

The Daily COVID-19 Literature Surveillance Summary

March 26, 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

Epidemiology

- [Children may also experience long-term effects of COVID-19 infections.](#) A letter to the editor conducted by researchers affiliated with the Department of Pediatrics at La Paz University Hospital in Madrid, Spain outlines their telephone consults performed from March to June 2020 for follow-up of children with COVID-19 infection, 8 of whom had long duration symptoms including low-grade fever, intense asthenia, and severe headache, requiring multiple ED visits but no hospital admission. Confirmation of SARS-CoV-2 infection was only confirmed in 2 out of 8 patients, however, delays in RT-PCR tests and shortages could cause under-diagnosis of COVID-19 and the stressful nature of the COVID-19 pandemic could also exacerbate these clinical symptoms. Though there is not a plethora of evidence, there is growing data suggesting the susceptibility of children to the long-term effects of COVID-19 infection.

Transmission & Prevention

- [COVID vaccines help reduce infections in vaccinated individuals at University of Texas Southwestern Medical Center.](#) A chief quality officer from the University of Texas Southwestern Medical Center (UTSW) reports findings in the first month of their COVID-19 vaccination program (December 15, 2020 to January 28, 2021) in which 59% of 23,234 eligible employees received at least 1 dose of either Pfizer or Moderna mRNA vaccines. They found most new infections (234 of 8969) occurred in non-vaccinated employees, with few (4 of 8121) in the fully vaccinated population ($p<0.01$). Authors suggest that mRNA vaccinations tremendously impact the rate of new SARS-CoV-2 infections and emphasize the importance of addressing vaccine hesitancy.
- [The Oxford-AstraZeneca COVID vaccine requires lower cost of manufacturing and storage but has potential links with rare adverse effects that required further investigation.](#) A team of journalists writing for Nature in March 2021 review updated data regarding the Oxford-AstraZeneca vaccine. Manufacturers reported overall efficacy of 76% with similar efficacy against variants and lower cost of manufacturing and storage compared to other vaccines. However, due to potential links between the vaccine and rare clotting conditions the authors suggest that more data analysis will be required before the vaccine is approved for use in the United States.
- [COVID vaccines are effective at preventing COVID-19 infections.](#) Researchers associated with UCLA and UCSD studied the incidence of COVID-19 in 36,659 vaccinated healthcare workers and found that 379 workers tested positive for SARS-CoV-2 through repeated nasal PCR testing, 71% of whom tested positive within 2 weeks after receiving the first dose. 37 workers tested positive after receiving the second dose, 22 of whom tested positive within the first week. Overall, the absolute risk of testing positive for SARS-CoV-2 after vaccination was 1.19% at UCSD and 0.97% at UCLA health systems, indicating that both doses or even one dose of the COVID-19 vaccine is indeed effective at preventing SARS-CoV-2 infection.
- [Patients with past SARS-CoV-2 infection have higher levels of antibodies after vaccination.](#) An immunology research team from Children's Mercy Kansas City used a multiplex bead-binding assay to assess antibody levels at baseline and 3 weeks after the first dose of the BNT162b2 (Pfizer) SARS-CoV-2 mRNA vaccine in 36 health care workers with laboratory-confirmed SARS-CoV-2 infection 30 to 60 days before they received the vaccine and 152 health care workers without past SARS-CoV-2 infection. After the first vaccine dose, they found that patients with past SARS-CoV-2 infection or seropositive status had higher levels of antibody to SARS-CoV-2 antigens as well as higher levels of neutralizing antibodies. Authors suggest further investigation into the duration of antibody responses and protective immunity measures is needed in order to confidently recommend an effective immunization program.

Management

- [Solid-organ transplant patients may have a reduced immune response to SARS-CoV-2 antigens.](#) A serological study conducted by researchers affiliated with multiple medical institutions in Spain and France analyzed 44 patients who were hospitalized with moderate/severe COVID-19 disease (28 solid-organ transplant (SOT) recipients and 16 immunocompetent (IC) patients), and found that SOT patients had lower IgG seroconversion rates (77% vs. 100%, $p=0.044$) and decreased reactive cytokine-producing T-cell frequencies to 4 main immunogenic SARS-CoV-2 antigens, indicating that SOT patients were delayed in achieving a strong immune response compared to immunocompetent patients. Worsening clinical outcomes were associated with a lesser SARS-CoV-2 reactive IL-2 producing T-cell response. Despite an initial delay in response, the serological and functional T-cell immune response were observed to be comparable to immunocompetent patients following COVID-19 infection, confirming the need for active immunization especially in SOT patients.

TABLE OF CONTENTS

DISCLAIMER.....	2
NOW LIVE!.....	2
LEVEL OF EVIDENCE.....	3
EXECUTIVE SUMMARY.....	4
TABLE OF CONTENTS.....	5
EPIDEMIOLOGY.....	6
SYMPTOMS AND CLINICAL PRESENTATION	6
Hypersensitivity reaction to Hyaluronic Acid Dermal filler following novel Coronavirus infection - a case report	6
<i>Pediatrics</i>	6
Long-term symptoms of COVID-19 in children.....	6
TRANSMISSION & PREVENTION.....	8
Early Evidence of the Effect of SARS-CoV-2 Vaccine at One Medical Center.....	8
Transmission dynamics and timing of key events for SARS-CoV-2 infection in healthcare workers.....	8
What scientists do and don't know about the Oxford-AstraZeneca COVID vaccine	9
DEVELOPMENTS IN TRANSMISSION & PREVENTION	9
SARS-CoV-2 Infection after Vaccination in Health Care Workers in California	9
Antibody Responses after a Single Dose of SARS-CoV-2 mRNA Vaccine	10
PREVENTION IN THE COMMUNITY	12
RT-PCR Screening Tests for SARS-CoV-2 with Saliva Samples in Asymptomatic People: Strategy to Maintain Social and Economic Activities while Reducing the Risk of Spreading the Virus	12
MANAGEMENT	13
ACUTE CARE	13
<i>Critical Care</i>	13
Interstitial Lung Disease Following COVID-19.....	13
SURGICAL SUBSPECIALTIES	14
<i>Transplant Surgery</i>	14
SARS-CoV-2-specific serological and functional T-cell Immune responses during acute and early COVID-19 convalescence in Solid Organ Transplant patients	14
R&D: DIAGNOSIS & TREATMENTS.....	17
DEVELOPMENTS IN TREATMENTS	17
Vitamin D3 to Treat COVID-19: Different Disease, Same Answer.....	17
ACKNOWLEDGEMENTS	18

