The Daily COVID-19 Literature Surveillance Summary

March 29, 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

- Seroprevalence of anti-SARS-CoV-2 antibodies may indicate positive impact from vaccines. A team from the Wuhan Center for Disease Control and Prevention conducted a cross-sectional assessment of the prevalence of anti-SARS-CoV-2 antibodies in a random sample of 9,542 Wuhan residents in April 2020, with two follow ups in June and October-December 2020. They found no significant decrease in IgG or neutralizing antibody titers in the 335 individuals who tested positive at the first appointment. Authors suggest the promise of durable immunity indicates vaccines could help prevent the resurgence of the epidemic in previously exposed populations.

Understanding the Pathology

- Can IgG antibodies be useful for passive immunization? Immunologists and pharmacists from several Chinese institutions used indirect ELISA to analyze IgM and IgG antibody levels in 32 COVID-19 patients from day 1 to day 24 of infection. They found that SARS-CoV-2 specific IgM was measurable for a shorter period (peaking at 20 days post-infection and beginning to fall around day 25), with IgG antibodies persisting throughout the time frame. The authors suggest IgG antibodies represents the primary immune response and propose its use for passive immunization treatment in COVID-19.

- Persistence of SARS-CoV-2 can be monitored through N-Antibody levels. Members of the LondonCOVID Group conducted a prospective SARS-CoV-2 serological study of 1,069 healthcare workers across 4 hospitals in London between March and July 2020. They found 29% (n=312) developed antibodies against nucleocapsid (N) protein (95% CI 26%–32%) which steadily increased and stabilized in the 12 weeks after the first seropositive test (Figure). Because anti-N antibody titers were similar between those with and without COVID-19 symptoms, authors suggest N antibody could be a reliable surveillance indicator for past infection with SARS-CoV-2.

- There is a trend of dropping anti-SARS-CoV-2 plaque reduction neutralization test titers over time in convalescent plasma donors. A team of microbiologists from the Canadian Blood Services in Alberta conducted Plaque Reduction Neutralization Tests (PRNT50) to detect levels of SARS-CoV-2 neutralizing antibodies in plasma products from 30 previously COVID-19 positive male blood donors with repeated donations. In 50% of the donors (n=15) they observed an eightfold drop in PRNT50 titers at 91-143 days from initial infection compared to peak PRNT50. Because SARS-CoV-2 antibodies titers appear to decline from peak values in 3-4 months, authors caution against relying on repeat donors when recruiting convalescent plasma donors.

R&D: Diagnosis & Treatments

- CRISPR-augmented RT-PCR may provide more sensitive tracking of circulating viral RNA of SARS-CoV-2 infection. Experts in molecular diagnosis and infectious disease from Tulane University, among others, evaluated the performance of a CRISPR-augmented RT-PCR for detecting SARS-CoV-2 in plasma samples from experimentally infected nonhuman primates (NHP) as well as 159 patients (adult and pediatric) with negative nasal swab RT-qPCR. Using nasopharyngeal swab RT-PCR as confirmatory tests, they found the assay accurately detected SARS-CoV-2 RNA in the blood of NHPs and humans. The test exhibited a 91.2% sensitivity and 99.2% specificity in the human patient cohort as compared to only 41% sensitivity with non-augmented RT-qPCR. Authors suggest SARS-CoV-2 can be reliably detected in the blood of patients negative nasal swab RT-qPCR and could improve detection of SARS-CoV-2 infection.

TABLE OF CONTENTS

EPIDEMIOLOGY

SEROPREVALENCE AND HUMORAL IMMUNE DURABILITY OF ANTI-SARS-COV-2 ANTIBODIES IN WUHAN, CHINA: A LONGITUDINAL, POPULATION-LEVEL, CROSS-SECTIONAL STUDY

He Z, Ren L, Yang J, Guo L, Feng L, Ma C, Wang X, Leng Z, Tong X, Zhou W, Wang G, Zhang T, Guo Y, Wu C, Wang Q, Liu M, Wang C, Jia M, Hu X, Wang Y, Zhang X, Hu R, Zhong J, Yang J, Dai J, Chen L, Zhou X, Wang J, Yang W, Wang C.. Lancet. 2021 Mar 20;397(10279):1075-1084. doi: 10.1016/S0140-6736(21)00238-5.
Level of Evidence: 4 - Local and current random sample surveys (or censuses)

BLUF

A team from the Wuhan Center for Disease Control and Prevention conducted a cross-sectional assessment of the prevalence of anti-SARS-CoV-2 antibodies in a random sample of 9,542 Wuhan residents in April 2020 (Figure 2), with two follow ups in June and October-December 2020. They found no significant decrease in IgG or neutralizing antibody titers in the 335 individuals who tested positive at the first appointment (Tables 1,2). Authors suggest the promise of durable immunity indicates vaccines could help prevent the resurgence of the epidemic in previously exposed populations.

ABSTRACT

BACKGROUND: Wuhan was the epicentre of the COVID-19 outbreak in China. We aimed to determine the seroprevalence and kinetics of anti-SARS-CoV-2 antibodies at population level in Wuhan to inform the development of vaccination strategies. METHODS: In this longitudinal cross-sectional study, we used a multistage, population-stratified, cluster random sampling method to systematically select 100 communities from the 13 districts of Wuhan. Households were systematically selected from each community and all family members were invited to community health-care centres to participate. Eligible individuals were those who had lived in Wuhan for at least 14 days since Dec 1, 2019. All eligible participants who consented to participate completed a standardised electronic questionnaire of demographic and clinical questions and self-reported any symptoms associated with COVID-19 or previous diagnosis of COVID-19. A venous blood sample was taken for immunological testing on April 14-15, 2020. Blood samples were tested for the presence of pan-immunoglobulins, IgM, IgA, and IgG antibodies against SARS-CoV-2 nucleocapsid protein and neutralising antibodies were assessed. We did two successive follow-ups between June 11 and June 13, and between Oct 9 and Dec 5, 2020, at which blood samples were taken. FINDINGS: Of 4600 households randomly selected, 3599 families (78 2%) with 9702 individuals attended the baseline visit. 9542 individuals from 3556 families had sufficient samples for analyses. 532 (5 6%) of 9542 participants were positive for pan-immunoglobulins against SARS-CoV-2, with a baseline adjusted seroprevalence of 6 92% (95% CI 6 41-7 43) in the population. 437 (82 1%) of 532 participants who were positive for pan-immunoglobulins were asymptomatic. 69 (13 0%) of 532 individuals were positive for IgM antibodies, 84 (15 8%) were positive for IgA antibodies, 532 (100%) were positive for IgG antibodies, and 212 (39 8%) were positive for neutralising antibodies at baseline. The proportion of individuals who were positive for pan-immunoglobulins who had neutralising antibodies in April remained stable for the two follow-up visits (162 [44 6%] of 363 in June, 2020, and 187 [41 2%] of 454 in October-December, 2020). On the basis of data from 335 individuals who attended all three follow-up visits and who were positive for pan-immunoglobulins, neutralising antibody levels did not significantly decrease over the study period (median 1/5 6 [IQR 1/2 0 to 1/14 0] at baseline vs 1/5 6 [1/4 0 to 1/11 2] at first follow-up [p=1 0] and 1/6 3 [1/2 0 to 1/12 6] at second follow-up [p=0 29]). However, neutralising antibody titres were lower in asymptomatic individuals than in confirmed cases and symptomatic individuals. Although titres of IgG decreased over time, the proportion of individuals who had IgG antibodies did not decrease substantially (from 30 [100%] of 30 at baseline to 26 [89 7%] of 29 at second follow-up among confirmed cases, 65 [100%] of 65 at baseline to 58 [92 1%] of 63 at second follow-up among symptomatic individuals, and 437 [100%] of 437 at baseline to 329 [90 9%] of 362 at second follow-up among asymptomatic individuals). INTERPRETATION: 6 92% of a cross-sectional sample of the population of Wuhan developed antibodies against SARS-CoV-2, with 39 8% of this population seroconverting to have neutralising antibodies. Our durability data on humoral responses indicate that mass vaccination is needed to effect herd protection to prevent the resurgence of the epidemic. FUNDING: Chinese Academy of Medical Sciences & Peking Union Medical College, National Natural Science Foundation, and Chinese Ministry of Science and Technology. TRANSLATION: For the Chinese translation of the abstract see Supplementary Materials section.

