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Epidemiology of Potential SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

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Epidemiology of Potential SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

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Keywords: Children, SARS-CoV-2, COVID-19, reinfection, epidemiology

Running title: SARS-CoV-2 Reinfection in Children.

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Abbreviations:

COVID-19: Coronavirus disease 2019

SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus 2

PCR-Q8: The Pediatric COVID Registry in Kuwait

WHO: World Health Organization.

PCR: polymerase chain reaction

IQR: interquartile range

Article summary: National-level study found that pediatric SARS-CoV-2 reinfection is uncommon, and estimated to be 1.02 (95% CI 0.71-1.45) infection per 100,000 person-days

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2 38 **Contributors' Statement:**
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6 40 **Drs Ali Abdulkareem, Danah Alsharrah, and Fatemah Alhaddad** conceptualized and designed
7
8
9 41 the study, curated the data, wrote the original draft of the paper, and revised the manuscript.
10

11 42 **Dr Abdullah Alkandari** conducted the formal analysis, and critically revised the manuscript
12

13 43 **Dr Saadoun Bin-Hasan:** conceptualized and designed the study, and critically revised the
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16 44 manuscript.
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18 45 **Drs Mona Al-Ahmad and Hashem Al-Hashemi:** conceptualized the study, participated in data
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20 46 curation, and revised the manuscript
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22 47 **Mohammed Alghounaim:** conceptualized and designed the study, supervised data collection,
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24
25 48 conducted initial analysis, and critically revised the manuscript.
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28 49 All authors approved the final manuscript as submitted and agree to be accountable for all aspects
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30 50 of the work.
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2 53 **Abstract**

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7 55 **Objective:** Subsequent protection from Severe acute respiratory syndrome-related coronavirus 2
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9 56 (SARS-COV-2) infection in pediatrics is not well reported in the literature. We aimed to describe
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11 57 the clinical characteristics and dynamics of SARS-CoV-2 PCR repositivity in children.

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16 59 **Methods:** This is a population-level retrospective cohort study included children 12 years and
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18 60 younger between February 28, 2020 and March 6, 2021. Patients were identified through multiple
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20 61 national-level electronic coronavirus disease 2019 (COVID-19) databases. SARS-CoV-2
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22 62 reinfection was defined as having two or more positive SARS-CoV-2 PCR done on a respiratory
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24 63 sample, at least 45 days apart. Clinical data was obtained from the Pediatric COVID-19 Registry in
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26 64 Kuwait (PCR-Q8). Descriptive statistics and incidence-sensitivity analyses were performed.

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32 66 **Results:** Thirty pediatric COVID-19 patients had SARS-CoV-2 reinfection at an incidence of 1.02
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34 67 (95% CI 0.71-1.45) infection per 100,000 person-days and a median time to reinfection of 83 days
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36 68 (IQR 62-128.75). The incidence of reinfection decreased to 0.78 (95% CI 0.52-1.17) and 0.47 (95%
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38 69 CI 0.28-0.79) per person-days when the minimum interval between PCR repositivity was increased
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41 70 to 60 and 90 days, respectively. The mean age of reinfected subjects was 8.5 years (IQR 3.7-10.3)
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43 71 and majority (70%) were female. Most children (55.2%) had asymptomatic reinfection. Fever was
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45 72 the most common presentation in symptomatic patients. One immunocompromised experienced two
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47 73 reinfection episodes.

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53 75 **Conclusion:** SARS-CoV-2 reinfection is uncommon in children. Previous confirmed COVID-19 in
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55 76 children seems to induce a protective immunity against future infections.

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79 **Strength and limitations of the study**

- 80 - Little is known about the risk of pediatric SARS-CoV-2 reinfection and children are more
- 81 likely to be asymptomatic and therefore not all positive cases are detected.
- 82 - Estimating the duration of immunity after the primary infection is crucial in planning health
- 83 care measures
- 84 - A population-level retrospective cohort study included children 12 years and younger was
- 85 performed and included SARS-CoV-2 reinfection and descriptive statistics were performed.

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2 87 **Introduction:**

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4 88 Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is a
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6 89 novel beta coronavirus that was first described in December 2019 and resulted in a pandemic of
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9 90 respiratory illness, coronavirus disease-2019 (COVID-19) ¹. By early May 2021, the pandemic has
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11 91 resulted in over 150 million cases worldwide and more than three million deaths reported by the
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13 92 World Health Organization (WHO)². Despite the widespread of COVID-19, children compromised
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15 93 less than 15% of all reported cases ³⁻⁵. Limited social interactions, and enhanced infection control
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17 94 measures such as school closure and online teaching, may have contributed to lower proportions of
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19 95 infected children ⁶. In addition, children are more likely to have asymptomatic or mild infection
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21 96 compared to adults and, therefore, may not be tested ⁷.
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27 98 Quantifying the duration of natural immunity after the primary SARS-CoV-2 infection has
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29 99 been crucial to address public health measures, to help predict the continuity of the pandemic, and
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32 100 to understand the effect of reinfection on disease severity. The first case of SARS-CoV-2
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34 101 reinfection was reported in August 2020 ⁸. Since then, interest in the exact risk and rate of
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36 102 reinfection has been increasing. Several reports estimated that reinfection occurs in less than 1% of
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39 103 previously infected individuals ⁹⁻¹¹. The duration between primary and secondary infection was
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41 104 reported to vary from 48 to 124 days in the first documented cases in literature ^{12, 13}. However, most
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43 105 of the reinfection studies focused mainly on the adult population. COVID-19 follows different
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45 106 disease dynamics in children, and studies addressing reinfection in this population are lacking.
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50 108 The first pediatric case of COVID-19 in Kuwait was identified in February 2020 ⁷. Since
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52 109 then, schools and daycare centers were closed, and classes were conducted virtually. In addition,
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55 110 commercial centers, gyms, and restaurants were open but with time restrictions and strict protective
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57 111 measures. Early in the pandemic, a national electronic COVID-19 testing database was created and
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59 112 included all SARS-CoV-2 test results of symptomatic individuals, contact tracing, and routine
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2 113 travel or hospitalization screening. Also, a national Pediatric COVID-19 Registry (PCR-Q8) was
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4 114 established for children aged 12 years and younger to better understand disease dynamics and
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6 115 update management protocols. This created the unique opportunity to investigate the possibility of
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9 116 reinfection with SARS-CoV-2, with an attempt to establish an average duration between the two
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11 117 positive results, potential factors linked to reinfection, and its clinical severity.
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13 118 14 15 16 119 17 18 120 **Methods:**

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20 121 A population-level retrospective cohort study was conducted in Kuwait between February
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22 122 28th, 2020, and March 6th, 2021. The national COVID-19 test result database was used to identify
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24 123 children younger than 12 years and had two or more subsequent positive SARS-CoV-2 polymerase
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26 124 chain reaction (PCR) tests done on a respiratory sample, at least 45 days apart. Subjects who had
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28 125 two or more positive SARS-CoV-2 PCR but less than 45 days in-between, and patients who
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30 126 fulfilled the WHO definition of the multisystem inflammatory syndrome in children (MIS-C) were
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32 127 excluded¹⁴.
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39 129 To assure the inclusion of all SARS-CoV-2 infected children into this study, the national
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41 130 COVID-19 testing database was used for initial patient identification. This database includes the
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43 131 results for all individuals who had SARS-CoV-2 PCR done on a respiratory specimen nationwide.
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45 132 SARS-CoV-2 PCR is typically done to confirm the diagnosis of symptomatic individuals, detect
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47 133 secondary infections in contact tracing, and identify infected subjects prior to hospitalization or
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49 134 travel. During the study period, the SARS-CoV-2 antigen was not routinely performed on pediatric
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51 135 samples. Also, serum SARS-CoV-2 IgG or IgM tests were not routinely done to confirm current or
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53 136 prior infection. A secondary search query was done on the PCR-Q8 registry, which included patient
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55 137 information from the following sources: hospital records, institutional quarantine centers, patient
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57 138 transport units, as well as all laboratories that provide SARS-CoV-2 PCR.
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The PCR-Q8 registry 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 categorized

based on WHO disease classification¹⁵. Infected children with mild or asymptomatic COVID-19

may not require hospitalization hence, clinical data in the registry may be lacking. For those

subjected, parents were contacted to complete missing disease-related data.

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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 February 28th, 2020 to

the second positive test or March 6th, 2021, whichever is first. However, individuals with the first

positive SARS-CoV-2 PCR starting January 1st, 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). Also, sensitivity analysis assessing the clinical

presentation and incidence of reinfection considering a minimum interval for PCR repositivity of 60

and 90 days.

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45 158 **Ethics:**

46 159 The study was approved by the ethical board of the Ministry of Health, Kuwait (reference no.

47 160 1607/2020). Verbal consent was obtained from parents who agreed to participate to complete

48 161 missing clinical data.

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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 were identified, of which, 30 patients had a repeat positive SARS-CoV-2 45 days or more after the first positive, 391 patients had their repeat test within 45 days and were excluded (figure 1). The incidence of reinfection was 1.02 (95% CI 0.71-1.45) 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 females (table 1). More than half (56.6%) of reinfection 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 days (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 second infection. Of those, three patients had mild or asymptomatic initial SARS-CoV-2 infection. One of the four patients was admitted for an acute exacerbation of asthma with three days history of fever. The median length of hospitalization was 9 days (IQR 5.75-13 days) and 6 days (IQR 3.75-6.75 days) for the first and second infection, 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

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2 189 severe pneumonia with prolonged hospital admission followed by a negative PCR test done in
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4 190 December. Interestingly, during her third infection in January 2021, she was asymptomatic and
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6 191 testing was done for screening before an outpatient appointment.
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11 193 Around half (46.6%) of reinfections occurred more than 90 days after the initial infection.