EPIDEMIOLOGY

SYMPTOMS AND CLINICAL PRESENTATION

HYPERSensitivity REACTION TO HYALURONIC ACID DERMAL FILLER FOLLOWING NOVEL CORONAVIRUS INFECTION - A CASE REPORT

Rowland-Warmann MJ.. J Cosmet Dermatol. 2021 Mar 18. doi: 10.1111/jocd.14074. Online ahead of print.

Level of Evidence: 5 - Case Report

BLUF

A case report by a dentist associated with Sinclair Pharma documents a delayed hypersensitivity reaction to nasal hyaluronic acid dermal filler in a 22-year-old female patient with COVID-19. Notably there was a 5-month time difference between the initial injection and testing positive for COVID-19 and symptoms included edema, erythema and tenderness which resolved in six days. The implication being that much like other flu-like illnesses, SARS-CoV-2 can appear to trigger an immunogenic reaction in those receiving hyaluronic acid dermal fillers and the risks must be relayed to the patients especially during this pandemic.

SUMMARY

- Risk factors for development of immunogenic reactions in those receiving hyaluronic dermal fillers includes: systemic infection, history of allergy, repeat treatment in same location (likely inducing trauma and free radical production)
- Management of immunogenic reaction: if mild, no treatment may be necessary. However, if symptoms persist, steroids can be used at 30-60mg daily with a 5-day taper. Notably, dermal filler swelling caused by SARS-CoV-2 has been treated with lisinopril 10mg for 3-5 days

ABSTRACT

The incidence of hypersensitivity reactions to hyaluronic acid dermal fillers is between 0.3 and 4.25%, mediated by T-lymphocytes. Flu-like illness can trigger immunogenic reactions at the site of filler placement. Cases of SARS-CoV-2 are significant, and pose a possible risk of inducing hypersensitivity. This case report is of a delayed type hypersensitivity after hyaluronic acid dermal filler treatment of the nose and subsequent infection with SARS-CoV-2. Risk factors for the development of such symptoms were identified as the presence of hyaluronic acid combined with flu-like illness and repeated treatment of one area. The case resolved without intervention. Clinicians should be mindful of the risk posed by the interaction of hyaluronic acid dermal filler with SARS-CoV-2 in light of the pandemic.

PEDIATRICS

LONG-TERM SYMPTOMS OF COVID-19 IN CHILDREN

Nogueira López J, Grasa C, Calvo C, García López-Hortelano M.. Acta Paediatr. 2021 Mar 20. doi: 10.1111/apa.15849. Online ahead of print.

Level of Evidence: 4 - Case-series

BLUF

A letter to the editor conducted by researchers affiliated with the Department of Pediatrics at La Paz University Hospital in Madrid, Spain outlines their telephone consults performed from March to June 2020 for follow-up of children with COVID-19 infection, 8 of whom had long duration symptoms including low-grade fever, intense asthenia, and severe headache, requiring multiple ED visits but no hospital admission (Table 1). Confirmation of SARS-CoV-2 infection was only confirmed in 2 out of 8 patients, however, delays in RT-PCR tests and shortages could cause under-diagnosis of COVID-19 and the stressful nature of the COVID-19 pandemic could also exacerbate these clinical symptoms. Though there is not a plethora of evidence, there is growing data suggesting the susceptibility of children to the long-term effects of COVID-19 infection.

ABSTRACT

We have read with great interest the article by Jonas F. Ludvigsson¹ reporting 5 cases of children with prolonged symptoms after being diagnosed of mild SARS-CoV-2 infection. There are many articles reviewing the long-term manifestations of COVID-19 in adult patients², but paediatric reports are still scarce.

FIGURES

	Constitutional / Long COVID-19 syndrome
Number of patients; n (%)	8 (11)
Gender; n (%)	
Male	4 (50)
Female	4 (50)
Age (months); median (IQR)	142 (117,8 - 166,8)
Comorbidities; n (%)	1 (12,5)
COVID-19 suspected or confirmed contact; n (%)	7 (87,5)
COVID-19 confirmation; n (%)	2 (25)
Days of symptoms before RT-PCR; median (IQR)	15,5 (4,3 - 26,3)
Hospital admission; n (%)	0
Blood test; median (IQR)	
Lymphocytes (cells/mm ³)	2355 (2057,8 - 2790)
D-Dimer (ng/mL)	290 (190 - 735)
LDH (U/L)	210 (205,3 - 282)
CRP (mg/L)	0,5 (0,5 - 0,5)
Procalcitonin (ng/mL)	0,02 (0,02 - 0,02)
Chest X-Ray; n (%)	
Normal	4 (50)
Interstitial infiltrates	2 (25)
Pneumonia	0
Not performed	2 (25)
Fever duration (days); median (IQR)	53,5 (12,3 - 64,5)
Symptom duration (days); median (IQR)	60 (37 - 70)
Follow-up time (days); median (IQR)	52,5 (25 - 60,5)
Telephone consultations; median (IQR)	11 (6,3 - 19)
New symptoms during follow-up; n (%)	6 (75)
Clinical worsening during follow-up; n (%)	4 (50)
> 1 visit to Emergency Department; n (%)	4 (50)

