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

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As of January 27, 2022 over 11.4 million children in the United States have tested positive for coronavirus disease 2019 (COVID-19).[1] COVID-19 cases among US children have seen an exponential increase in December 2021 and January 2022, a very short time period that far exceeds previous peaks of infection.[1] These recent data suggest the omicron (B.1.1.529) variant is more transmissible compared to the delta (B.1.617.2) and alpha (B.1.1.7) variants.[1] These data are particularly troubling as they coincide with school reopenings after the 2021 to 2022 holiday break across the country. Information about the durability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–specific natural immune responses in children is important to inform community-based transmission mitigation and pediatric vaccination strategies, for both current and potential future variants. However, the true incidence and longitudinal presence of natural (not-vaccine–induced) antibody response to SARS-CoV-2 infection is not known in the pediatric population because of the high proportion of asymptomatic infection[2] and prioritization of testing for adults and those with severe illness early in the pandemic. This is important information for the field because not all parents can or will choose to vaccinate their child.

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,[2–4] but briefly, it 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 health care systems, federally qualified health care 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 3 SARS-CoV-2 antibody tests over 6 to 8 months, or every 2 to 3 months, that includes the immunoassay for detection of antibodies to the SARS-CoV-2 nucleocapsid protein (Roche N-test). A value of ≥ 1 determined positive antibody status as per Roche.[5,6] 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 before each successive blood draw. This analysis included participants ages

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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 Ms Ross designed the data collection instruments and collected data. Michael Gonzalez programmed all survey questions in REDCap; Drs DeSantis, Leon-Novelo, and Mr Talebi and Ms Brito conducted and reviewed all analyses; Drs Swartz and Yaseen reviewed all analyses; Dr Wu, Mr Zhang, and Dr Omega-Njemnobi coordinated and supervised data collection and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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5 to 19 years old who have completed all 3 antibody assessments.

The association between the presence of SARS-CoV-2 nucleocapsid protein antibodies over the 3 test timepoints (~3 months apart) and predictors of interest was tested using a generalized additive model (GAM) with logit link, the predictor, and timepoint (an indicator for time points 2 and 3), with a participant-specific random effect to accommodate correlation. The GAM was fit using the *mgcv* package in R statistical software that reports a Wald-type *P* value for the significance of the association.[7] 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 institutional review board.

RESULTS

From our sample ($n = 218$; mean age 12.8 years, SD 3.6), 96% of those with evidence of nucleocapsid antibodies at baseline assessment (34.4% of the sample) continued to have antibodies >6 months later (mean 7.2 months, SD 1.55). Two children seroconverted from positive to negative status between their first and second antibody test, and no children seroconverted from positive to negative status between their second and third antibody test. Sixteen children seroconverted from negative to positive between their first and second antibody test, and 9 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 BMI group (underweight, healthy weight, overweight, obesity) over the 3 antibody measurement timepoints (Table 1).

N-test values to detect the presence of IgM, IgG, or IgA antibodies increased from baseline to timepoint 2 and slightly decreased from the timepoint 2 to the third immunoassay assessment. The subsequent downward trend was significant between timepoints 1 and 3 ($P = .002$) and timepoints 2 and 3 ($P < .001$) (Fig 1).

Because of the risk of a potential selection bias, a sensitivity analysis was conducted to test for any differences between participants who had all antibody assessments completed versus those who did not. Results showed no differences for all demographic variables with the exception of ethnicity. Hispanic participants were more likely to have all 3 assessments completed versus not completed (31.9% and 23.5%, respectively) versus non-Hispanic Whites (68.1% and 76.5%, respectively) ($P = .005$). (Supplemental Table 2).

TABLE 1 Sars-CoV-2 Antibody Status Over 3 Timepoints (Each Separated by ~3 Mo) by Symptom Status and Severity and Descriptive Characteristics

