

High frequency of SARS-CoV-2 infection in children admitted to academic hospitals in central South Africa

O P Khaliq, MMedSc, PhD ; S C Brown, MMed (Paeds), PhD ; B Pitso, MB ChB, MMed (Paeds) ;
N E Tabane, MB ChB, MMed (Paeds) 

Department of Paediatrics and Child Health, School of Clinical Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa

Corresponding author: O Khaliq (khaliqop@ufs.ac.za)

Background. During the COVID-19 pandemic, the Omicron variant was highly infectious in children, and resulted in high hospital admission rates in this population compared with other SARS-CoV-2 variants.

Objective. To investigate the prevalence of SARS-CoV-2 infection in children during the Omicron variant wave in Free State Province, South Africa (SA).

Methods. This prospective cross-sectional study was conducted from August 2022 to April 2023 in the Free State, SA. A total of 320 children admitted at Pelonomi Tertiary Hospital and Universitas Academic Hospital between the ages of 0 and 12 years were recruited. All participants were tested for SARS-CoV-2 using the nucleocapsid antibody rapid test. Parent and caregiver vaccination history was also collected.

Results. In our study, 46.8% of the children tested positive for SARS-CoV-2. The highest (60%) infection rate was observed in neonates. Children were admitted for various reasons, and none were screened for suspected SARS-CoV-2 on admission. Of the infected population, 28% were premature, 12.6% had gastrointestinal tract infections, 12% had respiratory conditions and 10% had central nervous system conditions. A total of 43.3% of the infected children were from vaccinated parents or caregivers.

Conclusion. Our study showed that a high number of hospitalised children tested positive for SARS-CoV-2 while admitted for conditions unrelated to COVID-19. Most, if not all, children did not exhibit COVID-19-specific symptoms, and this may be due to the Omicron variant, which was highly infectious but less virulent, and was associated with mild disease.

Keywords: SARS-CoV-2, Omicron variant, antibodies, children, admission diagnosis

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The COVID-19 pandemic affected the globe from 2020 to 2023, following its discovery in December 2019 in Wuhan, China.^[1] Globally, >2.6 million cases and 17 000 deaths were reported from 17 April 2023 to 14 May 2023.^[2] The virus has mutated rapidly since its discovery, resulting in different variants worldwide.^[3] However, vaccinations for COVID-19 were manufactured to protect individuals from severe complications after infection.^[4] The safety of these vaccines in children was unknown. Therefore, children under the age of 12 years were not vaccinated in South Africa (SA) until July 2023.

SA has had four variants since the emergence of COVID-19, and this study focused on the fourth variant, Omicron.^[3] The Omicron variant was first discovered in SA and Botswana in November 2021.^[5] This variant was reported to spread more rapidly than previous variants.^[6] Interestingly, infections were noted even in environments where COVID-19 safety protocols, such as wearing of masks, were observed.^[7] The Omicron variant was also reported to have high asymptomatic carriage, with mild disease patterns, making it difficult to detect and control.^[8]

During the emergence of the Omicron variant, the virus spread rapidly in adults and children, with higher admission numbers noted in paediatric wards in Germany.^[9] Another increase of paediatric admissions was noted in the USA.^[10] In Romania, paediatric cases also increased in children ($\geq 10\%$).^[11] Countries such as China, Korea, Japan and SA experienced increased paediatric admissions during the time of the Omicron variant.^[12-15]

The Omicron variant is involved with lower antibody neutralisation and lower vaccine effectiveness, resulting in risk

of re-infection.^[6] Moreover, antibody neutralisation is higher in children with mild infections than in adults with mild infections, and even higher in children ≤ 10 years of age than older children.^[16] Cloete *et al.*^[5] hypothesised that increased paediatric admissions were attributed to decreased frequency of mask use in children, and lower vaccination rates, as children ≤ 12 years were not vaccinated at the time of their study.^[15]

Children wore masks less frequently than adults because it was believed that they had a lower expression level of angiotensin-converting enzyme II (ACE2) and transmembrane protease serine 2 (TMPRSS2) (binding sites for the SARS-CoV-2 virus) than adults.^[17-19] The low expression of ACE2 receptors is suspected to result in mild symptoms in children. At the same time, other findings suggest that this could be due to children having fewer or no underlying conditions.^[20,21]

The immune response in children and adults is also reported to differ. Chou *et al.*^[22] have shown that children have stronger interferon (IFN) responses to SARS-CoV-2 and more T-cells than adults. The stronger IFN response to infection results in a lower cytokine storm, leading to mild infection.^[21] Furthermore, cytokine levels in children with mild COVID-19 were similar to those of healthy children, indicating that children only have a mild inflammatory response during infection.^[23] Children with mild COVID-19 infections are usually asymptomatic, and where not, have shorter hospitalisation stays than those with severe COVID-19 disease.^[24]

Wearing masks and performing COVID-19 screening before admission was no longer a standard procedure during 2022. At this

point, children were not yet vaccinated in SA. This study aimed to investigate the prevalence of COVID-19 infection in children aged 0 - 12 years during the Omicron variant wave in the Free State Province of SA, as this age group of children was not vaccinated until July 2023.

