

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Rubella virus infection and associated factors among pregnant women attending the antenatal care clinics of public hospitals in Hawassa City, Southern Ethiopia: a cross-sectional study
AUTHORS	Tamirat, Biniam; Hussien, Siraj; Shimelis, Techalew

VERSION 1 – REVIEW

REVIEWER	Karina Top Dalhousie University, Canada
REVIEW RETURNED	01-Apr-2017

GENERAL COMMENTS	<p>In this manuscript, the authors present the results of a rubella seroprevalence survey among pregnant women in southern Ethiopia and attempt to identify risk factors for rubella susceptibility (i.e., negative rubella IgG) and for rubella infection during pregnancy (i.e., positive rubella IgM). Demographic and reproductive characteristics are collected via patient questionnaire completed with the assistance of a nurse, but the data, particularly reproductive characteristics cannot be validated. The results suggest that 13.7% of pregnant women are susceptible to rubella (non-immune) while 2.3% have evidence of recent rubella infection (positive IgM) and may be at risk of transmitting the infection to their fetus. Overall, these results are important, highlighting the ongoing endemicity of rubella in Ethiopia and the need for immunization programs for children and women of reproductive age to prevent congenital rubella syndrome. The only risk factor for rubella susceptibility identified is residence in an urban area. However, the study may have been underpowered. The sample size was calculated based on a 50% estimated seroprevalence of rubella IgG, lower than the 86.3% observed seroprevalence, and did not account for the prevalence of the potential risk factors being measured. This limitation should be included in the discussion. Non-significant differences (at $p < 0.05$) in seropositivity rates between age groups/pregnancy trimester, etc, are discussed in much greater detail than is warranted when such differences are likely to be due to chance variation.</p> <p>The manuscript was difficult to follow and containing numerous typographical and grammatical errors. It would benefit from review by a native English speaker and use of clear, consistent terminology, particularly in regards to the primary outcomes, rubella IgG seropositivity (or protective immunity) and rubella IgM seropositivity (or recent exposure/infection).</p>
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	<p>Abstract:</p> <ol style="list-style-type: none">1. Page 2, lines 29-32: The differences in IgM seropositivity across age groups and pregnancy trimesters was not statistically significant and therefore could be simply due to chance. These two sentences should be removed and the authors should instead state that no statistically significant differences were observed across these categories.2. Page 2, Line 36: define "COR" <p>Introduction:</p> <ol style="list-style-type: none">1. Page 3, line 32: "Defects are rare after 20 weeks of gestation", please clarify as follows: "Congenital anomalies are rare if infection occurs after 20 weeks of gestation..."2. Page 4, lines 39-41: "In Ethiopia, sero-surveys are limited to inform on current status of rubella..." This is unclear. Have sero-surveys been conducted in Ethiopia to determine the prevalence of rubella immunity? If so, what were the findings? <p>Methods</p> <ol style="list-style-type: none">1. page 5, lines 30-32: "All pregnant women who attended the antenatal care clinics...during the study period were the study population". I think the authors mean that these women were the source population (i.e., the population from which the study subjects were drawn), since not all women who attended the clinics during the study period were recruited.2. Page 5, lines 32-34: "Pregnant women in the age range 15-49 years, or those who consented to participate, or had no major sickness to be interviewed were eligible..." Presumably subjects had to meet all of the above criteria, in which case, this sentence should be corrected as follows: "pregnant women 15-49 years of age who consented to participate AND had no major sickness that would prevent them from being interviewed were eligible." Could the authors define "major sickness"?3. Line 36-38: "However, none of the pregnant women approached..." This sentence should be moved to the results section.4. Page 5, lines 43-57: Sample size calculation: It is unclear why 50% sero-positivity rate was used as the basis for the sample size calculation when there were sero-surveys from neighboring countries showing much higher seroprevalence of rubella IgG. Those values would have provided a more accurate estimate of the sero-prevalence in Ethiopia. Did the authors try to power the study to be able to detect differences in seropositivity between subgroups (e.g., age groups)?5. Page 6, lines 4-6: Please specify the target recruitment at each hospital site.6. Page 6, line 16: please define: stillbirth, spontaneous abortion, and fetal death.7. Page 6, lines 35-36: IgG seropositivity indicates past infection/exposure to rubella, not "past or present", please correct.8. Page 6, lines 47-48: "the completeness of gathered data was checked immediately." Please clarify how the data were checked.9. Page 7, lines 11-16: Did the authors plan to do multivariable analysis? If so, what were the criteria for including variables in the multivariable models? If not, why was multivariable analysis not planned?
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	<p>Results</p> <ol style="list-style-type: none">1. page 7, lines 42-27: in addition to the women meeting the inclusion criteria, please indicate how many consented to participate and completed the survey. The response rate is the proportion of eligible women approached who completed the survey.2. Page 7 lines 8-9: "The sero-positivity rate for anti-rubella IgG was 86.3%, which indicated exposure to the infection." Positivity to either rubella IgM or IgG indicates exposure to the rubella virus. While IgM positivity indicates more recent infection (or re-infection), IgG positivity indicates distant exposure/infection with development of protective immunity. Please clarify this throughout the results and discussion sections.3. Page 8, lines 13-23 and lines 36-42: The differences in seropositivity between age groups, occupation, trimester, gravidity and parity are not statistically significant and therefore any differences observed in the point estimates are likely due to chance variation. The authors should clarify that IgM and IgG seropositivity were not significantly different across these variables.4. Page 8, lines 41-45: "the rates of anti-rubella IgG among women who reported a history of stillbirth..." The authors should avoid restating information from the tables in the text.5. Page 9, Table 1: anti-rubella IgG by age group – there are no data for rubella IgG positivity in women ≥ 35 years of age. What was the reference value for the crude ORs for IgG positivity by age group?6. Table 1: under rubella IgG for single marital status, the COR is 2.0 but the 95% CI is 9.0-51.6, please correct.7. Tables 1 & 2: Results are reported with varying precision (i.e., to between 1 and 3 decimal places). Please ensure that all percentages/ORs/confidence limits are reported with the same precision. <p>Discussion</p> <ol style="list-style-type: none">1. page 11, lines 24-25: "aimed to generate data on recent/acute and exposure to rubella..." As mentioned in point 2 under results above, this sentence should be clarified to differentiate between recent/acute exposure and past/remote exposure with development of protective immunity.2. Page 12, lines 10-11: What is the 95% confidence interval for the IgM seropositivity rate? Is 0.75%, as observed in Bangladesh, statistically significantly different from the 2% observed in this study?3. Page 12, lines 36-37: The results show that women in urban areas had 6.3-fold greater odds of protective immunity to rubella, not necessarily a higher rate of exposure.4. Page 12, lines 45-48: "The rate of exposure...appears to be decreasing with increasing age" – This conclusion is not supported by the results, which show no significant difference in seropositivity by age groups.5. Page 13, lines 5-9: Please remove "However, the positivity rate seems higher..." as any differences observed are likely due to chance, as discussed above.6. Page 14, lines 3-11: As mentioned in point 4 under methods, the authors should indicate that this study may not have been adequately powered to identify risk factors for seropositivity for rubella IgG.
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REVIEWER	Dr Aishatu B. Gubio Ahmadu Bello University Zaria Nigeria There is no competing interest
REVIEW RETURNED	14-May-2017
GENERAL COMMENTS	<ol style="list-style-type: none"> 1. create space between introduction and methods. 2. Sample size and sampling method line 14 correct word. 3. Data collection space. 4. somewhere in the discussions, a sentence to describe the risk factors should be included clearly before now talking about the risk factors 5. The abstract conclusion should be rephrased

