The Weekly COVID-19 Literature Surveillance Summary

June 25, 2021

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COVID-19 LST

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

- SARS-CoV-2-Specific Antibodies in Breast Milk After COVID-19 Vaccination of Breastfeeding Women: A prospective cohort study conducted by researchers in Israel including 84 breastfeeding women who received 2 doses of the Pfizer-BioNTech vaccine between December 23, 2020 and January 15, 2021 found positive levels of anti-SARS-CoV-2-specific IgA antibodies (ABs) in breast milk in 61.8% of samples 2 weeks after the first dose, 86.1% after 4 weeks, and 65.7% after 6 weeks as well as anti-SARS-CoV-2-specific IgG ABs in 91.7% at week 5 and 97% in weeks 5-6. There were no serious adverse events reported during the study period but 47 (55.9%) and 52 (61.9%) reported vaccine-related adverse events after the first and second dose, respectively. These findings suggest the antibodies found in breast milk showed strong neutralizing effects and potentially provide a protective effect in infants as protection against SARS-CoV-2 infection.

- Adverse pregnancy outcomes, maternal complications, and severe illness among U.S. delivery hospitalizations with and without a COVID-19 diagnosis: A multi-center retrospective cohort study conducted by researchers from the CDC COVID-19 Response Team and United States Public Health Service Corps investigated 489,471 pregnant patients who delivered at 703 hospitals between March and September 2020. 6,550 of those patients had confirmed COVID-19, which was associated with increased risk for severe adverse outcomes including ARDS, death, and sepsis, as well as preterm labor with preterm delivery, and longer hospitalization time. These findings signify the importance of implementation of mitigation strategies, counseling, and clinical attention to lessen the risk of SARS-CoV-2 infection for pregnant women given the increased risk for adverse events.

Transmission & Prevention

- Safety, Immunogenicity, and Efficacy of the BNT162b2 Covid-19 Vaccine in Adolescents: A research team from Cincinnati Children's Hospital (OH), Kaiser Permanente Vaccine Study Center (CA), and the California Research Foundation, San Diego (CA) funded by BioNTech and Pfizer used a multinational, placebo-controlled, observer-blinded trial of 30 µg of BNT162b2 delivered in two doses to determine immunogenicity in 12-to-15-year-old participants. 1131 received BNT162b2, and 1129 received placebo; there were no vaccine-related serious adverse events and few overall severe adverse events. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was determined by measuring neutralizing titers after dose 2. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100), and no COVID-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients (who did not have previous infection), while 16 cases occurred in placebo recipients. Overall, BNT162b2 vaccine in 12-to-15-year-olds produced a greater immune response than in young adults and was shown to be both safe and highly effective.

R&D: Diagnosis & Treatments

- Corticosteroid therapy for COVID-19: A systematic review and meta-analysis of randomized controlled trials: A systematic review and meta-analysis conducted by researchers in United States and India included 8 randomized-controlled studies conducted through March 10, 2021 with 7,737 patients, 2795 (36.1%) who received corticosteroids along with the standard of care (SOC) for treatment of moderate and severe-critical COVID-19 infection. The odds of mortality were significantly lower in patients who received corticosteroids compared to SOC (OR 0.85), and odds for need of mechanical ventilation were reduced with corticosteroids compared to SOC (OR 0.7), suggesting beneficial effects of corticosteroid treatment in moderate to severe COVID-19 infection.

- Interim Results of a Phase 1-2a Trial of Ad26.COV2.S Covid-19 Vaccine: An international team of researchers shared interim results from a Phase 1-2a clinical trial on the efficacy of the Ad26.COV2.S candidate vaccine, a replication-incompetent adenovirus vector encoding a SARS-CoV-2 spike (S) protein, in 403 individuals aged 15-55 (cohort 1) and 402 individuals aged >65 (cohort 3). Both cohorts received a high or low dose of the vaccine in a single-dose or two-dose schedule 56 days apart. The most common adverse reactions included fever, fatigue, headache, myalgia, and injection-site pain, which were more commonly reported in cohort 1 and in those who received the low dose. Neutralizing antibody titers against wild-type SARS-CoV-2 were present in more than 90% of participants on day 29 after the first dose, and a second dose increased titer by a factor of 2.6–2.9. These findings suggest that the Ad26.COV2.S vaccine is safe and effective in both younger and older adults with minimal side effects.

- Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With Coronavirus Disease 2019 (COVID-19; Metcovid): A Randomized, Double-blind, Phase IIb, Placebo-controlled Trial: Brazilian researchers conducted a randomized, double-blinded, placebo-controlled, Phase 2b trial between April 18 and June 16, 2020 to assess the efficacy of methylprednisolone (MP) in treating hospitalized COVID-19 patients. They performed modified intention to treat (mITT) analysis of 393 participants (194 in MP and 199 in placebo group) and found no significant difference in the primary outcome (28 day mortality) and secondary outcomes between the two groups. Post hoc analysis revealed lower 28 day mortality in ages over 60 in the MP group. Authors conclude that methylprednisolone did not lower mortality in hospitalized COVID-19 patients.

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SARS-COV-2-SPECIFIC ANTIBODIES IN BREAST MILK AFTER COVID-19 VACCINATION OF BREASTFEEDING WOMEN

Perl SH, Uzan-Yulzari A, Klainer H, Asiskovich L, Youngster M, Rinott E, Youngster I.. JAMA. 2021 May 18;325(19):2013-2014. doi: 10.1001/jama.2021.5782.

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

BLUF

A prospective cohort study conducted by researchers affiliated with multiple medical centers in Israel included 84 breastfeeding women who received 2 doses of the Pfizer-BioNTech vaccine between December 23, 2020 and January 15, 2021 and found positive levels of anti-SARS-CoV-2-specific IgA antibodies (ABs) in breast milk in 61.8% of samples 2 weeks after the first dose, 86.1% after 4 weeks, and 65.7% after 6 weeks as well as anti-SARS-CoV-2-specific IgG ABs in 91.7% at week 5 and 97% in weeks 5-6 (Figure 1). There were no serious adverse events reported during the study period but 47 (55.9%) and 52 (61.9%) reported vaccine-related adverse events after the first and second dose, respectively (Table 1). These findings suggest the antibodies found in breast milk showed strong neutralizing effects and potentially provide a protective effect in infants as protection against SARS-CoV-2 infection.

FIGURES

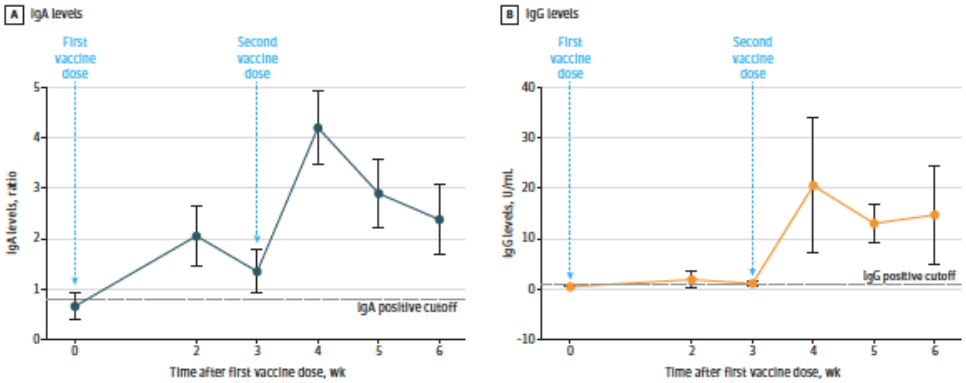

Figure 1. Changes in Levels of IgA and IgG in Breast Milk Over Time

A, All the comparisons between time points are P < .001. B, The comparison point at week 4 is P = .004; at week 5, P <.001; and at week 6, P = .005.

Data points represent means; error bars, 95%CIs.

	No. (%)
Study participants, No.	84
Maternal features	
Maternal age, mean (SD), y	34 (4)
No. of children, mean (SD)	2.36 (0.98)
Chronic diseases	22 (26.2)
Gestational diabetes	3 (3.6)
First vaccine adverse effects	47 (55.9)
Local pain	40 (47.6)
Fatigue	8 (9.5)
Fever	0
Other	12 (14.3)
Second vaccine adverse effects	52 (61.9)
Local pain	34 (40.5)
Fatigue	28 (33.3)
Fever	10 (11.9)
Other	22 (26.2)
Infant related features	
Vaginal delivery mode	78 (92.9)
Infant age at time of first maternal vaccine, mean (SD), mo	10.32 (7.31)
Birth week, mean (SD)	39.01 (1.95)
Birth weight, mean (SD), g	3175.27 (502.33)
Exclusive breastfeeding	35 (41.6)

Table 1. Maternal and Infant Characteristics

ADULTS

ADULTS HOSPITALIZED WITH COVID-19 -UNITED STATES, MARCH-JUNE AND OCTOBER-DECEMBER 2020: IMPLICATIONS FOR THE POTENTIAL EFFECTS OF COVID-19 TIER-1 VACCINATION ON FUTURE HOSPITALIZATIONS AND OUTCOMES

Sami S, Tenforde MW, Talbot HK, Lindsell CJ, Steingrub JS, Shapiro NI, Ginde AA, Douin DJ, Prekker ME, Erickson HL, Brown SM, Peltan ID, Gong MN, Khan A, Exline MC, Files DC, Gibbs KW, Rice TW, Casey JD, Grijalva CG, Stubblefield WB, Womack KN, Hager DN, Qadir N, Chang SY, Henning DJ, Wilson JG, Self WH, Patel MM; IVY Network Investigators.. Clin Infect Dis. 2021 May 12:ciab319. doi: 10.1093/cid/ciab319. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A team of researchers from the CDC COVID-19 Response Team conducted an observational study on 647 adults hospitalized due to COVID-19, 434 of whom were hospitalized during March 31 - June 4 2020, and 213 hospitalized during October 31 - December 31 2020. 91% of all hospitalized patients had at least one risk factor for severe COVID-19 (living in long-term care facilities (LTCFs), aged 65 years or more, or having at least 1 high-risk condition). A significant decrease in hospitalizations among people living in LTCFs was seen in the October-December cohort compared to the March-June group, suggesting that those in high-risk groups be prioritized for COVID-19 vaccination to reduce hospitalizations and prevent mortality.

ABSTRACT

BACKGROUND: Because of the increased risk for severe coronavirus disease 2019 (COVID-19), the Advisory Committee on Immunization Practices (ACIP) initially prioritized COVID-19 vaccination for persons in long-term care facilities (LTCF), persons aged >=65 years, and persons aged 16-64 years with high-risk medical conditions when there is limited vaccine supply. We compared characteristics and severe outcomes of hospitalized patients with COVID-19 in the United States between early and later in the pandemic categorized by groups at higher risk of severe COVID-19. METHODS: Observational study of sampled patients aged >=18 years who tested positive for SARS-CoV-2 and admitted to one of 14 academic hospitals in the United States during March-June and October-December 2020. Demographic and clinical information were gathered from electronic health record data. RESULTS: Among 647 patients, 91% met >=1 of the following risk factors for severe

COVID-19 [91% March-June (n=434); 90% October-December (n=213)]; 19% were LTCF residents, 45% were aged >=65-years, and 84% had >=1 high-risk condition. The proportion of patients who resided in a LTCF declined significantly (25% vs. 6%) from early to later pandemic periods. Compared with patients at lower risk for severe COVID-19, in-hospital mortality was higher among patients at high risk for severe COVID-19 (20% vs. 7%); these differences were consistently observed between March-June and October-December. CONCLUSIONS: Most adults hospitalized with COVID-19 were those recommended to be prioritized for vaccination based on risk for developing severe COVID-19. These findings highlight the urgency to vaccinate patients at high risk for severe COVID-19 and monitor vaccination impact on hospitalizations and outcomes.

CARDIOPULMONARY RECOVERY AFTER COVID-19: AN OBSERVATIONAL PROSPECTIVE MULTICENTRE TRIAL

Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, Kurz K, Koppelstätter S, Haschka D, Petzer V, Boehm A, Aichner M, Tymoszuk P, Lener D, Theurl M, Lorsbach-Köhler A, Tancevski A, Schapfl A, Schaber M, Hilbe R, Nairz M, Puchner B, Hüttenberger D, Tschurtschenthaler C, Aßhoff M, Peer A, Hartig F, Bellmann R, Joannidis M, Gollmann-Tepeköylü C, Holfeld J, Feuchtner G, Egger A, Hoermann G, Schroll A, Fritsche G, Wildner S, Bellmann-Weiler R, Kirchmair R, Helbok R, Prosch H, Rieder D, Trajanoski Z, Kronenberg F, Wöll E, Weiss G, Widmann G, Löffler-Ragg J, Tancevski I.. Eur Respir J. 2021 Apr 29;57(4):2003481. doi: 10.1183/13993003.03481-2020. Print 2021 Apr.
Level of Evidence: 3 - Local non-random sample

BLUF

A multidisciplinary team of researchers associated with Medical University of Innsbruck, Austria conducted an observational prospective study on the cardiopulmonary damage in 145 patients recovering from hospitalization due to COVID-19. 100 days after confirmed diagnosis, 41% of patients had persistent symptoms such as dyspnea (Figure 1) and 21% had a reduced diffusing lung capacity (p<0.001; Table 2), and 63% of patients had bilateral ground-glass opacities and/or reticulation in lower long lobes as seen on CT scans (Figure 2). Improvements in symptoms and CT findings were noted at 100 days compared to 60 days post-onset, but there was still significant cardiopulmonary damage indicating that the effects of COVID-19 may persist for a considerable period of time after recovery; further research is necessary to investigate the duration and severity of these effects.

ABSTRACT

BACKGROUND: After the 2002/2003 SARS outbreak, 30% of survivors exhibited persisting structural pulmonary abnormalities. The long-term pulmonary sequelae of coronavirus disease 2019 (COVID-19) are yet unknown, and comprehensive clinical follow-up data are lacking. METHODS: In this prospective, multicentre, observational study, we systematically evaluated the cardiopulmonary damage in subjects recovering from COVID-19 at 60 and 100 days after confirmed diagnosis. We conducted a detailed questionnaire, clinical examination, laboratory testing, lung function analysis, echocardiography, and thoracic low-dose computed tomography (CT). RESULTS: Data from 145 COVID-19 patients were evaluated, and 41% of all subjects exhibited persistent symptoms 100 days after COVID-19 onset, with dyspnea being most frequent (36%). Accordingly, patients still displayed an impaired lung function, with a reduced diffusing capacity in 21% of the cohort being the most prominent finding. Cardiac impairment, including a reduced left ventricular function or signs of pulmonary hypertension, was only present in a minority of subjects. CT scans unveiled persisting lung pathologies in 63% of patients, mainly consisting of bilateral ground-glass opacities and/or reticulation in the lower lung lobes, without radiological signs of pulmonary fibrosis. Sequential follow-up evaluations at 60 and 100 days after COVID-19 onset demonstrated a vast improvement of both, symptoms and CT abnormalities over time. CONCLUSION: A relevant percentage of post-COVID-19 patients presented with persisting symptoms and lung function impairment along with pulmonary abnormalities more than 100 days after the diagnosis of COVID-19. However, our results indicate a significant improvement in symptoms and cardiopulmonary status over time.

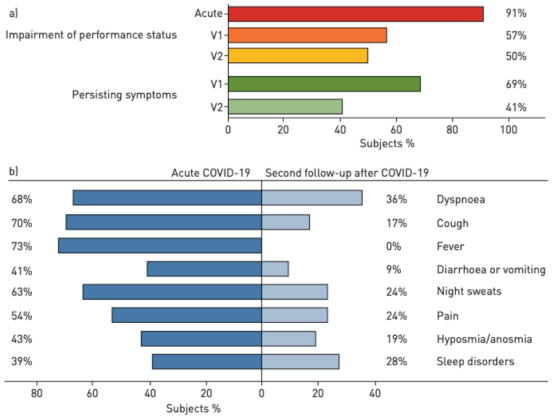

Figure 1. Symptom burden in the Development of Interstitial Lung Disease (ILD) in Patients with SARS-CoV-2 infection (CovILD) study cohort during acute coronavirus disease 2019 (COVID-19) and at follow-up. a) Using a standardised questionnaire, performance status and overall burden of symptoms were assessed for the time-point of disease onset, 60 days (V1), and 100 days (V2) after diagnosis of COVID-19. b) Symptom burden was assessed using a standardised questionnaire at COVID-19 onset and at 100 days post-COVID-19 diagnosis. All symptoms significantly improved over time (p<0.001 for all read-outs). nacute=145, nfollow-up=135

	First follow-up#	Second follow-up¶	p-value time change
Subjects	126	133	
Lung function impaired+	53 (42)	48 (36)	0.388
FVC L	3.6±1.0	3.7±0.9	**<0.001**
FVC <80% predicted	34 (27)	29 (22)	**0.049**
FEV_1 L	2.9±0.8	3.0±0.8	**0.001**
FEV_1 <80% predicted	28 (22)	30 (22)	1.000
FEV_1/FVC %	84±11	80±11	**<0.001**
FEV_1/FVC <70%	5 (4)	11 (8)	0.063
TLC L	6.2±1.3	6.2±1.3	0.881
TLC <80% predicted	14 (11)	15 (11)	0.791
D_{LCO} mmol·min^{-1}·kPa^{-1}	7.7±2.4	7.9±2.3	**<0.001**
D_{LCO} <80% predicted	39 (31)	28 (21)	**0.022**
P_{O_2} mmHg	79±10	78±9	0.864
P_{O_2} <75 mmHg	40 (32)	45 (37)	0.871

Data are presented as n, n (%) or mean±SD, unless otherwise stated. Bold type represents statistical significance. Wilcoxon signed-rank test and McNemar test were used to assess time-related differences. FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; P_{O_2}: partial pressure of oxygen assessed with blood gas analysis (without oxygen supplementation). #: 60 days after COVID-19 diagnosis; ¶: 100 days after COVID-19 diagnosis; +: lung function was considered impaired if FVC, FEV_1, FEV_1/FVC ratio, TLC or D_{LCO} were below the predicted normal.

