Author’s response to reviews

Title: Vaginal douching in Zambia: A risk or benefit to women in the fight against cervical cancer: A retrospective cohort stud

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Author’s response to reviews:

REVIEWER 1: KATIE O’BRIEN

Major concerns

1. I would have liked to see more information on the study sample. I know that it has been published on before, but the manuscript is missing a lot of key information, including how information on douching exposure and the covariates of interest were assessed, including the timing relative to when the VIA was performed. I also would have liked to have more information on who attends the screening clinics so that I could better understand how this sample is representative of the Zambian population. I additionally noticed that one key eligibility criteria - having at least one sexual partner - was not adequately described in the methods, which leads me to question what else may have been omitted.

Response: Thank you. More information has been provided on the source of the programmatic data- the Cervical Cancer Prevention Programme in Zambia (CCPPZ). A description of the type of women who access screening services has also been included. Please refer to Pg.4, lines 101-118.

2. The authors examine what type of douching is associated with cervical lesions, but never give us estimates for ever versus never, which I think is of primary importance. I also expected to see never douching as the referent group for the comparison of types of douche used. Point of clarification: douching with plain water is still douching if it involves a pressure system/ tubing, yes?
Response: Thank you for this observation. We only included women who indicated that they used either plain water or any solution. The suggestion of using “ever” vs “never” in our view seem to correspond to “yes” vs “no” douching. Including the “ever” vs “never” in addition will induce collinearity, hence the disentangling of categories, but we agree that the alternative would have been to replace this variable with the new suggested categorization, we chose to use the current categorization for this outcome.

3. There are some concerning errors in the only full paragraph on Page 6. First of all, I don't think women older than 49 are included, yet age groups 45-54 and 55 or older are both mentioned. Secondly, the current interpretation of the education category %s is incorrect: It should be that among those who douched, 41% had a secondary education and 36% had a primary education. (Rather than the % who douched among those with a secondary education, as described.)

Response: Thank you for this observation. This was an oversight on our part. We initially wanted to restrict participation in the study to women of reproductive age only, however, women older than 49 years old also screened for cervical cancer. We have standardized the age groups in all the Tables.

We have also taken note of the comment on interpretation of results from Table 1. Corrections have been made accordingly. Kindly refer to Pg.6, lines 155-164

4. Tables 1-3 could easily be combined. Table 2 could even be eliminated entirely, as the numbers are directly calculable from the n's provided in Table 1 and the estimates are not even discussed in the results. Further, since this is an observational study, I would assume that the effect estimates are subject to some confounding and am unsure of how to interpret the crude estimates anyway. Finally, it is not necessary to include both the 95% confidence intervals and the p-values: the 95% CI contains all of the information in the p-value, along with extra information about the precision of the estimate.

Response: Table 2 and 3 have been merged into one, please refer to Pg.7, line 179. We have also reported Odds ratios and the associated 95% confidence intervals. We agree with the reviewer that it is not necessary to include both the p-values and 95% confidence interval, however, we come from the school of thought that suggests that the strength of evidence if any is better presented by the p-value, hence we choose to present both, hope the reviewer will understand our thinking behind this presentation.

5. For variables that are continuous (e.g. age, number of sex partners, age @ debut, income), ORs for the continuous form of the variable and/or trend tests would help with interpretation.
Response: Thank you to the reviewer with this advice which we agree with, unfortunately, being programmatic data, this is how the information was collected, it is not possible for us to convert categorized information into continuous data, if we had continuous data, we would have worked with continuous data.

6. Table 5 could also be greatly reduced. Although the initial analysis is more about identifying what factors predict whether or not a woman douches, the second analysis is more directly about the association between douche and cervical lesions. As discussed above, I think the primary focus should be on ever vs. never douche with a secondary analysis on type of douching. The effect estimates for the other covariates are less interpretable in the current form as they are likely not appropriately adjusted for. For example, the association between age and cervical lesions cannot be confounded by any of the other factors in the table because nothing affects age. There may be other key covariates/confounders of the HIV-cervical lesion or occupation-cervical lesion associations that are not included here, making those difficult to interpret as well.

Response: We acknowledge the limitation of our study as perceived by the reviewer to estimate the effect of ever vs never douching on risk of abnormal cervical lesions. We will therefore mention this as a major limitation of this study in addition to unobserved confounders. Please refer to Pg.15-16, lines 282-284.

Minor comments

1. I noticed that a lot of women are missing HIV status. Normally I would discourage having a "missing" category in the tables as a covariate, as this results in a heterogeneous category of people that it is not appropriate to perform statistical tests on as a group. However, since so many women are missing this information, I understand why excluding these women is not a reasonable approach. That being said, I think you need to acknowledge this as a limitation in the discussion. If you can think of a reasonable alternative (imputation, exclusion of this variable from multivariable analyses), that might be informative, please consider adding that as a sensitivity analysis.

Response: Thank you. We wish to clarify that the category ‘unknown’ does not represent participants with missing data, rather, it represents women whose HIV status was unknown at the time of screening for cervical cancer.

