Durability of SARS-CoV-2 Antibodies from Natural Infection in Children and Adolescents

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45 **Abbreviations:**

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47 **COVID-19:** coronavirus disease 2019

48 **DSHS:** Department of State Health Services

49 **SARS-CoV-2:** severe acute respiratory syndrome coronavirus 2

50 **Texas CARES:** Texas COVID-19 Antibody Response Survey

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Contributors' Statement Page

Drs. Boerwinkle, Lakey, Pont, Shuford, and Valerio-Shewmaker conceptualized and designed the Texas CARES study.

Dr. Messiah drafted the initial manuscript and reviewed and revised the manuscript based on all other authors input.

Drs. Shewmaker, Kohl and Kelder and Jessica Ross designed the data collection instruments and collected data. Michael Gonzalez programmed all survey questions in REDCap.

Frances Brito carried out the initial analyses and reviewed and revised the manuscript. Drs. DeSantis, Swartz and Yaseen reviewed all analyses.

Leqing Wu, Shiming Zhang and Dr. Omega-Njemnobi coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Background. Recent data suggest the SARS-CoV-2 Delta (B.1.617.2) variant is more transmissible among children compared to the Alpha (B.1.1.7) variant. The true incidence and longitudinal presence of antibody response to SARS-CoV-2 infection is not known, however. We provided estimates of antibody response using Texas Coronavirus Antibody REsponse Survey (Texas CARES) data, a prospective population-based seroprevalence project designed to assess antibody status over time among the general population throughout the state.

Methods. In October 2020 Texas CARES began enrolling adults (aged 20-80 years) and children (aged 5-19 years). Participants were offered a series of three SARS-CoV-2 antibody tests over 6-8 months, or every 2-3 months that includes the immunoassay for detection of antibodies to the SARS-CoV-2 nucleocapsid protein (Roche N-test). Descriptive characteristics and COVID-19 infection-related symptom status was determined by questionnaire at the time of enrollment and prior to each successive blood draw. This analysis included participants ages 5-to-19 years old who have completed all three antibody assessments.

Results. From our sample (n=159; mean age 12.5 years, SD 3.6), 96% of those with evidence of nucleocapsid antibodies at baseline assessment continued to have antibodies > six months later (mean 7.0 months, SD 0.97). There was no difference in the presence of antibodies by symptom status (asymptotic versus symptomatic) or severity (mild-moderate versus severe), sex, age group, or body mass index group (underweight, healthy weight, overweight, obesity) over the three antibody measurement timepoints.

Conclusions. These results suggest that infection-induced antibodies persist and thus may provide some protection against future infection for at least half a year. 57.9% of the sample were negative for infection-induced antibodies at their third measurement point, suggesting a significant proportion of children have still not acquired natural infection.

Introduction

As of November 11, 2021 more than 6.6 million children in the United States have tested positive for COVID-19.[1] In early September, child COVID-19 cases peaked at 252,000 new cased per week and have declined since but remain extremely high. Since the first week of September, there have been almost 1.5 million additional child cases.[1] These recent data suggest the delta (B.1.617.2) variant is more transmissible among children compared to the alpha (B.1.1.7) variant.[1] These data are particularly troubling as they coincide with school openings across the country. Information about the durability of SARS-CoV-2-specific natural immune responses in children is important to inform school-and community-based transmission mitigation and pediatric vaccination strategies. However, the true incidence and longitudinal presence of antibody response to SARS-CoV-2 infection is not known in the pediatric population due to the high proportion of asymptomatic infection[2] and prioritization of testing for adults and those with severe illness early in the pandemic.

Methods

The Texas Coronavirus Antibody REsponse Survey (Texas CARES) is an ongoing prospective population-based seroprevalence project designed to assess antibody status over time among a volunteer population throughout the state. The design of Texas CARES has been described previously[2,3,4] but briefly, includes adults (aged 20-80 years) and children (aged 5-19 years). Texas CARES enrollment commenced in October 2020. Participants ages 5-to-19 years were recruited from large pediatric healthcare systems, Federally Qualified Healthcare Centers, urban and rural pediatric and family medicine practices, health insurance providers, and a social media campaign throughout the state of Texas. Participants were offered a series of three SARS-CoV-2 antibody tests over 6-8 months, or every 2-3 months, that includes the immunoassay for

detection of antibodies to the SARS-CoV-2 nucleocapsid protein (Roche N-test). The nucleocapsid test uses whole blood and has a sensitivity and specificity exceeding 97%.[5,6] Descriptive characteristics and COVID-19 infection-related symptom status were determined by questionnaire at the time of enrollment and prior to each successive blood draw. This analysis included participants ages 5-to-19 years old who have completed all three antibody assessments. The presence of SARS-CoV-2 nucleocapsid protein antibodies across the three test timepoints was explored via generalized linear mixed models with a logit link. Random effects for each participant were univariately fit. A likelihood ratio test was performed comparing each model to the intercept-only model to obtain a p-value. All protocols were reviewed and approved by the University of Texas Health Science Center's Committee for the Protection of Human Subjects, but also deemed public health practice by the Texas Department of State Health Services IRB.

