Author’s response to reviews

Title: Self-medication with Antibiotics for the Treatment of Menstrual Symptoms in Southwest Nigeria: A Cross-sectional Study

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Author’s response to reviews: see over
September 29, 2010

BMC Public Health
Melissa Norton, MD
Editor-in-Chief

Re: Revisions to MS: 1790606207373396

Dear Dr. Norton:

Thank you for providing us with the opportunity to revise our manuscript, MS: 1790606207373396, entitled “Self-medication with Antibiotics for the Treatment of Menstrual Symptoms in Southwest Nigeria: A Cross-sectional Study.”

During this second round of revisions, we have carefully gone through each of the reviewers’ and editor’s comments and addressed them. This entailed significantly shortening and tightening the new sections of the manuscript that were added in the first round of revisions (as suggested by the first reviewer), and adding additional details concerning our methodology (as suggested by the second reviewer). We have also added a number of new references that support and validate our sample size calculation approach, as well as our study design approach (as suggested by the second reviewer). To assist the editor in seeing the new changes, we have highlighted in blue the additions that were added during the first round of revisions and used “track changes” to highlight changes made during the second round of revisions.

We feel that this second revised manuscript is greatly improved. It offers novel data regarding antibiotic self-medication practices that would be of great interest to readers of BMC Public Health who are engaged in socio-behavioral research, women’s health research and antimicrobial resistance research, to name a few.

Thank you for your time and kind consideration. We look forward to hearing from you.

Sincerely yours,

Amy R. Sapkota, Ph.D, M.P.H.
Reviewer: Inge Gyssens

Reviewer's report:
The manuscript has improved. Most of the comments of the reviewers have been addressed. However, the added paragraphs are very lengthy and too many details are given.

Major Compulsory Revisions
1. The authors have added information on the setting and the survey instrument (administration) as requested. However, this could be presented in a more concise way, leaving out a number of details. In addition, since the survey instrument can be uploaded as supplementary material, there is no need to describe it in detail in the text. In general, they should try to reduce these paragraphs and the newly added paragraphs in the discussion by half.

Author’s response: We strongly agree with the reviewer and have gone through the manuscript and cut-back all of the newly added paragraphs by at least half (please see deletions in “track changes”). The only exception is in the discussion. In the first revised manuscript we completely rewrote the discussion including sections based on the reviewers’ initial suggestions. Instead of cutting the discussion completely in half, we have gone through and made it as concise as possible, while 1) retaining the information that was requested in the first round of reviews, and 2) adding information concerning the limitations of the study that were requested by the other reviewer in this round of reviews.

2. Please remove data included in the tables from the text in the results (prevalence of self-medication) and the discussion sections.

Author’s response: We agree with the reviewer that there was redundancy in the last version of the manuscript. As noted above, we have painstakingly gone through the manuscript and ensured that results only appear once, either in the text, tables or figures. This generally involved deleting portions of text in the results and discussion sections (please see deletions in “track changes”). We also deleted Figure 1, Panel A.

Minor Essential Revisions
1. Remove the subtitles in the discussion

Author’s Response: Subtitles have been removed in the discussion section.

2. Add a proper legend to table 2

Authors’ Response: We agree that the legend of Table 2 could be more detailed. The new legend reads: “Results of multivariate analysis of factors that may influence self-medication with antibiotics for the treatment of menstrual symptoms.”
3. Discussion. In the survey by Ogunfowokan the questions on self-management of dysmenorrhea were open ended. Therefore, "tetracycline" should be interpreted as the only cited antibiotic, and the prevalence of use probably much lower than in this study.

**Author's Response:** In response to the editor's concern noted in the middle of page 7 below, we have gone back to the raw data and calculated prevalence rates for each antibiotic used to treat menstrual symptoms (see the new last column of the new Table 3). This has enabled us to directly compare our results with those of Ogunfowokan and Babatunde. We have included this new comparison in the discussion section (lines 333-337).

“In this study, Ogunfowokan and Babatunde (2010) described that 1% of secondary school girls reported using tetracycline for the management of menstrual pain [33]. This is similar to our finding that 2.7% of our study participants specifically used tetracycline to treat several menstrual symptoms including cramps, and heavy flow (Table 3). However, since Ogunfowokan and Babatunde (2010) used a survey with open-ended questions on the self-management of menstrual symptoms and tetracycline was noted as the only cited antibiotic, the overall prevalence of antibiotic use for the treatment of menstrual symptoms is likely lower in the Ogunfowokan and Babatunde (2010) study compared to the present study.”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests
Reviewer's report

Reviewer: Abdelmoneim Awad

Reviewer's report:

General Comments
The paper is now much improved, and most of my remarks have been adequately addressed. However, I still have major concerns particularly related to the methods that should be addressed.

