PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19 symptom surveillance in immunocompromised children and young people in the UK: a prospective observational cohort study
AUTHORS	Shaunak, Meera; Patel, Ravin; Driessens, Corine; Mills, Lynne; Leahy, Alice; Gbesemete, Diane; Owens, Daniel; Lucas, JS; Faust, Saul; de Graaf, Hans

VERSION 1 – REVIEW

REVIEWER	Godelieve de Bree Amsterdam University Medical Center, location AMC
REVIEW RETURNED	19-Oct-2020

GENERAL COMMENTS	The authors describe a prospective observational cohort study among children and teenagers reporting symptoms of upper respiratory tract infections who are immunocompromised. In technical sense the study is well conducted. However, the interpretation of the data and the implications of the findings should be better described. I have several concerns: First, the main finding is that of all patients tested (110) none had COVID. But it is quite a substantial group (although the size of the cohort should be related to estimated total numbers (see also my comment below)) of children presenting with COVID-like symptoms. It is unclear what the implications are of this finding. I can imagine you would like a strategy that allows for early detection of COVID-19 in this patient group, but screening for symptoms is apparently not effective? This needs to be discussed. It would add to the study is a comparison (of symptoms) could be made with immunocompromised children with a proven SARS-CoV-2 infection. Are these data available through the ISARIC (Docherty et al BMJ) database. In the paper by Docherty it is shown that 310 people under age 18 were diagnosed with COVID. Additional question: To what extent is there overlap with centers that provided data to the study by Docherty and the present study? In the conclusion of the abstract (lines 50-54) the authors state that symptoms suggestive of SARS-CoV-2 were common. This implies… “ But the children do report symptoms suggestive of upper respiratory tract infection. How is this interpreted, was diagnostic testing for other respiratory viruses performed. Only if these were negative you could state that isolating measures were effective. Second, in the introduction (line 43) the authors mention the primary aim of the study which is assessment of frequency and severity of infection. Here also anxiety score should be added as aim.

	Third, an important conclusion is the high anxiety score. This is an important finding and should be more prominent in the abstract. Fourth, Results and discussion: Apparently only a minority of participants 110 of the 922 who reported symptoms were tested. How was it decided that participants should be tested: was it their own decision, or was the advice to get tested with symptoms? And if so, upon which symptoms. This should be explained in the methods section. Testing of only 110 out of 922 with symptoms could result in missing diagnoses. Minor comments Abstract line 55: comparison should be made with immunocompromised adults. Results: Lines 12-13 “by week 16, 1490…etc”. How does this compare to the total (estimated) number of children in care in the region / centers that contributed to the study. This would be relevant to mention and to discuss with respect also to potential bias in the study. Figure 2a: symptoms: often patients would report more than 2 symptoms. A Venn diagram would provide more insight. Table 1: how does it come that the number of patients in the upper row (“primary diagnosis”) is exactly the same in the lower row (“medication”), that does suggest that all patients use medication? Is it correct that there were 49 patients with diabetes and 82 patients use insulin (how is diabetes defined? Does not include steroid induced diabetes?) Results lines 35: 137 participants had medication suspended: what was the reason. Was the reason risk for COVID? Discussion Line 60: no participant: here should be added that 110 patients were tested Line 17: In the UK .. co-morbidity: the 43% with comorbidities: what was the proportion immunocompromised?

REVIEWER	Jérémie Rouger-Gaudichon University Hospital Centre Caen
REVIEW RETURNED	12-Nov-2020

GENERAL COMMENTS	This report is well-written and address an interesting question with an original method. The results provided here should be shared and published. However, the manuscript could be improved and some elements need to be precised. Please find below some commentaries and suggestions: 1) the authors stated that the primary objective was to assess the frequency and severity of COVID-19 in immunocompromised children. To answer to this question, the method appears to be not appropriate. The answers provided by the parents are declarative and it seems that the study mainly describe the frequency of symptoms that could be compatible with SARS-CoV-2 infection. To determine the frequency of the disease data should have retrieved directly from laboratory testing. Indeed, patients with symptoms obviously did not perform any test, and some asymptomatic children

