# The Daily COVID-19 Literature Surveillance Summary

## December 08, 2020

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# 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

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# EXECUTIVE SUMMARY

**Climate**

- No-fault compensation for vaccine injury. Are we looking at the other side of equitable access to Covid-19 vaccines? An opinion piece on COVID-19 vaccination explains that though there are 79 higher-income countries ready to pay for vaccine distribution in 92 lower-income countries, there is not yet an established method for injury compensation if an adverse vaccine event takes place. This suggests the need for an injury compensation plan in these lower-income countries by incorporating existing systems in wealthier countries, some World Health Organization programs, and the COVAX Facility, an international partnership to help support vaccine access in lower-income countries.

**Epidemiology**

- One study estimated SARS-CoV-2 seroprevalence in the US as of September 2020. This cross-sectional study, conducted primarily by US Centers for Disease Control and Prevention (Atlanta, Georgia), sampled 177,919 residual serum specimens from across all 50 United States, the District of Columbia, and Puerto Rico during 4 collection periods between July and September, 2020. They found that less than 10% of participants in 42 of 49 jurisdictions had detectable SARS-CoV-2 antibodies, with estimates of seropositivity projected in a given jurisdiction to range between fewer than 1% to 23%. This finding suggests a large variation in SARS-CoV-2 seroprevalence across jurisdictions and that most individuals do not exhibit SARS-CoV-2 antibodies from prior infection, highlighting the need for ongoing preventative practices (face masks, social distancing, etc.) and continued nationwide sera testing to inform SARS-CoV-2 epidemiology in the US.

**Understanding the Pathology**

- SARS-CoV-2 antibody and COVID-19 severity may vary with multisystem inflammatory syndrome in children (MIS-C). A group associated with Perelman School of Medicine at the University of Pennsylvania compared the antibody response to SARS-CoV-2 in 29 children with minimal (n=10) or severe COVID-19 (n=9) to those with MIS-C (n=10). They discovered that children with MIS-C have higher titers of IgG antibody than children with severe COVID-19 that effectively neutralize SARS-CoV-2 and may be due to longer time since onset of infection. This study is one of the first to study this immunological process in children in hopes of identifying pathophysiological pathways to investigate further.

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## NO-FAULT COMPENSATION FOR VACCINE INJURY - THE OTHER SIDE OF EQUITABLE ACCESS TO COVID-19 VACCINES

Halabi S, Heinrich A, Omer SB.. N Engl J Med. 2020 Dec 3;383(23):e125. doi: 10.1056/NEJMp2030600. Epub 2020 Oct 28.
Level of Evidence: 5 - Expert Opinion

### BLUF

An opinion piece on COVID-19 vaccination explains that though there are 79 higher-income countries ready to pay for vaccine distribution in 92 lower-income countries, there is not yet an established method for injury compensation if an adverse vaccine event takes place. This suggests the need for an injury compensation plan in these lower-income countries by incorporating existing systems in wealthier countries, some World Health Organization programs, and the COVAX Facility, an international partnership to help support vaccine access in lower-income countries.

# EPIDEMIOLOGY

## ESTIMATED SARS-COV-2 SEROPREVALENCE IN THE US AS OF SEPTEMBER 2020

Bajema KL, Wiegand RE, Cuffe K, Patel SV, Iachan R, Lim T, Lee A, Moyse D, Havers FP, Harding L, Fry AM, Hall AJ, Martin K, Biel M, Deng Y, Meyer WA 3rd, Mathur M, Kyle T, Gundlapalli AV, Thornburg NJ, Petersen LR, Edens C.. JAMA Intern Med. 2020 Nov 24. doi: 10.1001/jamainternmed.2020.7976. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