Table 2. Pulmonary function of coronavirus disease 2019 (COVID-19) patients at follow-up

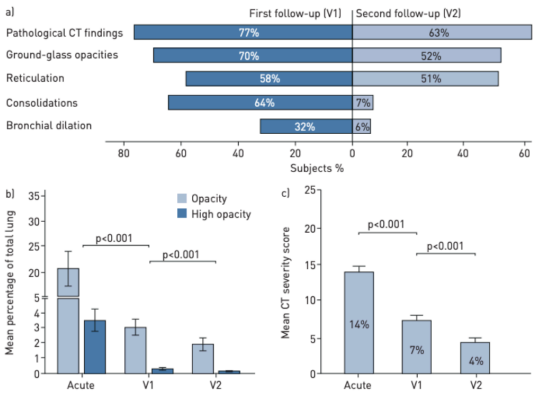

Figure 2. Chest computed tomography (CT) lung analysis at coronavirus disease 2019 (COVID-19) onset and follow-up. a) The pattern of pathological findings assessed with CT at 60 (V1) and 100 days (V2) after diagnosis of COVID-19. b) Automated analysis of lung opacities assessed on CT scans from the acute disease phase, 60 days and 100 days after COVID-19 diagnosis employing Syngo.via CT Pneumonia Analysis software (Siemens Healthineers, Erlangen, Germany). c) CT severity scoring by radiologists at COVID-19 onset, 60 days and 100 days after COVID-19 diagnosis. The severity score was calculated via CT evaluation by three independent radiologists who qualitatively graded lung impairment for each lobe separately (grade 0–5, with 0 for no involvement and 5 for massive involvement). A total score was achieved by summation of grades for all five lobes (maximum 25 points). Data are presented as mean±SE. nacute=23, nV1=145, nV2=135.

TEMPORAL DIFFERENCES IN CULTURABLE SARS-COV-2 FROM THE RESPIRATORY AND GASTRO-INTESTINAL TRACTS IN A PATIENT WITH MODERATE COVID-19

Audsley J, Holmes NE, Mordant FL, Douros C, Zufan SE, Nguyen THO, Kedzierski L, Rowntree LC, Hensen L, Subbarao K, Kedzierska K, Nicholson S, Sherry N, Thevarajan I, Tran T, Druce J.. Infect Control Hosp Epidemiol. 2021 May 10:1-10. doi: 10.1017/ice.2021.223. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

In a letter to the editor, infectious disease researchers associated with the University of Melbourne and Royal Melbourne Hospital present a case study of a 63-year-old HIV-positive male with SARS-CoV-2 RNA detected in RT-PCR of sputum on day 5 of symptoms and of feces on day 9. By day 53, when all RT-PCR were negative, neutralizing antibody development was detected and persisted at day 116 (Figure 1). These results indicate virus isolation in feces after respiratory cultures, suggesting that fecal-oral transmission of SARS-CoV-2 may still be a risk even after respiratory sputum samples are negative.

SUMMARY

- In addition to HIV, the patient has a history of ischemic heart disease, stage 3a chronic kidney disease, and previous non-Hodgkin's lymphoma that was treated.

FIGURES

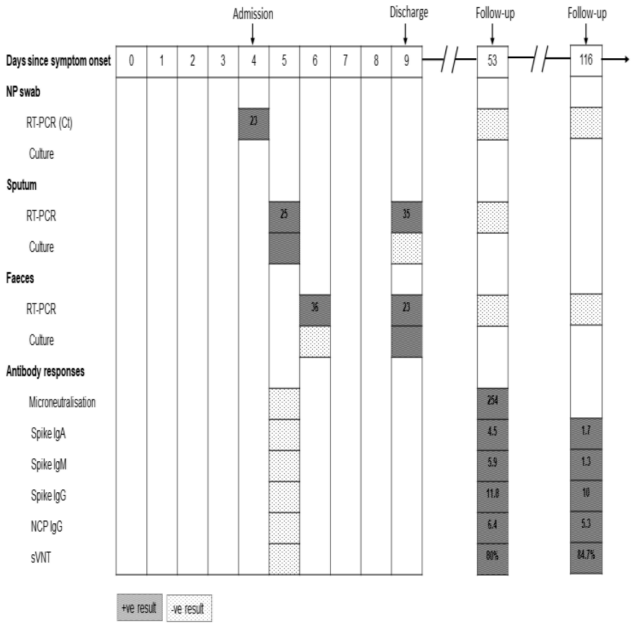

Figure 1. SARS-CoV-2 shedding, viral isolation and antibody development in a recovered COVID infected HIV-positive individual. Red rectangles indicate positive results and green rectangles indicate negative/undetected results. The numbers in RT-PCR rectangles are cycle threshold (Ct) values; while numbers in antibody response rectangles are titres for microneutralisation assays and index values for IgA/IgM/IgG Ig – immunoglobulin; NCP – nucleoscapsid; NP – nasopharyngeal; sVNT – surrogate virus neutralisation test

PREGNANT PERSONS

ADVERSE PREGNANCY OUTCOMES, MATERNAL COMPLICATIONS, AND SEVERE ILLNESS AMONG U.S. DELIVERY HOSPITALIZATIONS WITH AND WITHOUT A COVID-19 DIAGNOSIS

Ko JY, DeSisto CL, Simeone RM, Ellington S, Galang RR, Oduyebo T, Gilboa SM, Lavery AM, Gundlapalli AV, Shapiro-Mendoza CK.. Clin Infect Dis. 2021 May 12:ciab344. doi: 10.1093/cid/ciab344. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

A multi-center retrospective cohort study conducted by researchers from the CDC COVID-19 Response Team and United States Public Health Service Corps investigated 489,471 pregnant patients who delivered at 703 hospitals between March and September 2020. 6,550 of those patients had confirmed COVID-19, which was associated with increased risk for severe adverse outcomes including ARDS, death, and sepsis, as well as preterm labor with preterm delivery (Table 2), and longer hospitalization time (Figure 1). These findings signify the importance of implementation of mitigation strategies, counseling, and clinical attention to lessen the risk of SARS-CoV-2 infection for pregnant women given the increased risk for adverse events.

SUMMARY

COVID-19 infection among pregnant patients was associated with an increased risk for ARDS (adjusted risk ratio = 34.4), death (aRR = 17), sepsis (aRR = 13.6), mechanical ventilation (aRR = 12.7), shock (aRR = 5.1), ICU admission (aRR=3.6), acute renal failure (aRR = 3.5), thromboembolic disease (aRR = 2.7), adverse cardiac event/outcome (aRR = 2.2), and preterm labor with preterm delivery (aRR = 1.2)

ABSTRACT

BACKGROUND: Evidence on risk for adverse outcomes from COVID-19 among pregnant women is still emerging. We examined the association between COVID-19 at delivery and adverse pregnancy outcomes, maternal complications, and severe illness, whether these associations differ by race/ethnicity; and described discharge status by COVID-19 diagnosis and maternal complications. METHODS: Data from 703 hospitals in the Premier Healthcare Database during March-September 2020 were included. Adjusted risk ratios overall and stratified by race/ethnicity were estimated using Poisson regression with robust standard errors. Proportion not discharged home was calculated by maternal complications, stratified by COVID-19 diagnosis. RESULTS: Among 489,471 delivery hospitalizations, 6,550 (1.3%) had a COVID-19 diagnosis. In adjusted models, COVID-19 was associated with increased risk for: acute respiratory distress syndrome (adjusted risk ratio [aRR] = 34.4), death (aRR = 17.0), sepsis (aRR = 13.6), mechanical ventilation (aRR = 12.7), shock (aRR = 5.1), intensive care unit admission (aRR = 3.6), acute renal failure (aRR = 3.5), thromboembolic disease (aRR = 2.7), adverse cardiac event/outcome (aRR = 2.2) and preterm labor with preterm delivery (aRR = 1.2). Risk for any maternal complications or for any severe illness did not significantly differ by race/ethnicity. Discharge status did not differ by COVID-19; however, among women with concurrent maternal complications, a greater proportion of those with (versus without) COVID-19 were not discharged home. CONCLUSIONS: These findings emphasize the importance of implementing recommended mitigation strategies to reduce risk for SARS-CoV-2 infection and further inform counseling and clinical care for pregnant women during the COVID-19 pandemic.

Outcomes[b]	Diagnosis, No. (%)			Risk ratio (95% CI)	
	Total (N = 489,471)	COVID-19 (n = 6,550)	No COVID-19 (n = 482,921)	Unadjusted	Adjusted[c]
Any adverse pregnancy outcome[d]	20,774 (4.2)	372 (5.7)	20,402 (4.2)	1.3 (1.2–1.5)	1.2 (1.1–1.3)
Preterm labor with preterm delivery	17,707 (3.6)	315 (4.8)	17,392 (3.6)	1.3 (1.2–1.5)	1.2 (1.1–1.3)
Stillbirth	3,502 (0.7)	63 (1.0)	3,439 (0.7)	1.4 (1.1–1.7)	1.2 (1.0–1.6)
Any maternal complication[e]	3,691 (0.8)	291 (4.4)	3,400 (0.7)	6.3 (5.6–7.1)	6.3 (5.5–7.3)
Acute renal failure	775 (0.2)	41 (0.6)	734 (0.2)	4.1 (3.0–5.6)	3.5 (2.5–5.0)
Adverse cardiac event/ outcome[f]	1,601 (0.3)	41 (0.6)	1560 (0.3)	1.9 (1.4–2.6)	2.2 (1.6–2.9)
Thromboembolic disease[g]	546 (0.1)	19 (0.3)	527 (0.1)	2.7 (1.7–4.2)	2.7 (1.7–4.4)
Acute respiratory distress syndrome	644 (0.1)	218 (3.3)	426 (0.1)	37.7 (32.1–44.3)	34.4 (29.0–40.8)
Shock	404 (0.1)	30 (0.5)	374 (0.1)	5.9 (4.1–8.6)	5.1 (3.4–7.8)
Sepsis	476 (0.1)	85 (1.3)	391 (0.1)	16.0 (12.7–20.2)	13.6 (10.2–18.1)
Any maternal severe illness[h]	7,900 (1.6)	307 (4.7)	7,593 (1.6)	3.0 (2.7–3.3)	3.5 (2.8–4.3)
ICU admission	7,682 (1.6)	293 (4.5)	7,389 (1.5)	2.9 (2.6–3.3)	3.6 (2.8–4.5)
Mechanical ventilation	688 (0.1)	105 (1.6)	583 (0.1)	13.3 (10.8–16.3)	12.7 (9.2–17.5)
Discharge status					
Death	41 (0.0)	9 (0.1)	32 (0.0)	20.7 (9.9–43.4)	17.0 (8.2–35.4)
Discharged home	484,085 (98.9)	6,403 (97.8)	477,682 (98.9)	1.0 (1.0–1.0)	1.0 (1.0–1.0)
Discharged, other care	4,263 (0.9)	116 (1.8)	4,147 (0.9)	2.1 (1.7–2.5)	2.1 (1.8–2.6)
Other/missing[i]	1,082 (0.2)	22 (0.3)	1,060 (0.2)	1.5 (1.0–2.3)	1.4 (1.0–2.1)
Readmission within 30 days	5,933 (1.2)	99 (1.5)	5,834 (1.2)	1.3 (1.0–1.5)	1.2 (1.0–1.4)

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; RR = risk

Table 2. Adverse pregnancy outcomes and maternal complications associated with a documented COVID-19 diagnosis at delivery hospitalization — United States, March–September 2020a

Abbreviations: CI = confidence interval; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; RR = risk ratio.

a Premier Healthcare Database, 703 hospitals with delivery hospitalizations, March–September 2020.

b Outcomes are not mutually exclusive, with exception of discharge status categories.

c Adjusted for hospital (to account for within facility correlation), maternal age, race/ethnicity, primary payor, obesity, any diabetes, any hypertension, and asthma.

d Includes preterm labor with preterm delivery and stillbirth.

e Includes acute renal failure, adverse cardiac event/outcome, thromboembolic disease, acute respiratory distress syndrome, shock, and sepsis.

f Includes acute myocardial infarction, cardiomyopathy, heart failure/arrest during surgery or procedure, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, incident ventricular tachycardia, ischemia, pulmonary edema/acute heart failure, and atrial fibrillation/atrial flutter/supraventricular tachycardia.

g Includes deep vein thrombosis and other thromboembolic disease.

h Includes ICU admission, mechanical ventilation, and death.

i Includes "left against medical advice," "discharged to law enforcement," "still a patient," (n = 19) and "missing" (n = 107); none had a COVID-diagnosis.

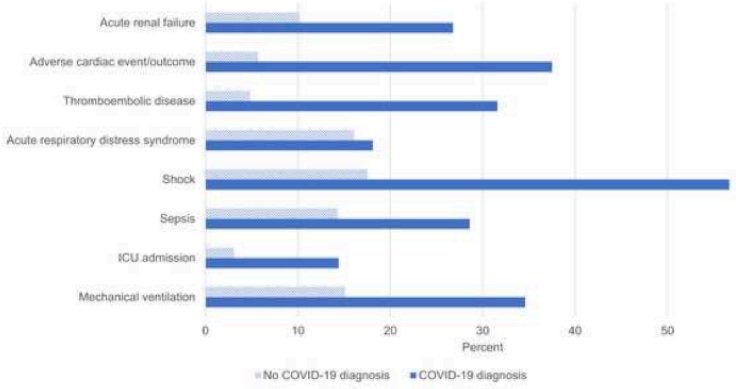

Figure 1. Percentage of women not discharged home a by selected maternal complications, stratified by COVID-19 diagnosis at delivery hospitalization — Premier Healthcare Database, United States, March–September 2020 b

a Women not discharged home includes women who expired, were discharged to another facility, or who had other or missing discharge status.

b Premier Healthcare Database, 703 hospitals with delivery hospitalizations, March–September 2020

SARS-COV-2 ACE2 AND TMPRSS2 RECEPTOR PROTEIN EXPRESSION PATTERNS THROUGHOUT GESTATION

Roberts DJ, Bebell LM, Edlow AG.. J Infect Dis. 2021 Apr 21:jiab164. doi: 10.1093/infdis/jiab164. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

An immunohistochemistry study conducted by researchers affiliated with Massachusetts General Hospital in Boston, MA examined patients who underwent therapeutic pregnancy termination or preterm delivery between January 1, 2019 and December 1, 2020 and found ACE2 expression (primary SARS-CoV-2 receptor) in the villous syncytiotrophoblast (ST), cytotrophoblast (CT) and extravillous trophoblasts (EVT) (Figure 1), favoring basal expression in 10/12 cases, circumferential expression in early gestation, and more polarized expression in later gestation (Table 1). TMPRSS2 (spike proteinase required for SARS-CoV-2 infection) was not commonly detected in villous tissues or placental endothelium (Figure 2). These findings suggest that polarized ACE2 expression away from maternal blood limits viral adhesion to ST and absence of TMPRSS2 in the ST limits viral entry into the villous trophoblast. However, due to circumferential ST expression in early gestation, even though maternal to fetal transmission of SARS-CoV-2 is rare, earlier gestation pregnancies may be more vulnerable to infection than later gestational pregnancies.

ABSTRACT

We previously demonstrated that the late gestation placental expression pattern of ACE2 (the primary SARS-CoV-2 receptor) is localized to the villous syncytiotrophoblast (ST), usually in a polarized membranous pattern at the ST base sparing the apical surface (that directly exposed to maternal blood). We found that the late gestation placental expression pattern of TMPRSS2 (the spike proteinase required for SARS-CoV-2 cellular infection), is usually absent in the trophoblast but rarely, weakly expressed in the placental endothelium. We now show the developmental protein expression patterns of ACE2 and TMPRSS2 by immunohistochemistry throughout gestation, from first through third trimester. We found TMPRSS2 expression was rarely detectable in villous endothelium and very rarely detectable in the ST across gestation. We found ACE2 expression varied during gestation with circumferential ST expression more common in early gestations and polarized expression more common in later gestation. Although this study is small, these preliminary results suggest that earlier gestation pregnancies may be more vulnerable to infection than later gestation pregnancies.

