


REGULAR ARTICLE

SARS-CoV-2 antibodies started to decline just four months after COVID-19 infection in a paediatric population

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Abstract

Aim: We evaluated the prevalence of paediatric severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections using antibody testing and characterised antibody titres by time from exposure.

Methods: This was a single-centre, prospective, cross-sectional cohort study. Patients under 18 years old were eligible to participate if they attended the paediatric emergency department at the tertiary Shaare Zedek Medical Center, Jerusalem, Israel, from 18 October 2020 to 12 January 2021 and required blood tests or intravenous access. SARS-CoV-2 seropositivity and antibody levels were tested by a dual-assay model.

Results: The study comprised 1138 patients (56% male) with a mean age of 4.4 years (interquartile range 1.3–11.3). Anti-SARS-CoV-2 antibodies were found in 10% of the patients. Seropositivity increased with age and 41% of seropositive patients had no known exposure. Children under 6 years of age had higher initial antibody levels than older children, followed by a steeper decline. The seropositivity rate did not vary during the study, despite schools re-opening. The findings suggest that children's immunity may start falling 4 months after the initial infection.

Conclusion: Immunity started falling after just 4 months, and re-opening schools did not affect infection rates. These findings could aid decisions about vaccinating paediatric populations and school closures.

KEYWORDS

antibody levels, asymptomatic infection, coronavirus, immunity, school closures

Abbreviations: AU, arbitrary units; IgG, immunoglobulin G; PCR, polymerase chain reaction; PED, paediatric emergency department.

Breuer and Raphael contributed equally to the work. Barak-Corren and Heiman contributed equally to the work.

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1 | BACKGROUND

COVID-19 is a highly infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it has become a major global public health challenge.¹ The disease is usually mild in children, and mortality and morbidity are significantly lower than in adults.^{2,3} Most children will have mild symptoms or asymptomatic infections,^{4,5} with younger children and chronic illness being the major risk factors for a more serious disease course.⁶ However, due to viral shedding, children may have significant potential to transmit the virus to other vulnerable populations, even if they have mild or no symptoms.⁷ Furthermore, children may go on to develop multisystem inflammatory syndrome in children,⁸ a syndrome that affects primarily school children. This syndrome is characterised by elevated inflammatory markers and can involve gastrointestinal, cardiovascular, haematopoietic and respiratory systems, as well as significant dermatological manifestations.⁸

The internationally accepted gold standard for identifying SARS-CoV-2 infections is real-time polymerase chain reaction (PCR) tests using nasopharyngeal swab samples.⁹ Serology testing is not appropriate for identifying acute COVID-19 and is primarily used for epidemiological purposes.¹⁰ The median time from a positive PCR to immunoglobulin G (IgG) seroconversion in children is 18 days,¹¹ which is longer than the six to 14 days in adults.¹² As a result, the sensitivity of SARS-CoV-2 serology assays have only been 57%–70% if performed less than 14 days from the time of infection.¹² The clinical significance of anti-SARS-CoV-2 antibody titre values is still being explored. Several studies have found that a correlation may exist between the severity of the primary disease, peak antibody titre values and the neutralising effect of these antibodies.¹³ However, uncertainty remains regarding the long-term serological response in children.

The purpose of this study was to evaluate the incidence of paediatric asymptomatic SARS-CoV-2 infections in Jerusalem, Israel, by using SARS-CoV-2 IgG antibody testing. In addition, when patients had a known history of SARS-CoV-2 infection, we sought to characterise antibody titres by the time from a positive PCR result and by the severity of the primary disease. Finally, we wanted to study the effect of closing schools on COVID-19 infections in children and adolescents under 18 years of age.