Table 1. Clinical characteristics of "constitutional syndrome" patients (long-COVID-19 syndrome)

TRANSMISSION & PREVENTION

EARLY EVIDENCE OF THE EFFECT OF SARS-COV-2 VACCINE AT ONE MEDICAL CENTER

Daniel W, Nivet M, Warner J, Podolsky DK.. N Engl J Med. 2021 Mar 23. doi: 10.1056/NEJMc2102153. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A chief quality officer from the University of Texas Southwestern Medical Center (UTSW) reports findings in the first month of their COVID-19 vaccination program (December 15, 2020 to January 28, 2021) in which 59% of 23,234 eligible employees received at least 1 dose of either Pfizer or Moderna mRNA vaccines. They found most new infections (234 of 8969) occurred in non-vaccinated employees, with few (4 of 8121) in the fully vaccinated population ($p<0.01$) (Figure 1A). Authors suggest that mRNA vaccinations tremendously impact the rate of new SARS-CoV-2 infections and emphasize the importance of addressing vaccine hesitancy.

FIGURES

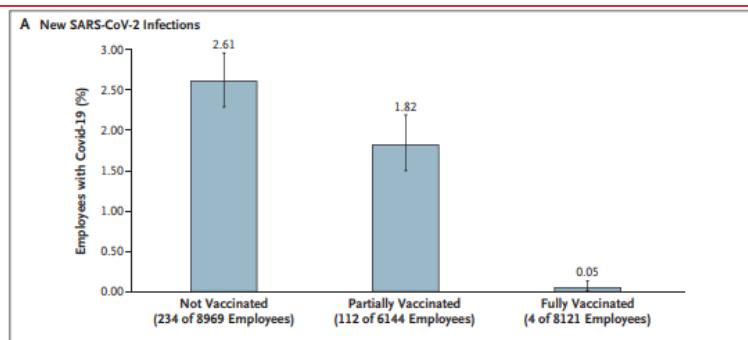


Figure 1. Early Results of SARS-CoV-2 Vaccination.

TRANSMISSION DYNAMICS AND TIMING OF KEY EVENTS FOR SARS-COV-2 INFECTION IN HEALTHCARE WORKERS

Emecen AN, Basoglu Sensoy E, Sezgin E, Yildirim Ustuner B, Keskin S, Siyve N, Celik SG, Bayrak G, Senturk Durukan N, Coskun Beyan A, Ergor A, Unal B, Ergor G.. Infect Dis (Lond). 2021 Mar 17:1-7. doi: 10.1080/23744235.2021.1900599. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

A retrospective cohort study conducted by infectious disease physicians and epidemiologists between March 19th 2020–November 1st 2020 aimed to evaluate the serial interval (summary) and incubation time of healthcare workers compared to the general populous. Some key results are that both the median serial interval and median incubation periods were shorter in healthcare workers compared to the general populous at 3.93 days and 3.99 days respectively (95% CI: 3.17-4.83, 95% CI: 3.25-4.84) (Table 2). The implication being that this shortened duration means stricter preventive measures should be taken to mitigate healthcare worker infection and thus quicker spread between one another.

SUMMARY

Serial interval is defined by the authors as “the time between symptom onsets in an infector-infectee pair”

ABSTRACT

BACKGROUND: Healthcare workers (HCWs) have increased risk for SARS-CoV-2 infection via contacts in hospitals, as well as via transmission in the community. Serial interval, which is defined as the time between symptom onsets in an infector-infectee pair, and the incubation period are key parameters in determining the control strategies for COVID-19. This study aimed to evaluate surveillance of HCWs and estimate the serial interval and incubation period of COVID-19. **METHODS:** A total of 149 HCWs and 36 certain infector-infectee pairs between 19th March 2020 and 1st November 2020 in a university hospital

were included in the study. Epidemiological characteristics were recorded. Serial interval and incubation period were estimated using parametric accelerated failure time models. RESULTS: Forty HCWs (26.8%) were detected via contact-based surveillance. Of 100 HCWs epidemiologically linked with a confirmed COVID-19 case, 36 (36%) had contact with a colleague. The median serial interval was 3.93 days (95% CI: 3.17-4.83). Of symptomatic HCWs, 97.5% had developed symptoms 13.71 (95% CI: 9.39-18.73) days after symptom onset of the primary case. The median incubation period was 3.99 (95% CI: 3.25-4.84) days. Of symptomatic HCWs, 97.5% developed symptoms within 9.49 (95% CI: 6.75-12.20) days after infection. CONCLUSIONS: The serial interval and the incubation period of COVID-19 in HCWs were shorter than in the general population. Rigorous contact tracing and isolation of infected HCWs could have resulted in shorter serial intervals. Implementation of more stringent in-hospital control measures focussed on transmission between HCWs should be considered.

FIGURES

Table 2. Estimates of serial interval and incubation period for log-normal, gamma and Weibull distribution ($n = 36$ pairs).

Distribution	Serial interval				Incubation period			
	2.5% per. (95% CI)	Median (95% CI)	97.5% per. (95%CI)	-2LL	2.5% per. (95%CI)	Median (95% CI)	97.5% per. (95%CI)	-2LL
Log-normal	1.13 (0.80-1.61)	3.93 (3.17-4.83)	13.71 (9.39-18.73)	170.1	1.68 (1.19-2.68)	3.99 (3.25-4.84)	9.49 (6.75-12.20)	70.0
Gamma	0.83 (0.53-1.37)	4.19 (3.43-5.24)	12.20 (8.94-15.67)	171.6	1.44 (0.99-2.36)	4.14 (3.42-4.90)	9.08 (6.58-11.33)	71.0
Weibull	0.55 (0.34-0.99)	4.30 (3.40-5.32)	12.08 (8.91-15.20)	173.7	0.95 (0.61-1.88)	4.24 (3.56-5.00)	9.00 (6.49-11.31)	73.7

CI: confidence interval; per.: percentile; -2LL: $-2 \times \log\text{-likelihood}$.