FIGURES

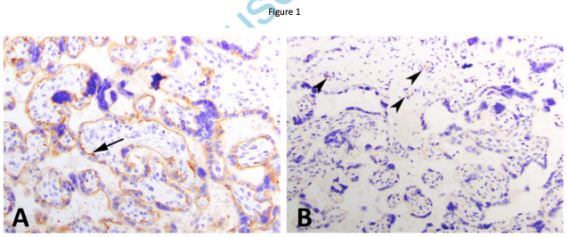

Figure 1. ACE2 and TMPRSS2 expression in the placenta of a woman testing negative for SARS- CoV-2 at 33 weeks 4 days (new figure from a case published in [14])
A. ACE2 expression showing polarized expression of ACE2 in the ST basally (towards the stromal side of the ST) cells (arrow) with absent apical expression. 20X.
B. TMPRSS2 expression showing very weak expression in the villous endothelium (arrowheads). 20X.
ST - syncytiotrophoblast

Case number	Gestational age (weeks)	Clinical history	ACE2 expression pattern in ST	TMPRSS2 expression
1	5 + 3d	TAB	~80 % circumferential,~20% polarized	Very weakly positive in ST and endometrial glands
2	7	TAB	Polarized	Negative
3	8	TAB	~75% polarized, ~25% circumferential	Negative
4	8 + 5d	TAB	Polarized	Negative
5	8 + 6d	TAB	~80% polarized, ~20% circumferential	Faint, villous endothelium
6	12	TAB, fetal anencephaly	Circumferential	Negative in ST, weakly positive in endometrial glands
7	18	PPROM	~80% polarized, ~20% circumferential	Negative
8	21	TAB, AV Canal defect	Polarized	Negative
9	23	TAB, fetal forebrain anomalies	~50% polarized, ~50% circumferential	Negative
10	28	PET with severe features	Polarized	Faint, villous endothelium
11	33	Chorio, NRFHT	~20% polarized, ~80% circumferential	Negative
12	36	IUGR, Breech, severe oligo	~80% polarized, ~20% circumferential	Negative

Table 1 Case Data

AV Canal – atrioventricular canal heart defect, Chorio – acute chorioamnionitis, d – days, IUGR – intrauterine growth restriction, NRFHT – non-reassuring fetal testing, oligo – oligohydramnios, PET – pre-eclampsia, PPROM – preterm premature rupture of membranes, ST – syncytiotrophoblast, TAB – therapeutic abortion

Figure 2

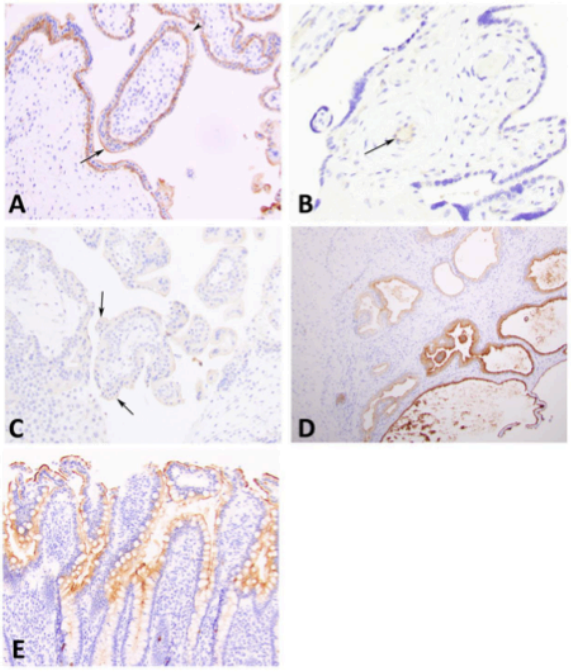

Figure 2. ACE2 and TMPRSS2 expression in early gestation

A. ACE2 expression in case 5 showing both polarized expression (arrowhead) and circumferential expression (arrow) in the same villous ST. 20X.

B. TMPRSS2 expression in case 10 showing weak staining in the villous endothelium (arrow). 40X.

C. TMPRSS2 expression in case 1 showing very weak expression in circumferentially in the villous ST (arrows). 20X.

D. TMPRSS2 control expression in prostatic epithelium. Note that weaker expression in some of the glandular epithelium is similar to that in B and C. 10X.

E. ACE2 control expression in small intestinal epithelium. 20X.

SAFETY, IMMUNOGENICITY, AND EFFICACY OF THE BNT162B2 COVID-19 VACCINE IN ADOLESCENTS

Frenck RW Jr, Klein NP, Kitchin N, Gurtman A, Absalon J, Lockhart S, Perez JL, Walter EB, Senders S, Bailey R, Swanson KA, Ma H, Xu X, Koury K, Kalina WV, Cooper D, Jennings T, Brandon DM, Thomas SJ, Türeci Ö, Tresnan DB, Mather S, Dormitzer PR, Şahin U, Jansen KU, Gruber WC; C4591001 Clinical Trial Group.. N Engl J Med. 2021 May 27. doi: 10.1056/NEJMoa2107456. Online ahead of print.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

A research team from Cincinnati Children's Hospital (OH), Kaiser Permanente Vaccine Study Center (CA), and the California Research Foundation, San Diego (CA) funded by BioNTech and Pfizer used a multinational, placebo-controlled, observer-blinded trial of 30 µg of BNT162b2 delivered in two doses to determine immunogenicity in 12-to-15-year-old participants. 1131 received BNT162b2, and 1129 received placebo; there were no vaccine-related serious adverse events and few overall severe adverse events. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was determined by measuring neutralizing titers after dose 2. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100) and no COVID-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients (who did not have previous infection), while 16 cases occurred in placebo recipients. Overall, BNT162b2 vaccine in 12-to-15-year-olds produced a greater immune response than in young adults and was shown to be both safe and highly effective.

ABSTRACT

BACKGROUND: Until very recently, vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) had not been authorized for emergency use in persons younger than 16 years of age. Safe, effective vaccines are needed to protect this population, facilitate in-person learning and socialization, and contribute to herd immunity. METHODS: In this ongoing multinational, placebo-controlled, observer-blinded trial, we randomly assigned participants in a 1:1 ratio to receive two injections, 21 days apart, of 30 mug of BNT162b2 or placebo. Noninferiority of the immune response to BNT162b2 in 12-to-15-year-old participants as compared with that in 16-to-25-year-old participants was an immunogenicity objective. Safety (reactogenicity and adverse events) and efficacy against confirmed coronavirus disease 2019 (Covid-19; onset, >=7 days after dose 2) in the 12-to-15-year-old cohort were assessed. RESULTS: Overall, 2260 adolescents 12 to 15 years of age received injections; 1131 received BNT162b2, and 1129 received placebo. As has been found in other age groups, BNT162b2 had a favorable safety and side-effect profile, with mainly transient mild-to-moderate reactogenicity (predominantly injection-site pain [in 79 to 86% of participants], fatigue [in 60 to 66%], and headache [in 55 to 65%]); there were no vaccine-related serious adverse events and few overall severe adverse events. The geometric mean ratio of SARS-CoV-2 50% neutralizing titers after dose 2 in 12-to-15-year-old participants relative to 16-to-25-year-old participants was 1.76 (95% confidence interval [CI], 1.47 to 2.10), which met the noninferiority criterion of a lower boundary of the two-sided 95% confidence interval greater than 0.67 and indicated a greater response in the 12-to-15-year-old cohort. Among participants without evidence of previous SARS-CoV-2 infection, no Covid-19 cases with an onset of 7 or more days after dose 2 were noted among BNT162b2 recipients, and 16 cases occurred among placebo recipients. The observed vaccine efficacy was 100% (95% CI, 75.3 to 100). CONCLUSIONS: The BNT162b2 vaccine in 12-to-15-year-old recipients had a favorable safety profile, produced a greater immune response than in young adults, and was highly effective against Covid-19. (Funded by BioNTech and Pfizer; C4591001 ClinicalTrials.gov number, NCT04368728.).

Efficacy End Point†	BNT162b2		Placebo		% Vaccine Efficacy (95% CI)‡
	No. of Participants with Event/Total No.§	Surveillance Time (No. at Risk)¶	No. of Participants with Event/Total No.§	Surveillance Time (No. at Risk)¶	
Covid-19 occurrence at least 7 days after dose 2 in participants without evidence of previous infection	0/1005	0.154 (1001)	16/978	0.147 (972)	100 (75.3–100)
Covid-19 occurrence at least 7 days after dose 2 in participants with or without evidence of previous infection	0/1119	0.170 (1109)	18/1110	0.163 (1094)	100 (78.1–100)

Table 3. Vaccine Efficacy against Covid-19 in Participants 12 to 15 Years of Age.*

* Results are for the efficacy population that could be evaluated, which included all eligible 12-to-15-year-old participants who received two doses of BNT162b2 or placebo as randomly assigned, with dose 2 received within the prespecified window, and had no major protocol deviations.

† Participants without evidence of previous infection were those who had no serologic or virologic evidence of past SARS-CoV-2 infection before 7 days after dose 2 (i.e., N-binding antibody testing [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2) and had negative NAAT results (nasal swab) at any unscheduled visit before 7 days after dose 2.

‡ The 95% confidence interval for vaccine efficacy was derived on the basis of the Clopper–Pearson method with adjustment for surveillance time.

§ The number of participants with a first occurrence of Covid-19 at 7 or more days after dose 2 and the total number of participants with data are shown.

¶ Total surveillance time in 1000 person-years for the given end point across all participants within each group of participants who were at risk for the end point is shown. The period for Covid-19 case accrual was from 7 days after dose 2 to the end of the surveillance period.

Age Group	No. of Participants	Geometric Mean 50% Neutralizing Titer (95% CI)†	Geometric Mean Ratio (95% CI), 12 to 15 Yr vs. 16 to 25 Yr‡
12–15 yr	190	1239.5 (1095.5–1402.5)	1.76 (1.47–2.10)
16–25 yr	170	705.1 (621.4–800.2)	—

Table 2. SARS-CoV-2 Serum Neutralization Assay Results 1 Month after Dose 2 of BNT162b2 among Participants without Evidence of Infection.

* Results are for the subset of participants in the dose 2 immunogenicity population that could be evaluated (i.e., participants who underwent randomization and received two BNT162b2 doses in accordance with the protocol, received dose 2 within the prespecified window, had at least one valid and determinate immunogenicity result from a blood sample obtained within 28 to 42 days after dose 2, and had no major protocol deviations) who had no evidence of previous SARS-CoV-2 infection. Participants without evidence of previous infection were those who had no serologic or virologic evidence (up to 1 month after receipt of the last dose) of past SARS-CoV-2 infection (i.e., N-binding antibody [serum] negative at vaccination visit 1 and SARS-CoV-2 not detected by NAAT [nasal swab] at vaccination visits 1 and 2) and had negative NAAT results (nasal swab) at any unscheduled visit up to 1 month after dose 2.

† Geometric mean titers and two-sided 95% confidence intervals were calculated by exponentiating the mean logarithm of the titers and the corresponding confidence intervals (based on the Student's t distribution). Assay results below the lower limit of quantitation were set to 0.5 times the lower limit of quantitation.

‡ The geometric mean ratio and two-sided 95% confidence intervals were calculated by exponentiating the mean difference of the logarithms of the titers (the 12-to-15-year-old cohort minus the 16-to-25-year-old cohort) and the corresponding confidence intervals (based on the Student's t distribution). The noninferiority criterion was met, since the lower boundary of the two-sided confidence interval for the geometric mean ratio was greater than 0.67.

ASSOCIATION OF MATERNAL SARS-COV-2 INFECTION IN PREGNANCY WITH NEONATAL OUTCOMES

Norman M, Navér L, Söderling J, Ahlberg M, Hervius Askling H, Aronsson B, Byström E, Jonsson J, Sengpiel V, Ludvigsson JF, Håkansson S, Stephansson O.. JAMA. 2021 May 25;325(20):2076-2086. doi: 10.1001/jama.2021.5775.
Level of Evidence: 3 - Cohort study or control arm of randomized trial

BLUF

In a cohort study of 88,159 newborn infants in Sweden between March 11, 2020 and January 31, 2021, researchers found that 2,323 (1.6%) were delivered by mothers who tested positive for SARS-CoV-2 during pregnancy. The relations between confounding and mediator variables were identified (Figure 1), and the data showed small increases in select neonatal morbidities with maternal SARS-CoV-2 infection in pregnancy (Figure 2 and 3).

ABSTRACT

Importance: The outcomes of newborn infants of women testing positive for SARS-CoV-2 in pregnancy is unclear. Objective: To evaluate neonatal outcomes in relation to maternal SARS-CoV-2 test positivity in pregnancy. Design, Setting, and Participants: Nationwide, prospective cohort study based on linkage of the Swedish Pregnancy Register, the Neonatal Quality Register, and the Register for Communicable Diseases. Ninety-two percent of all live births in Sweden between March 11, 2020, and January 31, 2021, were investigated for neonatal outcomes by March 8, 2021. Infants with malformations were excluded. Infants of women who tested positive for SARS-CoV-2 were matched, directly and using propensity scores, on maternal characteristics with up to 4 comparator infants. Exposures: Maternal test positivity for SARS-CoV-2 in pregnancy. Main Outcomes and Measures: In-hospital mortality; neonatal resuscitation; admission for neonatal care; respiratory, circulatory, neurologic, infectious, gastrointestinal, metabolic, and hematologic disorders and their treatments; length of hospital stay; breastfeeding; and infant test positivity for SARS-CoV-2. Results: Of 88 159 infants (49.0% girls), 2323 (1.6%) were delivered by mothers who tested positive for SARS-CoV-2. The mean gestational age of infants of SARS-CoV-2-positive mothers was 39.2 (SD, 2.2) weeks vs 39.6 (SD, 1.8) weeks for comparator infants, and the proportions of preterm infants (gestational age <37 weeks) were 205/2323 (8.8%) among infants of SARS-CoV-2-positive mothers and 4719/85 836 (5.5%) among comparator infants. After matching on maternal characteristics, maternal SARS-CoV-2 test positivity was significantly associated with admission for neonatal care (11.7% vs 8.4%; odds ratio [OR], 1.47; 95% CI, 1.26-1.70) and with neonatal morbidities such as respiratory distress syndrome (1.2% vs 0.5%; OR, 2.40; 95% CI, 1.50-3.84), any neonatal respiratory disorder (2.8% vs 2.0%; OR, 1.42; 95% CI, 1.07-1.90), and hyperbilirubinemia (3.6% vs 2.5%; OR, 1.47; 95% CI, 1.13-1.90). Mortality (0.30% vs 0.12%; OR, 2.55; 95% CI, 0.99-6.57), breastfeeding rates at discharge (94.4% vs 95.1%; OR, 0.84; 95% CI, 0.67-1.05), and length of stay in neonatal care (median, 6 days in both groups; difference, 0 days; 95% CI, -2 to 7 days) did not differ significantly between the groups. Twenty-one infants (0.90%) of SARS-CoV-2-positive mothers tested positive for SARS-CoV-2 in the neonatal period; 12 did not have neonatal morbidity, 9 had diagnoses with unclear relation to SARS-CoV-2, and none had congenital pneumonia. Conclusions and Relevance: In a nationwide cohort of infants in Sweden, maternal SARS-CoV-2 infection in pregnancy was significantly associated with small increases in some neonatal morbidities. Given the small numbers of events for many of the outcomes and the large number of statistical comparisons, the findings should be interpreted as exploratory.