	may also have an infection... 2) The authors may give more precisions or criticize in discussion the recruitment method: who decided the indication of flu vaccination, how much is it exhaustive if it only relies on practitionners' memory among centers? 3) The frequency of symptoms in the cohort is particularly high with no case of SARS-COV-2. The authors discussed this point but they may go further. They should notice that joint pain for instance is quite frequent comparatively with other symptoms, and may be frequent because of the studied population (auto-immune diseases requiring immunosuppressive treatments). 4) the figure 2 is an interesting way of showing the results. The authors should add a legend in the figure to favor the comprehension of the scale. 5) Did the authors see any correlation between parents' anxiety and the number or the type of symptoms presented by the children? 6) Some papers have indicated that immunocompromised children with cancer and/or HSCT history may be at risk of developing severe COVID-19. It should be mentionned in the discussion.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:
The authors describe a prospective observational cohort study among children and teenagers reporting symptoms of upper respiratory tract infections who are immunocompromised. In technical sense the study is well conducted. However, the interpretation of the data and the implications of the findings should be better described. I have several concerns:

First, the main finding is that of all patients tested (110) none had COVID. But it is quite a substantial group (although the size of the cohort should be related to estimated total numbers (see also my comment below)) of children presenting with COVID-like symptoms. It is unclear what the implications are of this finding. I can imagine you would like a strategy that allows for early detection of COVID-19 in this patient group, but screening for symptoms is apparently not effective? This needs to be discussed. It would add to the study is a comparison (of symptoms) could be made with immunocompromised children with a proven SARS-CoV-2 infection. Are these data available through the ISARIC (Docherty et al BMJ) database. In the paper by Docherty it is shown that 310 people under age 18 were diagnosed with COVID.
-Thank you for this comment. We have contacted the authors of the recommended paper and following additional analyses have added the following sentence in the discussion:" There was no significant difference in the presenting symptoms of the immunocompromised compared to the rest of the paediatric cohort (A. Docherty, personal communication)

Additional question: To what extent is there overlap with centres that provided data to the study by Docherty and the present study?
-Both studies have collected data from hospitals all over the UK. The overlap is extensive. We added a list of participating centres in supplementary online appendix B to make this clear.

In the conclusion of the abstract (lines 50-54) the authors state that symptoms suggestive of SARS-CoV-2 were common. This implies… " But the children do report symptoms suggestive of upper

respiratory tract infection. How is this interpreted, was diagnostic testing for other respiratory viruses performed. Only if these were negative you could state that isolating measures were effective.
-Thank you for this comment. Diagnostic testing for other respiratory viruses was not performed. We have removed this from the abstract conclusion.

Second, in the introduction (line 43) the authors mention the primary aim of the study which is assessment of frequency and severity of infection. Here also anxiety score should be added as aim.
-The primary objective of the study has been re-worded as per Reviewer 2's comment. A secondary objective relating to describing anxiety in this cohort has been added as recommended.

Third, an important conclusion is the high anxiety score. This is an important finding and should be more prominent in the abstract.
-The results section of the abstract has been re-arranged, giving the anxiety score finding more prominence.

Fourth, Results and discussion:
Apparently only a minority of participants 110 of the 922 who reported symptoms were tested. How was it decided that participants should be tested: was it their own decision, or was the advice to get tested with symptoms? And if so, upon which symptoms. This should be explained in the methods section. Testing of only 110 out of 922 with symptoms could result in missing diagnoses.
-The methods section has been expanded: added: "Study participants were advised that the study did not replace normal healthcare provision and were asked to follow government guidance and seek medical advice via emergency health care providers or the child's normal clinical team if concerns about symptoms arose. The study team did not provide advice on SARS-CoV-2 testing. During the study period testing was limited to patients possibly needing admission in the UK due to a national shortage."

Minor comments

Abstract line 55: comparison should be made with immunocompromised adults.
-Thank you for this comment. This is a very valuable addition, although we thought it would be better placed in the discussion. We added: While some adult patients on immunosuppressive biologics may not be at higher risk of severe disease (Fung et al, CID 2020), other analyses suggest that adults with malignancy, autoimmune conditions, asplenia and other immunosuppressive conditions are at greater risk of COVID-19 related death (Williamson et al Nature 2020).

Results: Lines 12-13 "by week 16, 1490…etc". How does this compare to the total (estimated) number of children in care in the region / centers that contributed to the study. This would be relevant to mention and to discuss with respect also to potential bias in the study.
- Thank you for this comment. We added in the limitations: "Although all subspecialties in each hospital were approached to take part in the study, not all decided to participate. This may have caused bias in the composition of the cohort." We have also added a new table to the supplementary online appendix B that shows recruitment number per centre.