Table 2. Estimates of serial interval and incubation period for log-normal, gamma and Weibull distribution ($n=36$ pairs).

WHAT SCIENTISTS DO AND DON'T KNOW ABOUT THE OXFORD-ASTRAZENECA COVID VACCINE

Mallapaty S, Callaway E.. Nature. 2021 Mar 24. doi: 10.1038/d41586-021-00785-7. Online ahead of print.

Level of Evidence: 5 - Opinion

BLUF

A team of journalists writing for Nature in March 2021 review updated data regarding the Oxford-AstraZeneca vaccine. Manufacturers reported overall efficacy of 76% with similar efficacy against variants and lower cost of manufacturing and storage compared to other vaccines. However, due to potential links between the vaccine and rare clotting conditions the authors suggest that more data analysis will be required before the vaccine is approved for use in the United States.

DEVELOPMENTS IN TRANSMISSION & PREVENTION

SARS-COV-2 INFECTION AFTER VACCINATION IN HEALTH CARE WORKERS IN CALIFORNIA

Keehner J, Horton LE, Pfeffer MA, Longhurst CA, Schooley RT, Currier JS, Abeles SR, Torriani FJ.. N Engl J Med. 2021 Mar 23. doi: 10.1056/NEJMc2101927. Online ahead of print.

Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

Researchers associated with UCLA and UCSD studied the incidence of COVID-19 in 36,659 vaccinated healthcare workers between December 16, 2020 - February 9, 2021 and found that 379 workers tested positive for SARS-CoV-2 through repeated nasal PCR testing, 71% of whom tested positive within 2 weeks after receiving the first dose (Table 1). 37 workers tested positive after receiving the second dose, 22 of whom tested positive within the first week. Overall, the absolute risk of testing positive for SARS-CoV-2 after vaccination was 1.19% at UCSD and 0.97% at UCLA health systems, indicating that both doses or even one dose of the COVID-19 vaccine is indeed effective at preventing SARS-CoV-2 infection.

FIGURES

Table 1. New SARS-CoV-2 Infections among Vaccinated Health Care Workers from December 16, 2020, through February 9, 2021.

Days after Vaccination	Vaccinated Persons		
	With New Infection (N = 379)	Tested (N = 14,604)*	Eligible for Testing (N = 36,659)†
	number	number (percent)	
Dose 1			
Days 1–7	145	5794	35,673 (97.3)
Days 8–14	125	7844	34,404 (93.8)
Days 15–21	57	7958	32,667 (89.1)
Day 22 or later, before dose 2	15	4286	32,327 (88.2)
Dose 2			
Days 1–7	22	5546	23,100 (63.0)
Days 8–14	8	4909	16,082 (43.9)
Day 15 or later	7	4167	14,990 (40.9)

* Shown are the numbers of unique health care workers who underwent testing (not the number of individual tests).

† Shown are the numbers and percentages of persons among 36,659 vaccinated health care workers who were eligible to undergo testing each week as of February 9, 2021.

Table 1. New SARS-CoV-2 Infections among Vaccinated Health Care Workers from December 16, 2020, through February 9, 2021.

ANTIBODY RESPONSES AFTER A SINGLE DOSE OF SARS-COV-2 mRNA VACCINE

Bradley T, Grundberg E, Selvarangan R, LeMaster C, Fraley E, Banerjee D, Belden B, Louiselle D, Nolte N, Biswell R, Pastinen T, Myers A, Schuster J.. N Engl J Med. 2021 Mar 23. doi: 10.1056/NEJMc2102051. Online ahead of print.

Level of Evidence: 3 - Local non-random sample

BLUF

An immunology research team from Children's Mercy Kansas City used a multiplex bead-binding assay to assess antibody levels at baseline and 3 weeks after the first dose of the BNT162b2 (Pfizer) SARS-CoV-2 mRNA vaccine in 36 health care workers with laboratory-confirmed SARS-CoV-2 infection 30 to 60 days before they received the vaccine and 152 health care workers without past SARS-CoV-2 infection. After the first vaccine dose, they found that patients with past SARS-CoV-2 infection or seropositive status had higher levels of antibody to SARS-CoV-2 antigens as well as higher levels of neutralizing antibodies (Figure 1). Authors suggest further investigation into the duration of antibody responses and protective immunity measures is needed in order to confidently recommend an effective immunization program.

