PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	SARS-CoV-2 transmissions in students and teachers – seroprevalence follow-up study in a German secondary school in November and December 2020
AUTHORS	Armann, Jakob Peter Kirsten, Carolin Galow, Lukas Kahre, Elisabeth Haag, Luise Dalpke, Alexander Lueck, Christian Berner, Reinhard

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Dr. Rachel Mary Hilliam Institution and Country: The Open University, Mathematics and Statistics, The Open University, Walton Hall, Milton Keynes, MK7 6AA, United Kingdom of Great Britain and Northern Ireland Competing interests:
REVIEW RETURNED	09-Feb-2021

GENERAL COMMENTS	This is an interesting study and well presented. It is not the usual sort of paper that the journal publishes, but then we are not in normal times and I think the readers of the journal will be interested in the findings. The statistics in the paper are appropriately carried out and correct conclusions drawn from this. However the study is one isolated school and indeed the first study visit data based on a single case. Because of a the lack of prevalence it is not easy to draw absolute conclusions and this should be made more explicit in the paper. Whilst the study does show that the increase in cases for this particular school is not larger than would be expected, there is still not a lot of evidence due to the relatively small numbers. Of course if the numbers had increased much more than expected then this might be some cause for concern - but again the small numbers are an issue. It would also be helpful to know if social distancing measures remained the same between the two time points. Also an explanation of what measures were put in place generally in Germany between those time points would also help readers (as these are very different in different countries). The conclusions are fine, but they do need to come with many more caveats about the size of the study. It is a helpful study and adds to a body of evidence, but it needs to be clear that there is not enough evidence from this study alone to make any definite statements, only suggestions based on this one school.

REVIEWER	Reviewer name: Dr. Claudia Insúa

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	Institution and Country: HOSPITAL DE NIÑOS DR PEDRO DE ELIZALDE, División Endocrinología, Hospital General de Niños Pedro de Elizalde, Ciudad Autónoma de Buenos Aires, Argentina. Competing interests: None
REVIEW RETURNED	11-Feb-2021

GENERAL COMMENTS	Considero de suma utilidad la publicación de este artículo, por lo oportuno de sus conclusiones a la problemática actual, la gran pregunta, si los niños aportan riesgo a la propagación de la enfermedad por Sars-Cov-2. El diseño del ensayo es bueno y el n, si bien es algo bajo no deja de aportar datos de interés teniendo en cuenta lo dificíl de obtener el consentimiento en la toma de muestras en pediatría así como la toma de una segunda muestra. English Translation: I consider the publication of this article very useful, due to the timeliness of its conclusions to the current problem, the big question, if children pose a risk to the spread of the disease by Sars-Cov-2. The design of the trial is good and the n, although it is somewhat low, does not cease to provide data of interest, taking into account the difficulty of obtaining consent in taking samples in pediatrics as well as taking a second sample.

REVIEWER	Reviewer name: Dr. Christian M Hedrich Institution and Country: University of Liverpool, Department of Women's & Children's Health, Institute of Live Course and Medical Sciences, University of Liverpool, Liverpool, UK Competing interests: None
REVIEW RETURNED	03-Feb-2021

GENERAL COMMENTS	The authors present a seroprevalence study from a school in Saxony, Germany, and conclude that school are no drivers of the pandemic. This study is therefore addressing a very important question that remains to be answered conclusively. This referee agrees with the authors' comments in relation to strengths. It is of certain benefit to include two time points, and the history of the pandemic in Saxony allowed one during a small first peak and another one during a second, mire severe spike of infections in the region. In relation to weaknesses/limitations, this referee has more concerns: 1) Preliminary evidence from several studies suggests that seropositivity is not stable in a large proportion of individuals, particularly in individuals with mild or no symptoms, such as children and young adults. 2) The combination of seroprevalence studies with T cell stimulation assays would be a more appropriate and informative approach. Appreciating that this is difficult and expensive, this referee (at least) recommends discussion of this limitation in the study. 3) It would be helpful to include information on a history of cold-like symptoms in table 2. Appreciating difficulties associated, it is difficult to extract this information form the results and discussion section. 4) Appreciating significant benefit of school opening for children, this referee suggests caution with the final sentence of the conclusions section, as this can only be claimed after a controlled comparative study. This could indeed be suggested as a result from this manuscript? 5) The entire manuscript could be slightly shortened and improved with the help of a native speaker.

