BMJ Open

Incidence of SARS-CoV-2 reinfection in a paediatric cohort in Kuwait

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ABSTRACT

Objective Subsequent protection from SARS-CoV-2 infection in paediatrics is not well reported in the literature. We aimed to describe the clinical characteristics and dynamics of SARS-CoV-2 PCR repositivity in children.

Design This is a population-level retrospective cohort study.

Setting Patients were identified through multiple national-level electronic COVID-19 databases that cover all primary, secondary and tertiary centres in Kuwait.

Participants The study included children 12 years and younger between 28 February 2020 and 6 March 2021. SARS-CoV-2 reinfection was defined as having two or more positive SARS-CoV-2 PCR tests done on a respiratory sample, at least 45 days apart. Clinical data were obtained from the Pediatric COVID-19 Registry in Kuwait.

Primary and secondary outcome measures The primary measure is to estimate SARS-CoV-2 PCR repositivity rate. The secondary objective was to establish average duration between first and subsequent SARS-CoV-2 infection. Descriptive statistics were used to present clinical data for each infection episode. Also, incidence-sensitivity analysis was performed to evaluate 60-day and 90-day PCR repositivity intervals.

Results Thirty paediatric patients with COVID-19 had SARS-CoV-2 reinfection at an incidence of 1.02 (95% CI 0.71 to 1.45) infection per 100 000 person-days and a median time to reinfection of 83 (IQR 62–128.75) days. The incidence of reinfection decreased to 0.78 (95% CI 0.52 to 1.17) and 0.47 (95% CI 0.28 to 0.79) per person-day when the minimum interval between PCR repositivity was increased to 60 and 90 days, respectively. The mean age of reinfected subjects was 8.5 (IQR 3.7–10.3) years and the majority (70%) were girls. Most children (55.2%) had asymptomatic reinfection. Fever was the most common presentation in symptomatic patients. One immunocompromised experienced two reinfection episodes.

Conclusion SARS-CoV-2 reinfection is uncommon in children. Previous confirmed COVID-19 in children seems to result in a milder reinfection.

INTRODUCTION

SARS-CoV-2 is a novel beta coronavirus that was first described in December 2019 and resulted in a pandemic of respiratory illness, COVID-19.[1] By early May 2021, the pandemic has resulted in over 150 million

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a national-level electronic database that included all SARS-CoV-2 test results that allowed data collection from variable sources and the detection of asymptomatically infected children.
⇒ The exact risk for SARS-CoV-2 reinfection is difficult to estimate as children are more likely to be asymptomatic; therefore, not all positive cases are detected.
⇒ Factors contributing to reinfection such as the circulating variants and the degree of community SARS- CoV-2 transmission were not addressed in this study.
⇒ Patients' symptoms and severity in this retrospective analysis were dependent on the accuracy of reporting in medical notes and parental recall of symptoms.
⇒ Due to limited genomic sequencing capacity, proving the direct causality between PCR repositivity and a genetically distinct virus was not possible.

cases worldwide and more than 3 million deaths reported by the WHO.[2] Despite the widespread outbreak of COVID-19, children comprised less than 15% of all reported cases.[3–5] Limited social interactions and enhanced infection control measures, such as school closure and online teaching, may have contributed to lower proportions of infected children.[6] In addition, children are more likely to have asymptomatic or mild infection compared with adults and, therefore, may not be tested.[7]

Quantifying the duration of natural immunity after the primary SARS-CoV-2 infection has been crucial to address public health measures, to help predict the continuity of the pandemic and to understand the effect of reinfection on disease severity. The first case of SARS-CoV-2 reinfection was reported in August 2020.[8] Since then, interest in the exact risk and rate of reinfection has been increasing. Several reports estimated that reinfection occurs in less than 1% of previously infected individuals.[9–11] The duration

between primary and secondary infection was reported to vary from 48 to 124 days in the first documented cases in literature.[12 13] However, most of the reinfection studies focused mainly on the adult population. COVID-19 follows different disease dynamics in children, and studies addressing reinfection in this population are lacking or limited.