FIGURES

Table 1

Baseline demographic and clinical characteristics and seroprevalence of antibodies against SARS-CoV-2 in the analysable population

	Analysable population at baseline	Individuals who tested positive for pan-immunoglobulins	Adjusted seroprevalence (95% CI)*
Overall	9542 (100%)	532/9542 (5·6%)	6·92% (6·41–7·43)
Sex			
Male	4658 (48·8%)	217/4658 (4·7%)	6·22% (5·53–6·91)
Female	4884 (51·2%)	315/4884 (6·4%)	7·70% (6·95–8·45)
Age group, years			
0–5	303 (3·2%)	14/303 (4·6%)	5·33% (2·80–7·86)
6–11	682 (7·1%)	23/682 (3·4%)	4·72% (3·13–6·31)
12–17	485 (5·1%)	16/485 (3·3%)	3·22% (1·65–4·79)
18–44	3905 (40·9%)	214/3905 (5·5%)	6·65% (5·87–7·43)
45–65	3340 (35·0%)	202/3340 (6·0%)	7·71% (6·81–8·61)
≥66	827 (8·7%)	63/827 (7·6%)	9·51% (7·51–11·51)
Occupation			
Health workers	83 (0·9%)	7/83 (8·4%)	14·83% (7·18–22·48)
Community workers	829 (8·7%)	34/829 (4·1%)	4·37% (2·98–5·76)
Volunteers in pandemic†	719 (7·5%)	36/719 (5·0%)	6·26% (4·49–8·03)
Other	7911 (82·9%)	455/7911 (5·8%)	7·22% (6·65–7·79)
Underlying disease‡			
No	7840 (82·2%)	426/7840 (5·4%)	6·70% (6·15–7·25)
Yes	1702 (17·8%)	106/1702 (6·2%)	7·92% (6·64–9·20)
Self-reported symptom§			
No	9118 (95·6%)	437/9118 (4·8%)	5·99% (5·50–6·48)
Yes	424 (4·4%)	95/424 (22·4%)	26·13% (21·95–30·31)
Visited hospital in the past 5 months			
No	9281 (97·3%)	454/9281 (4·9%)	6·11% (5·62–6·60)
Yes	261 (2·7%)	78/261 (29·9%)	36·65% (30·80–42·50)
Known contact with an individual with COVID-19 in the past 5 months			
No	9289 (97·3%)	474/9287 (5·1%)	6·33% (5·83–6·83)
Yes	253 (2·7%)	58/253 (22·9%)	26·81% (21·35–32·27)
Known contact with people with respiratory infections before enrolment			
No	9023 (94·6%)	447/9023 (5·0%)	6·19% (5·69–6·69)
Yes	519 (5·4%)	85/519 (16·4%)	19·55% (16·14–22·96)
Family size (number of people)			
1	816 (8·6%)	64/816 (7·8%)	8·34% (6·44–10·24)
2–3	4839 (50·7%)	288/4839 (6·0%)	6·91% (6·17–7·65)
≥4	3887 (40·7%)	128/3887 (3·3%)	6·53% (5·73–7·33)

Data are n (%) or n/N (%) unless otherwise indicated.

*Seroprevalence is adjusted for sex, age group, and district.

†Volunteers in the pandemic included, but are not limited to, drivers, cleaners in medical facilities, and construction workers who were involved in the implementation of prevention and control measures.

‡Underlying diseases included hypertension, pulmonary disease, cancer (undergoing chemotherapy), diabetes, cardiovascular disease, chronic kidney disease, chronic liver disease, and immunodeficiency disease, among others.

§Including fever or respiratory symptoms, or both.

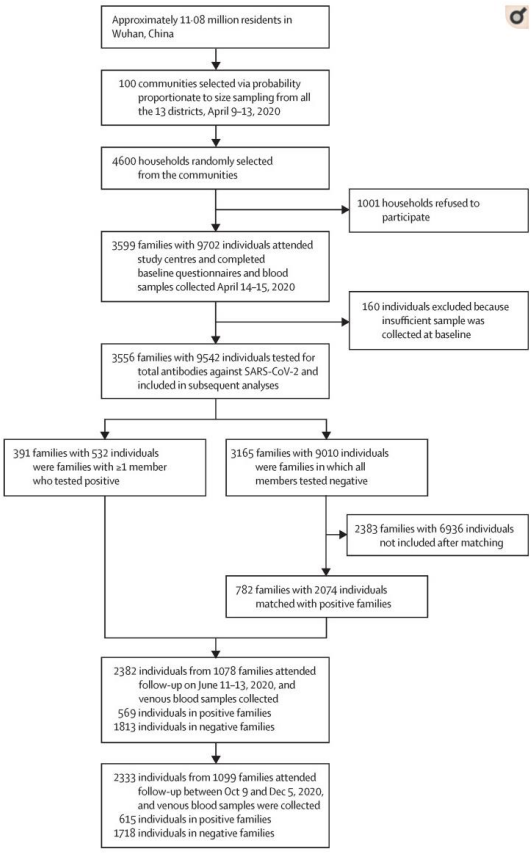
Table 2

Temporal changes in the proportion of participants who were positive for IgG, IgA, IgM, and neutralising antibodies among those who were positive for antibodies against SARS-CoV-2

	IgG	IgA	IgM	Neutralising antibodies
Baseline (n=532)	532 (100%)	84 (15·8%)	69 (13·0%)	212 (39·8%)
Confirmed cases (n=30)	30 (100%)	3 (10·0%)	2 (6·7%)	18 (60·0%)
Symptomatic infection (n=65)	65 (100%)	12 (18·5%)	3 (4·6%)	36 (55·4%)
Asymptomatic infection (n=437)	437 (100%)	69 (15·8%)	63 (14·4%)	158 (36·2%)
p value	NA	0·56	0·051	0·0009
First follow-up (n=363)	354 (97·5%)	36 (9·9%)	14 (3·9%)	162 (44·6%)
Confirmed cases (n=27)	27 (100%)	2 (7·4%)	0	15 (55·6%)
Symptomatic infection (n=56)	56 (100%)	6 (10·7%)	2 (3·6%)	35 (62·5%)
Asymptomatic infection (n=280)	271 (96·8%)	28 (10·0%)	12 (4·3%)	112 (40·0%)
p value	0·25	0·89	0·54	0·0042
Second follow-up (n=454)	413 (91·0%)	16 (3·5%)	7 (1·5%)	187 (41·2%)
Confirmed cases (n=29)	26 (89·7%)	0	0	17 (58·6%)
Symptomatic infection (n=63)	58 (92·1%)	0	1 (1·6%)	38 (60·3%)
Asymptomatic infection (n=362)	329 (90·9%)	18 (5·0%)	6 (1·7%)	132 (36·5%)
p value	0·92	0·092	0·78	0·0026

p values are for the comparison in proportions of patients in each symptom subgroup who were positive for each antibody at each timepoint, calculated using the χ^2 test. For the comparison of proportions of patients who are positive for neutralising antibodies: the p values were 0·84 at baseline, 0·71 at first follow-up and 0·94 at second follow-up for confirmed cases *vs* symptomatic individuals; 0·016 at baseline, 0·17 at first follow-up, and 0·030 at second follow-up for confirmed cases *vs* asymptomatic individuals, and 0·0046 at baseline, 0·0032 at first follow-up, and 0·0006 at second follow-up for symptomatic *vs* asymptomatic individuals.

Figure 2



Study profile

SUSTAINED NEUTRALISING ANTIBODIES IN THE WUHAN POPULATION SUGGEST DURABLE PROTECTION AGAINST SARS-COV-2

Strugnell R, Wang N.. Lancet. 2021 Mar 20;397(10279):1037-1039. doi: 10.1016/S0140-6736(21)00434-7.
Level of Evidence: 5 - Opinion

BLUF

Microbiologists from the University of Melbourne in Australia discuss a longitudinal cross-sectional study published by Zhenyu He and colleagues that examined the development and durability of SARS-CoV-2 neutralizing antibodies and estimated the penetration of the virus into the Wuhan community. The study found that 532 of 9542 participants (~5.6%) were positive for pan-immunoglobulins against SARS-CoV-2 at baseline, with 39.8% of the seropositive subgroup having detectable neutralizing antibodies. Authors suggest these findings highlight the importance of effective COVID-19 vaccines in the context of controlling the disease, especially given the relative paucity of antibodies produced via natural infection.

