

Long COVID prevalence, risk factors and impact of vaccination in the paediatric population: A survey study in Singapore

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ABSTRACT

Introduction: Information on the quality of health of children and younger persons (CYPs) after SARS-CoV-2 infection remains scarce, especially from Asia. In this study, we utilised an online survey to investigate Long COVID prevalence in CYPs in Singapore.

Method: The study was an anonymised online survey of physical and functional symptoms, made available from 14 October 2022 to 15 January 2023. Caregivers of CYPs aged 0 to 18 years were invited to complete the survey on behalf of their CYPs. Participants provided demographic information and their history of SARS-CoV-2 infection status to allow classification into cases and controls for analysis.

Results: A total of 640 completed responses were analysed, 471 (73.6%) were cases and 169 (26.4%) were controls. The prevalence of Long COVID ≥ 3 months post-infection was 16.8%. This decreased to 8.7% ≥ 6 months post-infection. Cases had higher odds of developing Long COVID (odds ratio [OR] 2.42, 95% confidence interval [CI] 1.31–4.74). The most common symptoms of Long COVID were persistent cough (7.4%), nasal congestion (7.6%) and fatigue (3.0%). Male gender was significantly associated with higher odds of Long COVID (adjusted OR 1.71 [1.04–2.83]). Vaccinated CYPs had lower odds of Long COVID but this was not statically significant (adjusted OR 0.65, 95% CI 0.34–1.25).

Conclusion: About 1 in 6 CYPs in Singapore developed Long COVID with persistence of 1 or more symptoms ≥ 3 months post-infection, and approximately half will recover by 6 months. Male gender was associated with higher odds of Long COVID, and vaccination could potentially be protective against Long COVID in CYPs.

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CLINICAL IMPACT

What is New

- The prevalence of Long COVID was 16.8% at 3 months in children with SARS-CoV-2 infection in multi-ethnic Singapore. This dropped to 8.7% at 6 months post-infection.
- Persistent cough, nasal congestion and fatigue were the most common symptoms.
- Male gender was predictive of Long COVID.

Clinical Implications

- Children with COVID-19 infection have more than twice the odds of developing persistent symptoms compared to children without previous COVID-19 infection.
- It is important to screen for persistent symptoms in children who have COVID-19 infection.

INTRODUCTION

On 5 May 2023, more than 3 years since the start of the COVID-19 pandemic, the World Health Organization (WHO) declared that COVID-19 no longer constituted a public health emergency.

Despite high numbers of children and younger persons (CYPs) having acute COVID-19,¹ information on the quality of health and well-being of CYPs after SARS-CoV-2 infection remains scarce, especially from Asia. Of interest is the phenomenon of Long COVID or postacute sequelae of COVID-19 (PASC), a heterogeneous, multisystemic condition, for which there are various definitions. In October 2021, WHO proposed a clinical definition for Long COVID in adults, stating that it generally occurs within 3 months from the onset of COVID-19, with symptoms lasting at least 2 months which cannot be explained by alternative diagnosis.² A research definition of Long COVID in CYPs was developed by Delphi consensus process, stating that Long COVID occurs in CYPs with a history of confirmed SARS-CoV-2 infection, with 1 or more persistent physical symptoms for a minimum duration of 12 weeks with an impact on everyday functioning.³

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Singapore is an island city-state in Southeast Asia with a resident population of 4.1 million as of 2022, and a CYP population below 20 years of 788,573 (19.4%).⁴ After its first case of COVID-19 on 23 January 2020,⁵ Singapore adopted a stringent COVID-19 testing, isolation and control strategy. A nationwide lockdown, termed as circuit breaker, was implemented from 7 April 2020 to 1 June 2020, during which all schools were closed as students shifted to home-based learning. Up until April 2022,^{6,7} close contacts of individuals with COVID-19 had to observe legally enforced stay-at-home restrictions with daily antigen rapid tests (ARTs), also known as health risk warning. Both polymerase chain reaction (PCR) (health facilities only) and ART testing were widely used for the diagnosis of COVID-19 over the course of the pandemic. ART kits were distributed widely to households in Singapore with self-testing recommended for anyone with symptoms of acute respiratory infections. All positive tests were required by law to be notified to the Ministry of Health.

Singapore experienced several waves of SARS-CoV-2 infections, driven by the delta variant (B.1.6172) from September 2021 to December 2021, followed by a larger wave from January 2022 to April 2022, driven by the omicron BA.1/BA.2 variant.⁸ Subsequent Omicron waves of BA.4/BA.5 and XBB followed. The pandemic vaccination programme for CYPs started in May 2021, with the introduction of mRNA COVID-19 vaccines for those aged 12–17 years. This was followed by a roll-out of mRNA vaccines to children aged 5–11 years in December 2021. In January 2022, a third mRNA vaccine dose (BNT162b2) as booster was recommended for children aged 12–17 years who had completed their second dose more than 5 months previously.⁹ Finally, in October 2022, COVID-19 vaccination was implemented for those aged 6 months to 4 years.

In this study, we utilised an online survey to collect data on the prevalence of Long COVID in CYPs in Singapore. We investigated factors associated with the development of Long COVID, including the protective effect of COVID-19 vaccination.