### BLUF

This cross-sectional study, conducted primarily by US Centers for Disease Control and Prevention (Atlanta, Georgia), sampled residual serum specimens (n=177,919) from across all 50 United States, the District of Columbia, and Puerto Rico during 4 collection periods between July and September, 2020. They found that less than 10% of participants in 42 of 49 jurisdictions had detectable SARS-CoV-2 antibodies, with estimates of seropositivity projected in a given jurisdiction to range between fewer than 1% to 23% (Figure 1, Table 1). This finding suggests a large variation in SARS-CoV-2 seroprevalence across jurisdictions and that most individuals do not exhibit SARS-CoV-2 antibodies from prior infection, highlighting the need for ongoing preventative practices (face masks, social distancing, etc.) and continued nationwide sera testing to inform SARS-CoV-2 epidemiology in the US.

### SUMMARY

Serum specimens were collected during 4 periods as follows: July 27 to August 13, August 10 to August 27, August 24 to September 10, and September 7 to September 24, 2020. This study stratified samples by age, gender, and location (metropolitan versus nonmetropolitan) and found that there was less than a 7% change across all jurisdictions from collection period 1 to 4 (Table 1).

### ABSTRACT

Importance: Case-based surveillance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection likely underestimates the true prevalence of infections. Large-scale seroprevalence surveys can better estimate infection across many geographic regions. Objective: To estimate the prevalence of persons with SARS-CoV-2 antibodies using residual sera from commercial laboratories across the US and assess changes over time. Design, Setting, and Participants: This repeated, cross-sectional study conducted across all 50 states, the District of Columbia, and Puerto Rico used a convenience sample of residual serum specimens provided by persons of all ages that were originally submitted for routine screening or clinical management from 2 private clinical commercial laboratories. Samples were obtained during 4 collection periods: July 27 to August 13, August 10 to August 27, August 24 to September 10, and September 7 to September 24, 2020. Exposures: Infection with SARS-CoV-2. Main Outcomes and Measures: The proportion of persons previously infected with SARS-CoV-2 as measured by the presence of antibodies to SARS-CoV-2 by 1 of 3 chemiluminescent immunoassays. Iterative poststratification was used to adjust seroprevalence estimates to the demographic profile and urbanicity of each jurisdiction. Seroprevalence was estimated by jurisdiction, sex, age group (0-17, 18-49, 50-64, and >=65 years), and metropolitan/nonmetropolitan status. Results: Of 177 919 serum samples tested, 103 771 (58.3%) were from women, 26 716 (15.0%) from persons 17 years or younger, 47 513 (26.7%) from persons 65 years or older, and 26 290 (14.8%) from individuals living in nonmetropolitan areas. Jurisdiction-level seroprevalence over 4 collection periods ranged from less than 1% to 23%. In 42 of 49 jurisdictions with sufficient samples to estimate seroprevalence across all periods, fewer than 10% of people had detectable SARS-CoV-2 antibodies. Seroprevalence estimates varied between sexes, across age groups, and between metropolitan/nonmetropolitan areas. Changes from period 1 to 4 were less than 7 percentage points in all jurisdictions and varied across sites. Conclusions and Relevance: This cross-sectional study found that as of September 2020, most persons in the US did not have serologic evidence of previous SARS-CoV-2 infection, although prevalence varied widely by jurisdiction. Biweekly nationwide testing of commercial clinical laboratory sera can play an important role in helping track the spread of SARS-CoV-2 in the US.

