Author's response to reviews

Title: Prevalence of asthma, rhinitis and eczema symptoms in rural and urban school-aged children from Oropeza Province - Bolivia: a cross-sectional study

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Author's response to reviews: see over
The Managing Editor

BMC Pulmonary Medicine

Dear Editor,

Please find attached in the journal page the revised version of the manuscript entitled “Prevalence of asthma, rhinitis and eczema symptoms in rural and urban school-aged children from Oropeza Province - Bolivia: a cross-sectional study”. Next we present the point-by-point response of the comments in the first revision of the paper:

Leila D Amorim

Reviewer's report:

Major Compulsory Revisions:
1. Selection of study population
The authors mentioned 185 registered schools, among which 36 were included in the study (30 in urban areas and 6 in rural areas). Some missing information is regarding:
(i) Distribution of all registered schools in rural and urban areas: 138 (75%) urban areas and 47(25%) in rural areas. This aspect has now been included in the revised version of the paper (page 6, paragraph 4).

(ii) Reasons for randomly selecting 43 schools out of 185.
The sampling strategy was according to the International Study of Asthma and Allergies Protocol in order to have representativeness of children in the region. We selected the number of schools required to achieve a sample size suggested considering 5% of significance level and 90% of statistical power (minimum sample size required 2016)(commented in point 1 (iii)).

Why the majority of schools are from urban areas?
There were more urban schools in the study because of their distribution in the source population.
(iii) A one-stage cluster sampling design is used, but it is not well described. Parameters considered for sample size calculation are missing. What is the intraclass correlation coefficient? What is the effect size?
We explain in more detail the sampling design in the revised version of the paper (page 6, paragraphs 4-6). We did not use intraclass correlation coefficient to calculate the sample size. The sample size calculation as recommended by the ISAAC study is rather based on finding differences between two centers than on one individual study. So in order to detect a 2% difference in the prevalence of severe asthma (3% in center A, 5% in center B) a sample size of 2016 participants would be needed in each center (alpha=0.05; power 95%). Our sample size estimation was based on this assumption.

2. Statistical methods
(i) Authors use chi-square tests and logistic regression models for data analysis. However, both methods assume independent observations coming from a random sampling scheme. Use of such methods for analysis of correlated data may lead to invalid and biased results. Since the data is clustered, extensions of those methodologies are required. There exists several statistical methods for handling correlated data (one reference is Shoukri and Chaudhary, 2007, Analysis of Correlated Data with SAS and R). For logistic regression models, authors might use GEE or random effects approaches.
AND
(iii) P-values in Table 1 should be revised with appropriate statistical method.

Although analysis of correlated data might be useful, we did not develop this kind of analysis. This limitation was included in the discussion (page 12, paragraph 1).

“Although a cluster sampling was used in the present study, methods for correlated data were not implemented as the cluster effect is not expected to be large [28]. Nevertheless, one has to bear in mind that this might limit the statistical power of our analyses [32].”

ii) In page 5, authors mentioned that they determined sample size based on 1% significance level. However, 95% confidence intervals are presented. Significance level used for sample size calculation should be the same used for statistical analysis.
This was corrected.
Minor Essential Revisions:

1. Response rate is reported to be 91%. Are you able to compare some information regarding two groups of individuals (those who participated and those who did not participated in the study) in order to assume that missing is at random?
Unlike this is not possible as we do not have any information on non-participants.

2. The study is highly unbalanced, with very large proportion of schools and students from urban areas, but the authors mentioned that they had a representative sample of children from urban and rural areas. Could you please explain with details about the representativeness of this sample for this population?
Considering the random sample of the schools, we assume that our sample is representative of the source population: 75% of schools in the source population are situated in urban environments as compared to 83% in our study population.

3. Authors should discuss potential selection bias and limitations of study.
Bias and limitations of the study are now discussed (page 11, paragraph 1; page 12, paragraph 2).

