20-Dec-2021
BMJ-2021-068898.R1
Comprehensive assessment of paediatric SARS-CoV-2 infection: A Danish population-based cohort study

Dear Ms. Kildegaard

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, and would be happy to consider it for publication if you could revise it according to the comments from the reviewers and the editorial team.

When you return your revised manuscript, please note that The BMJ requires an ORCID ID for corresponding authors of all research articles. If you do not have an ORCID ID, registration is free and takes a matter of seconds.

Yours sincerely,

Di Wang
Clinical Editor, the BMJ

T: 010 6410 0685
E: dwang@bmj.com
W:bmj.com/company
dwang@bmj.com

To start your revision, please click this link or log in to your account: *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=680560b474c14aff9c8818c86bfecd0a

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair); Richard Riley, Gary Collins, Angie Wade, Tim Cole; Jamie Kirkham; Rafael Perera; Julie Morris (statistical editors); Tim Feeney; Joseph Ross; Tiago Villanueva; Navjoyt Ladher; Nazrul Islam; Wim Weber; Di Wang; Jin-ling Tang (research editors)

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

1) As you mentioned, the screening rates varied. Might this not capture the full picture and downplay the impact of Covid on children? Please discuss on it.

2) Could you explain why in Table S7, the test negative group has higher absolute rate of many adverse outcomes (e.g. hospitalisation, ICU admission, Pneumonia, drug initiation, etc)? It does not seem plausible.

3) Table 1 should present the characteristics by test results (positive vs negative).

4) Why did you not consider a test-negative case control study design for vaccine efficacy?

5) Is it possible to also compare the outcomes by variants (e.g. alfa, delta) ? For example, by period of dominance or by sequencing (which would be better and more convincing, if you hae the data)?

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper. You may find the comments from Susi Kriemler and Richard Riley (statistician) particularly comprehensive and helpful.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:

Thank you for the opportunity to review this excellent study on the country-wide prevalence of SARS-CoV-2 infections in Denmark. I would like to compliment the authors for their work, for the careful interpretation of the results and thorough discussion including limitations of such a population-based cohort study. The study has a given design, and obviously and importantly compares PCR+ and PCR- youth. Although there were hospitalisations including ICU admissions, MIS-C and single neurological diseases withing 30 days of a positive PCR-Test, there was only a slight increase in health care use (physician visits) in the PCR+ compared to the PCR- group. Clear vaccination effectiveness was documented especially from 2months after vaccination on. The authors hypothesized that the increased health care use could be related to long COVID symptoms.

Overall, I think that the manuscript is very well and thoughtfully written. I would, nevertheless like to raise a few questions and comments for authors to consider.

The control population is not a random sample of all CYP in Denmark, but rather test-negative CYP. CYP doing the testing are likely slightly different from the general population: they might live in more urban settings, have better access to testing, perhaps higher socioeconomic position within families, etc. Presumably, the authors are trying to control for these unobserved characteristics by this choice of the control group or by calculating a propensity score as presented in the supplementary Table 2. Alternatively, perhaps this group was just more convenient to sample than general CYP population. As the control group plays a major role in the interpretation of results, the choice of both groups should be discussed in Methods and Discussion. This comment also refers to the comparison of vaccinated vs. non-vaccinated groups, in which you seem to have some socio-economic information.

The target population includes all CYP, tested in Denmark for SARS-CoV-2 at certain time periods. Perhaps this is detailed in the protocol, but it would be interesting to read also in the manuscript on a few further aspects: why were PCR-tests done in these children?

What were the testing criteria and setting during these months in Denmark? Particularly, asymptomatic children: were they (usually) tested due to contact tracing in families or regular screening at schools? Are the screening tests included in the eligible sample at all and equally distributed? Is it known if certain groups or minorities are underrepresented in tested populations in Denmark – and subsequently, in this study? Since having had a test is an inclusion criterion for the study population, it would be important to understand how exactly it might have affected the selection.