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REVIEWER	Reviewer name: Dr. Archana Koirala Institution and Country: Not applicable Competing interests: None
REVIEW RETURNED	03-Feb-2021

GENERAL COMMENTS	Dear authors, Thank you for your manuscript. Your research is important in the development of an understanding of the transmission of SARS-CoV-2 in educational settings. The major limitation of your study is that it is a single centre study and this needs to be acknowledged. You also need to describe to the reader in more detail, the setting (e.g. metropolitan/rural/surrounding population density/school classes and ventilation) and the mitigation strategies implemented within this school as they are key factors that contribute to transmission. Your paper would also benefit on some additional information on those who were seropositive, in particular, whether they may have attended school while infectious and source of infection. Please also review your wording (in particular within the Results section) to ensure it flows and is easy for the reader to understand. Lastly, the authors need to acknowledge that as numbers are low (the confidence interval for the (undetected:detected) is going to be wide) An additional citation of relevance: Tönshoff B, Müller B, Elling R, et al. Prevalence of SARS-CoV-2 Infection in Children and Their Parents in Southwest Germany. JAMA Pediatr. Published online January 22, 2021. doi:10.1001/jamapediatrics.2021.0001

VERSION 1 – AUTHOR RESPONSE

SARS-CoV-2 transmission in students and teachers – seroprevalence follow up study in a German secondary school in November and December 2020

Author's Response

Professor Imti Choonara and Dr. Angel Escobedo

Editor in Chief and Associate Editor

BMJ Peadiatrics Open

February 17th 2021

Dear Professor Choonara and Dr. Escobedo

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We thank you and the reviewers for the evaluation of our manuscript and your very helpful comments. We would like to address each query individually. Changes to the manuscript are highlighted with the track changes function in the manuscript.

Reviewer 1:

1)Preliminary evidence from several studies suggests that seropositivity is not stable in a large proportion of individuals, particularly in individuals with mild or no symptoms, such as children and young adults.

We added a paragraph addressing this concern and the current literature to our discussion

"There is some concern that the SARS-CoV-2 antibody response is not stable over time especially in asymptomatic individuals [14] leading to an underestimation of SARS-CoV-2 infection in seroprevalence studies. However, there are longitudinal studies of the SARS-CoV-2 antibody response kinetic in children [15] and adults [16]that show that antibody titers remain detectable for at least 62 days. Given the short intervals between exposure and first and second study visit of six to eight weeks and the fact that all seropositive participants in the first visit remained seropositive in the second visit we feel confident that the risk of missing a relevat number of infections due to vanishing antibody titers is low."

2) The combination of seroprevalence studies with T cell stimulation assays would be a more appropriate and informative approach. Appreciating that this is difficult and expensive, this referee (at least) recommends discussion of this limitation in the study.

The lack of additional immunological studies is now addressed within the limitations of the study

"In addition, there is a certain percentage of SARS-CoV-2 infected individuals who do not form detectable antibodies and are therefore not detected by a seroprevalence study. Additional immunological studies including T cell based assays would provide an even more comprehensive picture."

3) It would be helpful to include information on a history of cold-like symptoms in table 2. Appreciating difficulties associated, it is difficult to extract this information form the results and discussion section.

History of cold like symptoms is now included in table2 and added to the results section.

"92 participants reported an episode of cold like symptoms between study visits. Seroprevalence did not differ significantly between those with and without reported symptoms (7.6% vs. 6.2%)"

4) Appreciating significant benefit of school opening for children, this referee suggests caution with the final sentence of the conclusions section, as this can only be claimed after a controlled comparative study. This could indeed be suggested as a result from this manuscript?

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We formulated our conclusion more carefully now stating:

"The study could not provide evidence for a relevant silent, asymptomatic spread of SARS-CoV-2 in schools, neither in a low prevalence setting nor during a second, higher-incidence wave of the pandemic, adding to the evidence that educational settings do not play a crucial role in driving the SARS-CoV-2 pandemic – even if there are single imported cases. These results warrant further studies to evaluate if social distancing strategies such as the reduction of students of different classes mixing at school, paired with symptom-based screening strategies, contact tracing and quarantine measures for identified cases are as effective as full school closures, with less adverse effects on the student population."

5) The entire manuscript could be slightly shortened and improved with the help of a native speaker.

The language of the manuscript was improved with the help of a native speaker – changes are marked by the track changes function in the main document

Reviewer 2:

The major limitation of your study is that it is a single centre study and this needs to be acknowledged. You also need to describe to the reader in more detail, the setting (e.g. metropolitan/rural/surrounding population density/school classes and ventilation) and the mitigation strategies implemented within this school as they are key factors that contribute to transmission.

We rewrote the limitation section acknowledging this the single center design and added more detailed information on mitigation strategies as well as mean class size (23.8) to the Method section.

"There are several limitations to our study. Mainly that this is a single center study with a limited number of participants and a relevant loss of participants in the follow-up sampling. In addition, there is a certain percentage of SARS-CoV-2 infected individuals who do not form detectable antibodies and are therefore not detected by a seroprevalence study. Additional immunological studies would provide an even more comprehensive picture. "

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"Mitigation Strategies

The following mitigation strategies were implemented by the Federal State of Saxony and did not change during the study period:

Students were seated 1.5m apart in classrooms, mask wearing in common areas was strongly recommended for students and teachers but not mandated. Student mixing was decreased by a reduction in extracurricular activities.

