Pediatric Infection-Induced SARS-CoV-2 Seroprevalence Increases and Seroprevalence by Type of Clinical Care—September 2021-February 2022

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Abstract (Word Count: 200):

Background and Objectives
Trends in estimates of US pediatric SARS-CoV-2 infection-induced seroprevalence from commercial laboratory specimens may overrepresent children with frequent healthcare needs. We examined seroprevalence trends and compared seroprevalence estimates by testing type and diagnostic coding.

Methods
Cross-sectional convenience samples of residual sera between September 2021 and February 2022 from 52 U.S. jurisdictions were assayed for infection-induced SARS-CoV-2 antibodies; monthly seroprevalence estimates were calculated by age group. Multivariate logistic analyses compared seroprevalence estimates for specimens associated with ICD-10 codes and laboratory orders indicating well-child care with estimates for other pediatric specimens.

Results
Infection-induced SARS-CoV-2 seroprevalence increased in each age group; from 30% to 68% (1-4 years), 38% to 77% (5-11 years), and 40% to 74% (12-17 years). On multivariate analysis, patients with well-child ICD-10 codes were seropositive more often than other patients aged 1-17 years (adjusted prevalence ratio [aPR] 1.04; 95% CI 1.02-1.07); children aged 9-11 years receiving standard lipid screening were seropositive more often than those receiving other laboratory tests (1.05; 1.02-1.08).
Conclusions

Infection-induced seroprevalence more than doubled among children under 12 between September 2021 and February 2022, and increased 85% in adolescents. Differences in seroprevalence by care type did not substantially impact US pediatric seroprevalence estimates.

Keywords: (must add 3-10 key words here)
COVID-19; SARS-CoV-2; seroprevalence; serosurveillance; antibody; immunology

Word Count: 2860

Introduction

The COVID-19 pandemic, caused by SARS-CoV-2, has taken a tremendous toll in the United States; among children, there have been over 15 million reported cases and 1,794 deaths as of October 10, 2022[1]. The burden has been quantified in a number of ways, mostly focusing on case rates, hospitalizations, and reported deaths. However, these methods do not capture infections that were asymptomatic, not diagnosed, or not reported. The resulting under-capture of infections is particularly pronounced among the pediatric population, who are more likely to have asymptomatic or mild disease compared with older age groups[2].

The national commercial laboratory seroprevalence study is a repeated, cross-sectional national survey that estimates the proportion of the population who have infection-induced antibodies to SARS-CoV-2 in all 50 U.S. states, the District of Columbia, and Puerto Rico. This is the only national U.S. seroprevalence study that includes children. Assays detect anti-nucleocapsid (anti-N) antibodies [hereafter ‘infection-induced antibodies’], which are produced by the body in
response to infection but not in response to receipt of COVID-19 vaccines approved or authorized in the United States. The results from this analysis are publicly available online[3], where seroprevalence rates for the children aged 0-17 years are reported for the U.S. and for each jurisdiction with sufficient sample size. High seroprevalence among children as compared to other age groups had occurred prior to the study period for the present analysis; national seroprevalence estimates for children aged 0-17 years were significantly higher than all adult age groups between February 1 and July 11, 2021[3].

Because the national commercial laboratory seroprevalence study tests residual serum specimens that had been sent for clinical laboratory testing, the sample is more likely to include children with more frequent medical visits and increased healthcare access, which could potentially bias national seroprevalence estimates through over-representation of children with chronic or immunocompromising conditions. Since general exams and preventive or health maintenance services [hereafter ‘well-child care’] are recommended for all children, seroprevalence among the pediatric population presenting for well-child care would likely be more representative of general pediatric seroprevalence than that among those accessing healthcare for other reasons.

This study uses the ICD-10 codes and laboratory tests associated with pediatric specimens to explore potential biases of using commercial lab specimens to study seroprevalence of SARS-CoV-2 anti-N antibodies in this age group. ICD-10-CM codes corresponding with well-child care and lipid screenings among the recommended[4] age group (9-11 years) were used as proxies to identify well-child visits.
The objectives of this analysis were to describe the seroprevalence trends in more granular pediatric age groups corresponding to current pediatric vaccination recommendations and potential future vaccination considerations, and then compare the seroprevalence among specimens most likely to represent well-child care to that of other specimens.

Methods

Study design

The national commercial laboratory seroprevalence study included a convenience sample of blood specimens submitted to commercial laboratories for routine, clinical screening, or diagnostic testing between September 2021 and February 2022. Specimens for each state were selected by the designated commercial laboratory network, which used an internal algorithm to select specimens to optimize geographic distribution across the jurisdiction and a roughly equivalent sample size across five age groups (≤11, 12-17, 18-49, 50-64, and ≥65 years). Seroprevalence estimates for each monthly data collection period were adjusted for year of age, sex, and metropolitan status of county of residence using raking to create weights based on data from the 2018 American Community Survey 5-year population totals and bootstrap resampling to create confidence intervals. Differences in seroprevalence were considered to be statistically significant where confidence intervals did not overlap. Additional details of this methodology are published elsewhere. The data associated with each specimen result included patient age, sex, jurisdiction and county of residence, specimen collection date, laboratory tests ordered, and associated ICD-10-CM codes from the clinical encounter. Data on race, ethnicity, and vaccination status were not available. To decrease bias, specimens for which SARS-CoV-2 antibody testing had been ordered by the clinician were excluded from the study.
and all analyses. Specimens from those under one year of age were excluded from this study due to the potential for detection of maternal antibodies. Specimens were tested by the Roche Elecsys Anti-SARS-CoV-2 immunoassay, which measures pan-immunoglobulin antibody to the nucleocapsid protein of SARS-CoV-2 and has a mean time to sero-reversion of 737 days after initial infection[10]. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy (e.g., 45 C.F.R. part 46, 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq).

The distributions of the most common ICD codes associated with pediatric specimens were examined with descriptive methods. Two analyses were conducted to assess whether pediatric seroprevalence estimates produced by this study are similar between children seeking well-child care and those seeking other types of care. First, we defined children being tested for well-child care visits as those with one or more of the following ICD-10-CM codes: Z00 (General examination without complaint), Z71 (Encounter for health service, not elsewhere classified), and Z23 (Encounter for Immunization). We compared the infection-induced seroprevalence of specimens associated with well-child care visits to that of other pediatric specimens. Specimens that were associated with codes for other health concerns or conditions in addition to general health codes were included in the comparison group, since the laboratories drawn could have been for a reason besides well-child care, such as monitoring of a chronic condition. These groups were compared in an unweighted chi-square analysis, followed by a multivariate Poisson regression with robust variance adjusted for jurisdiction, sex, and metropolitan status. The same multivariate model was then applied to each pediatric age group. These analyses excluded specimens from children residing in one jurisdiction who did not submit pediatric specimens and
those in which more than 50% of pediatric specimens were submitted with no associated ICD-
10-CM codes (n=8). Specimens with no associated ICD-10-CM codes in the remaining
domains (n=5,338, representing 7% of pediatric specimens) were excluded from this
analysis.

The second analysis compared seroprevalence among children aged 9-11 who were getting a
lipid screening test to those whose specimens were associated with other types of testing. A lipid
screening for all children aged 9-11 years is strongly recommended by the National Heart, Lung,
and Blood Institute[4] and the American Academy of Pediatrics. Similar to the previous
analysis, an unweighted analysis was followed by a multivariate Poisson regression with robust
variance adjusted for jurisdiction, sex, and rural/urban status. Children with an ICD-10-CM code
for hyperlipidemia (n=603) were excluded from both groups since lipid panels in this group may
have been conducted due to monitoring of a chronic condition rather than as a well-child
screening. These analyses included 20 jurisdictions with at least 50 lipid screening specimens
for children aged 9-11 during the study period (AL, AR, AZ, CA, DC, DE, FL, IL, KY, MO,
MS, NC, NJ, NV, OH, PA, PR, SC, TN, and WI).

Results

Between September 2021 and February 2022, U.S. pediatric seroprevalence of infection-induced
SARS-CoV-2 antibodies increased from 45.1% (95% confidence interval [CI]: 44.0-46.0%) to
74.6% (95% CI: 73.5-75.6%) [3]. Over this time period, 86,677 pediatric specimens were tested
for anti-N antibodies (n= 6,096 aged 1-4 years; n=28,444 aged 5-11 years; n=52,137 aged 12-17 years).

The largest increase in national seroprevalence for each age group was seen during a period corresponding with the surge in cases due to the Omicron variant. Between December 2021 and February 2022, the seroprevalence among children aged 1-4 years increased from 33% (95% CI: 30-37%) to 68% (95% CI: 63-72%), seroprevalence among children aged 5-11 years increased from 47% (95% CI: 45-49%) to 77% (95% CI: 75-79%), and seroprevalence among adolescents aged 12-17 years increased from 46% (95% CI: 44-47%) to 74% (95% CI: 73-75%) (Figure 1). Examining relative increases between December 2021 and February 2022, seroprevalence among children aged 1-4 years increased by 106%, while seroprevalence in children aged 5-11 years and adolescents aged 12-17 years increased by 64% and 63%, respectively.