The authors also present results reweighted for representing the target population. Although it is possible to compare them with raw results, it would be convenient to summarize it in a sentence in Results, in a paragraph "Study representativeness". It seems that authors also collected ethnicity information (based on the information on vaccination among immigrant populations), which could be compared, if not with the target sample, then with general UK population for representativeness. Representativeness of socioeconomic backgrounds would be important too, at least via living address as proxy.

The authors provide information about mitigation and testing strategies in Denmark, but also timing of school holidays could have influenced the results (although – likely both for negative and positive participants). Since participants were recruited over more than a year, it would be interesting to see if results change when for instance 3-monthly sub-cohorts are analysed. E.g., are outcomes different for the different time periods? That would provide further important methodological insights, e.g., how sensitive population-based cohort studies might be to seasonal/epidemiological timing. Moreover, this could also be done for the time periods where different VOC mutations were prevalent. This approach would also allow to see whether there is a cohort effect in the controls which should not happen at all.

The authors matched the cohort only on the basis of the timing of the PCR testing and in sensitivity analyses also matched for year of birth and sex, if I understand correctly, in an effort to use pre-test characteristics. Therefore, matching by ethnicity, socio-economic state or previous illness was not done. However, assuming they should not change between testing and follow-up, they could maybe be used for matching as well. It would be great if you could justify your choice not to include them – as they would seem important to consider.

Figure 1 describes cases, testing, hospitalisations and vaccinations over time. I wonder whether you can comment on the ratio of cases and testing frequency that seems to have changed considerably over time. So, seemingly the number of cases does depend on testing frequency and cases when testing is relatively lower would be lower as well. On the other hand, the use of rapid tests may also have influenced prevalence based on PCR and could further contribute to the dark figure of cases.

Not only the number of tests done influences the number of cases and might be different among groups, but also the reason for testing. As mentioned already indication for PCR testing and possible confounding based on differential use of this indication seems important.

We do not have a lot of population-based information about MIS-C which does seem to be important in defining the SARS-CoV-2 burden of disease in CYP. Although I realize that n=27 cases is not a lot, I wonder whether the predominant VOC played a role. In our country we rarely see MIS-C with delta while it was still rare, but more common with previous mutations. Curious about your findings.

The other major burden of disease in SARS-CoV-2 is certainly Long COVID. I agree with the authors that data and the discussion about Long COVID is still very much discussed and debated. We do have some very good (controlled) studies now, that document long COVID to be a relevant side effect of SARS-CoV-2 infections. In the section "what is already known on this topic" you state that some evidence suggests that a substantial proportion of children experience persisting symptoms or sequelae to SARS-CoV-2 infection, but existing studies have major limitations, including responder bias and lack of control group. Perhaps this statement could be rephrased stating that long COVID in CYP exists, but with wide ranges of prevalence even in controlled studies (see CLoCK, Miller, Stephenson, Blankenburg, Molteni, Radtke). Ref 30 in your manuscript does not seem to be adequate. The whole discussion about long COVID is a bit difficult to follow and raises concerns. It seems to me that authors neglect the existence of controlled studies as mentioned above that are able to differentiate among SARS-CoV-2

specific symptomatology and confounders such as restrictions by the pandemic or other respiratory viruses.

Minor comments
Please define outcomes consistently. I understand that they were categorized into acute, intermediate and post-acute, but periods for intermediate overlap with acute and post-acute. Overlaps to compare time periods do not seem to make sense, but I may be wrong.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Susi Kriemler

Job Title: Prof

Institution: University of Zurich

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may

in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

Reviewer: 2

Recommendation:

Comments:
This study conducted a comprehensive assessment of SARS-CoV-2 infection in children and adolescents in Denmark based on the Nationwide Danish healthcare registers. The authors have assessed the risk of acute and post-acute adverse events following SARS-CoV-2 infection and evaluated the real-world effectiveness of the BNT162b2 mRNA vaccine. This is an excellent job about the SARS-CoV-2 infection in children and adolescents. The study has provided important implications for policymakers about epidemic prevention and control. However, I have some comments and hope these will help to improve this manuscript.
1. The authors have described the epidemic development in Denmark from 2020 to 2021 (Page 6, Line 35, Setting), and there were different epidemic stages. In Figure 1, the authors have presented the overview of the SARS-CoV-2 epidemic in Danish children and adolescents. I wonder whether the authors could add some information into Figure 1 to make the figure more informative, such as important time points of epidemic development described in the section of Setting, key prevention and control measures. Combining and visualization the average daily number and critical events in the development of the epidemic will help the readers easily get more information.
2. Page 7, Line 45-49: "Children who were not living in Denmark during the year prior to the index date or had previously been tested positive for SARS-CoV-2 were excluded from further analyses." Why did the authors exclude the children who were not living in Denmark during the year prior to the index date? One year prior to the index date?
3. Page 7, Line 57: How did the authors define the three periods? Is there a basis for classification? How did the authors choose day 0 to 29, day 0 to 59, and day 30 to 179? There were also some overlaps in these periods. I think the authors should clarify the point.
4. Page 11 Line 15: The authors have mentioned the information about whole genome sequencing of RT-PCR SARS-CoV2 tests. I think that the authors should describe the point in the Method part.

5. Page 11, Line 35-39: “The risk of hospitalization was similar in the second and third part of the pandemic, regardless of the predominant SARS-CoV-2 strain.” Did the second and third part represent Second wave and Alpha variant in Table S3, respectively? The descriptions should be consistent.
6. Page 13, Line 30-35: The authors have estimated vaccine effectiveness against documented SARS-CoV-2 infection. I want to know if it is possible to evaluate the effects of the vaccine for the risk of acute and post-acute adverse events.
7. Can the authors conduct a stratified analysis (stratified by SARS-CoV-2 variants or different stages of epidemics) based on the results in Figure 2? Because various measures in different stages might have significant effects on the outcomes in Figure 2, such as lockdown, vaccination, as the authors mentioned that reported risks associated with SARS-CoV-2 infection in children are highly dependent on the setting.
8. Page 15 Line 23: “In Denmark, two child fatalities have been registered within 30 days of a positive SARS-CoV-2 test, corresponding to a case fatality rate of 0.003%.” The authors should report case fatality in Denmark in the Results section.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Shunqing Xu

Job Title: Professor

Institution: State Key Laboratory of Environment Health (Incubation), Key Laboratory of Environment and Health, Ministry of Education, Key Laboratory of Environment and Health (Wuhan), Ministry of Environmental Protection, School of Public Health, Tongji Medical College, Huazhong University of Science and Technology, #13 Hangkong Road, Wuhan, 430030, Hubei, PR China.

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: No

Reviewer: 3

Recommendation:

Comments:
First, it is an excellent paper which presented a comprehensive data on COVID-19 epidemiology in children. However, I have some clarification regarding:

1. What is the exact number of MIS-C in this study? Is it 2 in 1000 (in discussion line 51) or 0.5 in 1000 (page 16 of 48) or 0.05% (abstract)? In comparison to data of the other country such as US, the incidence of MIS-C is 2 per 100,000. Why is the incidence of MIS-C higher in these settings?
2. I suggested to compare the mortality data to general child mortality data before pandemic in your country. And probably it is useful to address the inequality of healthcare service in other settings also contribute to children mortality in COVID-19 pandemic to become the lesson learned from this study
3. In table 1, the % of children hospitalized in age group 0-1 is 31%. In the settings, we know that the policy of swab in children is started from 2 years old of age. Please explain it more.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Nina Dwi Putri

Job Title: Dr

Institution: Faculty of Medicine, Universitas Indonesia

Reimbursement for attending a symposium?: Yes

A fee for speaking?: Yes

A fee for organising education?: Yes

Funds for research?: Yes

Funds for a member of staff?: Yes

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: I received funding as a field coordinator of ZF-2001 COVID-19 vaccine trial.

