classified as nonserious and 3% as serious, including three reports among women of cases of thrombosis in large arteries or veins accompanied by thrombocytopenia during the second week after vaccination. These three cases and the previously detected CVST cases are consistent with 17 cases of TTS, a newly defined condition. Approximately 338,700 Janssen COVID-19 vaccine recipients completed at least one v-safe survey during the week after vaccination; 76% reported a systemic reaction, 61% reported a local reaction, and 34% reported a health impact. Fatigue and pain were commonly reported symptoms in both VAERS and v-safe. The overall safety profile is consistent with preauthorization clinical trials data. Prompt review of U.S. vaccine safety data detected three additional cases of non-CVST TTS, in addition to the previously recognized CVST cases that initiated the pause in use of the Janssen COVID-19 vaccine. Ongoing monitoring of adverse events after COVID-19 vaccination, including vaccination with the Janssen single-dose vaccine, is essential for evaluating the risks and benefits of each vaccine.

FIGURES

TABLE 2. Characteristics of patients with evidence of thrombosis with thrombocytopenia syndrome* after receipt of Janssen COVID-19 vaccine — Vaccine Adverse Events Reporting System, United States, March–April, 2021

Patient	Age group, yrs	Days to symptom onset after vaccination	Initial signs and symptoms	Later signs and symptoms	Lowest platelet count†	Anti-PF4 antibody status§	Location of thrombus/occlusion
A	30–39	10	Headache, left-sided paresis	Headache, left-sided paresis	60,000/μL	Positive	Right carotid artery, left brachial vein, right femoral vein
B	50–59	11	Left leg swelling, bruising	Bilateral lower extremity swelling	15,000/μL	Not available	Left lower extremity deep vein, right femoral artery, left and right iliac arteries
C	30–39	6	Nausea, vomiting, shortness of breath, altered mental status	Nausea, vomiting, shortness of breath, altered mental status	20,000/μL	Not available	Portal vein, superior mesenteric and splenic arteries, pulmonary artery

Abbreviations: PF4 = platelet factor 4; TTS = thrombosis with thrombocytopenia syndrome.
* Patients with evidence of TTS not classified as cerebral venous sinus thrombosis. Brighton Collaboration's draft interim case finding definition for TTS: any patient presenting with acute venous or arterial thrombosis and new onset thrombocytopenia, with no known exposure to heparin or any other underlying condition or explanation for the condition. https://brightoncollaboration.us/wp-content/uploads/2021/04/TTS-Case-Finding-and-Definition-Process.v1.0-1-1.pdf
† Normal range = 150,000–450,000/μL.
§ The heparin:PF4 complex is the antigen in heparin-induced thrombocytopenia, an autoimmune reaction to administration of heparin, an anticoagulant. Anti-PF4 antibodies also have been found in patients with thrombosis who have no known exposure to heparin. Anti-PF4 antibodies have been detected in persons with thrombosis and thrombocytopenia after receipt of Janssen and AstraZeneca COVID-19 vaccines (Scully M, Singh D, Lown R, et al. Pathologic antibodies to platelet factor 4 after ChAdOx1 nCoV-19 vaccination. N Engl J Med 2021. Epub April 16, 2021).

TABLE 2. Characteristics of patients with evidence of thrombosis with thrombocytopenia syndrome* after receipt of Janssen COVID-19 vaccine — Vaccine Adverse Events Reporting System, United States, March–April, 2021

TABLE 3. V-safe enrollees who completed at least one survey and reported a local or systemic reaction or health impact on days 0–7 after receiving Janssen COVID-19 vaccine — United States, March 2–April 12, 2021

