

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Incidence of SARS-CoV-2 Reinfection in a Pediatric Cohort in Kuwait
AUTHORS	Alhaddad, Fatemah; Abdulkareem, Ali; Alsharrah, Danah; Alkandari, Abdullah; Bin-Hasan, Saadoun; Al-Ahmad, Mona; Al Hashemi, Hashem; Alghounaim, Mohammed

VERSION 1 – REVIEW

REVIEWER	Jessica Snowden University of Arkansas for Medical Sciences, Arkansas Children's Hospital
REVIEW RETURNED	01-Oct-2021

GENERAL COMMENTS	<p>The authors present a well-written manuscript describing the number of children with repeat positive COVID-19 test results in Kuwait. The ability to review the entire national dataset is a strength of the manuscript. In the discussion, the authors provide justification for the selection of 45 days as the cutoff point for "reinfection" for children with more than one positive test result in the dataset. However, there is no justification provided for the additional analyses at 60 and 90 days. Presumably the fact that the apparent "reinfection" rate decreases at 60 and 90 days reflects the likelihood that the patients with positive tests between 45-60 days reflect prolonged shedding rather than reinfection, however the authors do not provide any possible interpretation for that finding or for analyzing at the latter time points. The authors should (a) provide justification in the methods for the selection of the 45, 60, and 90 day time points; and (b) reframe the discussion to provide a more thorough explanation of the results.</p>
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REVIEWER	Rita Carsetti Bambino Gesù Children's Hospital, Rome, Diagnostic Immunology Unit
REVIEW RETURNED	16-Dec-2021

GENERAL COMMENTS	<p>This is a very interesting paper addressing the question of whether children may be reinfected by SARS-CoV-2. The Authors find that re-infection is rare in children 12 year-old or younger, with an observed rate of 1.02%.</p> <p>The retrospective cohort study included children who tested positive between February 28 2020 and March 6 2021, The surprising result is that median time to re-infection was 83 days. We normally assume that in adult reinfection is due to failure or decline of the immune response (see cited paper ref 16). The short time to re-infection observed here may indicate that the mostly asymptomatic or mild infections of children may fail to generate protective immune</p>
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	memory and strongly support the recommendation to vaccinate all children including those with previous infection. I believe that a short sentence about children immunity and avaccination should be added to the discussion.
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REVIEWER	Pier Piccaluga University of Bologna School of Medicine and Surgery, Department of Experimental, Diagnostic, and Experimental Medicine
REVIEW RETURNED	14-Jan-2022

GENERAL COMMENTS	<p>This is an interesting and well written article. The information are presented and discussed properly. The conclusions resonable and respectful of data.</p> <p>Minor: the cumulative incidence of reinfection is presented as number of infections per 100,000 previously infected person-days. It would be useful to know how many patients did experience reinfection,</p> <p>The Authors state that "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". Is 1.02 really similar to 0.13? Please discuss further</p> <p>Since most infections were asymptomatic in this age group, it would be useful to comment about possible strategies to avoid virus spread in such instances</p>
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VERSION 1 – AUTHOR RESPONSE

	Reviewer #1 Comments
R1_1	<p>-The authors present a well-written manuscript describing the number of children with repeat positive COVID-19 test results in Kuwait. The ability to review the entire national dataset is a strength of the manuscript.</p> <ul style="list-style-type: none"> We thank the reviewer for her time and effort in reviewing our study. <p>-In the discussion, the authors provide justification for the selection of 45 days as the cutoff point for "reinfection" for children with more than one positive test result in the dataset. However, there is no justification provided for the additional analyses at 60 and 90 days. Presumably the fact that the apparent "reinfection" rate decreases at 60 and 90 days reflects the likelihood that the patients with positive tests between 45-60 days reflect prolonged shedding rather than reinfection, however the authors do not provide any possible interpretation for that finding or for analyzing at the latter time points. The authors should (a) provide justification in the methods for the selection of the 45, 60, and 90 day time points; and (b) reframe the discussion to provide a more thorough explanation of the results.</p> <ul style="list-style-type: none"> We agree with the reviewer. It is difficult to establish whether the repositivity observed between 45 and 60 days is due persistent viral detection or reinfection. This fact was highlighted in the third paragraph of the discussion section (page 11, line 252): "A standard definition of SARS-CoV-2 reinfection is lacking. Traditionally, the detection of viable virus...". Also, to better explain the reviewer's points, the following sentences were added (page 12, line 265-268): "However, we observed a decline in the rate of repositivity from 1.02 to 0.47 per 100,000 previously infected person-days when the definition of PCR-repositivity increased from 45 to 90 days. As almost half of cases are asymptomatic, this finding could be due to persistent detection of viral particles by PCR."