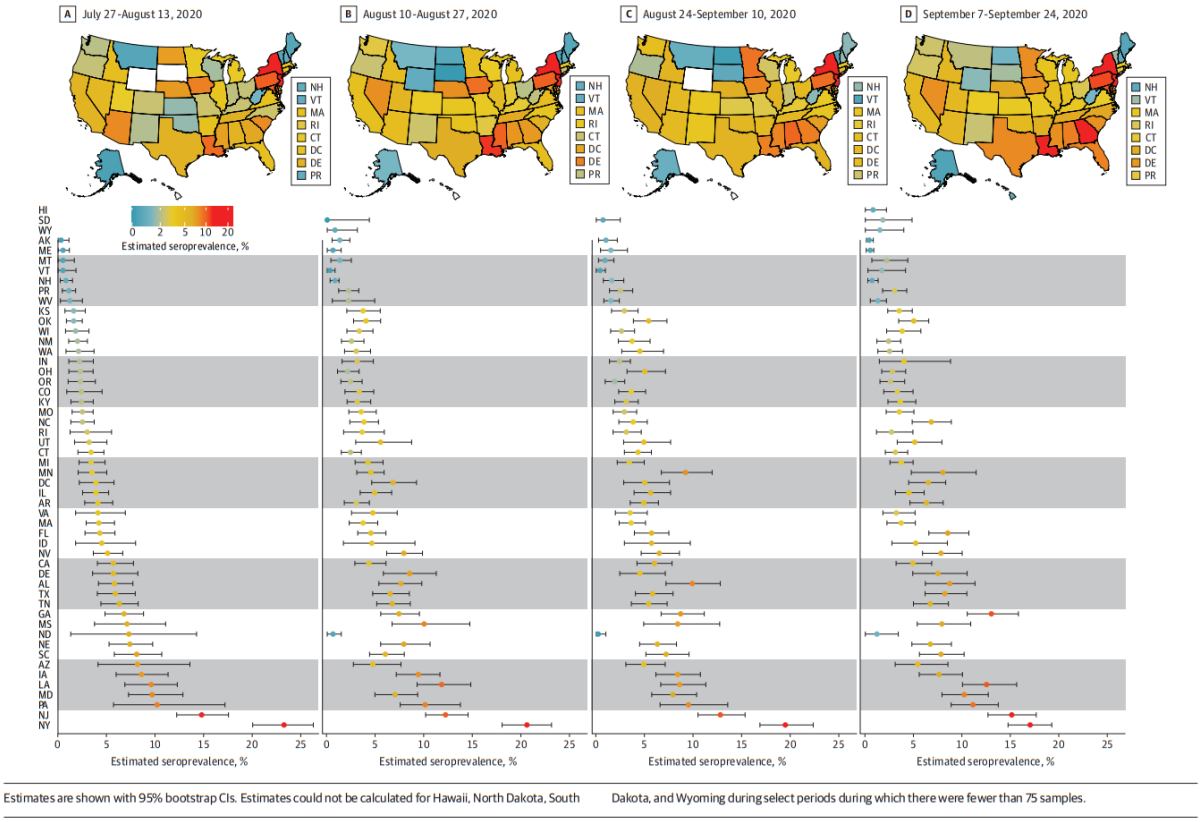


Figure 1. SARS-CoV-2 Prevalence Estimates by US Jurisdiction During Testing Periods From July 27 to August 13, August 10 to 27, August 24 to September 10, and September 7 to 24, 2020. Estimates are shown with 95% bootstrap CIs. Estimates could not be calculated for Hawaii, North Dakota, South Dakota, and Wyoming during select periods during which there were fewer than 75 samples.

