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Re: BMJ-2021-068898.R2

Dear Editors,

Thank you very much for the favourable evaluation of our manuscript on the course of the Danish SARS-CoV-2 pandemic, acute and post-acute effects of SARS-CoV-2 infection, and vaccine effectiveness in Danish children and adolescents. Please find below a point-by-point account of how we have addressed the issues raised by the editorial team and the reviewers. We appreciate the comments that have helped us to improve the manuscript. In addition to the changes prompted by the comments from the reviewers, we have extended follow-up until the end of October, which have led to a substantial increase in the number of children infected during the period where the delta variant was predominant, and in particular the number of BNT161b2 vaccine recipients in the vaccine effectiveness analysis. Finally, with the emergence of the new omicron variant, we would additionally like to offer to submit a subsequent research letter or otherwise supplement this submission regarding the risks related to omicron infection when these data become available during the early spring. However, we do not find it appropriate to postpone publication of the existing data.
Changes to the manuscript have been marked using the track changes function in Word. We hope that our revisions have enhanced our manuscript sufficiently to be acceptable for publication in your journal.

Sincerely,

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Comments from editorial team

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.

The level of screening most certainly affects the number of SARS-CoV-2 cases identified. Disregarding the first few months of the epidemic, where all countries including Denmark had a shortage of SARS-CoV-2 tests, Danish children and adolescents have been encouraged to undergo PCR-testing for SARS-CoV-2 throughout the epidemic in cases of symptoms that could be related to SARS-CoV-2 or if they had been in close contact with individuals positive for SARS-CoV-2. All tests were provided for free and were easily accessible nationwide. Consequently, the rates of testing among Danish children and adolescents have generally been very high. Nevertheless, some positive children are certain to go undiagnosed. We believe that such underdiagnosing will most likely primarily concern those with asymptomatic or very mild primary infection and those in the lowest risk of adverse events, although we do not yet fully know the association between initial severity of disease and immune-mediated complications such as MIS-C.
As a consequence of this, the number of children and adolescents with test-confirmed SARS-CoV-2 infection will naturally be lower than the total number of SARS-CoV-2 infections in society, as also indicated by recent Danish seroprevalence studies of SARS-CoV-2 that are referenced in the Discussion. As argued above, this is expected to mainly affect those with milder disease and thus mainly affect the denominator in our risk estimates, leading to a possible overestimation of the risks associated with SARS-CoV-2 infection in children, a concern which we have also included in the Discussion. Ultimately, we believe that using test-confirmed SARS-CoV-2 cases is the best approach leading to a clear target of inference as this population is clearly defined whereas the number of undetected infections is much more uncertain and difficult to estimate.

To aid readers, we have expanded the setting paragraph in the methods section to include more details on testing policies and added information on lock-down periods and major changes in testing strategies to Figure 1.

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.

Initially, we considered using the test negative group as our main control population. However, as detailed in the protocol amendments, we realized that this came with inherent biases, which led to us using the randomly sampled control population employed in the main analysis. For children and adolescents, testing of SARS-CoV-2 has been recommended in case of symptoms that could be related to SARS-CoV-2, because of contact with others with SARS-CoV-2 infection, before contacts to the health care system, and finally in the spring of 2021 weekly testing was recommended for school children. At the time of their negative test, children are therefore not necessarily representative of the background population. Some are presenting symptoms related to other respiratory viruses or, more importantly, otherwise in need of contact to the health care system, which explains the increased risk of many short-term outcomes (e.g. hospitalization, ICU admission and pneumonia).

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

As argued above, we do not believe that the test negative individuals are representative for the background population at the time of testing and thus the test negative population is not used as the primary comparator, i.e. reference cohort. We have, however, now included characteristics of the reference cohort in Table 1.

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

We believe that the cohort study design is an accepted and equally valid design for estimating vaccine effectiveness. We ultimately chose this design primarily because it allowed us to provide absolute effect sizes.

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 had the data)?