FIGURES

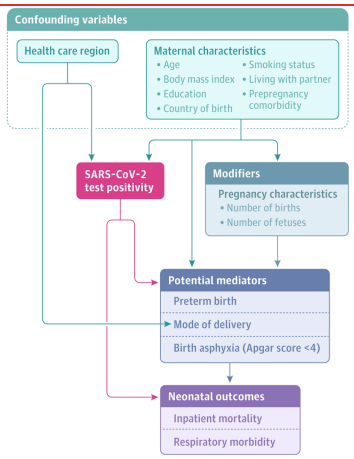

Figure 1. Conceptual Model of Relationships Between Maternal SARS-CoV-2 in Pregnancy, Birth Characteristics, and Neonatal Outcomes

Neonatal outcomes	Infants of SARS-CoV-2-positive mothers (n = 2323)	All infants of non-SARS-CoV-2-positive mothers (n = 85 836)	Matched infants of non-SARS-CoV-2-positive mothers (n = 9275)	Risk difference per 100 infants or median difference (95% CI)[a]	Conditional odds ratio (95% CI)
Resuscitation at birth					
Assisted ventilation (by mask or CPAP)	148 (6.4)	4232 (4.9)	470 (5.1)	1.3 (0.2 to 2.4)	1.28 (1.05 to 1.55)
Intubated at birth	14 (0.6)	251 (0.3)	29 (0.3)	0.3 (-0.0 to 0.6)	1.90 (1.00 to 3.59)
Admission to neonatal unit[b]	271 (11.7)	7351 (8.6)	776 (8.4)	3.3 (1.9 to 4.7)	1.47 (1.26 to 1.70)
Postterm	6/39 (15.4)	146/2042 (7.1)	16/268 (6.0)	9.4 (-2.3 to 21.1)	
Term or near-term	177/2194 (8.1)	5516/82 052 (6.7)	589/8830 (6.7)	1.4 (0.1 to 2.6)	
Preterm	88/90 (97.8)	1691/1742 (97.1)	171/177 (96.6)	1.2 (-2.9 to 5.2)	
Very preterm	38/38 (100)	650/675 (96.3)	61/66 (92.4)	7.6 (1.2 to 14.0)	
Admission hypothermia[c]	4/38 (10.5)	18/675 (2.7)	5/66 (7.6)	3.0 (-8.7 to 14.6)	
Neurologic disorders					
Hypoxic-ischemic encephalopathy stage 2-3[d]	3 (0.1)	82 (0.1)	7 (0.1)	0.1 (-0.1 to 0.2)	1.71 (0.44 to 6.63)
Neonatal convulsions	6 (0.3)	173 (0.2)	14 (0.2)	0.1 (-0.1 to 0.3)	1.71 (0.66 to 4.46)
Severe brain injury[e]	1/38 (2.6)	45/675 (6.7)	4/66 (6.1)	-3.4 (-11.1 to 4.3)	
Respiratory disorders and treatments					
Respiratory distress syndrome	29 (1.2)	508 (0.6)	50 (0.5)	0.7 (0.2 to 1.2)	2.40 (1.50 to 3.84)
Transient tachypnea of the newborn	33 (1.4)	893 (1.0)	117 (1.3)	0.2 (-0.4 to 0.7)	1.12 (0.76 to 1.65)
Meconium aspiration	3 (0.1)	117 (0.1)	13 (0.1)	-0.0 (-0.2 to 0.2)	0.92 (0.26 to 3.24)
CPAP	113 (4.9)	2985 (3.5)	348 (3.8)	1.1 (0.2 to 2.1)	1.32 (1.06 to 1.64)
Duration, d					
Median (IQR)	2 (1-4)	2 (1-3)	2 (1-2)	0 (0 to 0)	
Range	1-78	1-161	1-101		
Mechanical ventilation	23 (1.0)	435 (0.5)	46 (0.5)	0.5 (0.1 to 0.9)	2.04 (1.22 to 3.39)
Duration, d					
Median (IQR)	7 (2-8)	4 (2-9)	4 (2-8)	3 (∞ to 6)	
Range	1-23	1-70	1-70		
Surfactant administration[f]	16/38 (42.1)	283/675 (41.9)	28/66 (42.4)	-0.3 (-20.0 to 19.4)	
No. of administrations					
Median (IQR)	1 (1-2)	1 (1-2)	1 (1-2)	0 (0 to 0)	
Range	1-4	1-5	1-4		
Postnatal corticosteroids for lung disease[f]	2/38 (5.3)	62/675 (9.2)	7/66 (10.6)	-5.3 (-15.6 to 4.9)	
Need for oxygen at 28 d of postnatal age	0/38 (0)	11/675 (1.6)	3/66 (4.5)	-4.5 (-9.6 to 0.5)	
Any respiratory disorder[g]	65 (2.8)	1 557 (1.8)	184 (2.0)	0.8 (0.1 to 1.5)	1.42 (1.07 to 1.90)

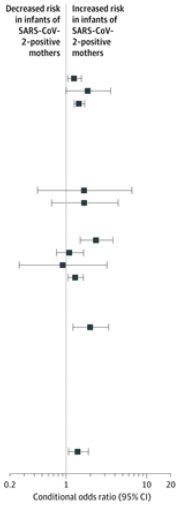

Figure 2. Neonatal Outcomes (Resuscitation at Birth, Admission to Neonatal Unit, Admission Hypothermia, Neurologic Disorders, and Respiratory Disorders and Treatments) Among Infants Born in Sweden (March 11, 2020–January 31, 2021) by Maternal SARS-CoV-2 Test Status in Pregnancy (Assessed as of March 8, 2021)

Neonatal outcomes	Infants of SARS-CoV-2-positive mothers (n = 2323)	All infants of non-SARS-CoV-2-positive mothers (n = 85 836)	Matched infants of non-SARS-CoV-2-positive mothers (n = 9275)	Risk difference per 100 infants or median difference (95% CI)[a]	Conditional odds ratio (95% CI)
Circulatory problems					
Persistent pulmonary hypertension	6 (0.3)	91 (0.1)	8 (0.1)	0.2 (-0.0 to 0.4)	3.00 (1.04 to 8.65)
Patent ductus arteriosus[b]	3/38 (7.9)	86/675 (12.7)	8/66 (12.1)	-4.2 (-15.9 to 7.4)	
Infections					
Pneumonia	3 (0.1)	85 (0.1)	8 (0.1)	0.0 (-0.1 to 0.2)	1.50 (0.40 to 5.65)
Sepsis (verified by blood culture)	4 (0.2)	75 (0.1)	7 (0.1)	0.1 (-0.1 to 0.3)	2.29 (0.67 to 7.81)
Antibiotic therapy	64 (2.8)	2119 (2.5)	190 (2.0)	0.7 (-0.0 to 1.4)	1.36 (1.02 to 1.82)
Metabolic or hematologic problems					
Hypoglycemia	54 (2.3)	1660 (1.9)	185 (2.0)	0.3 (-0.3 to 1.0)	1.17 (0.86 to 1.60)
Treated hyperbilirubinemia	84 (3.6)	2258 (2.6)	233 (2.5)	1.1 (0.3 to 1.9)	1.47 (1.13 to 1.90)
Blood transfusion	18 (0.8)	481 (0.6)	44 (0.5)	0.3 (-0.1 to 0.7)	1.64 (0.93 to 2.86)
Gastrointestinal disorder					
Surgery for necrotizing enterocolitis[b]	0/38 (0)	12/675 (1.8)	2/66 (3.0)	-3.0 (-7.2 to 1.1)	
In-hospital mortality					
Overall	7 (0.30)	96 (0.11)	11 (0.12)	0.2 (-0.1 to 0.4)	2.55 (0.99 to 6.57)
Gestational age <32 wk	4/38 (10.5)	56/675 (8.3)	8/66 (12.1)	-1.6 (-14.1 to 10.9)	
Length of hospital stay, d					
Infants not admitted for neonatal care					
Median (IQR)	2 (1-3)	2 (1-2)	2 (1-2)	0 (0 to 0)	
Range	0-24	0-28	0-20		
Missing data	187 (8.0)	4043 (4.7)	246 (2.7)		
Infants admitted for neonatal care					
Median (IQR)	6 (3-12)	6 (3-11)	6 (3-10)	0 (-2 to 7)	
Range	1-107	1-182	1-169		
Breastfeeding at discharge					
Yes	1888/2000 (94.4)	71 245/75 556 (94.3)	7873/8281 (95.1)	-0.7 (-1.8 to 0.4)	0.84 (0.67 to 1.05)
No	112/2000 (5.6)	4311/75 556 (5.7)	408/8281 (4.9)	0.7 (-0.4 to 1.8)	1.20 (0.96 to 1.50)
Missing data	323	10 280	994		
Positive SARS-CoV-2 test result in infant, by age					
Early neonatal (0-6 d)	16 (0.7)	2 (<0.1)	0	0.7 (0.4 to 1.0)	
Late neonatal (7-28 d)	5 (0.2)	47 (0.1)	4 (<0.1)	0.2 (-0.0 to 0.4)	
Postneonatal (>28 d)	1 (<0.1)	230 (0.3)	25 (0.3)	-0.2 (-0.4 to -0.1)	
Any postnatal age	22 (0.9)	279 (0.3)	29 (0.3)	0.6 (0.2 to 1.0)	

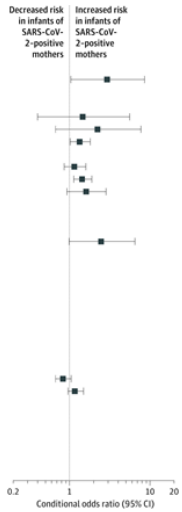

Figure 3. Neonatal Outcomes (Infections; Circulatory, Metabolic, Hematologic, and Gastrointestinal Problems; In-Hospital Mortality; Length of Hospital Stay; Breastfeeding; and Infant SARS-CoV-2 Test Status) Among Infants Born in Sweden (March 11, 2020–January 31, 2021) by Maternal SARS-CoV-2 Test Status in Pregnancy

JUST 2% OF SARS-COV-2-POSITIVE INDIVIDUALS CARRY 90% OF THE VIRUS CIRCULATING IN COMMUNITIES

Yang Q, Saldi TK, Gonzales PK, Lasda E, Decker CJ, Tat KL, Fink MR, Hager CR, Davis JC, Ozeroff CD, Muhlrad D, Clark SK, Fattor WT, Meyerson NR, Paige CL, Gilchrist AR, Barbachano-Guerrero A, Worden-Sapper ER, Wu SS, Brisson GR, McQueen MB, Dowell RD, Leinwand L, Parker R, Sawyer SL.. Proc Natl Acad Sci U S A. 2021 May 25;118(21):e2104547118. doi: 10.1073/pnas.2104547118.

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

BLUF

A cross-sectional study conducted at the University of Colorado Boulder from August 27, 2020 to December 11, 2020 testing 72,500 saliva samples from non-symptomatic individuals using qRT-PCR identified 1,405 positive COVID-19 cases. Comparison to published data of symptomatic, primarily hospitalized patients showed similar distributions of viral load (Figure 2). In both this campus population and published hospitalized patient populations, just 2% of individuals were found to harbor 90% of circulating virions (Figure 3), showing an asymmetric virion distribution. Authors highlight the importance of community screening for these viral superspreaders and the need to inform them of their infections status quickly to prevent further spread.

ABSTRACT

We analyze data from the fall 2020 pandemic response efforts at the University of Colorado Boulder, where more than 72,500 saliva samples were tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using qRT-PCR. All samples were collected from individuals who reported no symptoms associated with COVID-19 on the day of collection. From these, 1,405 positive cases were identified. The distribution of viral loads within these asymptomatic individuals was indistinguishable from what has been previously observed in symptomatic individuals. Regardless of symptomatic status, ~50% of individuals who test positive for SARS-CoV-2 seem to be in noninfectious phases of the disease, based on having low viral loads in a range from which live virus has rarely been isolated. We find that, at any given time, just 2% of individuals carry 90% of the virions circulating within communities, serving as viral "supercarriers" and possibly also superspreaders.

FIGURES

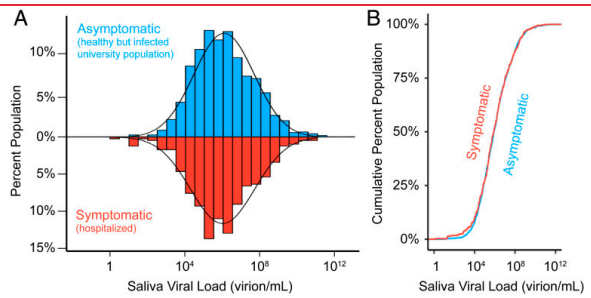

Figure 2. Viral load distributions are similar in asymptomatic and symptomatic populations. (A) A histogram of saliva viral loads in our asymptomatic campus population (n = 1,405, blue) compared to the same histogram of saliva viral loads from symptomatic (n = 404, red) individuals. The latter represents data compiled from the 10 studies in SI Appendix, Table S1. A log-normal probability density function is fitted onto the two distributions given the population mean and standard deviation. (B) Empirical cumulative distribution functions (ECDFs) of saliva viral load in the asymptomatic (n = 1,405, blue) and symptomatic (n = 404, red) populations. The similarity of the two ECDFs was assessed with the Kolmogorov–Smirnov test, which resulted in D statistic = 0.03, and P value = 0.97.

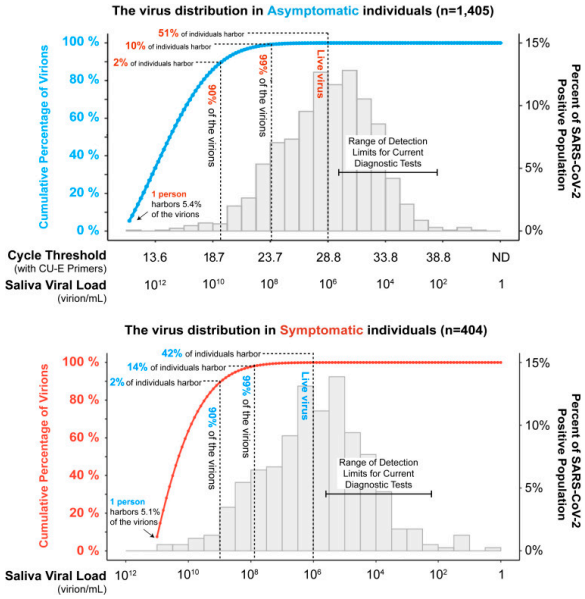

Figure 3. A small percentage of individuals are viral supercarriers. The histograms shown (right y axes) are the same as were shown in Fig. 2. Starting from the left of each histogram (i.e., those individuals with the highest viral loads), we calculated the accumulative percentage of total virions as a function of saliva viral load based on the probability density function of the distribution (blue and red lines, and left y axes). In both asymptomatic (blue line) and symptomatic populations (red line), the portion of population that harbors 90% and 99% of the circulating virus is highlighted by the dashed lines. We estimate that only around 50% (51% and 42% in the panels shown) of individuals who test positive for the virus actually harbor infectious virions, based on the observation that live virus has rarely been isolated from samples with viral loads of <106 virions per mL (28, 30–35). For context, the range of detection limits of common SARS-CoV-2 diagnostic testing paradigms (qRT-PCR, antigen testing, and reverse transcription loop-mediated isothermal amplification) are shown. All testing paradigms will capture virtually all infectious individuals and virions, in presymptomatic and symptomatic populations alike. Limits of detection are taken from refs. 50 to 52.

IMMUNOGENICITY OF COVID-19 MRNA VACCINES IN PREGNANT AND LACTATING WOMEN

Collier AY, McMahan K, Yu J, Tostanoski LH, Aguayo R, Ansel J, Chandrashekar A, Patel S, Apraku Bondzie E, Sellers D, Barrett J, Sanborn O, Wan H, Chang A, Anioke T, Nkolola J, Bradshaw C, Jacob-Dolan C, Feldman J, Gebre M, Borducchi EN, Liu J, Schmidt AG, Suscovich T, Linde C, Alter G, Hacker MR, Barouch DH.. JAMA. 2021 May 13. doi: 10.1001/jama.2021.7563. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

An exploratory, descriptive, prospective cohort study conducted at the Beth Israel Deaconess Medical Center by an OBGYN physician followed 103 women who received a COVID-19 vaccine (Moderna or Pfizer) from December 2020 through March 2021 and 28 women with confirmed infection from April 2020 through March 2021. CD4 and CD8 T-cell responses occurred in pregnant, lactating, and nonpregnant women following vaccination (Figure 3), with detectable binding and neutralizing antibodies in infant cord blood and breast milk (Figure 2). The small sample-size, failure to determine correlates of immunogenicity and protection, and lack of a control group warrant future studies with greater control and sample sizes.

ABSTRACT

Importance: Pregnant women are at increased risk of morbidity and mortality from COVID-19 but have been excluded from the phase 3 COVID-19 vaccine trials. Data on vaccine safety and immunogenicity in these populations are therefore limited. Objective: To evaluate the immunogenicity of COVID-19 messenger RNA (mRNA) vaccines in pregnant and lactating women, including against emerging SARS-CoV-2 variants of concern. Design, Setting, and Participants: An exploratory, descriptive, prospective cohort study enrolled 103 women who received a COVID-19 vaccine from December 2020 through March 2021 and 28 women who had confirmed SARS-CoV-2 infection from April 2020 through March 2021 (the last follow-up date was March 26, 2021). This study enrolled 30 pregnant, 16 lactating, and 57 neither pregnant nor lactating women who received either the mRNA-1273 (Moderna) or BNT162b2 (Pfizer-BioNTech) COVID-19 vaccines and 22 pregnant and 6 nonpregnant unvaccinated women with SARS-CoV-2 infection. Main Outcomes and Measures: SARS-CoV-2 receptor binding domain binding, neutralizing, and functional nonneutralizing antibody responses from pregnant, lactating, and nonpregnant women were assessed following vaccination. Spike-specific T-cell responses were evaluated using IFN-gamma enzyme-linked immunospot and multiparameter intracellular cytokine-staining assays. Humoral and cellular immune responses were determined against the original SARS-CoV-2 USA-WA1/2020 strain as well as against the B.1.1.7 and B.1.351 variants. Results: This study enrolled 103 women aged 18 to 45 years (66% non-Hispanic White) who received a COVID-19 mRNA vaccine. After the second vaccine dose, fever was reported in 4 pregnant women (14%; SD, 6%), 7 lactating women (44%; SD, 12%), and 27 nonpregnant women (52%; SD, 7%). Binding, neutralizing, and functional nonneutralizing antibody responses as well as CD4 and CD8 T-cell responses were present in pregnant, lactating, and nonpregnant women following vaccination. Binding and neutralizing antibodies were also observed in infant cord blood and breast milk. Binding and neutralizing antibody titers against the SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern were reduced, but T-cell responses were preserved against viral variants. Conclusion and Relevance: In this exploratory analysis of a convenience sample, receipt of a COVID-19 mRNA vaccine was immunogenic in pregnant women, and vaccine-elicited antibodies were transported to infant cord blood and breast milk. Pregnant and nonpregnant women who were vaccinated developed cross-reactive antibody responses and T-cell responses against SARS-CoV-2 variants of concern.