Results

From our sample (n=159; mean age 12.5 years, SD 3.6), 96% of those with evidence of nucleocapsid antibodies at baseline assessment continued to have antibodies > six months later (mean 7.0 months, SD 0.97). Two children seroconverted from positive to negative status between their first and second antibody test. Ten children seroconverted from negative to positive between their first and second antibody test, and six between their second and third tests, respectively. There was no difference in the presence of antibodies by symptom status (asymptotic versus symptomatic) or severity (mild-moderate versus severe), sex, age group, or body mass index group (underweight, healthy weight, overweight, obesity) over the three antibody measurement timepoints. (Table 1)

N-test values to detect the presence of IgM, IgG, or IgA antibodies increased from baseline to timepoint two and then decreased by the third immunoassay assessment. The subsequent

downward trend was significant between timepoints 1 and 3 (P=0.007) and timepoints 2 and 3 (P<0.001) (Figure1).

Discussion

The data reported here show that the majority of children followed for > six months and who had three successive antibody test results available for analysis retained SARS-CoV-2 antibodies over the entire time period regardless of age, sex, COVID-19 symptom status and severity, and body mass index. These results suggest that infection-induced antibodies persist and thus may provide some protection against future infection for at least half a year. We were unable to confirm COVID-19 infection prior to the baseline assessment, thus these data cannot confirm durability beyond six months. It should also be noted that well over half (57.9%) of the sample were negative for infection-induced antibodies at their third measurement point, suggesting a significant proportion of children are still immune-naïve to SARS-CoV-2 due to natural infection. As such, vaccines have an important role to play in providing protection against COVID-19 for children aged 12 years and older, and for those < 12 years as they become eligible.

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Data Sharing Statement

Texas CARES investigators are committed to data sharing. Granular results and user-specified data summaries are currently publicly available on the Texas CARES portal (https://sph.uth.edu/projects/texascares/dashboard). When baseline recruitment is complete, a deidentified individual level dataset will be available for download from the same portal.

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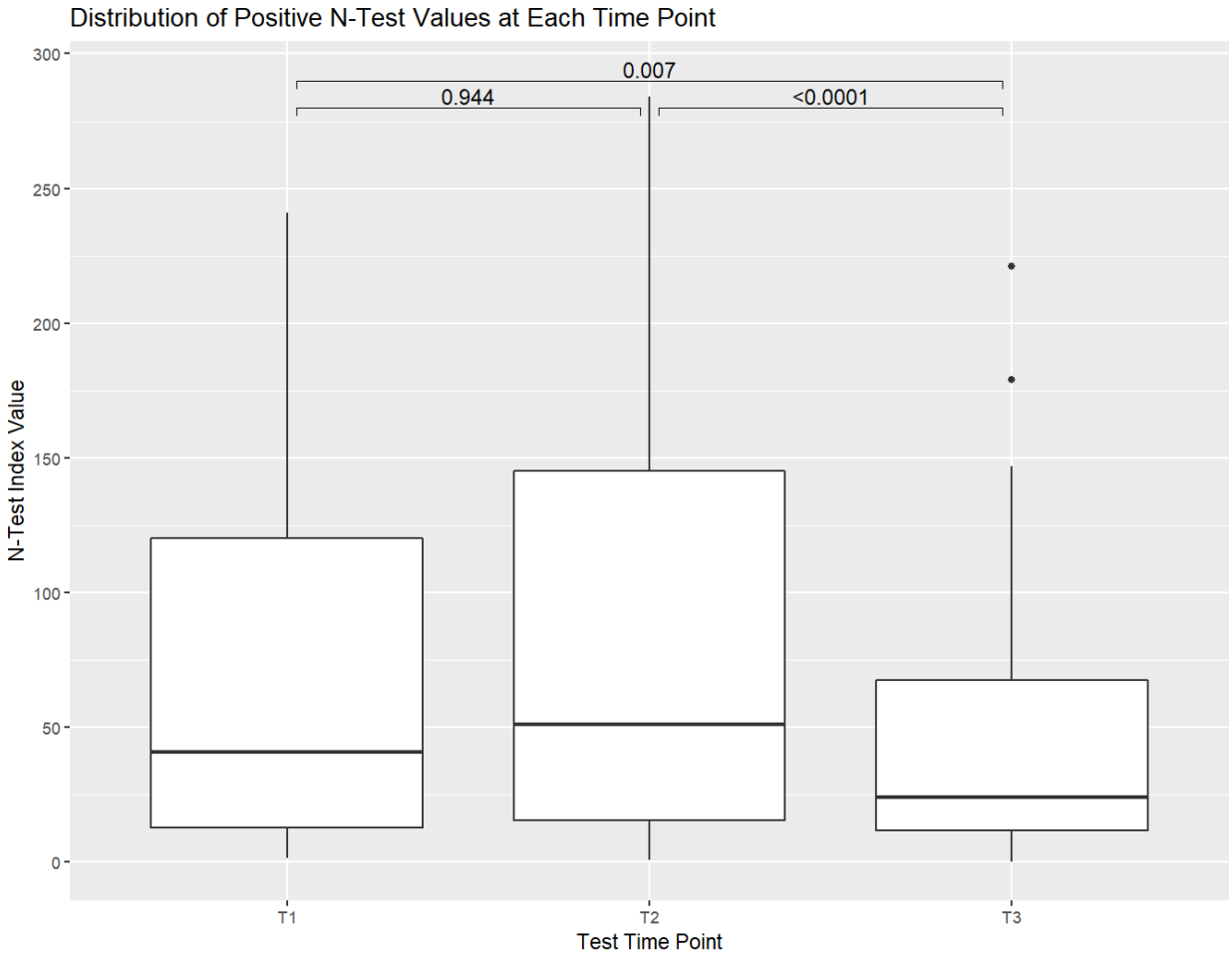
Table 1. Sars-CoV-2 antibody status over 3 timepoints (each separated by 2-3 months) by symptom status and severity and descriptive characteristics.

