

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The Effect of portable HEPA Filters on COVID-19 period prevalence – An observational quasi-interventional study in German kindergartens
AUTHORS	Falkenberg, Timo; Wasser, Felix; Zacharias, Nicole; Mutters, Nico; Kistemann, Thomas

VERSION 1 – REVIEW

REVIEWER	Theeten, Heidi Universiteit Antwerpen
REVIEW RETURNED	12-Apr-2023

GENERAL COMMENTS	<p>General comments: This is an interesting and relevant real-life study with the challenging goal to demonstrate the specific effect of HEPA filters as one of the interventions applied in kindergartens to reduce transmission of SARS-CoV-2 in the children. Although a quasi-interventional observational design is quite weak to obtain strong conclusions, the data would be interesting as any stronger design is hard to apply in this target group. Unfortunately, the data are not fully presented, the statistical analysis looks inadequate, and the discussion is not strong enough. The conclusion is probably correct but the link with the data should be better stated and the limitations of the design better discussed in order to evaluate the value of the study findings. Introduction and discussion sections could be shortened but the discussion's content should improve.</p> <p>Detailed comments and suggestions: Abstract: The number of children and kindergartens in intervention and control group should be added Introduction: Line 56 states "An experimental study by Zacharias et al. (8) using bacteriophages demonstrated that distance is a key factor in the transmission of virus laden aerosols..." The meaning and added value of this first observation is not clear, I would suggest to omit it. The second observation cited from the same reference is useful and sufficient. Line states that 10 on 11 studies about HEPA filters were not using SARS-CoV-2 particles but surrogates. This is according to the review of Liu et al, 2022 Portable HEPA Purifiers to Eliminate Airborne SARS-CoV-2: A Systematic Review - PubMed (nih.gov). Afterwards new studies have reported capacity of HEPA filters removing SARS-Cov2 particles however, Eg Effectiveness of HEPA Filters at Removing Infectious SARS-CoV-2 from the Air - PubMed (nih.gov) and Portable air cleaners and residential</p>
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	<p>exposure to SARS-CoV-2 aerosols: A real-world study - PubMed (nih.gov). But indeed no study yet has demonstrated an effect on incidence.</p> <p>Page 5 line 6 the sample size calculation is not fully clear: what is meant by “a population proportion of 15% is hypothesized”? Is sample size based on one prevalence estimate, or on a difference in prevalences? It should be the latter, as zero-incidence is not realistic in the intervention group.</p> <p>Methods:</p> <p>Until when was prospective registration continued? This is not mentioned.</p> <p>Line 41 mentions that incidence rates were calculated by dividing the number of cases by the total number of children, and that all cases were summed over the time period. Were re-infections excluded? If not, the calculated figure is a period prevalence and not an incidence.</p> <p>Line 46 states that a one-sided Wilcoxon rank test was used to compare between control and intervention group. Why was non-parametric testing used instead of parametric test such as chi-square? Non-parametric testing is more conservative. Why was no time-trend analysis included?</p> <p>Results</p> <p>Line 20 states that “During the actual childcare activities, which are occurring in the group setting, only 25% of kindergartens indicated childcare workers wearing facemasks. Consequently, in the majority of time no facemasks were worn” Do authors mean that kindergartens using facemask did so only 25% of time?</p> <p>Table 5 compares other preventive measures between control and intervention group. Although there is no significant difference for any of the measures, it is clear from the table that the trend is always towards less strict measures in the intervention group.</p> <p>P 7 line 10-20: most of the text is redundant (and even a bit confusing) as Table 4 is self-explicative, the paragraph could be shortened</p> <p>Table 5 with covid figures is very interesting, but its explanation in the text should improve. What is the min. incidence? Does min. incidence in the control group means that no child in the control group was ever diagnosed with covid before Nov 1st of 2021, so including the previous waves? Line 32 states that “The overall incidence rate of the entire sample population was 236 per 1,000 children for the time period from November 2021 to May 2022.” What is meant by the overall incidence rate? According to the methods section it should be a cumulative rate, but in the 6 months study period about 2/3 of the children were diagnosed with covid. Moreover the major part of the registration in the study period was retrospective, and Table 5 does not indicate what part of the figures was collected prospectively. Could the spectacular rise from Q3 to Max be due to more appropriate prospective reporting?</p> <p>It is not clear either on what figures the Wilcoxon rank test has been applied. From Table 5 could be inferred that the covid incidence in the intervention group was higher from the beginning, and it looks as if it increased faster in that group as well, but an appropriate time trend analysis should be applied to figure out. The results of the retrospective case reporting before November 2021 are lacking, as well as the figures about covid in child care workers. It is also not clear how many children were included in each part of the study period. Some may have left the kindergarten before the end of the period. How was this issue handled?</p>
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	<p>Discussion</p> <p>P8 line 35 states that For this reason, it appears that the use of preventive measures, such as facemasks frequent ventilation and surface decontamination remain important regardless of HEPA filters being used or not. Do the authors refer to their own data to state this and how?</p> <p>On line 38 is stated that The data obtained in our study might indicate that the use of HEPA filters leads to a reduction in preventive behavior, especially lower ventilation frequencies in the intervention group. However, practices were questioned only at the end of the observation period (march 2022) , and there might have been a difference in behavior from the beginning, as covid incidence at start (not clear if that is a point prevalence or covering the previous waves cfr earlier remark) is already substantially higher in the intervention group. Moreover, covid incidence in child care workers may have differed between control and intervention group but is not given. They are important sources of infection.</p> <p>Line 54 states that the background incidence is not a confounder, referring to mean 7-day incidence over the full period. However, there was a difference between control and intervention group from the start. What where the background incidences at the different time points of the study? Where they all comparable?</p> <p>The limitations section mentions that the heads of the kindergarten serving as contact points delivering the aggregated data might have underreported. Were they aware of all covid infections in their kindergarten? Did parents or workers have a duty to report covid infection to the head? Is there a possibility that parents would have reported more accurately in the kindergartens that were equipped with mobile filter units? This should be discussed.</p> <p>Other useful references for the discussion are SARS-CoV-2 aerosol transmission in schools: the effectiveness of different interventions - PubMed (nih.gov) and Ventilation Improvement Strategies Among K-12 Public Schools - The National School COVID-19 Prevention Study, United States, February 14-March 27, 2022 - PubMed (nih.gov), both stressing the necessity to combine different measures including ventilation and air filtering systems in order to reduce transmission.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer Comment	Response	Line number of change
Abstract: The number of children and kindergartens in intervention and control group should be added	The segregation of the sample size into intervention and control was added to the abstract	Line 14 & Line 16
Line 56 states “An experimental study by Zacharias et al. (8) using bacteriophages demonstrated that distance is a key factor in the transmission of virus laden	The section was shortened and restructured	Line 68 - 112