METHOD

Study design, setting and population

The study was an anonymised online survey which was made available from 14 October 2022 to 15 January 2023. Caregivers of CYPs aged 0 to 18 years residing in Singapore were invited via hospital posters and social media advertisements

to complete the online survey on behalf of their CYPs. The survey was based on a modified version of the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Paediatric COVID-19 questionnaire.¹⁰ Information recorded included basic demographic details; type of housing as a proxy for socioeconomic status; type and doses of COVID-19 vaccine received; date and details of prior SARS-CoV-2 infection, including type of diagnostic test (PCR or ART), symptoms and treatment. Clinical information regarding 28 physical and functional symptoms were recorded (present or absent, duration and severity assessed on a 5-category Likert scale). Caregivers of all CYPs, regardless of prior SARS-CoV-2 infection, were assessed using the same measures. Controls (SARS-CoV-2 negative CYPs) were asked specifically to complete survey questions based on their status during the 3 months prior to date of survey completion.

Case, control, vaccination and Long COVID definitions

Cases were defined as CYPs who reported confirmed SARS-CoV-2 infection via ART or PCR. Controls were individuals who reported not ever having a positive ART or PCR test from the start of the pandemic until the point of survey completion. CYPs were considered vaccinated if they had received 2 doses of COVID-19 vaccine 2 weeks prior to COVID-19 infection. For our main outcome analysis, we used the research definition of Long COVID in CYPs based on Stephenson et al.,³ i.e. a history of confirmed SARS-CoV-2 infection, with 1 or more persistent physical symptoms for a minimum duration of 3 months with an impact on everyday functioning.

Statistical methods and analysis

Univariable and multivariable analyses were performed to compare the prevalence of persistent symptoms in cases compared to controls. Factors included in the multivariable analysis were age, gender, ethnicity, type of residence (as a proxy for socioeconomic status), presence of comorbidities, and prior SARS-CoV-2 infection. Multivariable logistic regression was performed to assess the association between specific factors and the development of Long COVID in CYP with prior SARS-CoV-2 infection. Potential factors included in the model were predetermined before analysis from existing literature.^{11–13} They included prior SARS-CoV-2 infection, vaccination status prior to infection, gender, age, ethnicity, type of symptoms, number of symptoms and hospitalisation during

acute SARS-CoV-2 infection. We stratified the analyses into 2 age groups to reflect key educational stages (0–6 years and 7–18 years).

Pearson chi-square or Fisher exact tests were used to evaluate for differences between 2 categorical variables, Wilcoxon rank-sum test was used to determine if there was a difference between the medians of 2 groups. A *P* value of less than 0.05 was taken to be statistically significant. SPSS Statistics for Windows version 17.0 (SPSS Inc, Chicago, IL, US) was used.

Ethics approval

The above study was approved by the institutional review board (CIRB 2022/2296). Requirement for informed consent was waived in view of the anonymised nature of the survey.

Demographics and SARS-CoV-2 status

A total of 643 responses were recorded from 14 October 2022 to 15 January 2023. Of these, 3 caregivers had incomplete information about their child's prior SARS-CoV-2 infection and were excluded from further analysis. Of the 640 CYPs, the median age was 6 years (interquartile range

[IQR] 3–10 years). Chinese ethnicity made up 455 (71.1%) of total respondents, followed by Malays (n=82, 12.8%), Indians (n=53, 8.3%) and others, including Eurasians and those of mixed ethnicity (n=50, 7.8%). Four hundred and thirty-four (67.8%) of CYPs reside in government-subsidised housing, and the mean number of household members was 4.5 (1–12). Seventy-four (11.6%) CYPs had physician-diagnosed medical conditions (comorbidities); the 3 most common preexisting comorbidities were allergic rhinitis (n=16, 2.5%), eczema (n=16, 2.5%) and asthma (n=10, 1.6%). The demographic details of cases and controls did not differ significantly as shown in Table 1.

The study was made up of 471 (73.6%) cases, of whom 370 (78.6%) were confirmed by ART alone, 21 (4.5%) by PCR alone, and 80 (17.0%) by a combination of ART and PCR. Four hundred and thirty-six (92.6%) had 1 prior SARS-CoV-2 infection, 26 (5.5%) had 2 prior infections, and 9 (1.8%) had 3 or more previous infections. Most of the cases (96.8%) were infected from January 2022 during the first Omicron wave (BA.1/2/4/5 and XBB). The median number of symptoms experienced by cases during acute SARS-CoV-2 infection was 3

Table 1. Demographics of survey respondents.

	With previous SARS-CoV-2 infection n=471 (%)	Without previous SARS-CoV-2 infection n=169 (%)	<i>P</i> value
Age (median years, IQR)	6.0 (3.0–10.0)	5.7 (2.0–10.2)	0.08
Male	253 (53.7)	90 (53.3)	0.92
Ethnicity			0.60
Chinese	332 (70.5)	123 (72.8)	
Malay	58 (12.3)	24 (14.2)	
Indian	41 (8.7)	12 (7.1)	
Others	40 (8.5)	10 (5.9)	
Reside in government-subsidised housing	315 (66.9)	119 (70.4)	0.40
Number of household members (median, IQR)	4.0 (3.0–5.0)	4.0 (3.0–5.0)	0.52
School level			0.06
Preschool	218 (46.3)	70 (41.4)	
Primary school	140 (29.7)	48 (28.4)	
Secondary school	58 (12.3)	19 (11.2)	
Tertiary institution	18 (3.8)	7 (4.1)	
Home school	0 (0.0)	2 (1.2)	
Does not regularly attend school	37 (7.9)	23 (13.6)	
Any comorbidity	61 (13.0)	13 (7.7)	0.07
Received 1 or more dose of COVID-19 vaccine	228 (48.5)	80 (47.3)	0.81
mRNA COVID-19 vaccine	220 (46.7)	78 (46.2)	0.22
Sinovac vaccine	2 (0.4)	2 (1.2)	
Received 2 or more doses of COVID-19 vaccine	205 (43.5)	76 (45.0)	0.75
Received an influenza vaccine in past 1 year	147 (31.2)	59 (34.9)	0.38