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13 194 The incidence of reinfection decreased to 0.78 (95% CI 0.52-1.17) and 0.47 (95% CI 0.28-0.79) per
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15 195 infected person-days when the minimum acceptable duration between PCR repositivity was
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17 196 increased to 60 and 90 days, respectively. Also, there were more symptomatic children (64.3%)
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19 197 during the second infection using the 90-day definition when compared to the 45-day or 60-day
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Discussion

The exact risk and factors associated with SARS-CoV-2 reinfection in the pediatric 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 0.09-0.13 per 10,000 person-day^{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 subjects¹⁶. However, the epidemiology and disease dynamics of SARS-CoV-2 infection are different in children¹⁷. Therefore, using data generated from adult studies to infer on the pediatric population may not be accurate.

Magnitude and persistence of immunological responses conferred by SARS-CoV-2 infection can be variable based on age and medical comorbidities¹⁸. 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 neutralizing antibodies, the seropositivity was identified in all participants up to 53 days after infection¹⁹. However, the level of neutralizing antibodies varies greatly with disease severity and tend to wane over time^{20,21}. Few studies compared humoral responses between adults and children. Weisberg et. al. have shown that children exhibit lower antibody response compared to adults²². 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 infection²³. However, this testing method lacks sensitivity and is time consuming²⁴. In addition, due to the need of expertise

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2 227 and appropriate laboratory infrastructure, routine population-level testing using cell culture in not
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4 228 possible. For these reasons, the detection of genetically distinct SARS-CoV-2 in different infectious
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6 229 episodes or the use of the cycle threshold (Ct) value as a surrogate for viral load has been suggested
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9 230 ^{12, 13}. In Kuwait, genomic testing capacity is limited and retrieving patients' samples and laboratory
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11 231 data from several public and private laboratories was logistically challenging. In our study, a 45-day
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13 232 period between two-consecutive positive PCR test was selected based on the expected duration of
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15 233 molecular test positivity on a respiratory sample. Alsharrah et al. reported a median duration of
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18 234 PCR positivity among pediatric COVID-19 patients of 15 days, with maximum duration of 42 days
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25 237 To our knowledge, this is the first national-level cohort that estimates the risk of pediatric
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27 238 SARS-CoV-2 reinfection. Nevertheless, this study has some limitations. Due to limited genomic
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30 239 sequencing capacity, proving that PCR repositivity was caused by a genetically distinct virus was
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32 240 not possible. However, based on the expected duration of PCR-persistence in children mentioned
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34 241 above, one will not expect that PCR done on an upper respiratory specimen to remain positive
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36 242 beyond 45 days. Another limitation was the unavailability of some data recorded in the national
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39 243 pediatric COVID-19 registry. When data was missing, parents were contacted via the telephone,
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41 244 creating a recall bias. In addition, patients with mild upper respiratory tracts symptoms are
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43 245 underreported by parents. Therefore, mild cases are less likely to be tested and can be missed, and
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46 246 underestimate the reinfection rate. However, using the national level electronic record allowed the
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48 247 collection of data from variable sources and the detection of asymptotically infected
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50 248 children. Despite these limitations, this study has shown that reinfection is generally uncommon.
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53 249 Further studies that correlate degree of humoral and cellular immunity, along with wide genomic
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55 250 sequencing surveillance with risk of reinfection are needed to better understand and quantify the
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57 251 risk of repeat SARS-CoV-2 infection.
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2 253 **Acknowledgement:**
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6 255 Health, Kuwait, for her help in preparing this manuscript. We also thank the research group of the
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9 256 Pediatric COVID-19 Registry in Kuwait (PCR-Q8) for their contribution.
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2 258 **Table 1.** Demographic characteristics of the study population

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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]

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IQR, interquartile range.

Table 2. Clinical characteristics of the study population based on different defined intervals of polymerase chain reaction (PCR) repositivity

Variable	First Infection			Second Infection		
	Minimum interval of PCR repositivity			Minimum interval of PCR repositivity		
	45 days (n=30)	60 days (n=23)	90 days (n=14)	45 days (n=29)*	60 days (n=23)	90 days (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%)
Hospitalization 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%)
Diarrhea	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%)
Rhinorrhea	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%)
Hospitalization						
Length of stay in days [median, IQR]	5 (16.7%) 9 [5.75-13]	4 (17.4%) 9 [7.25-11]	3 (21.4%) 8 [6.5-9]	6 (20.7%) 6 [3-6]	5 (21.7%) 6 [3-6]	5 (35.7%) 6 [3-6]

IQR, interquartile range.

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2 *clinical data for one patient is missing
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Table 1. Demographic characteristics of the study population.

Table 2. Clinical characteristics of the study population based on different defined intervals of
polymerase chain reaction (PCR) repositivity.

Figure 1: Flow diagram of the study population

Figure 2: Duration between first SARS-CoV-2 infection and subsequent infections. The shaded
bars represent the duration between positive PCR results.

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3 **Figure 1:** Flow diagram of the study population
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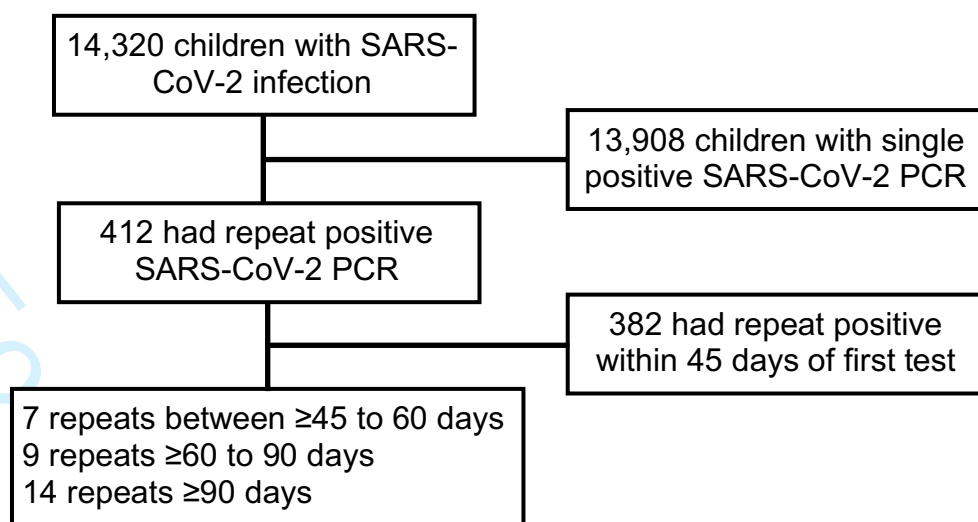
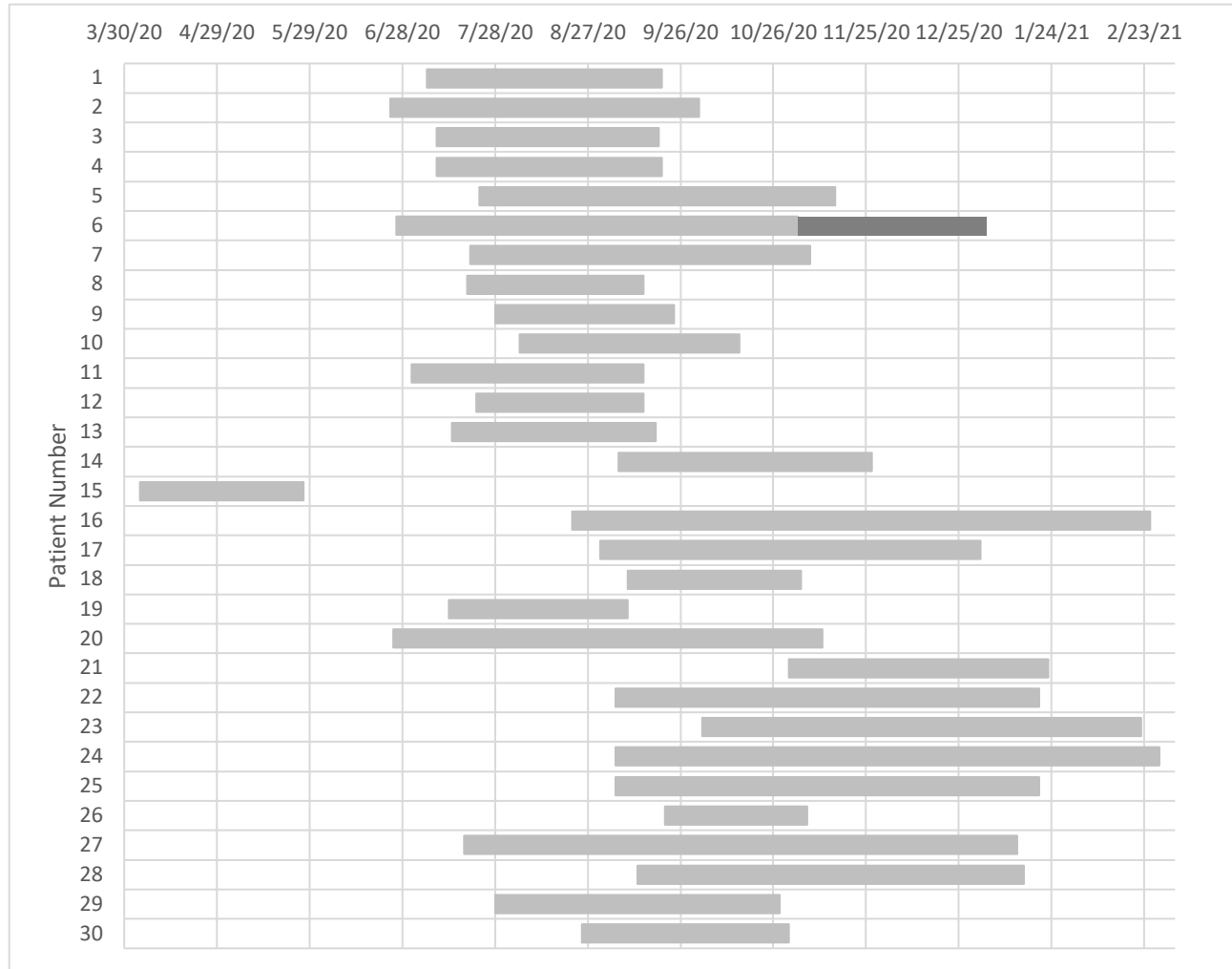


Figure 2: Duration between first SARS-CoV-2 infection and subsequent infections. The shaded bars represent the duration between positive PCR results.



