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Original Article

Seroprevalence of SARS-CoV-2 in self-reported COVID-19-free children

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KEYWORDS
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Abstract *Introduction:* COVID-19 poses risks and leads to complications for vulnerable populations, including children. Unreported cases of COVID-19 among children hinder our understanding of the true disease burden. In this study, we aimed to investigate the proportion of children who report no prior infection to SARS-CoV-2 but who nevertheless exhibit serological evidence of prior infection.
Methods: Between November 2022 and February 2023, we recruited children and adolescents under 19 years of age who lacked a prior history of SARS-CoV-2 infection. Participants underwent SARS-CoV-2 antibody testing to assess the presence of IgG antibodies specific to nucleocapsid (N) and spike (S) proteins. Demographic and contact information were also collected.
Results: Among 260 COVID-19-free children, the overall anti-N antibody positivity rate, which varied across age groups (4%—25%), was 9.2% (24/260). Contact with individuals who were positive for COVID-19, particularly the children's mothers, significantly increased the likelihood of antibody positivity. The median age of the 34 children who remained unvaccinated against COVID-19 was lower than that of the children who were vaccinated (6.5 vs. 9 years; $p < 0.001$). Until January 2024, the overall infection rate was 41.9% (99/236) among children who were negative for anti-N antibodies, irrespective of vaccination status or the presence of chronic disease.
Conclusion: We discovered previously undisclosed cases of SARS-CoV-2 infection among children. The risk of seropositivity increases substantially with household contact. Regarding

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children who report no prior exposure to COVID-19, clinicians must remain vigilant, as SARS-CoV-2 remains a concern.

Introduction

The COVID-19 pandemic has led to a significant global health crisis. While children typically experience milder symptoms than adults, they remain at risk of severe illness or long-term complications, including encephalitis and multisystem inflammatory syndrome in children (MIS-C).[1—3] When assessing the COVID-19 disease burden in children, relying solely on home antigen testing or self-reported symptoms may lead to underestimation.[4] Seroprevalence studies can provide valuable insights into the true scope of pediatric COVID-19.

Before 2021, seroprevalence studies in children primarily covered the spread of the original Wuhan strain and the Alpha variant, revealing rates that ranged from 1.4% to 36.2%.[5] Toward the end of 2021, before the Omicron wave, a meta-analysis revealed a pooled pediatric seroprevalence of approximately 52.8%—60.5%.[6] During the Omicron period, seroprevalence rates exhibited significant variation among countries. For example, in Montreal, Canada, the seroprevalence among 726 children was 58.4% between May and October 2022.[7] In Hong Kong, the seropositive rate among children aged 0—9 years surged from 0 to 70% from December 2021 to May 2022.[8] In Thailand, the seroprevalence among 5- to 7-year-old children increased from 9.1% during the pre-Omicron period to 48.8% during the Omicron period from January 2021 to December 2022.[9] The presence of different SARS-CoV-2 variants significantly impacts children's susceptibility to the virus. In addition, several other pivotal factors, including exposure levels, school closures, vaccination rates, seasonal shifts, herd immunity dynamics, geographical variations, and individual behaviors, collectively shape the dynamics underlying the seroprevalence of respiratory viruses.[10—12] In this context, seroprevalence studies conducted across a spectrum of clinical settings have consistently offered valuable insights.

In Taiwan, according to a recent study conducted in February 2021, the seroprevalence of SARS-CoV-2 has remained extremely low, with only 2 cases per 10,000 individuals (95% CI, 0.55—7.29).[13] There have been no seroprevalence studies specifically focusing on pediatric populations in Taiwan. As of 28 February 2023, a total of 2,092,408 cases of pediatric COVID-19 were reported. Despite the government's mandate to report confirmed cases and publicly disclose case numbers, identifying pediatric COVID-19 patients presents significant challenges. The reason for this is that the symptoms of COVID-19 overlap with those of other respiratory viruses commonly found in children, compounded by the limitations of antigen testing.[4,14] These challenges collectively contribute to the potential underestimation of COVID-19 cases among the pediatric population.

Our objective was to investigate the proportion of children who report no prior infection to SARS-CoV-2 but who eventially exhibit serological evidence of prior infection. To address the research gap, we conducted a targeted seroprevalence study. This study aimed to explore this unique population and analyze its characteristics to better understand the true burden of COVID-19 in children.