The first paediatric case of COVID-19 in Kuwait was identified in February 2020.[7] Since then, schools and daycare centres were closed, and classes were conducted virtually. In addition, commercial centres, gyms and restaurants were open but with time restrictions and strict protective measures. Early in the pandemic, a national electronic COVID-19 testing database was created and included all SARS-CoV-2 test results of symptomatic individuals, contact tracing, and routine travel or hospitalisation screening. Also, a national Pediatric COVID-19 Registry (PCR-Q8) was established for children aged 12 years and younger to better understand disease dynamics and update management protocols. This created the unique opportunity to investigate the possibility of reinfection with SARS-CoV-2, with an attempt to establish average duration between the two positive results, potential factors linked to reinfection and its clinical severity.

METHODS

A population-level retrospective cohort study was conducted in Kuwait between 28 February 2020 and 6 March 2021. The national COVID-19 test result database was used to identify children younger than 12 years and had two or more subsequent positive SARS-CoV-2 PCR tests done on a respiratory sample, at least 45 days apart. Subjects who had two or more positive SARS-CoV-2 PCR tests but less than 45 days in between, and patients who fulfilled the WHO definition of the multisystem inflammatory syndrome in children, were excluded.[14]

To assure the inclusion of all SARS-CoV-2-infected children into this study, the national COVID-19 testing database was used for initial patient identification. This database includes the results for all individuals who had SARS-CoV-2 PCR done on a respiratory specimen nationwide. SARS-CoV-2 PCR is typically done to confirm the diagnosis of symptomatic individuals, detect secondary infections in contact tracing, and identify infected subjects prior to hospitalisation or travel. During the study period, the SARS-CoV-2 antigen was not routinely performed on paediatric samples. Also, serum SARS-CoV-2 IgG or IgM tests were not routinely done to confirm current or prior infection. A secondary search query was done on the PCR-Q8, which included patient information from the following sources: hospital records, institutional quarantine centres, patient transport units, as well as all laboratories that provide SARS-CoV-2 PCR.

The PCR-Q8 retrospectively collected detailed individual-level demographic, laboratory and clinical characteristics of all children diagnosed with COVID-19 in Kuwait. The database was acquired to obtain demographic and clinical data. COVID-19 severity was categorised based on WHO disease classification.[15] Infected children with mild or asymptomatic COVID-19 may not require hospitalisation. Therefore, clinical data in the registry may be lacking or limited. For those subjects, parents were contacted to complete missing disease-related data.

Descriptive analysis was performed to compare between primary and secondary infections. To calculate incidence and to account for delayed presentation of reinfection, calculated days at risk included the period from the day of first positive SARS-CoV-2 PCR starting 28 February 2020 to the second positive test or 6 March 2021, whichever is first. However, individuals with the first positive SARS-CoV-2 PCR test starting 1 January 2021 were not included in the calculation due to limited time for reinfection to occur. Clopper-Pearson test was used to calculate the 95% CI. Analysis was done using GraphPad Prism (V.9.0). Due to the variability in established reinfection case definition, sensitivity analysis was used to assess the clinical presentation and incidence of reinfection considering a minimum interval for PCR repositivity of 60 and 90 days.[16]

Patient and public involvement

Patients were not included in the design, reporting or dissemination plans of our research. However, parents of children with PCR repositivity were contacted to complete missing data. This study was conducted to address epidemiological questions presented by the Pediatric COVID-19 Task Force (Ministry of Health, Kuwait). The initial concept and study plan was presented to the committee members, whose suggestions and comments were considered in the final study protocol.

Figure 1 Flow diagram of the study population.