FIGURES

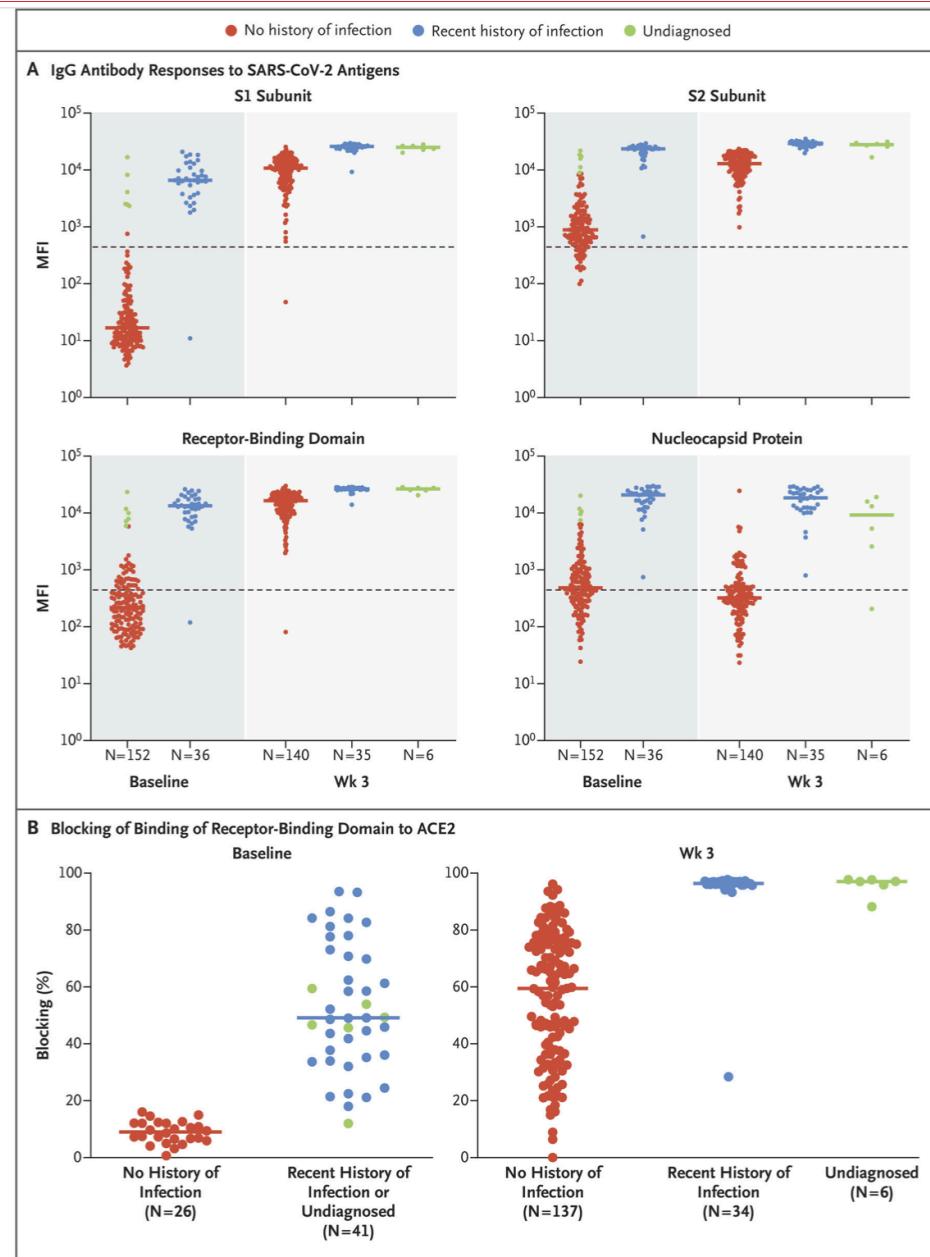


Figure 1. Antibody Response to SARS-CoV-2 mRNA Vaccine.

Panel A shows a multiplex bead-based antibody-binding assay that measures the IgG antibody response to four SARS-CoV-2 viral antigens (spike protein subunits S1 and S2, spike receptor-binding domain, and nucleocapsid protein). The median fluorescence intensity (MFI) is shown; background subtraction has been used to remove nonspecific signal. Participants designated as “undiagnosed” were those in the group with no history of SARS-CoV-2 infection who had antibody levels that matched those of participants with recent infection. The dashed line indicates a threshold determined by the sum of the mean and standard deviation for the negative control (i.e., beads without antigen). Panel B shows the results of a neutralization antibody proxy assay that determines the level of antibodies that block binding of the spike protein receptor-binding domain to the human host receptor angiotensin-converting enzyme 2 (ACE2), expressed as the percentage of binding that was blocked relative to a control with no plasma (representing maximum binding). The assay threshold for positivity was 30%. In both panels, each point represents a participant at baseline before receiving the vaccine or 3 weeks after receiving the first dose of vaccine and bars represent the group median. The numbers of participants in each group are shown below the graphs.

PREVENTION IN THE COMMUNITY

RT-PCR SCREENING TESTS FOR SARS-COV-2 WITH SALIVA SAMPLES IN ASYMPTOMATIC PEOPLE: STRATEGY TO MAINTAIN SOCIAL AND ECONOMIC ACTIVITIES WHILE REDUCING THE RISK OF SPREADING THE VIRUS

Oba J, Taniguchi H, Sato M, Takamatsu R, Morikawa S, Nakagawa T, Takaishi H, Saya H, Matsuo K, Nishihara H.. Keio J Med. 2021 Mar 19. doi: 10.2302/kjm.2021-0003-OA. Online ahead of print.

Level of Evidence: 5 - Review / Literature Review

BLUF

Physician scientists from the Keio University School of Medicine in Tokyo, Japan review literature regarding the use of saliva samples for RT-PCR screening for SARS-CoV-2. Authors argue that traditional nasopharyngeal swab samples used for RT-qPCR testing could be replaced by saliva sampling, which is less expensive and does not require trained medical staff to perform, and that pooled samples can facilitate large scale screening. Authors also introduce a new "social cut-off" standard for risk evaluation using cycle threshold (Ct) values from saliva sampling in RT-qPCR testing (Figure 2), suggesting not quarantining individuals with minimally infective Ct values can facilitate a faster, safer return to social and economic activities.

ABSTRACT

The year 2020 will be remembered for the coronavirus disease 2019 (COVID-19) pandemic, which continues to affect the whole world. Early and accurate identification of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is fundamental to combat the disease. Among the current diagnostic tests, real-time reverse transcriptase-polymerase chain reaction (RT-qPCR) is the most reliable and frequently used method. Herein, we discuss the interpretation of RT-qPCR results relative to viral infectivity. Although nasopharyngeal swab samples are often used for RT-qPCR testing, they require collection by trained medical staff. Saliva samples are emerging as an inexpensive and efficient alternative for large-scale screening. Pooled-sample testing of saliva has been applied for mass screening of SARS-CoV-2 infection. Current policies recommend isolating people with borderline cycle threshold (Ct) values ($35 < \text{Ct} < 40$), despite these Ct values indicating minimal infection risk. We propose the new concept of a "social cut-off" Ct value and risk stratification based on the correlation of Ct with infectivity. We also describe the experience of RT-qPCR screening of saliva samples at our institution. It is important to implement a scientific approach to minimize viral transmission while allowing economic and social activities to continue.