2 | METHODS

2.1 | Study design and population

A prospective, cross-sectional epidemiological survey was conducted between 18 October 2020 and 12 January 2021 in the paediatric emergency department (PED) of the Shaare Zedek Medical Center, a public, tertiary medical centre in Jerusalem, Israel. The area covered by the hospital had a high prevalence at the time of the study, with more than 4500 cumulative cases per one hundred thousand population. All patients under 18 years of age who

Key Notes

- This prospective, cross-sectional study found anti-severe acute respiratory syndrome coronavirus 2 antibodies in 10% of the children sampled, and 41% of the seropositive patients had no known exposure to the virus.
- Antibody levels began to fall four months after the initial infection and the seropositivity rate did not rise when schools re-opened.
- These findings are important when making decisions about vaccinating paediatric populations and ongoing school closures.

presented to the PED during the study period were eligible to participate if they required blood tests or intravenous access for any clinical reason. Parents and, or, legal guardians gave oral consent for subjects to participate in the study. The study was approved by the hospital's Institutional Research Ethics Board (reference number 0387-20-SZMC). Children under the age of three months were later excluded from the analysis, as antibodies detected in their blood may have been maternal antibodies that transferred through the placenta in-utero. Patients with blood samples that were unsuitable for laboratory testing, for technical reasons, were also excluded from the final analysis (Figure 1).

The accompanying parent or guardian filled out a comprehensive questionnaire in Hebrew or Arabic for each patient. This covered the patient's demographic background, their past medical history and specific COVID-19 information, such as their exposure to any individuals with the virus, previous PCR testing for SARS-CoV-2 and symptoms (Figure S1). All patients with positive serology results were contacted by telephone and given their results. Details from the questionnaire were confirmed during the same phone call, in particular the timing and source of the confirmed, or suspected, SARS-CoV-2 infection.

2.2 | Laboratory testing

All the blood samples were collected in a clot-activator test tube. Initial testing was conducted using the Abbott Architect SARS-CoV-2 IgG assay (Abbott Laboratories, Illinois, USA) according to the manufacturer's instructions. The presence or absence of IgG antibodies against the SARS-CoV-2 nucleocapsid protein was calculated by the system as an index of the chemiluminescent relative light unit in the reaction to the calibrator relative light unit. An index of 1.4 or greater was considered a positive result. All samples with positive or borderline (index 0.5–1.4) results were retested using the DiaSorin Liaison SARS-CoV-2 S1/S2 IgG assay (DiaSorin Spa, Piedmont, Italy), which tests antibodies against the spike protein of the virus. This assay calculates antibody concentrations, expressed as arbitrary

