Author's response to reviews

Title: Comparing antibiotic self-medication in two socio-economic groups in Guatemala City: a descriptive cross-sectional study

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Author's response to reviews: see over
Dear Maria Lourdes O.Catarroja, Tonilynn Manibo and the Journal Editorial Office-

My co-authors and I are pleased to send the revision to our paper entitled “Comparing antibiotic self-medication in two socio-economic groups in Guatemala City: a cross-sectional study” (MS: 1953187918134796). We thank the reviewers for their valuable comments that have helped improve the quality of our manuscript. Although most of the comments complement each other, in some instances we received contradictory comments (i.e. one reviewer asking for more details in the methodology while other reviewer asked for less detail). In such instances we opted to give more rather than less detail. Below are our responses to reviewers’ comments.

Responses to reviewer comments

Referee 1
1. I find this article limitedly interesting, as it adds only little new information to existing knowledge;

We revisited our literature review and recent publications that review the current knowledge on antibiotic self-medication and confirmed that the data from Low and Middle Income countries (LMIC), is extremely limited and contradictory. Given that this reviewer’s perception may reflect the perceptions of a segment of the journal’s readership, we updated and revised the manuscript’s introduction in order to highlight the knowledge gap this manuscript is contributing to fill.

2. Furthermore, there are some unacceptable limitations in the design which may derive large deviation results: First, two pharmacies are too limited to represent the retail pharmacy settings in one country; Second, more appropriate sampling method should be used to create a sample when we investigate the prevalence of self-medication in a specific population. The current sampling method is not enough to meet the goal. Third, the readers may be more interested in the factors which influence the self-medication practices based on knowledge, attitudes and practices design, however, this important model was not found in the article.

We revisited our methods section to make sure we are not giving the impression that the study reported in this manuscript aims at representing the country’s retail pharmacy settings. Rather than trying to represent the entire pharmaceutical retail sector, our study aimed at better understanding one of the features of such sector, namely the segmentation by socioeconomic strata how it is organized. We rephrased the manuscript methods to make sure that the readers will have clear expectations about the manuscript’s contribution.

We agree with the reviewer about the importance of carrying out a population-based study that analyzes factors associated with antimicrobial self-medication. The study we report here is one step in that direction, and
we are currently in the process of analyzing new data we collected, as well as designing a second phase of the study. However, the aims of the study reported in this manuscript were not to produce such population-based analysis. In the manuscript, we rephrased our methods to make sure we are clearly communicating what this study is about.

Referee 2
Major compulsory revisions
1. The conclusion in the abstract (lines 49-52 page 2) cannot be derived from the results. It is suggested to include the data about the similarities and differences between the two groups in the Results section.

We accept the comment and have made the following changes in the manuscript.

- Removed from abstract conclusion: Although respondents in both pharmacies were using the same types of antibiotics, and responded similarly about the risks of self-medicating, they were different in how often they self-medicated, where they purchased antibiotics, and from whom they sought advice.

- Abstract conclusion replaced with lines 66-69

Proportion of self-medication with antibiotics was high and similar in two pharmacies serving disparate socio-economic groups in Guatemala City. Additionally, self-medicating respondents were most often women and most commonly self-medicated with amoxicillin.

2. The time period of the self-medication practice is not specified in the methodology. As this influences the prevalence rates, it is essential to ascertain this.

We agree with the comment and made the following additions to the methodology of the manuscript:

- Lines 209-210 added to clarify (text added in “italics”): From May to August of 2013 we carried out a descriptive cross-sectional study in two pharmacies in Guatemala City.

- Line 274 added (text added in “italics”): The questionnaire was administered in a private area of the pharmacy from May to August of 2013, Monday through Friday between the hours of 9am and 4pm (until the target number of questionnaires were obtained).
3. Though the methodology is well explained, the validity and reliability of the questionnaire has not been commented upon. A more detailed description of the data collection tool will be welcomed.

We made the following changes in the manuscript in line with the reviewer’s comment.