Major Compulsory Revisions
I offer the following comments:

1. The authors did not indicate how were these 4 universities selected out of the 34 universities in Southwest Nigeria? Convenience sampling or random, if random, how?

Authors Response: To address the reviewer’s question, we have added the following sentence to the methods section (lines 120-121): “These universities were selected via convenience sampling.” The abstract was also changed to include the following statement (line 37-38): “The universities were selected by convenience…”

We have also acknowledged in the discussion section that this is a limitation of the study (lines 391-397):

“Another limitation of the study is that, while random sampling was completed at each university, the universities themselves were selected by convenience. In a study of this type, we did not have the ability to randomly select a sample of all Nigerian universities for inclusion in the study because we did not have the luxury of having collaborators present at every Nigerian university who could complete the necessary field work. As a result, it is unclear whether our findings are generalizable to other Nigerian universities.”

2. The authors described how the sample size was calculated, but still I have the following concerns:

a) The equation being used to allow an estimation of the prevalence and not to determine the difference in population for between different groups at 5% significance level. If, yes could they indicate the power of the study to detect this difference.

Author's Response: We sought additional advice from the editor with regards to how we should proceed with a response to this comment. The editor’s response was: “I agree with the author, especially since the primary focus was the prevalence rather than the determinants of use. Indeed, I would shorten the section by using references, rather than repeating the analysis in the text.”
To address the editor’s response, we have made the text of this section more concise, kept the references that were included in the initial revised manuscript and included additional references to support our approach (see details and added references in our response to “b” below).

b) I found it difficult to understand the way they follow in increasing the sample size by doubling it due to the clustered nature of sampling approach, increased by 5% to adjust for non-responses to reach 679. 680 can be divided by 4, so why 700 is chosen and then increased by 40 despite the fact that they have already considered the non-response previously. A reference must be included as an evidence for the validity of this.

Author’s Response: We sought additional advice from the editor with regards to how we should proceed with a response to this comment and s/he agreed that more details were needed to support our rationale.

To address the reviewer’s and editor’s comments, we have described more concisely how we arrived at our final sample size (lines 141-154):

“A sample size calculation was performed using the following equation: $n = \frac{(Z^2 \cdot P(1-P))}{(d^2)}$, where $n =$ sample size, $Z =$ Z statistic corresponding to a chosen level of confidence, $P =$ expected prevalence, and $d =$ precision [23]. In our calculation, we used $Z = 1.96$, $P = 0.3$ and $d = 0.05$. This calculation resulted in a sample size of 323. This sample size was doubled to account for the clustered nature of the study design [24,25], resulting in a sample size of 646. To account for non-responses, researchers typically increase the calculated sample size by anywhere from 5 to 20% [24,25]. We increased the sample size by 5% to account for non-responses, resulting in a sample size of 679. However, to be more conservative, we cushioned our sample size by an additional (arbitrary) ~10%, arriving at a total sample size, $n = 740$. This total sample size was divided by the number of clusters (4 universities) included in the study to determine how many surveys should be administered at each university [25,26]. This method of dividing the sample equally among clusters was in accordance with “generic cluster sample” design methods previously described by the WHO Department of Vaccines and Biologicals [26].

The additional references that we used to complete these calculations and validate our approach are as follows:


3. How were the numbers of students to be included in the study from each university calculated? I can see from table 1 that universities with less number of students as being mentioned in the methods represent 42.8% of the study population, which indicate that multi-stage cluster sample was not implemented appropriately in this study. The authors stated in the sample size calculation that the number was rounded up to a number to be divided by 4 (the number of universities) if this is the case, validity and generalisability of this study would be greatly affected. How can you ensure appropriate randomization through selection of the same number of students from a university with 25,000 students and another with 6,000 students.

Author's Response: We sought additional advice from the editor with regards to how we should proceed with a response to this comment and s/he agreed that more details were necessary.

Our goal was to collect 740 total surveys as discussed above. To accomplish this, we divided 740 by 4 (the total number of clusters or universities in the study) (lines 150-155). This was based on expert advice, as well as the following references that are also noted above:


In the above-cited reference, WHO defines samples devised by this method as “generic cluster samples” [26]. This type of sample is perfectly acceptable for the type of study that we conducted which sought to estimate the prevalence of self-medicated antibiotic use among ALL clusters and NOT among individual clusters or universities [26]. The same reference goes on to discuss that “A common modification to the cluster sample design is to select the clusters with probability proportionate to the size of some variable in the population, such as the population size…” [26]. This is the type of method that the reviewer is referring to. However, as indicated in the references that we have cited, the “generic cluster sample” that we chose to implement is also acceptable, again, particularly when the method is “not intended for calculation of estimates from individual clusters,” [26], something that we did not seek to do with this study.
We have added additional details regarding this issue to the revised manuscript (lines 150-155):

“This total sample size was divided by the number of clusters (4 universities) included in the study to determine how many surveys should be administered at each university [25,26]. This method of dividing the sample equally among clusters was in accordance with “generic cluster sample” design methods previously described by the WHO Department of Vaccines and Biologicals [26].