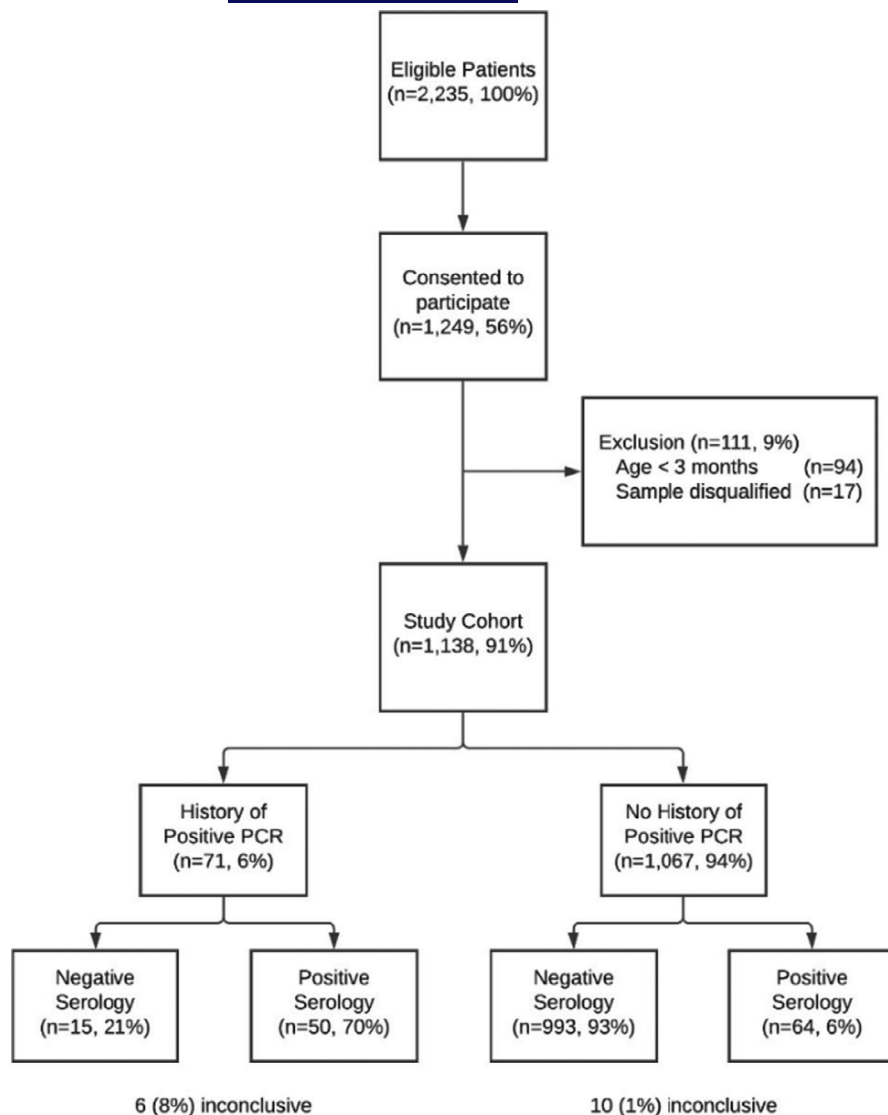


FIGURE 1 Study flow diagram. History of a positive PCR indicates a prior positive SARS-CoV-2 PCR on a nasopharyngeal swab test at the time of enrolment. Serology was only considered positive if antibodies were detected by both the Abbott Architect (anti-n protein IgG antibodies) and DiaSorin Liaison (anti-spike IgG antibodies) assays

units per millilitre (AU/mL): an AU/mL of 15 or greater is considered a positive result and 12–15 AU/mL is borderline. We used a dual-assay model in this study, which means that a patient was only considered positive for SARS-CoV-2 IgG antibodies if both assay tests produced a positive result. A positive Abbott assay, with a subsequent negative or borderline DiaSorin assay, or vice-versa, were considered inconclusive. All other results were considered negative. The manufacturers established that the tests' sensitivity and specificity approached 100% after 14 days from infection. Accordingly, seropositivity rates were not adjusted for imperfect test performance.

2.3 | Statistical analysis

The statistical analyses were conducted using SPSS Statistics for Windows, version 25.0. (IBM Corp, New York, USA). Continuous normally distributed variables, according to the Shapiro–Wilk test, were compared using the Student's *t*-test or one-way analysis of variance and presented as means and standard deviations (SD) and 95% confidence intervals (CI). Non-normally distributed variables were

compared using the Mann–Whitney *U* test and presented as medians with their corresponding interquartile range (IQR). Categorical variables were compared using the chi-square test or Fisher's exact test and presented as percentages with absolute values. Statistical tests were conducted using two-sided tests and *p* values of 0.05 or less were considered statistically significant. Finally, a multivariable logistic regression analysis was performed to study the risk factors for SARS-CoV-2 infection. The model's dependent variable was evidence of SARS-CoV-2 infection, due to either a positive serology test or a history of a positive SARS-CoV-2 PCR test. The independent variables were: gender, age, religion, ethnicity, number of parents and children in the home, housing density and if the child's educational institution remained open during lockdowns.

3 | RESULTS

There were 6264 patients treated in the PED during the 90-day study period. Blood tests and, or, intravenous access were obtained for 2235 patients (35%) and the parent or guardian of 1249 patients

(56%) provided consent to participate in the study. We excluded 111 patients (9%) and these comprised 94 infants under the age of 3 months and 17 with blood samples that were rejected by the laboratory. This means that there were 1138 patients (56% male) in the final study group (Figure 1), with a median age of 4.4 years (IQR 1.3–11.3). The cohort was similar to the general PED population during the study period (median age 4.6 [IQR 1.3–11.6] and 55.9% male, $p = 0.49$ and $p = 0.78$ respectively). Additional socio-demographic information is presented in Table 1.