SARS-COV-2 LINEAGES AND SUB-LINEAGES CIRCULATING WORLDWIDE: A DYNAMIC OVERVIEW

Cella E, Benedetti F, Fabris S, Borsetti A, Pezzuto A, Ciotti M, Pascarella S, Ceccarelli G, Zella D, Ciccozzi M, Giovanetti M.. Chemotherapy. 2021 Mar 18:1-5. doi: 10.1159/000515340. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Virologists, molecular epidemiologists, and other infectious disease experts from Italy, Brazil, and the United States reviewed literature and public data regarding SARS-CoV-2 lineages. They found the most common sub-lineage worldwide is B.1, with variants emerging in different regions (Figure 1). Because a recent variant (B.1.1.17) first detected in the UK has 17 acquired mutations that may influence infectivity, authors suggest continuous assessment of viral genomic changes is necessary for proper pandemic control, vaccine development, and treatment strategies.

ABSTRACT

BACKGROUND: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) originated in Wuhan, China, in early December 2019 has rapidly widespread worldwide, becoming one of the major global public health issues of the last centuries. Key Messages: Over the course of the pandemic, due to the advanced whole-genome sequencing technologies, an unprecedented amount of genomes have been generated, providing invaluable insights into the ongoing evolution and epidemiology of the virus during the pandemic. Therefore, this large amount of data played an important role in the SARS-CoV-2 mitigation and control strategies. Key Messages: The active monitoring and characterization of the SARS-CoV-2 lineages circulating worldwide is useful for a more specific diagnosis, better care, and timely treatment. In this review, a concise characterization of all the lineages and sub-lineages circulating and co-circulating across the world has been presented in order to determine the magnitude of the SARS-CoV-2 threat and to better understand the virus genetic diversity and its dispersion dynamics.

FIGURES

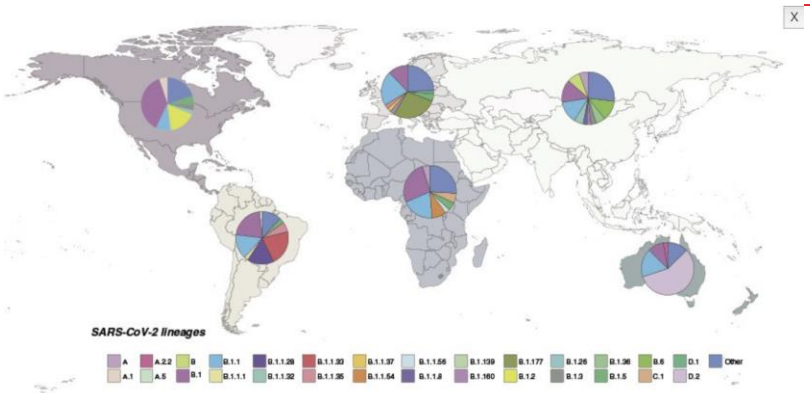


Fig.1: Worldwide lineage distribution. Lineage with a prevalence percentage <2% were grouped as “other.” (For details of the grouped lineages, see online suppl. Table 1.) SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

A NOVEL ALLELE, HLA-C*15:227, IDENTIFIED WHEN TYPING COVID-19 PATIENTS

Cheranev V, Loginova M, Jankevic T, Kutyavina S, Rebrikov D.. HLA. 2021 Feb 4. doi: 10.1111/tan.14199. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Experts in immunogenetics from the Center for Precision Genome Editing and Federal State Budget Research Institution in Russia describe their discovery of a novel human leukocyte antigen allele on the HLA-C gene in the peripheral blood of a COVID-19 patient using next generation sequencing. They sequenced nonsynonymous mutation (A → G) at position 368 that caused a change from TAT (Tyrosine) to TGT (Cysteine) at codon 99 in exon 3. Authors do not speculate on the allele's significance, but submitted it to the GenBank database as HLA-C*15:227 in September 2020.

ABSTRACT

HLA-C*15:227 differs from HLA-C*15:02:01:01 by a single nonsynonymous change (368A G Tyrosine 99 to Cysteine). This article is protected by copyright. All rights reserved.

SYMPTOMS AND CLINICAL PRESENTATION

PREGNANT PERSONS

PERSISTENCE OF SARS-COV-2 IN THE FIRST TRIMESTER PLACENTA LEADING TO TRANSPLACENTAL TRANSMISSION AND FETAL DEMISE FROM AN ASYMPTOMATIC MOTHER

Shende P, Gaikwad P, Gandhewar M, Ukey P, Bhide A, Patel V, Bhagat S, Bhor V, Mahale S, Gajbhiye R, Modi D.. Hum Reprod. 2021 Mar 18;36(4):899-906. doi: 10.1093/humrep/deaa367.
Level of Evidence: 5 - Case report

BLUF

Obstetrician-gynecologists and pathologists from ESI-PGIMSR and Model Hospital Andheri in Mumbai, India present the case of a 26-year old woman with a history of asymptomatic SARS-CoV-2 infection at gestational week 8 who presented with spontaneous abortion at 13 weeks. Pathology of the placenta showed detectable viral RNA in placental villi which appeared lysed and inflammatory with leukocyte infiltration (Figure 3). Because ultrasonography of the fetus showed extensive subcutaneous edema (Figure 4) and bilateral pleural effusions (Figure 1), with workup negative for other known causes of hydrops, authors suggest SARS-CoV-2 viral infection may lead to hydrops fetalis and fetal demise.

ABSTRACT

Coronavirus disease 2019 (COVID-19) is caused by infection of the respiratory tract by SARS-CoV-2 which survives in the tissues during the clinical course of infection but there is limited evidence on placental infection and vertical transmission of SARS-CoV-2. The impact of COVID-19 in first trimester pregnancy remains poorly understood. Moreover, how long SARS-CoV-2 can survive in placenta is unknown. Herein we report a case of a pregnant woman in the first trimester who tested positive for SARS-CoV-2 at 8 weeks of gestation although her clinical course was asymptomatic. At 13 weeks of gestation, her throat swab tested negative for SARS-CoV-2 but viral RNA was detected in the placenta and the Spike (S) proteins (S1 and S2) were immunolocalized in cytotrophoblast and syncytiotrophoblast cells of the placental villi. Histologically, the villi were generally avascular with peri-villus fibrin deposition and in some areas the syncytiotrophoblast layer appeared lysed. The decidua also had fibrin deposition with extensive leucocyte infiltration suggestive of inflammation. The SARS-CoV-2 crossed the placental barrier, as the viral RNA was detected in the amniotic fluid and the S proteins were detected in the fetal membrane. Ultrasonography revealed extensively subcutaneous edema with pleural effusion suggestive of hydrops fetalis and the absence of cardiac activity indicated fetal demise. This is the first study to provide concrete evidence of persistent placental infection of SARS-CoV-2 and its congenital transmission associated with hydrops fetalis and intrauterine fetal demise in early pregnancy.

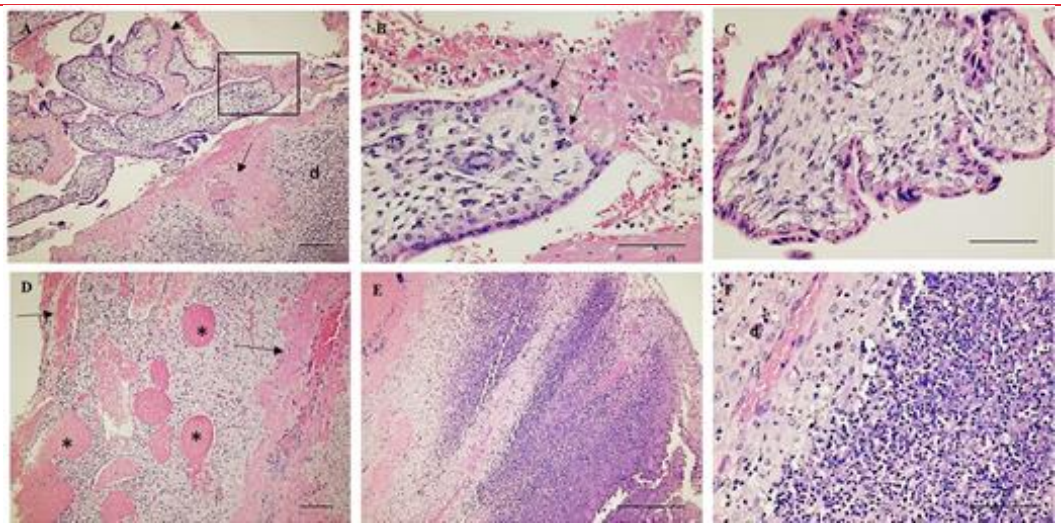


Figure 3. Histopathology of placenta and decidual tissue from a woman with asymptomatic SARS-CoV-2 infection in first trimester. (A–C) Placental villi and D–F is the decidual tissue stained with hematoxylin and eosin. (A) Lower magnification image showing fibrin deposition (arrow) in the intervillous space and decidua (d). Boxed area is enlarged in (B) showing lysis of syncytiotrophoblast cells in the villi (arrow), leukocyte infiltration in intervillous spaces and fibrin deposition. (C) Vacuolated avascular villi with vacuolated cells in the villus stroma. (D) Low magnification image showing shows dilated blood vessels (*) in the decidua and fibrin deposition (arrow). (E) Infiltration of immune cells in the decidual tissues. (F) Higher magnification of E showing leukocytes in the decidual bed (d). In all the images scale bar represents 100 µm.