2. In the first paragraph of the results section, please provide %s as well as the n's. The %s are easier to make sense of.

Response: Thank you for the advice. We have revised the first paragraph of the results section. Please refer to Pg.6, lines 155-164.
3. An OR of 1.6 should be interpreted as 1.6 AS likely not 1.6 times MORE likely (see page 8).

Response: Thank you for this correction. The interpretation of the ORs has been revised accordingly. Please refer Pg. 8, lines 183-201.

4. Table 4 could be omitted. Model selection methods are inherently biased and it adds no extra information to what is already seen in the previous tables. If kept, it might be helpful to re-frame as an attempt to build a predictive model for douching, rather than trying to interpret each covariate estimate on its own.

Response: We thank the reviewer for this comment. We have deleted Table 4. Please refer to Pg. 12.

5. The conclusions are very circumspect (e.g. "include messages to sensitize women against douching"). I'd prefer to see something a bit more direct (e.g. "public health messaging should describe the possible health risks of douching") while still avoiding causal language.

Response: Thank you for the caution. Our conclusion has been revised. Please refer to Pg. 16, lines 297-306.

REVIEWER 2: JOHANNES BERKHOF

1. p.4. A VIA positive result is replaced by cervical lesion in the results section. Why not use the term: VIA-positive result throughout the paper?

Response: Thank you for the comment. The VIA test is the screening test that was used while the term ‘abnormal cervical lesion’ has been used to refer to women who had a positive result upon screening. We have corrected this to ensure consistency throughout the paper.

2. p.5.1.11. Bivariate logistic regression analysis was employed to determine both the predictors of douching as well as identifying douches that were risk factors for abnormal cervical lesions. We used a significance level of 10% for adjustment variables to be entered in the multivariable analysis and the overall significance in the adjusted model was taken to be the traditional 5% significance level. This text is confusing. The paper only contains univariate logistic regressions with single or multiple covariates.
Response: Thank you for the comment. The description of the regression analysis has been revised. Please refer to Pg.5, lines 135-145.

3. p.5. 1.60. The majority were aged between 25-34 (3,999). 3,999 is not the majority of 11853.
Response: Thank you for this correction. The interpretation of results has been revised. Please refer to Pg. 6, lines 155-164.

4. The second paragraph on page 6, in which Table 1 is explained, leaves much to be improved. In particular:

l. 16. The highest proportion of women who douched were older (45-54 years old) and the elderly women (55 years or older) constituted the least proportion (14.4% and 5.2%), respectively. These numbers cannot be read from Table 1 and the sentences are not clear to me.

l.21.More women with secondary (41.1%) and primary education (35.5%) used some form of solution while only 17.6% with tertiary education used the same. I do not understand this sentence. The percentages do not relate to proportions of vaginal douching and seem to be misinterpreted: the percentages are column percentages but they seem to be interpreted as row percentages.

l. 24. Women with two to five sexual partners, house wives and those who never used a condom with their regular sexual partners constituted the majority of women who douched (66%, 45% and 51.2% respectively). 45% is not a majority.

Response: The interpretation of results from Table 1 has been revised. Please refer to Pg. 6, lines 155-164.

5. Table 2. HIV status is not statistically significantly associated with douching. See Table 1 where the p-value is 0.105. After adjusting for multiplicity, the p-value in Table 2 will be larger than 0.05. I consider the p-values in Table 2 confusing and suggest to remove them. Or only report p-values for all categories of a covariate together!

Response: Table 2 shows unadjusted odds ratios and adjusted odds ratios from a logistic regression model, the software (stata) we are using only gives odds ratios for each category compared to a reference category, this for us is desirable compared to the overall p-values.
6. Table 2 and 3. Please merge these tables into one Table.
Response: Thank you for the advice. Tables 2 and 3 have been merged. Please refer to Pg.9.

7. I do not see any additional value of Table 4, please discard.
Response: Thanks to the reviewer, we have deleted Table 4. Please refer to Pg.12-13.

8. The analysis of cervical lesions can also be improved.
Response: Thank you for this comment. We have improved the analysis of cervical lesions by including estimates from the univariate logistic regression analysis. Please refer to Pg.13-14.

Table 5: Why are not all covariates used that were also used in Table 2/3?
Response: In our analysis, we do not have priori explanatory variables, the analysis explanatory variables we used in this table explained the variation of the outcome better.

9. Table 5: Show both crude and adjusted odds ratios!
Response: Thank you for this comment. We have included both crude and adjusted odds ratios together with the associated 95% Cis and p-values. Please refer to Pg.13-14.

10. HIV- is reference category whereas in Table 2/3, HIV+ is reference category.
Response: Thank you for this observation. We have standardized the reference category for HIV status in all the Tables.

11. Only present p-value over all reference groups, not per reference group!
Response: The p-values we are presenting are for each category compared to a reference group, for categorical variables, this is a desirable presentation for us, other people may suggest something different.