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

Reviewer: 4

Recommendation:

Comments:
This registry-based study investigated the risk of acute and post-acute adverse events following SARS-CoV-2 infection and the effectiveness of the BNT162b2 mRNA vaccine among children and adolescents in Denmark. This topic is of public health importance. Data used in this study were obtained from various medical registries and data quality should be good. Overall, the study design appears to be valid. Below are my specific comments/suggestions:

1. The authors included children with RT-PCR test SARS-CoV-2 between 27 February 2020, to 31 July 2021 in the analysis of adverse events following SARS-CoV-2 infection. But as the authors mentioned, the test became widely available from July 2020. I suggest the authors exclude data between February and July 2020 to make the study population more 'representative'.

2. Could the authors provide the rationale for the use of "a reference cohort from the entire cohort of children under the age of 18 who were tested for SARSCoV-2 during the study period." One might ask why not just include all SARSCoV-2 negative children.

3. Page 7 of 48, Line 39-43. How was the reference cohort drawn? Randomly? What percentage? Were the positive cases also included in the sampling? But from lines 53-55, it seems only negative children were included for sampling. Suggest moving this sentence (lines 53-55) to Line 43.

Minor comments:
1. The title is a bit broad. I suggest the authors use a more specific title.
2. Please provide the numbers of total sample size and SARS-CoV-2 infection cases for the vaccine effectiveness assessment in the Abstract.
3. Page 10, line 29. "Only individuals with complete follow up were included". How did the authors define "complete follow up"? Only included children with SARSCoV-2 test?

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Huimin Xia

Job Title: Professor

Institution: Guangzhou Women and Children's Medical Center

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: No

Reviewer: 5

Recommendation:

Comments:
In this manuscript, the authors use Danish registry data to define population based risks for children in acute COVID (risk of hospitalization/ICU, acute complication like myocarditis or neuro issues, or MIS-C), and risks of having long effects of COVID (risk of needing follow up care). They compared children who tested positive for SARS-CoV-2 with children who tested negative. They also quantified real-life risk of testing positive for SARS-CoV-2 with and without documentation of vaccination. The key findings were that while risks of severe COVID/hospitalization/complication were low, the risk of MIS-C is notable (1:2000). There is an increased need for medical care post-COVID, suggesting long COVID, and vaccines are 88% after 2nd dose.

Overall, the authors have written a very clear, well organized and data supported manuscript. The data is highly informative and adds significant value. As a comprehensive report, I envision that this manuscript will serve as an important reference and justification for many pediatric COVID-19 related grants and manuscripts.

As the authors note, this manuscript does have biases included predominantly including a Caucasian population, and capturing medical information from the earlier part of delta transmission, and there were inherent limitations in who was tested. The authors address these concerns right of the bat in the discussion though.

Unfortunately, there was a peak of pediatric COVID as schools started in July, at least in the US, so this study missed that important and informative time period.

I would also argue that while the risk of COVID is low, 77-319 children (depending on the criteria the authors used) resulted in hospitalization for a vaccine-preventable illness. This carries significant healthcare implications and cost. This point seems to be lost in the policy implications section.

Overall, an excellent manuscript with informative data.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Lael Yonker

Job Title: Assistant Professor

Institution: Mass. General Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

Reviewer: 6

Recommendation:

Comments:

Thank you for the opportunity to review this interesting and informative research article, which is generally well written, and the authors have clearly worked very hard to produce this research. It's clearly an important and relevant topic.

I have read this from a statistical perspective, and have a number of comments for the authors to address in their revision. I do find some aspects confusing, as there are many comparisons going on here, including comparing positive versus negative (and ref group), and vaccinated versus unvaccinated, and I wonder what the 'best' reference group should be. Comments as follows:

1) The study is following up those who were PCR positive, but this depends on who is getting tested and who has access to tests, am I right? So could the sample be an unrepresentative sample of children?