4. Authors should estimate and present the intraclass correlation coefficient of the study.
This aspect was commented earlier.

5. Table 1 contains private type of school, which is not observed in rural areas. Please recategorize this variable.
Considering the descriptive purpose of this first table, we consider appropriate to show the different types of schools. For the analysis, this variable was categorized into public and private schools. This aspect was clarified in (page 9, paragraph 2).

Discretionary Revisions:
1. Include 95% CI in front of all confidence intervals cited throughout the text. Ok.
2. On page 9, correct word “statistically” (second last line) Ok.
3. Title of Table 2 is very long and confused. Please review it.
The title was changed accordingly (page 17):
Table 2: Prevalence, unadjusted and adjusted Odds Ratios comparing self-reported asthma, rhinitis and eczema in school aged children from rural and urban areas
Reviewer: Donna Rennie

Reviewer's report:
Major Compulsory Revisions
This is actually a study of asthma and allergic symptoms not diagnosis and the paper slips into the genre of diagnosis particularly in the discussion. This is misleading. Asthma symptoms and asthma diagnosis are not interchangeable particularly if based only on symptoms of wheeze as noted in this study. Please correct this throughout the paper including the discussion when referencing study findings.
Thank you for this comment. We have corrected this throughout the paper.

It is stated that the video questionnaire is much more indicative of asthma than report of symptoms. The validation of video responses has only been confirmed in 13 to 14 year olds and not with the age group identified in this study which is much more variable as far as age is concerned (9-15 years, mean age 11). This is potential misclassification bias and needs to be interpreted in reporting video and questionnaire results. I am not sure that these findings should be considered valid with the age range in this study. It may be just as likely that there is an under reporting of wheeze by video questionnaire.

These observations were included in the discussion (page 12, paragraph 4). Even if the video questionnaire has been validated only in children 13 to 14 year olds, it is unlikely that its validity decreases so much in this population (median 11 years). On the other hand, although there is the risk of misclassification bias, this would be expected to be present in a non-differential way between rural and urban areas.

Why are wheezing symptoms by questionnaire lower in urban than in rural (contrary to the hygiene hypothesis) populations? This is not discussed while the similarity between some of the findings and those from other studies are accepted as proof of the hygiene hypothesis working in this population. Is it possible this difference that the higher prevalence of wheezing in the rural children could due to differences in cooking and heating activities (biomass use) between rural and urban homes? What is the distribution of cough in the two populations?

There was no difference in the prevalence of cough in the written questionnaire (40.2% in urban areas, 41.7% in rural areas; p=0.5) while the prevalence in the video questionnaire was again lower in rural areas (7.8% in urban areas, 5.6% in rural areas, p=0.07). Therefore, we do assume that the validity of the video questionnaire is higher. This has been discussed on page 12 of the revised paper. In addition, we have added “Based on the video questionnaire…” when discussing the lower prevalence of asthma symptoms on page 13.
There may be another factor that should be mentioned as a potential reason for difference in geographical findings related to allergic symptoms. Given the extent of poverty noted in the study region (70%), which may also be considered a surrogate for living conditions, the presence of Helminths in the population may be an important contributor to the lower allergic symptoms seen in the rural children.

This aspect is now mentioned on page 13.

Minor Essential Revisions

Editorial:
Page 7 Severe eczema symptoms or severe eczema – rewrite to reflect a symptom if the eczema referred to is not from the ISAAC question about diagnosis. Ok

Complete the sentence on Chi Sq test which is used to test proportions or differences in prevalence of symptoms. The dependent variables should be referred to in that paragraph. Ok

Tables need to be formatted appropriately
Unfortunately we are not sure what the reviewer intended to say with this comment.

Discretionary revisions

The prevalence of symptoms from other Latin American ISAAC study groups deserves recognition in the introduction. This would add to the strength of the introduction.
These aspects were included in the Introduction (page 3, paragraph 3)

We are looking forward to your response and the comments of reviewers.

Yours sincerely,

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