FIGURES

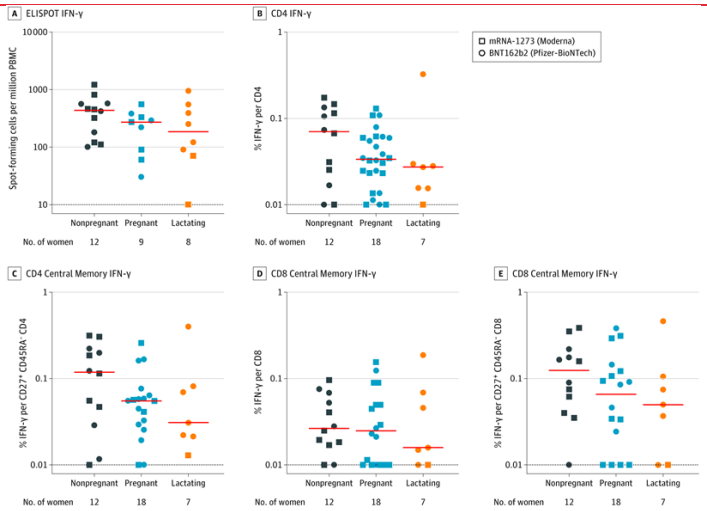

Figure 3. SARS-CoV-2 Spike–Specific Cellular Immune Responses in Vaccinated Pregnant, Lactating, and Nonpregnant Women

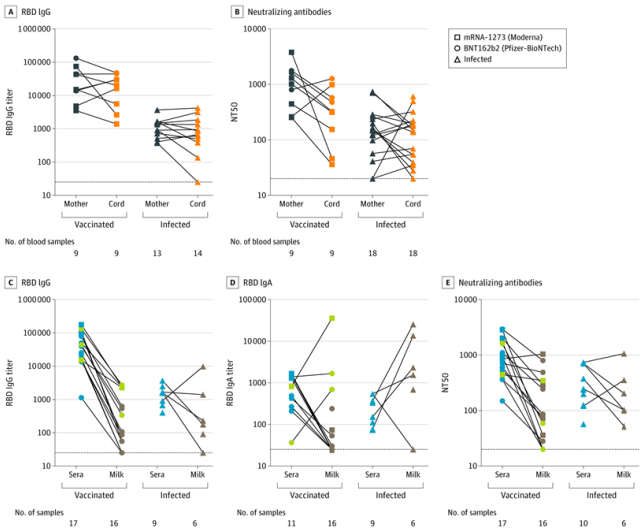

Figure 2. SARS-CoV-2 Binding and Neutralizing Antibody Responses in Infant Cord Blood and Breast Milk From Women Following Vaccination or Infection

PREVENTION IN THE COMMUNITY

HOUSEHOLD EXPOSURE TO SARS-COV-2 AND ASSOCIATION WITH COVID-19 SEVERITY: A DANISH NATIONWIDE COHORT STUDY

Broccia MM, de Knegt VEVE, Mills EHAEHA, Møller ALAL, Gnesin FF, Fischer TKTK, Zylyftari NN, Blomberg SNSN, Andersen MPMP, Schou MM, Fosbøl EE, Kragholm KK, Christensen HCHC, Polcwiartek LBLB, Phelps MM, Køber LL, Torp-Pedersen CC.. Clin Infect Dis. 2021 Apr 24:ciab340. doi: 10.1093/cid/ciab340. Online ahead of print.
Level of Evidence: 1 - Local and current random sample surveys (or censuses)

BLUF

A nationwide cohort study conducted by researchers in Denmark involving 15,063 multi-person households with 19,773 SARS-CoV-2 positive patients between 22 February and 6 October 2020 found 11,632 index cases with no secondary household infections, 3,421 index cases with secondary infections, and 4,710 secondary cases (Figure 1). Thus 22.8% of multi-person households with an index case, also had at least 1 secondary infection. See summary for critical COVID-19 infections. Analysis with Cox proportional hazards model revealed no significant association was found between household transmission of SARS-CoV-2 and COVID-19 infection severity, suggesting household members are not at higher risk for developing critical COVID-19 (Figure 2).

SUMMARY

Critical COVID-19 infection was found in
-2.9% of index cases with no secondary infection
-4.9% of index cases with secondary cases
-1.3% of secondary cases (Table 1)

ABSTRACT

BACKGROUND: Households are high-risk settings for the transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Severity of Coronavirus disease 2019 (COVID-19) is likely associated with the infectious dose of SARS-CoV-2 exposure. We therefore aimed to assess the association between SARS-CoV-2 exposure within households and COVID-19 severity. METHODS: We performed a Danish nationwide register-based cohort study including laboratory-confirmed SARS-CoV-2 infected individuals from 22 February to 6 October 2020. Household exposure to SARS-CoV-2 was defined as having one individual tested positive for SARS-CoV-2 within the household. Cox proportional-hazards models were used to estimate the association between 'critical COVID-19' within and between households with and without secondary cases. RESULTS: From 15,063 multi-person households, 19,773 SARS-CoV-2 positive individuals were included; 11,632 were categorized as index cases without any secondary household cases, 3,431 as index cases with secondary cases, i.e. 22.8% of multi-person households, and 4,710 as secondary cases. 'Critical COVID-19' occurred in 2.9 % of index cases living with no secondary cases, 4.9 % of index cases with secondary cases, and 1.3 % of secondary cases. The adjusted hazard ratio for 'critical COVID-19' among index cases versus secondary cases within the same household was 2.50 (95%CI=1.88-3.34), 2.27 (95%CI=1.77-2.93) for index cases in households with no secondary cases versus secondary cases, and 1.1 (95%CI=0.93-1.30) for index cases with secondary cases versus index cases without secondary cases. CONCLUSION: We found no increased hazard ratio of 'critical COVID-19' among household members of infected SARS-CoV-2 index cases.

FIGURES

Figure 1. Various types of SARS-CoV-2 positive household members.

Characteristics	Level	Index cases without secondary cases (n=11632)	Index cases with secondary cases (n=3431)	Secondary cases (n=4710)	Total (n=19773)
Composite outcome of critical COVID-19	Yes	341 (2.9)	167 (4.9)	60 (1.3)	568 (2.9)
Death within 30 days	Yes	127 (1.1)	59 (1.7)	15 (0.3)	201 (1.0)
Intensive care unit admission (NABE, NAB, BGA)	Yes	169 (1.5)	95 (2.8)	24 (0.5)	288 (1.5)
Severe acute respiratory syndrome (ICD-10: B97.2A)	Yes	264 (2.3)	129 (3.8)	48 (1.0)	441 (2.2)
Time period of positive test*	Limited test period	4,668 (40.1)	1,124 (32.8)	1,368 (29.0)	7,160 (36.2)
	Open test period	6,964 (59.9)	2,307 (67.2)	3,342 (71.0)	12,613 (63.8)
Sex	Female	6,350 (54.6)	1,767 (51.5)	2,474 (52.5)	10,591 (53.6)
	Male	5,282 (45.4)	1,664 (48.5)	2,236 (47.5)	9,182 (46.4)
Age	0-18	1,647 (14.2)	356 (10.4)	1,456 (30.9)	3,459 (17.5)
	19-39	4,037 (34.7)	933 (27.2)	1,067 (22.7)	6,037 (30.5)
	40-59	4,142 (35.6)	1,436 (41.9)	1,483 (31.5)	7,061 (35.7)
	60-79	1,584 (13.6)	595 (17.3)	609 (12.9)	2,788 (14.1)
	80-102	222 (1.9)	111 (3.2)	95 (2.0)	428 (2.2)
	Mean	39.96	44.65	35.87	39.80
Ethnicity	Danish	9,095 (78.2)	2,309 (67.3)	3,062 (65.0)	14,466 (73.2)
	Immigrant	1,782 (15.3)	858 (25.0)	943 (20.0)	3,583 (18.1)
	Descendant	755 (6.5)	264 (7.7)	705 (15.0)	1,724 (8.7)
Household members	2	4,807 (41.3)	1,302 (37.9)	1,302 (27.6)	7,411 (37.5)
	3-4	5,325 (45.8)	1,535 (44.7)	2,217 (47.1)	9,077 (45.9)
	>4	1500 (12.9)	594 (17.3)	1191 (25.3)	3,285 (16.6)
Comorbidities cf. Charlson Comorbidity Index	Yes	1428 (12.3)	558 (16.3)	516 (11.0)	2,502 (12.7)

Table 1. Characteristics of the study population

*The 'limited test period' from 22 February 2020 to 18 May 2020 covers a period of SARS-CoV-2 test accessibility for individuals at risk, while the 'open test period' from 19 May 2020 to 6 October 2020 covers SARS-CoV-2 test accessibility for all individuals in Denmark.

Accepted Manuscript

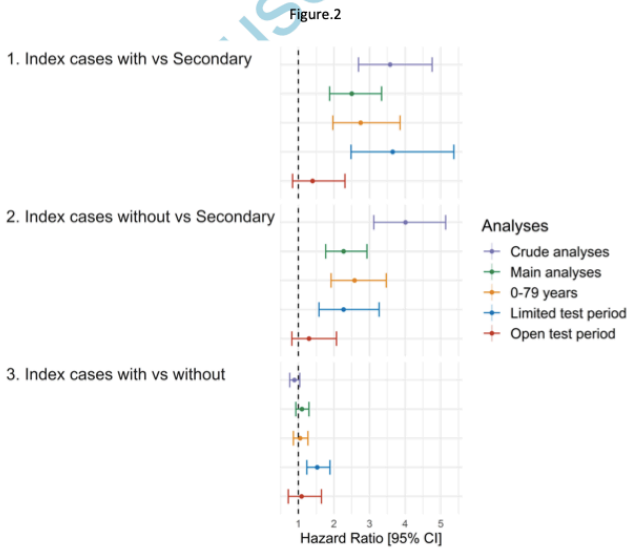

Figure 2. Association between SARS-CoV-2 exposure and critical COVID-19 specified by hazard ratios
Sub-cohorts were categorized as index cases with secondary cases (n = 3,431), index cases without any secondary household cases (n = 11,632), and secondary cases (n = 4,710). Table S4 shows the corresponding results in numbers.

REDUCED BNT162B2 MRNA VACCINE RESPONSE IN SARS-COV-2-NAIVE NURSING HOME RESIDENTS

Canaday DH, Carias L, Oyebanji OA, Keresztesy D, Wilk D, Payne M, Aung H, St Denis K, Lam EC, Rowley CF, Berry SD, Cameron CM, Cameron MJ, Wilson B, Balazs AB, Gravenstein S, King CL.. Clin Infect Dis. 2021 May 16:ciab447. doi: 10.1093/cid/ciab447. Online ahead of print.
Level of Evidence: 3 - Non-randomized controlled cohort/follow-up study

BLUF

A multidisciplinary team of researchers conducted a cohort study to analyze the antibody levels for spike, receptor binding domain (RBD), and virus neutralization after BNT162b2 mRNA vaccination in 149 nursing home (NH) residents (median age 76), 110 healthcare worker controls (median age 48), and 22 unvaccinated recently-infected convalescent controls (median age 53).
NH residents with no prior COVID-19 infection had significantly lower rates of neutralization titers (81% vs 99%), anti-spike levels, and anti-RBD levels than HCW controls. SARS-CoV-2 convalescent subjects had higher antibody titers compared to SARS-CoV-2-naive subjects in all groups. The lower titers among nursing home residents could lead to less protection from infection and suggests a lack of clarity how long any protection could last.

ABSTRACT

After BNT162b2 mRNA vaccination, antibody levels to spike, receptor binding domain (RBD) and virus neutralization were examined in 149 nursing home (NH) residents and 110 health care worker controls. SARS-CoV-2-naive NH residents median post-2nd vaccine dose antibody neutralization titers are 1/4 that of SARS-CoV-2-naive healthcare workers.

FIGURES

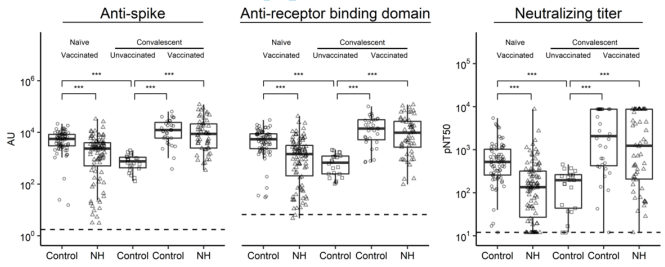

Figure 1. Humoral immune assessment of BNT162b2 mRNA vaccine vaccination in NH residents

COMPARABLE ENVIRONMENTAL STABILITY AND DISINFECTION PROFILES OF THE CURRENTLY CIRCULATING SARS-COV-2 VARIANTS OF CONCERN B.1.1.7 AND B.1.351

Meister TL, Fortmann J, Todt D, Heinen N, Ludwig A, Brüggemann Y, Elsner C, Dittmer U, Steinmann J, Pfaender S, Steinmann E.. J Infect Dis. 2021 May 16:jiab260. doi: 10.1093/infdis/jiab260. Online ahead of print.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

A laboratory study conducted by researchers affiliated with multiple medical institutions in Germany investigated the surface stability and inactivation profiles of the novel SARS-CoV-2 B.1.1.7 and B.1.351 variants compared to wild type (B.1.1.70) and found comparable susceptibility towards disinfection with heat (56 degree C), soap for 1-5 minutes, and 30% ethanol for 30 seconds (Figure 1). There was also comparable surface stability on steel, silver, copper, and face masks (Figure 2), indicating there was no enhanced surface stability of the variants compared to wild-type. These findings suggest how the current recommended hygiene measures are sufficient to combat the risk of SARS-CoV-2 variant transmission.

ABSTRACT

The emergence of novel SARS-CoV-2 B.1.1.7 and B.1.351 variants of concern with increased transmission dynamics has raised questions regarding stability and disinfection of these viruses. In this study, we analyzed surface stability and disinfection of the currently circulating SARS-CoV-2 variants B.1.1.7 and B.1.351 compared to the wild type. Treatment with heat, soap and ethanol revealed similar inactivation profiles indicative of a comparable susceptibility towards disinfection. Furthermore, we observed comparable surface stability on steel, silver, copper and face masks. Overall, our data support the application of currently recommended hygiene concepts to minimize the risk of B.1.1.7 and B.1.351 transmission.

FIGURES

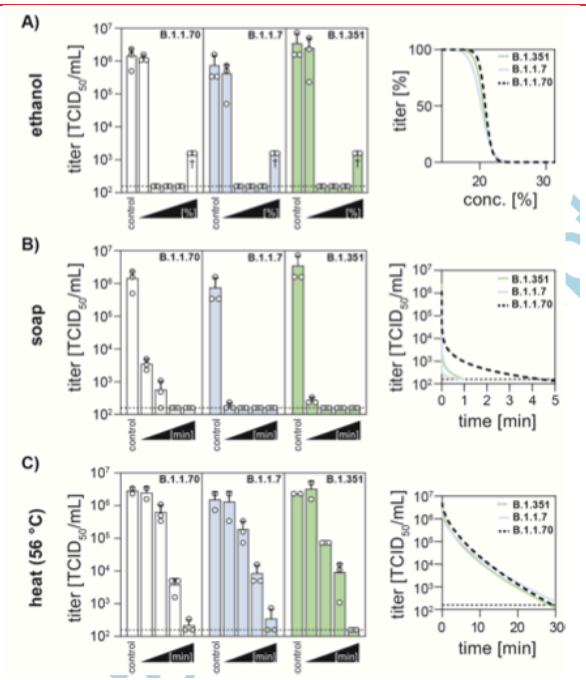

Figure 1: Inactivation of SARS-CoV-2 B.1.1.7 and B.1.351 variants compared to B.1.1.70 (wild type). Residual titer (TCID50/mL) of B.1.1.70 (white bars) B.1.1.7 (blue bars) and B.1.351 (green bars) variants after inactivation via A) ethanol (20%, 30%, 40%, 60% and 80%, left to right), B) soap for 30 s, 1, 5 and 10 min (left to right) and C) heat (56 °C) for 1, 5, 10 and 30 min (left to right). Depicted are the individual replicates as dots and the mean as bars ± SD; dashed line indicates lower limit of quantification (LLOQ) of the limiting dilution assay. † denotes elevated LLOQ due to cytotoxicity. Non-linear regression analyses were conducted using a four- parameter logistic model (A) or a fitted Weibull distribution model (B-C).

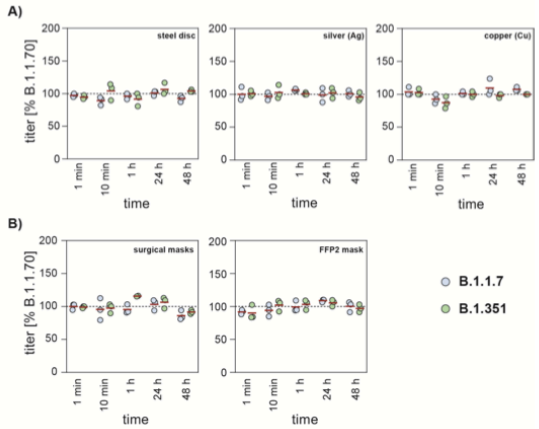

Figure 2: Relative stability of SARS-CoV-2 B.1.1.7 and B.1.351 variants to B.1.1.70 (wild type). SARS-CoV-2 stock solutions were applied on different surfaces and recovered after the indicated times and residual titer was assessed via limiting dilution assay (TCID50/mL). Normalized stability of B.1.1.7 (blue dots) and B.1.351 (green dots) variants on A) stainless steel discs and disks sputtered with copper or silver and B) on the inner layer of surgical masks and Filtering Face Piece 2 (FFP2) masks relative to wild type (dashed line). Depicted are the individual replicates as dots and the mean as red lines.

NEUROLOGY

FACTORS ASSOCIATED WITH COVID-19 IN PEOPLE WITH PARKINSON'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Chambergo-Michilot D, Barros-Sevillano S, Rivera-Torrejón O, De la Cruz-Ku GA, Custodio N.. Eur J Neurol. 2021 May 13. doi: 10.1111/ene.14912. Online ahead of print.