Denmark has sequenced the vast majority of SARS-CoV-2 tests from the fall of 2020 and onwards (in 2021 more than 90% have been sequenced). Due to data protection regulations, these results are not available on an individual-level nor stratified on age, but we used these results to define periods, where the B1.177, alpha and delta variant was dominant. We have now included analyses on all main outcomes stratified by these periods corresponding to the B1.177, alfa, and delta variant in the supplementary material, although evaluation of post-acute effects during the delta variant was not possible due to insufficient follow-up time. Further, and as per the comment from reviewer #1 below, we have presented the risk estimate for MIS-C by variant as part of the main manuscript.

Comments from the external peer reviewers

Reviewer #1

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.

Thank you for the positive comments and your thoughtful review.

1) 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.

Our permissions to study effects of SARS-CoV-2 infection are limited to individuals tested at some point for SARS-CoV-2. As the epidemic progresses, this group includes the vast majority of Danish children and adolescents. We have now included a supplementary table, stratified on age, of how many children have been tested out of the total Danish child population. As more than 84% of Danish children and adolescents thus are included in our study, we believe that our sample is representative of Danish children and adolescents. More importantly, the small subpopulation that has not at any point undergone testing for SARS-CoV-2 in a country with a very well-developed testing strategy, is considered unlikely to seek testing in case of symptoms, and thus represent a population that is not 'at risk' of the main criteria of interest across the analyses in our study: covid-19. We adjust for differences in baseline health and health care seeking behavior by applying propensity score-based weighting. We have now included immigration status to table 1 and in our propensity score model. Unfortunately, we do not have additional data on ethnicity or socioeconomic position. We have elaborated on our choice of reference group in the Methods section, and it is also addressed in the Discussion.

2) 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.

Unfortunately, we have no data on why an individual child had a PCR-test done at a certain time point, and we do not know whether a test was performed due to symptoms or as a screening. However, all tests are included in our data set regardless of the indication for testing. We have elaborated on the testing criteria used in Denmark in different periods of the epidemic in the Methods section and incorporated information on lock-down periods and major changes in testing strategies to Figure 1.

As argued above, 84% of Danish children and adolescents have been tested for SARS-CoV-2 at some point and are thus included in our study. Regardless of whether that individual was tested only once or multiple times, we have all both prior and subsequent data on drug use, health care utilization and hospital diagnoses. We therefore believe that the risk of selection bias is negligible in our setting.

3) 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.

We have weighted the reference cohort to represent the SARS-CoV-2 infected cohort to adjust for the small differences in baseline characteristics. The characteristics of the SARS-CoV-2 infected cohort and the reference cohort before and after propensity score-based weighting are presented in supplementary Table S4, including standardized mean differences. As argued above, we believe that our sample is representative of Danish children and adolescents and have elaborated on this in the Discussion. As suggested, we have now also included immigration status in our models.

4) 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.

Thank you for this suggestion. As outlined in our response above (editorial comment #5), we have now included analyses on all main outcomes by time periods corresponding to the B1.177, alpha, and delta variant in the supplementary material and have presented the risk of MIS-C by variant in the main manuscript. Regarding seasonality, we have further tried to mitigate this bias by sampling a temporally aligned reference cohort as described in the Methods section p 7, lines 25-28.

5) 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.

For the main reference cohort, we randomly assigned each individual an index date from the distribution of test dates among SARS-CoV-2 positive children to ensure that the two cohorts were temporally aligned. We then applied propensity score-based weighting to adjust for differences in age, sex, medical history, and now also immigration status. We chose to apply weights instead of matching not to exclude data on SARS-CoV-2 negative individuals, and believe that weighting is at least an equally valid tool for confounder adjustment as matching.

6) 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 have included a figure of the positive percentage over time in our supplementary material (Figure S1). As further discussed in our response to the editorial comment #1, we expect that increased testing primarily increases the identified number of individuals with asymptomatic or very mild SARS-CoV-2 infection and that the dark figure of cases leads to an overestimation of the risks associated with SARS-CoV-2 infection There is, however, not a linear trend between the number of tests and positive cases, as illustrated by Figure 1 during the spring of 2021, when the average number of daily test were at their highest, but the number of SARS-CoV-2 cases was at a low stable rate.