Methods

Study population enrollment

Between November 2022 and February 2023, during the predominance of the SARS-CoV-2 Omicron variant, we recruited children and adolescents under 19 years of age who had no prior history of SARS-CoV-2 infection via convenience sampling. Recruiting younger children and adolescents posed significant challenges due to family hesitancy about blood sampling and the busy schedules of senior high school students. As a result, we did not impose any restrictions on participant characteristics other than age. The recruitment process began by sending emails and recruitment documents, including a registration link, to schools, day care centers, and kindergartens. For these documents, participants provided their contact information, name, age, and school affiliation. The research team proactively contacted the teaching and administrative staff of these institutions to explain the recruitment needs and request their assistance. Parents were subsequently contacted by the schools.

After receiving responses, the researchers screened the basic demographic data of the individuals and conducted phone interviews with the parents within one week. During these interviews, the researchers provided a detailed explanation of the experimental procedures and the process used for blood sampling. Upon confirming the participants' willingness to participate in the study during the interviews, the researchers proceeded to verify that the participants had not previously tested positive for COVID-19 (i.e., had negative rapid tests or negative PCR results).

Once the participants' eligibility was established, the researchers implemented the informed consent process and administered the questionnaire. The questionnaire included personal information, medical history, vaccination records, COVID-19 contact history (contacts are defined as any daily interactions without wearing masks), and a question regarding the number of cohabitants. Furthermore, the parents were instructed to inform the researchers if SARS-CoV-2 infection was confirmed prior to scheduled blood sampling. The children included in the study were followed untill January 2024 from the time of enrollment. If the enrolled children who were negative for

anti-N antibodies had SARS-CoV-2 infection, as confirmed either by rapid antigen or PCR tests after blood sampling, they were also asked to inform the researchers.

SARS-CoV-2 antibody testing

In this study, we used SARS-CoV-2 IgG assays (Abbott, Lake Forest Illinois) to assess the presence of IgG antibodies specific to nucleocapsid (N) and spike (S) proteins associated with the SARS-CoV-2 virus. Chemiluminescent microparticle immunoassay (CMIA) technology, which involves an automated, two-step process, was utilized. The sensitivity of the CMIA was 90.3% (95% CI: 76.4%—96.4%), and the specificity was 98.8% (95% CI: 93.8%—99.8%).[15] To determine whether IgG antibodies to SARS-CoV-2 were present or absent in the sample, we compared the chemiluminescent relative light unit (RLU) in the reaction to the calibrator RLU. The calibrator RLU, as calculated by the system, served as an index (signal/cutoff, S/C). If the chemiluminescent RLU exceeded a cutoff value of 1.40 (S/C) for IgG anti-N antibodies or 50.0 AU/mL for IgG anti-S antibodies, the measurement was considered to be positive.

Statistical analysis

The characteristics of the study variables were summarized using descriptive statistics. The frequency and percentage are reported for categorical variables, while the median and interquartile range (IQR) are reported for numerical variables. To analyze the categorical variables, the chi-squared test and Fisher's exact test were used. For non-normally distributed numerical variables, the Mann–Whitney U test was used to compare distributions between two independent groups. We used multivariable logistic regression models to identify variables that were independently associated with anti-N antibody positivity. The models were adjusted for demographics and contact history. Adjusted odds ratios (aORs), 95% confidence intervals (CIs), and corresponding p values were calculated for each variable included in the models. To determine statistical significance, we used a threshold of $p < 0.05$. All the statistical analyses were conducted using SPSS version 26.0 software (IBM Corp., Armonk, NY, USA).

Ethical approval

This study was approved by the Research Ethics Committee of National Taiwan University Hospital (202206053RINC).

Results

Vaccination rate

A total of 260 children who self-reported not having previously tested positive for COVID-19 were included in the study. Fig. 1 illustrates the distribution of these children across different age groups, along with COVID-19 vaccination rates, calculated as the number of children who received at least one dose of an mRNA vaccine divided by the total number of children. Among the participants, 182 (70%) were elementary school-aged. The overall vaccination rate among participants was 86.9% (226/260). For children aged 5 years or younger, the vaccination rate was 64.9%. For children aged 6 years or older, the vaccination rates consistently remained high, ranging from 81% to 100%.

