Author's response to reviews

Title: Risk factors for cervical precancerous lesions and determinants of screening attendances in Dar es Salaam, Tanzania

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Version: 2 Date: 12 August 2012

Author's response to reviews: see over
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Title: CERVICAL CANCER SCREENING IN DAR ES SALAAM, TANZANIA – A SITUATIONAL ANALYSIS

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Version: 2 Date: 12August 2012
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Reviewer: Megan Smith

Reviewer's report:
Major Compulsory Revisions

1. Subjects and methods section, paragraph 2: I understand that there may be a parallel manuscript in preparation describing the recruitment of the reference group in more detail (given the reference “(Kahesa et al forthcoming)”), however as that is not available. I feel that some more details are required here about the study. For example: over which time period were participants recruited? How were they approached (eg via a home visit, via telephone, some other method?)? Where did they need to attend to have samples collected for HPV / HIV testing? How were they interviewed (eg face to face, by phone) and by whom (eg study personnel, nurse)? Why were the three municipalities chosen? It mentions that the reference group was chosen using a national household survey, but there is no reference given for the survey, and so it is not possible to determine the methods and representativeness of that survey. Some of these questions relate to the sub-group of screened women also – for example were all women screened from February to June 2008 invited to participate, or was some sort of sampling used?

We have revised the subjects and methods section in paragraph 2 and describe in detail the recruitments of the reference group.

2. Discussion – The discussion does not really examine either the strengths or the weaknesses of this study. In particular, it does not discuss potential biases in the study. I think for example that there would need to be some discussion regarding how representative the sub-population of women from the screened group may be of screened in women generally, and likewise the representativeness of the reference group of unscreened women. For example, the unscreened women are from three municipalities within Dar es Salaam, but it is unclear where the screened women lived.

The weakness and strength of the study has been added in the discussion section

3. A table comparing the characteristics of the overall group of screened women with the subgroup of screened women who were interviewed etc would be very valuable. It would give some idea, for example, of how representative the subgroup is of the larger population of screened women.

A new Table 1, which compares the subgroup of screened women with the entire group of screened women in terms of socioeconomic information, has been added

4. The authors state in the abstract and the results section that there was no significant association between HR-HPV infection and screening attendance, but that there was for HIV infection. However given that HIV+ women are over-represented in the screened group (for reasons explained by the authors) and there was a strong association between HIV positivity and HR-HPV positivity, this seems surprising. You would expect a group with an over-representation of women who were HIV+ to also have a higher proportion of women who were HR-HPV+ (after adjusting for age, which the authors did). It seems very likely that HIV is a potential confounder when attempting to examine the relationship between HR-HPV and screening attendance, since it is associated with both of these factors. In order to make a conclusion about whether there is or is not an association between HR-HPV and screening attendance, I think that HIV status should be adjusted for. Then
you could get an idea if, among HIV negative women, those who attended screening were more or less likely to be HR-HPV+. Note that while the information in Table 3 shows the relationship between HIV, HR-HPV and screening attendance, this is insufficient to address this point because (unlike in Table 2), age has not been adjusted for.

5. Following on from item 4, couldn’t a multiple logistic regression analysis have been done in such a way that all variables were used in the same model, or tried and an explanation of which were left out and why (rather than adjusting for age only)? This would have dealt with queries in the readers’ minds such as the potential for confounding between HIV and HR-HPV, which adjusting for age only has not.

We have re-analyzed our data as suggested and our estimate did change a bit. We assessed confounding and interaction and all factors were considered for multivariate analysis. We used the chunk test to see if there was interaction by comparing the -2LL (negative two log likelihood) of the reduced model (no interaction terms) and the full model (with interaction terms). We found no significant difference between these two models and concluded that there was no interaction. All variables were tested for confounding since they were not effect modifiers. We noted the odds ratio for HIV and HPV when each of the variables was left out of the model and also when it was put back in the model. The variables that changed the odds ratio of HIV-1 and HPV by more than 10% were considered confounders. The variables were tested singly and also as groups of confounders. All statistical tests were two-sided. We also perform stratified analysis of HR-HPV and HIV infection among screened and unscreened women.

Minor Essential Revisions

6. Introduction, paragraph 1 – The comments regarding the rates of cervical cancer in Australia and New Zealand are not consistent with the best available data from those countries. The sentence claims that age-standardised incidence in both of these settings (as well as in the North America) is “less than 6 per 100,000.” I assume that these would have been standardised using the WHO population? In that case, the most recent rate for New Zealand (for 2008) is 7.1 per 100,000 women, and rates have been over 6 per 100,000 women since at least as far back as 1995 (presumably longer, as rates have been dropping since then due to screening). In Australia, age-standardised incidence for the most recent year available (also 2008) is 6.0 per 100,000 women. In some recent years incidence has fallen below 6 per 100,000, but the data suggest that it has been reasonably stable at around 6 per 100,000 since around 2001. So I think in neither of these cases would it be really accurate to say rates were “less than 6.0…”

We have revised paragraph 1 and now it is read as age standardized incidence rate in North America and Australia/New Zealand is less than 8 per 100,000.