Changes in testing strategy have primarily been driven by developments in SARS-CoV-2 transmission. Thus, when Denmark like the rest of Europe experienced increased SARS-CoV-2 transmission in the fall of 2020, the Danish Health Care Authorities repeatedly encouraged Danish citizens to undergo testing in cases of symptoms that could be related to SARS-CoV-2 or if they had been in close contact with individuals positive for SARS-CoV-2. When Denmark experienced a second lock-down in January and February testing rates and SARS-CoV-2 transmission fell abruptly. In the spring of 2021, there were relatively low and stable rates of SARS-CoV-2 infection among children and adolescents, despite of high numbers of tests reflecting that school children were encouraged to undergo weekly testing after returning to schools. This information has now been added to the methods section to aid interpretation.

Use of antigen testing was very limited in children and adolescents until the spring of 2022 and has since been used mainly for children aged 12 years of above and only for asymptomatic testing. If tested positive on an antigen test, children were encouraged to undergo subsequent PCR-testing and 84% with a positive antigen test for SARS-CoV-2 underwent PCR-testing within 2 days of the antigen test.

7) 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.

Again, thank you for this suggestion. We have now included the risk for MIS-C by SARS-CoV-2 variant as also outlined above and report no difference in the occurrence of MIS-C across dominating SARS-CoV-2 strain.

8) 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.

Thank you for these comments. We have updated our literature search and references on long COVID. We have made the following change to the discussion: "There is an increasing amount of literature reporting on persisting symptoms following infection, such as fatigue, headache, cognitive difficulties, myalgia, and cough persisting in anywhere from 4 to 66% of children with SARS-CoV-2 infection.[31] Because these symptoms are highly prevalent in childhood and adolescence and may have been exaggerated by the negative effects of lockdown measures on children's well-being, comparison with non-SARS-CoV-2 infected individuals is crucial in order not to overestimate the prevalence of "long-COVID". Emerging controlled studies on persistent symptoms after SARS-CoV-2 infection, all report increased risk of symptoms after both four and twelve weeks, but with wide ranges of prevalence and risk differences ranging from 0.8% to 13.1% among SARS-CoV-2 infected children and controls. [32–37] We did not have information on symptom-based outcomes, but…"

Minor comments

9) 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.

Thank you for this comment. We have had a lengthy discussion amongst the authors as how to best define the outcome windows to capture and characterise adverse events related to SARS-CoV-2 infection. To increase specificity, we chose to limit acute complications as hospitalisations, ICU treatment etc. to the 0-29 day time window, as events beyond this period are likely not related to the primary SARS-CoV-2 infection. However, this time window was not applicable when reporting on the risk of post-infectious complications to SARS-CoV-2 infection such as MIS-C which usually occurs weeks after the primary infection. We chose the two-month intermediate time window to ensure capture of complications such as MIS-C. We acknowledge that this window overlaps with the primary risk window of 0-29, however, as some complications such as MIS-C can occur during a longer window, this was ultimately found to be the most relevant risk window.
The single outcome is, however, not reported across overlapping time periods. Thus, the risk of hospitalization is only reported in the acute (0-29 day) and post-acute period (30-179 day).

Reviewer #2

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.

Thank you.

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.

Thank you for this very useful suggestion. We have now added time points to Figure 1 and expanded the 'Setting' paragraph in the methods section to include more details on Danish testing policies over time.

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?

We chose to exclude these children from analyses to ensure preexposure data on drug prescriptions, hospitalisations, and health care utilization, and this has been added to the Methods section. Further, we have rephrased the sentence to "… not living <u>continuously</u> in Denmark during the one year prior to their 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.

We ultimately chose to operate with these time periods to maximize capture of adverse events related to SARS-CoV-2 infection in all phases of the epidemic. No outcome is, however, reported across overlapping time periods. We have provided a more detailed reasoning behind our choices in the response to comment 9 from reviewer #1 above.

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.

Thank you for this suggestion. We have added information on whole genome sequencing of RT-PCR SATS-CoV-2 tests to the methods section on page 6, line 7-10: "Using data from Danish large-scale genome sequencing of SARS-CoV-2 available from the Global Initiative in Sharing All Influenza Data (GISAID), we also evaluated the risk of study outcomes across dominating SARS-CoV-2 strains."