*Patient 6 had two episodes of reinfection

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Incidence of SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

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Running title: SARS-CoV-2 Reinfection in Children.

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Abbreviations:

COVID-19: Coronavirus disease 2019

SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus 2

PCR-Q8: The Pediatric COVID Registry in Kuwait

WHO: World Health Organization.

PCR: polymerase chain reaction

IQR: interquartile range

Article summary: National-level study found that pediatric SARS-CoV-2 reinfection is uncommon, and estimated to be 1.02 (95% CI 0.71-1.45) infection per 100,000 person-days

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2 38 **Contributors' Statement:**
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6 40 **Drs Ali Abdulkareem, Danah Alsharrah, and Fatemah Alhaddad** conceptualized and designed
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8
9 41 the study, curated the data, wrote the original draft of the paper, and revised the manuscript.
10

11 42 **Dr Abdullah Alkandari** conducted the formal analysis, and critically revised the manuscript
12

13 43 **Dr Saadoun Bin-Hasan:** conceptualized and designed the study, and critically revised the
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16 44 manuscript.
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18 45 **Drs Mona Al-Ahmad and Hashem Al-Hashemi:** conceptualized the study, participated in data
19
20 46 curation, and revised the manuscript
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22 47 **Dr Mohammed Alghounaim:** conceptualized and designed the study, supervised data collection,
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25 48 conducted initial analysis, and critically revised the manuscript.
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28 49 All authors approved the final manuscript as submitted and agree to be accountable for all aspects
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30 50 of the work.
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1
2 53 **Abstract**

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7 55 **Objective:** Subsequent protection from severe acute respiratory syndrome-related coronavirus 2
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9 56 (SARS-COV-2) infection in pediatrics is not well reported in the literature. We aimed to describe
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11 57 the clinical characteristics and dynamics of SARS-CoV-2 PCR repositivity in children.

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16 59 **Methods:** This is a population-level retrospective cohort study included children 12 years and
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18 60 younger between February 28, 2020 and March 6, 2021. Patients were identified through multiple
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20 61 national-level electronic coronavirus disease 2019 (COVID-19) databases. SARS-CoV-2
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22 62 reinfection was defined as having two or more positive SARS-CoV-2 PCR done on a respiratory
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24 63 sample, at least 45 days apart. Clinical data was obtained from the Pediatric COVID-19 Registry in
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26 64 Kuwait (PCR-Q8). Descriptive statistics and incidence-sensitivity analyses were performed.

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32 66 **Results:** Thirty pediatric COVID-19 patients had SARS-CoV-2 reinfection at an incidence of 1.02
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34 67 (95% CI 0.71-1.45) infection per 100,000 person-days and a median time to reinfection of 83 days
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36 68 (IQR 62-128.75). The incidence of reinfection decreased to 0.78 (95% CI 0.52-1.17) and 0.47 (95%
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38 69 CI 0.28-0.79) per person-days when the minimum interval between PCR repositivity was increased
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41 70 to 60 and 90 days, respectively. The mean age of reinfected subjects was 8.5 years (IQR 3.7-10.3)
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43 71 and majority (70%) were female. Most children (55.2%) had asymptomatic reinfection. Fever was
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45 72 the most common presentation in symptomatic patients. One immunocompromised experienced two
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47 73 reinfection episodes.

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53 75 **Conclusion:** SARS-CoV-2 reinfection is uncommon in children. Previous confirmed COVID-19 in
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55 76 children seems to induce a protective immunity against future infections.

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2 79 **Data availability statement:**
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4 80 Data are available upon reasonable request
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9 82 **Strength and limitations of the study**
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11 83 - This study used a national-level electronic database that included all SARS-CoV-2 test
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13 84 results that allowed data collection from variable sources and the detection of
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15 85 asymptotically infected children.
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18 86 - The result highlights that SARS-CoV-2 reinfection is uncommon in children.
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20 87 - The exact risk for SARS-CoV-2 reinfection is difficult to estimate as children are more
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22 88 likely to be asymptomatic, and therefore not all positive cases are detected.
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25 89 - Patients' symptoms and severity in this retrospective analysis were dependent on the
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27 90 accuracy of reporting in medical notes and parental recall of symptoms.
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30 91 - Due to limited genomic sequencing capacity, proving the direct causality between PCR
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32 92 repositivity and a genetically distinct virus was not possible.
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2 94 **Introduction:**

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4 95 Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is a
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6 96 novel beta coronavirus that was first described in December 2019 and resulted in a pandemic of
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9 97 respiratory illness, coronavirus disease-2019 (COVID-19) ¹. By early May 2021, the pandemic has
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11 98 resulted in over 150 million cases worldwide and more than three million deaths reported by the
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13 99 World Health Organization (WHO)². Despite the widespread of COVID-19, children compromised
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16 100 less than 15% of all reported cases ³⁻⁵. Limited social interactions, and enhanced infection control
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18 101 measures such as school closure and online teaching, may have contributed to lower proportions of
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20 102 infected children ⁶. In addition, children are more likely to have asymptomatic or mild infection
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23 103 compared to adults and, therefore, may not be tested ⁷.

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27 105 Quantifying the duration of natural immunity after the primary SARS-CoV-2 infection has
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29
30 106 been crucial to address public health measures, to help predict the continuity of the pandemic, and
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32 107 to understand the effect of reinfection on disease severity. The first case of SARS-CoV-2
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34 108 reinfection was reported in August 2020 ⁸. Since then, interest in the exact risk and rate of
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36 109 reinfection has been increasing. Several reports estimated that reinfection occurs in less than 1% of
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39 110 previously infected individuals ⁹⁻¹¹. The duration between primary and secondary infection was
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41 111 reported to vary from 48 to 124 days in the first documented cases in literature ^{12, 13}. However, most
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43 112 of the reinfection studies focused mainly on the adult population. COVID-19 follows different
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46 113 disease dynamics in children, and studies addressing reinfection in this population are lacking.

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50 115 The first pediatric case of COVID-19 in Kuwait was identified in February 2020 ⁷. Since
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53 116 then, schools and daycare centers were closed, and classes were conducted virtually. In addition,
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55 117 commercial centers, gyms, and restaurants were open but with time restrictions and strict protective
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57 118 measures. Early in the pandemic, a national electronic COVID-19 testing database was created and
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59 119 included all SARS-CoV-2 test results of symptomatic individuals, contact tracing, and routine
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2 120 travel or hospitalization screening. Also, a national Pediatric COVID-19 Registry (PCR-Q8) was
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4 121 established for children aged 12 years and younger to better understand disease dynamics and
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6 122 update management protocols. This created the unique opportunity to investigate the possibility of
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9 123 reinfection with SARS-CoV-2, with an attempt to establish an average duration between the two
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11 124 positive results, potential factors linked to reinfection, and its clinical severity.
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13 125 14 15 16 126 17 18 127 **Methods:**