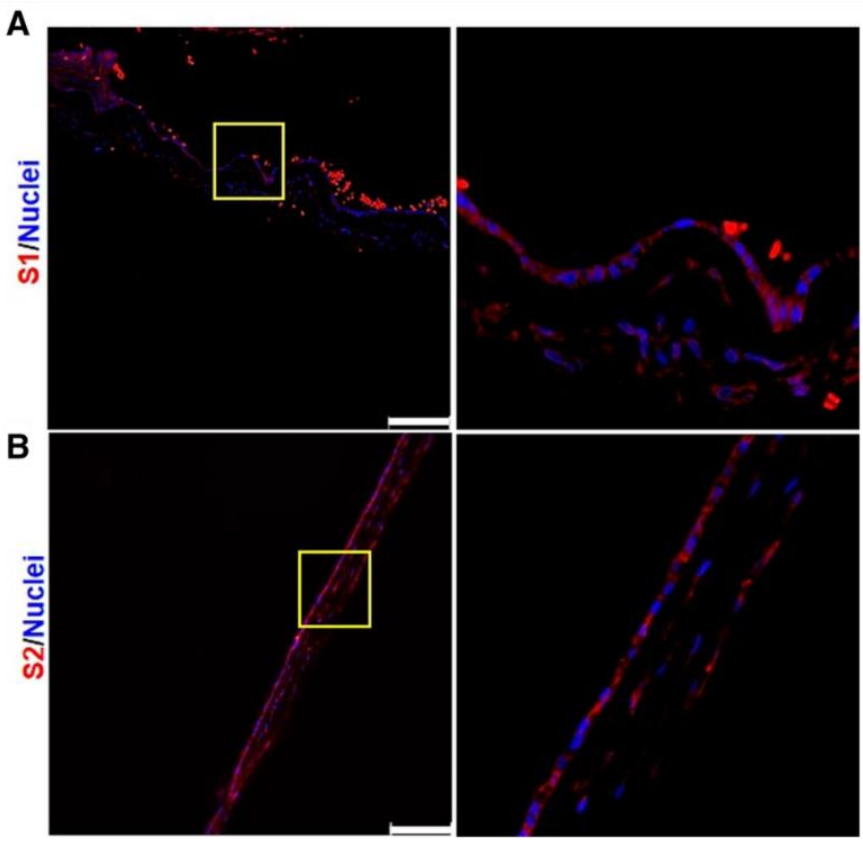


Figure 4. Detection of spike proteins of SARS-CoV-2 in first trimester fetal membrane from a woman with asymptomatic COVID-19 in first trimester. Paraffin sections were immunostained for Spike proteins S1 (A) and S2 (B) of SARS-CoV-2 using monoclonal antibodies. Boxed area is enlarged in the next panel to show the specific cell types. Scale bar represents 100 µm.

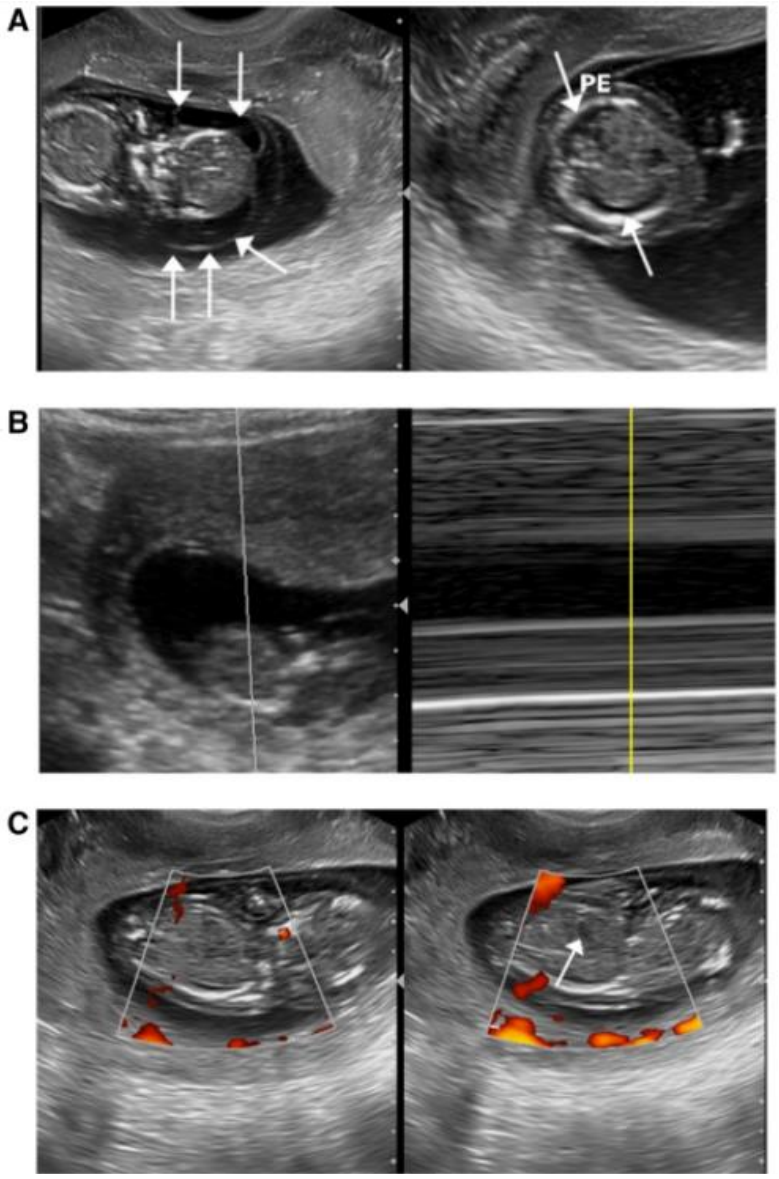


Figure 1. Transabdominal ultrasound at 13 weeks of amenorrhea showing hydrops fetalis and demise in a pregnant woman who was positive for SARS-CoV-2 at 8 weeks of gestation. (A) Extensive subcutaneous edema (white arrows) and pleural effusion (PE). (B) Images showing absent cardiac activity. (C) Absence of blood flow in the fetal heart (arrow).

PROFILE OF SPECIFIC ANTIBODIES TO THE SARS-COV-2

Mou D, Feng H, Cao R, Weng X, Zhao L, Yang L, Jin R, Chen W.. J Med Microbiol. 2021 Mar 18. doi: 10.1099/jmm.0.001335. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Immunologists and pharmacists from several Chinese institutions used indirect ELISA to analyze IgM and IgG antibody levels in 32 COVID-19 patients from day 1 to day 24 of infection (Table 1)(Summary). They found that SARS-CoV-2 specific IgM was measurable for a shorter period (peaking at 20 days post-infection and beginning to fall around day 25), with IgG antibodies persisting throughout the time frame (Figure 1). The authors suggest IgG antibodies represents the primary immune response and propose its use for passive immunization treatment in COVID-19.

SUMMARY

Patient enrollment criteria: epidemiological history, body fever, and Ct value of SARS-CoV-2 in the throat swab less than 38

ABSTRACT

In this work, we studied the profile of IgM and IgG antibody responses to SARS-CoV-2 in 32 patients with COVID-19 from day 1 to day 24. IgM remained measurable for a much shorter period than IgG, suggesting that IgG antibody may represent the primary immune response.