RESULTS

During the study period, there were 14 320 documented SARS-CoV-2 infections in children younger than 12 years in Kuwait, accounting for 2 954 372 person-days of follow-up. Among those, 421 children with repeat positive SARS-CoV-2 PCR tests were identified, of which, 30 patients had a repeat positive SARS-CoV-2 45 days or more after the first positive test; 391 patients had their repeat test within 45 days and were excluded (figure 1). The incidence of reinfection was 1.02 (95% CI 0.71 to
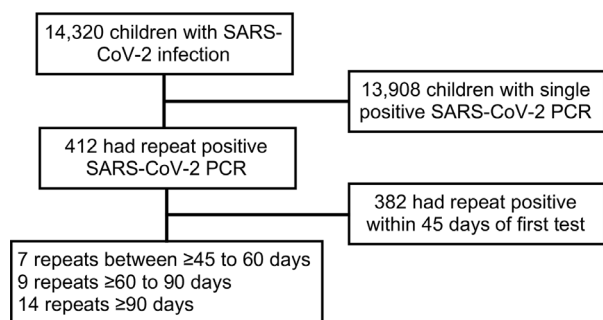
Table 1 Demographic characteristics of the study population

Variable	Population (n=30)
Age (median, IQR)	8.6 years (3.7–10.3)
Male	9 (30%)
Comorbid conditions	
Asthma	2 (6.7%)
Diabetes	1 (3.3%)
Healthy	17 (56.7%)
Neurological disease	3 (10%)
Other	5 (16.7%)
Preterm	1 (3.3%)
Time between 2 episodes	
First positive PCR to reinfection (median, IQR)	83 days (62–128.75)
Symptom onset of first episode to reinfection (median, IQR)	83 days (62.5–130.5)

1.45) infection per 100 000 previously infected person-days. The mean age of the reinfection cohort was 8.5 (IQR 3.7–10.3) years and majority (70%) were girls (table 1). More than half (56.6%) of reinfected patients were not

known to have any chronic comorbid conditions at the time of the first or second infection.

The median time between the two episodes of infection as evident by the sample collection date was 83 (IQR 62–128.75) days (figure 2). Majority of the patients had asymptomatic infection during the first and second episodes, 43.3% and 53.3%, respectively (table 2). In symptomatic patients, fever, cough and shortness of breath were the most commonly reported symptoms. One (3.3%) patient had severe pneumonia during the first infection, whereas four (13.3%) patients had severe pneumonia during the second infection. Of those, three patients had mild or asymptomatic initial SARS-CoV-2 infection. One of the four patients was admitted for acute exacerbation of asthma with a 3-day history of fever. The median length of hospitalisation was 9 (IQR 5.75–13) days and 6 (IQR 3.75–6.75) days for the first and second infections, respectively. None of the subjects received care in an intensive care unit.

One female patient previously diagnosed with hypereosinophilic syndrome on low-dose prednisone had three episodes of SARS-CoV-2 infections. Her first infection was in July 2020 where she was admitted for 10 days as a case of severe pneumonia followed by two negative PCR tests done in August. Her second infection was in November 2020 when she was also admitted for severe pneumonia

Figure 2 Duration between first SARS-CoV-2 infection and subsequent infections. The shaded bars represent the duration between positive PCR results. Patient 6 had two episodes of reinfection.

Table 2 Clinical characteristics of the study population based on different defined intervals of PCR repositivity