Event	Percentage of enrollees reporting reaction or health impact								
	Days 0–7*	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Total enrollees, no. (%) of enrollees reporting†	338,765 (100)	207,483 (61)	259,535 (77)	261,096 (77)	251,676 (74)	238,946 (71)	225,427 (67)	209,958 (62)	202,138 (60)
Reaction reported									
Fatigue	59.1	17.9	56.3	26.2	16.7	12.8	11.0	9.8	9.0
Injection site pain	57.9	31.6	48.5	39.1	30.1	21.5	13.7	7.9	5.0
Headache	52.2	13.0	50.8	19.9	10.8	8.1	7.6	7.5	7.4
Myalgia	47.8	9.0	47.9	19.2	9.7	6.6	5.3	4.6	4.4
Fever	34.7	4.8	37.0	8.3	2.8	1.8	1.4	1.2	1.2
Chills	34.2	5.5	35.7	6.7	2.3	1.4	1.2	1.0	1.0
Joint pain	26.1	3.5	25.3	8.9	4.5	3.3	2.8	2.6	2.4
Nausea	18.7	3.8	15.7	5.4	3.5	2.6	2.1	1.9	1.7
Diarrhea	9.4	0.9	4.3	3.4	2.7	2.1	1.7	1.5	1.5
Swelling	9.3	1.8	4.6	4.6	4.4	3.9	2.9	2.1	1.5
Abdominal pain	7.4	0.9	5.0	2.2	1.6	1.3	1.2	1.1	1.1
Redness	7.4	1.2	2.5	4.0	4.1	3.4	2.4	1.6	1.0
Itching	7.1	1.2	1.8	2.6	3.2	3.0	2.5	1.8	1.4
Vomiting	2.1	0.2	1.6	0.4	0.2	0.2	0.2	0.2	0.2
Rash	1.9	0.2	0.5	0.6	0.6	0.6	0.6	0.6	0.6
Any injection site reaction§	60.7	33.1	50.3	41.8	33.1	24.1	15.9	9.7	6.6
Any systemic reaction¶	76.4	29.8	74.8	44.1	28.9	22.3	19.7	18.2	17.3
Any health impact**	33.9	4.8	33.2	9.7	5.1	3.8	3.3	3.1	3.1
Unable to perform normal daily activities	28.3	3.8	27.7	7.4	4.0	3.0	2.6	2.5	2.5
Unable to work	17.0	1.8	16.3	4.5	2.0	1.3	1.0	1.0	0.9
Needed medical care	1.4	0.1	0.4	0.2	0.3	0.3	0.3	0.4	0.4
Telehealth	0.53	0.02	0.16	0.09	0.11	0.12	0.11	0.12	0.12
Clinic	0.40	0.03	0.05	0.05	0.07	0.10	0.11	0.12	0.12
Emergency visit	0.31	0.04	0.08	0.05	0.06	0.06	0.07	0.07	0.06
Hospitalization	0.04	0.00	0.01	0.01	0.01	0.01	0.01	0.01	0.01

* Proportion of enrollees who reported a reaction or health impact at least once during postvaccination days 0–7.
† Enrollees were able to respond on multiple days.
§ Injection site pain, swelling, redness, or itching.
¶ Fatigue, headache, myalgia, fever, chills, nausea, diarrhea, abdominal pain, vomiting, or rash at injection site.
** A health impact was defined as being unable to perform normal daily activities, being unable to work, or receiving medical care.

TABLE 3. V-safe enrollees who completed at least one survey and reported a local or systemic reaction or health impact on days 0–7 after receiving Janssen COVID-19 vaccine — United States, March 2–April 12, 2021

PREVENTION IN THE HOSPITAL

SARS-COV-2 INFECTION IN ASYMPTOMATIC VACCINATED-HEALTHCARE WORKERS

Damiani V, Mandatori D, De Fabritiis S, Bibbò S, Ferrante R, Di Giuseppe F, Ruggieri AG, Di Camillo C, Buccolini C, Pizzi D, Fazii P, Stuppia L, De Laurenzi V.. Infect Control Hosp Epidemiol. 2021 May 10:1-6. doi: 10.1017/ice.2021.224. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A research brief by researchers affiliated with G. D'Annunzio University of Chieti-Pescara and Spirito Hospital of Pescara, Italy discusses 7 health care workers (HCWs) who tested positive for SARS-CoV-2 after receiving both doses of the BNT162b2 vaccine between January - March 2021, all of whom were asymptomatic within 36 days of the second vaccination (Table 1). This highlights that despite vaccination, HCWs should maintain precautions to avoid spread of infection, although larger studies are still necessary.