FIGURES

Table 1. Information of 32 patients

Characteristic	Mild (*N*=23)	Moderate (*N*=5)	Severe (*N*=4)	Total (*N*=32)
Age-yr				
Median (IQR)	42 (31–52)	62 (58–68)	61 (58–68)	47 (33–58)
Range	25–59	52–70	48–69	25–70
Female sex-no. (%)	15 (65)	5 (100)	2 (50)	22 (69)

*The values shown are based on available data.
†Mild: symptomatic but not affecting daily activities; Moderate: symptomatic and slightly affects daily life; Severe: seriously affects daily life.
IQR, interquartile range; yr, year.

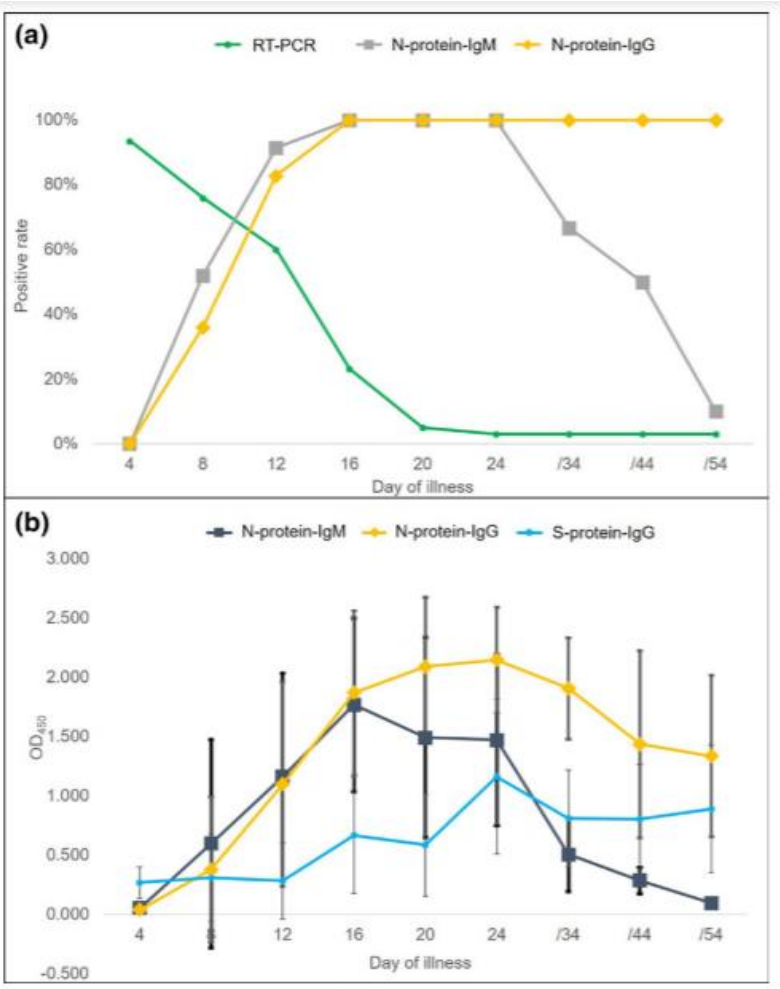


Fig. 1. Profile of IgM and IgG antibody responses to SARS-CoV-2. (a) Positive rate of IgM and IgG antibody responses to SARS-CoV-2 and viral RNA of SARS-CoV-2 in the patients over the course of illness. (b) OD_{450} of IgM, IgG antibody responses to SARS-CoV-2 and IgG antibody to SARS-CoV-2 spike RBD protein in the patients over the course of illness.

PERSISTENCE OF SARS-COV-2 N-ANTIBODY RESPONSE IN HEALTHCARE WORKERS, LONDON, UK

Shrotri M, Harris RJ, Rodger A, Planche T, Sanderson F, Mahungu T, McGregor A, Heath PT; LondonCOVID Group, Brown CS, Dunning J, Hopkins S, Ladhani S, Chand M.. Emerg Infect Dis. 2021 Mar 18;27(4):1155-1158. doi: 10.3201/eid2704.204554. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Members of the LondonCOVID Group conducted a prospective SARS-CoV-2 serological study of 1,069 healthcare workers across 4 hospitals in London between March and July 2020. They found 29% (n=312) developed antibodies against nucleocapsid (N) protein (95% CI 26%–32%) which steadily increased and stabilized in the 12 weeks after the first seropositive test (Figure). Because anti-N antibody titers were similar between those with and without COVID-19 symptoms, authors suggest N antibody could be a reliable surveillance indicator for past infection with SARS-CoV-2.

ABSTRACT

Prospective serosurveillance of severe acute respiratory syndrome coronavirus 2 in 1,069 healthcare workers in London, UK, demonstrated that nucleocapsid antibody titers were stable and sustained for <12 weeks in 312 seropositive participants. This finding was consistent across demographic and clinical variables and contrasts with reports of short-term antibody waning.

FIGURES

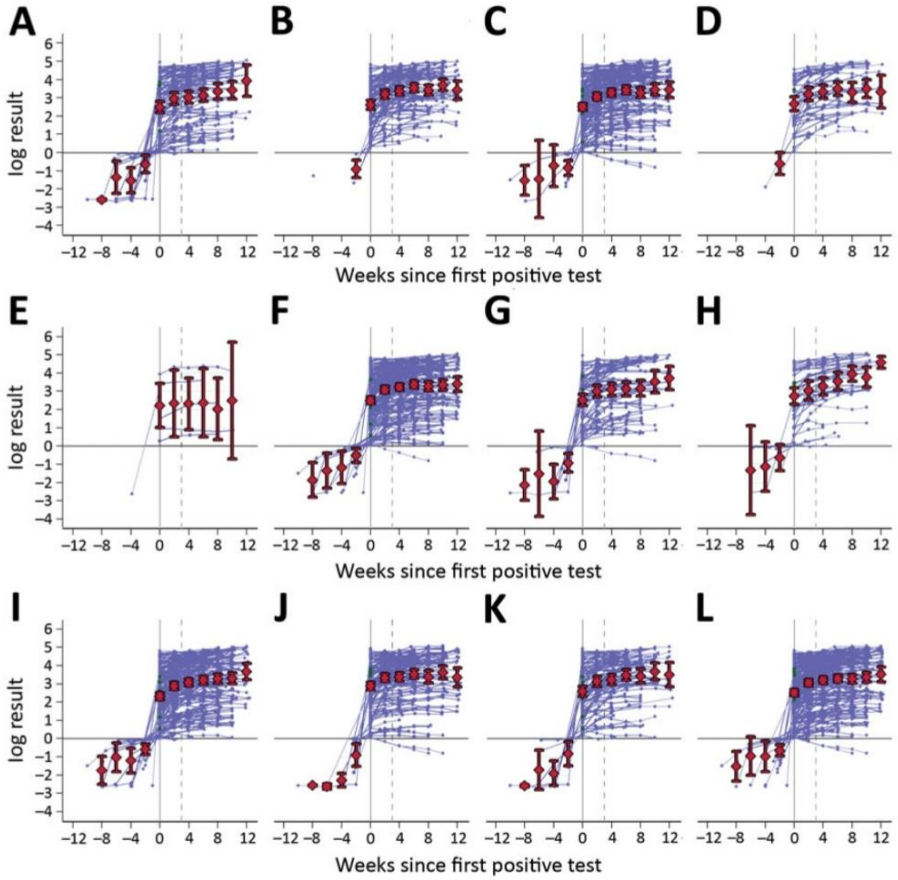


Figure: "log antibody titers over time in participants with >1 positive test result by subgroups in study of nucleocapsid-antibody response in healthcare workers, London, UK. Subgroups are as follows: A) no self-reported illness (n = 99), B) coronavirus disease (COVID-19) diagnosis (n = 94), C) respiratory illness (n = 175), D) other illness (n = 43), E) immunocompromised (n = 6), F) general hospital employee (n = 204), G) emergency department employee (n = 71), H) intensive care unit employee (n = 38), I) age <40 years (n = 185), J) age >40 years (n = 127), K) male sex (n = 95), L) female sex (n = 217). Times are with respect to the date of the first positive test (week 0), and week 4 is indicated by dashed lines; previous negative results are also included. Individual responses are indicated by blue lines; mean titers with 95% CI for the mean are shown in red".

