

Peer Review File

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Reviewer Comments

The paper titled “Association between vaccinations and clinical manifestations in children with COVID-19” is interesting. Pediatric COVID-19 patients with BCG vaccinations exhibit similar clinical manifestations compared to those without BCG vaccinations, and the severity of symptoms in pediatric patients may be related to the maturity of immune function. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1: The number of children without BCG vaccination in China is limited, and the number of children not vaccinated with BCG in this study is also very small, and the statistical results may be biased. The comparison with children in other countries should be increased, and the results are more credible.

Reply 1: Thanks for your comments, we acknowledged that the number of children not vaccinated with BCG in this study was very small, and the statistical results may be biased because of this small sample size of children without BCG vaccination. The number of children without BCG vaccination in China is limited because it is free and mandatory to vaccinate BCG at birth in China according to the Chinese policy. We agreed that the comparison with children in other countries should be increased and the results will be more credible, we will try our best to look up the potential cooperation pediatric hospital in future, we have addressed this important issue in the limitation section (see Page 11, lines 262-264).

Changes in the text: We have modified our text as “according to the Chinese policy,

the comparison with children in other countries should be increased and the results will be more credible, we will try our best to look up the potential cooperation pediatric hospital in future” (see Page 11, lines 262-264)

Comment 2: Will children have the problem of long intestinal detoxification? Are anal swabs more appropriate than nasopharyngeal swabs as a treatment effectiveness and determining the time to terminate isolation?

Reply 2: According to our previous study (Emerg Microbes Infect. 2020;9(1):1233-1237.), although we did not conduct strictly paired time-course analysis, we noticed that some cases were persistently negative in throat swabs and others were persistently negative in anal swabs. Thus, similar to SARS-CoV and MERS coronavirus (Lancet Gastroenterol Hepatol. 2020;5(4): 335-337.), we suspect that fecal-oral transmission is also one route for SARS-CoV-2 infection and long intestinal detoxification may occur in some cases.

According to the study conducted by Gong et al in 10 pediatric patients, they reported that testing on anal swabs remained detectable well even after throat testing was negative and suggested the possibility of fecal-oral transmission besides respiratory transmission (Nat Med. 2020;26(4):502-505). According to our previous study (Emerg Microbes Infect. 2020;9(1):1233-1237.), we suspect that decreased viral loads in anal swabs may indicate the resolution phase of SARS-CoV-2 infection and has the potential to be used for monitoring the effectiveness of therapeutic responses as which negatively correlated with Tregs, IgM, and IgG.

Changes in the text: We didn't modify our text.

Comment 3: The current situation of the foreign epidemic situation is very severe, and it is constantly evolving and changing. What is the significance of this research to the global situation of COVID-19?

Reply 3: As the reviewer said the current situation of the foreign epidemic situation is very severe, we are trying to investigate the association of BCG vaccination and COVID-19 infection in children, the significance of this research is that the findings of

this study may provide evidence of the science decision for government, especially in the field of BCG vaccination, it may be helpful to control the COVID-19 epidemic in the global situation.

Changes in the text: We have modified our manuscript as “it may be helpful to control the COVID-19 epidemic in the global situation.” in the discussion section (see Page 12, lines 279-280)

Comment 4: What are the human genetic factors related to COVID-19 infection susceptibility and disease severity? What are the special factors for children?

Reply 4: ACE2 or TMPRSS2 DNA polymorphisms were likely associated with genetic susceptibility of COVID-19, ACE2 polymorphisms were found to be associated with cardiovascular and pulmonary conditions by altering the angiotensinogen-ACE2 interactions, such as p.Arg514Gly in the African/African-American population. Unique but prevalent polymorphisms (including p.Val160Met (rs12329760), an expression quantitative trait locus in TMPRSS2, offer potential explanations for differential genetic susceptibility to COVID-19 as well as for risk factors, including those with cancer and the high-risk group of male patients.(BMC Med . 2020, 18(1):216. Hum Genomics. 2020, 14(1):17.)

Special factors for children may be related to the immunity. The immune system of children is still developing and may respond to pathogens differently comparing to that in adults. In the present study, we found that the percentage of asymptomatic COVID-19 infections increased with age. Children will conduct many vaccines and have a more active innate immune response and fewer underlying disorders. So children maybe more vulnerable to the SARS-COV-2 virus.

Changes in the text: We have modified our text as “ACE2 or TMPRSS2 DNA polymorphisms were likely associated with genetic susceptibility of COVID-19(21-22)”. (see Page 10, lines 228-229)

Comment 5: Children are as likely to be infected with COVID-19 as adults, but the importance of children in spreading the virus is still uncertain. What are the

symptoms that children are more likely to have than adults?

Reply 5: Although children are as likely to be infected with COVID-19 as adults, but the infection rate of children is less than adults, it may be less exposure to the virus. The symptoms that children are more likely to be fever and/or cough than adults, and less dizziness, headache, abdominal pain, diarrhea, nausea, vomiting, loss of appetite. (Wu Q, et al. Pediatrics. 2020;146(1). Ma, N., et al. 2020; JAMA Ophthalmol 138(10): 1079-1086.)

Changes in the text: we have modified our text as “The symptoms that children are more likely to be fever and/or cough than adults.” (see Page 10, lines 220-221)

Comment 6: There are several imported cases in this study, and these cases need further analysis and comparison.

Reply 6: Thanks for your kind suggestion, we have compared the eight imported cases with Chinese cases in Wuhan, the percentage of BCG vaccination (5/8) for imported confirmed cases is much lower than that of China (239/248), and the asymptomatic rate (5/8) is higher than that of Chinese cases (92/248). we added this in the results section (see Page 9, lines 194-197)

Changes in the text: we have modified our text as advised “We have compared the eight imported cases with Chinese cases in Wuhan, the percentage of BCG vaccination (5/8) for imported confirmed cases is much lower than that of China (239/248), and the asymptomatic rate (5/8) is higher than that of Chinese cases (92/248).”(see Page 9, lines 198-201)

Comment 7: There have been many studies on COVID-19. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.

Reply 7: To the best of our knowledge, this is the first original study on the association of BCG vaccinations and clinical manifestations in children with COVID-19, we have searched in PubMed with keywords (Bacillus Calmette Guerin[Title])

AND (COVID–19[Title]), there are only some commentary or review article in adult. (Weng, C. H., et al. Epidemiol Infect. 2020,148: e140. Ten Doesschate, T., et al. Trials. 2020,21(1): 481.)

Changes in the text: We have modified our text as “the association of BCG vaccinations and clinical manifestations in children with COVID–19” in the introduction section (see Page 5, line 111-112.)

Comment 8: There are many uncertainties in retrospective research, which increase the deviation of research results. How to explain and solve this problem?

Reply 8: We agreed that many uncertainties exist in retrospective research, however in the current retrospective study, the symptoms and age were recorded in the electronic health record, and the vaccination status was recorded in the specific vaccine management system, the deviation is relatively low.

Changes in the text: We have modified our limitation as “however in the current retrospective study, the symptoms and age were recorded in the electronic health record, and the vaccination status was recorded in the specific vaccine management system, the deviation is relatively low.” (see Page 12, lines 269-272)