| | No. (%)[a] | | | |
|---|---|---|---|---|
| Characteristic | Period 1 | Period 2 | Period 3 | Period 4 |
| Total samples | 38 776 | 45 907 | 45 327 | 47 909 |
| Dates of specimen collection[b] | July 27-August 13, 2020 | August 10-27, 2020 | August 24-September 10, 2020 | September 7-24, 2020 |
| Sex | | | | |
| Male | 16 024 (41.3) | 18 794 (40.9) | 18 983 (41.9) | 20 343 (42.5) |
| Female | 22 751 (58.7) | 27 112 (59.1) | 26 344 (58.1) | 27 564 (57.5) |
| Age category, y | | | | |
| 0-17 | 6700 (17.3) | 6920 (15.1) | 6484 (14.3) | 6612 (13.8) |
| 18-49 | 11 237 (29.0) | 14 571 (31.8) | 14 079 (31.1) | 15 157 (31.6) |
| 50-64 | 10 367 (26.8) | 12 514 (27.3) | 12 426 (27.4) | 13 207 (27.6) |
| ≥65 | 10 408 (26.9) | 11 856 (25.9) | 12 316 (27.2) | 12 933 (27.0) |
| Assay[c] | | | | |
| Abbott ARCHITECT | 18 467 (47.6) | 20 436 (44.5) | 22 378 (49.4) | 23 534 (49.1) |
| Ortho VITROS | 15 334 (39.6) | 17 708 (38.6) | 16 116 (35.6) | 16 100 (33.6) |
| Roche Elecsys | 4975 (12.8) | 7763 (16.9) | 6833 (15.1) | 8275 (17.3) |
| Metropolitan status[d] | | | | |
| Nonmetropolitan | 5932 (15.3) | 6339 (13.8) | 6807 (15.0) | 7212 (15.1) |
| Metropolitan | 32 828 (84.7) | 39 555 (86.2) | 38 500 (85.0) | 40 671 (84.9) |

[a] Percentages calculated out of nonmissing values for all periods. Missing values in period 1 included sex (n = 1), age (n = 64), and metropolitan status (n = 16). Missing values in period 2 included sex (n = 1), age (n = 46), and metropolitan status (n = 13). Missing values in period 3 included age (n = 22) and metropolitan status (n = 20). Missing values in period 4 included sex (n = 2) and metropolitan status (n = 26).

[b] Because laboratories completed biweekly sampling 3 days apart, the total number of days included in each period across all jurisdictions was more than 2 weeks. There were 207 missing dates in period 1, 216 missing dates in period 2, 236 missing dates in period 3, and 226 missing dates in period 4.

[c] Abbott ARCHITECT SARS-CoV-2 IgG, Ortho-Clinical Diagnostics VITROS Anti-SARS-CoV-2 IgG, and Roche Elecsys Anti-SARS-CoV-2.

[d] Determined by the 2013 Rural-Urban Continuum Codes classification.[23] Counties identified by Rural-Urban Continuum Codes 1 to 3 were designated metropolitan and 4 to 9 were designated nonmetropolitan.

Table 1. Demographic and Assay Characteristics of Sampled Populations in 50 US States, Washington DC, and Puerto Rico During 4 Periods of SARS-CoV-2 Testing From July 27 to September 10, 2020

# ADULTS

## HIGHER VIRAL LOADS IN ASYMPTOMATIC COVID-19 PATIENTS MIGHT BE THE INVISIBLE PART OF THE ICEBERG

Hasanoglu I, Korukluoglu G, Asilturk D, Cosgun Y, Kalem AK, Altas AB, Kayaaslan B, Eser F, Kuzucu EA, Guner R.. Infection. 2020 Nov 24. doi: 10.1007/s15010-020-01548-8. Online ahead of print.
Level of Evidence: 4 - Local non-random sample

### BLUF

Physicians and Scientists primarily from Yildirim Beyazit University School of Medicine (Turkey) analyzed the viral loads of 6 sample types (nasopharyngeal/oropharyngeal (NP+OP), saliva, oral cavity, rectal, and urine) of 60 patients (360 total samples) with laboratory-confirmed COVID-19 from May 1-May 30th, 2020 in Ankara City Hospital and Infectious Disease Clinical Microbiology Clinic. They found that "PCR positivity rates were 80%, 50%, 13.3%, 8.3%, and 1.7% for NP+OP, saliva, oral cavity, rectal, and urine samples, respectively". They also found that NP+OP viral loads of asymptomatic patients were higher than viral loads in symptomatic patients (p=0.0141, Figure 1), and patients with more severe disease had decreased viral loads despite other factors associated with a low prognosis (p=0.0015, Figure 6). The authors suggest the need for further virological and immunological investigations to understand the dynamics of SARS-CoV-2 viral load and its relationship to disease severity.