7. Introduction, paragraph 3: Could more information be provided about the reach of the screening service offered at ORCI – for example is it national, regional, or just within Dar es Salaam? If it is not limited to women in Dar es Salaam, Is there any information on what approximate proportion of women would be from outside Dar es Salaam use this service? It would be informative to compare this with where women in the reference group were from.

We have added information on the screening services offered in Dar es Salaam in paragraph 3.
8. Table 3: There appears to be an error in the first row of column labels – both are labeled as those who participated in the screening program; it appears that the right column should be the 845 women who did not participate, and that this is where the ** footnote should go.

The table 3 has been revised and re-analysed

Discretionary Revisions
1. Introduction, paragraph 3: Does the routine screening service at ORCI (ie that offered after the initial project ended 2005) include both VIA and VILI (as in the Initial phase) or VIA only? It would be good to clarify this point.
2. Methods, VIA status and socioeconomic and reproductive characteristics sub-section, paragraph 1: Similar to the previous point – were women screened by VIA and VILI, or by VIA only? The text as it stands could mean either of these things, so please clarify this point.

We have clarified the use of VIA test as screening method at ORCI

3. Methods, Cervical risk factors and screening attendance sub-section, paragraph 4: It would be useful to explain very briefly the rationale for re-testing samples which were positive on the Trinity Biotech’s Uni-Gold Recombigen test using Abbott determine HIV-1/2.

We have explained briefly the rationale behind re-testing positive samples by using Abbott determine HIV-1/2.

4. Results, paragraph 1: For greater clarity re which group of screened women is being referred to, I would suggest changing “7%...of the screened women were found...” to “7%...of the women screened during the period 2002-2008 were found...”

We have revised the text as suggested

5. Table 2: It seems that uptake of the voluntary HIV test was quite high in both groups (>=90%) – this could potentially be highlighted as a strength.

We have considered emphasizing the high uptake of voluntary HIV test may as a strength but has decided against

Reviewer: Ju-Fang Shi
Reviewer's report:

1. Background
Why doing this study is not well defined, the authors should add some sentences to explain the specific significance of the current analysis.

We have revised the last paragraph of the background section and know it read as “With the aim of describing risk factors for VIA positivity and determinants of screening attendances in Dar es Salaam, Tanzania, this paper present the results from a comparative analysis performed among women who are reached and not reached by the screening program”.

2. Methods
Page 4, Study population: The 845 reference women have received HPV DNA HC2 screening, thus, in theory, they were HPV test screened women rather than unscreened women. It would be important that the authors provide further detailed information for the recruitment process of the reference group to exclude those attending the current study just for a free HC2 screening. Otherwise, the results of Table 2 and table 3 in Results are supposed to be the differences between “VIA screened women” and “HC2 screening women”, rather than between “the screened” and “the unscreened”. Figure 1 should be explained further.

We have described in detail the recruitment process in the methodology section. Regarding changing the names of the two groups which are compared in table 2, now seen as table 3, to “VIA screened women” and “HC2 screening women” – the rationale for categorizing our study population as “screened” and “unscreened” is that the main purpose of the study was to explore socioeconomic and clinical factors associated with screening attendance. We have thus not changed the name of the study groups.

3. Page 4, Data collection: The clinical management for VIA positive women and whether colposcopy has been used for diagnosis should be specified. If histologically confirmed results are available, then it would probably be a better outcome of the study than VIA, considering its accuracy.

4. We have mentioned that the colposcopy was not used and also highlighted the shortcoming of VIA in the discussion section.

5. Results
Table 1, 2 & 3: to be consistent, please always put the reference groups (subgroup with OR=1.00) on the same side (either top or bottom, usually top).

We have revised the tables

6. Discussion
Page 8: The findings that low education, high parity, younger age at first sexual intercourse (a surrogate of being married at a young age in some populations) were associated with being VIA positive are consistent with the results of the prior studies by IARC. However, the association between a status of Widowed/Separated and risk of cervical lesions is not suggested. The authors
should extend the discussion on this factor further and make conclusion cautiously. In addition, parity-associated is not well-interpreted in this section. Limitations of the study should be discussed, for example, the issue of VIA performance.

The discussion on low education, high parity, younger age at first sexual intercourse has been extended and limitation of VIA performance is described in the discussion section

7. Minor Essential Revisions
Title
“Situational analysis” is not one of types of study design, an alternative name should be given (following BMC’s Instructions for authors “the title should include the study design”)

The title has been changed to Risk factors for cervical precancerous lesions and determinants of screening attendances in Dar es Salaam

8. Abstract
Background information needs to be added, following BMC’s Instructions for authors

We have added background information as instructed

9. First line: “cervical precancerous lesions” or “cervical precancerous lesions and cancer”?

It was meant for cervical precancerous lesions

10. Background
More information on burden of cervical cancer and demographic data (e.g. total number of women aged 25-59, the population coverage of the routine screening program if possible) from the study population should be given.

The burden of cervical cancer in Tanzania has been described in more detail as suggested

11. Methods
Page 4, Study population: the authors mentioned that “In all, 1599 women were found to be eligible for the study and a total of 845 women aged 25-59 were enrolled”, then what are the criteria behind this? The term of “Figure 1” should appear in the 2nd paragraph of the study population.

