The Host Response to SARS-CoV-2 Differs Upon Age of Infection

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Introduction

- Infection with SARS-CoV-2 and the resultant host immune response has been primarily characterized in middle and older aged populations due to the severity of disease in these age groups. Children have experienced significantly lower rates of hospitalization and death compared to adults in response to SARS-CoV-2 infection. The etiology of these age-associated patterns remains unknown.
- Studies evaluating the viral load and magnitude of the humoral response, as a cause of disease severity, have varied. Prior studies have shown that viral loads are similar or slightly lower in children compared to adults[1,2]. Antibody responses have been shown to be both higher and lower after primary infection in children compared to adults [3,4].
- In this study, we measured nasopharyngeal SARS-CoV-2 RNA abundance and Spike-specific IgG responses across the age-spectrum to further define aspects of the age-dependent host immune response in a cohort of beneficiaries of the U.S. Military Health system across the United States.

Methods

Study Design

- This study was conducted as part of the Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) study. EPICC is a longitudinal cohort study examining SARS-CoV-2 clinical and immunologic outcomes amongst beneficiaries of the U.S. Military Health System.

Study Population

- From March of 2020-March of 2022, individuals presenting with COVID-19-like symptoms were enrolled from ten U.S military treatment facilities.
- All age groups were enrolled.
- Demographic and clinical data were collected from participants, in addition to nasopharyngeal swabs and peripheral blood samples.
- For this analysis, only individuals with a positive SARS-CoV-2 PCR were included.

Laboratory Methods

- Magnitude of viral RNA was measured by quantitative PCR (qPCR) from nasopharyngeal samples, and SARS-CoV-2-specific antibodies were measured from serum with multiplex microsphere immunoassay.[5]

Statistical Analysis

- Nonparametric tests were used to determine differences in RNA abundance and IgG magnitude between age strata.

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Results

Table 1. Demographics of participants with primary SARS-CoV-2 infection

Age cohort	0-4	5-11	12-17	18-22	23-44	45-64	65+
N	36	76	47	206	1310	572	175
Median age	3.1	8.4	15.4	21.0	33.0	53.7	69.6
Sex							
Male	21 (58.3%)	37 (48.7%)	28 (59.6%)	127 (61.7%)	767 (58.5%)	349 (61.0%)	110 (62.9%)
Female	15 (41.7%)	39 (51.3%)	19 (40.4%)	77 (37.4%)	506 (38.6%)	210 (36.7%)	64 (36.6%)
Missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.0%)	37 (2.8%)	13 (2.3%)	1 (0.6%)
Race							
Asian	0 (0.0%)	7 (9.2%)	2 (4.3%)	5 (2.4%)	67 (5.1%)	36 (6.3%)	7 (4.0%)
Black	1 (2.8%)	4 (5.3%)	4 (8.5%)	30 (14.6%)	149 (11.4%)	90 (15.7%)	24 (13.7%)
Hispanic or Latino	13 (36.1%)	15 (19.7%)	15 (31.9%)	68 (33.0%)	307 (23.4%)	125 (21.9%)	34 (19.4%)
Other	2 (5.6%)	9 (11.8%)	7 (14.9%)	13 (6.3%)	125 (9.5%)	26 (4.5%)	11 (6.3%)
White	20 (55.6%)	41 (53.9%)	19 (40.4%)	90 (43.7%)	662 (50.5%)	295 (51.6%)	99 (56.6%)
Severity							
Mild	36 (100.0%)	74 (97.4%)	46 (97.9%)	198 (96.1%)	1204 (91.9%)	371 (64.9%)	86 (49.1%)
Hospitalized	0 (0.0%)	2 (2.6%)	1 (2.1%)	8 (3.9%)	104 (7.9%)	195 (34.1%)	74 (44.3%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	6 (1.0%)	15 (8.6%)

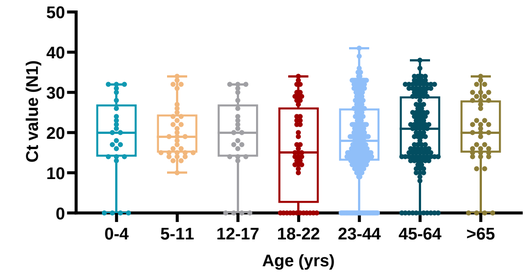


Figure 1. In outpatients, viral abundance from respiratory specimen collected within 7 days post symptom onset did not differ between age groups. P=0.1417 by Kruskal-Wallis test.