Students were not allowed to attend school when they were tested positive for SARS-CoV-2, had close contact to an infected individual within 14 days or showed symptoms of a respiratory infection – with the exception of an isolated runny or stuffed nose – until symptoms resolved for more than 48h or tested negative for SARS-CoV-2.

These measures were not part of the study protocol nor assessed or controlled by the study team."

Your paper would also benefit on some additional information on those who were seropositive, in particular, whether they may have attended school while infectious and source of infection.

Unfortunately, we do not have data on individual school attendance for the 247 students during the study period. Students who were tested positive themselves or lived in a household with a SARS-CoV-2 infected person were not allowed to attend school during a 14 day officially mandated quarantine. Students who had no knowledge of their infection most likely attended school but this was not tracked per study protocol.

Please also review your wording (in particular within the Results section) to ensure it flows and is easy for the reader to understand.

The language of the manuscript was improved with the help of a native speaker – changes are marked by the track changes function in the main document

Lastly, the authors need to acknowledge that as numbers are low (the confidence interval for the (undetected:detected) is going to be wide)

Limited numbers of participants are now addressed in the limitations of the study

"There are several limitations to our study. Mainly that this is a single center study with a limited number of participants and a relevant loss of participants in the follow-up sampling. In addition, there is a certain percentage of SARS-CoV-2 infected individuals who do not form detectable antibodies and are therefore not detected by a seroprevalence study. Additional immunological studies would provide an even more comprehensive picture. "

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An additional citation of relevance:
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This Reference is now mentioned in our introduction together with the recently published study by Stringhini et al.

"…some studies showing lower SARS-CoV-2 seroprevalence in young children compared to adults [8, 9]. "

Reviewer 3:

The statistics in the paper are appropriately carried out and correct conclusions drawn from this. However the study is one isolated school and indeed the first study visit data based on a single case. Because of a the lack of prevalence it is not easy to draw absolute conclusions and this should be made more explicit in the paper.

Whilst the study does show that the increase in cases for this particular school is not larger than would be expected, there is still not a lot of evidence due to the relatively small numbers. Of course if the numbers had increased much more than expected then this might be some cause for concern - but again the small numbers are an issue.

We formulated our conclusion more carefully now stating:

"The study could not provide evidence for a relevant silent, asymptomatic spread of SARS-CoV-2 in schools, neither in a low prevalence setting nor during a second, higher-incidence wave of the pandemic, adding to the evidence that educational settings do not play a crucial role in driving the SARS-CoV-2 pandemic – even if there are single imported cases. These results warrant further studies to evaluate if social distancing strategies such as the reduction of students of different classes mixing at school, paired with symptom-based screening strategies, contact tracing and quarantine measures for identified cases are as effective as full school closures, with less adverse effects on the student population."

And rewrote the limitation section.

"There are several limitations to our study. Mainly that this is a single center study with a limited number of participants and a relevant loss of participants in the follow-up sampling. In addition, there is a certain percentage of SARS-CoV-2 infected individuals who do not form detectable antibodies and are therefore not detected by a seroprevalence study. Additional immunological studies would provide an even more comprehensive picture. "

It would also be helpful to know if social distancing measures remained the same between the two time points. Also an explanation of what measures were put in place generally in Germany between those time points would also help readers (as these are very different in different countries).

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and added more detailed information on mitigation strategies to the method section

"Mitigation Strategies

The following mitigation strategies were implemented by the Federal State of Saxony and did not change during the study period:

Students were seated 1.5m apart in classrooms, mask wearing in common areas was strongly recommended for students and teachers but not mandated. Student mixing was decreased by a reduction in extracurricular activities.

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These measures were not part of the study protocol nor assessed or controlled by the study team."

The conclusions are fine, but they do need to come with many more caveats about the size of the study. It is a helpful study and adds to a body of evidence, but it needs to be clear that there is not enough evidence from this study alone to make any definite statements, only suggestions based on this one school.

Please see above.

Reviewer 4:

I consider the publication of this article extremely useful, due to the timeliness of its conclusions to the current problem, the big question, whether children pose a risk to the spread of the disease by Sars-Cov-2. The trial design is good and the n, although somewhat low, still provides data of interest taking into account how difficult it is to obtain consent in taking samples in pediatrics as well as taking a second sample.

We appreciate this assessment of our work and agree wholeheartedly.

Editor in Chief Comments to Author :

Title delete "Low risk of undetected". Our titles do not convey results

The title was changed to

"SARS-CoV-2 transmissions in students and teachers – seroprevalence follow up study in a German secondary school in November and December 2020"

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