- Line 260-263 (text added in “italics”)
  *The instrument was validated by interviewing approximately 20 consumers with the aim of detecting comprehension problems and to assess if the questions responded to the research aims. The instrument consisted of 22 questions: 21 multiple choice and 1 open ended question.*

4. What about the operational definition of self-medication and antibiotics in the questionnaire?

We accept reviewer’s comments. We have added a description in the manuscript’s methods section clarifying the operational definition of self-medication in the methodology section

- Lines 235-243 were added:

  *Costumers who purchased antibiotics without a prescription were invited to participate in the study. Informed consent was obtained and participants were given a brief verbal definition of the practice of self-medication and the opportunity to ask any questions regarding the study, or self-medication with antibiotics. Participants were asked to complete the questionnaire which consisted of a brief introduction of study objectives and a definition of self-medication: “Self-medication occurs when patients obtain and use medications without a prescription from a doctor, meaning that patients make a personal decision to seek treatment for their illness.”*

The operational definition of “antibiotic” was the following:
Medications that are commonly used and included World Health Organizations model List of Essential Medications, as well as on the national “basic list” of medications. In short, these are medications available in Guatemala used to treat bacterial and protozoal infections. We included the following medications: Amoxicillin, Tetracycline, Trimethoprim-sulfamethoxazol, Erithromycin, Ciprofloxacin, Cefadroxil, Cefixime, Amoxicillin/Clavulanic Acid, Azithromycin, Secnidazol, Albendazol, Metronidazol, Levofloxacin, Ceftriaxone, Clarithromycin. We included albendazole in order to confirm anecdotal evidence of its’ over-use in Guatemala. Additionally there is evidence for resistant cases of giardia that have been reported worldwide.
With this in mind, we added the following text to the manuscript in the methodology section Lines 269-273

*We defined antibiotics as the following: Medications that treat bacterial and protozoal infections, and that are found on the World Health Organizations (WHO) Model list of Essential medicines, and the Guatemalan national “basic list” of medications [26,27].*

5. Were all the participants clear about what constitutes self-medication?

Numerous steps were taken in order to ensure participants’ comprehension of self-medication. Prior to beginning the study, participants were given a brief verbal definition of self-medication. As part of the consent process, participants read a short definition describing self-medication: “Self-medication occurs when patients obtain and use medications without a prescription from a doctor.” And finally, participants were given the opportunity to ask questions to the field-researcher regarding self-medication before filling out the study questionnaire.

6. Were the antibiotics specified by trade name or generic names?

We clarify by adding the following text to the methodology:

- Line 243-245

*We determined which antibiotics were being used for self-medication by documenting the generic name of the antibiotic at the time participant purchased the medication*

7. Were the respondents allowed multiple choices for each statement or single choice?

We accept this comment and clarify that multiple choices were allowed for three questions. In order to be more precise regarding this point in the manuscript, we added the following text to the manuscript’s methods section:

- Lines 264-267

*Multiple responses were allowed for the following items: 1. Respondent symptoms provoking self-medication, 2. Reasons for self-medicating, and 3. Locations where respondents purchased antibiotics for self-medicating.*
• Additionally, in table three, we added the symbol * to these items in order to indicate that multiple responses were allowed.

8. The data about reading the drug labels has been included in the results. However, this is not mentioned in the questionnaire details.

   We agree with this comment and have added text in three places within the manuscript to clarify:

   • First, to the manuscript’s methods section (added text in “italics”):
     Lines 266-270
     
     We gathered information about frequency of self-medication, symptoms that provoked self-medication, with which antibiotics patients self-medicated, whom they went to for advice upon self-medicating and if respondents read the antibiotic information handout.

   • Second, to the discussion, we added line 465 to emphasize the type of information patients may read (added text in “italics”):

     Participants do not read the antibiotic information handout associated with the medications they purchase, regardless of their socioeconomic status.

   • Third, in table three we have changed the title of the section referring to reading the antibiotic information handout.

     The title for this section in table 3 has been changed from: “how patients inform themselves”,
     And is now written as: regarding the antibiotic information handout

9. How was the prevalence of self-medication calculated?

   We realize that the term prevalence was not communicating well our results, so we have opted to clarify by using the term “proportion”. The numerator was the number of participants who affirmed previously having self-medicated with antibiotics, and the denominator was the total of participants included in the study.

   The following changes have been made:
   • Abstract (results), line 62 and now reads:
Proportion of self-medication was 79% in the Suburban pharmacy and 77% in City Center pharmacy.

- Abstract (conclusions) lines 66-67:
  Proportion of self-medication with antibiotics was high and similar in two pharmacies serving disparate socio-economic groups in Guatemala City.

- Lines 205-207 of the background. The following sentence has been changed to read (changes in “italics”):
  In this study we aimed to compare the magnitude of antibiotic self-medication and the characteristics of those who self-medicate with antibiotics in two pharmacies serving disparate socio-economic communities in Guatemala City.

- Line 203 from original manuscript omitted to avoid confusion (see deleted text in track changes, line 245):
  (The following text omitted: Additionally, all patients who arrived to the pharmacy to purchase antibiotics were tallied in order to calculate the prevalence of self-medication with antibiotics.)