SARS-CoV-2 antibody testing

The children included in the study underwent SARS-CoV-2 antibody testing. Fig. 2 displays the distribution of anti-N antibody positivity across the different age groups. The

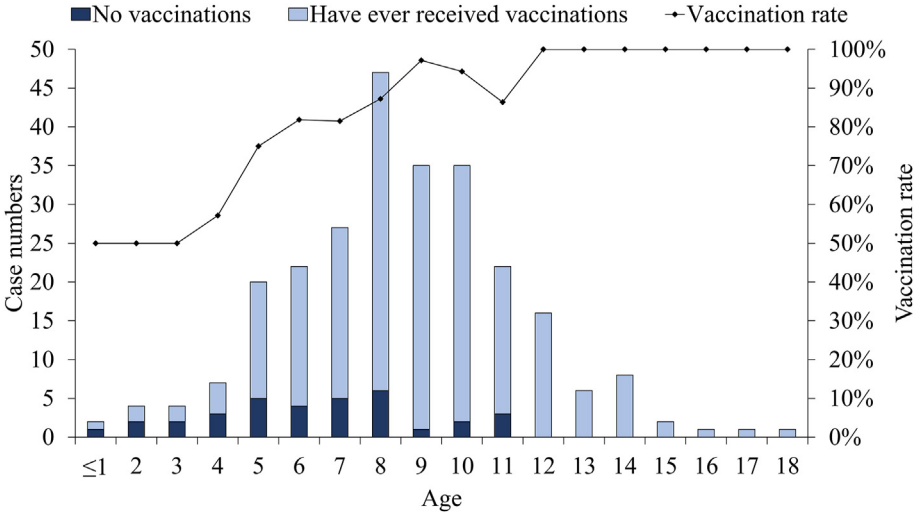

Figure 1. The distribution of 260 children who self-reported not having previously had COVID-19 across different age groups and the COVID-19 vaccination rates (in terms of at least one dose).
The dark blue bars represent individuals who had not received any COVID-19 vaccine, while the light blue bars represent individuals who had received at least one dose of a COVID-19 vaccine. The black line indicates the vaccination rate for each age group. The overall vaccination rate was 86.9% (226/260).

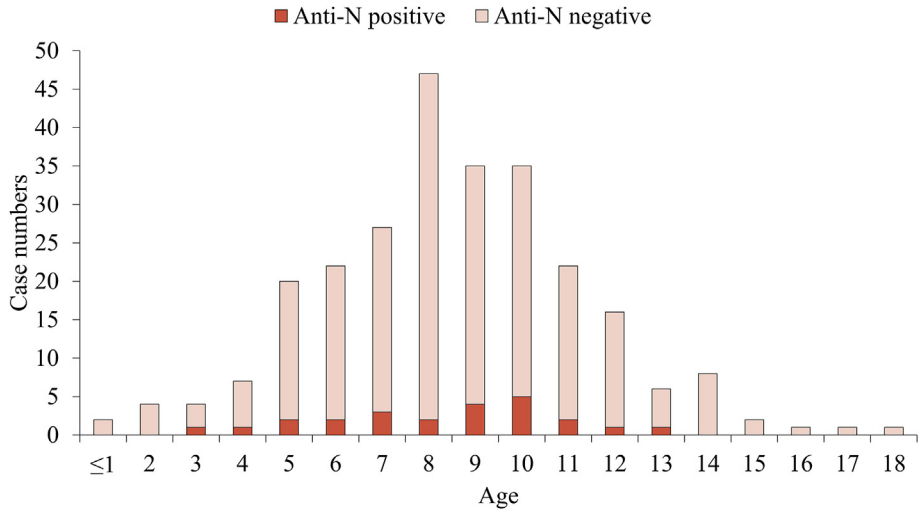

Figure 2. The distribution of anti-N antibody positivity across different age groups.
Dark red bars indicate individuals with anti-N antibodies, while light red bars represent individuals who lacked anti-N antibodies. The overall positivity rate was 9.2% (24/260).

overall positivity rate across all age groups was 9.2% (24/260). No children aged less than 3 years or older than 13 years tested positive for anti-N antibodies. However, for children between 3 and 13 years of age, the positivity rates ranged from 4% to 25%.

Table 1 provides an overview of the demographic information and contact histories of the children who underwent SARS-CoV-2 antibody testing. We compared the characteristics of children who tested positive for anti-N antibodies ($n = 24$) with those of children who tested negative ($n = 236$). Age, sex, underlying chronic disease status, body mass index (BMI), vaccination status, and the number of cohabitants or siblings living together were balanced between the two groups. The SARS-CoV-2 anti-S antibody titers differed significantly between the two groups: the anti-N antibody-positive group had a median titer of 24057.7 AU/mL (IQR: 11854.2–38009.7), while the anti-N antibody-negative group had a median titer of 3422.6 AU/mL (IQR: 820.9–13207.3, $p < 0.001$).