Overall, 114 (10%) patients had anti-SARS-CoV-2 antibodies in both assays and another 16 (1.6%) had inconclusive test results. A positive serology test result was associated with older age (median 7.6 vs. 3.8 years, $p < 0.001$), self-identifying as a Muslim (21% vs. 14%, $p = 0.05$) or an ultra-orthodox Jew (69% vs. 50%, $p < 0.001$) and a larger family size (mean 7.08 ± 3.2 vs. 6.09 ± 2.5 , $p = 0.004$) (Table 1). The rate of seropositivity increased by age, from 13/219 (5.9%) samples from infants under one year of age to 68/490 (13.8%) from adolescents aged 12 to 18 years (Figure S2). When these variables were adjusted using a logistic regression model, only four variables were significantly associated with the virus: older age, larger family size and Muslim and ultra-orthodox Jewish religions. Other patient characteristics, such as gender, housing density and whether the child's school was open or closed during lockdowns were insignificant (Table S1).

Of the 114 seropositive patients, only 50 (44%) had a known history of a PCR-confirmed SARS-CoV-2 infection. Another 17 (15%) had not been tested but strongly suspected that they had contracted the virus due to clinical symptoms or exposure to a first-degree relative or non-relative with COVID-19. Thus, 47 (41%) seropositive patients had no knowledge of any prior infection or exposure. Of note, only 17/73 (23%) of the patients who suspected they had COVID-19 were seropositive for anti-SARS-CoV-2 antibodies. In addition, of the 179 (16%) patients with first-degree relatives who tested positive for SARS-CoV-2, only 57 (31%) were seropositive.

3.1 | Patients with a previously confirmed infection

A history of PCR-confirmed SARS-CoV-2 infection was reported in 71 (6%) patients and only 50 (70%) of those had anti-SARS-CoV-2 antibodies. The 26 (37%) of those who were asymptomatic at the time of their PCR-confirmed infection were more likely to be seronegative, but this was not statistically significant ($p = 0.34$) (Table 2). Of note, the five patients with multisystem inflammatory syndrome in children had higher antibody levels than all the other seropositive patients (Abbot index 5.3 vs. 3.9, $p = 0.053$ and DiaSorin 108.9 vs. 84.8 AU/mL, $p = 0.096$), but this was not statistically significant.

3.2 | Time from infection and antibody levels

The time interval between the primary infection, established by the initial positive SARS-CoV-2 PCR test, and the serology testing

significantly affected the sensitivity of the anti-SARS-CoV-2 antibody assay. There was a peak sensitivity rate of 47/54 (87%) when it was taken 22–119 days after the infection, ($p < 0.001$, Table 2). The same temporal effect was also noted in the levels of antibodies detected over time, with significantly lower antibody levels in samples taken more than 4 months after the infection. Samples taken within 22–119 days of the infection showed higher antibody levels than tests taken within 21 days or more than 120 days after the initial infection: Abbott index 3.2 versus 0.7 within 21 days ($p = 0.001$) and 3.2 versus 1.2 after 120 days ($p = 0.005$) and DiaSorin levels 80 versus 25 AU/mL within 21 days ($p = 0.015$) and 80 versus 57 AU/mL after 120 days ($p = 0.1$) (Figure 2A, Table S2). The antibody levels were also affected by the age of the patient. Children under the age of 6 years had higher antibody levels than older children in the first 60 days after infection, followed by a steeper decline in antibody levels (Figure 2B and C, Table S2).

3.3 | School closures and virus infections

Attending school was not associated with an increased risk of infection. The weekly rate of seropositive cases did not vary over the study period, even though the re-opening of schools coincided with the start of the study (Figure S3). In addition, only 9/71 (12%) of the patients with a history of a SARS-CoV-2 infection reported that they contracted the infection at school. Finally, 152/816 (19%) respondents said they still attended school during lockdown. The rate of SARS-CoV-2 seropositive cases in this cohort was not different to the children who stayed at home during lockdown: 3% versus 7.5% for day care or preschool children aged 0–6 years old ($p = 0.19$), 14% versus 13% for elementary school children aged 6 to 12 ($p = 0.82$) and 15% versus 14% for high school children aged 12 to 18 ($p = 0.83$). Overall, there were no differences in the seroprevalence rate between children who went to school, stayed at home during lockdown or whose parents did not answer this question (13%, 13%, and 12%, respectively, $p = 0.809$) (Table 1).