IQR: interquartile range

(IQR 2–4), with fever ($n=373$, 79.2%), cough ($n=256$, 54.5%), rhinorrhoea ($n=249$, 52.9%), sore throat ($n=209$, 44.4%) and fatigue ($n=154$, 32.7%) as the most common symptoms. Twenty-two (4.7%) of cases had asymptomatic infection. Eighteen (3.8%) of cases required hospitalisation for acute SARS-CoV-2 infection, 2 (0.4%) required oxygen supplementation, and 2 (0.4%) required intensive care.

Prevalence and clinical manifestation of Long COVID

The prevalence of at least 1 persistent symptom lasting beyond 3 months (Long COVID) in cases was 16.8% (Table 2). Compared to controls, cases had higher odds of developing Long COVID (OR 2.42, 95% CI 1.31–4.74). These odds remained significant after multivariable adjustment (OR 2.43, 95% CI 1.31–4.51). The most common persistent symptoms experienced by CYPs with Long COVID were persistent cough (7.4%), nasal congestion or runny nose (7.6%), and fatigue (3.0%). Persistent cough and nasal congestion or runny nose were significantly more likely in cases compared to controls (OR 2.76, 95% CI 1.06–7.18; OR 3.39, 95% CI 1.18–9.76, respectively) (Table 2). Higher rates of difficulty breathing, palpitations, dizziness or light headedness, insomnia, hypersomnia, loss of concentration, memory problems, fatigue or tiredness and skin rash were also reported by CYPs with COVID-19 after 3 months, but these were not significantly different statistically from controls (Table 2).

The overall odds of cases reporting at least 1 symptom as severe or very severe were higher in cases than controls but this was not statistically significant (OR 1.49, 95% CI 0.70–3.17) (Table 2). Long COVID symptoms with higher point estimate odds of being reported as being severe or very severe included nasal congestion (OR 3.69, 95% CI 0.46–29.43), persistent cough (OR 6.21, 95% CI 0.81–47.59), prolonged school absence beyond 2 and 4 weeks (OR 1.25, 95% CI 0.67–2.32 and OR 1.08, 95% CI 0.44–2.63, respectively) (Table 2).

Prevalence of Long COVID symptoms up to 6 months post-infection

Fig. 1(a) shows the reported prevalence of Long COVID symptoms (1, 2 and 3 symptoms) at 3, 4 and 6 months post-infection. There was a consistent downward trend of CYPs with Long COVID from 3 to 6 months regardless of the number of persistent symptoms. Prevalence of CYPs with Long COVID due to 1 persistent symptom had decreased progressively from 16.8% to 8.7%. The proportion of cases at 6 months post-infection who still reported at least 1, 2 and 3 symptoms

were 8.7%, 3.8% and 1.3%, respectively. The proportion of cases at 3 months and 6 months post-infection who had reported persistent cough decreased progressively from 7.4% to 2.1%, and those who had reported fatigue also decreased from 3.0% to 1.1% (Fig. 1(b)). Of 474 CYPs with prior COVID-19 infection, 64 (13.5%) reported that they have not fully recovered from COVID-19.

Predictive factors for Long COVID

Table 3 summarises the analysis of the relationships between specific factors and development of Long COVID in CYPs. Male gender was significantly associated with higher odds of Long COVID in cases in univariate analysis and remained so after adjustments in multivariate analysis (OR 1.71, 95% CI 1.04–2.83 and OR 1.69, 95% CI 1.01–2.81, respectively). All other factors, including age, ethnicity, housing type, any comorbidity, number of symptoms during acute infection and COVID-19 hospitalisation, were not found to be significantly associated with Long COVID for CYPs in our study. Although not statistically significant, cases who were vaccinated had lower odds of Long COVID (adjusted OR 0.65, 95% CI 0.34–1.25) compared to cases who were unvaccinated, and cases of older age had higher odds of Long COVID compared to those of younger age (adjusted OR 1.78, 95% CI 0.94–3.37).

DISCUSSION

To our knowledge, this is the first study from Asia documenting Long COVID in CYPs. CYPs with COVID-19 infection in a multi-ethnic paediatric population in Singapore had a more than 2-fold increase in the odds of developing Long COVID. The prevalence of Long COVID was 16.8% at 3 months but this dropped to 8.7% at 6 months post-infection. Persistent cough, nasal congestion or runny nose, and fatigue were the most common symptoms reported in CYPs with Long COVID. After adjusting for potential confounders, male gender was found to be predictive of developing Long COVID in CYPs. Vaccinated CYPs were less likely to progress to Long COVID but the difference was not statistically significant.

The reported prevalence of Long COVID in CYPs ranges widely from 2% to 67%^{11,14,15} due to differences in Long COVID definitions and study methodologies. Our reported rate of 16.8% is lower than studies of persistent symptoms in CYPs 3 months post SARS-CoV-2 infection which have reported prevalence of 23–67%.^{13,15} Due to the widespread availability and recommended use of ART kits in Singapore,¹⁶ the infection status of our survey population was highly verified. Almost all CYPs with prior SARS-CoV-2 infection in our study

Table 2. Comparative analysis of Long COVID and persistent symptoms in children and younger persons (CYPs) with and without prior SARS-CoV-2 infection.