- Line 308, results
  The proportion of self-medication with antibiotics was high in both pharmacies.

- Line 382, discussion
  Proportion of self-medication was high and similar in both pharmacies, despite the differences in monthly income and education level.

- Line 540, conclusion
  The high proportion and factors contributing to self-medication with antibiotics in Guatemala City are similar in two disparate socio-economic pharmacies.

Minor essential revisions:
10. Abstract: Lines 21, 22 on Page 2: it is recommended to give expansion of the abbreviation.
   - We accept this comment and have added lines 21-23 to the abstract to define the terms OECD and LMIC:

   High prevalence of self-medication has been reported in Organization for Economic Co-operation and Development (OECD) countries and Low to Middle Income Countries (LMIC), but there is mixed evidence.
regarding gender, socio-economic status, and literacy level and the role they play in self-medicating practice.

11. The rest of the abstract and the article are quite well written. The Background gives a very elaborate and good justification of investigating research outcomes. It is suggested to include the reference for statement 113-114 page 5.

- We have added in the following three citations to support the statement numbered as 12-14 in lines 146


12. The discussion elaborates the recent research done on this topic and provides valid comparisons between other studies and the currently derived data. In all the Tables and the manuscript, it is being recommended that the significant p values can be highlighted rather than adding another column with all p values.

We accept this comment and added the following modifications in tables 1 and 3.
- p-values have been removed, and asterisks have been added to highlight significant differences in the tables. In the text of the manuscript, p-values have been mentioned only when calculated as less than 0.01.

13. The correctness and citation style of the References needs to be looked into e.g.: Ref 14.

We have made corrections to the references in response to this reviewer.

14. In general most of the references are recent. However, Ref 6, 7 and 20 are quite old and can be replaced with other recent studies.

There is little recent information available in Latin America regarding self-medication with antibiotics and so we rely on these older studies...
to define some important points in Latin America. For example, reference 6 (drug utilization research group) is a multi-center study from 1992. To our knowledge, there has been no similar study published with same power in this region. Reference 7 (Automedicacion en una poblacion urbana de Cuernavaca) is the most recent article published mentioning gender and self-medication in Latin America.

We agree with replacement of article 21 with article 10 in the following instance:

- In Lines 170-172 we have taken out the following reference and left only reference 10 (in “italics”):

In Latin America the difficulty in access to health care as a result of low-income can often result in self-medication [10] although this has not been clearly established.

Reference 21 in original manuscript has been omitted:

Lines 170-172 makes reference solely to this citation:

Referee 3

Major Compulsory Revisions

1. Abstract: Methods – “We used a questionnaire to gather information about frequency of self-medication, symptoms that provoked self-medication, with which antibiotics patients self-medicated, and who they went to for advice about self-medicating... “ This refers to a composition of the questionnaire. It is better to clearly explain the basic methodology (study setting, design, study population, etc) used without going into excessive detail.

We accept this comment and have changed the text in the methods section.

- Lines 31-35 have been changed to the following (changed text in “italics”)

We conducted a descriptive, cross-sectional study in two Guatemala City pharmacies: one Suburban pharmacy and one City Center pharmacy. We gathered information about frequency of self-medication, characteristics of self-medication, income and education
of those self-medicating. We compared proportions between the two pharmacies, using two-sample z-test and chi square test as appropriate.

2. Abstract: Results – the authors mentioned the socio-demographic characteristics of the study participants. However, prevalence of antibiotic self medication and factors associated with it, reasons and source for self-medication, etc need to be mentioned.

In response to this comment, we made some changes to the manuscript. First, we clarified the research design and aims by adding the qualifier “descriptive” to the study design. With this change we try to emphasize that this study was not designed for analyzing statistical associations with risk factors. Second, we have changed the background section of the abstract so that it is in accordance with the methods and results section of the abstract. Third, we made results on reasons and source for self-medication more visible in the results section.

- Lines 26-28: Background of the abstract replaced with the following text (new text in “italics”)

   We aimed to compare the magnitude of antibiotic self-medication and the characteristics of those who self-medicate with antibiotics in two pharmacies serving disparate socio-economic communities in Guatemala City.

3. The authors directly compared the socio-demographic characteristics of the study participants of the two areas. However, it is extremely important to perform a further statistical analysis first to identify factors associated with antibiotic self medication separately and then compare the results of the two areas.

Although we agree with the reviewer about the importance of analyzing the statistical association of self-medication with different independent variables (risk factors), we did not design this study with that aim in mind. We are working on designing a study that examines those risk factors at the population level, and the study reported here was one step in that direction.