19
20 128 A population-level retrospective cohort study was conducted in Kuwait between February
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22 129 28th, 2020, and March 6th, 2021. The national COVID-19 test result database was used to identify
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25 130 children younger than 12 years and had two or more subsequent positive SARS-CoV-2 polymerase
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27 131 chain reaction (PCR) tests done on a respiratory sample, at least 45 days apart. Subjects who had
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30 132 two or more positive SARS-CoV-2 PCR but less than 45 days in-between, and patients who
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32 133 fulfilled the WHO definition of the multisystem inflammatory syndrome in children (MIS-C) were
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34 134 excluded ¹⁴.
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39 136 To assure the inclusion of all SARS-CoV-2 infected children into this study, the national
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41 137 COVID-19 testing database was used for initial patient identification. This database includes the
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43 138 results for all individuals who had SARS-CoV-2 PCR done on a respiratory specimen nationwide.
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46 139 SARS-CoV-2 PCR is typically done to confirm the diagnosis of symptomatic individuals, detect
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48 140 secondary infections in contact tracing, and identify infected subjects prior to hospitalization or
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50 141 travel. During the study period, the SARS-CoV-2 antigen was not routinely performed on pediatric
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53 142 samples. Also, serum SARS-CoV-2 IgG or IgM tests were not routinely done to confirm current or
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55 143 prior infection. A secondary search query was done on the PCR-Q8 registry, which included patient
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57 144 information from the following sources: hospital records, institutional quarantine centers, patient
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59 145 transport units, as well as all laboratories that provide SARS-CoV-2 PCR.
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4 147 The PCR-Q8 registry retrospectively collected detailed individual-level demographic,
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6 148 laboratory and clinical characteristics of all children diagnosed with COVID-19 in Kuwait. The
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9 149 database was acquired to obtain demographic and clinical data. COVID-19 severity was categorized
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11 150 based on WHO disease classification¹⁵. Infected children with mild or asymptomatic COVID-19
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13 151 may not require hospitalization. Therefore, clinical data in the registry may be lacking. For those
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16 152 subjected, parents were contacted to complete missing disease-related data.
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20 154 Descriptive analysis was performed to compare between primary and secondary infections.
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23 155 To calculate incidence and to account for delayed presentation of reinfection, calculated days at risk
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25 156 included the period from the day of first positive SARS-CoV-2 PCR starting February 28th, 2020 to
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27 157 the second positive test or March 6th, 2021, whichever is first. However, individuals with the first
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30 158 positive SARS-CoV-2 PCR starting January 1st, 2021, were not included in the calculation due to
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32 159 limited time for reinfection to occur. Clopper-Pearson test was used to calculate the 95% CI.
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34 160 Analysis was done using GraphPad Prism (v. 9.0). Due to the variability in established reinfection
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36 161 case definition, sensitivity analysis assessing the clinical presentation and incidence of reinfection
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39 162 considering a minimum interval for PCR repositivity of 60 and 90 days¹⁶.

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43 164 **Patient and public involvement statement:**

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45 165 Patients were not included in the design, reporting or dissemination plans of our research.
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48 166 However, parents of children with PCR repositivity were contacted to complete missing data. This
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50 167 study was conducted to address epidemiological questions presented by the Pediatric COVID-19
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53 168 Task Force (Ministry of Health, Kuwait). The initial concept and study plan was presented to the
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55 169 committee members, whose suggestions and comments were considered in the final study protocol
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2 172 **Ethics:**
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4 173 The study was approved by the ethical board of the Ministry of Health, Kuwait (reference no.
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6 174 1607/2020). Verbal consent was obtained from parents who agreed to participate to complete
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9 175 missing clinical data.
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1 2 177 **Results**

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4 178 During the study period, there were 14,320 documented SARS-CoV-2 infections in children
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6 179 younger than 12 years in Kuwait, accounting for 2,954,372 person-days of follow-up. Among those,
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9 180 421 children with repeat positive SARS-CoV-2 PCR were identified, of which, 30 patients had a
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11 181 repeat positive SARS-CoV-2 45 days or more after the first positive, 391 patients had their repeat
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13 182 test within 45 days and were excluded (figure 1). The incidence of reinfection was 1.02 (95% CI
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16 183 0.71-1.45) infection per 100,000 previously infected person-days. The mean age of the reinfection
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18 184 cohort was 8.5 (IQR 3.7-10.3) years and majority (70%) were females (table 1). More than half
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20 185 (56.6%) of reinfection patients were not known to have any chronic comorbid conditions at the time
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23 186 of the first or second infection.

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27 188 The median time between the two episodes of infection as evident by the sample collection
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30 189 date was 83 days (IQR 62-128.75 days) (figure 2). Majority of the patients had asymptomatic
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32 190 infection during the first and second episodes, 43.3% and 53.3% respectively (table 2). In
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34 191 symptomatic patients, fever, cough and shortness of breath were the most commonly reported
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36 192 symptoms. One (3.3%) patient had severe pneumonia during the first infection, whereas, four
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39 193 (13.3%) patients had severe pneumonia during second infection. Of those, three patients had mild or
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41 194 asymptomatic initial SARS-CoV-2 infection. One of the four patients was admitted for an acute
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43 195 exacerbation of asthma with three days history of fever. The median length of hospitalization was 9
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46 196 days (IQR 5.75-13 days) and 6 days (IQR 3.75-6.75 days) for the first and second infection,
47
48 197 respectively. None of the subjects received care in an intensive care unit.

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52 199 One female patient previously diagnosed with hypereosinophilic syndrome on low-dose
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55 200 prednisone, had three episodes of SARS-CoV-2 infections. Her first infection was in July 2020
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57 201 where she was admitted for 10 days as a case of severe pneumonia followed by two negative PCR
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59 202 tests done in August. Her second infection was in November 2020 when she was also admitted for

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2 203 severe pneumonia with prolonged hospital admission followed by a negative PCR test done in
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4 204 December. Interestingly, during her third infection in January 2021, she was asymptomatic and
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6 205 testing was done for screening before an outpatient appointment.
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11 207 Around half (46.6%) of reinfections occurred more than 90 days after the initial infection.
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13 208 The incidence of reinfection decreased to 0.78 (95% CI 0.52-1.17) and 0.47 (95% CI 0.28-0.79) per
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15 209 infected person-days when the minimum acceptable duration between PCR repositivity was
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18 210 increased to 60 and 90 days, respectively. Also, there were more symptomatic children (64.3%)
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20 211 during the second infection using the 90-day definition when compared to the 45-day or 60-day
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2 215 **Discussion**

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6 217 The exact risk and factors associated with SARS-CoV-2 reinfection in the pediatric population
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9 218 are still not well understood. We found that a second SARS-CoV-2 infection is uncommon in
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11 219 children with a rate of 1.02 reinfection per 100,000 previously infected person-days and a median
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13 220 time to reinfection of 83 days. The finding of this study is similar to previous reports which showed
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15
16 221 a reinfection incidence in adults of 0.9-1.3 per 100,000 person-day^{9, 11}. Similarly, in a large Danish
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18 222 cohort, prior SARS-CoV-2 provided on average 80.5% protection against repeat infection. The
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20 223 estimated protection differed between different age groups ranging from 47.1% in individuals older
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22 224 than 65 years of age to 82.7% in younger subjects¹⁷. However, the epidemiology and disease
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25 225 dynamics of SARS-CoV-2 infection are different in children¹⁸. Therefore, using data generated
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27 226 from adult studies to infer on the pediatric population may not be accurate.

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32 228 Magnitude and persistence of immunological responses conferred by SARS-CoV-2
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34 229 infection can be variable based on age and medical comorbidities¹⁹. Hence, estimating the duration
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36 230 of protective immunity after acquiring SARS-CoV-2 infection has been the focus of several studies.
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39 231 In an adult study, looking at the neutralizing antibodies, the seropositivity was identified in all
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41 232 participants up to 53 days after infection²⁰. However, the level of neutralizing antibodies varies
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43 233 greatly with disease severity and tend to wane over time^{21, 22}. Few studies compared humoral
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46 234 responses between adults and children. Weisberg et. al. have shown that children exhibit lower
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48 235 antibody response compared to adults²³. However, the incidence of reinfections observed in this
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50 236 study was similar to previously reported adult patients.

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55 238 A standard definition of SARS-CoV-2 reinfection is lacking. Traditionally, the detection of
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57 239 viable virus by cell culture has been the standard to ascertain active infection²⁴. However, this
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59 240 testing method lacks sensitivity and is time consuming²⁵. In addition, due to the need of expertise

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2 241 and appropriate laboratory infrastructure, routine population-level testing using cell culture in not
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4 242 possible. For these reasons, the detection of genetically distinct SARS-CoV-2 in different infectious
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6 243 episodes or the use of the cycle threshold (Ct) value as a surrogate for viral load has been suggested
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9 244 ^{12, 13}. In Kuwait, genomic testing capacity is limited and retrieving patients' samples and laboratory
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11 245 data from several public and private laboratories was logistically challenging. In our study, a 45-day
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13 246 period between two-consecutive positive PCR test was selected based on the expected duration of
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16 247 molecular test positivity on a respiratory sample. Alsharrah et al. reported a median duration of
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18 248 PCR positivity among pediatric COVID-19 patients of 15 days, with maximum duration of 42 days
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20 249 ⁷. However, we observed a decline in the rate of repositivity from 1.02 to 0.47 per 100,000
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23 250 previously infected person-days when the definition of PCR-repositivity increased from 45 to 90
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25 251 days. As almost half of cases are asymptomatic, this finding could be due to persistent detection of
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27 252 viral particles by PCR.

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32 254 Asymptomatic SARS-CoV-2 infection is common in pediatrics. We found that around half
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34 255 of infections (43.3% in initial infection and 55.2% in reinfection) remained asymptomatic on
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36 256 follow-up. This finding is similar to other studies ²⁶. High proportion of silent infection may pose an
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39 257 important public health concern and limit the effectiveness of transmission mitigation efforts. Also,
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41 258 the possibility of reinfection within a relatively short period of time as observed in this study may
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43 259 be an overlooked source of community transmission. Real-world COVID-19 vaccine effectiveness
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46 260 data showed that reinfection is more common in unvaccinated adults²⁷. These findings support the
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48 261 recommendation to offer vaccination to those previously infected.