Figure 2a: symptoms: often patients would report more than 2 symptoms. A Venn diagram would provide more insight.
-Thank you for your comment. We have replaced the heatmap with the suggested Venn diagram titled: Venn diagram depicting the association between fever, cough, shortness of breath and sore throat during the study period
Table 1: how does it come that the number of patients in the upper row ("primary diagnosis") is exactly the same in the lower row ("medication"), that does suggest that all patients use medication?

Is it correct that there were 49 patients with diabetes and 82 patients use insulin (how is diabetes defined? Does not include steroid induced diabetes?)
-Thank you for your comment. We removed the total number in the medication part as this does not make sense. As diabetes is sometime a comorbidity of another primary disease there are more patients on insulin than patients with a primary diagnosis of diabetes. To clarify this we added to the results section: “When patients had more than one diagnosis, the primary diagnosis is reported.”

Results lines 35: 137 participants had medication suspended: what was the reason. Was the reason risk for COVID?
-Yes – this has been added to the manuscript.

Discussion Line 60: no participant: here should be added that 110 patients were tested - -This has been added to the manuscript.

Line 17: In the UK .. co-morbidity: the 43% with comorbidities: what was the proportion immunocompromised?
-8% had a haematological/ oncological or immunological co-morbidity and could be presumed immunocompromised. This has been added to the manuscript.
Reviewer 2

Comments to the Author
This report is well-written and address an interesting question with an original method. The results provided here should be shared and published. However, the manuscript could be improved and some elements need to be precised. Please find below some commentaries and suggestions:

1) the authors stated that the primary objective was to assess the frequency and severity of COVID-19 in immunocompromised children. To answer to this question, the method appears to be not appropriate. The answers provided by the parents are declarative and it seems that the study mainly describe the frequency of symptoms that could be compatible with SARS-CoV-2 infection. To determine the frequency of the disease data should have retrieved directly from laboratory testing. Indeed, patients with symptoms obviously did not perform any test, and some asymptomatic children may also have an infection...
-The primary objective has been re-worded as follows: “to describe the frequency of symptoms compatible with SARS-CoV-2 infection in immunocompromised children and young people in the UK during the SARS-CoV-2 pandemic”

2) The authors may give more precisions or criticize in discussion the recruitment method: who decided the indication of flu vaccination, how much is it exhaustive if it only relies on practitionners' memory among centers?
- Added to explain the indication for vaccination: following the Immunisation against infectious disease UK governmental guidance (Green book Chapter 19, page 14 https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/931139/Green_book_chapter_19_influenza_V7_OCT_2020.pdf). All patients with these conditions are cared for by specialised teams in hospitals. To make this clear we changed “centres” to “hospitals”.

3) The frequency of symptoms in the cohort is particularly high with no case of SARS-COV-2. The authors discussed this point but they may go further. They should notice that joint pain for instance is quite frequent comparatively with other symptoms, and may be frequent because of the studied population (auto-immune diseases requiring immunosuppressive treatments).
-We have added this point to the discussion – specifically that symptoms of SARS-CoV-2 infection overlap with those of chronic disease exacerbations and medication side-effects. Common symptoms may reflect the contribution of certain diagnoses to the cohort.

4) the figure 2 is an interesting way of showing the results. The authors should add a legend in the figure to favor the comprehension of the scale.
-Thanks for this comment. As suggested by the first reviewer we have replaced the figure by a Venn diagram and have amended the legend accordingly.

5) Did the authors see any correlation between parents' anxiety and the number or the type of symptoms presented by the children?
-Thank you for this suggestion. We looked at the data and found no correlation between parent' anxiety and the number of symptoms. We added "the correlation between number of symptoms and anxiety was not significant using cross-sectional Pearson correlation".

6) Some papers have indicated that immunocompromised children with cancer and/or HSCT history may be at risk of developing severe COVID-19. It should be mentioned in the discussion.
-We have included some reviews which show that although these children are prone to infection, they are not very much affected by SARS-CoV-2. We added the following reference (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7361142/) reporting that the incidence of COVID-19 disease is lower after haematopoietic stem cell transplantation in children than in adults to the discussion. We have also added the following reference (https://doi.org/10.1038/s41416-020-01181-0) that reports that children with cancer and SARS-CoV-2 infection do not appear at increased risk of severe infection compared to the general paediatric population.

VERSION 2 – REVIEW

REVIEWER	Jérémie Rouger CHU Caen, Normandie, France
REVIEW RETURNED	19-Jan-2021

GENERAL COMMENTS	Thank you for your anwers. I hope I helped you to improve the manuscript