The precision of the estimate varied by age group. Over the study period, the confidence intervals for the seroprevalence estimates for the children aged 5-11 years and adolescents aged 12-17 years are similar, and while their confidence intervals overlap with each other they do not overlap with those of any of the adult age groups (Figure 1). While the median confidence intervals of estimates among children aged 5-11 years and adolescents aged 12-17 years were each 3 percentage points (median monthly sample sizes: 4609 and 8590, respectively) the median confidence interval of the seroprevalence estimate for children aged 1-4 years was 7 percentage points (median monthly sample size: 1104). The confidence interval for children aged 1-4 years overlapped with that of the youngest adult age group, 18-49 years, throughout the study period.
Among pediatric specimens in the study, the most commonly associated ICD-10-CM code for all age groups was Z001 (Encounter for pediatric health examination), which was recorded for 18% of visits associated with specimens among children aged 1-4 years, 20% of visits for children aged 5-11 years, and 14% of visits for adolescents aged 12-17 years. Other ICD-10-CM codes varied by age group, but most corresponded to common pediatric complaints or concerns seen in outpatient general practice (supplemental table 1). Laboratory tests associated with each group were similar (supplemental table 2). In unweighted analysis, the infection-induced seroprevalence among pediatric patients whose specimen was drawn in association with well-child care codes exclusively (n=6279; 53.1%) differed by only 1.2 percentage points from that of pediatric patients whose specimens were associated with other codes (n=65,211; 51.9%; p=0.052). Seroprevalence was between 1.0 and 2.3 percentage points higher among children seeking well-child care in each pediatric age subgroup studied, though differences were not significant: 1-4 years (46.2% and 43.9%, p=0.42), 5-11 years (54.9% and 53.8%, p=0.34), and 12-17 years (52.6% and 51.6%, p=0.25) (Table 1). On a multivariate analysis adjusting for sex, jurisdiction, and metropolitan status, pediatric patients with well-child care codes had a higher prevalence of seropositivity compared with pediatric patients whose laboratory tests were ordered in association with other ICD-10-CM codes (adjusted prevalence ratio [aPR] =1.04; 95% CI 1.02-1.07). On analysis by pediatric age subgroup, the only age group with a significant difference was among children aged 12-17 years (aPR= 1.05; 95% CI 1.01-1.08) (Table 2). While the prevalence ratio was above 1 for children aged 1-4 years and 5-11 years, the sample sizes were smaller and the results were not significant.
Among patients aged 9-11 years without a hyperlipidemia diagnosis, Z001 (Encounter for pediatric health examination) was the most common ICD-10-CM code associated with both groups, noted for 33% of specimens on whom a lipid screen had been ordered and 11% of the comparison group. In the comparison group, the most common associated tests were complete metabolic panels, complete blood counts, and thyroid hormone levels. Among the top 10 diagnosis codes, four others were common to both groups (screening for nutritional, metabolic of endocrine disorders; pediatric BMI; obesity, unspecified; and vitamin D deficiency). The most frequent diagnoses among children in the lipid screening group included additional ICD-10-CM codes used for obesity or weight gain, as well as screening codes for diabetes or diseases of the blood or blood-forming organs. The most frequent diagnoses among children in the comparison group included ICD-10-CM codes corresponding to fatigue, abdominal pain, and developmental concerns (supplemental table 3). On analysis of pediatric patients aged 9-11 years without hyperlipidemia on whom a lipid screening test had been ordered, seroprevalence (n=5224; 57.9%) was higher than that among the comparison group (n=6301; 52.4%; p<0.001) (Table 3). On a multivariate analysis adjusting for sex, jurisdiction, and metropolitan status, those whose blood specimen was associated with a routine lipid screening had higher prevalence of seropositivity for infection-induced antibodies compared with those whose blood was drawn for other types of laboratory tests (aPR=1.05; 95% CI 1.02-1.08) (Table 4).