Physical symptom	CYP with prior SARS-CoV-2 infection n=471 (%)	CYP without prior SARS-CoV-2 infection n=169 (%)	Univariable analysis		Multivariable* analysis	
			P value	OR (95% CI)	P value	OR (95% CI)
Presence of at least 1 symptom lasting ≥3 months	79 (16.8)	13 (7.7)	0.004	2.42 (1.31–4.74)	0.005	2.43 (1.31–4.51)
Presence of at least 1 symptom reported as severe/very severe	37 (7.9)	9 (5.3)	0.28	1.52 (0.72–3.21)	0.30	1.49 (0.70–3.17)
Nasal congestion	112 (23.8)	64 (37.9)	<0.001	0.51 (0.35–0.75)	0.001	0.51 (0.35–0.75)
≥3 months	36 (7.5)	5 (3.0)	0.03	2.71 (1.05–7.04)	0.04	2.76 (1.06–7.18)
Severe/very severe	11 (2.3)	1 (0.6)	0.20	4.01 (0.52–31.36)	0.22	3.69 (0.46–29.43)
Disturbed/loss of smell	7 (1.5)	0 (0.0)	0.20	NA	1.00	NA
≥3 months	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Disturbed/loss of taste	8 (1.7)	1 (0.6)	0.46	2.90 (0.36–23.38)	0.33	2.83 (0.35–22.90)
≥3 months	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Difficulty breathing	25 (5.3)	9 (5.3)	0.99	1.00 (0.46–2.18)	1.00	0.99 (0.45–2.20)
≥3 months	9 (1.9)	1 (0.6)	0.47	3.27 (0.41–26.03)	0.25	3.36 (0.42–28.87)
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.81	0.73 (0.06–8.83)
Chest tightness	8 (1.7)	0 (0.0)	0.12	NA	1.00	NA
≥3 months	4 (0.8)	0 (0.0)	0.58	NA	1.00	NA
Severe/very severe	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Chest pain	3 (0.6)	0 (0.0)	0.57	NA	1.00	NA
≥3 months	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Palpitations	11 (2.3)	2 (1.2)	0.53	2.00 (0.44–9.10)	0.49	1.73 (0.37–8.00)
≥3 months	6 (1.3)	1 (0.6)	0.68	2.17 (0.26–18.14)	0.60	1.77 (0.21–15.27)
Severe/very severe	3 (0.6)	0 (0.0)	0.57	NA	1.00	NA
Persistent cough	96 (20.4)	32 (18.9)	0.74	1.10 (0.70–1.71)	0.57	1.14 (0.72–1.81)
≥3 months	35 (7.4)	4 (2.4)	0.02	3.31 (1.16–9.46)	0.23	3.39 (1.18–9.76)
Severe/very severe	16 (3.4)	1 (0.6)	0.05	5.91 (0.78–44.89)	0.08	6.21 (0.81–47.59)
Headache	15 (3.2)	3 (1.8)	0.43	1.82 (0.52–6.37)	0.36	1.81 (0.51–6.43)
≥3 months	7 (1.5)	0 (0.0)	0.20	NA	1.00	NA
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.75	0.67 (0.06–7.78)
Dizziness or light-headedness	13 (2.8)	4 (2.4)	1.00	1.17 (0.38–3.64)	0.91	0.94 (0.29–3.03)
≥3 months	7 (1.5)	1 (0.6)	0.69	2.53 (0.31–20.75)	0.45	2.26 (0.27–19.16)
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Blurred vision or problems seeing	1 (0.2)	1 (0.6)	0.46	0.36 (0.02–5.75)	0.39	0.26 (0.01–5.51)

Table 2. Comparative analysis of Long COVID and persistent symptoms in children and younger persons (CYPs) with and without prior SARS-CoV-2 infection. (Cont'd)

Physical symptom	CYP with prior SARS-CoV-2 infection n=471 (%)	CYP without prior SARS-CoV-2 infection n=169 (%)	Univariable analysis		Multivariable* analysis	
			P value	OR (95% CI)	P value	OR (95% CI)
≥3 months	0 (0.0)	1 (0.6)	0.26	NA	0.99	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Problems with balance	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.66	0.57 (0.05–6.77)
≥3 months	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Joint pain or swelling	7 (1.5)	0 (0.0)	0.20	NA	1.00	NA
≥3 months	3 (0.6)	0 (0.0)	0.57	NA	1.00	NA
Severe/very severe	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Muscle pain or ache	16 (3.4)	2 (1.2)	0.18	2.94 (0.67–12.91)	0.15	3.00 (0.67–13.35)
≥3 months	5 (1.1)	0 (0.0)	0.33	NA	1.00	NA
Severe/very severe	3 (0.6)	0 (0.0)	0.57	1.36 (1.30–1.43)	1.00	NA
Tingling feeling “pins and needles”	5 (1.1)	0 (0.0)	0.33	NA	1.00	NA
≥3 months	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Insomnia	11 (2.3)	6 (3.6)	0.40	0.65 (0.24–1.79)	0.46	0.68 (0.24–1.90)
≥3 months	4 (0.8)	1 (0.6)	1.00	1.44 (0.16–13.00)	0.73	1.50 (0.15–14.73)
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Hypersomnia	5 (1.1)	1 (0.6)	1.00	1.80 (0.21–15.54)	0.64	1.69 (0.19–15.12)
≥3 months	4 (0.8)	1 (0.6)	1.00	1.44 (0.16–13.00)	0.79	1.35 (0.15–12.34)
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Fainting or black outs	2 (0.4)	2 (1.2)	0.29	0.36 (0.05–2.55)	0.18	0.25 (0.03–1.91)
≥3 months	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Severe/very severe	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Loss of concentration	11 (2.3)	1 (0.6)	0.20	4.02 (0.52–31.36)	0.26	3.31 (0.41–26.50)
≥3 months	6 (1.3)	1 (0.6)	0.68	2.17 (0.26–18.14)	0.53	2.00 (0.24–16.94)
Severe/very severe	0 (0.0)	1 (0.6)	0.26	NA	0.99	NA
Memory problems	11 (2.3)	2 (1.2)	0.53	2.00 (0.44–9.10)	0.66	1.43 (0.30–6.91)
≥3 months	7 (1.5)	1 (0.6)	0.69	2.53 (0.31–20.75)	0.53	1.99 (0.23–17.04)
Severe/very severe	1 (0.2)	2 (1.2)	0.17	0.18 (0.02–1.97)	0.07	0.07 (0.004–1.28)
Problems with finding right words when speaking	9 (1.9)	1 (0.6)	0.47	3.27 (0.41–26.03)	0.33	2.81 (0.35–22.79)
≥3 months	6 (1.3)	0 (0.0)	0.35	NA	1.00	NA
Severe/very severe	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Fatigue or tiredness	36 (7.6)	11 (6.5)	0.72	1.19 (0.59–2.39)	0.73	1.13 (0.56–2.30)

