



# Seroprevalence of SARS-COV-2 antibodies among school-age children in the Swabi district of Pakistan

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## ABSTRACT

**OBJECTIVES:** To determine the seroprevalence of SARS-CoV-2 antibodies (IgM, IgG) in school-age children and identify the predominant symptoms in seropositive children in the Swabi district of Khyber Pakhtunkhwa, Pakistan.

**METHODS:** This descriptive cross-sectional study was conducted from November 2020 to May 2021. Blood samples from 246 randomly selected children (aged 5-16 years) in Swabi district of Pakistan were analyzed using ELISA. The study focused on the general pediatric population, excluding those over 16 years, with chronic illnesses, or whose parents declined participation. Data was collected through a structured questionnaire.

**RESULTS:** Among 246 participants, 5 (2.03%) individuals tested positive for IgM and 58 (23.6%) for IgG antibodies, totaling 63 (25.6%) participants with both IgM and IgG antibodies. Mean age of seropositive and seronegative children was  $11.2 \pm 3.0$  and  $10.3 \pm 2.98$  years respectively ( $p=0.030$ ). Out of 63 seropositive children, 51 (80.96%) were symptomatic, and 12 (19.04%) were asymptomatic. Common symptoms among seropositive individuals included fever (98.0%,  $n=50/51$ ), cough (88.02%,  $n=45/51$ ), sore throat (78.4%,  $n=40/51$ ), coryza (66.7%,  $n=34/51$ ), myalgia (60.8%,  $n=31/51$ ), and loss of smell and taste (49.0%,  $n=25/51$ ). The mean antibody titer was  $20.9 \pm 10.41$  IU/ml and  $13.35 \pm 5.6$  IU/ml for symptomatic and asymptomatic individuals respectively ( $p=0.013$ ).

**CONCLUSION:** In our study, approximately one fourth of the participants tested positive for SARS-CoV-2 antibodies, predominantly IgG. Females exhibited higher seropositivity than males, with a significant association between seropositivity and exposure to confirmed COVID-19 cases. Symptomatic cases comprised 80.95% of seropositive individuals, with predominant symptoms of fever, cough, and sore throat. Symptomatic individuals had a higher mean antibody titer.

**KEYWORDS:** Seroepidemiologic Studies (MeSH); Seroprevalence (MeSH); Immunity (MeSH); Serosurvey (Non-MeSH); Immune Surveillance (Non-MeSH); SARS-CoV-2 (MeSH); COVID-19 (MeSH); Antibodies (MeSH); Immunoglobulin G (MeSH); Immunoglobulin M (MeSH)

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## INTRODUCTION

In early 2020, as the coronavirus disease 2019 (COVID-19) pandemic began to sweep across the globe. The initial data revealed that children accounted for only around 1-3% of confirmed coronavirus disease 2019 (COVID-19) cases, with fewer critical cases and fatalities.<sup>1,2</sup> This led to the assumption that children were less susceptible and had a low risk of being

infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>3</sup> Evidence from countries affected early in the crisis, found low levels of SARS-CoV-2 antibodies, between 0% to 5%, in children.<sup>4</sup> Since the severity of the symptoms was partially dependent upon the strength of SARS-CoV-2 immune response, it was initially presumed that children fail to mount antibody responses post-recovery from asymptomatic or mildly symptomatic

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infection.<sup>5</sup> More recently, strong evidence has emerged which demonstrates that children are susceptible to SARS-CoV-2, and are capable of producing protective, and potentially lasting, antibody defenses, post-recovery from asymptomatic or mild infection.<sup>6</sup>

It has become widely accepted that a majority of children experience an asymptomatic, or mild course of illness. Thus, there is concern that earlier findings have been grossly underestimated, due to low testing rates in children.<sup>7,8</sup> The clinical manifestations of SARS-CoV-2 infection that lead to COVID-19 in children are distinct from those observed in adults.<sup>9</sup> Compared to more specific symptoms in adults, children do not always display symptoms suggestive of typical illness due to SARS-CoV-2.<sup>9</sup> According to the literature, the most common symptoms of COVID-19 caused by SARS-CoV-2 in children are fever, cough, sore throat, headache, loss of sense of smell or taste, gastrointestinal issues, runny nose, and fatigue.<sup>10,11</sup>

As of May 2021, official reports documented 93,000 cases of SARS-CoV-2 infection in Pakistani children and adolescents aged 1 to 20 years. Nevertheless, a significant gap exists in the available data regarding the seroprevalence of SARS-CoV-2 antibodies among children in Pakistan. Thus, it is hard to accurately gauge the true number of cases, or proportion of asymptomatic infections, within this age

group.<sup>12</sup> Given the milder and often asymptomatic nature of the disease in pediatric cases, undetected infections may contribute significantly to SARS-CoV-2 infection transmission.