Discussion

Children have experienced a high burden of SARS-CoV-2 infection, with an overall national seroprevalence of over 74% among US children aged 0-17 years in February 2022[3], higher than any other age group. Seroprevalence estimates among children aged 5-11 and 12-17 years
were significantly higher than that of all adult age groups for each month of the study period. The seroprevalence of children aged 1-4 years had the widest confidence interval and was not significantly different from seroprevalence among adults aged 18-49 years. From December 2021 through February 2022, a period that reflects the surge in infections due to the Omicron variant, the largest recorded absolute increases in infection-induced antibody seroprevalence have been seen in all age groups. Seroprevalence among older children, for whom vaccines are available but vaccination rates are lower compared to adult age groups[11], increased by over 60% over this period. The seroprevalence among children aged 1-4 years, for whom no vaccines were approved during the study period, more than doubled from December 2021 through February 2022.

Overall, children whose laboratory tests were ordered in association with well-child care codes were slightly more likely to test positive for infection-induced SARS-CoV-2 antibodies compared with those whose laboratory tests were associated with other ICD-10-CM codes. Adolescents (12-17 years) presenting for well-child care were also significantly more likely to test seropositive; the lack of a significant difference in the two younger age groups may be related to the smaller sample sizes in these groups. Children aged 9-11 years who received a lipid screening test had significantly higher seroprevalence than other children in this age group. One possible reason for these findings is that families with children with chronic conditions which require more frequent and focused visits and laboratory monitoring may be more likely to adopt consistent mitigation measures, including vaccination and mask use, than other families. While these findings reach statistical significance, the prevalence ratios reflect that the size of the differences are small from an epidemiologic perspective.
Seroprevalence among children exceeded adult infection-induced antibody seroprevalence prior to the study period[3]. However, only 17.5% of reported COVID-19 cases are among those aged 0-17, while children make up 22.3% of the U.S. population[1]. As of May 12, 2022, the cumulative case rate in the pediatric population was reported as 17,467 cases per 100,000 population, or 17.5%[12]. The increased ratio of estimated infections to reported cases among children, compared with adults, has been reported in several states[13]. Those findings, combined with our findings regarding the representativeness of these data, reinforce the importance of seroprevalence to more fully capture the SARS-CoV-2 infection burden among the pediatric population.

This study has six main limitations. First, we were restricted to an internal comparison due to the lack of a nationally representative serosurvey. The population studied may still differ from the general population in terms of access to medical care, frequency of care-seeking, and other factors, as most pediatric well-child care visits outside the 9-11 year age group do not require lab draws in the absence of clinical concerns. Second, it is difficult to understand the full clinical picture of a visit based on ICD-10-CM codes alone, as codes are occasionally omitted in error. This may have resulted in misclassification of some visits as well-child care as opposed to other types of care. Third, there are no race or ethnicity data available for specimens, and therefore we could not stratify or control for these important demographic variables, which are known to be significantly associated with COVID-19 case rates and vaccination rates. Fourth, not all children develop detectable anti-N antibodies after infection, but the rate of lack of seroconversion and whether this occurs more or less frequent than adults is unknown[14,15]. It is possible that burden of infection may be under-captured by seroprevalence data in children who develop a
level of anti-N antibodies that falls below the assay cut point[16]. Fifth, while specimens were
selected with attention to geographic representativeness in each jurisdiction, they were not a
probabilistic sample, which may impact generalizability of findings. Finally, there are
limitations to analyses based on lipid screenings, as practices may vary. While the National
Heart, Lung and Blood Institute and American Academy of Pediatrics strongly recommend
screening of all children aged 9 to 11 years, this has not been universally recommended or
adopted in practice. The U.S. Preventative Services Task Force and American Academy of
Family Physicians endorse a more targeted approach[17], and practices have been found to vary
among practicing pediatricians[18]. Therefore, as indicated by our ICD-10-CM code
comparison, pediatric patients remain more likely to get a lipid screening if they have risk
factors, such as a weight medically classified as overweight or obese. These differences likely
limit the utility of lipid screening as a proxy for well-child care visits.

Conclusion

Taken together, these findings indicate that the high seroprevalence estimates among pediatric
age groups in the national seroprevalence study likely approximate seroprevalence in the U.S.
pediatric population seeking well-child care. There are only small differences between children
likely to be seeking care for general exams and preventive or health maintenance services as
compared with those seeking services due to acute symptoms or chronic conditions, indicating
that results do not have an epidemiologically important bias due to the care type sought by
children in the sample. This information is important to contextualize data on seroprevalence,
nationally and by jurisdiction, and to better understand infection burden during consideration of
potential future pediatric vaccine recommendations.
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Figure 1: Infection-induced SARS-CoV-2 antibody seroprevalence* by age group — U.S., September 2021- February 2022