The recruitment in the method section has been described in more detail as suggested

12. Page 5, Ethics: Please indicate what clinical management was provided if women were found to have cervical cancer.

The ethic section has been revised and indicates the clinical management of invasive cervical cancer

Results
13. Typos: Page 11, Table 2, sub-heading of the very right column: age-adjusted…
Page 13, Table 3, sub-heading of second column: did not participate...
Socioeconomic status is a general measure based on individual or population’s income, education and occupation but does not cover other significant factors of parity and age for first marriage. To be specific, the authors should try to avoid using the general term, in both abstract and main text.

The table 2 and 3 has been revised, it now appears as table 3 and 4 respectively. The use of socioeconomic status has been changed to determinants of VIA status

14. Discretionary Revisions
The initial screening project by Ngoma et al. Int J Gynaecol Obstet 2010 found a better performance of VILI compared with VIA (the sensitivity for the detection of CIN2+ were 60.6% (95% CI, 42.1–77.1) for VIA and 93.9% (95% CI, 79.8–99.3) for VILI). It would be great if the authors explained further why the ORCI chose VIA only as the screening test for routine service. Some data on detection rates of CIN2+ from this national screening program would be interesting to see.

The rationale of use VIA instead of VILI has been explained
Title: Cervical cancer screening in Dar es Salaam, Tanzania - A situational Analysis

Reviewer: elisabete weiderpass

1. The authors state in the abstract and discussion: "Women who are of poor socioeconomic status are more likely to be VIA positive and thus at risk of developing cervical cancer”. Does poor socioeconomic status also include high parity and being married at a young age? If so, how do the authors know that a woman with high parity or married at a young age has a poor socioeconomic status?

Basic socioeconomic factors included are marital status, age and education level. High parity may also be considered a surrogate measure of socio economic status since the number of child birth has direct relationship with resources distribution within the family. In addition, high parity may also be associated with poor educational level. However, we acknowledge that socioeconomic status may be considered a too general term to use and have therefore avoided using it in the text. We are instead referring to the specific determinants - as suggested by one of the other reviewers

2. Introduction:
   • Reference nr 1 is lacking information
   We have change reference no 1 to new reference Arbyn et al World wide burden of cervical cancer in 2008, Ann oncology (2011) 22(12) 2675-86

3. A screening program based on Pap smears requires different steps, …
   The sentence has been changed to: “A screening program based on Pap smears requires several steps, …. 

4. VIA is not usually recommended for postmeonpausal women. What is the rationale for screening women through age 59 years?

We extended the age to 59 years since we wanted to get the epidemiological pattern of the disease and a cut off point for using VIA test among women in Dar es Salaam (the results have been published in a parallel paper).
Reviewer's report
Title: Cervical cancer screening in Dar es Salaam, Tanzania - A situational analysis
Reviewer: Dorota Gertig

1. The study methods and selection of participants should be described in more detail. I found it hard to follow the selection of participants and also Figure 1. Figure 1 does not include the numbers for the screened population (n=14,107) and I don't understand why only 83 of 396 women accepted screening at OCRI? It is also unclear how HIV testing and HR-HPV testing was performed on the reference group sample as these women did not undergo screening? How were the cervical samples obtained from unscreened women? I note that the recruitment of the reference group is being published elsewhere but more detail is required in this manuscript.

We have revised the subjects and methods section in paragraph 2 and describe in detail the recruitments of the reference group

2. Statistical methods-although it is stated that multiple logistic regression was used to adjust the risk estimates, it appears that only age was adjusted for in the model, thus there is potential confounding by other factors of interest. A full model should be constructed and all variables which are associated with the outcome of interest should remain in the model. At present, all of the variables in the tables could potentially be confounded by each other (eg association between educational level could be confounded by parity, first sexual intercourse and age at marriage etc).

This issue has been addressed in the response to one of the other reviewers comments

Minor essential revisions:
3. Table 3: The table heading appears to repeat n=890 twice and ** is missing in the table.

We have revised table 3 (which now appears as table 4)

4. P8 para 2 states that "most likely excess risk among lower Socioeconomic groups is related to sexual behaviour" however I think it more likely this is related to lack of access to services or lack of health knowledge.

5. p8 par 3 The analysis between HR-HPV and HIV is cross sectional thus it is not possible to state temporality. I would suggest rewording to state they are significantly "associated" in this study.
6. p8 par 4 states that HIV positive women were more likely to participate in the screening program. However, this reflects the lack of detail in methods and recruitment as I'm not sure how HIV stats was determined in the non-screened women and whether there could be a selection bias in this group. The possibility of selection bias has been stated as a limitation of our study in the discussion section. The HIV prevalence among women who had not attended screening is in line with HIV prevalence rate reported among the general population of women living in Dar es Salaam. This may indicate that in terms of HIV positivity, the sample of unscreened women may be considered a representative subsample.

7. Table 3 Would be interesting to stratify this table by age. Since age did not show any significant confounding effect with regards to HIV and HPV in the multivariate analysis, as stated above, we found no need of performing age stratified analyses.