### ABSTRACT

PURPOSE: SARS-CoV-2 virus dynamics in different hosts and different samples and their relationship with disease severity have not been clearly revealed. The aim of this study is to evaluate the viral loads of 6 different sample types (nasopharyngeal/oropharyngeal combined, oral cavity, saliva, rectal, urine, and blood) of patients with different ages and clinics, to reveal the relationship between disease course and SARS-CoV-2 viral load, and differences in viral loads of asymptomatic and symptomatic patients. METHODS: Nasopharyngeal/oropharyngeal, oral cavity, saliva, rectal, urine, and blood samples are collected from patients who were hospitalized with diagnosis of COVID-19 on admission. Laboratory analysis were carried out at Public Health Institute of Turkey Virology Reference and Research Laboratory. RESULTS: A total of 360 samples from 60 patients were obtained on admission. Fifteen (25%) of the patients were asymptomatic while 45 (75%) were symptomatic. A significant difference was found between mean ages of asymptomatic vs symptomatic patients (26.4 and 36.4, respectively, p = 0.0248). No PCR positivity were found in blood. Only one asymptomatic patient had positive PCR result for urine sample. Viral loads of asymptomatic patients were found to be significantly higher (p = 0.0141) when compared with symptomatic patients. Viral load had a significant negative trend with increasing age. A significant decrease in viral load was observed with increasing disease severity. CONCLUSION: In conclusion, this study demonstrates that asymptomatic patients have higher SARSCoV-2 viral loads than symptomatic patients and unlike in the few study in the literature, a significant decrease in viral load of nasopharyngeal/oropharyngeal samples was observed with increasing disease severity. Factors associated with poor prognosis are found to be significantly correlated with low viral load.

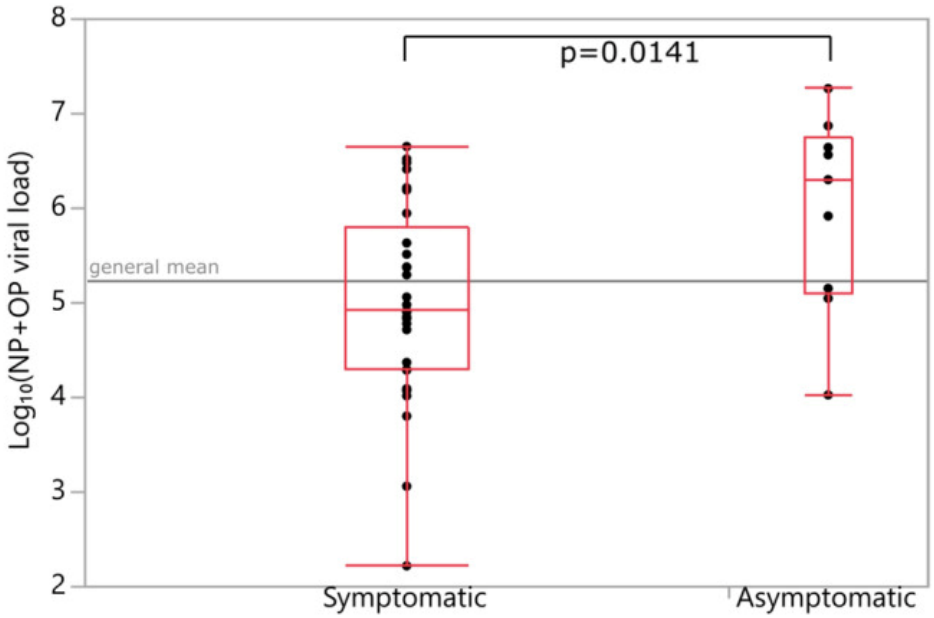


Figure 1. Viral loads of NP (Nasopharyngeal)+OP (Oropharyngeal) samples (Student's t-test)