4. In Tables 1 & 3 – Most of the percentages are not correct (for example, for the age group 20-29 in City Center: 77/197 = 39% but in table 35%; married: 88/197=44.7% but in table 40%).
We accept the comments and have changed the erroneous percentages in the table to reflect improvements.

5. The discussion and conclusion need to be improved based on the further statistical analysis will be performed rather than comparing percentages.

We improved the discussion and conclusion based on the multiple comments and changes we made to the manuscript. However, we did not carry out the suggested statistical analysis (statistical association with risk factors) because the design of the study and the study aims are not in line with such analysis.

6. As limitations of the study, what about sample size and the nature of study design? The sample size of each area is too small to detect important associations between socio-demographic factors and antibiotic self-medication. A cross-sectional study was employed in this study, which might suffer from temporal relationship establishment with some variables and could not provide much more substantial evidence of causality.

We agree with this comment (which is why we did not perform the statistical analysis suggested by the reviewer) and added the following to the limitations of the study:

- Lines 524-529 of the discussion, we have added the following text (new text in italics):

> Limitations of this study include those inherent to the cross-sectional research design, as well as the use of purposeful sampling for selecting the pharmacies. The study is not population-based and therefore its results cannot be assumed to be generalizable to all pharmacies in Guatemala City or to Guatemala City. The study did not ask qualitative questions that allowed participants to provide their own explanations and meanings around self-medication.

**Minor Essential Revisions**

1. The writing would benefit from thorough editing and review for grammatical errors.

We appreciate your feedback, the manuscript has been revised and edited by an expert in English grammar and literature and we have made changes accordingly to the manuscript.

2. Lines 113 & 114: The authors say “In contrast, men have shown to self-medicate more frequently than women in Nepal, Syria, and the United Arab Emirates.” They need to provide a reference for this statement.
We have now included Citations included as references 12-14 in lines
• Line 146 added references [12-14]

**Discretionary Revisions**

1. The title might be changed to “Antibiotic self-medication practices in two disparate socio-economic communities in Guatemala City” to focus on the prevalence rates and factors associated with antibiotic self-medication since these are very crucial to increase awareness about the negative consequences of antibiotic misuse among the general population, encourage pharmacy professionals in controlling the problem of irrational antibiotic use by involving in giving education to their clients about the drugs for self-medication and the hazards associated with self-medication with antibiotics, and for the regulatory bodies to enforce antibiotic policies and then to take measures such as strict prescription policy.

We agree with this comment in the sense that the title needs to be revisited. In order to appropriately reflect the study design, we have changed the title to: “Comparing antibiotic self-medication in two socio-economic groups in Guatemala City: a *descriptive* cross-sectional study”

• Line 2, The title has been changed to (changed text in “*italics*”)
Comparing antibiotic self-medication in two socio-economic groups in Guatemala City: a *descriptive* cross-sectional study

**Referee 4**

1. The authors should add some precisions about the regulatory framework (see comments) Comments: An important point of the context in which the study has been led is that people acquire easily antibiotics in pharmacies without prescription. Yet, in the article, there are two places where the law is mentioned but not with the same idea. It should be made clear what the law is exactly on this subject. The authors write: "there is no law requiring a medical prescription in order to purchase antibiotics" (lines 71-72); and further: "there is currently no law in Guatemala requiring the continual presence of a pharmacist in the pharmacy" (line 356). So the reader may wonder: does it mean that people manage to get antibiotics as the pharmacist is not present, or is the law explicitly saying that antibiotics are not prescription drugs? These clarifications should be welcome because it is not quite clear for the reader if people may acquire antibiotics easily because there is no legal obligation for the presence of the pharmacist (who could check the appropriateness of dispensing the antibiotics), or if the law permits the antibiotics being sold without a prescription. In the latter case, does the notion of "drugs available on prescription only" even exist in Guatemala? So
it should be made clear what the law on the subject is exactly, to help the reader understand the significance of the authors’ point when, in conclusion, they suggest a regulation of the sales of antibiotics.

Based on our results, it is not clear if people are self-medicating with antibiotics because there is no law or because there is no pharmacist in the pharmacies, but improvement in either or both may help regulate antibiotic use. We appreciate the feedback regarding the confusion in the regulation of antibiotics in Guatemala. We accept the comment and have added the following text to clarify the lack of regulations regarding antibiotic sales in Guatemala.

- Lines 96-100 added to the background to clarify the laws surrounding prescription use. (added lines shown in “italics”)

The misuse and abuse of antibiotics in this scenario pose a serious risk to infectious disease control and public health in general [1, 2], especially in countries like Guatemala. In this country, narcotics are the only type of medication requiring a prescription for purchase; antibiotics are sold essentially as over-the-counter medications in Guatemala.