Level of Evidence: 2 - Systematic review of surveys that allow matching to local circumstances

BLUF

A systematic review and meta-analysis conducted by researchers in Peru included 6 articles published through April 1, 2021 (Table 1) and found a 2% prevalence of COVID-19 in patients with Parkinson's disease. COVID-19 infection was associated with obesity (OR: 1.79), pulmonary disease (OR: 1.92), COVID-19 contact (OR: 41.77), hospitalization (OR: 11.78), and death (OR: 11.23) in patients with Parkinson's disease (Table 2, Part 2), whereas vitamin D supplementation (OR: 0.50) was associated with decreased risk. During the pandemic, there has been an increase in prevalence of worsening motor symptoms, as well as non-motor symptoms including emotional status, anxiety, and sleep disorders (Table 2, Part 4). These findings highlight the increased COVID-19 mortality in Parkinson's disease both medically and socially with increased isolation and subsequent decrease in quality of life, and health policies should be established to prevent these patients from developing complications.

ABSTRACT

BACKGROUND: There is a debate about whether there is an increased risk of COVID-19 infection in people with Parkinson's disease (PD), possibly due to associated factors. This study aimed to systematically review the factors associated with COVID-19 in people with PD. METHODS: The search was carried out in PubMed, Scopus, and Web of Science until November 2020 (updated until April 1, 2021). Observational studies that analyzed factors associated with COVID-19 in people with PD were selected and revised. RESULTS: The authors included six studies (4 case-controlled studies and 2 cross-sectional studies) in the qualitative and quantitative syntheses. Authors found that the following factors were associated with COVID-19 in people with PD: obesity (OR: 1.79, 95% CI: 1.07 to 2.99, I2 : 0%), any pulmonary disease (OR: 1.92, 95% CI: 1.17 to 3.15, I2 : 0%), COVID-19 contact (OR: 41.77, 95% CI: 4.77 - 365.56, I2 : 0%), vitamin D supplementation (OR: 0.50, 95% CI: 0.30 to 0.83, I2 : 0%), hospitalization (OR: 11.78, 95% CI: 6.27 to 22.12, I2 : 0%), and death (OR: 11.23, 95% CI: 3.92 to 32.18, I2 : 0%). Authors did not find significant association between COVID-19 and hypertension, diabetes, cardiopathy, cancer, any cognitive problem, dementia, chronic obstructive pulmonary disease, renal or hepatic disease, smoking, and tremor. CONCLUSIONS: Meta-analyses were limited by the number of events and some methodological limitations. Despite that, the authors assessed available evidence, and the results may be useful in future health policies.

FIGURES

Author	Year	Design	Country	Population	PD diagnosis criteria	COVID-19 diagnosis criteria	Case/exposed definition	Control/non-exposed definition	Matching factors
Del Prete	2020	Case-controlled study	Italy	PD patients	MDS-PD	Laboratory[1]	PD patients with COVID-19	PD patients without COVID-19	Age and disease duration
Fasano	2020	Case-controlled study	Italy	PD patients	MDS-PD	Confirmed: molecular test Probable: COVID-19-related symptoms	PD patient with confirmed/probable COVID-19	PD patients without COVID-19	NR
Brown	2020	Cross-sectional study	All continents[2]	PD and non-PD patients	NR	Laboratory[1]	Patients with COVID-19	Patients without COVID-19	DA
Santos-García	2020	Cross-sectional study	Spain	PD patients	NR	Laboratory[1]	PD patients with COVID-19	PD patients without COVID-19	DA
Cilia	2020	Case-controlled study	Italy	PD patients	NR	Laboratory[1]	PD patients with COVID-19	PD patients without COVID-19	Sex, age and disease duration
Sainz-Amo	2020	Case-controlled study	Spain	PD patients	MDS-PD	Laboratory[1]	PD patients with COVID-20	PD patients without COVID-20	NR

Table 1. Characteristics of included studies.

D: Parkinson disease. MDS-PD: Movement Disorder Society Clinical Diagnostic Criteria for PD. NR: not reported. DA: does not apply. 1 Authors did not specific a method. 2 About 80% of responses came from the United States.

Group	Author	Smoking (%)	Obesity (%)	Hypertension (%)	Diabetes (%)	Cardiopathy (%)	Cancer (%)	Renal or hepatic dysfunction (%)	Any pulmonary disease (%)	COPD (%)	COVID-19 contact (%)	Dyslipidemia (%)	Arrhythmia (%)
PD patients with COVID-19	Del Prete	NR	NR	71.43	42.86	28.57	14.29	0	0	NR	42.86	NR	NR
PD patients without COVID-19		NR	NR	0	7.14	14.29	7.14	14.29	0	NR	0	NR	NR
PD patients with COVID-19	Fasano	5.7	18.1	41.9	7.6	NR	0.9	NR	5.7	5.7	NR	NR	NR
PD patients without COVID-19		4.6	10.9	38.7	8	NR	3.3	NR	1.7	1.7	NR	NR	NR
PD patients with COVID-19	Brown	5.9	NR	25	NR	20	NR	NR	14	NR	NR	NR	NR
PD patients without COVID-19		1.6	NR	31	NR	8.2	NR	NR	8.1	NR	NR	NR	NR
PD patients with COVID-19	Santos-García	6.7	NR	26.7	20	3	0	NR	14.3	NR	14.8	64.3	20
PD patients without COVID-19		8.3	NR	24.3	9.7	65	3.1	NR	9.4	NR		24.1	12.7
PD patients with COVID-19	Cilia	0	8.3	33.3	0	8.3	16.7	8.3	8.3	8.3	50	NR	NR
PD patients without COVID-19		8.3	5.5	44.4	5.5	13.9	8.3	13.9	11.1	11.1	0	NR	NR
PD patients with COVID-19	Sainz-Amo	NR	NR	49	21	15	8	8	10	NR	NR	NR	NR
PD patients without COVID-19		NR	NR	42	12	19	2	2	8	NR	NR	NR	NR

Table 2, Part 2: Characteristics of population of included studies.

Group	Author	Psychiatric symptoms							Worsening following the onset of the pandemic				Hospitalization (%)	Death (%)
		Bad mood/depression (%)	Anxiety (%)	Pain (every day) (%)	Cognitive problems (%)	Somnolia (%)	Hallucinations (%)	Behavioral disorders (%)	Motor symptoms (%)	Mood (%)	Anxiety (%)	Sleep disorders (%)		
PD patients with COVID-19	Del Prete	NR	NR	NR	NR	NR	NR	NR	29.8	24.7	20	20.2	57.14	14.29
PD patients without COVID-19		NR	NR	NR	NR	NR	NR	NR					0	0
PD patients with COVID-19	Fasano	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	17.1	8.7
PD patients without COVID-19		NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	27.2	7.6
PD patients with COVID-19	Brown	NR	NR	NR	NR	NR	NR	NR	55	51	NR	59	3.8	NR
PD patients without COVID-19		NR	NR	NR	NR	NR	NR	NR	41	39	NR	32	NR	NR
PD patients with COVID-19	Santos-García	57.1	50	26.7	30.5	6.7	6	15.4	40.7	NR	31.3	41.4	5	3
PD patients without COVID-19		38.6	41.8	50.4	35.2	15.2	23.4	30.6		NR			NR	NR
PD patients with COVID-19	Cilia	NR	NR	NR	0	8	NR	NR	NR	NR	NR	NR	NR	6
PD patients without COVID-19		NR	NR	NR	8.3	8.3	NR	NR	NR	NR	NR	NR	NR	6
PD patients with COVID-19	Sainz-Amo	NR	NR	NR	38	36	NR	NR	NR	NR	NR	NR	NR	21
PD patients without COVID-19		NR	NR	NR	14	14	NR	NR	NR	NR	NR	NR	NR	NR

Table 2, Part 4: Characteristics of population of included studies.

MEDICAL SUBSPECIALTIES

CARDIOLOGY

COVID AND CARDIOVASCULAR DISEASE: WHAT WE KNOW IN 2021

Chilazi M, Duffy EY, Thakkar A, Michos ED.. Curr Atheroscler Rep. 2021 May 13;23(7):37. doi: 10.1007/s11883-021-00935-2.
Level of Evidence: 5 - Review / Literature Review

BLUF

A literature review conducted by researchers affiliated with Johns Hopkins University and School of Medicine investigated the short-term and long-term consequences of SARS-CoV-2 infection on the heart and found myocardial injury in COVID-19 is correlated with severity of critical illness instead of virally-induced myocardial damage. Given the low prevalence of COVID-19 myocarditis, cardiac MRI should be used in cases where there could be immediate procedural implications, such as re-vascularization, ablation, valvular interventions, or concern for malignancy (Figure 2). Persistent Long COVID-19 symptoms are present in an estimated 20-30% of outpatients and up to 80% of hospitalized patients, and follow-up can be done with serial electrocardiograms and echocardiogram for monitoring (Figure 3). These findings further the knowledge base regarding cardiovascular implications of COVID-19 infection but could benefit from future investigation (Figure 4).

ABSTRACT

PURPOSE OF REVIEW: Coronavirus disease 2019 (COVID-19) has been the cause of significant global morbidity and mortality. Here, we review the literature to date of the short-term and long-term consequences of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection on the heart. RECENT FINDINGS: Early case reports described a spectrum of cardiovascular manifestations of COVID-19, including myocarditis, stress cardiomyopathy, myocardial infarction, and arrhythmia. However, in most cases, myocardial injury in COVID-19 appears to be predominantly mediated by the severity of critical illness rather than direct injury to myocardium from viral particles. While cardiac magnetic resonance imaging remains a powerful tool for diagnosing acute myocarditis, it should be used judiciously in light of low baseline prevalence of myocarditis. Guiding an athletic patient through return to play (RTP) after COVID-19 infection is a challenging process. More recent data show RTP has been a safe endeavor using a screening protocol. "Long COVID" or post-acute sequelae of SARS-CoV-2 infection has also been described. The reported symptoms span a large breadth of cardiopulmonary and neurologic complaints including fatigue, palpitations, chest pain, breathlessness, brain fog, and dysautonomia including postural tachycardia syndrome (POTS). Management of POTS/dysautonomia primarily centers on education, exercise, and salt and fluid repletion. Our understanding of the impact of COVID-19 on the cardiovascular system is constantly evolving. As we enter a new age of survivorship, additional research is needed to catalogue the burden of persistent cardiopulmonary symptoms. Research is also needed to learn how acute management may alter the likelihood and prevalence of this chronic syndrome.

FIGURES

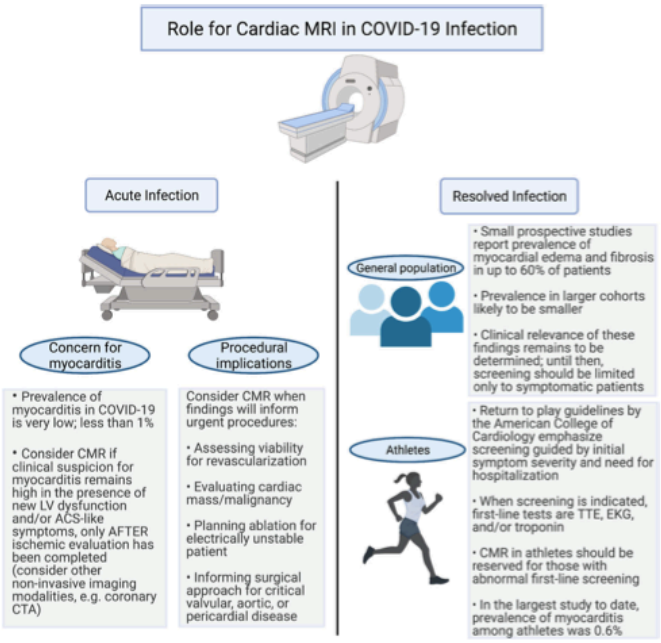

Figure 2. Review of the role and indications for cardiac magnetic resonance (CMR) imaging in acute and resolved infection, both in the general population and more specifically in athletes. Abbreviations: LV left ventricular, ACS acute coronary syndrome, CCTA coronary computed tomography angiography, TTE transthoracic echocardiography, EKG electrocardiogram

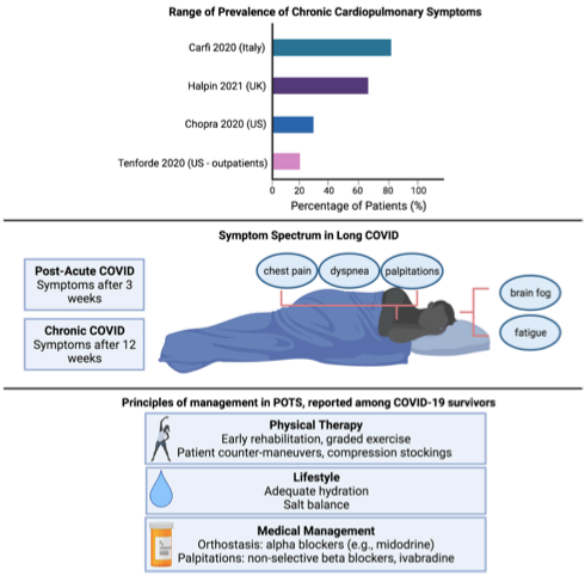

Figure 3. Review of the prevalence of long COVID, definitions and symptomatic manifestations, and current principles of management for potential COVID/postural orthostatic tachycardia syndrome overlap

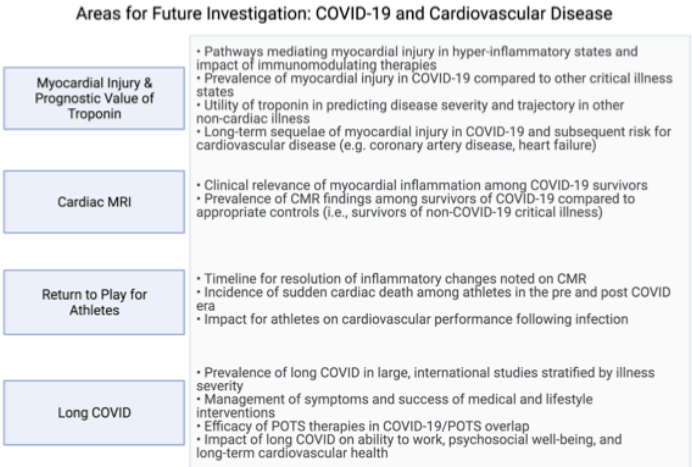

Figure 4. Suggestions for future areas of investigation in the domains explored in this review. Abbreviations: POTS postural orthostatic tachycardia syndrome, CMR cardiac magnetic resonance

EPITOPE-SPECIFIC ANTIBODY RESPONSES DIFFERENTIATE COVID-19 OUTCOME AND VARIANTS OF CONCERN

Voss C, Esmail S, Liu X, Knauer MJ, Ackloo S, Kaneko T, Lowes LE, Stogios PJ, Seitova A, Hutchinson A, Yusifov F, Skarina T, Evdokimova E, Loppnau P, Ghiabi P, Hajian T, Zhong S, Abdoh H, Hedley BD, Bhayana V, Martin CM, Slessarev M, Chin-Yee B, Fraser DD, Chin-Yee I, Li SS.. JCI Insight. 2021 Jun 3:148855. doi: 10.1172/jci.insight.148855. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

Researchers from Western University and University of Toronto assessed patient-specific antibody response to SARS-CoV and found that antibody responses to the S(811-825), S(881-895) and N(156-170) epitopes (Spike (S) or Nucleocapsid (N)) negatively or positively correlated with clinical severity or patient survival (Figure 2, 5, 6). They also found two mutations, P681H and S235F, associated with the B.1.1.7 variant changed the specificity of the associated epitopes. Overall they determined that epitope-resolved antibody testing can also be used to predict clinical outcomes and epitope peptides can be used to detect antibodies against variants of concern.

ABSTRACT

BACKGROUND: The role of humoral immunity in the coronavirus disease 2019 (COVID-19) is not fully understood owing, in large part, to the complexity of antibodies produced in response to the SARS-CoV-2 infection. There is a pressing need for serology tests to assess patient-specific antibody response and predict clinical outcome. METHODS: Using SARS-CoV-2 proteome and peptide microarrays, we screened 146 COVID-19 patients plasma samples to identify antigens and epitopes. This enabled us to develop a master epitope array and an epitope-specific agglutination assay to gauge antibody responses systematically and with high resolution. RESULTS: We identified linear epitopes from the Spike (S) and Nucleocapsid (N) protein and showed that the epitopes enabled higher resolution antibody profiling than the S or N protein antigen. Specifically, we found that antibody responses to the S(811-825), S(881-895) and N(156-170) epitopes negatively or positively correlated with clinical severity or patient survival. Moreover, we found that the P681H and S235F mutations associated with the coronavirus variant of concern B.1.1.7 altered the specificity of the corresponding epitopes. CONCLUSIONS: Epitope-resolved antibody testing not only affords a high-resolution alternative to conventional immunoassays to delineate the complex humoral immunity to SARS-CoV-2 and differentiate between neutralizing and non-neutralizing antibodies, it may potentially be used to predict clinical outcome. The epitope peptides can be readily modified to detect antibodies against variants of concern (VOC) in both the peptide array and latex agglutination formats. FUNDING: Ontario Research Fund (ORF)-COVID-19 Rapid Research Fund, the Toronto COVID-19 Action Fund, Western University, the Lawson Health Research Institute, the London Health Sciences Foundation, and the AMOSO Innovation Fund.