2) I find the reference group confusing. Does it include people that might also be positive? And if not, then how does it differ from the subsequent analyses that only include test negative as a reference group? Please add more clarity.

3) Related point: late in the results we see "In sensitivity analyses using a cohort of SARS-CoV-2 test-negative children as comparators, SARS-CoV-2 positive children were no longer at increased risk of hospitalisation within the first month of testing and the signals indicating increased initiation of bronchodilating agents during the post-acute phase was also attenuated" – so this raises doubt in my mind as to the choice of the reference group. Are those that tested negative not more reliably negative and so a better reference group to focus on than the one chosen to be the main reference group?

4) "The risk of MIS-C within two months of SARS-CoV-2 infection was 0.05% (N=27)" – but the denominator is 60692 and so this should be 0.04%? (0.04445%) – perhaps rather give to 2 decimal places, so 0.045%. Please check other calculations and rounding.

5) Confidence intervals are needed around the %s shown in the abstract and in the whole paper. For example, for the above I work out the 95% CI is 0.029% to 0.065%.

6) For the general reader, I would suggest giving the actual manufacturer name (Pfizer) for the BNT162b2 mRNA vaccine too for the reader in the abstract and paper.

7) "with MIS-C occurring in one of 2000 children" – change to in ABOUT one in 2000 children

8) "The BNT162b2 mRNA vaccine was effective in preventing documented SARS-CoV-2 infection for up to three months after the first dose." – this implies it is NOT effective after three months, but the authors do not focus on evaluations post 3 months. So this needs to be worded better.

9) There is no mention of missing data in covariates or how it was handled in the analyses – in particular, toward the propensity score matching if one of the covariates was missing,

10) "Only individuals with complete follow up were included" – the impact of potentially informative censoring is considered in a sensitivity analysis. The results are shown in Table S11 and I think should also be included in the main article for completeness (even though results are very similar). Though, the number at risk will change for each analysis? This is not clear from the table, as it gives just one set of events and number at risk for each of the two groups.

11) Excuse my ignorance from a non-statistical perspective, but in Figure 3 why would the vaccinated people not get infected? I thought it was more that vaccine led to more mild symptoms after infection, not that there is no infection at all. Should this be labelled % diagnosed?

12) A related point but in the what this study adds, it says "The BNT162b2 mRNA vaccine was effective in preventing documented SARS-CoV- 2 infection for up to three months after first dose" – this implies it

completely prevents infection in anyone – surely this is not correct? It might reduce risk of infection, or reduce risk of symptoms? But not completely prevent?

13) Figure 2 – why are some outcomes give as events n < 5 and others given as events =0?

14) Figure 2 - CIs are needed around the %s

15) PERR=prior event rate ratio adjusted rate ratio. This is quite hard to follow. Might be easier to refer to it as a ratio of rate ratios (RRR)?

16) Table 2 please add a footnote to explain better what is meant by baseline and follow-up.

17) Table 1 "stratified one whether the infection led to hospitalization" – should rather be "stratified BY whether the infection led to hospitalization"?

18) How are adjusted risk differences calculated? As this is either conditional on assumed values of the adjustment factors, or somehow averaged over all individuals (marginal risk difference). Please clarify.

19) Abstract, in the results where it says "The estimated vaccine effectiveness …" please make it clear what the reference group is.

20) "For comparison, we matched 10 unvaccinated individuals to each vaccinated individual based on birthyear, sex and municipality on the date of vaccination." – also adjusted for is immigration status. But generally, these seems a limited set of confounders to adjust for (e.g. comorbidities, smoking, etc). I wonder if the authors could comment on this potential limitation?

21) The results section of the main paper would benefit from sub-headings to break up the text and aid with the flow for the reader.

I hope these comments are helpful to the authors and I look forward to seeing the revision
Richard Riley
Professor of Biostatistics and Acting Chief Statistics Editor for BMJ

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Richard Riley

Job Title: Prof of Biostatistics

Institution: Keele University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes