Author’s response to reviews

Title: Comparative effectiveness of school-based caries prevention: A prospective cohort study

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Author’s response to reviews:

Thank you for submitting the paper entitled "Comparative effectiveness of school-based caries prevention: A prospective cohort study". Although the theme is important, reviewers gave important comments. Would you please respond to the comments.

Thank you for your consideration and review—we have responded to the author comments below.

Reviewer reports:

Yusuke Matsuyama (Reviewer 1): Dear authors,

Thank you for the opportunity to review this paper. In this study, treatment group received primary and secondary prevention program whereas control group received primary prevention program only. In this study,

- The primary prevention program consisted: a twice-yearly dental evaluation conducted by a dental hygienist, oral hygiene instruction, prophy, fluoride varnish, and glass ionomer sealants placed on permanent first and second molars.
The secondary prevention program consisted: glass ionomer interim therapeutic restorations (ITRs) placed on all asymptomatic teeth with carious lesions.

Thus, simply saying, the effectiveness of ITR in addition to primary prevention on untreated dental caries and caries experience was evaluated. The result showed that ITR was effective to decrease untreated dental caries but not effective to reduce caries experience. This seems to be reasonable. However, there are a lot of problems to be considered.

We sincerely thank the author for his/her helpful comments and for reviewing our manuscript. We have responded to the comments below and made the necessary modifications and additions to the manuscript.

Major comments

#1

Necessary information as epidemiological research is lacked. e.g. how was the target population chosen, how was the treatment assigned, duration of follow-up time, etc. I recommend following guidelines such as CONSORT though this study does not seem to be RCT.

While this was not an RCT, we have added detailed epidemiologic information for the prospective cohort study to the Methods section that summarizes the target population, treatment follow-up, intervention assignment, and other factors, using the STROBE checklist for observational cohort studies. This information can be found in throughout the expanded Methods section.

#2
Generalized additive model was applied to evaluate nonlinearity of the effect of increased intensity of care (line 86; this means ITR?) on reduction in dental decay; however, the reason why non-linear relationship was expected is unclear. Please describe the reason to choose GAM and the benefit of finding non-linear relationship. On line 105, it is described that "GAMs are useful in the analysis of longitudinal data because of their flexibility in modeling nonlinear effects." But longitudinal data itself does not necessary mean non-linear relationship. Or, if there is any benefit for policy makers or scientific perspective, I feel that is sufficient reason to apply GAM but there was no explanation of it.

We agree with this assessment—the use of GAMs to explore nonlinear trends in decay and the effects of different prevention types is due to the fact that there is little long-term analysis of caries prevention that studies caries over time with different treatment agents (or in schools), limited mostly to one or two years. As such, it is not clear if caries trends or the effects of prevention are consistently linear, which would be a simplifying assumption. Thus, we used GAMs to explore the long-term trends and long-term effects. We have expanded the manuscript (See second paragraph, midway through, beginning with “Notably, there is…”) to include this information, as well as some additional information in the last paragraph of the Background section.

#3

One of outcomes is total observed caries experience (TOCE). TOCE was calculated as the sum of all observed decayed or filled teeth observed over the course of the study, regardless of exfoliation.

I could not understand the difference between TOCE and DFT. Please explain it.

We created TOCE specifically for the analysis of longitudinal caries prevention programs, and have published about the outcome in JTR Clinical & Translational Research (DOI
and have another paper about TOCE in revise and resubmit at the Journal of Public Health Dentistry. In our previous work, we determined that DMFT/dmft are biased in longitudinal studies (either cohort or RCTs) of caries prevention due to exfoliation and do not adequately reflect accumulated decay across both primary and permanent dentitions. Other outcomes (e.g., untreated decay or the proportion of sound surfaces) are similarly biased. TOCE avoids these biases and has been shown to be useful in prevention research, with consistent estimates for combined or when analyzed separately by primary and permanent dentition. We have added detailed discussion about TOCE in the second paragraph in the Methods section and clarify how it differs.

#4

In discussion, it is described that "In addition to treatment of existing cavities, interim restorations can reduce the levels of cariogenic oral bacteria, preventing the progression of decay and lowering the rate of secondary caries [14]." The description in the paragraph is redundant, but before staring the discussion, is the outcome of this study (TOCE) able to obtain secondary caries? If not, following discussion of the effect of ITR to reduce secondary caries would not be necessarily.

Yes, it can. We’ve reframed the sentence to be clearer.

#5

Short detail of intervention should be described in abstract.

This has been added.
#6

Conclusion in abstract was not understandable or not matched with objective.

We have re-written the conclusion to more accurately reflect the objective and be clearer.

Minor comments

#1

Line 65: The prevalence of dental caries would be in top ten but I am not sure DALYs due to dental caries is in top ten among all diseases. Please check the reference.

We have changed this statement to include the exact statistics from the reference.

#2

Line 81: How long do you expect as "long-term"? If there is studies in short-term effect, please describe it.

We have clarified the duration and included additional references showing the literature gap.

#3

Line 109: why same coefficients were expected though the outcome is different?
In this case, the coefficients refers to the covariates in the model. We have simplified this to just refer to the smoothed terms.

#4

Line 110: In this function, what do x and \( \pi \) mean?

The x variable is time (which includes the interaction effect with treatment group \( z \)) and \( \pi \) is the probability of untreated decay as defined in the standard logit function. We have added this information.

#4

Line 137: What do the percentages mean (person-level or tooth level)?

Person-level, this has been changed.

#5

Line 162: "evidence of comparative effectiveness in community-based settings is limited" but how limited it is? Number of studies is limited? The design is poor?

We meant to imply that many of the prevention agents are limited to clinical studies, but the usefulness in large-scale pragmatic settings (like schools) is largely limited to sealants or fluoride, or is of limited follow-up. We have made this clarification.
Line 184: "ITRs may be more effective at reducing the subsequent risk of decay on teeth that are adjacent to the tooth that was recently restored." I guess you can analyze it using the data because the data include tooth-level information.

We agree—we are focusing on whole-mouth health in this paper but plan on doing individual rates of change and risk in specific teeth in a subsequent project.

Table 2A: Age and visit did not included in the model?

These are included in the model, but cannot be shown in Table 2A because they are no longer parametric coefficients—as described in the analysis section, smoothed terms were used for these coefficients so parametric coefficients could not be estimated. We show them in the non-smoothed standard (GEE) model for comparison. Table 3 has the nonparametric EDFs for smoothed terms. We’ve added this as a note to Table 2.

Figure 1 &2: Why does the range of x-axis different between Figures? What does y-axis mean? At the left end of the graph seems to be more than 0. What does this mean?

The x-axes reflect the number of visits in analysis. The y-axis thus changed because, for untreated decay, the baseline decay was included as a covariate and not included in the longitudinal analysis (models included baseline decay as a confounder and thus time began at T=1). The y-axis refers to the smoothed coefficients at each observation as estimated by the
GAM. As the effective degrees of freedom for untreated decay were estimated to be approximately linear (close to 1), we elected in the revised manuscript to simplify and have the figures only for TOCE over time by treatment group.

Satoru Haresaku (Reviewer 2): Comments to the Author

The manuscript addresses an interesting field of research. It is important to have effective and research based intervention programs about primary and secondary caries prevention.

However I have some major concerns about this manuscript.

We would like to thank the reviewer for his/her time and for reviewing the manuscript and providing comments and suggestions. We have responded below and made the necessary changes and additions in the manuscript.

- The information of the subjects were insufficient to prove the effectiveness of the caries prevention. There was no subjects' information regarding the use of water fluoridation and socio-economic status although socio-economic status was described in limitation. The information would have been one of the most important confounding factors in the present study. In addition, there was no information that when and where the survey was conducted, and that how many schools participated.

We have included additional information in the revised manuscript about the subject population, eligibility criteria, and selection. We note specifically that while child-level race/ethnicity was unavailable, all children were from Title 1 schools across the full study sample so we do not anticipate significant differences in race and do not believe it to be a confounder with these two groups. To address your other point, we further adjusted for water fluoridation in the revised
analyses, the results did not appreciably change to affect results. We note the number of schools and where the study was conducted in the revised Methods.

- There was no information that how subjects were divided to the experimental group or the control group. Selection bias might have occurred in the present study.

We have discussed selection bias in the updated Discussion and provided information regarding treatment assignment in the Methods (paragraph one). As both cohorts were from low-income children, of the same age, with no significant differences in baseline oral health status, we don’t consider selection bias to be at work. We expect children of both groups to be consenters and non-consenters. The non-randomization of treatment is a limitation but one common to open cohorts.

- TOCE is not common to evaluate the status of dental caries. DMFT or dmft were usually used in epidemiological study for caries prevention. You need to explain why TOCE was used.

We have added further information about TOCE in the Methods section (this was also requested by the first reviewer). We created TOCE specifically for the analysis of longitudinal caries prevention programs, and have published about the outcome in JTR Clinical & Translational Research (DOI 10.1177/2380084417750612) and have another paper about TOCE in revise and resubmit at the Journal of Public Health Dentistry. In our previous work, we determined that DMFT/dmft are biased in longitudinal studies (either cohort or RCTs) of caries prevention due to exfoliation and do not adequately reflect accumulated decay across both primary and permanent dentitions. Other outcomes (e.g., untreated decay or the proportion of sound surfaces) are similarly limited. TOCE avoids these limitations and has been shown to be useful in prevention research, with consistent estimates for combined or when analyzed separately by primary and
permanent dentition. We have added detailed discussion about TOCE in the second paragraph in the Methods section and clarify how it differs.

- The statistical results were mainly described in discussion and the epidemiological discussion was not enough. This may result from the shortage of the subjects' information.

We have reduced some of the focus on the statistical interpretation in the discussion and added more to the epidemiologic interpretation of the results.