FIGURES

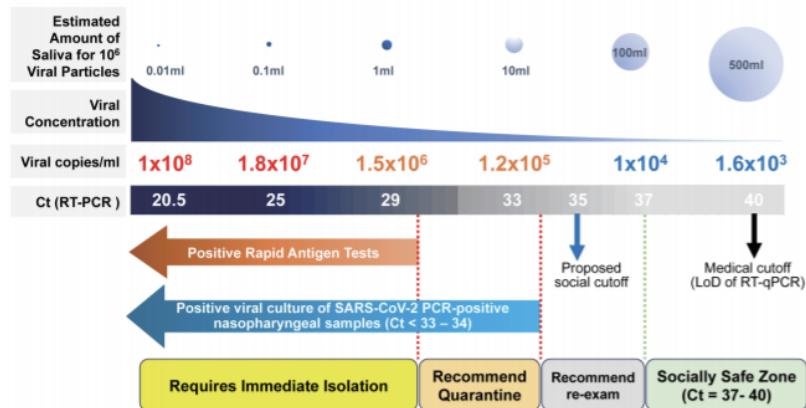


Figure 2. Proposed risk stratification based on RT-qPCR Ct values and rapid antigen testing. Viral copies/ml were estimated from RTqPCR Ct values using the formula provided by Wyllie et al.²² The estimated amount of saliva required to contain 10^6 viral copies and the corresponding viral concentrations are shown. Data for positive viral cultures of SARS-CoV-2 PCR-positive nasopharyngeal samples ($\text{Ct} < 33\text{--}34$) are from La Scola et al.²⁶ and Singanayagam et al.²⁹ A new social cut-off²²; at Ct values >35 is proposed based on these two and other studies showing the correlation between Ct values and viral culture recovery rates,^{26,28} thereby allowing individuals to continue their social activities with follow-up testing recommended. The limit of detection (LoD) is generally considered to be the lowest concentration of target that can be detected in 95% of repeat measurements. Note that LoDs of currently approved RT-qPCR kits for SARS-CoV-2 vary significantly,^{25,32} and the medical cut-off shown in the figure should be interpreted with caution. Ct, cycle threshold.

MANAGEMENT

ACUTE CARE

CRITICAL CARE

INTERSTITIAL LUNG DISEASE FOLLOWING COVID-19

Cottin V, Lafitte C, Sénéchal A, Traclet J.. Am J Respir Crit Care Med. 2021 Mar 18. doi: 10.1164/rccm.202006-2466IM. Online ahead of print.

Level of Evidence: 5 - Case Report

BLUF

Respiratory specialists in Lyon, France conducted a case-study of a 73-year old man who was treated for endobronchial hamartochondroma with a rigid bronchoscopy, while having no parenchymal abnormalities seen on chest CT (Figure 1A,B). One year later, he was admitted for viral pneumonia with COVID-19, with CT showing extensive ground glass opacities (Figure 1C,D). A follow-up CT 8 weeks later showed persistent ground-glass attenuation and linear opacities (Figure 1E,F) which improved with prednisone treatment (Figure 1G,H). These findings suggest that glucocorticoids may improve persistent post-COVID-19 interstitial lung disease.

SUMMARY

- Patient had a history of smoking, mitral valve replacement, atrial fibrillation, diabetes insipidus, hypertension, and chronic kidney disease.
- Force vital capacity (FVC) at time of bronchoscopy was 88% of predicted value and diffusing capacity of the lung for carbon monoxide (DLco) was 63% of predicted value.
- At 8 week follow-up, FVC was 64% and DLco was 38% of predicted value.
- After prednisone treatment, FVC was 76% and DLco was 49% of predicted value.

FIGURES

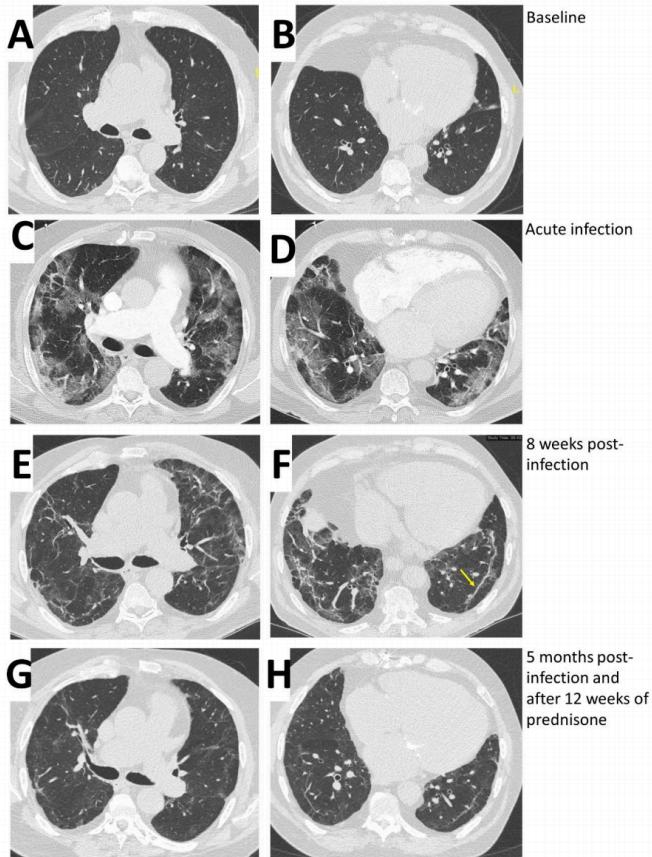


Figure 1. Computed tomography one year before COVID-19 infection showing normal lung parenchyma (A, B), at the time of COVID-19 infection showing extensive ground glass attenuation (C, D), eight weeks following COVID-19 infection showing persistent groundglass attenuation and linear opacities (arrow) (E,F) and 5 months following COVID-19 infection demonstrating improvement after prednisone therapy. A, C, E, G: axial views below the carina; B, D, F, H: axial views in the lung bases.