SUMMARY

- All cases were confirmed with genetic sequencing or PCR testing and reasonably belong to the B.1.1.7 lineage

FIGURES

ID	Date of Vaccination		Date of Testing		Results of TaqPath Positive Test			Lineage	Detection Method	Mutations		
	First Dose	Second Dose	Positive	Negative	ORF 1ab	N	S			E484K	N501Y	Δ69/70
HCW 1	13/01/21	-	19/01/21	20/01/21	28.949	29.201	ND	B.1.1.7	NGS	No	Yes	Yes
HCW 2	05/01/21	28/01/21	01/02/21	02/02/21	31.656	31.720	ND	B.1.1.7	NGS	No	Yes	Yes
HCW 3	04/01/21	26/01/21	01/03/21	12/03/21	18.318	17.463	ND	B.1.1.7	NGS	No	Yes	Yes
HCW 4	10/01/21	31/01/21	06/02/21	17/02/21	35.823	34.976	ND	B.1.1.7	Allplex	No	Yes	Yes
HCW 5	13/01/21	03/02/21	06/02/21	17/02/21	36.236	36.911	ND	B.1.1.7	Allplex	No	Yes	Yes
HCW 6	03/01/21	24/01/21	16/02/21	17/02/21	31.645	31.213	ND	B.1.1.7	Allplex	No	Yes	Yes
HCW 7	05/01/21	26/01/21	02/03/21	13/03/21	15.894	15.866	ND	B.1.1.7	Allplex	No	Yes	Yes

Table 1. Vaccination status, qRT-PCR results and NGS summary.
SARS-CoV-2 qRT-PCR results are shown as ct values. ND denotes not determined ct value.
NGS: indicates that next generation sequencing of the entire viral genome was performed
Allplex: indicates that the presence of Δ69/70, N501Y and E484K were evaluated using AllplexTM SARS-CoV-2 Variants I Assay

BNT162B2 MRNA COVID-19 VACCINE EFFECTIVENESS AMONG HEALTH CARE WORKERS

Benenson S, Oster Y, Cohen MJ, Nir-Paz R.. N Engl J Med. 2021 May 6;384(18):1775-1777. doi: 10.1056/NEJMc2101951. Epub 2021 Mar 23.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A letter to the editor from researchers affiliated with Hadassah Hebrew University Medical Center (HHUMC) in Jerusalem investigated efficacy of the BNT162b2 vaccine among HHUMC health care workers. They discusses how 689 out of 6680 (10.3%) workers had been infected with COVID-19 through January 31, 2021, similar to the overall rates in Jerusalem which has the highest COVID-19 incidence in Israel. The trend in weekly incidence of COVID-19 decreased dramatically and remained low after 4 weeks (Table 1) despite the B.1.1.7 variant surge in up to 80% of cases. These findings suggest the effectiveness of the BNT162b2 vaccine among high-incidence areas and against variants.

SUMMARY

- Two doses of the Pfizer-BioNTech vaccine were administered beginning December 20, 2020 and within 8 weeks, 5297 of 6252 workers (84.7%) received the first dose and 98.9% received the second dose.