4 | DISCUSSION

We found an overall 10% seropositivity rate among children in this large, prospective cohort of paediatric patients presenting to the PED in a region with a high prevalence of COVID-19 cases. Seroprevalence rates varied from 7.7% for children under the age of 6 years to 16.4% in older children. Of the seropositive patients, 41% had no known past exposure to COVID-19, indicating a significant rate of undetected, asymptomatic infection and carriage in children.¹⁴ This was similar to the rate in a large meta-analysis.¹⁵ The paediatric seroprevalence rate found in this study was higher than previously reported in Israel¹⁶ and similar to other areas worldwide that have been heavily affected by COVID-19.¹⁷ This was in contrast to studies from earlier in the pandemic, which demonstrated

TABLE 1 Demographics and characteristics of the patients, with a comparison of seropositive and seronegative patients

Characteristic	All patients	Patients with positive serology results (dual assay)	Patients with negative serology results	p Value
	n = 1138 (100%)	n = 114 (10%)	n = 1008 (88.6%)	
Age median [IQR]	4.4 [1.3–11.3]	7.6 [2.6–14.9]	3.8 [1.2–10.8]	<0.001
Age groups n (%)				
3–12 months	219 (19)	13 (11)	201 (20)	0.005
1–3 years	283 (25)	21 (18)	259 (25)	
3–6 years	146 (12)	12 (10)	134 (13)	
6–12 years	222 (20)	30 (26)	190 (19)	
12–18 years	268 (24)	38 (33)	224 (22)	
Gender n (%)				
Male	639 (56)	72 (63)	558 (55)	0.112
Female	499 (44)	42 (36)	450 (44)	
Ethnicity/religion n (%)				
Jewish	901 (79)	73 (64)	815 (81)	0.005
Ultra-orthodox	451 (50)	51 (69)	387 (47)	<0.007
Traditional	274 (30)	9 (12)	265 (32)	
Secular	60 (6)	2 (3)	58 (7)	
Other/no answer	116 (12)	11 (15)	104 (12)	
Muslim	160 (14)	24 (21)	133 (14)	
Christian	10 (1)	1 (1)	9 (1)	
Other/unknown	67 (6)	16 (14)	49 (5)	
Family and housing				
Number of parents and children in household (SD)	6.2 (2.6)	7 (3.2)	6 (2.5)	0.004
Number of rooms	4 [3–5]	4 [3–5]	4 [3–5]	0.3
Size of residence (m ²)	100 [80–120]	103 [84–120]	100 [80–120]	0.33
Housing density				
per room	1.3 [1–2]	1.5 [1–2]	1.3 [1–1.8]	0.02
per size (m ²)	17 [12–24]	16 [1–22]	17 [12–24]	2.6
Chronic disease n (%)	140 (12)	12 (10)	126 (12)	0.73
Attended school during lockdowns n (%)	152 (13)	15 (13)	134 (13)	0.809
Reason for PED referral n (%)				
Infectious disease	730 (64)	69 (61)	661 (66)	0.21
Non-infectious disease	159 (14)	24 (21)	135 (13)	0.09
Trauma	176 (15)	16 (12)	160 (16)	0.58

Note: Inconclusive results (n = 16, 1.4%) were not included in this comparison. Values shown with square brackets represent median and interquartile range (IQR).

Abbreviations: PED, paediatric emergency department; SD, standard deviation.

significantly lower seroprevalence in children.¹⁸ The high seropositivity rate we observed among ultra-orthodox Jews and Muslims contributed to the total seroprevalence rate found in this study. Previous studies have described how religious affiliation and communal ceremonies may have influenced SARS-CoV-2 transmission.¹⁹ We also found that a larger family size was associated with seropositivity and this may provide another explanation for the high seroprevalence rate in this group.