	Timepoint 1 (N=159)		**Timepoint 2** (N=159)		**Timepoint 3** (N=159)		p-value[a]
	Positive	Negative	Positive	Negative	Positive	Negative	
	53 (33.3%)	106 (66.6%)	61 (38.4%)	98 (61.6%)	67 (42.1%)	92 (57.9%)	
Symptom Status							0.498
Symptomatic	25 (50.0%)	30 (29.4%)	26 (44.8%)	29 (30.9%)	26 (40.6%)	29 (33.0%)	
Asymptomatic	25 (50.0%)	72 (70.6%)	32 (55.2%)	65 (69.1%)	38 (59.4%)	59 (67.0%)	
Missing	3	4	3	4	3	4	
Symptom Severity[b]							0.872
Mild-Moderate	21 (87.5%)	24 (80.0%)	21 (84.0%)	24 (82.8%)	21 (84.0%)	24 (82.8%)	
Severe	3 (12.5%)	6 (20.0%)	4 (16.0%)	5 (17.2%)	4 (16.0%)	5 (17.2%)	
Sex							0.942
Males	22 (42.3%)	43 (40.6%)	25 (41.7%)	40 (40.8%)	28 (42.4%)	37 (40.2%)	
Females	30 (57.7%)	63 (59.4%)	35 (58.3%)	58 (59.2%)	38 (57.6%)	55 (59.8%)	
Age Group							0.977
5-9 years	15 (28.3%)	23 (21.7%)	16 (26.2%)	22 (22.4%)	17 (25.4%)	21 (22.8%)	
10-14 years	20 (37.7%)	48 (45.3%)	25 (41.0%)	43 (43.9%)	30 (44.8%)	38 (41.3%)	
15-19 years	18 (34.0%)	35 (33.0%)	20 (32.8%)	33 (33.7%)	20 (29.9%)	33 (35.9%)	
Body Mass Index Group[c]							0.117
Underweight	1 (2.1%)	4 (4.0%)	1 (1.8%)	4 (4.3%)	2 (3.3%)	3 (3.4%)	
Healthy	31 (64.6%)	66 (65.3%)	37 (66.1%)	60 (64.5%)	40 (65.6%)	57 (64.8%)	
Overweight	8 (16.7%)	21 (20.8%)	10 (17.9%)	19 (20.4%)	11 (18.0%)	18 (20.5%)	
Obesity	8 (16.7%)	10 (9.9%)	8 (14.3%)	10 (10.8%)	8 (13.1%)	10 (11.4%)	
Missing	5	5	5	5	6	4	

[a]p value calculated from likelihood ratio test

[b]Percent of symptomatic children total

[c]Based on standardized body mass index percentiles adjusted for age and sex (https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm)



271 **Figure 1.** Boxplots of N-test values at each time point.

272 Boxplot for the N-test values across the three timepoints for the sample that were positive at the first timepoint
273 (N=53). The N-test value denotes prior COVID-19 infection. Each box represents data falling between the 25th and
274 the 75th percentiles. The horizontal bar within the box represents the median, and the whiskers extend 1.5 times the
275 interquartile range below the 25th and above the 75th percentiles, and the points that lie beyond the whiskers can
276 be considered extreme values.

277 P values calculated by Wilcoxon Signed Rank test. Note that this is not a test for the difference in medians, but
278 rather a non-parametric test for differences in sets of pairs.

279 *significant at the p=0.05 level

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