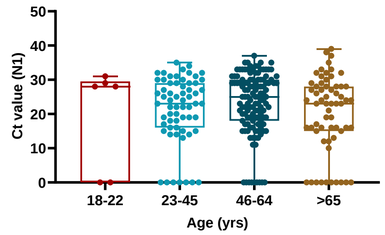
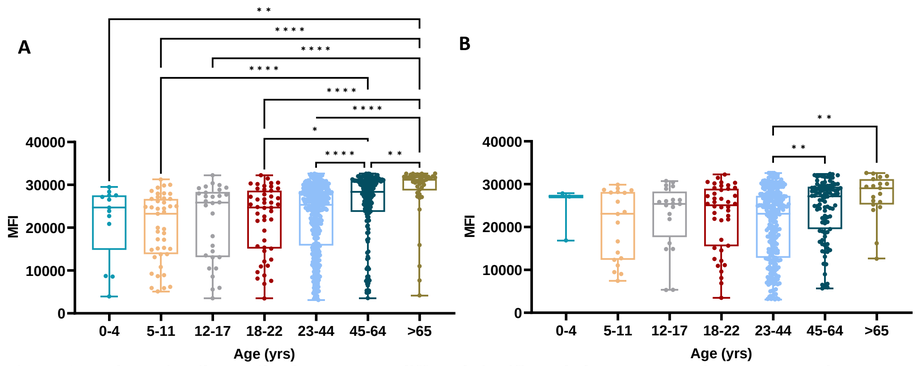


Figure 2. In hospitalized patients, viral abundance from respiratory specimen collected within 7 days post symptom onset did not differ between age groups. <18 years age groups not shown as hospitalization was rare in these age groups. P=0.4236 by Kruskal-Wallis test.



Proportion seropositive		
Age (yrs)	0-30 days	35-90 days
0-4	15/18 (83.3%)	3/5 (60.0%)
12-17	26/27 (96.3%)	18/18 (100.0%)
18-22	65/72 (90.3%)	46/48 (95.8%)
23-44	380/409 (92.9%)	263/281 93.6%)
45-64	172/180 9 (95.6%)	99/102 (97.1%)
5-11	45/47 (95.7%)	22/23 (95.7%)
65+	42/46 (91.3%)	19/19 (100%)

Table 2. Proportion of individuals in each group with MFI above the limit of detection at time tested post symptom onset.

Figure 3. Early anti-spike antibody response differed significantly by age group in contrast to late responses in those with mild disease. **3A.** IgG magnitude (median fluorescence intensity, MFI) at 0-30 days post symptom onset (DPSO). P <0.0001 by Kruskal-Wallis. **3B.** IgG MFI at 35-90 DPSO. P < 0.0001 by Kruskal-Wallis. MFI below limit of detection (<3000) has not been graphed and are considered non-responders. * represents P ≤ 0.05, ** represents P ≤ 0.01, *** represents P ≤ 0.001, **** P ≤ 0.0001

Conclusions

- Viral RNA abundance during acute infection did not correlate with age in individuals who experienced mild COVID-19. Comparing younger adults to older adults, there was also no difference in viral abundance in hospitalized patients. These findings are similar to prior studies for SARS-CoV-2. Interestingly, these findings for SARS-CoV-2 diverge from other respiratory viruses such as respiratory syncytial virus and influenza where children tend to have higher viral abundance.
- Among those with mild or asymptomatic disease, a higher magnitude of spike-specific antibodies correlated with older age at early time points. The comparison was less robust at convalescent time points.
- Together, these data show that acute viral abundance does not correlate with age, while the magnitude of antibody response does, implicating host immunity in pathogenesis.
- Defining age-dependent immunity against SARS-CoV-2 has the potential to identify key immunologic responses that can be used to optimize treatment and vaccine strategies.

Acknowledgements

Disclaimer: The contents of this publication are the sole responsibility of the author (s) and do not necessarily reflect the views, opinions, or policies of Uniformed Services University of the Health Sciences (USUHS); the Department of Defense (DoD); the Departments of the Army, Navy, or Air Force; the Defense Health Agency, Brooke Army Medical Center; Walter Reed National Military Medical Center; Naval Medical Center San Diego; Madigan Army Medical Center; United States Air Force School of Aerospace Medicine; Fort Belvoir Community Hospital; William Beaumont Army Medical Center; Tripler Army Medical Center; Naval Medical Center Portsmouth; the Henry M. Jackson Foundation for the Advancement of Military Medicine Inc; the National Institutes of Health. Mention of trade names, commercial products, or organizations does not imply endorsement by the U.S. Government. The investigators have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46.

Funding: This work was supported by awards from the Defense Health Program (HU00012020067) and the National Institute of Allergy and Infectious Disease (HU00011920111). The protocol was executed by the Infectious Disease Clinical Research Program (IDCRP), a Department of Defense (DoD) program executed by the Uniformed Services University of the Health Sciences (USUHS) through a cooperative agreement by the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. (HJF). This project has been funded in part by the National Institute of Allergy and Infectious Diseases at the National Institutes of Health, under an interagency agreement (Y1-AI-5072).

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