4. The use of two methods of sampling for recruitment of study participants is also another limitation of this study.

Author’s Response: We agree with the reviewer that this is a limitation. We have noted this in the discussion (lines 387-390):

“The fact that surveys were administered in residence halls or lecture halls depending on the university is also a limitation. However, the data show that survey administration in either residence halls or lecture halls was not a factor that influenced the findings.”

5. I read the survey instrument carefully and I noticed that there are no direct, clear questions about the use of antibiotics without consultation of a medical doctor? Could the authors explain why they did not include the following two direct questions: (i) In the past 3 months, have you taken any antibiotic to treat menses symptoms without medical (doctor) consultation? (ii) In the past 3 months, have you taken any pain relieving medications such as aspirin or ibuprofen to relieve menses symptoms without medical (doctor) consultation?. The non-inclusion of these questions will make it hard to estimate accurately the prevalence of self-medication.

Author’s Response: We recognize that our study has limitations and we have made our best effort to recognize and state these limitations outright. However, we request that the manuscript be evaluated based on scientific merit, rather then “how the study should have been conducted,” as the later approach tends to be subjective and is not the norm of a standard peer-review process. To resolve this issue, we sought additional advice from the editor who commented “I agree with the author--it is too late to change the instrument now. Indeed, asking what was used, and then why, is probably better than a compound question. I have a larger concern about whether the students knew what an antibiotic was. Can the authors use their data from question 12 to present a prevalence for any named antibiotic, eg providing a total in Table 3? It is of great concern that the numbers there are so small, raising a question in my mind about the validity of the aggregate answers, and thereby their overall main finding.”

To address the editor’s comment, we have used the raw data from question 12 to present a prevalence rate for each named antibiotic (see the final column of the new Table 3). It was clear from the surveys that nearly all “users” would only check off one antibiotic for either one or multiple symptoms for question 12 (ie. almost nobody used
multiple antibiotics). Thus, we could, in essence, add the individual prevalence rates for each antibiotic checked in question 12 to give us a crude estimate of the overall prevalence of self-medicated antibiotic use for menstrual symptoms. If this is done, we arrive at a crude estimate of 19%, which is similar to the overall prevalence rate of 24% that we originally calculated using answers to questions 11, 12 and 13.

Nonetheless, we believe that using our original approach provides a better estimation of prevalence, because it captures the respondents who checked YES to question 11, “Have you EVER taken ANY ANTIBIOTICS to treat menses symptoms?” and/or checked a box regarding time of use in question 13, and then left question 12 blank for whatever reason. Moreover, the fact that our initial pilot study (Ojo KK, Sapkota A: Self-prescribed use of antimicrobials during menstrual periods: a disturbing new example of information poverty in Nigeria. Journal of Infection in Developing Countries 2007, 1: 123-124.) found an overall prevalence of self-medicated antibiotic use for menstrual symptoms of 40% (2 out of 5 interviewed women) among a similar population in Nigeria, leads us to believe that the prevalence estimate reported in the present study is likely conservative.

As to the editor’s concern about whether students knew what an antibiotic was, we have already included this as a potential limitation in the discussion section (lines 385-387).

The author stated that they used questions 11, 12 and 13 to estimate the prevalence of self-medication with antibiotics. Since there was no question to indicate the frequency of use (i.e., 1st or 2nd or 3rd time…etc to use the antibiotic), in addition to the fact that 21% reported that they had seen a doctor, there is high possibility that most of the 24% that were estimated to be self-medicated were prescribed the antibiotic by a medical doctor. However, the response to the question that only 6% reported that it was recommended by a doctor or nurse may indicate the possibility that those who were self-medicated is about 18%. The authors needs to explain in details with percentages how the three questions were used to calculate the prevalence of self-medication with antibiotics for review process.

Author’s Response: We sought additional advice from the editor with regards to how we should proceed with a response to this comment and s/he stated: “I agree with the reviewer. I would not re-do things, and s/he is not suggesting the prevalence need be calculated differently. The manuscript is simply unclear about it. Rather than being defensive, the authors should simply state the facts. In most places, increasing clarity requires shortening the manuscript, and tightening, not providing more detail.”

This clarification has been provided in the following text (lines 196-202):

“Responses to three questions in the second section (questions 11, 12 and 13 shown on the uploaded questionnaire) were used to calculate the prevalence of recent antibiotic usage for menstrual symptoms. If a participant answered “Yes” to question 11 or checked off any box in questions 12 or 13, they were considered a “user” of antibiotics for the treatment of menstrual symptoms. “Self-medication” with antibiotics
was verified using the participants qualitative answers to the open-ended question at the end of the questionnaire (question 22).”