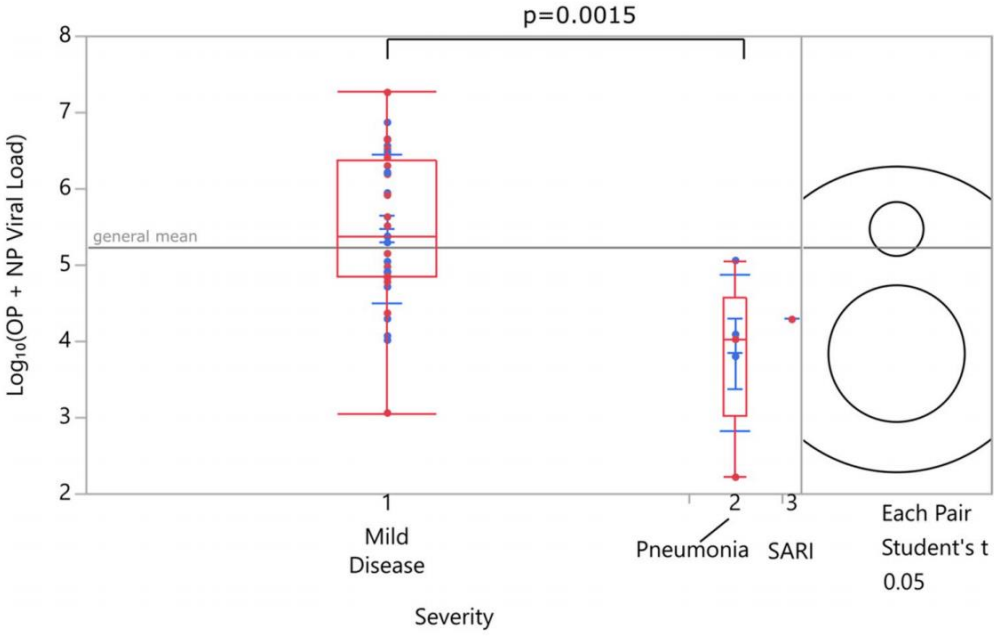


Figure 6. Viral load vs disease severity (SARI: severe acute respiratory illness, NP:Nasopharyngeal, OP: Oropharyngeal)

# UNDERSTANDING THE PATHOLOGY

## SARS-COV-2 ANTIBODY RESPONSES IN CHILDREN WITH MIS-C AND MILD AND SEVERE COVID-19

Anderson EM, Diorio C, Goodwin EC, McNerney KO, Weirick ME, Gouma S, Bolton MJ, Arevalo CP, Chase J, Hicks P, Manzoni TB, Baxter AE, Andrea KP, Burudpakdee C, Lee JH, Vella LA, Henrickson SE, Harris RM, Wherry EJ, Bates P, Bassiri H, Behrens EM, Teachey DT, Hensley SE.. J Pediatric Infect Dis Soc. 2020 Dec 2:piaa161. doi: 10.1093/jpids/piaa161. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

### BLUF

A group associated with Perelman School of Medicine at the University of Pennsylvania compared the antibody response to SARS-CoV-2 in 29 children with minimal (n=10) or severe COVID-19 (n=9) to those with MIS-C (multisystem inflammatory syndrome in children) (n=10) in April and May 2020. They discovered that children with MIS-C have higher titers of IgG antibody than children with severe COVID-19 (Figure 1) that effectively neutralize SARS-CoV-2 and may be due to longer time since onset of infection. This study is one of the first to study this immunological process in children in hopes of identifying pathophysiological pathways to investigate further.

### ABSTRACT

SARS-CoV-2 antibody responses in children remain poorly characterized. Here, we show that pediatric patients with multisystem inflammatory syndrome in children (MIS-C) possess higher SARS-CoV-2 spike IgG titers compared to those with severe coronavirus disease 2019 (COVID-19), likely reflecting a longer time since onset of infection in MIS-C patients.