Table 2. Comparative analysis of Long COVID and persistent symptoms in children and younger persons (CYPs) with and without prior SARS-CoV-2 infection. (Cont'd)

Physical symptom	CYP with prior SARS-CoV-2 infection n=471 (%)	CYP without prior SARS-CoV-2 infection n=169 (%)	Univariable analysis		Multivariable* analysis	
			P value	OR (95% CI)	P value	OR (95% CI)
≥3 months	14 (3.0)	3 (1.8)	0.58	1.70 (0.48–5.97)	0.50	1.56 (0.43–5.60)
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.32	0.24 (0.01–4.07)
Poor appetite	32 (6.8)	15 (8.9)	0.39	0.75 (0.40–1.42)	0.36	0.74 (0.39–1.41)
≥3 months	9 (1.9)	0 (0.0)	0.12	NA	1.00	NA
Severe/very severe	4 (0.8)	3 (1.8)	0.39	0.48 (0.11–2.14)	0.37	0.50 (0.11–2.30)
Diarrhea	11 (2.3)	12 (7.1)	0.004	0.31 (0.14–0.72)	0.005	0.29 (0.12–0.68)
≥3 months	0 (0.0)	0 (0.0)	NA	NA	NA	NA
Severe/very severe	0 (0.0)	2 (1.2)	0.07	NA	0.99	NA
Stomach or abdominal pain	12 (2.5)	5 (3.0)	0.78	0.86 (0.30–2.47)	0.65	0.78 (0.27–2.28)
≥3 months	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.68	0.59 (0.05–6.93)
Severe/very severe	1 (0.2)	0 (0.0)	1.00	NA	1.00	NA
Feeling nauseous or persistent vomiting	9 (1.9)	4 (2.4)	0.75	0.80 (0.24–2.64)	0.48	0.64 (0.19–2.18)
≥3 months	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.63	0.53 (0.04–6.85)
Severe/very severe	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Constipation	7 (1.5)	7 (4.1)	0.04	0.35 (0.12–1.01)	0.08	0.37 (0.13–1.10)
≥3 months	1 (0.2)	3 (1.8)	0.06	0.12 (0.01–1.14)	0.042	0.09 (0.01–0.91)
Severe/very severe	2 (0.4)	1 (0.6)	1.00	0.72 (0.07–7.95)	0.82	0.76 (0.06–8.90)
Skin rash	12 (2.5)	11 (6.50)	0.02	0.38 (0.15–0.87)	0.02	0.35 (0.15–0.83)
≥3 months	5 (1.1)	1 (0.6)	1.00	1.80 (0.21–15.54)	0.63	1.69 (0.19–14.76)
Severe/very severe	2 (0.4)	0 (0.0)	1.00	NA	1.00	NA
Missed school due to persistent symptoms	106 (22.5)	59 (34.9)	0.002	0.54 (0.34–0.79)	0.002	0.55 (0.37–0.81)
Missed school ≥2 weeks	48 (10.2)	15 (8.9)	0.62	1.17 (0.53–2.14)	0.49	1.25 (0.67–2.32)
Missed school ≥2 weeks	20 (4.2)	7 (4.1)	0.95	1.03 (0.43–2.47)	0.87	1.08 (0.44–2.63)

CI: confidence interval; CYP: children and younger person; NA: not applicable; OR: odds ratio

≥ more than or equal

*Adjusted for age (0–6 years or 7–18 years), gender, ethnicity (Chinese or non-Chinese), housing type (government-subsidised or non-subsidised housing), presence of comorbidities, and prior SARS-CoV-2 infection