This study was conducted to furnish documented seroprevalence data for SARS-CoV-2 antibodies (IgM and IgG) in children. The objective was to estimate antibodies and identify the most frequently occurring symptoms associated with seropositivity in a randomly selected sample of the pediatric population in the Swabi district of the Khyber Pakhtunkhwa province, Pakistan. The findings intended to contribute to estimating previous infections, understanding symptom patterns, and informing government policymakers on preventive measures like school closures, quarantine, and lockdown implementation.

## METHODS

This descriptive cross-sectional sero-epidemiological study was conducted between November 26, 2020, and May 3, 2021 at the Swabi district of Khyber Pakhtunkhwa province of Pakistan. Study was approved by the ethical board of Khyber Medical University Peshawar (DIR/KMU-EB/000832/SC dated May 26, 2021).

The laboratory analysis was performed in haematology department of KMU while the participants were included from district Swabi. Eligible participants included were children, aged between 5 to 16 years old, and those that did not report chronic diseases or genetic ailments while unwilling and those with chronic illnesses were excluded from the study. The target sample size, of 246 participants, was calculated using the OpenEpi calculator, based on apriori seroprevalence of SARS-CoV-2 antibodies of 20.0%, a population size of 1.62 million people.<sup>13,14</sup> A purposefully designed questionnaire was completed by the parents/guardians at the time of enrolment, which included information on demographics, clinical history, and any history of exposure to a confirmed COVID-19 case. In case any participant had been symptomatic, we collected data relating to the symptoms, including details of any visits to the doctor, or a hospital, and results of RT-PCR tests, if

taken.

District Swabi is one of the largest, and most populous districts in Pakistan, consisting of 1.62 million people.<sup>14</sup> The district is further divided into 56 union councils, out of which, 6 were selected randomly by lottery method, including the union councils Kotha, Sheikh Dheri, Maniri, Tarakai, Topi East, and Zaida. By enlisting the help of the local 'Nazims', we sent out invitations for participation in our study to families residing in these union councils. Consenting families were briefed about the objectives of this study, and written informed consent was obtained from the guardians of all enrolled participants.

Samples for serological analysis were collected at designated sites. Phlebotomy was performed by trained medical nurses under aseptic conditions, and blood samples were obtained in gel tubes containing clot activators. All further analyses were performed at the Department of Haematology, Institute of Basic Medical Sciences, KMU. The cold chain during the whole process was maintained. Anti-SARS-CoV-2 antibodies were detected in blood sera using commercially available manual COVID-19 ELISA IgG (Vircell®, Spain, Cat GI032), and IgM+IgA kits (Vircell®, Spain, Cat MAI032). These tests were performed by a well-trained biotechnologist. These assays target the spike protein (S) of SARS-CoV-2. The IgG assays have an overall sensitivity of 90.0% and specificity of 98.0%; for IgM+A assays, an overall sensitivity of 92.0%, and specificity of 99.0% has been reported, according to the manufacturers. Values above the manufacturer's cut-off value were considered positive. The antibody index was calculated using the formula: (antibody serum optical density (OD) / cutoff mean OD) × 10. Values for antibody index >6 IU/ml were considered positive, whereas values < 4 IU/ml were considered negative; values between 4-6 IU/ml were equivocal and considered negative. An in-house assessment of the specificity of the assays was carried out using ten blood samples (collected and stored in a deep freezer at -70°C as part of another study in 2018) as negative controls. All

ten pre-pandemic samples were tested negative for SARS-CoV-2 IgM and IgG.

Data was recorded and analyzed using IBM SPSS version 26. Comparisons of categorical variables were performed using Chi-square tests. Continuous variables, between seropositive and seronegative participants, were analyzed using independent samples t-tests. All differences were considered statistically significant if they resulted in p-values of < 0.05.

## RESULTS

The demographic characteristics of participants are listed in Table I. Total 246 children were enrolled of school-going age, between 5 to 16 years old, in a symptom-independent manner, from the district Swabi.

We demonstrated that 2% (n=5) of our participants were seropositive for SARS-CoV-2 IgM, whereas 23.6% (n=58) were seropositive for SARS-CoV-2 IgG antibodies. Since IgM seropositivity in our sample was very low, characteristics of IgM seropositive participants were grouped with IgG seropositive participants, and further statistical analyses were performed for comparison between characteristics of seropositive (IgG/IgM +ve), and seronegative participants. Results from our serological analysis are displayed in Table II.

The mean age of seropositive and seronegative participants was 11.2±3.00 years and 10.3±2.98 years respectively (p=0.030). Among female participants, 33.0% (29/88) were seropositive for SARS-CoV-2 antibodies, while 21.5% (34/158) of male participants were found to be seropositive (p=0.036). We did not find a significant difference in the distribution of seropositive cases between the 6 union councils of district Swabi, investigated in our study (p=0.604). There was a statistical association between seropositivity and exposure history, with significantly higher seropositivity found in participants reporting exposure to a confirmed COVID-19 case, compared to those that did not (p <0.001). However, no participant in our cohort had a history hospitalization, for their

**Table I: Demographic features of the study participants (n=246)**

Variables		Frequency (%)
Gender	Male	158 (64.2%)
	Female	88 (35.8%)
History of RT-PCR* confirmed	Yes	19 (7.7%)
	No	227 (92.3%)
RT-PCR test done	Yes	0 (0%)
	No	246 (100%)
Hospitalization in past 6 months	Yes	0 (0%)
	No	246 (100%)
Union councils	Kotha	45 (18.3%)
	Sheikh Dheri	44 (17.9%)
	Maniri	35 (14.2%)
	Tarakai	46 (18.7%)
	Topi east	46 (18.7%)
	Zaida	30 (12.2%)

\* RT-PCR: Reverse Transcription Polymerase Chain Reaction

symptoms. Similarly, none of the participants had been tested by reverse transcription polymerase chain reaction (RT-PCR) for SARS-CoV-2 confirmation.

Of all participants who tested positive for SARS-CoV-2, 80.95% (n=51/63) experienced symptoms, while 19.05%

(n=12/63) remained asymptomatic. The prevalent symptoms among seropositive children are detailed in Table III. The most frequently reported symptoms included fever (98%), cough (88.2%) and sore throat (78.4%). The mean antibody titer was 20.9±10.41 IU/ml and 13.35±5.6 IU/ml for symptomatic and asymptomatic

individuals respectively (p=0.013).

## DISCUSSION

This is the first study conducted on children from one of the populous districts of Khyber Pakhtunkhwa, Pakistan. Recently, strong evidence has emerged that demonstrates that children are likely to be infected with SARS-CoV-2 and are capable of producing protective anti-body defenses in response.<sup>8-10,15</sup> Although the timeline of immune responses in children is not clearly understood, antibodies against SARS-CoV-2 are estimated to persist for a 5- to 8-month period.<sup>9,16-18</sup> It can be assumed that seropositive children in our cohort were either in the active phase of infection or had unknowingly recovered from COVID-19. It has been well established that a large majority of children experience a mild course of SARS-CoV-2 illness or remain asymptomatic.<sup>8-10</sup> Due to low symptom burden, there is concern that many infected children may not have been tested, causing a significant proportion of cases to remain undetected.<sup>15-16</sup> This may especially be true for many low middle income countries, such as Pakistan, where testing strategies rarely actively target asymptomatic infection due to limited resources, symptom-based referrals, and narrow criteria for who can get an RT-PCR test.

**Table II: Comparison of demographic and clinical parameters of seropositive and seronegative children (n=246)**

Variables		Seropositive (n=63)	Seronegative (n=183)	P Value
Age in years (mean ± SD)		11.2 (± 3.00)	10.3 (± 2.98)	0.030*
Gender	Male (n=158)	34 (21.5%)	124 (78.5%)	0.036**
	Female (n=88)	29 (33%)	59 (67%)	
Union council	Kotha (n=45)	10 (22.2 %)	35 (77.8%)	0.604**
	Sheikh Dheri (n=44)	15 (34.1%)	29 (65.9%)	
	Maniri (n=35)	11 (31.4%)	24 (68.6%)	
	Tarakai (n=46)	9 (19.6%)	37 (80.4%)	
	Topi East (n=46)	11 (23.9%)	35 (76.1%)	
	Zaida (n=30)	7 (23.3%)	23 (76.7%)	
Hx of contact with PCR*** positive COVID-19 case	Yes (n=19)	18 (94.7%)	1 (5.3%)	<0.001**
	No (n=227)	45 (19.8%)	182 (80.2%)	

\*Independent t test, \*\*Chi square test, \*\*\*Polymerase Chain Reaction

**Table III: Symptoms pattern in seropositive children**

Symptoms	Frequency (n=51)	Percentage
Fever	50	98
Cough	45	88.2
Sore throat	40	78.4
Coryza	34	66.7
Myalgia	31	60.8
Loss of smell and taste	25	49
Vomiting and diarrhea	4	7.8

We observed elevated levels of IgG and IgM against SARS-CoV-2 in our pediatric cohort, compared to most existing evidence.<sup>20</sup> However, our results are different from several recent studies in showing that seroprevalence in children is higher than what was reported earlier during the pandemic.<sup>2</sup> IgG/IgM antibodies against SARS-CoV-2, as high as 70.0%, have been reported in children from Iquitos, Peru.<sup>21</sup> Like our results, a large study from India reported 24.1% seroprevalence of SARS-CoV-2 IgG, in children aged between 10 and 17 years.<sup>22</sup> Another study from New York indicated seroprevalence levels of 16.5% among its pediatric population.<sup>16</sup> During this study, samples were obtained during a phase when Pakistan's second wave in district Swabi was receding from its peak. Following two brief closure periods, schools have predominantly remained open since September 2020, implementing essential preventive measures. This could be a potential explanation for the high seroprevalence levels found in this study. Nonetheless, this analysis reveals a glaring gap between the low number of children being tested for SARS-CoV-2 in district Swabi and the high seroprevalence levels in our cohort. Data shows that, between September 2020 to May 2021, 9,106 children were tested in district Swabi for SARS-CoV-2 by RT-PCR, but only 235 positive cases were identified. In this study, a significantly large proportion (81%) of seropositive participants recalled experiencing some symptoms, but none visited a hospital, nor were they tested. Based on these findings, it may be stated that the number of children infected with SARS-

CoV-2 has been underestimated in district Swabi.

Evidence suggests that fever and cough are the most common symptoms.<sup>11,23</sup> This is concurred by our analysis, as fever (98%) and cough (90%) were the most frequently noticed symptoms in our cohort, although our observed frequencies are higher than reported values in the literature. Another major study shows loss of smell and taste in 40% of children, among a large cohort infected with SARS-CoV-2 in the UK.<sup>24</sup> Like this, in our study, loss of smell and taste was reported by 49% of seropositive children. Consistent with several studies, our findings indicate that, in comparison to adults, children often present with vague clinical presentations of SARS-CoV-2.<sup>24</sup>

Although most major surveys indicate that seroprevalence levels in children do not differ by gender, female children in our study were found to have a significantly higher risk of being seropositive than male children (p-value: 0.036) which could also be a sample size effect.<sup>22,25</sup> The results of this study have revealed that a significant age-dependent increase in seropositivity is noted, with the mean age of seropositive participants being approximately one year older compared to seronegative participants (p-value: 0.030) (Table II). This could be partially influenced by the expression of angiotensin-converting enzyme 2 (ACE2), the main receptor in human cells for the entry of SARS-CoV-2. ACE2 receptors in children have a lower affinity for SARS-CoV-2, making entry into host cells more difficult.<sup>23,26</sup> Expression, and affinity of ACE2

increase throughout childhood, which could be the reason why older children in our cohort had a higher risk of being seropositive.<sup>26</sup> However, it is not currently known to what extent ACE2 expression dictates the clinical presentations of COVID-19. According to several studies, the strength of the SARS-CoV-2 antibody responses elicited by an individual is tied to the severity of their symptoms.<sup>3,16</sup> This was reflected in our findings, as antibody titers were found to be significantly higher in children who recalled experiencing symptoms (p:0.013).

## LIMITATIONS AND STRENGTHS

A strength of this study is the timely collection of samples post the subsiding of the second epidemic wave, enhancing the likelihood of detecting antibodies in recently infected children. However, caution is warranted in generalizing findings due to the study's focus on a specific pediatric population in one location, limiting applicability to diverse demographics and epidemic timelines in other regions.

This study has several limitations, including the enrollment of participants irrespective of symptom history or known exposure, potentially leading to an overestimation of seroprevalence. The likelihood of missed infections exists due to the necessary post-exposure interval for SARS-CoV-2 antibodies to form. Additionally, detectable antibody levels may not be present in some children infected with SARS-CoV-2, and previously seropositive participants could have experienced waning immunity, aligning with observations concerning the decline of SARS-CoV-2 antibody levels following recovery.

## CONCLUSION

In this study of 246 school-going children (ages 5–16) in Swabi district, about one fourth of the participants were tested positive for SARS-CoV-2 antibodies, and the majority were positive for SARS-CoV-2 IgG. Females had a higher seropositivity (33%) than males (21.5%). Seropositivity was significantly associated with exposure to a confirmed COVID-19 case.

Symptomatic cases constituted 80.95% of seropositive individuals, with common symptoms being fever (98%), cough (88.2%), and sore throat (78.4%). Asymptomatic cases accounted for 19.05%. The mean antibody titer was higher in symptomatic individuals. No participants had a history of hospitalization, and none were tested by RT-PCR. The study highlights the prevalence and characteristics of SARS-CoV-2 in school-going children, emphasizing the need for continued research and surveillance in this population.

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## AUTHORS' CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under:

**MA, MNK:** Concept and study design, acquisition, analysis and interpretation of data, drafting the manuscript, approval of the final version to be published

**MI, SAA & Su:** Acquisition of data, drafting the manuscript, approval of the final version to be published

**YMY:** Concept and study design, analysis and interpretation of data, critical review, approval of the final version to be published

*Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

## CONFLICT OF INTEREST

Authors declared no conflict of interest, whether financial or otherwise, that could influence the integrity, objectivity, or validity of their research work.

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## DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request



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