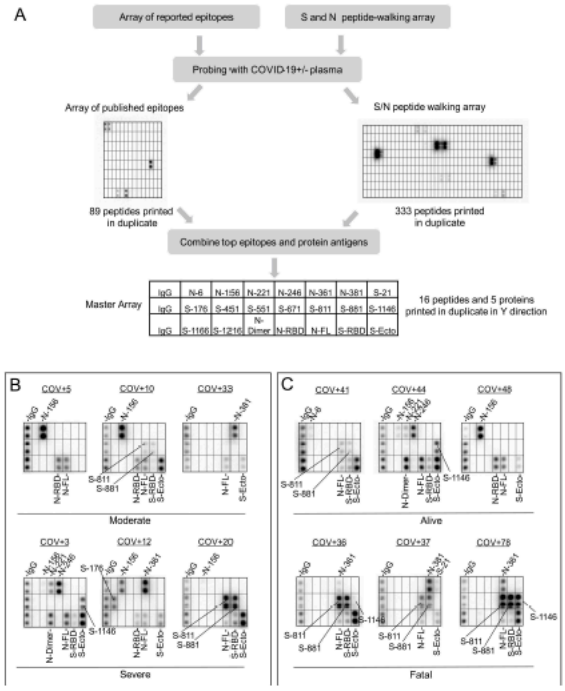

Figure 2. Identification of SARS-CoV-2 epitopes and epitope-resolved antibody profiling. **(A)** Workflow for identifying antigenic epitopes by peptide arrays and the layout of a master array for SARS-CoV-2 antibody profiling. **(B, C)** Representative images of epitope-resolved antibody profiles for the different groups of COVID-19 patients (n=65 unique patient samples).

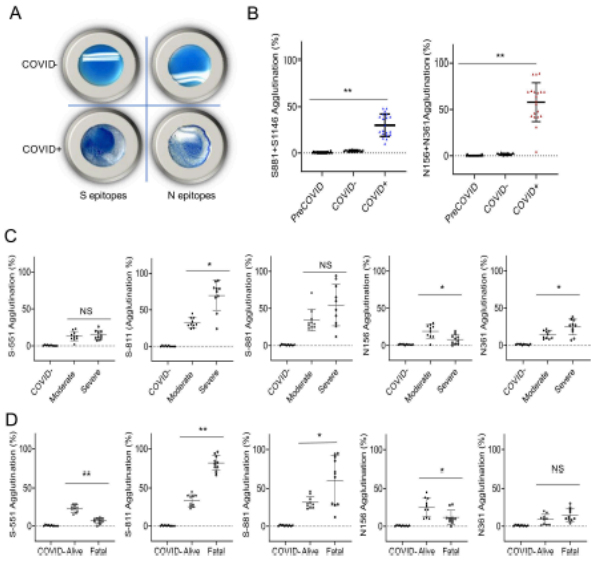

Figure 5. Rapid epitope-dependent agglutination assay for SARS-CoV-2 antibodies effectively differentiated patient groups. **(A)** Latex bead agglutination assay to gauge antibody responses to SARS-CoV-2. The latex beads were coated with one or more biotinylated S or N epitope peptides and mixed with SARS-CoV-2 -negative (COVID-, top) or -positive (COVID+, bottom) plasma. The presence of antibodies against the epitopes promoted the agglutination of the latex beads. Images shown were taken after 2 min incubation at room temperature. **(B)** Epitope-based latex agglutination assay distinguished COVID-19+ from COVID-19- or preCOVID-19 plasma. The epitope peptides used were: S-811 and S-1146 from the spike and N-156 and N-361 from the nucleocapsid protein. **(C)** Correlation of disease severity with antibody responses to the S-811, N-156 and N-361 epitopes determined by latex bead agglutination. **(D)** Correlation of disease outcome with antibody responses to the S-551, S-811, S-881 and N-156 epitopes determined by latex bead agglutination. P values calculated based on unpaired one-tail Student t-test with Welch's correction (no assumption of equal SD) (n=20 for B; n=10 for C & D). *p<0.05, **p<0.002. Error bars represent the standard deviation.

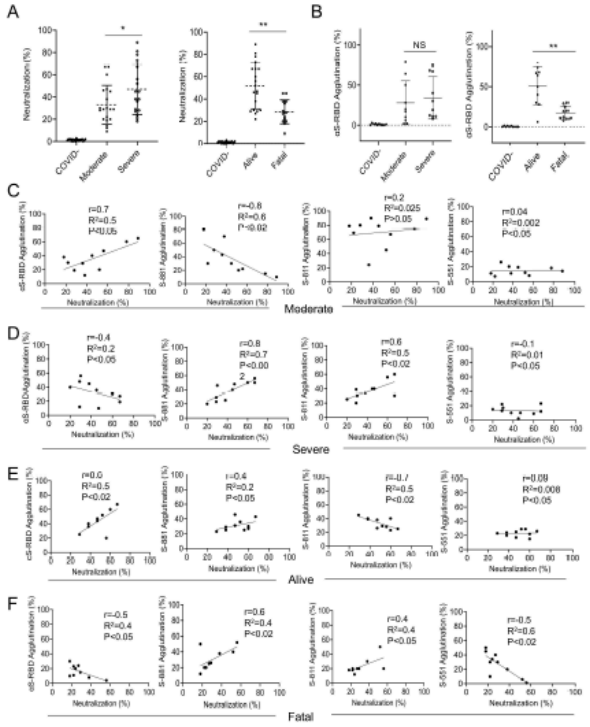

Figure 6. Antibody specificity predicts neutralization efficiency and disease outcome. (A) Correlation of neutralization efficiency with clinical severity (left) or outcome (right). *, p<0.05; **, p<0.01. **(B)** Correlation of S-RBD-antibody response measured by latex agglutination with COVID-19 severity (left) or outcome (right). **, p<0.01. Error bars represent standard deviation. **(C-F)** Pearson (r) correlation between epitope-dependent agglutination and neutralization. The coefficient of determination (R^2) was calculated based on linear regression analysis. Confidence interval (CI): 95%. The p-values were calculated using a two-tailed t-distribution with n – 2 degrees of freedom (n=10). P-values are shown on each graph.

SARS-COV-2 INFECTIVITY BY VIRAL LOAD, S GENE VARIANTS AND DEMOGRAPHIC FACTORS AND THE UTILITY OF LATERAL FLOW DEVICES TO PREVENT TRANSMISSION

Lee LYW, Rozmanowski S, Pang M, Charlett A, Anderson C, Hughes GJ, Barnard M, Peto L, Vipond R, Sienkiewicz A, Hopkins S, Bell J, Crook DW, Gent N, Walker AS, Peto TEA, Eyre DW.. Clin Infect Dis. 2021 May 11:ciab421. doi: 10.1093/cid/ciab421. Online ahead of print.
Level of Evidence: 3 - Non -randomized controlled cohort/follow-up study

BLUF

A large-scale retrospective cohort study in the UK examined SARS-CoV-2 2,974,596 contacts of 1,064,004 index cases between September 1, 2020 and February 28, 2021 in England within 10 days of index case positive test. They found that infectivity increased with increased index case viral load/lower Ct (11.7% transmission to contacts at Ct=15 and 4.5% at Ct=30) and that infection with B.1.1.7 increased transmission 1.55 fold. Transmission was most likely in household contacts and household visitors and least likely after outdoor contact, with children being less likely than adults to test positive or transmit infection (Figure 2).

SUMMARY

The researchers utilized four lateral flow devices to simulate the proportion of cases with PCR-positive contacts and results ranged from detecting 83-89.5% of cases with PCR-positive contacts (Figure 5), indicating that lateral flow devices can be used to diagnose the majority of cases that lead to onward transmission with rapid and regular screens; however, further prospective studies are required to corroborate and extrapolate these findings.

ABSTRACT

BACKGROUND: How SARS-CoV-2 infectivity varies with viral load is incompletely understood. Whether rapid point-of-care antigen lateral flow devices (LFDs) detect most potential transmission sources despite imperfect clinical sensitivity is unknown. METHODS: We combined SARS-CoV-2 testing and contact tracing data from England between 01-September-2020 and 28-February-2021. We used multivariable logistic regression to investigate relationships between PCR-confirmed infection in contacts of community-diagnosed cases and index case viral load, S gene target failure (proxy for B.1.1.7 infection), demographics, SARS-CoV-2 incidence, social deprivation, and contact event type. We used LFD performance to simulate the proportion of cases with a PCR-positive contact expected to be detected using one of four LFDs. RESULTS: 231,498/2,474,066(9%) contacts of 1,064,004 index cases tested PCR-positive. PCR-positive results in contacts independently increased with higher case viral loads (lower Ct values) e.g., 11.7%(95%CI 11.5-12.0%) at Ct=15 and 4.5%(4.4-4.6%) at Ct=30. B.1.1.7 infection increased PCR-positive results by ~50%, (e.g. 1.55-fold, 95%CI 1.49-1.61, at Ct=20). PCR-positive results were most common in household contacts (at Ct=20.1, 8.7%[95%CI 8.6-8.9%]), followed by household visitors (7.1%[6.8-7.3%]), contacts at events/activities (5.2%[4.9-5.4%]), work/education (4.6%[4.4-4.8%]), and least common after outdoor contact (2.9%[2.3-3.8%]). Contacts of children were the least likely to test positive, particularly following contact outdoors or at work/education. The most and least sensitive LFDs would detect 89.5%(89.4-89.6%) and 83.0%(82.8-83.1%) of cases with PCR-positive contacts respectively. CONCLUSIONS: SARS-CoV-2 infectivity varies by case viral load, contact event type, and age. Those with high viral loads are the most infectious. B.1.1.7 increased transmission by ~50%. The best performing LFDs detect most infectious cases.

FIGURES

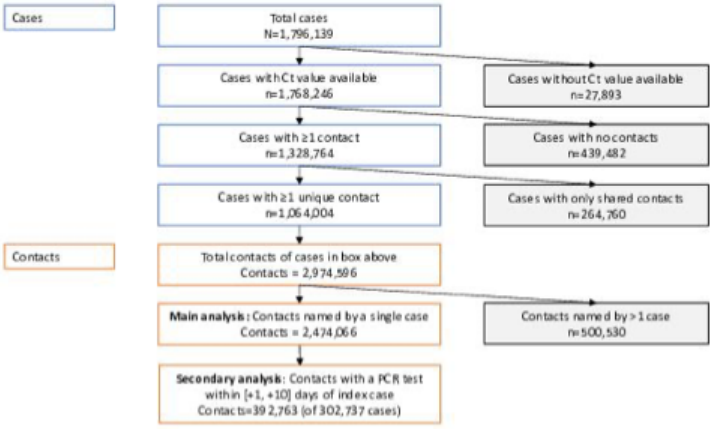

Figure 1. Index cases and contacts in England, 01 September 2020 to 28 February 2021.

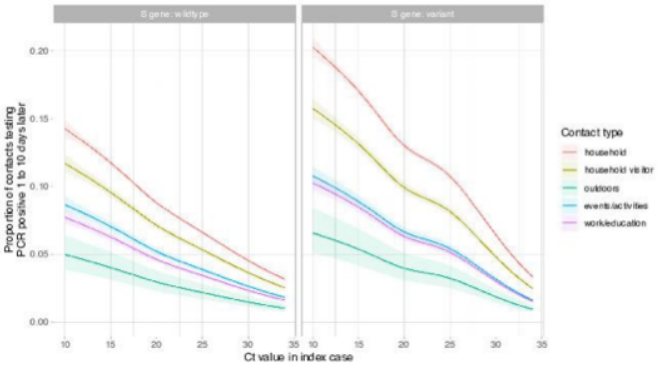

Figure 2. Relationship between PCR cycle threshold (Ct) value in cases and the proportion of their contacts with a PCR positive result, by contact type and S gene target failure. Model predictions are plotted after adjustment for index case age (set to the median value, 35 years), case ethnicity (set to white), index of multiple deprivation score at contact's home address (set to median, 14,465), incidence at contact's home address (set to median 350 cases per 100,000 population per week) and index case sex (set to female). The shaded area indicates the 95% confidence interval.

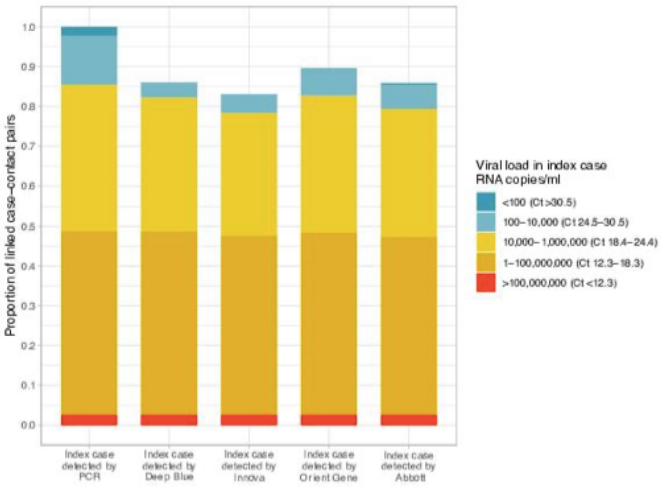

Figure 5. Simulated proportion of cases with a PCR-positive contact detected using four lateral flow devices (LFD). The proportion of cases detected by estimated PCR viral load (PCR cycle threshold, Ct value) is shown in the PCR column. The number of cases with a PCR-positive contact who would be detected using each LFD is shown for 4 LFDs.

DEVELOPMENTS IN TREATMENTS

CORTICOSTEROID THERAPY FOR COVID-19: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

Pulakurthi YS, Pederson JM, Saravu K, Gupta N, Balasubramanian P, Kamrowski S, Schmidt M, Vegivinti CTR, Dibas M, Reierson NL, Pisipati S, Joseph BA, Selvan PT, Dmytriw AA, Keesari PR, Sriram V, Chittajallu S, Brinjikji W, Katamreddy RR, Chibbar R, Davis AR, Malpe M, Mishra HK, Kallmes KM, Hassan AE, Evanson KW.. Medicine (Baltimore). 2021 May 21;100(20):e25719. doi: 10.1097/MD.0000000000025719.
Level of Evidence: 1 - Systematic review of randomized trials or n-of-1 trials

BLUF

A systematic review and meta-analysis conducted by researchers in United States and India included 8 randomized-controlled (RCT) studies conducted through March 10, 2021 with 7,737 patients, 2795 (36.1%) who received corticosteroids along with the standard of care (SOC) for treatment of moderate and severe-critical COVID-19 infection. The odds of mortality were significantly lower in patients who received corticosteroids compared to SOC (OR 0.85) (Figure 2) and odds for need of mechanical ventilation were reduced with corticosteroids compared to SOC (OR 0.7) (Figure 3), suggesting beneficial effects of corticosteroid treatment in moderate to severe COVID-19 infection.

ABSTRACT

BACKGROUND: Corticosteroid treatment is an effective and common therapeutic strategy for various inflammatory lung pathologies and may be an effective treatment for coronavirus disease 2019 (COVID-19). The purpose of this systematic review and meta-analysis of current literature was to investigate the clinical outcomes associated with corticosteroid treatment of COVID-19. METHODS: We systematically searched PubMed, medRxiv, Web of Science, and Scopus databases through March 10, 2021 to identify randomized controlled trials (RCTs) that evaluated the effects of corticosteroid therapies for COVID-19 treatment. Outcomes of interest were mortality, need for mechanical ventilation, serious adverse events (SAEs), and superinfection. RESULTS: A total of 7737 patients from 8 RCTs were included in the quantitative meta-analysis, of which 2795 (36.1%) patients received corticosteroids plus standard of care (SOC) while 4942 (63.9%) patients received placebo and/or SOC alone. The odds of mortality were significantly lower in patients that received corticosteroids as compared to SOC (odds ratio [OR] = 0.85 [95% CI: 0.76; 0.95], P = .003). Corticosteroid treatment reduced the odds of a need for mechanical ventilation as compared to SOC (OR = 0.76 [95% CI: 0.59; 0.97], P = .030). There was no significant difference between the corticosteroid and SOC groups with regards to SAEs and superinfections. CONCLUSION: Corticosteroid treatment can reduce the odds for mortality and the need for mechanical ventilation in severe COVID-19 patients.

FIGURES

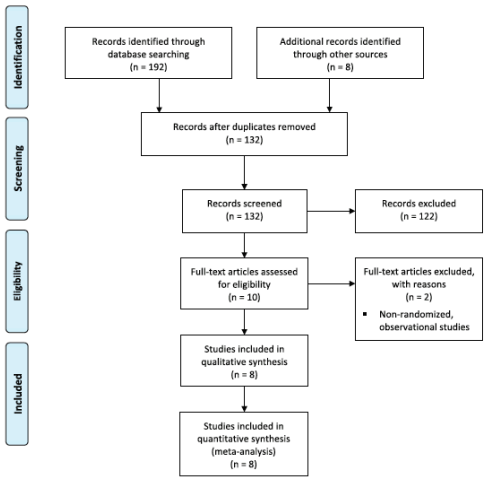

Figure 1. PRISMA diagram of search records and included studies

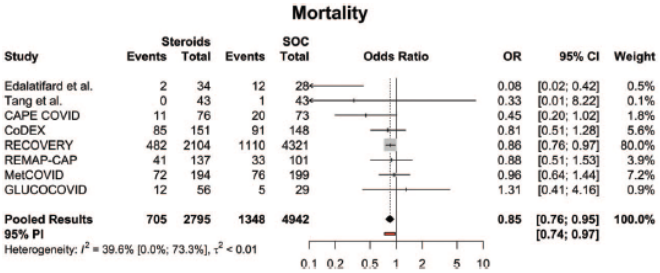

Figure 2. Forest plot of subgroup comparisons of mortality rates. Pooled results were computed using restricted effects maximum likelihood with 95% confidence intervals (CIs) computed using the Q-profile method. A 95% prediction interval (PI) was also computed (see red bar). OR = odds ratio, SOC = standard of care.