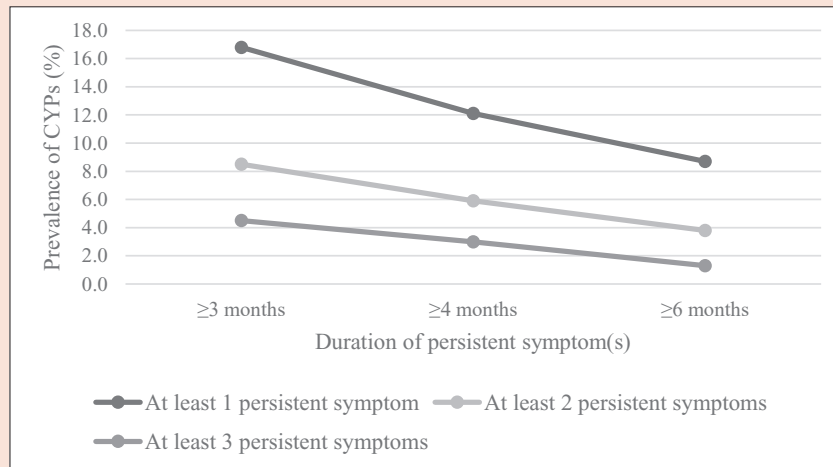
Bold numbers indicate statistical significance.

cohort had infection during the period of omicron variant dominance, and vast majority experienced mild or asymptomatic COVID-19 infection, with only 3.8% reporting hospitalisation for acute infection. This is representative of the disease course of acute COVID-19 infection in children.¹⁷

Persistent cough, nasal congestion or runny nose, and fatigue were the most common symptoms reported in CYPs with Long COVID in our cohort.

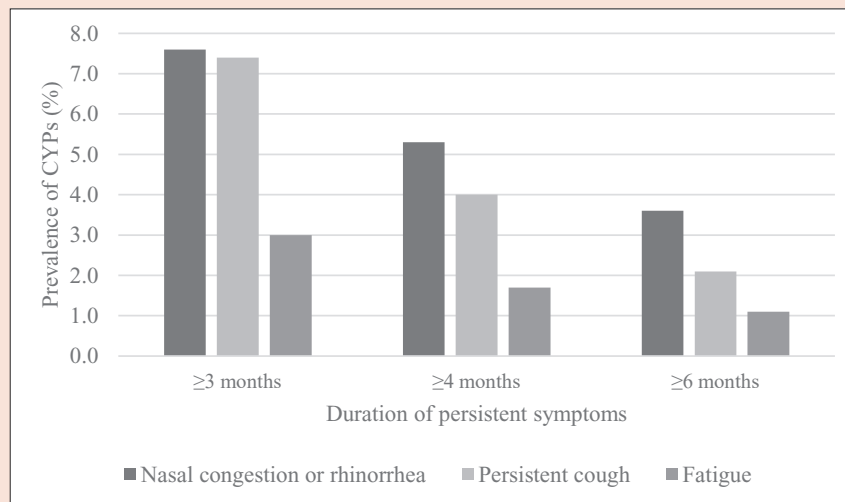
Our rates were similar to published studies where the proportion of Long COVID with persistent cough and nasal congestion or rhinorrhoea were 7.0%¹⁸ and 7.5%,¹¹ respectively. Loss of taste and smell were common symptoms (6–29%) of Long COVID in earlier studies involving CYP with infections during the period of delta variant dominance.^{11,19,20} Only 1 case (0.2%) each was reported in our study and this is in-keeping with

Fig. 1(a). Prevalence of persistent symptoms beyond 3, 4 and 6 months in children and younger persons (CYPs) with prior SARS-CoV-2 infection.



CYPs: children and younger persons

Fig. 1(b). Prevalence of common symptoms persistent beyond 3, 4 and 6 months in children and younger persons (CYPs) with prior SARS-CoV-2 infection.



CYPs: children and younger persons

the different symptomatology of infections caused by different SARS-CoV-2 variants.^{21,22}

Meta-analysis of Long COVID studies involving CYPs have also reported high prevalence of sleep disorders, cognitive difficulties and headaches.^{11,20} In our study, prevalence of persistent insomnia, hypersomnia, headache, loss of concentration and memory problems were higher in CYPs with COVID-19 after 3 months but these were not statistically significant compared to controls, possibly due to our smaller study sample size. Fatigue has been reported to affect 21–76% of CYPs with Long COVID,^{14,18,19,23,24} higher than CYPs

of our cohort (3%). These differences may be explained in part by differing study populations and social restrictions in place in various countries during the COVID-19 pandemic, and different tools used to measure cognitive and functional changes used in different studies. Nevertheless, cognitive and functional difficulties in CYPs should be further explored in future studies.

Notably, both cases and controls reported prevalence of various symptoms surveyed in this study which persisted beyond 3 months, including fatigue, headache, insomnia and poor appetite. This is similar to observations in Long COVID

Table 3. Analysis of factors associated with Long COVID in children and younger persons (CYPs) with prior SARS-CoV-2 infection.

Factor	At least 1 symptom persistent beyond 3 months			
	Univariable analysis		Multivariable analysis*	
	P value	OR (95% CI)	P value	OR (95% CI)
Gender				
Female		1.00		1.00
Male	0.03	1.71 (1.04–2.83)	0.04	1.69 (1.01–2.81)
Age				
Younger age (0–6 years)		1.00		1.00
Older age (7–18 years)	0.25	1.32 (0.82–2.15)	0.08	1.78 (0.94–3.37)
Ethnicity				
Chinese		1.00		1.00
Non-Chinese	0.47	1.21 (0.72–2.03)	0.73	1.10 (0.65–1.87)
Housing type				
Government-subsidised residence		1.00		1.00
Private residence	0.41	0.80 (0.47–1.36)	0.35	0.77 (0.44–1.36)
Presence of any preexisting comorbidity				
No comorbidity		1.00		1.00
Any comorbidity	0.24	0.61 (0.27–1.39)	0.21	0.58 (0.25–1.35)
Vaccination status				
Unvaccinated		1.00		1.00
Vaccinated [#]	0.67	0.89 (0.54–1.49)	0.20	0.65 (0.34–1.25)
Number of symptoms during acute SARS-CoV-2 infection				
Less than 4 symptoms		1.00		1.00
4 or more symptoms	0.07	1.56 (0.96–2.55)	0.11	1.51 (0.91–2.51)
Hospitalisation for acute SARS-CoV-2 infection				
No hospitalisation		1.00		1.00
Hospitalisation	0.53	1.44 (0.46–4.50)	0.37	1.71 (0.53–5.54)