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52 263 To our knowledge, this is the first national-level cohort that estimates the risk of pediatric
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55 264 SARS-CoV-2 reinfection. Nevertheless, this study has some limitations. Due to limited genomic
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57 265 sequencing capacity, proving that PCR repositivity was caused by a genetically distinct virus was
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59 266 not possible. However, based on the expected duration of PCR-persistence in children mentioned

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2 267 above, one will not expect that PCR done on an upper respiratory specimen to remain positive
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4 268 beyond 45 days. Another limitation was the unavailability of some data recorded in the national
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6 269 pediatric COVID-19 registry. When data was missing, parents were contacted via the telephone,
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9 270 creating a recall bias. In addition, patients with mild upper respiratory tracts symptoms are
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11 271 underreported by parents. Therefore, mild cases are less likely to be tested and can be missed, and
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13 272 underestimate the reinfection rate. However, using the national level electronic record allowed the
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16 273 collection of data from variable sources and the detection of asymptotically infected
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18 274 children. Despite these limitations, this study has shown that reinfection is generally uncommon.
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20 275 Further studies that correlate degree of humoral and cellular immunity, along with wide genomic
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23 276 sequencing surveillance with risk of reinfection are needed to better understand and quantify the
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25 277 risk of repeat SARS-CoV-2 infection.
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2 279 **Acknowledgement:**
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6 281 Health, Kuwait, for her help in preparing this manuscript. We also thank the research group of the

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9 282 Pediatric COVID-19 Registry in Kuwait (PCR-Q8) for their contribution.
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1
2 284 **Table 1.** Demographic characteristics of the study population

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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]

286 IQR, interquartile range.

Table 2. Clinical characteristics of the study population based on different defined intervals of polymerase chain reaction (PCR) repositivity

Variable	First Infection			Second Infection		
	Minimum interval of PCR repositivity			Minimum interval of PCR repositivity		
	45 days (n=30)	60 days (n=23)	90 days (n=14)	45 days (n=29)*	60 days (n=23)	90 days (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%)
Hospitalization 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%)
Diarrhea	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%)
Rhinorrhea	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%)
Hospitalization						
Length of stay in days [median, IQR]	5 (16.7%) 9 [5.75-13]	4 (17.4%) 9 [7.25-11]	3 (21.4%) 8 [6.5-9]	6 (20.7%) 6 [3-6]	5 (21.7%) 6 [3-6]	5 (35.7%) 6 [3-6]

IQR, interquartile range.

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2 *clinical data for one patient is missing
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43 378 **Table 1.** Demographic characteristics of the study population.

45 379 **Table 2.** Clinical characteristics of the study population based on different defined intervals of
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48 380 polymerase chain reaction (PCR) repositivity.

50 381 **Figure 1:** Flow diagram of the study population

52 382 **Figure 2:** Duration between first SARS-CoV-2 infection and subsequent infections. The shaded
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54 383 bars represent the duration between positive PCR results.

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Figure 1: Flow diagram of the study population

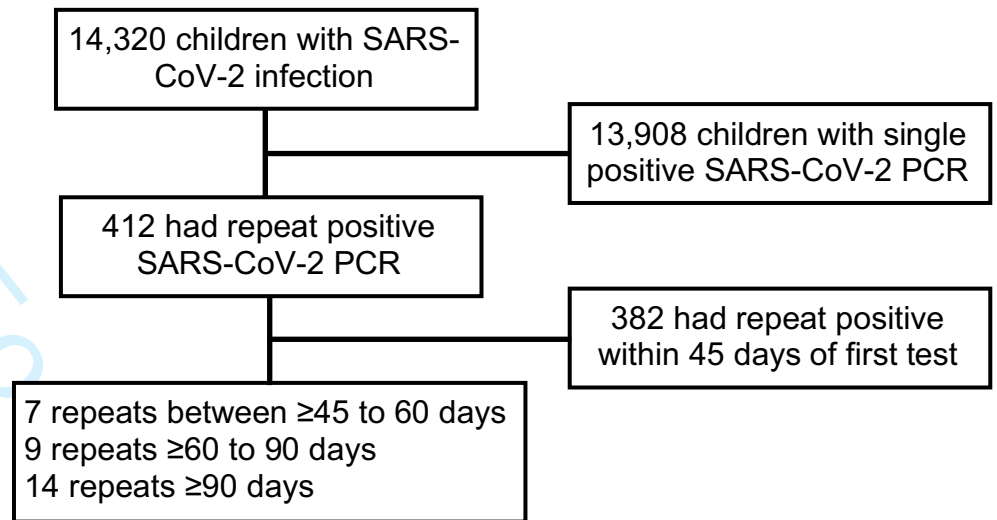
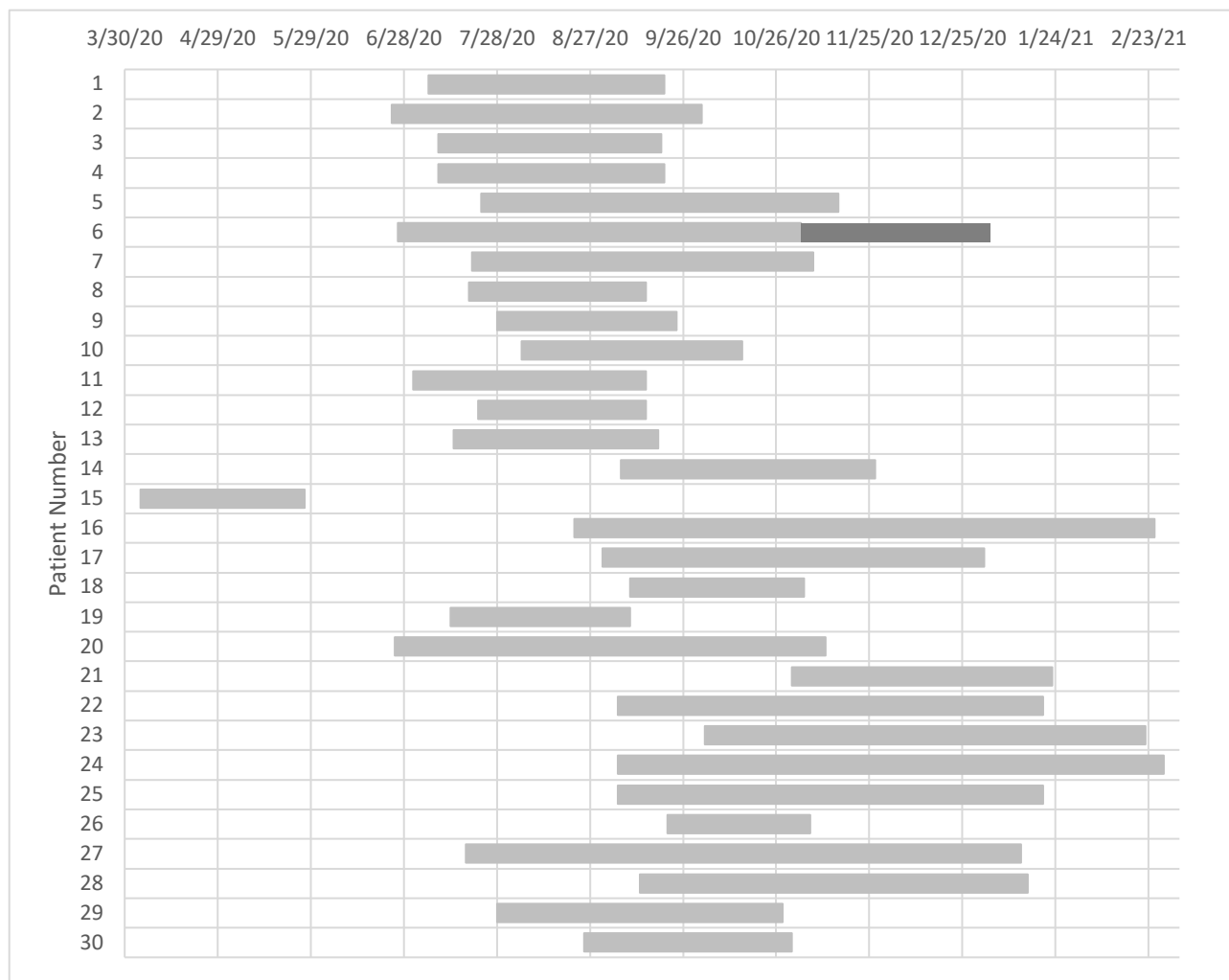


Figure 2: Duration between first SARS-CoV-2 infection and subsequent infections. The shaded bars represent the duration between positive PCR results.



*Patient 6 had two episodes of reinfection

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Manuscript number (if known): Not known

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Incidence of Potential SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page and line number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	P 1, L 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P 6, L 105-123
Objectives	3	State specific objectives, including any prespecified hypotheses	P 7, L 132-134
Methods			
Study design	4	Present key elements of study design early in the paper	P 7, L 138
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Dates: P7, L139 Exp: P7, L 146 Data: P8, 157
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P 7, L138 and P8, L 157
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Exclusion: P 7, L142
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	NA
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P 7, L 146 Outcome: P7, L140
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P8, L157
Bias	9	Describe any efforts to address potential sources of bias	Potential recall bias is mentioned in limitation
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P 8, L165
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	NA
		(b) Describe any methods used to examine subgroups and interactions	P8, L 170
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	NA
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	P8, L 170

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Results			Page and line number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P 9, L 183
		(b) Give reasons for non-participation at each stage	P 9, L187
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P 9, L 193
		(b) Indicate number of participants with missing data for each variable of interest	Table 1- no missing data Table 2 – indicated by *
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	P9, L 184
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	P9, L183- 190
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P9, L187
		(b) Report category boundaries when continuous variables were categorized	done
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P 10, L213
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11, L 223
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12, L272
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11, 234- P12 L269
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12, L 280
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P1, L15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

1
2 available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at
3 <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is
4 available at www.strobe-statement.org.
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Incidence of SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

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Incidence of SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

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Keywords: Children, SARS-CoV-2, COVID-19, reinfection, epidemiology

Running title: SARS-CoV-2 Reinfection in Children.