In terms of contact with COVID-19-positive individuals within their families, the anti-N antibody-positive children had more contacts with confirmed COVID-19 in their families than did the anti-N antibody-negative children (1 vs. 0, $p = 0.002$). However, no significant differences were observed between the two groups in terms of the number of cohabitants or siblings living together. A greater percentage of children in the anti-N antibody-positive group had contact with people who had tested positive for COVID-19 in general (83.3% vs. 49.6%, $p = 0.002$). Most of the COVID-19-positive individuals the children had contact with were adults (70.8% vs. 44.5%, $p = 0.01$). A significantly greater proportion of children had contact with their parents in this respect (66.7% vs. 37.3%, $p = 0.01$), specifically their mothers (58.3% vs. 24.2%, $p < 0.001$) and fathers (54.2% vs. 27.1%, $p = 0.01$). No significant differences were observed between the two groups in terms of contact with siblings living together (33.3% vs. 22.0%, $p = 0.21$).

To identify factors that were independently associated with anti-N antibody positivity, we conducted a multivariable logistic regression analysis. Prior to running the analysis, we assessed multicollinearity among the predictor variables using the variance inflation factor (VIF). Predictor variables demonstrating high VIF values (ranging from 7.65 to 11.36), specifically "any contact", "contact with adults", and "contact with parents", were considered to indicate multicollinearity and were consequently excluded from the analysis to mitigate the risk of collinearity. The results are presented in Table 2. Having received a COVID-19 vaccination did not correlate with the absence of anti-N antibodies, suggesting that prior vaccination did not confer protection against infection in the studied population. However, various types of COVID-19 contact histories were significantly associated with the likelihood of testing positive for anti-N antibodies. After adjusting for other variables, contact with certain cohabitants, especially the children's mothers, who had tested positive for COVID-19 significantly increased the possibility of testing positive for anti-N antibodies (aOR: 3.9, 95% CI: 1.3–11.1, $p = 0.01$).

Factors associated with family attitudes toward COVID-19 vaccination in children without a prior history of SARS-CoV-2 infection

In Table 3, we show the factors that influenced the rate of vaccine uptake. Most children (88.1%) in the vaccinated group had received more than two vaccine doses. The 34 children who had not received any COVID-19 vaccine had a younger median age than did those who had received a COVID-19 vaccine (6.5 vs. 9 years; $p < 0.001$). Furthermore, a greater proportion of children who had not received any vaccine were younger (elementary school-aged; <6 years old) than children who had received vaccines (38.2% vs. 10.6%, $p < 0.001$). The prevalence of chronic diseases was comparable between the two groups (44.1% vs. 46.7%, $p = 0.78$).

Table 1 Demographic information and COVID-19 contact history of children who underwent SARS-CoV-2 antibody testing.

	Anti-N Ab positivity (N = 24)	Anti-N Ab negativity (N = 236)	P value
Age (years)	9.4 (7.1—10.3)	9.0 (7.3—10.9)	0.82
Females, number (%)	15 (62.5%)	122 (51.7%)	0.31
Chronic disease	9 (37.5%)	111 (47.2%)	0.36
BMI (kg/m^2)	15.9 (15.2—19.5)	16.2 (14.9—18.4)	0.67
Vaccination	23 (95.8%)	203 (86.0%)	0.34
Number of doses	2 (2—3)	2 (2—3)	0.09
More than two doses	20 (83.3%)	179 (75.8%)	0.61
SARS-CoV-2 anti-S Ab titers (AU/mL)	24057.7 (11854.2—38009.7)	3422.6 (820.9—13207.3)	<0.001
Number of cohabitants	4 (4—5)	4 (4—5)	0.44
Number of siblings living together	1 (1)	1 (1)	0.73
Positive cases of COVID-19 within the family	1 (0—2)	0 (0—1)	0.002
COVID-19 contact history			
Any contact	20 (83.3%)	117 (49.6%)	0.002
Contact with adults	17 (70.8%)	105 (44.5%)	0.01
Contact with grandparents	1 (4.2%)	22 (9.3%)	0.71
Contact with parents	16 (66.7%)	88 (37.3%)	0.01
Contact with mother	14 (58.3%)	57 (24.2%)	<0.001
Contact with father	13 (54.2%)	64 (27.1%)	0.01
Contact with siblings	8 (33.3%)	52 (22.0%)	0.21

Continuous variables are described as medians (IQRs) and were tested using the Kruskal—Wallis H test. Categorical variables are presented as numbers (%) and were tested using the chi-square test.
Abbreviations: Ab, antibody; BMI, body mass index.