	Time Point 1 ($N = 218$)		Time Point 2 ($N = 218$)		Time Point 3 ($N = 218$)		
	Positive 75 (34.4)	Negative 143 (65.6)	Positive 89 (40.8)	Negative 129 (59.2)	Positive 98 (44.9)	Negative 120 (55.1)	*P*[a]
Symptom status							
Symptomatic	33 (45.8)	38 (27.3)	37 (43.0)	34 (27.2)	37 (38.9)	34 (29.3)	.38
Asymptomatic	39 (54.2)	101 (72.7)	49 (57.0)	91 (72.8)	58 (61.1)	82 (70.7)	Ref
Missing	3	4	3	4	3	4	
Symptom severity[b]							
Mild-moderate	28 (84.8)	31 (81.6)	30 (81.1)	29 (85.3)	30 (81.1)	29 (85.3)	Ref
Severe	5 (15.2)	7 (18.4)	7 (18.9)	5 (14.7)	7 (18.9)	5 (14.7)	96
Sex							
Males	36 (48.6)	64 (44.8)	41 (46.6)	59 (45.7)	46 (47.4)	54 (45.0)	.89
Females	38 (51.4)	79 (55.2)	47 (53.4)	70 (54.3)	51 (52.6)	66 (55.0)	Ref
Age group, y							
5–9	20 (26.7)	28 (19.6)	21 (23.6)	27 (20.9)	23 (23.5)	25 (20.8)	.76
10–14	27 (36.0)	66 (46.2)	36 (40.4)	57 (44.2)	43 (43.9)	50 (41.7)	Ref
15–19	28 (37.3)	49 (34.3)	32 (36.0)	45 (34.9)	32 (32.7)	45 (37.5)	.93
BMI group[c]							
Underweight	1 (1.4)	6 (4.4)	1 (1.2)	6 (5.0)	2 (2.2)	5 (4.4)	.68
Healthy	45 (65.2)	93 (68.9)	56 (67.5)	82 (67.8)	60 (66.7)	78 (68.4)	Ref
Overweight	11 (15.9)	26 (19.3)	14 (16.9)	23 (19.0)	16 (17.8)	21 (18.4)	.93
Obesity	12 (17.4)	10 (7.4)	12 (14.5)	10 (8.3)	12 (13.3)	10 (8.8)	.55
Missing	6	8	6	8	8	6	

All values provided as *n* (%) unless otherwise indicated. Ref, reference.

[a] *P* from logistic GAM model with presence of Sars-CoV-2 antibody as response, timepoint (categorical) and the variable on the left as predictors with participant specific random effect.

[b] Percent of symptomatic children total.

[c] Based on standardized BMI percentiles adjusted for age and sex.

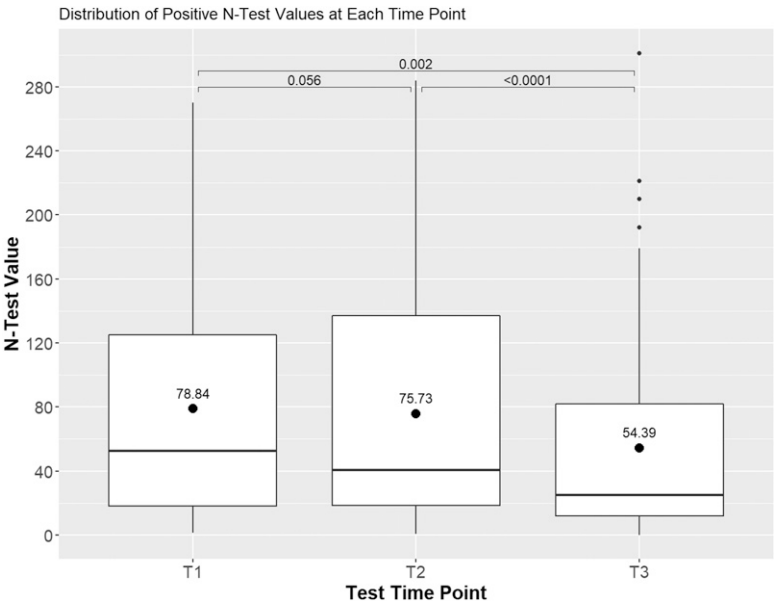

FIGURE 1

Boxplots of *N*-test values at each time point. Boxplot for the *N*-test values across the 3 timepoints for the sample that were positive at the first timepoint ($N = 75$). The *N*-test value denotes previous COVID-19 infection. Each box represents data falling between the 25th and the 75th percentiles. The horizontal bar within the box represents the median, and the whiskers extend 1.5 times the interquartile range below the 25th and above the 75th percentiles, and the points that lie beyond the whiskers can be considered extreme values. The black dots in each box represent the mean value. *P* values calculated by Wilcoxon rank test. Note that this is not a test for the difference in medians, but rather a nonparametric test for differences in sets of pairs. *Significant at the $P = .05$ level. T1, timepoint 1; T2, timepoint 2; T3, timepoint 3.

DISCUSSION

The data reported here show that most children followed for >6 months and who had 3 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 BMI. These results suggest that infection-induced antibodies persist and thus may provide some protection against future infection for at least half a year. Although there is 1 study among adults suggesting that SARS-CoV-2 vaccination may blunt the development of antibodies to the nucleocapsid after subsequent natural infection,[8] this study included only a modest number of pediatric participants who were vaccinated (7.3% at timepoint 1, 9.6% at timepoint 2, and 17.9% at timepoint 3), making it challenging to draw the same conclusions. We were unable to confirm COVID-19 infection before the baseline assessment, thus these data cannot confirm durability beyond 7 months. It should also be noted that well over one-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 because of natural infection. As such, vaccines have an important role to play in providing protection against COVID-19 for children aged ≥5 years, and for those <5 years as they become eligible.

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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.

ABBREVIATIONS

COVID-19: coronavirus disease 2019
DSHS: Department of State Health Services
GAM: generalized additive model
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2
Texas CARES: Texas COVID-19 Antibody Response Survey

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