<p>aerosols...” The meaning and added value of this first observation is not clear, I would suggest to omit it. The second observation cited from the same reference is useful and sufficient.</p>		
<p>Line states that 10 on 11 studies about HEPA filters were not using SARS-CoV-2 particles but surrogates. This is according to the review of Liu et al, 2022 Portable HEPA Purifiers to Eliminate Airborne SARS-CoV-2: A Systematic Review - PubMed (nih.gov). Afterwards new studies have reported capacity of HEPA filters removing SARS-Cov2 particles however, Eg Effectiveness of HEPA Filters at Removing Infectious SARS-CoV-2 from the Air - PubMed (nih.gov) and Portable air cleaners and residential exposure to SARS-CoV-2 aerosols: A real-world study - PubMed (nih.gov). But indeed no study yet has demonstrated an effect on incidence.</p>	<p>The wording was altered to reflect the more recent publication of Ueki et al. that demonstrated that also infectious SARS-CoV-2 is removed by HEPA filters.</p>	<p>Line 77 - 80</p>
<p>Page 5 line 6 the sample size calculation is not fully clear: what is meant by “a population proportion of 15% is hypothesized”? Is sample size based on one prevalence estimate, or on a difference in prevalences? It should be the latter, as zero-incidence is not realistic in the intervention group.</p>	<p>The formulation was corrected, indeed a 15% difference in population proportion was hypothesized</p>	<p>Line 153</p>
<p>Methods: Until when was prospective registration continued? This is not mentioned.</p>	<p>This information was previously omitted, as only the data of the Omicron wave was reported. Now, we have added a half sentence specifying the completion date of the documentation</p>	<p>Line 172</p>

<p>Line 41 mentions that incidence rates were calculated by dividing the number of cases by the total number of children, and that all cases were summed over the time period. Were re-infections excluded? If not, the calculated figure is a period prevalence and not an incidence.</p>	<p>It was not possible to control for reinfection, as the data was collected fully anonymous. We have corrected the terminology throughout the paper and are now referring to “period prevalence”</p>	<p>Lines 1, 11, 25, 26, 37, 114, 181, 182, 184, 187, 246, 247, 249, 250, 251, 258, 266, 316, 344, 346, 347, 349, 350</p>
<p>Line 46 states that a one-sided Wilcoxon rank test was used to compare between control and intervention group. Why was non-parametric testing used instead of parametric test such as chi-square? Non-parametric testing is more conservative. Why was no time-trend analysis included?</p>	<p>The Wilcoxon rank test was utilized as the required conditions for parametric tests were not confirmed. As the data is not distributed normally it was necessary to use a non-parametric test. Although the test is more conservative, the result is very clear with a p-value of 0.989, clearly no significant difference was found. We did not show a time-trend analysis as we only presented the data for the Omicron wave. As you indicated that a time-trend would be useful for data interpretation, we have now added a graphic illustrating the period prevalence for all COVID-19 waves. This graphic illustrates that no significant difference was evident between the control and intervention group throughout the pandemic</p>	<p>Line 188-190 Figure 1 Line 239- 246</p>
<p>Line 20 states that “During the actual childcare activities, which are occurring in the group setting, only 25% of kindergartens indicated childcare workers wearing facemasks. Consequently, in the majority of time no facemasks were worn” Do authors mean that kindergartens using facemask did so only 25% of time?</p>	<p>Here we are referring to the percentage of kindergartens that had a policy requiring childcare workers to wear facemasks during childcare activities in the group setting. Only in 25% of kindergartens such a policy existed in the remaining 75% of kindergartens no facemasks were worn during childcare activities.</p>	<p>Line 206-207</p>

	The wording was slightly altered to make this more clear	
Table 5 compares other preventive measures between control and intervention group. Although there is no significant difference for any of the measures, it is clear from the table that the trend is always towards less strict measures in the intervention group.	Yes, in the table it does become evident that although no significant difference was observed that the intervention group tends to have slightly less strict preventive measures. This leads to the hypothesis that the use of HEPA filters may reduce the uptake of other preventive measures. This has been discussed in the discussion section (Line 313 – 317 & line 325 – 327)	No change
P 7 line 10-20: most of the text is redundant (and even a bit confusing) as Table 4 is self-explicative, the paragraph could be shortened	The paragraph was shortened	Line 227 - 231
Table 5 with covid figures is very interesting, but its explanation in the text should improve. What is the min. incidence? Does min. incidence in the control group means that no child in the control group was ever diagnosed with covid before Nov 1st of 2021, so including the previous waves? Line 32 states that “The overall incidence rate of the entire sample population was 236 per 1,000 children for the time period from November 2021 to May 2022.” What is meant by the overall incidence rate? According to the methods section it should be a cumulative rate, but in the 6 months study period about 2/3 of the children were diagnosed with covid. Moreover the major part of the registration in the study period was retrospective, and Table 5 does not indicate what part	Table 5 was changed to avoid confusion. In the table, as specified in its title only the data from the Omicron wave (November 2021 – May 2022) was presented. The min. and max. refer to the lowest and highest prevalence rates observed in the kindergarten. Thus, the min. of 0 in the control group means that there was a kindergarten that did not experience any cases during the time period from November 2021 to May 2022. Q1 and Q3 refer to the quartiles of the data. This has no temporal implication but only refers to the distribution during the omicron wave. The wording “overall incidence rate” was changed to “period prevalence”. As kindergartens had to officially report COVID cases among their children and staff, the retrospective and	Line 247, Line 258-260