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.

We agree and have now used the same wording in the description of periods throughout the manuscript.

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.

Preliminary analyses showed that there had only been <5 hospitalisations 30 days after SARS-CoV-2 infection among 12-17 year-olds in the period between 1 May 2021 and 31 October 2021 where we evaluated vaccine effectiveness. We therefore decided that our study was not powered to evaluate the risk of hospitalisations and other 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.

As outlined in our response to the editorial comment #5, we have now included analyses on all main outcomes by the B1.177, alfa, and delta variant in the supplementary material and have presented the risk of MIS-C by variant in the main manuscript.

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.

The number of fatalities registered within 30 days of a positive SARS-CoV-2 test comes from an external source (Statens Serum Institute) and therefore it is not reported in the results section.

Reviewer #3

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

Thank you for your comments.

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?

We have revised the wording, so the risk of MIS-C is reported consistently throughout the manuscript. The incidence of 2 per 100,000 reported in the US by authors as Belay ED et al. (PMID: 33821923) is the cumulative incidence of MIS-C among all American children and adolescents. This number is largely affected by the measurement point in the epidemic and by national developments of the epidemic. We therefore chose to report the risk of MIS-C as the number of MIS-C cases among children and adolescents with confirmed SARS-CoV-2 infection.

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

In the discussion, we have argued that the substantial geographic disparities in outcomes related to COVID-19 can be related to "differences in national management of the epidemic, access to health care, testing capacity and issues of race, social inequality, and underlying child health." According to Statistics Denmark, Danish all-cause child mortality has been stable around 0.03% during the past five years. Because there have only been two child fatalities reported so far in Denmark in relation to SARS-CoV-2 infection, and as it is uncertain whether these are directly caused by SARS-CoV-2 infection, we have chosen not to include this comparison in the final manuscript.

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.

In table 1, the percentages are calculated vertically, meaning that 31% of all children hospitalised with SARS-CoV-2 infection are in the age group 0-1 year. If instead starting from the number of children infected, 3.5% (98/2,784) of SARS-CoV-2 infected children aged 0-1 years are hospitalised, which is somewhat higher than in the remaining age groups. This is highlighted in the Results section.

Reviewer #4

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:

Thank you for your positive comments and review.

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'.

One of our main aims of this study was to describe the entire burden of the SARS-CoV-2 epidemic in Danish children and adolescents. Therefore, we have chosen also to include the first part of the epidemic. However, the main results are now also provided stratified by period (corresponding to dominating variants; see above), which allows the reader to assess risks after the initial period.

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.

We initially considered using the test negative group as our main comparison group, but realised that this came with risk of important biases. We have provided the full argument for this in our response to editorial comment #2. All children tested at some point for SARS-CoV-2 are, however, eligible for inclusion in the reference group.

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.

The reference cohort was sampled among all children or adolescents under the age of 18 years who were tested for SARS-CoV-2 during the study period, meaning that both positive and negative cases were included in the sampling. Each child was then given a randomly sampled index date from the distribution of test dates among SARS-CoV-2 positive children to ensure that the two cohorts were temporally aligned. Children with a previous positive SARS-CoV-2 test were excluded from the reference cohort and children were censored from the reference cohort, if they later tested positive for SARS-CoV-2. This has now been clarified in the Methods section. The lines 53-54 refers to the sensitivity analysis where we compared SARS-CoV-2 test positive children to children who tested negative for SARS-CoV-2.

Minor comments:
4) The title is a bit broad. I suggest the authors use a more specific title.

Thank you for this suggestion. However, we feel that the title is just, given that the manuscript covers many different aspects of the SARS-CoV-2 epidemic in Danish children and adolescents, describing both the course of the Danish SARS-CoV-2 epidemic, the dominating SARS-CoV-2 strains, characteristics of children hospitalised with SARS-CoV-2 and the acute and post-acute risk associated with infection as well as effectiveness of the BNT162b2 vaccine. Should the editors wish for us to provide a more specific title, however, we will of course comply.

5) Please provide the numbers of total sample size and SARS-CoV-2 infection cases for the vaccine effectiveness assessment in the Abstract.

