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Sarah E. Messiah, PhD, MPH, Stacia DeSantis, PhD, Luis Leon-Novelo, PhD, Yashar Talebi MS, Frances Brito, MS, Harold W. Kohl, III, PhD, MSPH, Melissa Valerio-Shewmaker, PhD, Jessica Ross, BS, Michael D. Swartz, PhD, Ashraf Yaseen, PhD, Steven H. Kelder, PhD, MPH, Shiming Zhang, MS, Onyinye S. Omega-Njemnobi, MD, PhD, Michael O. Gonzalez, MPH, Leqing Wu, MS, Eric Boerwinkle, PhD, David Lakey, MD, Jennifer A. Shuford, MD, Stephen J. Pont, MD

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

Sarah E. Messiah, PhD, MPH[a,b], Stacia DeSantis, PhD[c], Luis Leon-Novelo, PhD[c], Yashar Talebi MS[c], Frances Brito, MS[c], Harold W. Kohl, III, PhD, MSPH[d,e], Melissa Valerio-Shewmaker, PhD[f], Jessica Ross, BS[c], Michael D. Swartz, PhD[c], Ashraf Yaseen, PhD[c], Steven H. Kelder, PhD, MPH[d], Shiming Zhang, MS[c], Onyinye S. Omega-Njemnobi, MD, PhD[d], Michael O. Gonzalez, MPH[c], Leqing Wu, MS[c], Eric Boerwinkle, PhD[c], David Lakey, MD[g], Jennifer A. Shuford, MD[h], Stephen J. Pont, MD[h]

Affiliations: [a]The University of Texas Health Science Center at Houston, School of Public Health in Dallas, Dallas, TX, USA; [b]Center for Pediatric Population Health, The University of Texas Health Science Center at Houston, School of Public Health and Children's Health System of Texas, Dallas, TX, USA; [c]The University of Texas Health Science Center at Houston, School of Public Health in Houston, Houston, TX, USA; [d]The University of Texas Health Science Center at Houston, School of Public Health in Austin, Austin, TX, USA; [e]University of Texas at Austin, Austin, TX, USA; [f]The University of Texas Health Science Center at Houston, School of Public Health in Brownsville, Brownsville, TX, USA; [g]The University of Texas System, Austin, TX, USA; [h]Texas Department of State Health Services, Austin, TX, USA

Address correspondence to: Sarah E. Messiah, The University of Texas Health Science Center at Houston, School of Public Health in Dallas, 2777 N Stemmons Fwy, Dallas, TX (Sarah.E.Messiah@uth.tmc.edu)**,** 972-546-2919

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Clinical Trials Registration: N/A

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.

Abbreviations:

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

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.

Drs. DeSantis, Leon-Novelo, and Mr Talebi and Ms. Brito conducted and reviewed all analyses.

Drs. 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.

Introduction

As of January 27, 2022 over 11.4 million children in the United States (US) have tested positive for 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 re-openings after the 2021-22 holiday break across the country. Information about the durability of 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 due to 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 as 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[2,3,4] 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). 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 prior to each successive blood draw. This analysis included participants ages 5-to-19 years old who have completed all three antibody assessments.

The association between the presence of SARS-CoV-2 nucleocapsid protein antibodies over the 3 test timepoints (approximately 3 months apart) and predictors of interest was tested using a generalized additive model (GAMM) 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 IRB.

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 > six 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 nine 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 slightly decreased from the timepoint two to the third immunoassay assessment. The subsequent downward trend was significant between timepoints 1 and 3 (P=0.002) and timepoints 2 and 3 (P<0.001) (Figure 1).

Due to 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%, 23.5% respectively) versus non-Hispanic whites (68.1%, 76.5% respectively) (p=0.005). (Supplemental Table 1).

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. While there is one 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 prior to the baseline assessment, thus these data cannot confirm durability beyond seven 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 5 years and older, and for those < 5 years as they become eligible.

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References

1. American Academy of Pediatrics and the Children's Hospital Association. Children and COVID-19: State Data Report. https://www.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ Accessed February 4, 2022.
2. Messiah SE, Valerio-Shewmaker MA, DeSantis, SM, et al. Estimated Prevalence of SARS-CoV-2 Antibodies in the Texas Pediatric Population, 2021. Preprints with the *Lancet*. Available at SSRN: http://dx.doi.org/10.2139/ssrn.3868061
3. Valerio-Shewmaker MA, DeSantis SM, et al. Strategies to estimate prevalence of SARS-CoV-2 antibodies in a Texas vulnerable population: results from phase I of the Texas Coronavirus Antibody REsponse Survey (TX CARES). medRxiv [Preprint]. 2021 Jul medRxiv doi: https://doi.org/10.1101/2021.08.04.21261613
4. DeSantis SM, León-Novelo LG, Swartz MD, et al. Estimation of total immunity to SARS-Cov-2 in Texas. medRxiv [Preprint]. 2021 medRxiv doi: https://doi.org/10.1101/2021.08.05.21261610
5. Roche. Elecsys® Anti-SARS-CoV-2. Package Insert 2020-07, V9.0; Material Numbers 09203095190 and 09203079190. US Food and Drug Administration https://www.fda.gov/media/137605/download
6. Roche. Elecsys® Anti-SARS-CoV-2 S. Package Insert 2020-12, V1.0; Material Numbers 09289267190 and 09289275190. US Food and Drug Administration https://www.fda.gov/media/144037/download
7. Wood, S. N. (2011). Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. In Journal of the Royal Statistical Society (B) (Vol. 73, Issue 1, pp. 3–36).
8. Allen N, Brady M, Carrion Martin AI, et al. Serological markers of SARS-CoV-2 infection; anti-nucleocapsid antibody positivity may not be the ideal marker of natural infection in vaccinated individuals. J Infect. 2021;83(4):e9-e10.

