Author's response to reviews

Title: Helicobacter pylori infection in pregnant women in four districts of Uganda: role of geographic location, education and water sources

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Author's response to reviews: see over
We appreciate the interest in our study and the helpful comments from the reviewers that have enabled us improve our manuscript. We have responded to the comments on the manuscript entitled: Helicobacter pylori infection in pregnant women in four districts of Uganda: role of geographic location, education and water sources. We have addressed the reviewers’ comments as follows, including the changed text as it appears in the revised manuscript indicated by red font.

Reviewer: Ishag Adam

Major compulsory

Reviewer Comment 1 (R1C1): It is a long non-compact manuscript

Author Response 1 (AR1): The manuscript is 3476 words; we feel 3500 is standard for original research articles in many journals

R1C2: Authors have to focus on prevalence and associated risk factors of H. pylori during pregnancy.

AR2: We appreciate this comment and we believe the main focus on the article is on the prevalence and risk factors of H. pylori in our study population. We included some information that could be considered peripheral; however, it provides useful background information for the reader. For example, we included some information on the relationship between H. pylori and anemia (Lines 59-62); this provides the justification for the study. We also included information on diagnosis of H. pylori (Lines 68-74); this was to justify our choice of test for H. pylori infection. Our discussion of the low prevalence in Apac (Lines 225-260) is quite lengthy because this was an unexpected result.

R1C3: The first paragraph which is not related directly to the topic can be omitted.

AR3: We appreciate this comment and have omitted the following content from the first paragraph:

Helicobacter pylori infection is associated with factors such as domestic overcrowding[7-9] and low educational attainment [10-14] which are typical of low
socio-economic status; however, at least one study reports an association of the infection with higher social economic status[15].

The first paragraph now reads as follows:

*Helicobacter pylori* infection has a major role in the development of gastritis and peptic ulcers and is an important risk factor for gastric cancer[1]. The prevalence of *H. pylori* infection is persistently higher in developing countries than in developed countries[2] and can vary by ethnicity[3-5], place of birth, and socioeconomic factors even among persons living in the same country[6]. Data on *H. pylori* infection in Uganda are limited and are not representative of the general population: the prevalence was 74% in patients with dyspepsia referred for endoscopy[7] and 86% in patients with cancer and benign tumors[8]. Additional data are from a low-income urban setting in Kampala City, Uganda where the prevalence of *H. pylori* infection in children twelve years and below was 44.3% based on a stool antigen test [9] and was 63% based on a serological test in children aged 1-10 years [10]. While these data are informative, the coverage in terms of geographical location and age-group is limited. Additionally, to our knowledge, there is no data from apparently healthy, non-referred adults.

**R1C4:** Likewise the method is vague and long and need to be summarized.

**AR4:** We appreciate the reviewer’s concern. We believe the details in the Methods section help a reader have a better understanding of the results. For example details about ethnic groups in Uganda (Lines 82-84) will help the reader appreciate the findings about ethnicity and *H. pylori* infection. We are happy to consider omitting some content/details were necessary.

**R1C5:** Results it has been mentioned that education and residence are protective factors, I suggest to reword it to look the reverse that illiteracy (low educational level) and urban residence are associated with *H. pylori*

**AR5:** We appreciate this comment and have revised the manuscript to reflect this as follows:

**Abstract (Lines 33-35)**

Urban residence (AOR=1.71; 95% CI: 1.13-2.60) and no formal education (AOR=1.95; 95% CI: 1.03-3.67) were also independently associated with *H. pylori* infection.

**Results (Lines 191-193)**

Women enrolled at urban health facilities had 1.79 times higher odds of *H. pylori* infection compared to women enrolled at rural centers; this difference reduced but remained significant after controlling for location.

**Results (Lines 195-198)**

The odds of *H. pylori* infection among women with no education relative to women with some formal education was not significant in the univariate analysis, however, when location was controlled for, the odds ratio was 1.98 (95% CI: 1.08-3.63, p=0.03) relative to women with some formal education.
Urban residence (adjusted OR=1.71; 95% CI: 1.13-2.60, p=0.02) and no education (AOR=1.95; 95% CI: 1.03-3.67, p=0.04) each had an independent and positive association with \textit{H. pylori} infection (Table 3).

Discussion (Line 279)
Having no formal education was positively associated with \textit{H. pylori} infection.

Reviewer: Marion Rowland

**Reviewer's report:**

**R2C1:** This is a very interesting manuscript and highlights the declining prevalence of \textit{H. pylori} in less developed regions of the world.

**AR6:** We appreciate the reviewer’s interest. We believe that the widely accepted assumption that the prevalence of \textit{H. pylori} in less developed countries is very high has blinded us to possible deviations from this general rule.