	First infection			Second infection		
	Minimum interval of PCR repositivity			Minimum interval of PCR repositivity		
	45 days	60 days	90 days	45 days	60 days	90 days
Variable	(n=30)	(n=23)	(n=14)	(n=29)*	(n=23)	(n=14)
Disease severity						
Asymptomatic	13 (43.3%)	12 (52.2%)	8 (57.1%)	16 (55.2%)	12 (52.2%)	5 (35.7%)
Mild illness	15 (33.3%)	9 (39.1%)	4 (28.6%)	9 (31%)	7 (30.4%)	5 (35.7%)
Mild pneumonia	1 (3.3%)	1 (4.3%)	1 (7.1%)	0	0	0
Severe pneumonia	1 (3.3%)	1 (4.3%)	1 (7.1%)	4 (13.8%)	4 (17.4%)	4 (28.6%)
Reason for testing						
Close contact testing	13 (43.3%)	12 (52.2%)	8 (57.1%)	6 (20.7%)	5 (21.7%)	4 (28.6%)
Hospitalisation screening	5 (16.7%)	4 (17.4%)	3 (21.4%)	7 (24.1%)	6 (26.1%)	5 (35.7%)
Suspected COVID-19	12 (40%)	7 (30.4%)	3 (21.4%)	6 (20.7%)	5 (21.7%)	4 (28.6%)
Travel screening	1 (3.3%)	0	0	10 (34.5%)	7 (30.4%)	1 (7.1%)
Symptoms						
Abdominal pain	2 (4%)	1 (3.1%)	1 (5%)	0	0	0
Cough	4 (8.2%)	4 (12.5%)	3 (15%)	8 (20.5%)	8 (21.6%)	7 (21.9%)
Diarrhoea	2 (4%)	2 (6.3%)	2 (10%)	0	0	0
Fever	16 (32.6%)	11 (34.4%)	6 (30%)	12 (30.8%)	10 (27%)	8 (25%)
Headache	2 (4%)	2 (6.3%)	1 (5%)	1 (2.6%)	1 (2.7%)	1 (3.1%)
Loss of smell	4 (8.2%)	1 (3.1%)	0	1 (2.6%)	1 (2.7%)	1 (3.1%)
Loss of taste	4 (8.2%)	1 (3.1%)	0	1 (2.6%)	1 (2.7%)	1 (3.1%)
Myalgia	4 (8.2%)	3 (9.4%)	3 (15%)	1 (2.6%)	1 (2.7%)	1 (3.1%)
Rhinorrhoea	4 (8.2%)	3 (9.4%)	1 (5%)	8 (20.5%)	8 (21.6%)	7 (21.9%)
Shortness of breath	3 (6.1%)	2 (6.3%)	2 (10%)	3 (7.7%)	3 (8.1%)	3 (9.4%)
Sore throat	3 (6.1%)	2 (6.3%)	1 (5%)	3 (7.7%)	3 (8.1%)	2 (6.3%)
Vomiting	1 (2%)	0	0	1 (2.6%)	1 (2.7%)	1 (3.1%)
Hospitalisation	5 (16.7%)	4 (17.4%)	3 (21.4%)	6 (20.7%)	5 (21.7%)	5 (35.7%)
Length of stay in days (median, IQR)	9 (5.75–13)	9 (7.25–11)	8 (6.5–9)	6 (3–6)	6 (3–6)	6 (3–6)

*Clinical data for one patient is missing.

with prolonged hospital admission followed by a negative PCR test done in December. Interestingly, during her third infection in January 2021, she was asymptomatic and testing was done for screening before an outpatient appointment.

Around half (46.6%) of reinfections occurred more than 90 days after the initial infection. The incidence of reinfection decreased to 0.78 (95% CI 0.52 to 1.17) and 0.47 (95% CI 0.28 to 0.79) per infected person-day when the minimum acceptable duration between PCR repositivity was increased to 60 and 90 days, respectively. Also, there were more symptomatic children (64.3%) during the second infection using the 90-day definition when compared with the 45-day or 60-day minimum interval.

DISCUSSION

The exact risk and factors associated with SARS-CoV-2 reinfection in the paediatric population are still not well understood. We found that a second SARS-CoV-2 infection is uncommon in children with a rate of 1.02 reinfection per 100 000 previously infected person-days and a median time to reinfection of 83 days. The finding of this study is similar to previous reports, which showed a reinfection incidence in adults of 0.9–1.3 per 100 000 person-days.[9 11] Similarly, in a large Danish cohort, prior SARS-CoV-2 provided on average 80.5% protection against repeat infection. The estimated protection differed between different age groups ranging from 47.1% in individuals older than 65 years of age to 82.7% in younger subjects.[17] However, the epidemiology and disease dynamics of SARS-CoV-2 infection are different in children.[18] Therefore, using data generated from adult studies to infer on the paediatric population may not be accurate.