FIGURES

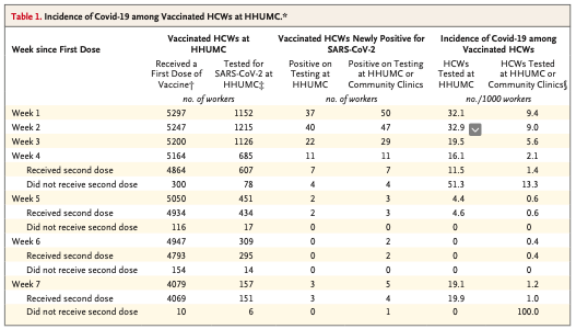


Table 1. Incidence of Covid-19 among Vaccinated HCWs at HHUMC.*

Week since First Dose	Vaccinated HCWs at HHUMC		Vaccinated HCWs Newly Positive for SARS-CoV-2		Incidence of Covid-19 among Vaccinated HCWs	
	Received a First Dose of Vaccine†	Tested for SARS-CoV-2 at HHUMC‡	Positive on Testing at HHUMC	Positive on Testing at HHUMC or Community Clinics	HCWs Tested at HHUMC	HCWs Tested at HHUMC or Community Clinics§
	no. of workers		*no. of workers*		*no./1000 workers*	
Week 1	5297	1152	37	50	32.1	9.4
Week 2	5247	1215	40	47	32.9	9.0
Week 3	5200	1126	22	29	19.5	5.6
Week 4	5164	685	11	11	16.1	2.1
Received second dose	4864	607	7	7	11.5	1.4
Did not receive second dose	300	78	4	4	51.3	13.3
Week 5	5050	451	2	3	4.4	0.6
Received second dose	4934	434	2	3	4.6	0.6
Did not receive second dose	116	17	0	0	0	0
Week 6	4947	309	0	2	0	0.4
Received second dose	4793	295	0	2	0	0.4
Did not receive second dose	154	14	0	0	0	0
Week 7	4079	157	3	5	19.1	1.2
Received second dose	4069	151	3	4	19.9	1.0
Did not receive second dose	10	6	0	1	0	100.0

Table 1. Incidence of Covid-19 among Vaccinated HCWs at HHUMC.*

* Health care workers (HCWs) were tested at the Hadassah Hebrew University Medical Center (HHUMC), community clinics, or both loca- tions. Positive results on testing at community clinics were reported by the local office of the Israeli Ministry of Health to the Hadassah Infection Prevention and Control Unit.

† At each week since the first dose, the number of HCWs represents the number at risk (i.e., those who were not infected during the previous week). ‡ HCWs who were tested more than once per week were counted only once.

§ The denominator used to calculate incidence among the vaccinated HCWs tested at HHUMC or community clinics was the number of

HCWs who received a first dose of vaccine. Systematic testing of all vaccinated HCWs was not performed; therefore, some positive cases may have been missed.

MEDICAL SUBSPECIALTIES

ENDOCRINOLOGY

COVID-19 AND THE PITUITARY

Frara S, Allora A, Castellino L, di Filippo L, Loli P, Giustina A.. Pituitary. 2021 May 3. doi: 10.1007/s11102-021-01148-1. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review by endocrine specialists from San Raffaele Vita-Salute University and IRCC Hospital, Italy found that diabetes mellitus, obesity, and vertebral fractures are the most common endocrine manifestations in COVID-19 patients, and ACE2 mRNA expression in the pituitary, pituitary apoplexy, and hyponatremia are the most common pituitary manifestations. Research has yet to be done on the effect of COVID-19 on pituitary conditions such as acromegaly, Cushing's Syndrome, hypopituitarism, and adrenal insufficiency but these may be risk factors for severe COVID-19.

ABSTRACT

BACKGROUND: Despite COVID-19 being identified as severe respiratory viral infection, progressively many relevant endocrine manifestations have been reported greatly contributing to the severity of the clinical presentation. Systemic involvement in COVID-19 is due to the ubiquitous expression of angiotensin-converting enzyme 2 (ACE2) receptor, responsible for the entry in the cells of SARS-CoV-2, Several reports in humans and animal models showed a significant ACE2 mRNA expression in hypothalamus and pituitary cells. Moreover, higher mortality and poorer outcomes have been widely described in COVID-19 patients with obesity, diabetes and vertebral fractures, which are all highly prevalent in subjects with pituitary dysfunctions. AIM: To review the main endocrine manifestations of COVID-19 with their possible implications for pituitary diseases, the possible direct and indirect involvement of the pituitary gland in COVID-19, the impact of COVID-19 on the management of established pituitary diseases which can be already at increased risk for worse outcomes and on neurosurgical activities as well as vaccination. CONCLUSIONS: Our review underlines that there could be a specific involvement of the pituitary gland which fits into a progressively shaping endocrine phenotype of COVID-19. Moreover, the care for pituitary diseases need to continue despite the restrictions due to the emergency. Several pituitary diseases, such as hypopituitarism and Cushing disease, or due to frequent comorbidities such as diabetes may be a risk factor for severe COVID-19 in affected patients. There is the urgent need to collect in international multicentric efforts data on all these aspects of the pituitary involvement in the pandemic in order to issue evidence driven recommendations for the management of pituitary patients in the persistent COVID-19 emergency.