Infection rate after enrollment among children who were negative for anti-N antibodies

Until January 2024, 99 children who were negative for anti-N antibodies were reported to have been infected with SARS-CoV-2. The overall infection rate was 41.9% (99/236), irrespective of factors such as vaccination status, age, or the presence of chronic disease.

Discussion

In our study, we investigated the seroprevalence of SARS-CoV-2 among children who reported being COVID-19-free. Our findings indicated a seroprevalence of 9.2% within this group. Household contact represented a primary risk factor for SARS-CoV-2 infection. The cumulative infection rate after a 4-month follow-up period reached 17.8%, suggesting a significant ongoing transmission rate regardless of age. In this context, vaccine coverage was low among children younger than 6 years, indicating the limited protection of this age group.

Based on the latest data from the Taiwan Government Open Data Platform, we identified a total of 2,092,408 reported cases of COVID-19 in children as of 28 February 2023. At that time, there were 3,645,509 people younger than 18 years of age in Taiwan.[16] Based on these data, we estimated that the SARS-CoV-2 infection rate among individuals under 18 years of age was approximately 57.4% by 28 February 2023. According to the seroprevalence data from our analysis, among children who did not self-report previously having COVID-19, approximately 9.2% (24/260) had been infected. In addition, the infection rate 4 months after enrollment was approximately 41.9% (99/236). By taking these two factors into account, we further estimated that the actual infection rate among children in Taiwan

Table 2 Multivariable logistic regression analysis for children who self-reported being COVID-19-free but later tested positive for anti-N antibodies.

Predictors	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Sex (female)	0.6 (0.3—1.5)	0.31	0.7 (0.3—1.7)	0.41
Received COVID-19 vaccines	3.7 (0.5—28.6)	0.34	3.0 (0.4—24.0)	0.31
COVID-19 contact history				
Contact with grandparents	0.4 (0.1—3.3)	0.71	0.4 (0.1—3.2)	0.38
Contact with mother	4.4 (1.9—10.4)	<0.001	3.9 (1.3—11.1)	0.01
Contact with father	3.2 (1.4—7.5)	0.01	1.8 (0.7—4.7)	0.23
Contact with siblings	1.8 (0.7—4.4)	0.21	0.7 (0.2—2.0)	0.51

Abbreviations: OR, odds ratio.

Table 3 Characteristics of vaccinated and unvaccinated children who underwent SARS-CoV-2 antibody testing in our study.

	Had not received any COVID-19 vaccine (N = 34)	Had received COVID-19 vaccines (N = 226)	P value
Sex (female ratio)	18 (52.9%)	119 (52.7%)	0.98
Age (years)	6.5 (5—8)	9 (7—10)	<0.001
Before elementary school age (<6 years old)	13 (38.2%)	24 (10.6%)	<0.001
Number of family numbers	4 (3—5)	4 (4—5)	0.98
Number of siblings	1 (1—2)	1 (1—1)	0.26
Chronic disease	15 (44.1%)	105 (46.7%)	0.78
Vaccination status			
Number of doses	0 (0)	2 (2—3)	<0.001
More than two doses	0 (0%)	199 (88.1%)	<0.001

Continuous variables are described as medians (IQRs) and were tested using the Kruskal—Wallis H test. Categorical variables are presented as numbers (%) and were tested using the chi-square test.

reached 77.6% (57.4% + 42.6% x [123/260]) by January 2024.

It is important to note that the total infection rate may have been overestimated, as cases of reinfection were also included in the data. However, the reinfection rate was considerably lower in children than in adults, ranging from 0.12% to 0.18%.[17,18] Therefore, this effect seems to be minimal. Nevertheless, due to the limited sample size, making such an assumption may introduce some biases. To mitigate this, larger-scale studies incorporating sophisticated mathematical modeling are necessary for a more accurate assessment. After 20 March 2023, the Taiwan CDC no longer required SARS-CoV-2 infections to be reported the government; accordingly, the actual number of infections could no longer be counted. In this context, our data provide valuable evidence concerning the presence of unreported COVID-19 cases among children.