	<ul style="list-style-type: none"> Regarding the use of 45-, 60-, and 90- day intervals, 45-day interval was selected based on our previous experience in a cohort of pediatric patient who had regular PCR testing. The remaining intervals were selected based on case definitions established by different European countries. The reasoning and a reference were added to the methods section (page 8, line 178). The point of doing sensitivity analysis was to highlight the points raised here by the reviewer.
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	Reviewer #2 Comments
R2_1	<p>-This is a very interesting paper addressing the question of whether children may be reinfected by SARS-CoV-2. The Authors find that re-infection is rare in children 12 year-old or younger, with an observed rate of 1.02%. The retrospective cohort study included children who tested positive between February 28 2020 and March 6 2021, The surprising result is that median time to re-infection was 83 days. We normally assume that in adult re-infection is due to failure or decline of the immune response (see cited paper ref 16). The short time to re-infection observed here may indicate that the mostly asymptomatic or mild infections of children may fail to generate protective immune memory and strongly support the recommendation to vaccinate all children including those with previous infection. I believe that a short sentence about children immunity and a vaccination should be added to the discussion.</p> <ul style="list-style-type: none"> We thank the reviewer for her time and effort in reviewing our study. We agree with the reviewer on the importance of COVID-19 vaccination to those with recent infection. A paragraph addressing reinfection concerns related to public health and vaccination was added to the discussion section (page 12, line 270): "Asymptomatic SARs-CoV-2 infection is common in pediatrics. We found that around half of infections (43.3% in initial infection and 55.2% in reinfection) remained asymptomatic on follow-up. This finding is similar to other studies. High proportion of silent infection may pose an important public health concern and limit the effectiveness of transmission mitigation efforts. Also, the possibility of reinfection within a relatively short period of time as observed in this study may be an overlooked source of community transmission. Real-world COVID-19 vaccine effectiveness data showed that reinfection is more common in unvaccinated adults. These findings support the recommendation to offer vaccination to those previously infected."

	Reviewer #3 Comments
R3_1	<p>-This is an interesting and well written article. The information are presented and discussed properly. The conclusions reasonable and respectful of data. Minor: the cumulative incidence of reinfection is presented as number of infections per 100,000 previously infected person-days. It would be useful to know how many patients did experience reinfection,</p> <ul style="list-style-type: none"> We thank the reviewer for his time and effort in reviewing our study. As indicated in our Results section: (page 9, line 193), 30 patients had repeat positive SARS-Cov-2 45 days or more after the first positive swab.
R3_2	<p>-The Authors state that "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". Is 1.02 really similar to 0.13? Please discuss further</p>

	<ul style="list-style-type: none"> Each number had different denominator. We thank the reviewer for highlighting a source of potential misinterpretation. The denominator was changed to be matching in both numbers (page 11, line 235).
R3_3	<p>- Since most infections were asymptomatic in this age group, it would be useful to comment about possible strategies to avoid virus spread in such instances.</p> <p>We agree with the reviewer that comment of public health measures to control the outbreak is relevant. A paragraph discussing potential public health concerns and COVID-19 vaccination has been added to the discussion section.(page 12, line 270):</p> <p>“Asymptomatic SARs-CoV-2 infection is common in pediatrics. We found that around half of infections (43.3% in initial infection and 55.2% in reinfection) remained asymptomatic on follow-up. This finding is similar to other studies. High proportion of silent infection may pose an important public health concern and limit the effectiveness of transmission mitigation efforts. Also, the possibility of reinfection within a relatively short period of time as observed in this study may be an overlooked source of community transmission. Real-world COVID-19 vaccine effectiveness data showed that reinfection is more common in unvaccinated adults. These findings support the recommendation to offer vaccination to those previously infected.”</p>

VERSION 2 – REVIEW

REVIEWER	Jessica Snowden University of Arkansas for Medical Sciences, Arkansas Children’s Hospital
REVIEW RETURNED	23-Feb-2022

GENERAL COMMENTS	<p>The authors present a national cohort study of COVID-19 in children, describing the frequency of a repeat positive PCR test in children with a history of COVID-19. Given our increasing appreciation of the impact the COVID-19 pandemic has had on children, studies like this are important to understanding the epidemiology of COVID-19. Enthusiasm for the publication is limited by (1) lack of justification of the choice of 45 days as a definition of reinfection, which is inconsistent with the standard guideline of 90-days used by most other groups and supported with only one citation; and (2) conclusions reported in the discussion and abstract that are not justified by the results of this study, particularly given the differences observed when using a 45- versus 90-day definition of reinfection. In particular, the abstract states that previous infection appears to convey immunity, which is not addressed in this study. Many factors contribute to reinfection, including exposures, variants, community levels of infection, vaccination, etc, none of which are addressed in this study. Paragraph 4 in the discussion states that the possibility of reinfection within a short period of time could be a source of community transmission. Again, no data in this study supports that conclusion. Additionally, there are multiple grammatical errors throughout the manuscript and copy editing is strongly suggested.</p>
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REVIEWER	Rita Carsetti Bambino Gesù Children’s Hospital, Rome, Diagnostic Immunology Unit
REVIEW RETURNED	01-Mar-2022