SURGICAL SUBSPECIALTIES

TRANSPLANT SURGERY

ANTIBODY RESPONSE TO 2-DOSE SARS-COV-2 MRNA VACCINE SERIES IN SOLID ORGAN TRANSPLANT RECIPIENTS

Boyarsky BJ, Werbel WA, Avery RK, Tobian AAR, Massie AB, Segev DL, Garonzik-Wang JM.. JAMA. 2021 May 5. doi: 10.1001/jama.2021.7489. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

In a research letter, surgery and pathology specialists associated with Johns Hopkins University School of Medicine discuss their study on antibody responses by 2-dose SARS-CoV-2 mRNA vaccination in 658 transplant recipients. At a median of 21 days after dose 1, antibody was detected in 98 participants (15%) with median antibody levels of > 250 U/mL (Roche Elecsys anti–SARS-CoV-2 S enzyme immunoassay) and 9.23 arbitrary units (EUROIMMUN enzyme immunoassay) (Figure). Antibodies were detected in 357 participants (54%) after a median of 29 days after dose 2, with a median antibody level of 142.1 U/mL

(Roche) and 6.48 arbitrary units (EUROIMMUN). These results suggest that although a higher antibody response was noted after dose 2, transplant recipients still have a substantial risk of acquiring COVID-19.

SUMMARY

- Use of antimetabolite immunosuppression was associated with poor antibody responses.

FIGURES

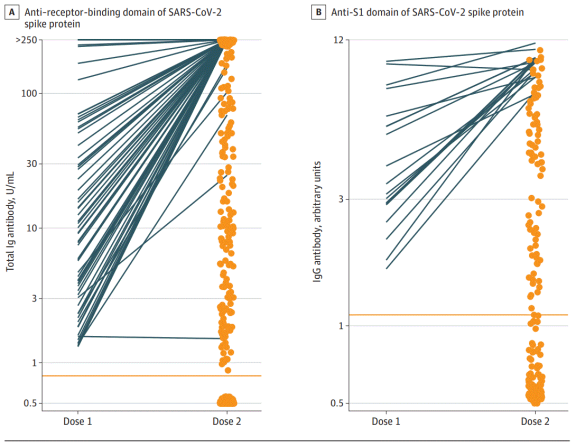


Figure. Antibody Levels of Study Participants After 2-Dose Series of SARS-CoV-2 mRNA Vaccine

SARS-COV-2 RNAEMIA PREDICTS CLINICAL DETERIORATION AND EXTRAPULMONARY COMPLICATIONS FROM COVID-19

Ram-Mohan N, Kim D, Zudock EJ, Hashemi MM, Tjandra KC, Rogers AJ, Blish CA, Nadeau KC, Newberry JA, Quinn JV, O'Hara R, Ashley E, Nguyen H, Jiang L, Hung P; Stanford COVID-19 Biobank Study Group, Blomkalns AL, Yang S.. Clin Infect Dis. 2021 May 5:ciab394. doi: 10.1093/cid/ciab394. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A prospective cohort study conducted by researchers from Stanford University School of Medicine collected plasma and analyzed quantitative (qPCR) and digital PCR (dPCR) to quantify SARS-CoV-2 RNA from 191 patients who presented to the ED with COVID-19 infection. Twenty-three percent (44/191) of SARS-CoV-2 positive patients had viral RNA detected in plasma by dPCR compared to 1.4% (2/147) by qPCR, indicating than dPCR is more sensitive than qPCR for detection of SARS-CoV-2 RNAemia. Compared with non-RNAemic patients, those with RNAemia were more likely to develop severe disease (odds ratio 6.72 [95% CI, 2.45 – 19.79]) (Figure 2), and require hospital admission (90.9% vs 70.1%, difference = 20.8% [95% CI, 8.1%-33.6%]), and tended toward higher rates of all EPC categories ($p < 0.05$) (Figure 4). These findings demonstrate how RNAemia on presentation could serve as an indicator for early therapies to be administered for the patients at highest risk for severe COVID-19 infection and deterioration.