CI: confidence interval; OR: odds ratio

[#]Vaccinated: receipt of 2 COVID-19 vaccine doses at least 2 weeks prior to SARS-CoV-2 infection

*Adjusted for age (0–6 years or 7–18 years), gender, ethnicity (Chinese or non-Chinese), housing type (government-subsidised or non-subsidised housing), presence of comorbidities, vaccination status, number of symptoms during acute SARS-CoV-2 infection (<4 symptoms or ≥4 symptoms), and hospitalisation for acute SARS-CoV-2 infection.

Bold numbers indicate statistical significance.

studies involving both adult^{25,26} and paediatric populations,^{15,19,27} suggesting that symptoms are unlikely to be exclusive due to the specific consequence of SARS-CoV-2 infection. The pandemic and control measures used to limit its spread, such as school closures, social isolation and home-based learning, would have had a significant

impact on the well-being of CYPs. It is clear that many CYPs experienced a range of physical and functional changes during the COVID-19 pandemic that warrant further investigation and intervention.

After adjusting for potential confounders, male gender was found to be predictive of developing

Long COVID in CYPs in our study. Studies in paediatric populations have contrasting results with regard to the association of gender and risk of Long COVID.^{13,15,28,29} More studies in CYPs are needed to confirm the association between gender and Long COVID.

Studies in adults have shown a protective effect of vaccination against Long COVID.³⁰ Our study found that CYPs who were vaccinated were less likely to have Long COVID in both univariable analysis (crude OR 0.89, 95% CI 0.54–1.49) and multivariable analysis after adjustment for potential confounders (adjusted OR 0.65, 95% CI 0.34–1.25). However, the association did not meet statistical significance, similar to a study by Morello et al. which reported reduced risk of Long COVID in vaccinated children (OR 0.60, 95% CI 0.33–1.11).¹² Further studies are required to study the protective effect of 3 or more doses of COVID-19 vaccines on Long COVID in children, as the third dose is introduced to greater numbers of CYPs.

This study has limitations, including the cross-sectional nature of the questionnaire. Data on symptoms and testing were retrospective and hence, prone to recall bias. Persons who had persistent symptoms might also be more likely to respond to the survey. Our use of controls mitigated these factors, but may not have fully eliminated them. As it was an internet-based survey, there could have been selection bias, favouring those with internet access. Self-reported symptoms can also be biased by age since younger children are not able to express their emotional and functional status adequately compared to older children.

It was also possible that infections were missed in controls. However, the strict legally-enforced contact tracing and testing systems in place with easily accessible ART and PCR testing in Singapore reduced the likelihood of such false negative misclassification. Even after the end of legal enforcement in April 2022, ART testing with self-isolation continued to be recommended as a national policy for individuals with symptoms of respiratory tract infection, and implemented in all healthcare settings, educational settings and offices. There was a risk of false-positives tested by ART alone without confirmation with PCR. However, ART kits have been shown to perform well with high sensitivity and specificity for the diagnosis of COVID-19.³¹ We adjusted for known potential confounders of gender, ethnicity, medical history, or type of residence (socioeconomic status), but may have missed unknown confounders.

CONCLUSION

In conclusion, we found that approximately 1 in 6 CYPs in Singapore developed Long COVID with persistence of 1 or more symptoms after 3 months post-infection. Reassuringly, about half will recover by 6 months with prevalence falling to about 1 in 11. Commonly reported Long COVID symptoms included cough, nasal congestion and fatigue. Vaccination could potentially be protective against Long COVID in CYPs, but the findings did not reach statistical significance. More research is needed to identify risk factors for the development of Long COVID in CYPs.

Conflict of interest (including financial disclosure)

The authors have no conflict of interest to disclose.

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REFERENCES

1. United Nations International Children's Emergency Fund. Child mortality and COVID-19, March 2023. <https://data.unicef.org/topic/child-survival/covid-19>. Accessed 29 June 2023.
2. World Health Organization. Post COVID-19 condition (Long COVID), 7 December 2022. <https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition>. Accessed 29 June 2023.
3. Stephenson T, Allin B, Nugawela MD, et al. Long COVID (post-COVID-19 condition) in children: a modified Delphi process. *Arch Dis Child* 2022;107:674-80.
4. Department of Statistics, Singapore. Population and population structure. <https://www.singstat.gov.sg/find-data/search-by-theme/population/population-and-population-structure/latest-data>. Accessed 29 June 2023.
5. The Straits Times. Singapore confirms first case of Wuhan virus; second case likely, 23 January 2020. <https://www.straitstimes.com/singapore/health/singapore-confirms-first-case-of-wuhan-virus>. Accessed 29 June 2023.
6. Ministry of Health, Singapore. Implementation of Stay-Home Notice, 17 February 2020. <https://www.moh.gov.sg/news-highlights/details/implementation-of-new-stay-home-notice>. Accessed 29 June 2023.
7. The Straits Times. Singapore announces major easing of Covid-19 rules from April 26: What you need to know, 22 April 2022. <https://www.straitstimes.com/singapore/singapore-announces-major-easing-of-covid-19-rules-from-april-26-what-you-need-to-know>. Accessed 29 June 2023.
8. Ng OT, Marimuthu K, Lim N, et al. Analysis of COVID-19 Incidence and Severity Among Adults Vaccinated With 2-Dose mRNA COVID-19 or Inactivated SARS-CoV-2 Vaccines With and Without Boosters in Singapore. *JAMA Netw Open* 2022;5:e2228900.