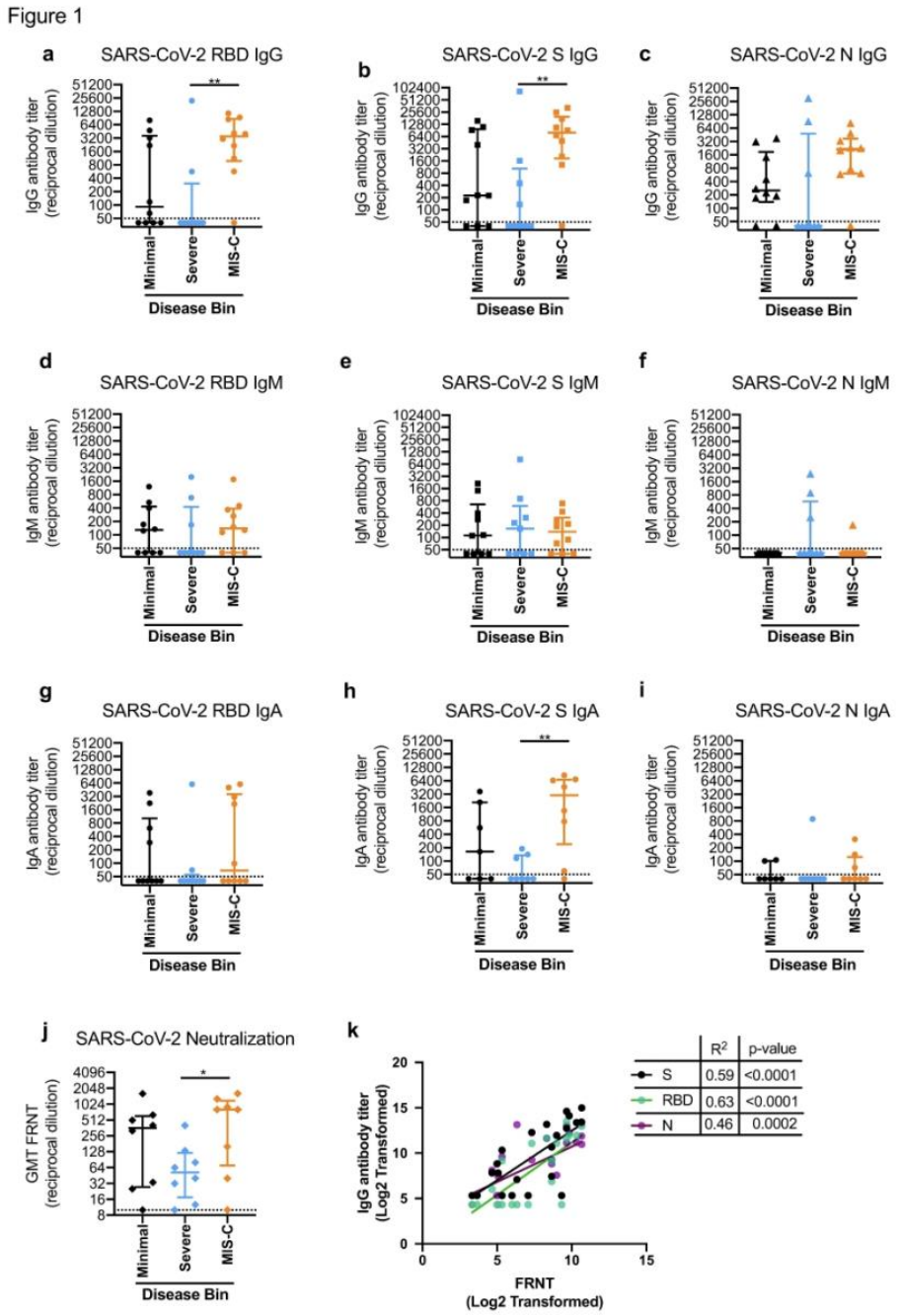


Figure 1. Serum SARS-CoV-2 antibody levels in pediatric COVID-19 patients. Antibody titers expressed as reciprocal serum dilution against SARS-CoV-2 antigens in pediatric patients with minimal disease (n=10), severe disease (n=9) and multisystem inflammatory syndrome (MIS-C; n=10). Line and error bars represent median antibody titer and interquartile range per disease phenotype. Titers against the SARS-CoV-2 receptor binding domain (S-RBD) IgG (a), IgM (d), and IgA (g). Titers against SARS-CoV-2 full length spike protein (S) IgG (b), IgM (e), and IgA (h). Titers against SARS CoV-2 nucleocapsid protein (N) IgG (c) and IgM (f) and IgA (i). Note: IgA S and N antibodies were measured in a subset of samples with sufficient volume; N=23). (j) Neutralization activity of sera against SARS-CoV-2 spike pseudo-typed vesicular stomatitis virus (VSV) expressed as the geometric mean of the reciprocal dilution foci reduction neutralization titer (GMT FRNT; N=24). (k) Linear regressions of Log2 transformed SARS-CoV-2 IgG titers (S, S-RBD, and N) and FRNT neutralization titers (R2 = 0.59, 0.63, 0.4; p<0.0001, p<0.0001, and p=0.0002, respectively). Dashed lines denote the lower limit of detection at a reciprocal dilution of 50. Unpaired t-test of log2 transformed titers **p<0.001

## HEALTHCARE-ASSOCIATED SARS-COV-2 TRANSMISSION IN A NEONATAL UNIT: THE IMPORTANCE OF UNIVERSAL MASKING, HAND HYGIENE AND SYMPTOM SCREENING IN CONTAINMENT

Holgate SL, Dramowski A, van Niekerk M, Hassan H, Prinsloo Y, Bekker A.. J Pediatric Infect Dis Soc. 2020 Dec 2:piaa160. doi: 10.1093/jpids/piaa160. Online ahead of print.
Level of Evidence: 4 - Case-series