Conflict of Interest Disclosures: The authors no conflicts of interest to disclose

Funding: None

Abbreviations:

COVID-19: Coronavirus disease 2019

SARS-CoV-2: Severe acute respiratory syndrome-related coronavirus 2

PCR-Q8: The Pediatric COVID Registry in Kuwait

WHO: World Health Organization.

PCR: polymerase chain reaction

IQR: interquartile range

Article summary: National-level study found that pediatric SARS-CoV-2 reinfection is uncommon, and estimated to be 1.02 (95% CI 0.71-1.45) infection per 100,000 person-days

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2 38 **Contributors' Statement:**
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6 40 **Drs Ali Abdulkareem, Danah Alsharrah, and Fatemah Alhaddad** conceptualized and designed
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8
9 41 the study, curated the data, wrote the original draft of the paper, and revised the manuscript.
10

11 42 **Dr Abdullah Alkandari** conducted the formal analysis, and critically revised the manuscript
12

13 43 **Dr Saadoun Bin-Hasan:** conceptualized and designed the study, and critically revised the
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16 44 manuscript.
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18 45 **Drs Mona Al-Ahmad and Hashem Al-Hashemi:** conceptualized the study, participated in data
19
20 46 curation, and revised the manuscript
21

22 47 **Dr Mohammed Alghounaim:** conceptualized and designed the study, supervised data collection,
23
24
25 48 conducted initial analysis, and critically revised the manuscript.
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28 49 All authors approved the final manuscript as submitted and agree to be accountable for all aspects
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30 50 of the work.
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1
2 53 **Abstract**

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6 55 **Objective:** Subsequent protection from severe acute respiratory syndrome-related coronavirus 2
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9 56 (SARS-COV-2) infection in pediatrics is not well reported in the literature. We aimed to describe
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11 57 the clinical characteristics and dynamics of SARS-CoV-2 PCR repositivity in children.

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13 58 **Design:** This is a population-level retrospective cohort study

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16 59 **Setting:** Patients were identified through multiple national-level electronic coronavirus disease
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18 60 2019 (COVID-19) databases that covers all primary, secondary and tertiary centers in Kuwait.

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20 61 **Participants:** The study included children 12 years and younger between February 28, 2020 and
21
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23 62 March 6, 2021. SARS-CoV-2 reinfection was defined as having two or more positive SARS-CoV-2
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25 63 PCR done on a respiratory sample, at least 45 days apart. Clinical data was obtained from the
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27 64 Pediatric COVID-19 Registry in Kuwait (PCR-Q8).

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30 65 **Primary and secondary outcome measures:** The primary measure is to estimate SARS-CoV-2
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32 66 PCR repositivity rate. The secondary objective was to establish average duration between first and
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34 67 subsequent SARS-CoV-2 infection. Descriptive statistics was used to present clinical data for each
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36 68 infection episode. Also, incidence-sensitivity analysis was performed to evaluate 60- and 90-day
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38 69 PCR repositivity intervals.

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41 70 **Results:** Thirty pediatric COVID-19 patients had SARS-CoV-2 reinfection at an incidence of 1.02
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43 71 (95% CI 0.71-1.45) infection per 100,000 person-days and a median time to reinfection of 83 days
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45 72 (IQR 62-128.75). The incidence of reinfection decreased to 0.78 (95% CI 0.52-1.17) and 0.47 (95%
46
47 73 CI 0.28-0.79) per person-days when the minimum interval between PCR repositivity was increased
48
49 74 to 60 and 90 days, respectively. The mean age of reinfected subjects was 8.5 years (IQR 3.7-10.3)
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51 75 and the majority (70%) were females. Most children (55.2%) had asymptomatic reinfection. Fever
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53 76 was the most common presentation in symptomatic patients. One immunocompromised
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55 77 experienced two reinfection episodes.
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2 79 **Conclusion:** SARS-CoV-2 reinfection is uncommon in children. Previous confirmed COVID-19 in
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4 80 children seems to result in a milder reinfection.

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10 82 **Data availability statement:**

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12 83 No additional data available.

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17 85 **Strength and limitations of the study**

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19 86 - This study used a national-level electronic database that included all SARS-CoV-2 test
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21 results that allowed data collection from variable sources and the detection of
22 87 asymptotically infected children.
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24 88 - The exact risk for SARS-CoV-2 reinfection is difficult to estimate as children are more
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26 89 likely to be asymptomatic, therefore not all positive cases are detected.
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28 90 - Factors contributing to reinfection such as the circulating variants, and the degree of
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30 91 community SARS- CoV-2 transmission were not addressed in this study.
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32 92 - Patients' symptoms and severity in this retrospective analysis were dependent on the
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34 93 accuracy of reporting in medical notes and parental recall of symptoms.
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36 94 - Due to limited genomic sequencing capacity, proving the direct causality between PCR
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38 95 repositivity and a genetically distinct virus was not possible.
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2 98 **Introduction:**

3
4 99 Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) is a
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6 100 novel beta coronavirus that was first described in December 2019 and resulted in a pandemic of
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9 101 respiratory illness, coronavirus disease-2019 (COVID-19) ¹. By early May 2021, the pandemic has
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11 102 resulted in over 150 million cases worldwide and more than three million deaths reported by the
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13 103 World Health Organization (WHO)². Despite the widespread of COVID-19, children compromised
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16 104 less than 15% of all reported cases ³⁻⁵. Limited social interactions, and enhanced infection control
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18 105 measures such as school closure and online teaching, may have contributed to lower proportions of
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20 106 infected children ⁶. In addition, children are more likely to have asymptomatic or mild infection
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23 107 compared to adults and, therefore, may not be tested ⁷.

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27 109 Quantifying the duration of natural immunity after the primary SARS-CoV-2 infection has
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30 110 been crucial to address public health measures, to help predict the continuity of the pandemic, and
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32 111 to understand the effect of reinfection on disease severity. The first case of SARS-CoV-2
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34 112 reinfection was reported in August 2020 ⁸. Since then, interest in the exact risk and rate of
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36 113 reinfection has been increasing. Several reports estimated that reinfection occurs in less than 1% of
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39 114 previously infected individuals ⁹⁻¹¹. The duration between primary and secondary infection was
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41 115 reported to vary from 48 to 124 days in the first documented cases in literature ^{12, 13}. However, most
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43 116 of the reinfection studies focused mainly on the adult population. COVID-19 follows different
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45
46 117 disease dynamics in children, and studies addressing reinfection in this population are lacking/or
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48 118 limited.

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52 120 The first pediatric case of COVID-19 in Kuwait was identified in February 2020 ⁷. Since
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55 121 then, schools and daycare centers were closed, and classes were conducted virtually. In addition,
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57 122 commercial centers, gyms, and restaurants were open but with time restrictions and strict protective
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60 123 measures. Early in the pandemic, a national electronic COVID-19 testing database was created and

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2 124 included all SARS-CoV-2 test results of symptomatic individuals, contact tracing, and routine
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4 125 travel or hospitalization screening. Also, a national Pediatric COVID-19 Registry (PCR-Q8) was
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6 126 established for children aged 12 years and younger to better understand disease dynamics and
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9 127 update management protocols. This created the unique opportunity to investigate the possibility of
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11 128 reinfection with SARS-CoV-2, with an attempt to establish an average duration between the two
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13 129 positive results, potential factors linked to reinfection, and its clinical severity.
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20 132 **Methods:**

22
23 133 A population-level retrospective cohort study was conducted in Kuwait between February
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25 134 28th, 2020, and March 6th, 2021. The national COVID-19 test result database was used to identify
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27 135 children younger than 12 years and had two or more subsequent positive SARS-CoV-2 polymerase
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30 136 chain reaction (PCR) tests done on a respiratory sample, at least 45 days apart. Subjects who had
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32 137 two or more positive SARS-CoV-2 PCR but less than 45 days in-between, and patients who
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34 138 fulfilled the WHO definition of the multisystem inflammatory syndrome in children (MIS-C) were
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36 139 excluded ¹⁴.
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41 141 To assure the inclusion of all SARS-CoV-2 infected children into this study, the national
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43 142 COVID-19 testing database was used for initial patient identification. This database includes the
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46 143 results for all individuals who had SARS-CoV-2 PCR done on a respiratory specimen nationwide.
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48 144 SARS-CoV-2 PCR is typically done to confirm the diagnosis of symptomatic individuals, detect
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50 145 secondary infections in contact tracing, and identify infected subjects prior to hospitalization or
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53 146 travel. During the study period, the SARS-CoV-2 antigen was not routinely performed on pediatric
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55 147 samples. Also, serum SARS-CoV-2 IgG or IgM tests were not routinely done to confirm current or
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57 148 prior infection. A secondary search query was done on the PCR-Q8 registry, which included patient
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2 149 information from the following sources: hospital records, institutional quarantine centers, patient
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4 150 transport units, as well as all laboratories that provide SARS-CoV-2 PCR.
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9 152 The PCR-Q8 registry retrospectively collected detailed individual-level demographic,
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11 153 laboratory and clinical characteristics of all children diagnosed with COVID-19 in Kuwait. The
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13 154 database was acquired to obtain demographic and clinical data. COVID-19 severity was categorized
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16 155 based on WHO disease classification¹⁵. Infected children with mild or asymptomatic COVID-19
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18 156 may not require hospitalization. Therefore, clinical data in the registry may be lacking/or limited.
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20 157 For those subjected, parents were contacted to complete missing disease-related data.
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25 159 Descriptive analysis was performed to compare between primary and secondary infections.
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27 160 To calculate incidence and to account for delayed presentation of reinfection, calculated days at risk
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30 161 included the period from the day of first positive SARS-CoV-2 PCR starting February 28th, 2020 to
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32 162 the second positive test or March 6th, 2021, whichever is first. However, individuals with the first
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34 163 positive SARS-CoV-2 PCR starting January 1st, 2021, were not included in the calculation due to
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36 164 limited time for reinfection to occur. Clopper-Pearson test was used to calculate the 95% CI.
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39 165 Analysis was done using GraphPad Prism (v. 9.0). Due to the variability in established reinfection
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41 166 case definition, sensitivity analysis assessing the clinical presentation and incidence of reinfection
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43 167 considering a minimum interval for PCR repositivity of 60 and 90 days¹⁶.
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48 169 **Patient and public involvement statement:**