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

	Time point 1 *(N=218)*		*Time point 2* *(N=218)*		*Time point 3* *(N=218)*		*p-value*[a]
	Positive	Negative	Positive	Negative	Positive	Negative	
	75 (34.4%)	143 (65.6%)	89 (40.8%)	129 (59.2%)	98 (44.9%)	120 (55.1%)	
Symptom Status							
Symptomatic	33 (45.8%)	38 (27.3%)	37 (43.0%)	34 (27.2%)	37 (38.9%)	34 (29.3%)	0.38
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%)	0.96
Sex							
Males	36 (48.6%)	64 (44.8%)	41 (46.6%)	59 (45.7%)	46 (47.4%)	54 (45.0%)	0.89
Females	38 (51.4%)	79 (55.2%)	47 (53.4%)	70 (54.3%)	51 (52.6%)	66 (55.0%)	Ref
Age Group							
5-9 years	20 (26.7%)	28 (19.6%)	21 (23.6%)	27 (20.9%)	23 (23.5%)	25 (20.8%)	0.76
10-14 years	27 (36.0%)	66 (46.2%)	36 (40.4%)	57 (44.2%)	43 (43.9%)	50 (41.7%)	Ref
15-19 years	28 (37.3%)	49 (34.3%)	32 (36.0%)	45 (34.9%)	32 (32.7%)	45 (37.5%)	0.93
Body Mass Index Group[c]							
Underweight	1 (1.4%)	6 (4.4%)	1 (1.2%)	6 (5.0%)	2 (2.2%)	5 (4.4%)	0.68
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%)	0.93
Obesity	12 (17.4%)	10 (7.4%)	12 (14.5%)	10 (8.3%)	12 (13.3%)	10 (8.8%)	0.55
Missing	6	8	6	8	8	6	

[a]p value 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 body mass index percentiles adjusted for age and sex