*Seroprevalence to antibodies to the SARS-CoV-2 nucleocapsid protein

Note: Shading indicates confidence interval for each trend line. Estimates are weighted to approximate the general population on the characteristics of age, sex, and metropolitan status.
Table 1. Infection-induced SARS-CoV-2* seroprevalence (unweighted) among pediatric specimens collected by commercial laboratories associated with well-child care visits or other visit types — U.S., September 2021-February 2022

| Age     | Well-child visit ICD-10 codes§ | ICD10 codes indicative of other visit types | Chi-square P-value |
|---------|-------------------------------|--------------------------------------------|--------------------|
|         | Unweighted seroprevalence     | Unweighted seroprevalence                  |                    |
|         | n (95% CI)                    | n (95% CI)                                 |                    |
| All (1-17) | 6279 53.1% (51.9%, 54.4%)  | 65211 51.9% (51.5%, 52.2%)                  | 0.05               |
| 1-4     | 370 46.2% (41.1%, 51.4%)      | 3872 43.9% (42.3%, 45.5%)                  | 0.42               |
| 5-11    | 2503 54.9% (52.9%, 56.8%)     | 20967 53.8% (53.1%, 54.5%)                 | 0.34               |
| 12-17   | 3406 52.6% (50.9%, 54.3%)     | 40372 51.6% (51.1%, 52.1%)                 | 0.25               |

*Antibodies to the SARS-CoV-2 nucleocapsid protein

§ [Z00 (General examination without complaint), Z71 (Encounter for health service, not elsewhere classified), and Z23 (Encounter for Immunization)]; specimens included in this analytic group are exclusively associated with ≥1 of these ICD-10 codes
Table 2. Adjusted prevalence ratio (aPR) of infection-induced SARS-CoV-2 antibody in sera from well-child care§ visits to that in sera from other visits—U.S., September 2021-February 2022*

| Well-child care ICD-10 codes only§ | 95% CI    | P-value |
|-----------------------------------|-----------|---------|
| aPR                               |           |         |
| All                               |           |         |
| All (1-17)                        | 1.04      | 1.02, 1.07 | **0.002** |
| Subgroups                         |           |         |
| 1-4                               | 1.06      | 0.94, 1.20 | 0.320    |
| 5-11                              | 1.02      | 0.98, 1.06 | 0.404    |
| 12-17                             | 1.05      | 1.01, 1.08 | **0.010** |

* Seroprevalence of antibodies to the SARS-CoV-2 nucleocapsid protein among pediatric specimens collected by commercial laboratories. Multivariate Poisson regression with robust variance used to estimate association included jurisdiction of residence, sex, and urbanicity of residence as covariates.

§ Comparison between seroprevalence of specimens exclusively associated with ≥1 of three ICD-10 codes [Z00 (General examination without complaint), Z71 (Encounter for
health service, not elsewhere classified), and Z23 (Encounter for Immunization) and specimens associated with any other ICD-10 codes

Table 3. Infection-induced SARS-CoV-2 seroprevalence* (unweighted) among specimens collected by commercial laboratories from children aged 9-11 years stratified by associated lab test—U.S., September 2021-February 2022

| Age  | Lipid screening test | No lipid screening test | Chi-square | P-value |
|------|----------------------|-------------------------|------------|---------|
|      | n                   | Unweighted seroprevalence (95% CI) | n | seroprevalence (95% CI) |            |
| 9-11 | 5224                | 57.9% (56.6%, 59.2%) | 6301 | 52.4% (51.1%, 53.6%) | <0.001 |

*Antibodies to the SARS-CoV-2 nucleocapsid protein
Table 4. Adjusted prevalence ratio (aPR) of infection-induced SARS-CoV-2 antibody in sera for standard lipid screenings to that in sera for other laboratory tests among children aged 9-11 years—U.S., September 2021-February 2022*

| Standard Lipid Screening§ | aPR | 95% CI       | p-value |
|---------------------------|-----|-------------|---------|
| Had lipid screening test   | 1.05| 1.02, 1.08  | 0.004   |

* Seroprevalence of antibodies to the SARS-CoV-2 nucleocapsid protein among specimens collected by commercial laboratories from patients aged 9-11 years.

Multivariate Poisson regression with robust variance used to estimate association included jurisdiction of residence, sex, and urbanicity of residence as covariates.

§ Comparison between seroprevalence of specimens associated with lipid screening panels and specimens associated only with other laboratory tests
Figure 1
178x89 mm (x DPI)