SURGICAL SUBSPECIALTIES

TRANSPLANT SURGERY

SARS-COV-2-SPECIFIC SEROLOGICAL AND FUNCTIONAL T-CELL IMMUNE RESPONSES DURING ACUTE AND EARLY COVID-19 CONVALESCENCE IN SOLID ORGAN TRANSPLANT PATIENTS

Favà A, Donadeu L, Sabé N, Pernin V, Gonzalez-Costello J, Lladó L, Meneghini M, Garcia-Romero E, Cachero A, Torija A, Rodriguez-Urquia R, Crespo E, Teubel I, Melilli E, Montero N, Manonelles A, Preyer R, Strecker K, Ovize A, Lozano JJ, Sidorova J, Cruzado JM, Le Quintrec M, Thaunat O, Bestard O.. Am J Transplant. 2021 Mar 23. doi: 10.1111/ajt.16570. Online ahead of print.

Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

A serological study conducted by researchers affiliated with multiple medical institutions in Spain and France analyzed 44 patients who were hospitalized with moderate/severe COVID-19 disease (28 solid-organ transplant (SOT) recipients and 16 immunocompetent (IC) patients), and found that SOT patients had lower IgG seroconversion rates (77% vs. 100%, p=0.044)

(Figure 5) and decreased reactive cytokine-producing T-cell frequencies to 4 main immunogenic SARS-CoV-2 antigens (Figure 3C), indicating that SOT patients were delayed in achieving a strong immune response compared to immunocompetent patients. Worsening clinical outcomes were associated with a lesser SARS-CoV-2 reactive IL-2 producing T-cell response (Figure 7). Despite an initial delay in response, the serological and functional T-cell immune response were observed to be comparable to immunocompetent patients following COVID-19 infection, confirming the need for active immunization especially in SOT patients.

ABSTRACT

The description of protective humoral and T-cell immune responses specific against SARS-CoV-2 has been reported among immunocompetent (IC) individuals developing COVID-19 infection. However, its characterization and determinants of poorer outcomes among the at-risk Solid Organ Transplant (SOT) patient population has not been thoroughly investigated. Cytokine-producing T-cell responses such as IFN-gamma, IL-2, IFN-gamma/IL-2, IL-6, IL-21 and IL-5 against main immunogenic SARS-CoV-2 antigens and IgM/IgG serological immunity were tracked in SOT (n=28) during acute infection and at 2 consecutive time-points over the following 40 days of convalescence and were compared to matched IC (n=16) patients admitted with similar moderate/severe COVID-19. We describe the development of a robust serological and functional T-cell immune responses against SARS-CoV-2 among SOT patients, similarly to IC patients during early convalescence. However, at the infection onset, SOT displayed lower IgG seroconversion rates (77% vs 100%; p=0.044), despite no differences on IgG titers, and a trend towards decreased SARS-CoV-2-reactive T-cell frequencies, especially against the membrane protein (7[0-34] vs 113[15-45] p=0.011, 2[0-9] vs 45[5-74], p=0.009 and 0[0-2] vs 13[1-24], p=0.020, IFN-gamma, IL-2 and IFN-gamma/IL-2 spots, respectively). In summary, our data suggest that despite a certain initial delay, SOT achieve comparable functional immune responses than the general population after moderate/severe COVID-19.

FIGURES

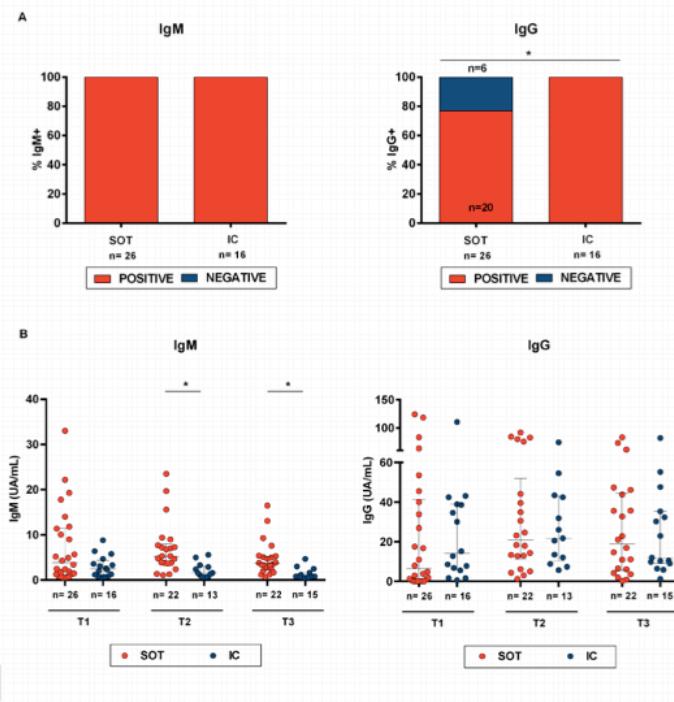


Figure 5: IgM and IgG antibody responses to SARS-CoV-2.

Figure 5A: Percentage at T1 of SOT and IC patients with detectable SARS-CoV-2-specific IgM and IgG class-switching.
 *p<0.05 (Chi-Square Test).

Figure 5B: IgM and IgG titers for every time point and study group (SOT and IC). *p<0.05 (Mann-Whitney test analysis).