A TREND OF DROPPING ANTI-SARS-COV-2 PLAQUE REDUCTION NEUTRALIZATION TEST TITERS OVER TIME IN CANADIAN CONVALESCENT PLASMA DONORS

Drews SJ, Devine DV, McManus J, Mendoza E, Manguiat K, Wood H, Girardin R, Dupuis A, McDonough K, Drebot M..
Transfusion. 2021 Mar 18. doi: 10.1111/trf.16364. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

BLUF

A team of microbiologists from the Canadian Blood Services in Alberta conducted Plaque Reduction Neutralization Tests (PRNT50) to detect levels of SARS-CoV-2 neutralizing antibodies in plasma products from 30 previously COVID-19 positive male blood donors with repeated donations. In 50% of the donors (n=15) they observed an eightfold drop in PRNT50 titers at 91-143 days from initial infection compared to peak PRNT50 (Figure 1). Because SARS-CoV-2 antibodies titers appear to

decline from peak values in 3-4 months, authors caution against relying on repeat donors when recruiting convalescent plasma donors.

ABSTRACT

BACKGROUND: Convalescent plasma products are a potential passive immunotherapy for Coronavirus disease 2019 (COVID-19) disease. Various approaches have been utilized to determine the concentration of Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-neutralizing antibodies in plasma products. The Canadian Blood Services used Plaque Reduction Neutralization Test 50 (PRNT50) -generated values to qualify convalescent plasma donations supporting clinical trials in Canada. This manuscript describes changes in PRNT50 titers of repeat male plasma donations collected approximately 1-4 months after onset of COVID-19 signs and symptoms in donors. STUDY DESIGN AND METHODS: Men were eligible to donate if they: met standard criteria, were < 67 years of age, reported a previous SARS-CoV-2-positive nucleic acid test, and recovered and were symptom free for at least 28 days prior to donation. Repeat donation analysis required at least one original and one repeat donation where a PRNT50 was performed. RESULTS: From April 29, 2020 to July 25, 2020, 156 donors donated once, with 78 (50%) of the donated plasma having PRNT50 titers of >=1:160. Thirty-seven (23.7%) of the donated plasma had a titer of 1:40 or 1:80 (individuals donating this plasma were asked to donate a second time only). A total of 30 donors (19.2%) had repeat donations. Of the repeat donors, 15 (50%) had at least an eightfold change from peak to trough PRNT50 titers within greater than 90 days after onset of COVID-19 symptoms. CONCLUSIONS: Blood operators cannot infer that SARS-CoV-2 PRNT50 will remain high in repeat plasma donors 3-4 months after onset of COVID-19 symptoms.

FIGURES

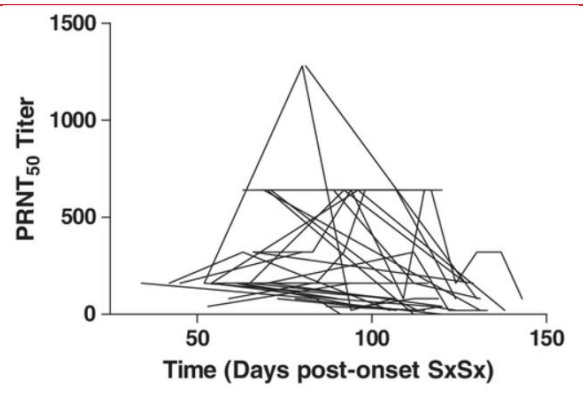


Figure 1

A trend to dropping plaque reduction neutralization test 50% (PRNT50) titers over time in repeat donors. Lines represent PRNT50 values from each donor plotted against time after onset of signs and symptoms. For presentation purposes, individual data points are not indicated but are presented in Table 1

TRANSMISSION & PREVENTION

PREVENTION IN THE COMMUNITY

PREGNANT PEOPLE'S PARADOX-EXCLUDED FROM VACCINE TRIALS DESPITE HAVING A HIGHER RISK OF COVID-19 COMPLICATIONS

Rubin R.. JAMA. 2021 Mar 16;325(11):1027-1028. doi: 10.1001/jama.2021.2264.
Level of Evidence: 5 - Opinion

BLUF

A medical reporter for the Journal of the American Medical Association reviews the indeterminate guidelines proposed by the World Health Organization, United States Centers for Disease Control and pharmaceutical companies regarding COVID-19 vaccinations in pregnant women. Although there is an obvious risk of severe COVID-19 in this population, the author suggests vaccine safety in pregnant women remains uncertain largely due to routine obstacles preventing inclusion of pregnant women in clinical research.

PREVENTION IN THE HOSPITAL

SARS-COV-2 IS ASSOCIATED WITH HIGH VIRAL LOADS IN ASYMPTOMATIC AND RECENTLY SYMPTOMATIC HEALTHCARE WORKERS

McEllistrem MC, Clancy CJ, Buehrle DJ, Singh N, Lucas A, Sirianni V, Decker BK.. PLoS One. 2021 Mar 18;16(3):e0248347. doi: 10.1371/journal.pone.0248347. eCollection 2021.
Level of Evidence: 3 - Local non-random sample

BLUF

Infectious disease physicians from the University of Pittsburgh and VA Pittsburgh Health System compared RT-PCR cycle threshold (Ct) values and symptom duration between 13 healthcare workers (HCW), 12 outpatients, and 28 inpatients who had a positive nasopharyngeal swab for SARS-CoV-2 between June 24 and August 23, 2020. Almost half (46.2%) of HCWs who tested positive were asymptomatic; no symptomatic HCWs (n=6) had symptoms for more than a week while half (6/12) of symptomatic inpatients had symptoms for at least one week (p = 0.04)(Figure 1). Median Ct value in HCW was not significantly different from outpatients with COVID-19 (23.2 vs 29; no p-value), but was significantly different from inpatients (23.2 vs 34.0; p = 0.003)(Figure 2). Because HCWs had high viral loads and were likely to be asymptomatic, authors suggest employee infection prevention programs should promote maintaining distance separation and consistent personal protection equipment usage at work.

ABSTRACT

BACKGROUND: Healthcare workers (HCW) are at increased risk of SARS-CoV-2 infection from both patients and other HCW with coronavirus disease 2019 (COVID-19). RT-PCR cycle threshold (Ct) values of SARS-CoV-2 <= 34 and the first 7-9 days of symptoms are associated with enhanced infectivity. We determined Ct values and duration of symptoms of HCW with a positive SARS-CoV-2 test. As HCW often assume their greatest risk of acquiring SARS-CoV-2 is working on a COVID-19 unit, we also determined Ct values and symptom duration of inpatients with a positive SARS-CoV-2 test. METHODS: From 6/24/2020-8/23/2020, Ct values and duration of symptoms from 13 HCW, 12 outpatients, and 28 inpatients who had a positive nasopharyngeal swab for SARS-CoV-2 were analyzed. RESULTS: Among HCW with a positive SARS-CoV-2 test, 46.2% (6/13) were asymptomatic and requested testing due to an exposure to someone with COVID-19; 83.3% (5/6) of those exposures occurred in the community rather than in the hospital. The median Ct value of HCW was 23.2, and 84.6% (11/13) had a Ct value <= 34. The median Ct value of 29.0 among outpatients with COVID-19 did not significantly differ from HCW. In contrast, inpatients with a positive SARS-CoV-2 test had a median Ct value of 34.0 (p = 0.003), which translated into a median ~1,000-fold lower viral load than observed in HCW. Among those with symptoms related to COVID-19, no (0/6) HCW compared to 50% (6/12) of inpatients had symptoms for at least one week (p = 0.04). CONCLUSIONS: At our institution, asymptomatic COVID-19 accounted for nearly half of the cases among HCW. Symptomatic HCW had high viral loads and short duration of symptoms, both of which are associated with peak infectivity. Infection prevention programs should educate HCW on these

findings in an effort to increase adherence to the requirement to maintain six feet separation in workspaces and breakrooms, in addition to consistently wearing personal protection equipment.