<p>of the figures was collected prospectively. Could the spectacular rise from Q3 to Max be due to more appropriate prospective reporting?</p>	<p>prospective data collection did not affect the quality of reporting.</p>	
<p>It is not clear either on what figures the Wilcoxon rank test has been applied. From Table 5 could be inferred that the covid incidence in the intervention group was higher from the beginning, and it looks as if it increased faster in that group as well, but an appropriate time trend analysis should be applied to figure out.</p>	<p>No time trend is shown in table 5. The Wilcoxon rank test was performed on the data of the Omicron wave, comparing the mean prevalence rate of the intervention and control group. The COVID-19 prevalence was not higher from the beginning and also did not increase faster. A time trend analysis was added to illustrate that the control and intervention group did not show any significant difference throughout the pandemic.</p>	<p>Line 188 -190 Figure 1 Figure 2</p>
<p>The results of the retrospective case reporting before November 2021 are lacking, as well as the figures about covid in child care workers. It is also not clear how many children were included in each part of the study period. Some may have left the kindergarten before the end of the period. How was this issue handled?</p>	<p>The study only presents the data for the Omicron wave, as the HEPA filters were only installed during summer 2021. Nonetheless, figures illustrating the data of the entire pandemic have been added to illustrate that there was no difference between the intervention and control group throughout the pandemic. We have added the data of the childcare workers, however, also in their case no significant difference was observed. The sample population was consistent throughout the period without any children leaving the kindergarten during the period.</p>	<p>Line 199-200 Figure 1 Figure 2 Table 6 (line 261-263)</p>
<p>P8 line 35 states that For this reason, it appears that the use of preventive measures, such as facemasks frequent ventilation and surface</p>	<p>This refers to our own data. As you have pointed out in one of your previous comments, it appears that (although not all significant) the intervention group</p>	<p>Line 295 - 298</p>

<p>decontamination remain important regardless of HEPA filters being used or not. Do the authors refer to their own data to state this and how?</p>	<p>practices less strict preventive measures compared to the control group. Thus, it appears that such preventive measures are important regardless of the use of HEPA filters. It is further hypothesized that the use of HEPA filters may result in lower adherence to preventive measures. The wording was altered to more clearly articulate this point.</p>	
<p>On line 38 is stated that The data obtained in our study might indicate that the use of HEPA filters leads to a reduction in preventive behavior, especially lower ventilation frequencies in the intervention group. However, practices were questioned only at the end of the observation period (march 2022) , and there might have been a difference in behavior from the beginning, as covid incidence at start (not clear if that is a point prevalence or covering the previous waves cfr earlier remark) is already substantially higher in the intervention group.</p>	<p>We do not have data to confirm that a change in preventive behavior occurred. You are right that we only have the data on prevention behavior from one time-point. Nonetheless, this data leads to the suspicion that less strict preventive measures were followed in the intervention group. We used the formulation “it is suspected” to clearly state that this is not confirmed.</p> <p>Do note that there was no difference in COVID-19 prevalence throughout the time period. Thus the prevalence of the intervention group was in fact not higher at the beginning.</p>	<p>No change</p>
<p>Moreover, covid incidence in child care workers may have differed between control and intervention group but is not given. They are important sources of infection.</p>	<p>We have added the data for the childcare workers, however, no difference in prevalence rates was observed for them.</p>	<p>Line 253-257 Line 261-263</p>
<p>Line 54 states that the background incidence is not a confounder, referring to mean 7-day incidence over the full period. However, there was a difference between control and</p>	<p>We have added the time trend analysis, to highlight that there was no difference between the intervention and control group throughout the reporting period. Also prior to</p>	<p>Figure 1 Figure 2 Line 324 – 326 Line 338 – 339</p>

<p>intervention group from the start. What were the background incidences at the different time points of the study? Were they all comparable?</p> <p>The limitations section mentions that the heads of the kindergarten serving as contact points delivering the aggregated data might have underreported. Were they aware of all covid infections in their kindergarten? Did parents or workers have a duty to report covid infection to the head? Is there a possibility that parents would have reported more accurately in the kindergartens that were equipped with mobile filter units? This should be discussed.</p>	<p>the installation of the HEPA filters no difference was observed. The 7-day incidence was not significantly different between the districts.</p> <p>During the reporting time there was mandatory reporting of COVID-19 cases, therefore the kindergarten heads should be aware of all cases. The data obtained corresponds to the data submitted to the local health authorities by the kindergarten heads. Nonetheless, we note that there is a possibility that parents did not report a sick child to the head of kindergarten. Thus, the limitation is mentioned.</p>	
<p>Other useful references for the discussion are SARS-CoV-2 aerosol transmission in schools: the effectiveness of different interventions - PubMed (nih.gov) and Ventilation Improvement Strategies Among K-12 Public Schools - The National School COVID-19 Prevention Study, United States, February 14-March 27, 2022 - PubMed (nih.gov), both stressing the necessity to combine different measures including ventilation and air filtering systems in order to reduce transmission.</p>	<p>Thank you, we have added the reference of Villers et al. to the discussion.</p>	<p>Line 306 - 307</p>