Less than a third (29%) of the patients with a PCR-confirmed virus infection did not have conclusive positive serology test results. The nucleocapsid-based antibody test was chosen as the primary screening antibody test for this study, based on preliminary studies that found it showed superior sensitivity to spike-based antibody kits.²⁰ This was in accordance with the Israeli Ministry of Health guidelines for SARS-CoV-2 serology testing at the time of the study. Overall, our dual-assay model only had a sensitivity of 70% for

TABLE 2 Demographic and clinical characteristics of patients with a past PCR-confirmed SARS-CoV-2 infection

Characteristic	All patients	Positive Serology	Negative Serology	Inconclusive Serology	p Value
	n = 71 (100%)	n = 50 (70%)	n = 15 (21%)	n = 6 (8%)	
Age median [IQR]	10.8 [3–15]	10.8 [4–15]	6.8 [2–13]	7.2 [1–16]	0.18
Gender n (%)					
Male	40 (56)	28 (56)	8 (53)	4 (67)	0.85
Female	31 (44)	22 (44)	7 (47)	2 (33)	
Symptoms n (%)					
Weakness	45 (63)	33 (66)	8 (53)	4 (66)	0.34
Fever	22 (31)	16 (32)	5 (33)	1 (16)	0.83
Sore throat	21 (29)	17 (34)	3 (20)	1 (16)	0.2
Smell/taste loss	13 (18)	10 (20)	3 (20)	0 (0)	0.79
Rhinorrhoea	13 (18)	10 (20)	1 (6)	2 (33)	0.15
Cough	12 (17)	8 (16)	3 (20)	1 (16)	0.9
Headache	12 (17)	7 (14)	5 (33)	0 (0)	0.16
Days since COVID-19 infection n (%)					
0–21	10 (14)	6 (12)	3 (20)	1 (16)	0.63
22–59	8 (11)	1 (2)	6 (40)	1 (16)	<0.001
60–89	24 (33)	22 (44)	1 (6)	1 (16)	0.008
90–119	11 (15)	10 (20)	1 (6)	0 (0)	0.22
120+	19 (26)	15 (30)	4 (26)	0 (0)	0.80
	9 (13)	2 (4)	3 (20)	4 (67)	0.04

Abbreviation: IQR, interquartile range.

detecting anti-SARS-CoV-2 antibodies in patients with a history of COVID-19. This poor sensitivity was pronounced in samples taken within 21 days of infection (13% sensitivity) or after 120 days of infection (22% sensitivity). Samples taken 21–119 days after infection had a dual-assay sensitivity of 87%, which was slightly lower than the 90%–97% described in adults.¹² However, it is important to note that a lack of detectable antibodies does not necessarily correlate to a lack of neutralising ability and specific, acquired SARS-CoV-2 immunity may still exist.^{21,22} Of note, no correlation was found between symptomatic and asymptomatic COVID-19 cases and the level of anti-SARS-CoV-2 antibodies.²³

We found that the temporal trend of anti-SARS-CoV-2 antibodies over time in children was different to the trends in adults. Children experienced a delayed initial rise in antibody levels, followed by a rapid decline and even the disappearance of detectable antibodies 4 months after the initial infection. This was particularly pronounced in children under the age of 6 years (Figure 2). These findings are in contrast to the current evidence in adults,²⁴ and may point to children having a distinct, weaker long-term immune response.²⁵ That latter study focused on a pseudo-virus *in vitro* assay of antibodies from the serum of children who had reduced neutralising activity compared to those taken from adults. The results may indicate reduced serological protection and susceptibility to recurrent infection in the paediatric population.²⁵ This attenuated immune response may lead to an underestimation of the true rate of prior, undetected virus infections in children, as negative serology test results will be interpreted as a lack of past infection, and not as

a patient recovering from COVID-19 with undetectable antibodies. This may also have implications for studies exploring long COVID-19 in children,²⁶ as a cohort of seronegative children may not represent a reliable control group.²⁷ In addition, this may have implications on the efficacy and lasting, long-term immunogenicity of SARS-CoV-2 vaccines in the paediatric population.