FIGURES

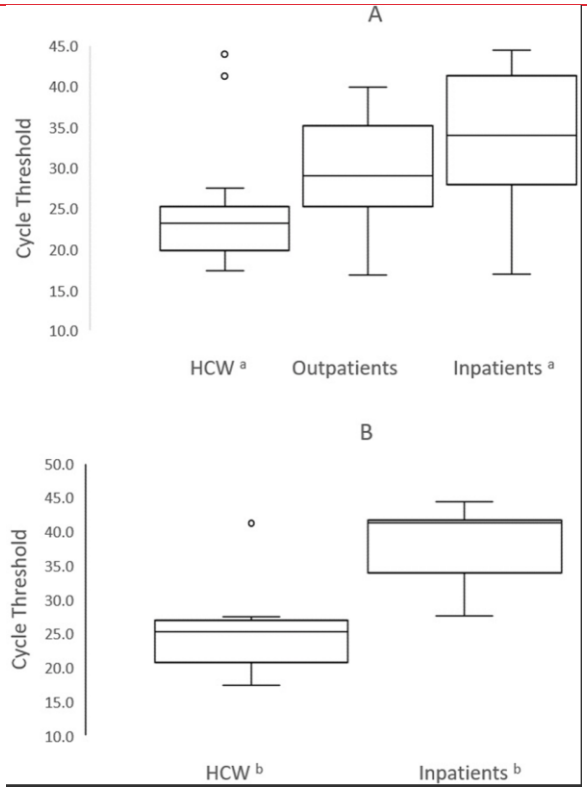


Fig 1. Comparison of the cycle threshold values of healthcare workers (HCW), outpatients, and inpatients with a positive RT-PCR SARS-CoV-2 test.

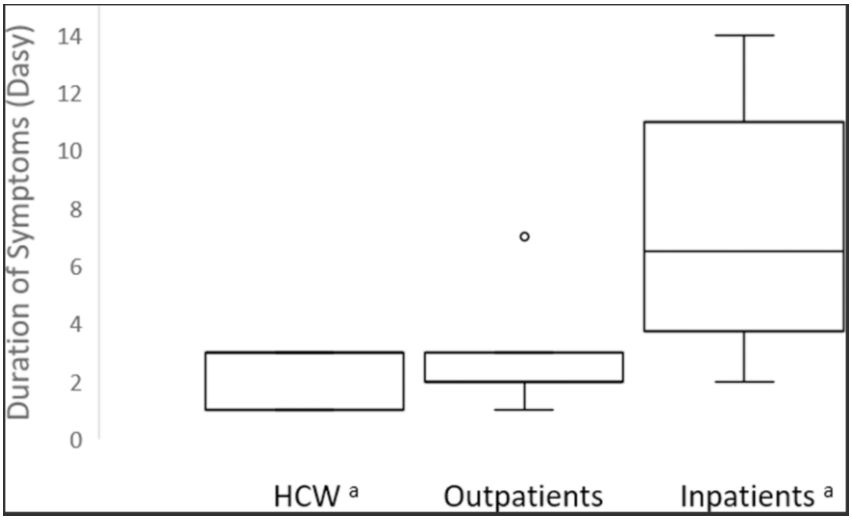


Fig 2. Duration of symptoms prior to symptom duration prior to a positive SARS-CoV-2 test among Heathcare Workers (HCW), outpatients, and inpatients, a p value 0.04.

CRITICAL CARE

AN UNEXPECTED CASE OF RECURRENCE OF PULMONARY EMBOLISM IN A PATIENT RECOVERED FROM COVID19 IN FULL REGIMEN DOSE OF DIRECT ORAL ANTICOAGULANT DRUG

D'Elia E, Gori M, Grosu A, Iorio A, Lorini FL, Falanga A, Di Marco F, Senni M.. BMC Pulm Med. 2021 Mar 24;21(1):102. doi: 10.1186/s12890-021-01453-2.
Level of Evidence: 5 - Case report

BLUF

A team of cardiovascular experts from the Hospital Papa Giovanni XXIII, in Bergamo, Italy present the case of a 51-year old male recently recovered from COVID-19 complicated by right pulmonary embolism on dagibatran who presented with palpitations, chest pain, and shortness of breath. Computed tomography angiogram showed marked endoluminal filling of the right and left pulmonary artery suggestive of extensive pulmonary embolism (Figures 1, 2). Patient received tissue plasminogen activator, symptomatically improved, and was later discharged on low molecular weight heparin. The authors suggest direct oral anticoagulants may not satisfactorily address hypercoaguability in COVID-19 patients and recommend randomized clinical trial studies to evaluate anticoagulation regimens.

FIGURES

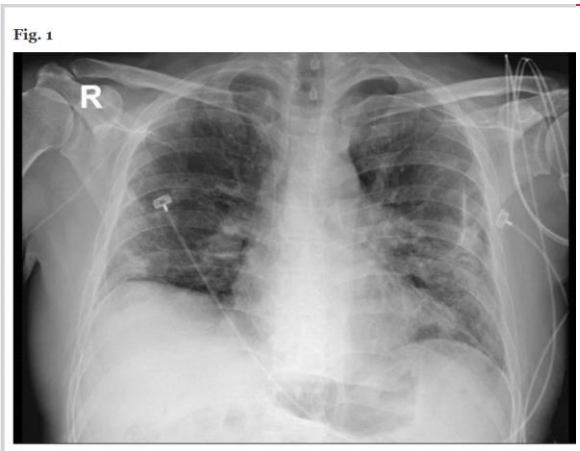


Figure 1.
Chest X Ray showing bilateral interstitial infiltrates with accentuation of the vascular plot, in the absence of pleural effusion

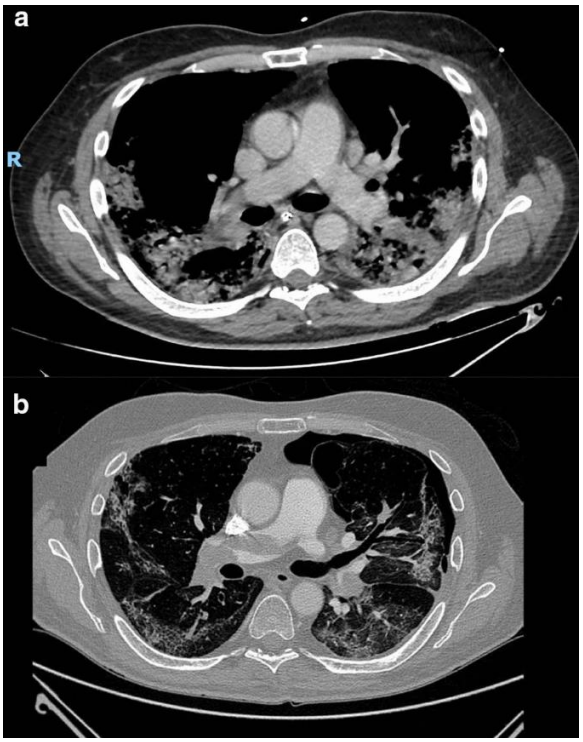


Figure 2.
Computed tomography angiogram during the first hospital admission showing a focal filling defect affecting the pulmonary artery branch for the lower right lobe with thromboembolic outbreak (a). Computed tomography angiogram at the time of hospital re-admission showing extensive defect of endoluminal filling of the right and left pulmonary artery with extension to their main branches (b)

SENSITIVE TRACKING OF CIRCULATING VIRAL RNA THROUGH ALL STAGES OF SARS-COV-2 INFECTION

Huang Z, Ning B, Yang HS, Youngquist BM, Niu A, Lyon CJ, Beddingfield BJ, Fears AC, Monk CH, Murrell AE, Bilton SJ, Linhuber JP, Norton EB, Dietrich ML, Yee JK, Lai W, Scott JW, Yin XM, Rappaport J, Robinson JE, Saba NS, Roy CJ, Zwezdaryk KJ, Zhao Z, Hu TY.. J Clin Invest. 2021 Feb 9:146031. doi: 10.1172/JCI146031. Online ahead of print.
Level of Evidence: 3 - Non-consecutive studies, or studies without consistently applied reference standards

BLUF

Experts in molecular diagnosis and infectious disease from Tulane University, among others, evaluated the performance of a CRISPR-augmented RT-PCR for detecting SARS-CoV-2 in plasma samples from experimentally infected nonhuman primates (NHP) as well as 159 patients (adult and pediatric) with negative nasal swab RT-qPCR (Figure 1). Using nasopharyngeal swab RT-PCR as confirmatory tests, they found the assay accurately detected SARS-CoV-2 RNA in the blood of NHPs (Figure 2) and humans. The test exhibited a 91.2% sensitivity and 99.2% specificity in the human patient cohort (Figure 4) as compared to only 41% sensitivity with non-augmented RT-qPCR. Authors suggest SARS-CoV-2 can be reliably detected in the blood of patients negative nasal swab RT-qPCR and could improve detection of SARS-CoV-2 infection.