- Lines 499-503 added to the end of the discussion section in order to clarify that we do not know if self-medication occurs because of availability or accessibility

Trained health care professionals do not monitor the sale and dispensing of antibiotics in Guatemala to patients in community pharmacies, and there is no law requiring a prescription for antibiotic use. Both factors, absence of health care professionals in the pharmacy and lack of regulations, may contribute to irrational use of antibiotics and antimicrobial resistance.

2. A question: In the references cited on lines 135-139, about the fact that patients are often unaware of potential problems, risks, side effects, resistance, etc., which types of patients do these studies refer to? Are they patients from all social milieus?

We accept this comment and added the term LMIC to clarify. (LMIC defined previously in manuscript as Low to Middle Income Countries)

- In line 174 LMIC added to clarify (shown in “italics”)
When practicing self-medication, patients “in LMIC” are often unaware of potential problems that may arise, and this may expose them to risks [19] including side effects, antimicrobial resistance, or worsening of symptoms [7, 9, 13, 20].

3. Some figures in table 3 are strange.
   1°) the total of percentages concerning the "frequency of self-medication" amounts to more than 100%
   2°) these figures do not correspond to those on line 228.

Thank you for bringing this to our attention, the figures in table 3 have been corrected and are in agreement with those reported in the text.

4. The authors assert that people have no awareness of risks associated with antibiotics while the answers collected ant the figures reported don’t allow to make such an interpretation. They should make a statement involving a more cautious attitude with this issue. Comments from reviewer: The analysis made from the figures about risk perception is a bit quick: the authors say that people perceive little or no risk. Yet, when they are asked how self-medication can effect one’s health (1 negative effect, 10 positive effect), the figures show, for the first group, that 17% respond 2-4 (on a scale of 10), and 20% respond 5. This shows mixed feelings. Can one reasonably conclude that people see the effects of self-medication only as positive, when 37% have a mixed opinion? Besides, the fact they perceive a positive effect of self-medicating on their health doesn’t imply they do not perceive any risks. It may be precisely to avoid risks that they seek advice near other people. People may experience side effects of antibiotics or be conscious of their negative effects without renouncing self-medicating with this drug. Their decision to self-medicate with antibiotics may result from a personal assessment of the benefit/risk balance, but it doesn't mean they have no awareness of the risks of self-medication. (On this subject, though this study is a quantitative one, the discussion might benefit from including some references on qualitative data on the subject. For instance, the study about “Managing Medicinal Risks in Self-Medication”, Drug Safety). So, it would appear to be prudent to say that these answers do not imply people have no awareness of the risk associated with self-medication, as studies have shown the feeling of this risk doesn’t prevent people from self-medicating.

We accept this comment. In order to be clearer about the perceptions respondents’ have when self-medicating, we have chosen to omit the use of the word “risk”. Instead, we use the phrases “positive-effect” or “negative-effect” as indicated below. In regards to the comment concerning 37% of respondents having a mixed opinion, we would like to emphasize that the majority of respondents perceive that self-medication has a positive effect on their health. With the revisions we have made
below, we hope that the emphasis on the majority of respondents is clearer.

- Lines 353-356 of results (sentence using the word “risk” omitted. Also, risk replaced by “negative effect”)

Participants were asked to rate, on a scale of 1-10, the effect self-medication could have on one’s health (1 being a negative effect and 10 being a positive effect). Sixty-three percent of Suburban and 65% of City Center participants responded marking 6 and above, perceiving little or no negative effect in self-medication (see table 3).

- Starting at line 416 through 426 of discussion. The following paragraph has been changed to reflect the reviewers comments (changes shown in italics)

The majority of respondents in both pharmacies indicated that self-medication had a positive effect on their health. Previous studies have emphasized the dangers in self-medicating with antibiotics. Side effects, incorrect drugs or dosages and antibiotic resistances are all factors that make the practice problematic [1, 7, 29]. But regardless of possible risks, the majority of participants perceive that self-medication has a positive effect on their health. One review of local LMIC pharmacy interventions to improve the standards of service places an emphasis on the educational services pharmacists may provide in order to improve outcomes [20]. These types of services must go beyond classifying medication use as “good or bad” [30]. Patient awareness surrounding the how, why and when to use antibiotics as well as the risks surrounding self-medication with antibiotics may be created through educational initiatives. These types of proposals can be targeted toward specific population needs based on demographic characteristics we have described.