9. Yung CF, Pang D, Kam KQ, et al. BNT162b2 vaccine protection against omicron and effect of previous infection variant and vaccination sequence among children and adolescents in Singapore: a population-based cohort study. *Lancet Child Adolesc Health* 2023;7:463-70.
10. ISARIC. ISARIC Global COVID-19 paediatric follow-up. <https://isaric.org/research/covid-19-clinical-research-resources/paediatric-follow-up>. Accessed 29 June 2023.
11. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. *Sci Rep* 2022;12:9950.
12. Morello R, Mariani F, Mastrantoni L, et al. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. *EClinicalMedicine* 2023;59:101961.
13. Nugawela MD, Stephenson T, Shafran R, et al. Predictive model for long COVID in children 3 months after a SARS-CoV-2 PCR test. *BMC Med* 2022;20:465.
14. Molteni E, Sudre CH, Canas LS, et al. Illness duration and symptom profile in symptomatic UK school-aged children tested for SARS-CoV-2. *Lancet Child Adolesc Health* 2021;5:708-18.
15. Stephenson T, Pinto Pereira SM, Shafran R, et al. Physical and mental health 3 months after SARS-CoV-2 infection (long COVID) among adolescents in England (CLoCK): a national matched cohort study [published correction appears in *Lancet Child Adolesc Health*. 2022 Jul;6:e21]. *Lancet Child Adolesc Health* 2022;6:230-9.
16. gov.sg. Promoting regular self-testing, 7 November 2022. <https://www.gov.sg/article/regular-self-testing-for-all-and-expansion-of-the-booster-vaccination-strategy>. Accessed 29 June 2023.
17. Li B, Zhang S, Zhang R, et al. Epidemiological and Clinical Characteristics of COVID-19 in Children: A Systematic Review and Meta-Analysis. *Front Pediatr* 2020;8:591132.
18. Buonsenso D, Munblit D, Pazukhina E, et al. Post-COVID Condition in Adults and Children Living in the Same Household in Italy: A Prospective Cohort Study Using the ISARIC Global Follow-Up Protocol. *Front Pediatr* 2022;10:834875.
19. Borch L, Holm M, Knudsen M, et al. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. *Eur J Pediatr* 2022;181:1597-607.
20. Behnood SA, Shafran R, Bennett SD, et al. Persistent symptoms following SARS-CoV-2 infection amongst children and young people: A meta-analysis of controlled and uncontrolled studies. *J Infect* 2022;84:158-70.
21. Ekroth AKE, Patrzylas P, Turner C, et al. Comparative symptomatology of infection with SARS-CoV-2 variants Omicron (B.1.1.529) and Delta (B.1.617.2) from routine contact tracing data in England. *Epidemiol Infect* 2022;150:e162.
22. Menni C, Valdes AM, Polidori L, et al. Symptom prevalence, duration, and risk of hospital admission in individuals infected with SARS-CoV-2 during periods of omicron and delta variant dominance: a prospective observational study from the ZOE COVID Study. *Lancet* 2022;399:1618-24.
23. Asadi-Pooya AA, Nemati H, Shahisavandi M, et al. Long COVID in children and adolescents [published correction appears in *World J Pediatr* 2022]. *World J Pediatr* 2021;17:495-9.
24. Say D, Crawford N, McNab S, et al. Post-acute COVID-19 outcomes in children with mild and asymptomatic disease. *Lancet Child Adolesc Health* 2021;5:e22-e23.
25. Taquet M, Dercon Q, Luciano S, et al. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLoS Med* 2021;18:e1003773.
26. Wanga V, Chevinsky JR, Dimitrov LV, et al. Long-Term Symptoms Among Adults Tested for SARS-CoV-2 - United States, January 2020-April 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1235-41.
27. Rao S, Lee GM, Razzaghi H, et al. Clinical Features and Burden of Postacute Sequelae of SARS-CoV-2 Infection in Children and Adolescents. *JAMA Pediatr* 2022;176:1000-9.
28. Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, et al. Long COVID in Children: Observations From a Designated Pediatric Clinic. *Pediatr Infect Dis J* 2021;40:e509-e511.
29. Pazukhina E, Andreeva M, Spiridonova E, et al. Prevalence and risk factors of post-COVID-19 condition in adults and children at 6 and 12 months after hospital discharge: a prospective, cohort study in Moscow (StopCOVID). *BMC Med* 2022;20:244.
30. Gao P, Liu J, Liu M. Effect of COVID-19 Vaccines on Reducing the Risk of Long COVID in the Real World: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2022;19:12422.
31. Kam KQ, Maiwald M, Chong CY, et al. SARS-CoV-2 antigen rapid tests and universal screening for COVID-19 Omicron variant among hospitalized children. *Am J Infect Control* 2023;51:255-60.