The magnitude and persistence of immunological responses conferred by SARS-CoV-2 infection can be variable based on age and medical comorbidities.[19] Hence, estimating the duration of protective immunity after

acquiring SARS-CoV-2 infection has been the focus of several studies. In an adult study, looking at the neutralising antibodies, the seropositivity was identified in all participants up to 53 days after infection.[20] However, the level of neutralising antibodies varies greatly with disease severity and tends to wane over time.[21 22] Few studies compared humoral responses between adults and children. Weisberg *et al* have shown that children exhibit lower antibody response compared with adults.[23] However, the incidence of reinfections observed in this study was similar to previously reported adult patients.

A standard definition of SARS-CoV-2 reinfection is lacking. Traditionally, the detection of viable virus by cell culture has been the standard to ascertain active infection.[24] However, this testing method lacks sensitivity and is time-consuming.[25] In addition, due to the need for expertise and appropriate laboratory infrastructure, routine population-level testing using cell culture is not possible. For these reasons, the detection of genetically distinct SARS-CoV-2 in different infectious episodes or the use of the cycle threshold value as a surrogate for viral load has been suggested.[12 13] In Kuwait, genomic testing capacity is limited and retrieving patients' samples and laboratory data from several public and private laboratories was logistically challenging. In our study, a 45-day period between two consecutive positive PCR tests was selected based on established definition in previously published studies and the expected duration of molecular test positivity on a respiratory sample.[26–29] Alsharrah *et al* reported median duration of PCR positivity among paediatric patients with COVID-19 of 15 days, with maximum duration of 42 days.[7] However, we observed a decline in the rate of repositivity from 1.02 to 0.47 per 100 000 previously infected person-days when the definition of PCR repositivity increased from 45 to 90 days. As almost half of cases are asymptomatic, this finding could be due to persistent detection of viral particles by PCR.

Asymptomatic SARS-CoV-2 infection is common in paediatrics. We found that around half of infections (43.3% in initial infection and 55.2% in reinfection) remained asymptomatic on follow-up. This finding is similar to other studies.[30] High proportion of silent infection may pose an important public health concern and limit the effectiveness of transmission mitigation efforts. Also, the possibility of reinfection within a relatively short period of time as observed in this study may be an overlooked source of community transmission. Further epidemiological studies are needed to assess the risk of transmission in patients with PCR repositivity within 90 days. Real-world COVID-19 vaccine effectiveness data showed that reinfection is more common in unvaccinated adults.[31] These findings support the recommendation to offer vaccination to those previously infected.

To our knowledge, this is the first national-level cohort that estimates the risk of paediatric SARS-CoV-2 reinfection. Nevertheless, this study has some limitations. Due to limited genomic sequencing capacity, proving that PCR repositivity was caused by a genetically distinct virus was not possible. However, based on the expected duration of PCR persistence in children mentioned above, one will not expect that PCR done on an upper respiratory specimen to remain positive beyond 45 days. Also, the effect of different SARS-CoV-2 variants on the risk of reinfection was difficult to assess. Another limitation was the unavailability of some data recorded in the national PCR-Q8. When data were missing, parents were contacted via the telephone, creating a recall bias. In addition, patients with mild upper respiratory tract symptoms are underreported by parents. Therefore, mild cases are less likely to be tested and can be missed, and underestimate the reinfection rate. However, using the national-level electronic record allowed the collection of data from variable sources and the detection of asymptomatically infected children. Lastly, the exact incidence of reinfection is dependent on several factors that may be difficult to control in cohort studies and may affect data generalisability. These factors include rate of SARS-CoV-2 transmission in the community and pre-existing population immunity. However, the effect of existing immunity is limited in our cohort as it included paediatric patients who were followed from the start of the pandemic. Despite these limitations, this study has shown that reinfection is generally uncommon. Further studies that correlate degree of humoral and cellular immunity, along with wide genomic sequencing surveillance, with risk of reinfection are needed to better understand and quantify the risk of repeat SARS-CoV-2 infection.

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