Our study began immediately after a month-long nationwide Israeli lockdown, between 18 September and 17 October 2020, in contrast to previous large paediatric seroprevalence studies, which were conducted during extended lockdown periods when infection rates were low.¹⁸ Interestingly, there was a relatively stable week-by-week seropositivity rate despite the gradual re-opening of schools during the study period. In addition, school closures were not uniformly or completely enforced during this lockdown. This included a government-approved strategy to keep schools open for children with special needs and the children of essential workers. It also included children who attended schools that remained open in defiance of government-mandated closures.²⁸ The 152 children who reported that they continued to attend school during the lockdown period did not have an increased risk of infection and this remained when the data were corrected for all other patient characteristics. These results were consistent with other findings that children were mostly infected by a first-degree relative in their home (55%) and that there were relatively low rates of infection in childcare facilities and schools (12%).^{29,30} These data may encourage policymakers to carefully reconsider widespread school closures.³¹

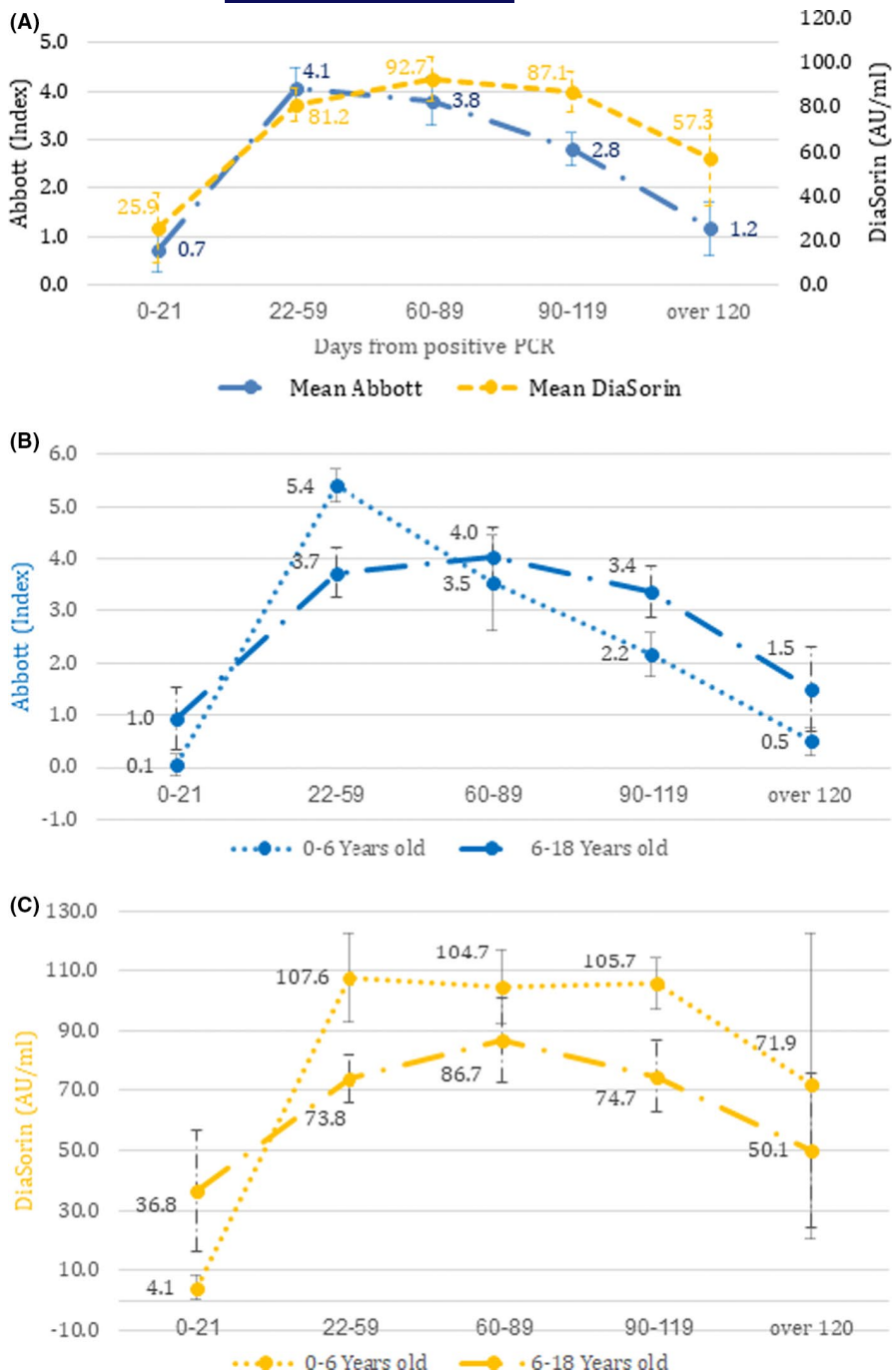


FIGURE 2 Antibody titre levels by time from infection. (A) Mean antibody levels and standard error, for both Abbott and DiaSorin assays, of all patients with a past PCR confirmed SARS-CoV-2 infection ($n = 71$). (B) Antibody levels obtained using the Abbott assay, divided by older ($n = 47$) or younger ($n = 24$) than 6 years old. (C) Antibody levels obtained using the DiaSorin assay, divided by older ($n = 40$) or younger than 6 years old ($n = 17$)

4.1 | Strengths and limitations

The strengths of this study included its large, prospective, population-based cohort in a region with high rates of SARS-CoV-2 infections and a diverse paediatric population. This enabled us to identify asymptomatic carriers and to characterise the serological response over time. We also noted that previous studies found lower rates of unknown, asymptomatic infections in children.³² Moreover, we were able to assess the role schools played in infections among children in a way that was not possible in previous studies. Other strengths of this study were the comprehensive patient questionnaire and further telephone-based epidemiological investigations of

seropositive children, as well as the use of two distinct SARS-CoV-2 antibody assays.