ABSTRACT

BACKGROUND: The determinants of COVID-19 disease severity and extrapulmonary complications (EPCs) are poorly understood. We characterized relationships between SARS-CoV-2 RNAemia and disease severity, clinical deterioration, and specific EPCs. METHODS: We used quantitative (qPCR) and digital (dPCR) PCR to quantify SARS-CoV-2 RNA from plasma in 191 patients presenting to the Emergency Department (ED) with COVID-19. We recorded patient symptoms, laboratory markers, and clinical outcomes, with a focus on oxygen requirements over time. We collected longitudinal plasma samples from a subset of patients. We characterized the role of RNAemia in predicting clinical severity and EPCs using elastic net regression. RESULTS: 23.0% (44/191) of SARS-CoV-2 positive patients had viral RNA detected in plasma by dPCR, compared to 1.4% (2/147) by qPCR. Most patients with serial measurements had undetectable RNAemia within 10 days of symptom onset, reached maximum clinical severity within 16 days, and symptom resolution within 33 days. Initially RNAaemic patients were more likely to manifest severe disease (OR 6.72 [95% CI, 2.45 - 19.79]), worsening of disease severity (OR 2.43 [95% CI, 1.07 - 5.38]), and EPCs (OR 2.81 [95% CI, 1.26 - 6.36]). RNA load correlated with maximum severity (r = 0.47 [95% CI, 0.20 - 0.67]). CONCLUSIONS: dPCR is more sensitive than qPCR for the detection of SARS-CoV-2 RNAemia, which is a robust predictor of eventual COVID-19 severity and oxygen requirements, as well as EPCs. Since many COVID-19 therapies are initiated on the basis of oxygen requirements, RNAemia on presentation might serve to direct early initiation of appropriate therapies for the patients most likely to deteriorate.

FIGURES

Figure 2

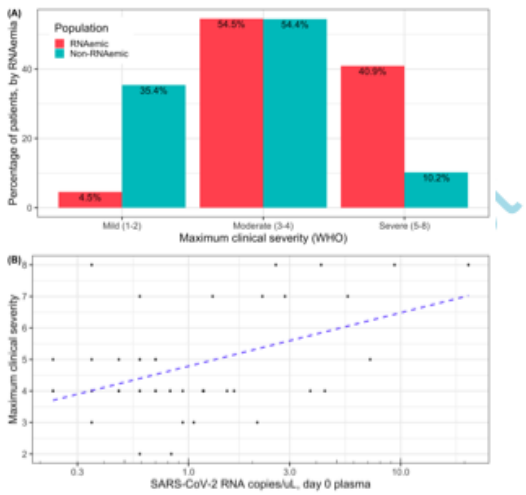


Figure 2. SARS-CoV-2 RNAemia and clinical severity. (A). RNAemic patients had higher mean maximum WHO scores (4.80) than non-RNAemic patients (3.24, difference = 1.56 [95% CI of difference, 1.00 – 2.11]). 40.9% of RNAemic patients developed severe disease, compared to 10.2% of non-RNAemic patients (difference = 30.7% [95% CI of difference, 13.9% - 47.5%]). 4.5% of initially RNAemic patients had mild disease, compared to 35.4% of non-RNAemic patients (difference = 30.8% [95% CI of difference, 19.5% - 42.2%]). Equivalent proportions of both RNAemic (54.5%) and non-RNAemic (54.4%) patients had disease of moderate severity. (B). Among patients with detectable RNAemia at time of enrollment (n=44), patients with higher plasma RNA concentrations manifested more severe disease (r = 0.47 [95% CI, 0.20 – 0.67]). RNA concentrations in RNAemic patients were distributed approximately log-normally, so were log-scaled for depiction and calculation of correlation. Dashed blue line shows linear correlation between log-scaled plasma RNA concentration and maximum clinical severity.

Figure 4

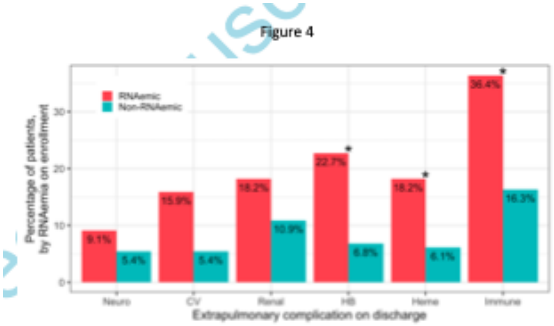


Figure 4. Presence of extrapulmonary complications, by RNAemia. 56.8% (25/44) of patients RNAemic on enrollment patients developed one or more extrapulmonary complications by hospital discharge, compared to 30.6% (45/147) of non-RNAemic patients (difference in proportions = 26.2% [95% CI, 8.3% - 44.1%]). RNAemic patients tended toward higher rates of extrapulmonary complications across systems, though only differences in rates of hepatobiliary (HB), hematologic, and immunologic complications were individually statistically significant at $p < 0.05$ (chi-squared tests for equality of proportions with continuity correction). CV = cardiovascular, HB = hepatobiliary.