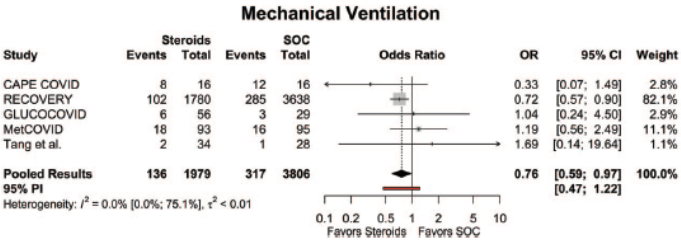

Figure 3. Forest plot of subgroup comparisons of need for mechanical ventilation. Pooled results were computed using restricted effects maximum likelihood with 95% confidence intervals (CIs) computed using the Q-profile method. A 95% prediction interval (PI) was also computed (see red bar). OR = odds ratio, SOC = standard of care.

INTERIM RESULTS OF A PHASE 1-2A TRIAL OF AD26.COV2.S COVID-19 VACCINE

Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, Stoop J, Tete S, Van Damme W, Leroux-Roels I, Berghmans PJ, Kimmel M, Van Damme P, de Hoon J, Smith W, Stephenson KE, De Rosa SC, Cohen KW, McElrath MJ, Cormier E, Scheper G, Barouch DH, Hendriks J, Struyf F, Douoguih M, Van Hoof J, Schuitemaker H.. N Engl J Med. 2021 May 13;384(19):1824-1835. doi: 10.1056/NEJMoa2034201. Epub 2021 Jan 13.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

An international team of researchers shared interim results from a phase 1-2a clinical trial on the efficacy of the Ad26.COV2.S candidate vaccine, a replication-incompetent adenovirus vector encoding a SARS-CoV-2 spike (S) protein, in 403 individuals aged 15-55 (cohort 1) and 402 individuals aged >65 (cohort 3). Both cohorts received a high or low dose of the vaccine in a single-dose or two-dose schedule 56 days apart. The most common adverse reactions included fever, fatigue, headache,

myalgia, and injection-site pain, which were more commonly reported in cohort 1 and in those who received the low dose (Figure 1). Neutralizing antibody titers against wild-type SARS-CoV-2 were present in more than 90% of participants on day 29 after the first dose, and a second dose increased titer by a factor of 2.6–2.9 (Figure 2). These findings suggest that the Ad26.COV2.S vaccine is safe and effective in both younger and older adults with minimal side effects.

SUMMARY

Data from cohort 2 is not reported in this article and is exploring efficacy of 1 versus 2 dose schedules.

ABSTRACT

BACKGROUND: Efficacious vaccines are urgently needed to contain the ongoing coronavirus disease 2019 (Covid-19) pandemic of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A candidate vaccine, Ad26.COV2.S, is a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full-length and stabilized SARS-CoV-2 spike protein. METHODS: In this multicenter, placebo-controlled, phase 1-2a trial, we randomly assigned healthy adults between the ages of 18 and 55 years (cohort 1) and those 65 years of age or older (cohort 3) to receive the Ad26.COV2.S vaccine at a dose of 5x1010 viral particles (low dose) or 1x1011 viral particles (high dose) per milliliter or placebo in a single-dose or two-dose schedule. Longer-term data comparing a single-dose regimen with a two-dose regimen are being collected in cohort 2; those results are not reported here. The primary end points were the safety and reactogenicity of each dose schedule. RESULTS: After the administration of the first vaccine dose in 805 participants in cohorts 1 and 3 and after the second dose in cohort 1, the most frequent solicited adverse events were fatigue, headache, myalgia, and injection-site pain. The most frequent systemic adverse event was fever. Systemic adverse events were less common in cohort 3 than in cohort 1 and in those who received the low vaccine dose than in those who received the high dose. Reactogenicity was lower after the second dose. Neutralizing-antibody titers against wild-type virus were detected in 90% or more of all participants on day 29 after the first vaccine dose (geometric mean titer [GMT], 224 to 354) and reached 100% by day 57 with a further increase in titers (GMT, 288 to 488), regardless of vaccine dose or age group. Titers remained stable until at least day 71. A second dose provided an increase in the titer by a factor of 2.6 to 2.9 (GMT, 827 to 1266). Spike-binding antibody responses were similar to neutralizing-antibody responses. On day 14, CD4+ T-cell responses were detected in 76 to 83% of the participants in cohort 1 and in 60 to 67% of those in cohort 3, with a clear skewing toward type 1 helper T cells. CD8+ T-cell responses were robust overall but lower in cohort 3. CONCLUSIONS: The safety and immunogenicity profiles of Ad26.COV2.S support further development of this vaccine candidate. (Funded by Johnson & Johnson and the Biomedical Advanced Research and Development Authority of the Department of Health and Human Services; COV1001 ClinicalTrials.gov number, NCT04436276.).

Figure 1. Solicited Adverse Events in Cohorts 1 and 3 after the First Vaccine Dose.

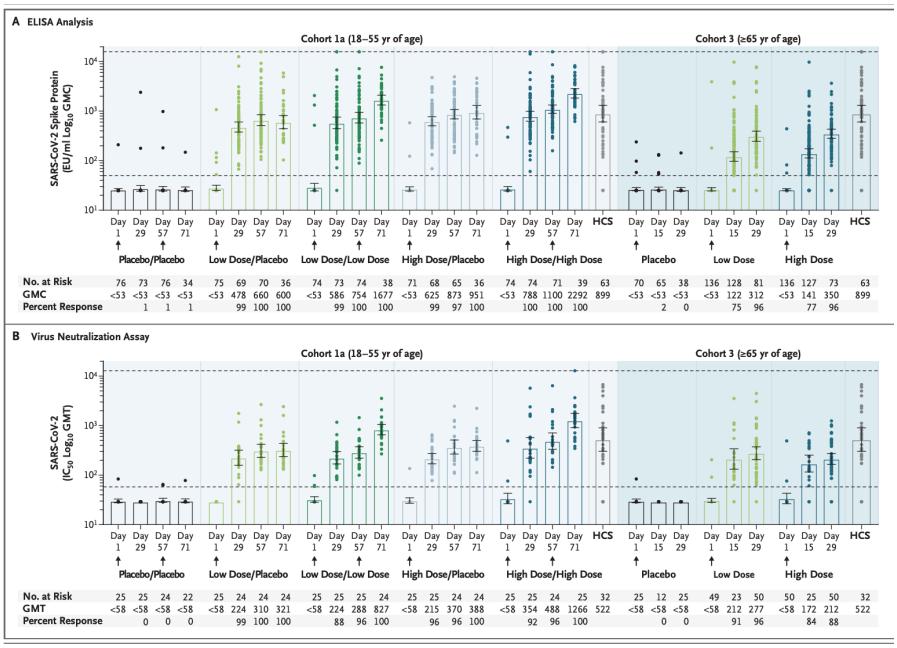

Figure 2. Humoral Immunogenicity.

METHYLPREDNISOLONE AS ADJUNCTIVE THERAPY FOR PATIENTS HOSPITALIZED WITH CORONAVIRUS DISEASE 2019 (COVID-19; METCOVID): A RANDOMIZED, DOUBLE-BLIND, PHASE IIB, PLACEBO-CONTROLLED TRIAL

Jeronimo CMP, Farias MEL, Val FFA, Sampaio VS, Alexandre MAA, Melo GC, Safe IP, Borba MGS, Netto RLA, Maciel ABS, Neto JRS, Oliveira LB, Figueiredo EFG, Oliveira Dinelly KM, de Almeida Rodrigues MG, Brito M, Mourão MPG, Pivoto João GA, Hajjar LA, Bassat Q, Romero GAS, Naveca FG, Vasconcelos HL, de Araújo Tavares M, Brito-Sousa JD, Costa FTM, Nogueira ML, Baía-da-Silva DC, Xavier MS, Monteiro WM, Lacerda MVG; Metcovid Team.. Clin Infect Dis. 2021 May 4;72(9):e373-e381. doi: 10.1093/cid/ciaa1177.
Level of Evidence: 2 - Randomized trial or observational study with dramatic effect

BLUF

Brazilian researchers conducted a randomized, double-blinded, placebo-controlled, phase 2b trial between April 18-June 16, 2020 to assess the efficacy of methylprednisolone (MP) in treating hospitalized COVID-19 patients (Figure 1). They performed modified intention to treat (mITT) analysis of 393 participants (194 in MP and 199 in placebo group) and found no significant difference in the primary outcome (28 day mortality) and secondary outcomes (summary) between the two groups. Post hoc analysis revealed lower 28 day mortality in ages over 60 in the MP group (Tables 1,2). Authors conclude that methylprednisolone did not lower mortality in hospitalized COVID-19 patients.

SUMMARY

Metacovis is a randomized, double-blinded, placebo-controlled, phase 2b trial conducted from April 18-June 16, 2020 to assess the efficacy of methylprednisolone (MP) in treating hospitalized COVID-19 patients more than 18 years of age. They randomized 416 participants and performed mITT analysis in 393 participants with 194 in MP (twice daily for 5 days) and 199 in the placebo arm.

Primary outcome: 28 day mortality
Secondary outcomes: early mortality, need for endotracheal intubation, and PaO2/FiO2 less than 100 on day 7

They found:
- No significant differences in the 28 day mortality by group. 76/199 in placebo and 72/194 in MP (p=0.629).
- Subgroup analysis revealed decreased mortality in MP arm for patients over 60 years old.
- Radiologic evidence of Bronchiolitis Obliterans with Organizing Pneumonia and pulmonary fibrosis did not differ significantly between MP and placebo
- No increased occurrence of sepsis in the MP group
- Requirement of more insulin in MP arm

ABSTRACT

BACKGROUND: Steroid use for COVID-19 is based on the possible role of these drugs in mitigating the inflammatory response, mainly in the lungs, triggered by SARS-CoV-2. This study aimed at evaluating at evaluating the efficacy of methylprednisolone (MP) among hospitalized patients with suspected COVID-19. METHODS: Parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial was performed with hospitalized patients aged >= 18 years with clinical, epidemiological and/or radiological suspected COVID-19, at a tertiary care facility in Manaus, Brazil. Patients were randomly allocated (1:1 ratio) to receive either intravenous MP (0.5 mg/kg) or placebo (saline solution), twice daily, for 5 days. A modified intention-to-treat (mITT) analysis was conducted. The primary outcome was 28-day mortality. ClinicalTrials Identifier NCT04343729. FINDINGS: From April 18 to June 16, 2020, 647 patients were screened, 416 randomized, and 393 analyzed as mITT, MP in 194 and placebo in 199 individuals. SARS-CoV-2 infection was confirmed by RT-PCR in 81.3%. Mortality at day 28 was not different between groups. A subgroup analysis showed that patients over 60 years in the MP group had a lower mortality rate at day 28. Patients in the MP arm tended to need more insulin therapy, and no difference was seen in virus clearance in respiratory secretion until day 7. CONCLUSION: The findings of this study suggest that a short course of MP in hospitalized patients with COVID-19 did not reduce mortality in the overall population.

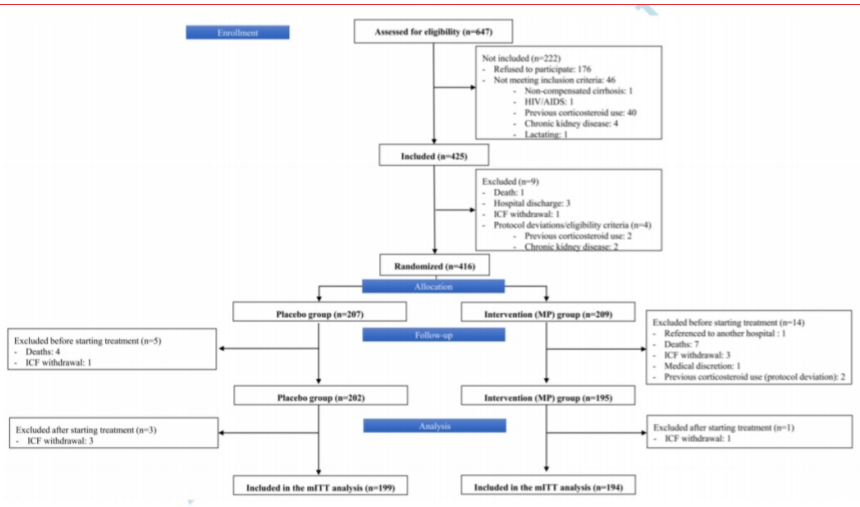

Figure 1: "Trial profile. Eligible participants were allocated at a 1:1 ratio to receive MP (0.5 mg/kg/day) or placebo twice daily, for 5 days. MP, Methylprednisolone; mITT, modified intention to treat".

Variable	Total n=393	Placebo n=199	MP n=194	HR (95%CI) / Absolute Difference (95% CI)	*P*
Primary outcome					
28-day mortality, %	148/393 (37.7%)	76/199 (38.2%)	72/194 (37.1%)	0.924 (0.669 - 1.275)	0.629
Secondary and exploratory outcomes					
7-day mortality, %	79/393 (20.1%)	47/199 (23.6%)	32/194 (16.5%)	0.677 (0.432 - 1.061)	0.089
14-day mortality, %	116/393 (29.5%)	63/199 (31.7%)	53/194 (27.3%)	0.821 (0.570 - 1.183)	0.290
Presence of viral RNA in the naso/oropharyngeal swab on day 5, %	135/283 (47.7%)	66/139 (47.5%)	69/144 (47.9%)	0.43 (-11.1 - 11.9)	0.942
Presence of viral RNA in the naso/oropharyngeal swab on day 7, %	111/212 (52.4%)	50/95 (52.6%)	61/117 (52.1%)	-0.49 (-13.7 - 12.8)	0.943
Need for IMV until day 7, %	34/188 (18.1%)	16/95 (16.8%)	18/93 (19.4%)	2.6 (-8.6 - 13.6)	0.654
Proportion of patients with oxygenation index (PaO_2/FiO_2)<100 until day 7, %	34/111 (30.6%)	13/51 (25.5%)	21/60 (35.0%)	9.51 (-7.70 - 25.59)	0.279
Pulmonary fibrosis after day 7, %	15/56 (26.8%)	3/22 (13.6%)	12/34 (35.3%)	21.7 (-2.4 - 40.7)	0.074
BOOP after day 7, %	36/56 (64.3%)	17/22 (77.3%)	19/34 (55.9%)	-21.4 (-42.1 - 4.3)	0.103
Positive blood culture on day 7, %	16/196 (8.2%)	7/88 (8.0%)	9/108 (8.3%)	0.3 (-8.1 - 8.3)	0.923
Need for insulin therapy until day 28, %	189/347 (54.5%)	86/174 (49.4%)	103/173 (59.5%)	10.1 (-0.4 - 20.3)	0.059
Sepsis until day 28	151/393 (38.4%)	77/199 (38.7%)	74/194 (38.1%)	-0.6 (-10.1 - 9.0)	0.911
Length of hospitalization (days), median (IQR)	9 (7 - 13)	9 (7 - 12)	10 (7 - 13)	-	0.296

HR: Hazard Ratio; CI: Confidence interval

IQR, interquartile range; BOOP=Bronchiolitis Obliterans with Organizing Pneumonia; IMV, invasive mechanical ventilation

Table 2: "Primary, secondary and post hoc exploratory outcomes".

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Subgroup	Placebo n=199	MP n=194	HR (95%CI)	*P*
Age > 60 years	52/84 (61.9%)	34/73 (46.6%)	**0.634 (0.411 - 0.978)**	**0.039**
Invasive mechanical ventilation	57/67 (85.1%)	53/66 (80.3%)	0.808 (0.555 - 1.176)	0.266
Non-invasive oxygen therapy	19/90 (21.1%)	18/98 (18.4%)	0.818 (0.429 - 1.558)	0.541
qSOFA ≥2	52/70 (74.3%)	53/76 (69.7%)	0.850 (0.579 - 1.246)	0.404
Lymphocytes ≤876 × 10^9/L	54/87 (62.1%)	45/88 (51.1%)	0.693 (0.466 - 1.029)	0.056
IL-6 >77 pg/mL	57/82 (69.5%)	51/81 (63.0%)	0.755 (0.517 - 1.102)	0.319
Ferritin >940 ng/mL	52/83 (62.7%)	47/90 (52.2%)	0.738 (0.497 - 1.096)	0.304
C-reactive protein >80 mg/L	35/65 (53.8%)	34/74 (45.9%)	0.745 (0.465 - 1.195)	0.344
SARS-CoV-2 positive PCR	69/157 (43.9%)	70/161 (43.5%)	0.953 (0.683 – 1.329)	0.777

HR: Hazard Ratio; CI: Confidence interval; Cut-off levels were defined as lower and higher than the median.

Table 3: "Death on day 28 per post-hoc defined subgroups".

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