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50 170 Patients were not included in the design, reporting, or dissemination plans of our research.
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53 171 However, parents of children with PCR repositivity were contacted to complete missing data. This
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55 172 study was conducted to address epidemiological questions presented by the Pediatric COVID-19
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57 173 Task Force (Ministry of Health, Kuwait). The initial concept and study plan was presented to the
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59 174 committee members, whose suggestions and comments were considered in the final study protocol
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Ethics:

The study was approved by the ethical board of the Ministry of Health, Kuwait (reference no. 1607/2020). Verbal consent was obtained from parents who agreed to participate to complete missing clinical data.

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1
2 182 **Results**

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4 183 During the study period, there were 14,320 documented SARS-CoV-2 infections in children
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6 184 younger than 12 years in Kuwait, accounting for 2,954,372 person-days of follow-up. Among those,
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8 185 421 children with repeat positive SARS-CoV-2 PCR were identified, of which, 30 patients had a
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10 186 repeat positive SARS-CoV-2 45 days or more after the first positive, 391 patients had their repeat
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12 187 test within 45 days and were excluded (figure 1). The incidence of reinfection was 1.02 (95% CI
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14 188 0.71-1.45) infection per 100,000 previously infected person-days. The mean age of the reinfection
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16 189 cohort was 8.5 (IQR 3.7-10.3) years and majority (70%) were females (table 1). More than half
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18 190 (56.6%) of reinfection patients were not known to have any chronic comorbid conditions at the time
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20 191 of the first or second infection.
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27 193 The median time between the two episodes of infection as evident by the sample collection
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29 194 date was 83 days (IQR 62-128.75 days) (figure 2). Majority of the patients had asymptomatic
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31 195 infection during the first and second episodes, 43.3% and 53.3% respectively (table 2). In
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33 196 symptomatic patients, fever, cough and shortness of breath were the most commonly reported
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35 197 symptoms. One (3.3%) patient had severe pneumonia during the first infection, whereas, four
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37 198 (13.3%) patients had severe pneumonia during second infection. Of those, three patients had mild or
38
39 199 asymptomatic initial SARS-CoV-2 infection. One of the four patients was admitted for an acute
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41 200 exacerbation of asthma with three days history of fever. The median length of hospitalization was 9
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43 201 days (IQR 5.75-13 days) and 6 days (IQR 3.75-6.75 days) for the first and second infection,
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45
46 202 respectively. None of the subjects received care in an intensive care unit.
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52 204 One female patient previously diagnosed with hypereosinophilic syndrome on low-dose
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54 205 prednisone, had three episodes of SARS-CoV-2 infections. Her first infection was in July 2020
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56 206 where she was admitted for 10 days as a case of severe pneumonia followed by two negative PCR
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58 207 tests done in August. Her second infection was in November 2020 when she was also admitted for
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2 208 severe pneumonia with prolonged hospital admission followed by a negative PCR test done in
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4 209 December. Interestingly, during her third infection in January 2021, she was asymptomatic and
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6 210 testing was done for screening before an outpatient appointment.
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11 212 Around half (46.6%) of reinfections occurred more than 90 days after the initial infection.
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13 213 The incidence of reinfection decreased to 0.78 (95% CI 0.52-1.17) and 0.47 (95% CI 0.28-0.79) per
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15 214 infected person-days when the minimum acceptable duration between PCR repositivity was
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18 215 increased to 60 and 90 days, respectively. Also, there were more symptomatic children (64.3%)
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20 216 during the second infection using the 90-day definition when compared to the 45-day or 60-day
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23 217 minimum interval.
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2 220 **Discussion**

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6 222 The exact risk and factors associated with SARS-CoV-2 reinfection in the pediatric population
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9 223 are still not well understood. We found that a second SARS-CoV-2 infection is uncommon in
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11 224 children with a rate of 1.02 reinfection per 100,000 previously infected person-days and a median
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13 225 time to reinfection of 83 days. The finding of this study is similar to previous reports, which showed
14
15 226 a reinfection incidence in adults of 0.9-1.3 per 100,000 person-day^{9,11}. Similarly, in a large Danish
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17 227 cohort, prior SARS-CoV-2 provided on average 80.5% protection against repeat infection. The
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19 228 estimated protection differed between different age groups ranging from 47.1% in individuals older
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21 229 than 65 years of age to 82.7% in younger subjects¹⁷. However, the epidemiology and disease
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23 230 dynamics of SARS-CoV-2 infection are different in children¹⁸. Therefore, using data generated
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25 231 from adult studies to infer on the pediatric population may not be accurate.

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27 232

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30 233 Magnitude and persistence of immunological responses conferred by SARS-CoV-2
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32 234 infection can be variable based on age and medical comorbidities¹⁹. Hence, estimating the duration
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34 235 of protective immunity after acquiring SARS-CoV-2 infection has been the focus of several studies.
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36 236 In an adult study, looking at the neutralizing antibodies, the seropositivity was identified in all
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38 237 participants up to 53 days after infection²⁰. However, the level of neutralizing antibodies varies
39
40 238 greatly with disease severity and tend to wane over time^{21,22}. Few studies compared humoral
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42 239 responses between adults and children. Weisberg et. al. have shown that children exhibit lower
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44 240 antibody response compared to adults²³. However, the incidence of reinfections observed in this
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46 241 study was similar to previously reported adult patients.

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49
50 243 A standard definition of SARS-CoV-2 reinfection is lacking. Traditionally, the detection of
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52 244 viable virus by cell culture has been the standard to ascertain active infection²⁴. However, this
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54 245 testing method lacks sensitivity and is time consuming²⁵. In addition, due to the need of expertise

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2 246 and appropriate laboratory infrastructure, routine population-level testing using cell culture in not
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4 247 possible. For these reasons, the detection of genetically distinct SARS-CoV-2 in different infectious
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6 248 episodes or the use of the cycle threshold (Ct) value as a surrogate for viral load has been suggested
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9 249 ^{12, 13}. In Kuwait, genomic testing capacity is limited and retrieving patients' samples and laboratory
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11 250 data from several public and private laboratories was logistically challenging. In our study, a 45-day
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13 251 period between two-consecutive positive PCR test was selected based on established definition in
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16 252 previously published studies and the expected duration of molecular test positivity on a respiratory
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18 253 sample ²⁶⁻²⁹. Alsharrah et al. reported a median duration of PCR positivity among pediatric COVID-
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20 254 19 patients of 15 days, with maximum duration of 42 days ⁷. However, we observed a decline in the
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23 255 rate of repositivity from 1.02 to 0.47 per 100,000 previously infected person-days when the
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25 256 definition of PCR-repositivity increased from 45 to 90 days. As almost half of cases are
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27 257 asymptomatic, this finding could be due to persistent detection of viral particles by PCR.
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32 259 Asymptomatic SARS-CoV-2 infection is common in pediatrics. We found that around half
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34 260 of infections (43.3% in initial infection and 55.2% in reinfection) remained asymptomatic on
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36 261 follow-up. This finding is similar to other studies ³⁰. High proportion of silent infection may pose an
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39 262 important public health concern and limit the effectiveness of transmission mitigation efforts. Also,
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41 263 the possibility of reinfection within a relatively short period of time as observed in this study may
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43 264 be an overlooked source of community transmission. Further epidemiological studies are needed to
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46 265 assess the risk of transmission in patients with PCR repositivity within 90 days. Real-world
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48 266 COVID-19 vaccine effectiveness data showed that reinfection is more common in unvaccinated
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50 267 adults³¹. These findings support the recommendation to offer vaccination to those previously
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53 268 infected.