### BLUF

This article describes two preterm neonate patients and six staff who all experienced the same exposure to and tested positive for COVID-19 in one neonatal intensive care unit (NICU) at the Tygerberg Hospital NICU in Cape Town, South Africa in April 2020 to emphasize the importance of outbreak containment measures. After contact tracing and further investigation, it was determined that despite infection prevention policies, there were initial delays in staff screening, testing, and COVID-19 testing data, as well as lack of full adherence to universal masking that led to spread of infection and staffing shortages, suggesting the importance of refining and fully implementing protocols.

### ABSTRACT

Following exposure to a health care worker with an influenza-like illness, two preterm neonates and six staff members developed symptoms and tested positive for SARS-CoV-2. This neonatal unit COVID-19 outbreak occurred prior to implementation of universal masking and symptom screening policies. Both neonates and all staff recovered, with no further healthcare-associated SARS-CoV-2 transmission following implementation of effective outbreak containment measures.

# MANAGEMENT

## ACUTE CARE

## CRITICAL CARE

### SARS-COV-2-TRIGGERED IMMUNE REACTION: FOR COVID-19, NOTHING IS AS OLD AS YESTERDAY'S KNOWLEDGE

Welte T.. Am J Respir Crit Care Med. 2020 Dec 3. doi: 10.1164/rccm.202011-4194ED. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

#### BLUF

A pulmonologist from Hannover, Germany writes that the evolution of disease progression in individuals with COVID-19 has been compared with influenza and SARS Coronavirus 2002/2003 but has differed in many ways. After analyzing various studies, the author states that the primary damage caused by SARS Coronavirus 2 is the triggered immune response, which differs based on organ system but is mainly found in the lungs as pulmonary vasculitis. For this reason, anti-inflammatory inhalation therapies targeted at the lungs, as opposed to antiviral therapies, might prove to be more useful against the second phase of COVID-19.

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