6. The authors described how the study questionnaire was piloted. The validity and reliability measures of this instrument should be included in the manuscript.

**Author’s Response:** No validity testing was done. We conducted focus groups, modified the survey accordingly and went forward with the study.

7. In table (2), the results of the multivariate logistic regression for age, public/private universities and marital status should be included even if there are no significant differences. The numbers of each subcategory should be indicated (i.e, yes (n=), No (n=), Lab science, public health or medicine n=...etc). Since the responses for cramps and other symptoms include 5-point scale, the combining of mild, moderate, severe and extreme would not be appropriate to include for multivariate analysis. I would suggest to be deleted, if the authors would like to include, hence I would suggest 3 groups (none, mild+ moderate, and severe + Extreme).

**Author’s Response:** To address the reviewer’s comment, the results for all variables that were included in the final multivariate logistic model have been included in the revised Table 2, along with the numbers of participants in each subcategory. (NOTE: Not all variables that were insignificant by univariate analyses were included in the final multivariate model. Inclusion or exclusion was based on subsequent effects on R² values.)

The reviewer’s view that collapsing variables (such as the responses for cramps and other symptoms) into 2 groups is not appropriate is in contrast to his/her initial suggestion that appeared in the first round of reviews: “…It is preferred to classify your data of each predictive variable to 2 or 3 groups after that you can compare between the groups to predict factors associated with self-medication.” The regression analysis was modified to specifically respond to the reviewer’s initial suggestion (first round). Furthermore, collapsing categorical data into binary variables is a perfectly acceptable approach to follow.

8. Figures 1 A and B to be deleted since they will not add much significance to what have been already included in the text and tables.

**Author’s Response:** We sought additional advice from the editor with regards to how we should proceed with a response to this comment and s/he stated: “Present results only once—figures, tables, or text. Do not repeat. Personally, I like graphics and so would not necessarily delete the figures. But, the manuscript needs tightening, and the removal of redundancy.”

To address this comment, we have removed Figure 1, Panel A, kept the remainder of the figures and ensured that results are not repeated in multiple places in the
manuscript. This involved deleting portions of text in both the results and discussion sections (please see deletions in “track changes”).

9. Could the authors explain how do they reach the conclusion that this study reported that 1 out of 4 university women surveyed in Southwest Nigeria self-medicate with antibiotics. I would suggest to be deleted.

Author’s Response: The overall prevalence rate that we are reporting in this study is 24%. This equates to approximately 1 out of 4 participants (25%) (ie. “1 out of 4 university women who were surveyed in Southwest Nigeria...”). To address the reviewer’s concern, we have added the word “approximately” to the conclusion section of the abstract (line 59), as well as the discussion section of the main text (line 296).

Minor Essential Revisions

10. I would suggest the following changes to the results section of the abstract:
The response rate is 95.4%. Eighty-six percent (95% CI: 83-88%) of participants experienced menstrual symptoms, and 39% (95% CI: 36-43%) reported using analgesics to treat them. Overall, 24% (95% CI: 21-27%) of participants reported self-mediated use of antibiotics to treat the menstrual symptoms: Factors associated with this usage were: lower levels of education (Odds Ratio (OR): 2.8, 95% CI: 1.1-7.1, p-value:0.03); non-science major (OR: 1.58, 95% CI: 1.03-2.50, p-value: 0.04); usage of analgesics (OR: 3.17, 95% CI: 2.07-4.86, 52 p-value: <0.0001); and mild to extreme heavy bleeding (OR: 1.64, 95% CI: 1.01-2.67, p-value: 0.05) and acne (OR: 1.57, 95% CI: 0.98-2.54, p-value: 0.06). Ampicillin, tetracycline, ciprofloxacin and metronidazole were used to treat the most symptoms. Doctors or nurses (6%, 95% CI: 4-7%), friends (6%, 95% CI: 4-7%) and family members (7%, 95% CI: 5-8%) were most likely to recommend the use of antibiotics for menstrual symptoms, while these drugs were most often obtained from local chemists or pharmacists (10.2%, 95% CI: 8-12%).

Author’s Response: We have followed the reviewer’s advice and added the response rate to this section of the abstract (line 43), deleting the initial first sentence. However, we prefer to keep the details regarding the types of menstrual symptoms that were treated: “Overall, 24% (95% CI: 21-27%) of participants reported self-mediated use of antibiotics to treat the following menstrual symptoms: cramps, bloating, heavy bleeding, headaches, acne, moodiness, tender breasts, backache, joint and muscle pain” (lines 45-48).

11. P-values < 0.0001 to be changed to < 0.001, which also indicate the high significance.

Author’s Response: These p-values have been modified throughout the manuscript.

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.