This study had several limitations. The single-site sample collection may have led to a geo-demographic population bias, as seroprevalence in other regions with different rates of infection may have been different. Similarly, these findings may only apply to the SARS-CoV-2 variants in Israel at the time of the study. Of note, the study only included Israeli residents and patients from the Palestinian Authority were not represented in this cohort. Also, voluntary enrolment in the study may have led to selection bias, as the parents of patients with a past history of exposure to SARS-CoV-2 may have been more interested in participating in the study. Thus,

the true rate of seroprevalence may be lower than reported here. On the other hand, since the assays used in this study were not 100% sensitive and specific, the true seropositivity rate in the general population may be somewhat different to our results. It is worth noting that the Abbott assay used in this study is intended to be used for the qualitative, and not quantitative, detection of antibodies, unlike the DiaSorin assay. Despite this, we have demonstrated significant differences in the test values, with respect to the time from infection, and our results can help guide clinicians when they are interpreting the results of this assay. In addition, this study sampled the paediatric population presenting to the PED for varied reasons, and may not reflect the general, healthy paediatric population. Nevertheless, refusal to participate in the study was minimal. This was because of the high infection rates in the region before and during the study, rising public awareness that children are often asymptomatic and the fact that serological tests were not easily accessible at the time of the study. Moreover, our findings on the serological responses over time, as well as differences in seropositivity rates among different age groups, were not site-specific and not affected by these biases. This means that they should be generalisable to broader paediatric populations. We did not collect data on the parents' occupation, as well as the child's involvement in extra-curricular group activities, which may have had an effect on the rate of seropositivity. These data may have revealed additional risk factors for infection.

5 | CONCLUSION

This study found that 41% of children with SARS-CoV-2 antibodies had no known or suspected exposure to the virus. We also found that anti-SARS-CoV-2 antibodies declined rapidly in young children and even disappeared 4 months after the initial infection. This may indicate a distinct immune response pattern among children, which may be important when weighing up the cost-effectiveness and advantages of vaccinating healthy paediatric populations. In addition, we did not find that opening schools increased the infection rates among children. These findings, along with the ongoing vaccination of adults, may help policymakers to decide whether to keep schools open and restore an element of normalcy and stability in the lives of children worldwide.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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