**R2C2:** The study included 500 women but it is unclear what percentage of the total attendance at antenatal clinics during the time frame this represents.

**AR7:** We appreciate this comment. The 500 women represent only a small proportion of the women attending ANC. Unfortunately we did not collect data on the total attendance at antenatal clinics. The only way to access this data if records are still available at the health facilities is to physically travel to each facility. It is now not logistically possible to go back to the health facilities in the diverse regions. However, this was designed as a cross-sectional study with sample size calculation based on expected prevalence. We believe that without the additional information regarding total ANC attendance our findings are still valid and add to the body of knowledge.

**R2C3:** It is unusual that the prevalence of \textit{H. pylori} declines in older women 16% compared to 53% in the youngest age group. Similarly the prevalence decreases with increasing parity.

**AR8:** We thank the reviewer for this comment. While the prevalence of \textit{H. pylori} infection in the oldest age group is 16%, we note that this group had 6 women and 3 of them were from Apac where the prevalence of infection was very low. Similarly, Apac made up nearly 25% of the women with parity 3+, and only 16% of the women with parity \(\leq 2\). Adjusting for location seemed to eliminate the association between \textit{H. pylori} infection and age, and between \textit{H. pylori} infection and parity. Just to note that Farag et al [18] found \textit{H. pylori} infection associated with younger age.

**R2C4:** While the authors did not consider PPIs when enrolling participants, they should state the proportion of women taking PPIs in the study. Could this explain the unexpected low prevalence in older women?

**AR9:** We appreciate this comment and acknowledge that this is a limitation of the study (Lines 301-303). We are not in a position to state the proportion of women taking PPIs in the study because we did not ask specifically about PPIs considering that these were pregnant women in our low income setting who would not be likely to be taking a variety of medication.
We do not think that this limitation could have led to the low prevalence among the older women. While the prevalence of *H. pylori* infection in the oldest age group is 16%, we note that this group had 6 women, 3 of who were from Apac where the prevalence of infection was very low.

**R2C5:** Similarly the highest wealth quintile has the highest prevalence of *H. pylori* and this is also unexpected, as most infectious diseases are more prevalent among lower socio-economic groups. Is education a better marker of income than wealth index used in this study in Uganda.

**AR10:** We appreciate this comment. We noted that while the highest wealth quintile had the highest prevalence of *H. pylori* infection, this association was eliminated after controlling for location (Lines 265-268). We also noted that the context of low social-economic status is important. Rural areas in our setting have a significantly higher proportion of people in the lower wealth quintiles relative to urban areas. As the same time, rural areas in our setting are characterised by less community crowding as compared to urban areas. Although urban areas are characterised by higher social economic status relative to rural areas, in our setting densely-populated slum communities are typical of our urban areas and this is where infectious diseases such as *H. pylori* infection are more likely to spread (Lines 270-277). We also noted that the study in Pemba, Zanzibar by Farag et al. [18] found a similar association.

**R2C6:** In a multiple logistic regression model all factors in the model should be included simultaneously in the final model. It appears from Table 3 that each characteristic is examined individually using logistic regression. This reviewer feels that further analysis is required and the final model should include the numbers and the unadjusted odds ratios.

**AR11:** We presented the numbers and unadjusted odds ratios in Table 2. Lines 165-167 in the Methods section state: The risk factors associated with *H. pylori* following univariate and/or bivariate analysis (at p ≤ 0.05) were entered into a multivariable logistic regression to select the final set of independent risk factors. The foot-note below Table 3 states: Adjusting for location, residence, education, water source. These are factors that met the criteria for inclusion into the final model and they were included simultaneously in the final model. We believe that this addresses the reviewer’s concerns and further analysis is not needed.

**R2C7:** The differences in the type of water supply should be clarified as this reviewer cannot fully appreciate the difference between a public tap and a public well; a river or a spring/borehole.

**AR12:** Because of concerns about the length of the manuscript we provide the definitions here for now, but we are happy to include them if it is deemed necessary. 

**Public tap:** piped municipal water accessed using a tap/valve. The tap is open for everyone in the community to use; it is a community resource. This is referred to as an improved water source.

**Well:** a hole in the ground made to access sub-surface water. A public well is accessible by everyone in the community; it is a community resource.

**River:** a river is a natural water course that flows to a larger water body eg ocean, lake or another river.
Spring: a concentrated discharge of ground water that appears as a flow of water at the surface; ground water flowing naturally at the surface of the earth. Springs may be protected to reduce contamination.

Borehole: a narrow shaft bored into the ground to access water. A vertical pipe is installed and water is manually pumped out of the borehole by the individuals that need it.

Minor

R2C7: While this work is very well referenced the list of references could be more focused.

AR13: We have attempted to reduce on the number of references.

We thank you for your interest in our study

Corresponding Author