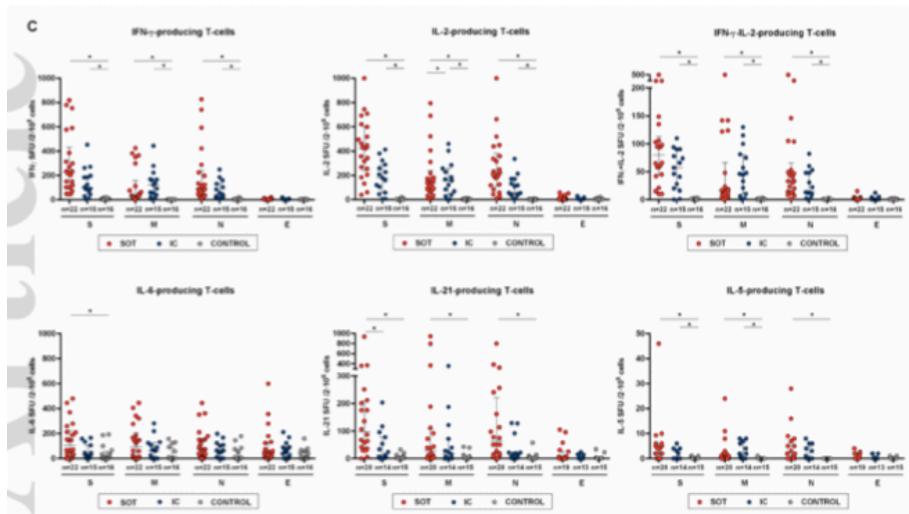


Figure 3. Cytokine profile of T-cell responses against main structural SARS-CoV-2 proteins Spike (S), Membrane (M), Nucleoprotein (N) and Envelope (E). Frequencies of IFN-gamma, IL2, IFN-gamma/IL2, IL6, IL5 and IL21 producing T cells were assessed among the three study group samples at different time points. * $p<0.05$, calculated with Kruskall-Wallis’ test.

Figure 3C. T3=49; 43-53 days after symptom onset.

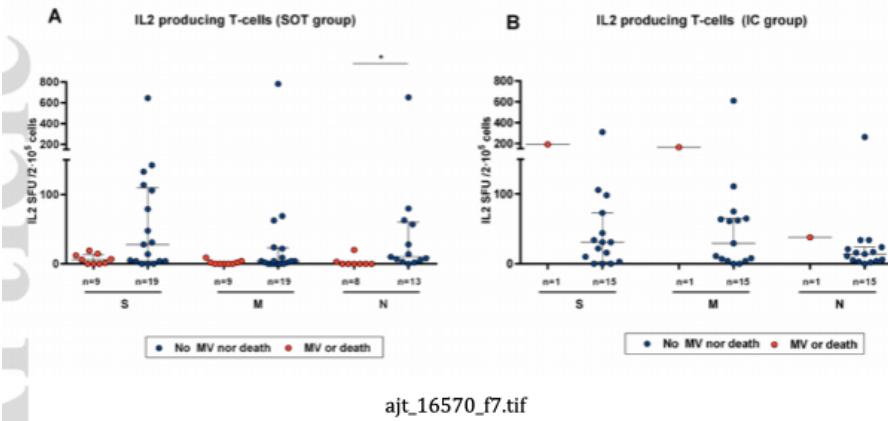


Figure 7. Baseline SARS-CoV-2-specific IL2-producing T-cell frequencies and clinical outcomes in SOT and IC patients with severe COVID19 infection. IL2-producing frequencies between patients with a poor outcome (VM or death) and those with a favorable clinical evolution.

Figure 7A. SOT patients ** $p<0.05$ (analyzed by Mann-Whitney U Test).

Figure 7B. IC patients. Only one IC patient required mechanical ventilation.

R&D: DIAGNOSIS & TREATMENTS

DEVELOPMENTS IN TREATMENTS

VITAMIN D3 TO TREAT COVID-19: DIFFERENT DISEASE, SAME ANSWER

Leaf DE, Ginde AA.. JAMA. 2021 Mar 16;325(11):1047-1048. doi: 10.1001/jama.2020.26850.

Level of Evidence: 5 - Expert Opinion

BLUF

An editorial piece penned by a pair of physicians associated with Brigham and Women's Hospital and the University of Colorado School of Medicine discusses the results of a recent JAMA published study (Murai, et al.) about vitamin D3 having no benefit as therapy in COVID-19 patients versus placebo group. The authors agree with the findings of the study showing no significant change in hospital length of stay between the treatment and placebo group, while also emphasizing the study's limitations of being underpowered, excluding key patient demographics, and containing ambiguous data. The implication being that while new therapies need to be assessed with an open mind, current vitamin D therapy appears to not be efficacious in patients with COVID-19.

SUMMARY

- In vitro research shows that vitamin D and its metabolites show antimicrobial and anti-inflammatory effects
- COVID-19 pandemic has sparked interest in vitamin D as therapy especially given its action on ACE2 upregulation which would be beneficial to those already infected with COVID-19
- Furthermore, while the authors believe the study in focus is beneficial to research at large, it should be noted the study was under-powered, excluded key patient demographics like ICU and ventilated patients, many patients did not have vitamin D deficiencies and finally, the study did not measure the active metabolites of vitamin D, only levels of 25(OH)D

ACKNOWLEDGEMENTS

CONTRIBUTORS

Ankita Dharmendran
Brad Mott
Hamza Sultan
Michael Wang
Nicolas Longobardi
Renate Meckl

EDITORS

John Michael Sherman
Julia Ghering
Maresa Woodfield

SENIOR EDITORS

Allison Hansen
Avery Forrow

SENIOR EXECUTIVE EDITOR

Ann Staudinger Knoll

CHIEF EDITOR

Charlotte Archuleta

ADVISOR

Will Smith