We have added the total number of vaccine recipients to the abstract. Due to word limitations in the Abstract, we could not report the number for SARS-CoV-2 infection cases (778 after the first dose, 359 after the second dose), but these are available in Table S12.

6) 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?

In all analyses, we only included individuals with complete follow-up, meaning we required 1, 2 and 1-6 months follow-up in respective analyses and either a full 21 days of follow-up after the first vaccine dose or full 60 days of follow-up after the second dose in vaccine analyses. All follow-up ended on October 31, 2021. For analyses of 30-day outcomes, we thus included individuals until October 02, 2021. In analyses of the intermediate two-month time-window, we included individuals until September 02, 2021, and so forth.

Reviewer #5

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.

Thank you for these positive comments.

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.

1) 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.

We have now updated the manuscript to include the most recent data available in the Danish registries. This has allowed us to extend the follow-up until the end of October, substantially increasing the number of children infected during the period where delta transmission was predominant.

2) 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.

Thank you for this comment. We have added this point to the policy implications section.

Overall, an excellent manuscript with informative data.

Reviewer #6

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?

The study includes all Danish children and adolescents who have been tested at some point for SARS-CoV-2 during the epidemic. At this point, this includes the vast majority of Danish children and adolescents (84%), and we therefore believe that our sample is representative. We have, however, included a supplementary table, stratified on age, of how many children have been tested out of the total Danish Child population. As described in the Methods section, all tests were provided for free and were easily accessible. To aid readers in their interpretation, we have further elaborated on testing strategies under Setting in the Methods section and included key changes in testing strategy to Figure 1.

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.

We have now rephrased the Methods section to add more clarity.
As described in further detail in our response to reviewer #4 (comment 3), the reference cohort was sampled among all children or adolescents who were tested for SARS-CoV-2 at some point during the study period, meaning that both children tested positive and negative were included in the sampling. This approach was different from the one applied in our sensitivity analysis where we included a comparator group of children at the date of their negative SARS-CoV-2 test. Please see our response to editorial comment #2 of why this approach came with inherent biases.

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?

As also argued in our response to editorial comment #2, we wanted to compare the risk associated with SARS-CoV-2 infection to the background risk. At the time of their negative test, children are, however, not necessarily representative of the background population. Some are presenting with symptoms related to other respiratory viruses or tested because they are in otherwise need of contact to the health care system, which explains their increased risk of e.g. hospitalisation. This ultimately led us to choose the randomly sampled reference cohort used in the main analysis.

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.

We have checked and corrected rounding of numbers throughout the manuscript.

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%.

We have added confidence intervals to the risk estimates throughout the manuscript.

Comment 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.

We agree and have added this to the manuscript.

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

We agree and have changed the wording accordingly.

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.

We agree and have rephrased this sentence in the manuscript.

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,

None of the included covariates had missing data. This has now been clarified in the manuscript.

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.

We have updated supplementary now Table S12 so it includes the number at risk for each analysis and added a sentence to the Results section on the results of the sensitivity analysis.

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?

Vaccination against COVID-19 is expected to reduce the risk of SARS-CoV-2 as well as to limit severeness of symptoms if infected. We agree that the label could be more clear, and have changed the label to "Documented SARS-CoV-2 infection (%)".

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?

We have rephrased this sentence in the "what this study adds" section.

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

As stated in the figure legend, we cannot report counts less than five because of Danish Data Protection legislation. We are, however, allowed to report if there are no events at all.

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

These have now been added.

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)?

PERR refers to a specific method, and we have therefore found it inappropriate to change the wording.

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

This has been added to the table legend.

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

This has been corrected.

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.

Risk differences are estimated in the SMR-weighted population using binomial regression with an identity link and a single independent variable (exposure status). The estimand is the average treatment effect amongst the treated. This has been clarified in the Methods section.

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

This has been clarified in the abstract.

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?

Due to the nationwide roll-out of vaccines, where vaccines are offered to children only on the basis of age, we do not believe that other of our measured covariates are strong confounders influencing both the likelihood for choosing to receive a vaccine and the chances of attracting SARS-CoV-2.

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.

We agree and have now added subheadings to the Results section.