Methods

Study design and study population

A total of 320 participants aged 0 - 12 years were included in the study. No admissions were done primarily for COVID-19. No patients were excluded. The study occurred in Bloemfontein, at the Pelonomi and Universitas Academic hospitals, from August 2022 to April 2023. Ethical permission was obtained from the University of the Free State before the commencement of the study (ref. no. UFS-HSD2022/1456/2609) in accordance with the Declaration of Helsinki. Informed consent was obtained from parents and legal guardians, and assent was obtained from children >7 years of age. This prospective cross-sectional study consisted of children admitted for various reasons; interestingly, none were admitted for suspected SARS-CoV-2 infection. Participants were randomly recruited from general paediatric wards and specialised wards such as paediatric oncology, cardiology and paediatric intensive care units at both hospitals. Their COVID-19 status was unknown during recruitment as SARS-CoV-2 screening upon admission was no longer standard practice during the period that the study was conducted. The children were categorised into different age groups (<1 month, 1 - 12 months, 13 - 60 months, 61 - 144 months). Babies who were born prematurely and were admitted for ≥ 1 month were categorised in the 1-month - 12-month group. Children were tested for SARS-CoV-2 antibodies following consent from their parents or caregivers. The nucleocapsid antibody testing technique (Roche) was used to measure the presence of antibodies (IgG/IgM rapid COVID test) in children. A drop of blood was obtained on admission during their routine daily blood withdrawal procedures. SARS-CoV-2 infection in children was confirmed by the presence of both immunoglobulin G (IgG) and immunoglobulin M (IgM) antibodies. The results include all children tested, with and without COVID-19 infection.

Data analysis

Data were analysed using a descriptive-quantitative approach. The frequencies and percentages for categorical data, mean, standard deviation, medians and percentiles for numerical data were analysed using SAS Software, version 9.4 (SAS Institute Inc., USA).

Results

This study occurred during the fourth wave of COVID-19 (Omicron), which started in December 2021. A total of 320 children were included in the study during the period from August 2022 to April 2023. The COVID-19 status of all recruited children according to the various age groups and parent/caregiver COVID-19 vaccination status is depicted in Table 1.

Overall, 46.8% ($n=150$) of the children had both IgM and IgG antibodies, indicating active or recent infection. The infection rate was higher (60%) in neonates (<1 month) than in other age groups. In infants aged 1 - 12 months, 21.3% were infected; in toddlers between 13 and 60 months, 11.3% were infected; while 8% of the children aged 61 - 72 months were infected (Table 1).

The COVID-19 vaccination history of all parents or caregivers included in the study showed that 61.3% had received the COVID-19 vaccination. Almost half (43.4%) of all children who tested positive for COVID-19 came from vaccinated parents or caregivers, while 41% came from unvaccinated ones.

In neonates, prematurity was the most common reason that children were admitted in both infected (32.2%) and uninfected groups (37.3%). However, slightly more infected children tended to have gastrointestinal tract (GIT) infection diagnoses (14.4%) than in the uninfected group (9.3%). Interestingly, almost double the number of neonates in the uninfected group were diagnosed with respiratory conditions compared with the infected group (24.0% v. 11.1%) (Table 2).

More of these infants were admitted owing to complications related to their prematurity (40.6%) in the infected group than the uninfected group (5.4%). These babies were born prematurely and had been admitted for >1 month. GIT conditions were accountable for only 16.5% of admissions in the infected group, compared with 43.2% in the uninfected group (Table 2).

In the 13 - 60-month cohort, 18.6% of the infected children were diagnosed with respiratory conditions, compared with 14.6% in the uninfected group. The most common respiratory conditions in the infected group were asthma, diffuse alveolar haemorrhage and recurrent chest infections. In the 61 - 144-month group, the most common diagnoses in infected children were related to the central nervous system (CNS) and respiratory conditions (33.3%). In contrast, in the uninfected group, the most common reason for admission was haematological and oncological conditions (52.6%) (Table 2). The most common CNS conditions were seizures, while respiratory conditions were asthma and lower respiratory tract infections.

Confidence intervals were calculated to determine the relation between age in months, parents/caregiver infection history and parent/caregiver vaccination history. Table 3 shows that in all the different age groups, there is no relationship between SARS-CoV-2 infection history of parents/caregivers and the infection of the children. However, there is a relationship between the age of the children and their SARS-CoV-2 infection, as well as the vaccination history of the parents/caregivers and infection in the children (Table 3).

Discussion

This study aimed to investigate the prevalence of SARS-CoV-2 infection in unvaccinated children during the Omicron variant (fourth wave). Results show that just under half of the children included in the study had both IgM and IgG antibodies present, indicating current or recent active infection. However, they were admitted for other conditions. All positive cases found in the study were incidental, as none of these children were tested for SARS-CoV-2 upon admission, or admitted due to infection.

The highest infection rates were noted in neonates <1 month (60%), followed by infants aged 1 - 12 months and toddlers, aged 13 - 60 months, and the lowest infection rates were observed in children between 61 - 144 months. These results differ from a multicentre observational study conducted in SA in the Tshwane district that investigated clinical profiles of all children infected with SARS-CoV-2 (6 287 children ≤ 19 years of age) during the fourth wave (Omicron variant). Of the infected children, 14% were aged 0 - 4 years, 20% were aged 5 - 9 years, 32% were aged 10 - 14 years, and 34% were aged 15 - 19 years.^[15] The infection rates increased with age while in our study, the rates decreased with age. Furthermore, of the three COVID-19 waves, the highest rates of infection were noted in the fourth wave (Omicron).^[22]

According to the Centers for Disease Control and Prevention update on COVID-19 in children and adolescents ≤ 18 years, 11.8% of children were infected during the fourth wave of COVID-19 in January 2022 in SA.^[25] Furthermore, a paediatric registry in the USA

Table 1. Child SARS-CoV-2 infection and parent/caregiver SARS-CoV-2 infection and vaccination history (N=320)

Age (months)	Total SARS-CoV-2 infections (%)	Total SARS-CoV-2 uninfected (%)	Parent/caregiver infected previously (%)	Parent/caregiver uninfected previously (%)	Parent/caregiver vaccinated (%)	Parent/caregiver unvaccinated (%)
0 - 144 (n=320)	46.8	53.1	12.5	87.5	61.3	38.8
<1 (n=165)	60	44.1	10.3	89.7	61.8	38.2
1 - 12 (n=69)	21.3	21.7	17.4	82.6	53.6	46.4
13 - 60 (n=55)	11.3	22.3	10.9	89.1	70.9	29.1
61 - 144 (n=31)	8	11.2	19.4	80.6	54.8	45.2

reported that 24% of children aged between 5 and 11 years tested positive for SARS-CoV-2.^[16]

The infection rate of the neonates in the current study is also high compared with a study published in Iran, which had an infection rate of 6.1% in neonates.^[26] A study in the UK reported that the incidence of SARS-CoV-2 was 5.6 per 10 000 live births. Of these neonates, 42% had severe SARS-CoV-2 infection.^[27] Our results may have had a higher infection rate in neonates because the majority of the study population comprised neonates (51.6%). The presence of SARS-CoV-2 antibodies in circulation determined infection.

The presence of both antibodies represents a recent infection, as research shows that the IgM antibody is detected 4 days following infection and reaches its peak on the 20th day, after which it drops. Conversely, IgG rises 7 days after infection until the 25th day, but remains detectable 4 weeks after infection.^[28] IgM is the first line of defence against viruses, while IgG maintains long-term immunity after viral infection.^[29] A study conducted in China in 2020 showed that in patients with SARS-CoV-2 infection, IgM antibodies appear early and peak before IgG. IgM was reported to linger in the system for 3 weeks, while IgG antibodies remained in the system longer.^[28]

Children included in the study were admitted for reasons other than suspected SARS-CoV-2 infection, and none were tested before admission; therefore, their infection status was unknown upon admission. In December 2021, the paediatric population of hospital admissions due to SARS-CoV-2 infection was ~18% (462/2 550) in the Tshwane district.^[15] Of these admissions, the most common conditions associated with positive antibodies were seizures (20%), acute gastroenteritis (20%), respiratory infections (14%) and bronchopneumonia (15%). The current study's admission diagnoses differed among the different age groups. In these, the reasons for admission were prematurity (28%), GIT conditions (12.6%), respiratory conditions (12%) and CNS conditions (10%). However, whether the admission diagnoses were due to SARS-CoV-2 infection in these children is unknown, as this study was only focused on infection rates. This study adds new knowledge because most SA studies underreport neonatal data.^[1,2]

Another study recruited 97 SARS-CoV-2-positive children admitted to a hospital in India.^[30] Some of the children were admitted due to COVID-19, while others were admitted for other reasons but tested positive for SARS-CoV-2 upon admission. The study population was aged 1 - 18 years. The total sample size of the study was lower (n=97) than the current study (n=320). The study found that 30.93% of the children were asymptomatic, while 68.04% were symptomatic. These results differ from the current study as all 46.8% (n=150/320) SARS-CoV-2 infected children were asymptomatic, indicating mild disease.

Studies show that pregnant women infected with SARS-CoV-2 are at a higher risk of preterm deliveries.^[31-34] Another multicentre study conducted in Saudi Arabia described the clinical outcomes of mothers infected with SARS-CoV-2 and their neonatal outcomes. The authors found that out of 204 neonates, 15.5% (n=31) were born prematurely.^[35] In the current study, 32.2% of the SARS-CoV-2-infected babies were premature. These babies may have been infected via vertical transmission before birth, or the infection may have been acquired in hospital. There are different ways in which vertical transmission can occur, leading to preterm birth.^[36] SARS-CoV-2 is transmitted through faecal contamination of the birth canal, which can infect the neonate during labour. Vertical transmission via the ACE2 receptors found in the placenta can also affect gaseous exchange and lead to other complications, such as intrauterine death and perinatal asphyxia.^[35] However, the likelihood of transmission to the fetus is minimal due to the presence of the placental barrier.^[37] Some researchers state that vertical transmission to the fetus might be possible through other receptors (dipeptidyl peptidase-4 inhibitor (DDP4) and cluster of differentiation (CD147) and proteases (Furin).^[38,39]

In a study by Allotey *et al.*,^[32] the rate of preterm births in women infected with COVID-19 was 17%, which is lower than in the current study. Furthermore, in the current study, mothers were not tested for SARS-CoV-2; therefore, their SARS-CoV-2 status was unknown. However, their maternal COVID-19 vaccination history was collected, and 61.8% of the mothers with premature deliveries were vaccinated. The rates of COVID-19-vaccinated adults in the Tshwane district were lower than in this study (32%).^[15] Our results align with reports published by the SA National Department of Health, which found that 65 - 80% of the adult population had a positive result due to a previous infection or COVID-19 vaccination.^[40] A study conducted in Israel from April 2020 to March 2021 revealed that antenatal vaccination with the Pfizer vaccine demonstrated elevated IgG titers, and these antibodies were transferred to the fetus through the placenta.^[41] Maternal transfer of anti-SARS-CoV-2 antibodies was found in neonatal circulation 2 weeks after the first dose, indicating neonatal immunity during pregnancy. Equally, another study showed that the transfer of SARS-CoV-2 IgG and IgM was possible via breastmilk. Notably, both antibodies in neonatal circulation may indicate neonatal immunity more than an active infection.^[18] However, in the current study, information on breastfeeding was not collected to confirm this finding.

According to Beharier *et al.*,^[41] it is difficult to confirm whether antibodies found in neonates following delivery may be due to the placental transfer of a seropositive mother or to immune response following the COVID-19 vaccine. The study reported no

Table 2. Admission diagnoses of all children tested for COVID-19 (N=320)

Age, months	SARS-CoV-2 infected	n (%)	SARS-CoV-2 uninfected	n (%)
<1 (n=165)	Neonatal infection	10 (11.1)	Neonatal infection	7 (9.3)
	Prematurity	29 (32.2)	Prematurity	28 (37.3)
	GIT condition	13 (14.4)	GIT condition	7 (9.3)
	CNS condition	7 (7.7)	CNS condition	7 (9.3)
	Endocrine condition	4 (4.4)	Endocrine condition	3 (4.0)
	Respiratory conditions	10 (11.1)	Respiratory condition	18 (24.0)
	Congenital abnormalities	3 (3.3)	Congenital abnormalities	4 (5.3)
	Dermatology	2 (2.2)	Not recorded	1 (1.3)
	Oncology	2 (2.2)		
	Toxicity	2 (2.2)		
1 - 12 (n=69)		32 (46)		37 (54)
	Prematurity	13 (40.6)	Prematurity	2 (5.4)
	GIT condition	5 (15.6)	GIT condition	16 (43.2)
	CNS condition	2 (6.3)	CNS condition	1 (2.7)
	CVS condition	2 (6.3)	CVS condition	2 (5.4)
	Malnutrition	2 (6.3)	Malnutrition	6 (16.2)
	Infections	2 (6.3)	Infections	2 (5.4)
	Endocrine condition and CNS condition	2 (6.3)	Oncological conditions	1 (2.7)
	Renal condition	1 (3.1)	Haematological condition	1 (2.7)
	Malnutrition and GIT condition	1 (3.1)	Respiratory condition	3 (8.1)
	Malnutrition and respiratory conditions	2 (6.3)	Not recorded	1 (2.7)
	Myalgia	1 (3.1)		
	Respiratory conditions	2 (6.3)		
	Other	1 (3.1)		
	Not recorded	1 (3.1)		
13 - 60 (n=55)		17 (31)		38 (69)
	GIT condition	1 (5.9)	GIT condition	3 (7.3)
	CNS condition	3 (17.6)	CNS condition	5 (12.2)
	Respiratory conditions	3 (17.6)	Respiratory conditions	6 (15.8)
	Malnutrition	2 (11.8)	Malnutrition	1 (6.3)
	Toxicity	2 (11.8)	Toxicity	3 (7.3)
	Renal conditions	2 (11.8)	CVS condition	1 (2.4)
	Congenital and respiratory condition	2 (11.8)	CVS and respiratory conditions	1 (2.4)
	Oncology conditions	3 (17.6)	Dermatology	2 (4.9)
			Haematology and oncology	10 (26.3)
			Endocrine condition	1 (2.4)
			CNS and GIT condition	1 (2.4)
			Prematurity	2 (4.9)
			Infection	3 (7.3)
61 - 144 (n=31)		12 (38)		19 (62)
	Respiratory conditions	3 (25.0)	Respiratory conditions	4 (21.1)
	CNS	4 (33.3)	CVS condition	1 (5.3)
	Haematological conditions	3 (25.0)	Congenital abnormalities	1 (5.3)
	Not recorded	2 (16.6)	Hematology and oncology	10 (52.6)
			Ear, nose, throat	1 (5.3)
			Not recorded	2 (10.5)

GIT = gastrointestinal, CNS = central nervous system; CVS = cardiovascular system.

significant difference between maternal and neonatal antibody titers in vaccinated mothers compared with previously infected mothers who had recently recovered.

Strengths

As far as we are aware, this is the first prevalence study of SARS-CoV-2 infection in children in SA. All studies published on COVID-19 in children include all children with known SARS-

CoV-2 infection, and they all report on symptoms and outcome. The current study, however, included all admissions regardless of SARS-CoV-2 infection status. None of the children included had a known COVID-19 status.

Limitations

Our study included all children admitted to a hospital ward between 0 and 12 years old. Our results showed the highest SARS-CoV-2

Table 3. Confidence intervals

Age (months)	Confidence interval
0 - 144	1.19 - 1.35
COVID-19 test	1.47 - 1.58
SARS-CoV-2 infection history	1.09 - 1.17
Vaccination history	1.33 - 1.44
<1	
COVID-19 test	1.44 - 1.56
SARS-CoV-2 infection history	1.08 - 1.16
Vaccination history	1.33 - 1.45
1 - 12	
COVID-19 test	1.46 - 1.87
SARS-CoV-2 infection history	0.98 - 1.27
Vaccination history	1.13 - 1.54
13 - 60	
COVID-19 test	1.31 - 1.92
SARS-CoV-2 infection history	0.92 - 1.38
Vaccination history	1.07 - 1.69
61 - 144	
COVID-19 test	1.35 - 1.97
SARS-CoV-2 infection history	0.96 - 1.54
Vaccination history	1.08 - 1.74

infection rate in the <1 month population, which is often under-reported. However, the mothers of the neonates were not tested for SARS-CoV-2 infection on admission. Therefore, the study cannot confirm whether the antibodies detected were due to vertical transmission. Furthermore, COVID-19 vaccination status was obtained verbally, and the timing of the vaccination was not recorded. Feeding practices, such as breastfeeding, were not recorded. The results may be under-reported because the study only included inpatients, and the majority of the children were neonates. This may also introduce some bias. There is no evidence that the reasons for admission were related to COVID-19.

Conclusion

A substantial number of hospitalised children were infected with SARS-CoV-2. All infected children did not have COVID-19-specific symptoms and were admitted for conditions entirely unrelated to COVID-19. This may be due to the Omicron variant, which is highly infectious, less virulent and associated with mild disease. Noting the high infection rates in the study, vaccination of all children for COVID-19 is recommended, as vaccinating parents alone does not protect the children from infection.

Data availability. The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available owing to ethical restrictions.

Declaration. None.

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Author contributions. OPK: conceptualisation, investigations, data collection, writing and editing. BP: results interpretation, writing and editing.

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Conflicts of interest. None.

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