GENERAL COMMENTS	The revised version of the paper can be accepted for publication.
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REVIEWER	Pier Piccaluga University of Bologna School of Medicine and Surgery, Department of Experimental, Diagnostic, and Experimental Medicine
REVIEW RETURNED	09-Feb-2022

GENERAL COMMENTS	no further comments
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VERSION 2 – AUTHOR RESPONSE

	Reviewer #1 Comments
R1_1	<p>The authors present a national cohort study of COVID-19 in children, describing the frequency of a repeat positive PCR test in children with a history of COVID-19. Given our increasing appreciation of the impact the COVID-19 pandemic has had on children, studies like this are important to understanding the epidemiology of COVID-19. Enthusiasm for the publication is limited by</p> <p>(1) lack of justification of the choice of 45 days as a definition of reinfection, which is inconsistent with the standard guideline of 90-days used by most other groups and supported with only one citation</p> <p>We thank the reviewer for the time placed on reviewing our study and her constructive comments.</p> <p>To date, there is still some controversy on the most appropriate duration between subsequent positive PCR to define a reinfection. However, several cohort studies among adults reported that persistent PCR positivity becomes very unlikely after 6-weeks (42 days) (Sethurman et al, JAMA. 10.1001/jama.2020.8259; Wajnberg, Lancet Microbe, 10.1016/S2666-5247(20)30120-8). This finding was similar to what we described among a pediatric cohort that was serially tested until 2 negative consecutive PCR (Alsharrah, JMV. 10.1002/jmv.26684). This factor, along with rapid decline in humoral responses after 30 days of infection, lead several authors to consider 45 days as the cutoff duration to consider reinfection (Cohen and Burbelo, CID. 10.1093/cid/ciaa1866) and the same definition was used as a primary measure (Abu-Raddad, CID. 10.1093/cid/ciaa1846) or part of sensitivity analysis (Qureshi, CID. 10.1093/cid/ciab345)</p> <p>We agree with the reviewer that the exact duration for reinfection need a consensus agreement among expert. In view of absence of clear definitions we opted to perform a sensitivity analysis of all three established durations (45, 60, 90 days). We modified the manuscript to include the abovementioned references. Now it read: “In our study, a 45-day period between two-consecutive positive PCR test was selected based on established definition in previously published studies and the expected duration of molecular test positivity on a respiratory sample ²⁶⁻²⁹.”</p>

R1_2	<p>(2) conclusions reported in the discussion and abstract that are not justified by the results of this study, particularly given the differences observed when using a 45- versus 90-day definition of reinfection. In particular, the abstract states that previous infection appears to convey immunity, which is not addressed in this study. Many factors contribute to reinfection, including exposures, variants, community levels of infection, vaccination, etc, none of which are addressed in this study.</p> <p>Paragraph 4 in the discussion states that the possibility of reinfection within a short period of time could be a source of community transmission. Again, no data in this study supports that conclusion. Additionally, there are multiple grammatical errors throughout the manuscript and copy editing is strongly suggested.</p> <p>We agree with the reviewer on the point that our paper did not evaluate the risk of reinfection, rather the incidence alone. Hence, it is inaccurate to assume the protective role of previous infection on the subsequent exposure. For this reason, the conclusion in the abstract was modified</p> <p>Also, we agree that some factors related to the risk of reinfection were not addressed in the paper. Other factors contributing to reinfection were not part of the primary nor the secondary objectives of the study. This point was added to the limitation section.</p> <p>Finally, regarding the point stating that the possibility of reinfection within a short period of time could be a possible source of community transmission, we agree with the reviewer that we did not assess the risk of transmission from reinfected patients. However, transmission from asymptotically infected individuals is well documented. We added a sentence to address the reviewer's comment: "Further epidemiological studies are needed to assess the risk of transmission in patients with PCR repositivity within 90 days."</p> <p>We reviewed the manuscript for grammar errors and corrected accordingly.</p>

	Reviewer #2 Comments
R2_1	-Thank you for your effort in reviewing our paper

	Reviewer #3 Comments
R3_1	-Thank you for your effort in reviewing our paper