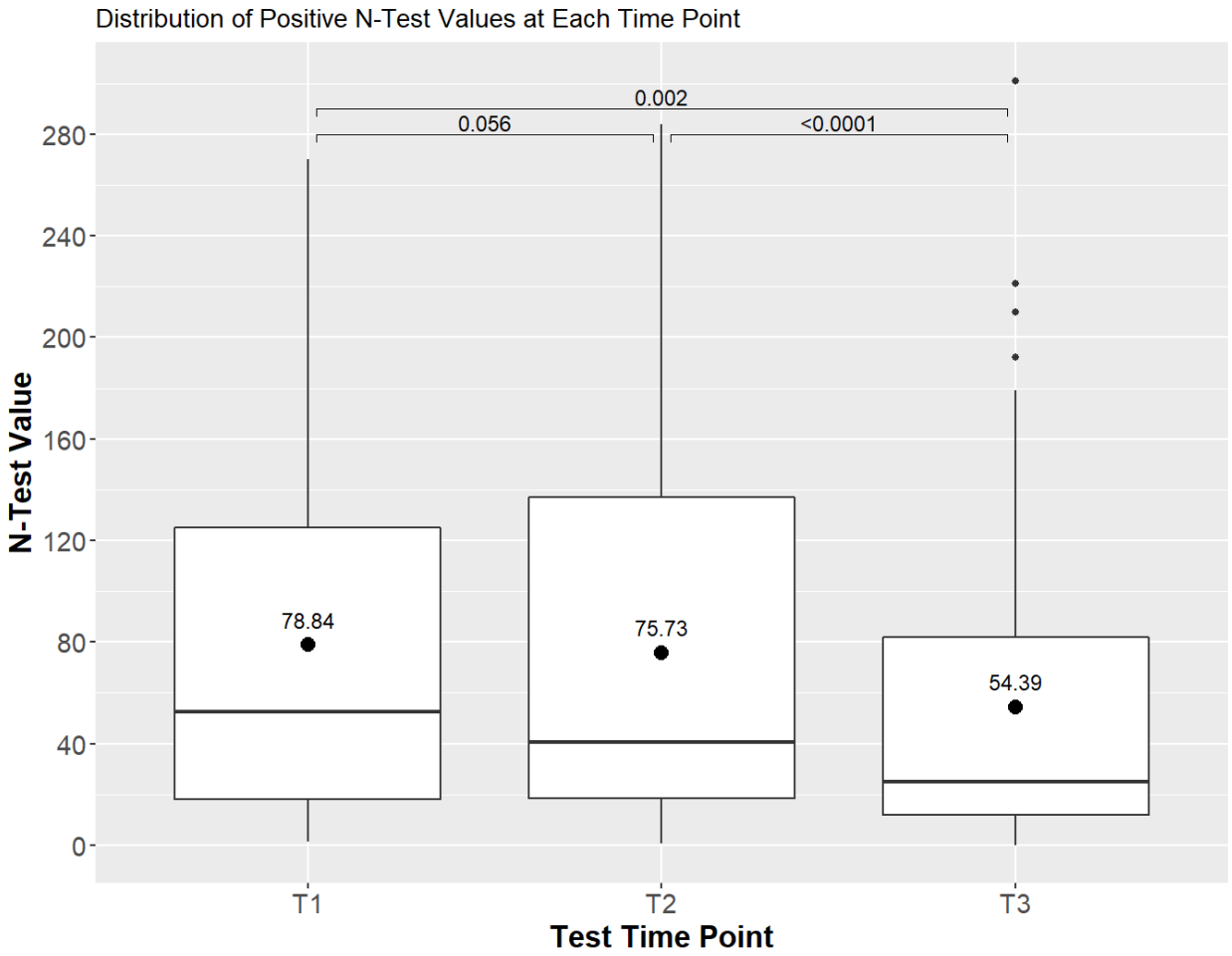

Figure 1. Boxplots of N-test values at each time point.

Boxplot for the N-test values across the three timepoints for the sample that were positive at the first timepoint (N=75). The N-test value denotes prior 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 Signed Rank test. Note that this is not a test for the difference in medians, but rather a non-parametric test for differences in sets of pairs.

*significant at the p=0.05 level

Supplemental Table 1. Sensitivity Analysis Comparing Those with All Available Data Points Versus Those With Not All Available Data Points.

	Participants with all time points (N=218)	Participants missing time points (N=5551)	Total (N=5769)	p value
Symptomatic/Asymptomatic				0.215[1]
Asymptomatic	140 (66.4%)	3188 (62.1%)	3328 (62.3%)	
Symptomatic	71 (33.6%)	1943 (37.9%)	2014 (37.7%)	
Missing	7	420	427	
Symptom Severity				0.995[1]
Mild/Moderate	59 (83.1%)	1624 (83.1%)	1683 (83.1%)	
Severe	12 (16.9%)	331 (16.9%)	343 (16.9%)	
Missing	147	3596	3743	
Age				0.522[1]
10-14 years	93 (42.7%)	2162 (38.9%)	2255 (39.1%)	
15-19 years	77 (35.3%)	2133 (38.4%)	2210 (38.3%)	
5-9 years	48 (22.0%)	1256 (22.6%)	1304 (22.6%)	
Missing	0	0	0	
Gender				0.631[1]
Female	117 (53.9%)	2810 (50.7%)	2927 (50.8%)	
Male	100 (46.1%)	2736 (49.3%)	2836 (49.2%)	
None of these describe me	0 (0.0%)	1 (0.0%)	1 (0.0%)	
Missing	1	4	5	
Ethnicity				0.005[1]
Hispanic	68 (31.9%)	1272 (23.5%)	1340 (23.8%)	
Non-Hispanic	145 (68.1%)	4145 (76.5%)	4290 (76.2%)	
Missing	5	134	139	
Race				0.587[1]
American Indian or Alaskan Native	1 (0.5%)	26 (0.5%)	27 (0.5%)	
Asian	10 (4.7%)	382 (7.1%)	392 (7.0%)	
Black	4 (1.9%)	165 (3.1%)	169 (3.0%)	
Hawaiian or Other Pacific Islander	0 (0.0%)	7 (0.1%)	7 (0.1%)	
Multi-racial	15 (7.1%)	303 (5.6%)	318 (5.7%)	
White	182 (85.8%)	4497 (83.6%)	4679 (83.7%)	
Missing	6	171	177	
BMI Category				0.286[1]
Normal	138 (67.6%)	3174 (63.5%)	3312 (63.6%)	
Obese	22 (10.8%)	743 (14.9%)	765 (14.7%)	
Overweight	37 (18.1%)	841 (16.8%)	878 (16.9%)	
Underweight	7 (3.4%)	243 (4.9%)	250 (4.8%)	
Missing	14	550	564	
fully vaccinated at				
T1	16 (21.1%)	1413 (81.8%)	1429 (79.2%)	
T2	21 (27.6%)	304 (17.6%)	325 (18.0%)	

T3	39 (51.3%)	11 (0.6%)	50 (2.8%)	
Missing	142	3823	3965	
latest vaccine status				
full	76 (35.0%)	1728 (33.7%)	1804 (33.7%)	
no dose provided	1 (0.5%)	14 (0.3%)	15 (0.3%)	
no vaccine name or dose	0 (0.0%)	13 (0.3%)	13 (0.2%)	
none	135 (62.2%)	3092 (60.2%)	3227 (60.3%)	
one dose and no name provided	0 (0.0%)	2 (0.0%)	2 (0.0%)	
partial	5 (2.3%)	286 (5.6%)	291 (5.4%)	
Missing	1	416	417	

[1]Pearson's Chi-squared test