Contact history, particularly household contact history, plays a significant role in the dynamics underlying the transmission of COVID-19. It was reported that the household secondary attack rate was much greater for SARS-CoV-2 than for SARS-CoV-1 or MERS-CoV.[19] Examining the impact of contact history on underreported cases provides valuable insights into the potential sources of undetected infections. Household contact, which represents a primary mode of transmission, can contribute to a high secondary attack rate due to shared living spaces and close interactions. Additionally, reduced use of personal protective equipment may be a feature of these settings. Consequently, household contact plays a pivotal role in disease transmission. Furthermore, mothers in Taiwan often serve as the primary caregivers for children and engage in close contact with them during daily activities. This close relationship results in an increased likelihood of infectious disease transmission from mothers to children compared to other family members. Therefore, it is crucial to be vigilant of secondary transmission when mothers are diagnosed with COVID-19. Conversely, sick children are often isolated from their siblings by their parents to prevent cross-infection and household clustering, potentially reducing the transmission of SARS-CoV-2 among siblings.

In the early stages of the COVID-19 pandemic, children under the age of 10 years exhibited lower susceptibility to COVID-19 than did adults. However, the risk of infection in adolescents and high school students is more comparable to that in adults.[20] Children and adolescents are more susceptible to the Delta and Omicron variants than to previous strains.[21,22] In Taiwan, strict measures such as mandatory surgical mask wearing, school closures, and online distance learning were implemented as mitigation and prevention strategies during the COVID-19 pandemic. However, the Taiwanese government announced a moratorium on class suspensions due to confirmed cases on 12 September 2022. The overall infection rate (17.8%) observed during the 4-month follow-up period reflects the actual infection rate among children in real-world scenarios after the relaxation of prevention and control measures.

While children face a lower risk of severe disease from COVID-19 than adults do, vaccination remains an effective measure for preventing severe illness, MIS-C, and the debilitating effects of long COVID.[23] Our study highlights a significant trend in family behaviors toward COVID-19 vaccination—it tends to be all or none. Once a child's parents decide to initiate vaccination and the child receives the first dose, they are more inclined to complete the vaccination course. However, our findings also revealed lower vaccine coverage among younger children than among children in other age groups. This discrepancy is consistent with a previous study on vaccine hesitancy.[24] Understanding how family decisions regarding vaccination uptake influence public health policy implementation is imperative, highlighting the need for further investigation in this area.

Our study has several limitations. First, most children who participated in the study were recruited from two cities in northern Taiwan, which may limit the generalizability of our findings to the entire country. Second, we did not use randomized sampling, potentially introducing selection bias. Moreover, regarding certain age groups, such as toddlers and teenagers, the sample sizes were relatively small, which could affect the overall representativeness of our results. Third, we did not conduct a follow-up assessment of anti-N antibody positivity after enrollment.

Consequently, it is possible that the infection rate may have been underestimated. Finally, the utilization of CMIA may have introduced certain considerations that affect the interpretability of the data. These include assay sensitivity during the early stages of infection or in individuals with mild or asymptomatic cases, potential cross-reactivity, and variability in the antibody response. Moreover, anti-N antibodies may diminish over time, particularly in nonsevere cases, leading to a rapid decline in antibody titers. This could result in an underestimation of overall seropositivity.

Conclusion

Our study revealed a significant number of unreported SARS-CoV-2 infections among 9.2% enrolled children, highlighting the importance of household transmission. Contact with individuals who were positive for COVID-19, particularly the children's mothers, substantially increased the likelihood of anti-N antibody positivity. Regarding children who report no prior exposure to COVID-19, clinicians must remain vigilant, as SARS-CoV-2 remains a concern.

CRediT authorship contribution statement

Hsiao-Lun Huang: Validation, Writing — original draft. **Chun-Yi Lu:** Data curation, Investigation. **Yun-Chung Liu:** Data curation, Formal analysis, Software. **Tu-Hsuan Chang:** Conceptualization, Formal analysis, Investigation, Resources, Software, Validation, Writing — original draft, Writing — review & editing, Data curation, Funding acquisition, Methodology, Visualization. **Ting-Yu Yen:** Investigation. **Kuan-Ying A. Huang:** Investigation. **Hung-Jen Tang:** Resources. **Luan-Yin Chang:** Conceptualization, Data curation, Funding acquisition, Methodology, Resources, Supervision, Validation, Writing — review & editing. **Li-Min Huang:** Funding acquisition, Resources.

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