DEVELOPMENTS IN TREATMENTS

REMDESIVIR FOR CORONAVIRUS DISEASE 2019 (COVID-19): A SYSTEMATIC REVIEW WITH META-ANALYSIS AND TRIAL SEQUENTIAL ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Okoli GN, Rabbani R, Copstein L, Al-Juboori A, Askin N, Abou-Setta AM.. Infect Dis (Lond). 2021 May 11:1-9. doi: 10.1080/23744235.2021.1923799. Online ahead of print.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

Researchers from University of Manitoba, Canada conducted a systematic review and meta-analysis on 5 studies examining remdesivir use in COVID-19 treatment (Table 1). Results indicated that a 10-day course of 100 mg remdesivir did not reduce all-cause mortality (RR 0.94, 95% CI 0.82-1.07; I^2=0%) or clinical progression of COVID-19 (RR 0.82, 95% CI 0.40-1.66; I^2=0%) (Figure 3). A 5-day course improved clinical progression (RR 1.05, 95% CI 1.01–1.10), but trial sequential analysis was inconclusive (Figure 4). This suggests that despite use of remdesivir for COVID-19 patients, no significant benefits are seen after 10 days of use in comparison to no treatment/placebo.

ABSTRACT

BACKGROUND: In view of many unanswered clinical questions regarding treatment of COVID-19 with remdesivir, we systematically identified, critically appraised and summarized the findings from randomized controlled trials (RCTs) of remdesivir for COVID-19. METHODS: We searched relevant databases/websites (up to September 2020) and selected English-language RCT publications of remdesivir for COVID-19. We conducted meta-analysis using an inverse variance, random-effects model in addition to trial sequential analysis (TSA) for the efficacy outcomes: all-cause mortality, viral burden and clinical progression. Safety outcomes were diarrhoea, nausea, and vomiting. We calculated the relative risk (RR) and 95% confidence interval (CI) for all outcomes. Statistical heterogeneity was calculated using the I2 statistic. RESULTS: We included five RCTs (7540 participants) from 7237 citations. Most (80%) were of an unclear to high risk of bias. There was no evidence of a significant improvement with remdesivir (100 mg, 10 days) regarding all-cause mortality (RR 0.94, CI 0.82-1.07; I2 = 0%; 4 RCTs; 7143 patients), clinical progression (RR 1.08, CI 0.99-1.18; I2 = 70.4%; 3 RCTs; 1692 patients), or diarrhoea (RR 0.82, CI 0.40-1.66; I2 = 0%; 2 RCTs; 630 patients). Nausea occurred more often with remdesivir (RR 2.77, CI 1.28-6.03; I2 = 0%; 2 RCTs; 630 patients). TSA showed that the required information size was not reached for firm conclusions to be drawn. CONCLUSIONS AND RELEVANCE: There is insufficient evidence to support the use of remdesivir for treatment of COVID-19. More high-quality RCTs are needed for a stronger evidence. Until then, remdesivir should remain an experimental drug for COVID-19.

FIGURES

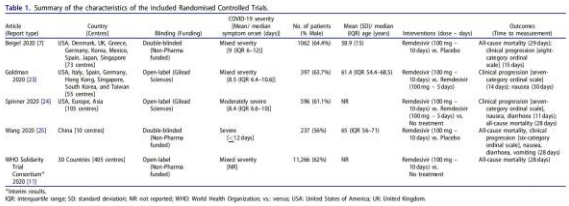


Table 1. Summary of the characteristics of the included Randomised Controlled Trials.