ABSTRACT

BACKGROUND: Circulating SARS-CoV-2 RNA may represent a more reliable indicator of infection than nasal RNA, but RT-qPCR lacks diagnostic sensitivity for blood samples. METHODS: A CRISPR-augmented RT-PCR assay that sensitively detects SARS-CoV-2 RNA was employed to analyze viral RNA kinetics in longitudinal plasma samples from nonhuman primates (NHP) after virus exposure; to evaluate the utility of blood SARS-CoV-2 RNA detection for COVID-19 diagnosis in adults cases confirmed by nasal/nasopharyngeal swab RT-PCR results; and to identify suspected COVID-19 cases in pediatric and at-risk adult populations with negative nasal swab RT-qPCR results. All blood samples were analyzed by RT-qPCR to allow direct comparisons. RESULTS: CRISPR-augmented RT-PCR consistently detected SARS-CoV-2 RNA in the plasma of experimentally infected NHPs from 1 to 28 days post-infection, and these increases preceded and correlated with rectal swab viral RNA increases. In a patient cohort (n=159), this blood-based assay demonstrated 91.2% diagnostic sensitivity and 99.2% diagnostic specificity versus a comparator RT-qPCR nasal/nasopharyngeal test, while RT-qPCR exhibited 44.1% diagnostic sensitivity and 100% specificity for the same blood samples. This CRISPR-augmented RT-PCR assay also accurately identified COVID-19 patients with one or more negative nasal swab RT-qPCR result. CONCLUSION: Results of this study indicate that sensitive detection of SARS-CoV-2 RNA in blood by CRISPR-augmented RT-PCR permits accurate COVID-19 diagnosis, and can detect COVID-19 cases with transient or negative nasal swab RT-qPCR results, suggesting that this approach could improve COVID-19 diagnosis and the evaluation of SARS-CoV-2 infection clearance, and predict the severity of infection.

FIGURES

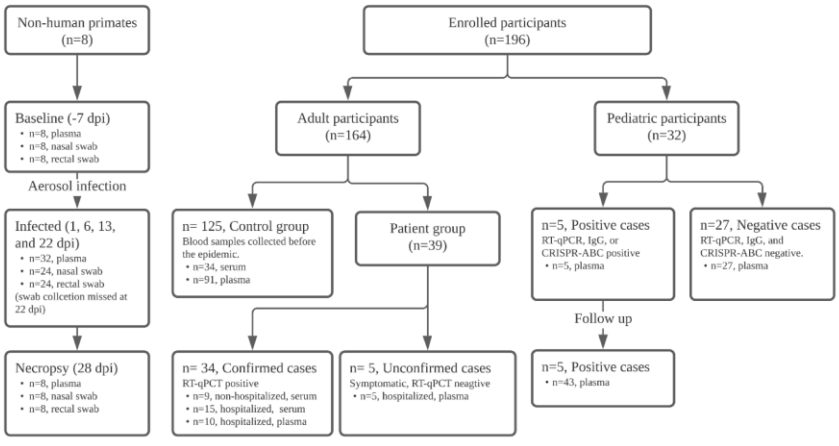


Figure 1. Flow diagram describing the numbers and disposition of the study subjects.

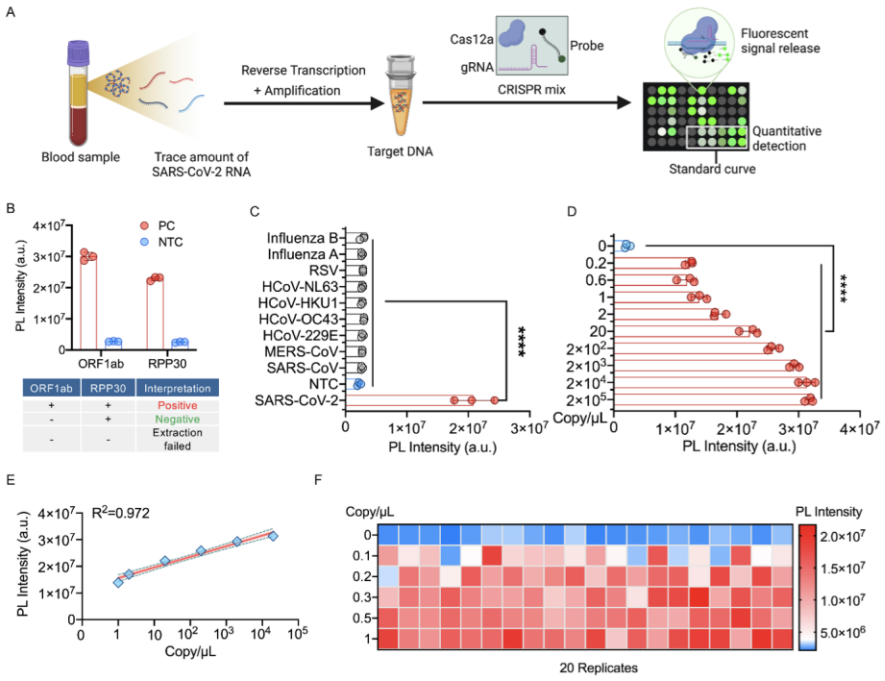


Figure 2. Analytical validation of the CRISPR-ABC assay. (**A**) CRISPR-ABC assay schematic. A SARS-CoV-2 ORF1ab target amplified from plasma RNA is quantified by comparing target- and CRISPR-mediated probe cleavage against that produced by a standard curve generated by RT-PCR of SARS-CoV-2 ORF1ab RNA samples of known concentration. (**B**) CRISPR-ABC signal in positive control (PC; 10^4 copies/µL) and no template control (NTC; nuclease-free water) samples. (**C**) CRISPR-ABC specificity with healthy human plasma spiked with or without indicated virus RNA or virions. (**D**) Limit of detection and (**E**) linear range of the assay. Shading denotes the 95% confidence interval of the fitted line. (**F**) CRISPR-ABC reproducibility for replicate plasma samples spiked with 0 to 1 copies/µL of inactivated SARS-CoV-2 virus. Graphs present the mean ± SD of three technical replicates for each sample. (****, $p < 0.0001$ for a difference between the zero-concentration sample and all other groups by one-way ANOVA adjusted for multiple comparisons).

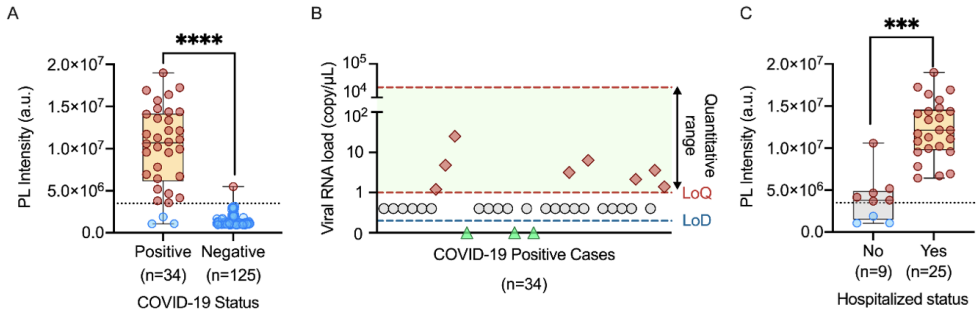


Figure 4. Plasma CRISPR-ABC results of adult COVID-19 cases. (**A**) CRISPR-ABC signal in baseline blood samples of 34 adults with COVID-19 diagnosed by nasal or nasopharyngeal RT-qPCR and 125 archived blood samples collected before the COVID-19 pandemic; (**B**) SARS-CoV-2 RNA copy number in these 34 COVID-19 subjects; (**C**) Comparison of CRISPR-ABC signal values of blood samples from hospitalized (n=25) and non-hospitalized COVID-19 patients (n=9) by a general linear model analysis adjusted for age. Panel A and C present as box plots with maximum, Q3, median, Q1, and minimum value of PL intensity of different group. Dotted lines indicate the positive result threshold. Dashed lines in panel A indicate the linear range and LoQ and LoD of the CRISPR-ABC assay. All samples were analyzed in triplicate. (****, $p < 0.0001$ by Mann-Whitney U test; ***, $P<0.001$ by general linear model analysis adjusting for age and symptom duration differences between these groups).

ACKNOWLEDGEMENTS

CONTRIBUTORS

Hamza Sultan
Krithika Kumarasan
Leah Merker
Michael Wang
Nicolas Longobardi
Reza Aghaei

EDITORS

Maresa Woodfield

SENIOR EDITORS

Avery Forrow

SENIOR EXECUTIVE EDITOR

Thamanna Nishath

CHIEF EDITOR

Brennan Enright

ADVISOR

Will Smith