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57 270 To our knowledge, this is the first national-level cohort that estimates the risk of pediatric
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59 271 SARS-CoV-2 reinfection. Nevertheless, this study has some limitations. Due to limited genomic

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2 272 sequencing capacity, proving that PCR repositivity was caused by a genetically distinct virus was
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4 273 not possible. However, based on the expected duration of PCR-persistence in children mentioned
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6 274 above, one will not expect that PCR done on an upper respiratory specimen to remain positive
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9 275 beyond 45 days. Also, the effect of different SARS-CoV-2 variants on the risk of reinfection was
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11 276 difficult to assess. Another limitation was the unavailability of some data recorded in the national
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13 277 pediatric COVID-19 registry. When data was missing, parents were contacted via the telephone,
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16 278 creating a recall bias. In addition, patients with mild upper respiratory tracts symptoms are
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18 279 underreported by parents. Therefore, mild cases are less likely to be tested and can be missed, and
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20 280 underestimate the reinfection rate. However, using the national level electronic record allowed the
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23 281 collection of data from variable sources and the detection of asymptotically infected children.
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25 282 Lastly, the exact incidence of reinfection is dependent on several factors that may be difficult to
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27 283 control in cohort studies and may affect data generalizability. These factors include rate SARS-
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30 284 CoV-2 transmission in the community, and preexisting population immunity. However, the effect of
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32 285 existing immunity is limited in our cohort as it included pediatric patients that were followed from
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34 286 the start of the pandemic. Despite these limitations, this study has shown that reinfection is
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36 287 generally uncommon. Further studies that correlate degree of humoral and cellular immunity, along
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39 288 with wide genomic sequencing surveillance with risk of reinfection are needed to better understand
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41 289 and quantify the risk of repeat SARS-CoV-2 infection.
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2 291 **Acknowledgement:**
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4 292 We would like to thank Dr. Hessa Alkandari, chair of the pediatric council in the Ministry of

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6 293 Health, Kuwait, for her help in preparing this manuscript. We also thank the research group of the

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9 294 Pediatric COVID-19 Registry in Kuwait (PCR-Q8) for their contribution.
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1
2 296 **Table 1.** Demographic characteristics of the study population

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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]

6 298 IQR, interquartile range.

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Table 2. Clinical characteristics of the study population based on different defined intervals of polymerase chain reaction (PCR) repositivity

Variable	First Infection			Second Infection		
	Minimum interval of PCR repositivity			Minimum interval of PCR repositivity		
	45 days (n=30)	60 days (n=23)	90 days (n=14)	45 days (n=29)*	60 days (n=23)	90 days (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%)
Hospitalization 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%)
Diarrhea	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%)
Rhinorrhea	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%)
Hospitalization						
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]

IQR, interquartile range.

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14 314 [covid-19-infections/children-and-covid-19-state-level-data-report/](https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/). Published May 10, 2020.
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49 395 Delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections
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55 401 **Table 1.** Demographic characteristics of the study population.

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58 402 **Table 2.** Clinical characteristics of the study population based on different defined intervals of
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60 403 polymerase chain reaction (PCR) repositivity.

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2 404 **Figure 1:** Flow diagram of the study population

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4 405 **Figure 2:** Duration between first SARS-CoV-2 infection and subsequent infections. The shaded

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6 406 bars represent the duration between positive PCR results.

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3 **Figure 1:** Flow diagram of the study population
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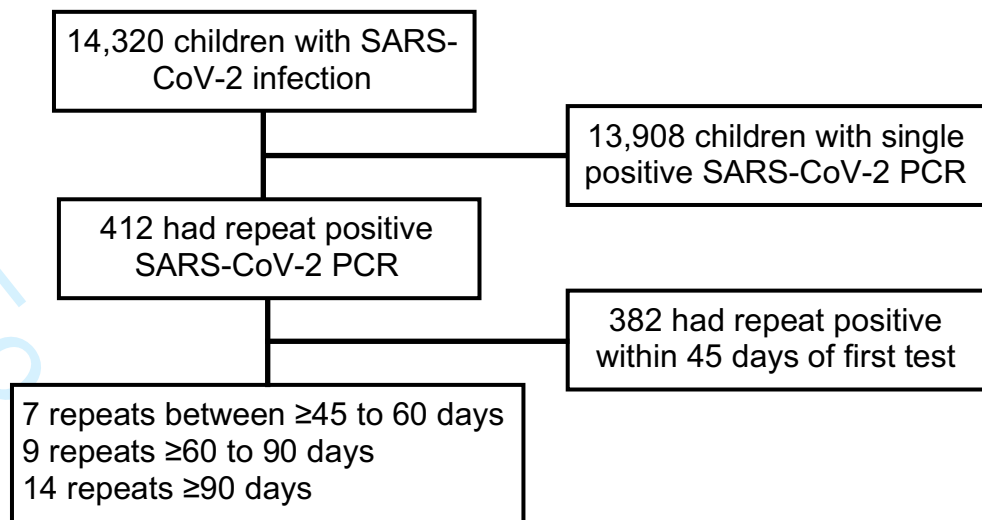
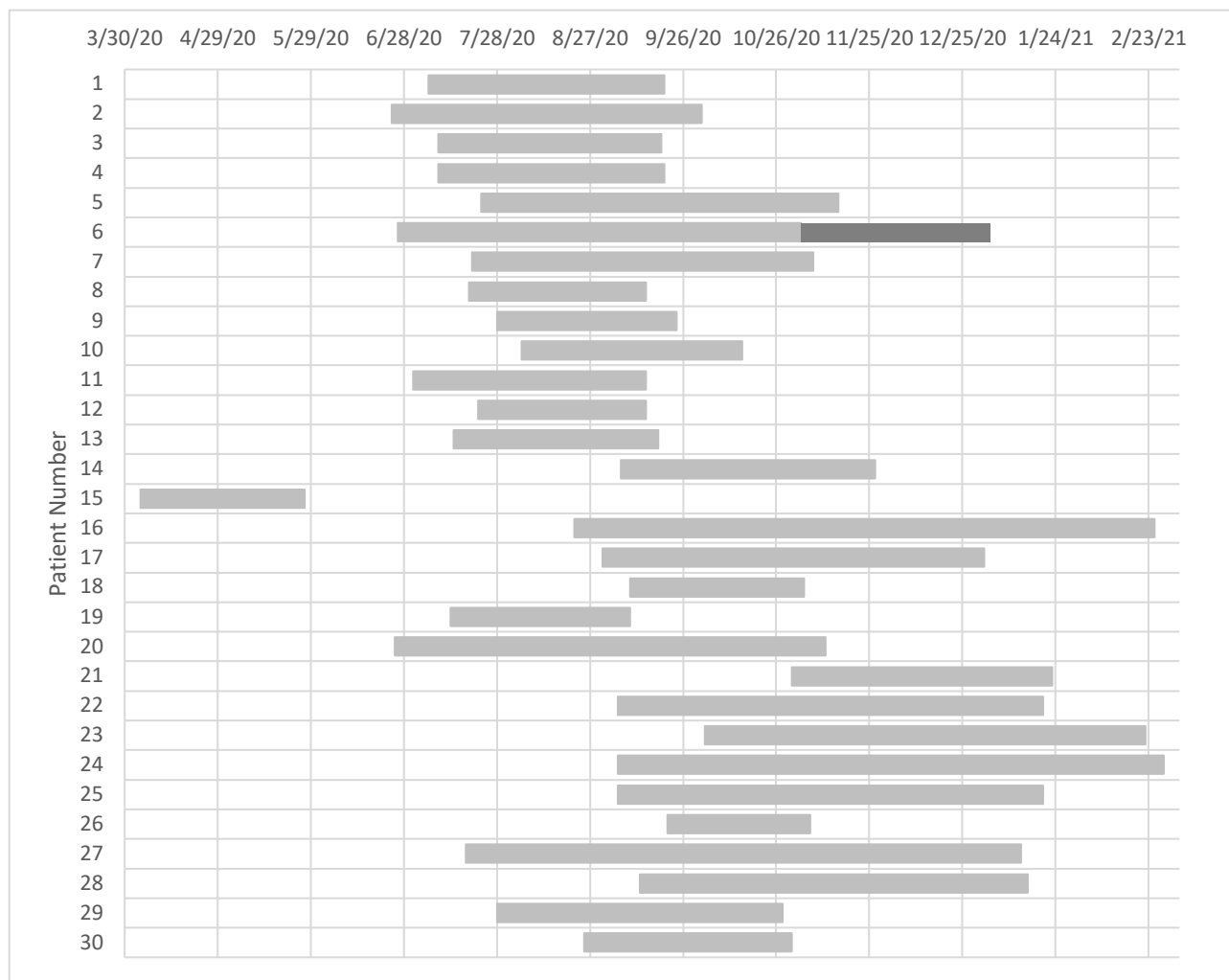


Figure 2: Duration between first SARS-CoV-2 infection and subsequent infections. The shaded bars represent the duration between positive PCR results.



*Patient 6 had two episodes of reinfection

Incidence of Potential SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page and line number
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	P 1, L 1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	P 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	P 6, L 105-123
Objectives	3	State specific objectives, including any prespecified hypotheses	P 7, L 132-134
Methods			
Study design	4	Present key elements of study design early in the paper	P 7, L 138
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Dates: P7, L139 Exp: P7, L 146 Data: P8, 157
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	P 7, L138 and P8, L 157
		<i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	Exclusion: P 7, L142
		<i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	NA
		<i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	P 7, L 146 Outcome: P7, L140
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P8, L157
Bias	9	Describe any efforts to address potential sources of bias	Potential recall bias is mentioned in limitation
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	P 8, L165
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	NA
		(b) Describe any methods used to examine subgroups and interactions	P8, L 170
		(c) Explain how missing data were addressed	NA
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	NA
		<i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	
		<i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	P8, L 170

Results			Page and line number
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	P 9, L 183
		(b) Give reasons for non-participation at each stage	P 9, L187
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	P 9, L 193
		(b) Indicate number of participants with missing data for each variable of interest	Table 1- no missing data Table 2 – indicated by *
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	P9, L 184
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	P9, L183- 190
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	P9, L187
		(b) Report category boundaries when continuous variables were categorized	done
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	P 10, L213
Discussion			
Key results	18	Summarise key results with reference to study objectives	P11, L 223
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P12, L272
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P11, 234- P12 L269
Generalisability	21	Discuss the generalisability (external validity) of the study results	P12, L 280
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P1, L15

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely

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available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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