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Article (Report type)	Country (Centres)	Blinding (Funding)	COVID-19 severity (Mean/ median symptom onset (days))	No. of patients (% Male)	Mean (SD)/ median (IQR) age (years)	Interventions (dose – days)	Outcomes (Time to measurement)
Beigel 2020 [7]	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore (73 centres)	Double-blinded (Non-Pharma funded)	Mixed severity (9 (IQR 6–12))	1062 (64.4%)	58.9 (15)	Remdesivir (100 mg – 10 days) vs. Placebo	All-cause mortality (29 days); clinical progression (eight-category ordinal scale) (15 days)
Goldman 2020 [23]	USA, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan (55 centres)	Open-label (Gilead Sciences)	Mixed severity (8.5 (IQR 6.4–10.6))	397 (63.7%)	61.4 (IQR 54.4–68.5)	Remdesivir (100 mg – 10 days) vs. Remdesivir (100 mg – 5 days)	Clinical progression (seven-category ordinal scale) (14 days); nausea (30 days)
Spinner 2020 [24]	USA, Europe, Asia (105 centres)	Open-label (Gilead Sciences)	Moderately severe (8.4 (IQR 6.6–10))	596 (61.1%)	NR	Remdesivir (100 mg – 10 days) vs. Remdesivir (100 mg – 5 days) vs. No treatment	Clinical progression (seven-category ordinal scale), nausea, diarrhoea (11 days); all-cause mortality (28 days)
Wang 2020 [25]	China (10 centres)	Double-blinded (Non-Pharma funded)	Severe (< 12 days)	237 (56%)	65 (IQR 56–71)	Remdesivir (100 mg – 10 days) vs. Placebo	All-cause mortality, clinical progression (six-category ordinal scale), nausea, diarrhoea, vomiting (28 days)
WHO Solidarity Trial Consortium* 2020 [11]	30 Countries (405 centres)	Open-label (Non-Pharma funded)	Mixed severity (NR)	11,266 (62%)	NR	Remdesivir (100 mg – 10 days) vs. No treatment	All-cause mortality (28 days)

*Interim results.
IQR: interquartile range; SD: standard deviation; NR: not reported; WHO: World Health Organization; vs.: versus; USA: United States of America; UK: United Kingdom.

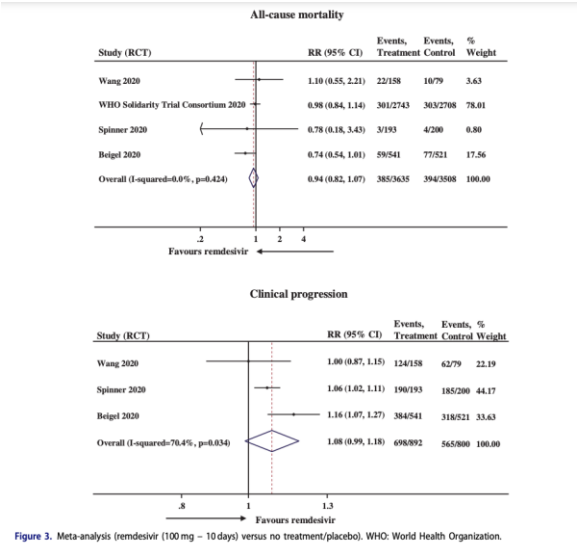

Figure 3. Meta-analysis (remdesivir (100 mg – 10 days) versus no treatment/placebo). WHO: World Health Organization.

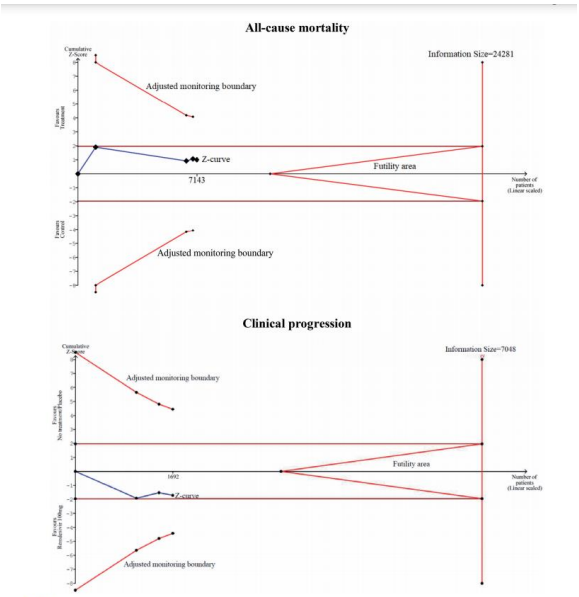

Figure 4. Trial sequential analysis.

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