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

Comment 1: In this manuscript, the authors present the results of a rubella seroprevalence survey among pregnant women in southern Ethiopia and attempt to identify risk factors for rubella susceptibility (i.e., negative rubella IgG) and for rubella infection during pregnancy (i.e., positive rubella IgM). Demographic and reproductive characteristics are collected via patient questionnaire completed with the assistance of a nurse, but the data, particularly reproductive characteristics cannot be validated. The results suggest that 13.7% of pregnant women are susceptible to rubella (non-immune) while 2.3% have evidence of recent rubella infection (positive IgM) and may be at risk of transmitting the infection to their fetus. Overall, these results are important, highlighting the ongoing endemicity of rubella in Ethiopia and the need for immunization programs for children and women of reproductive age to prevent congenital rubella syndrome.

Response: Thanks for your positive comments on the importance of this study

Comment 2: The only risk factor for rubella susceptibility identified is residence in an urban area. However, the study may have been underpowered. The sample size was calculated based on a 50% estimated seroprevalence of rubella IgG, lower than the 86.3% observed seroprevalence, and did not account for the prevalence of the potential risk factors being measured. This limitation should be included in the discussion.

Response: We have now specified the suggested limitation in the discussion section

Comment 3: Non-significant differences (at $p < 0.05$) in seropositivity rates between age groups/pregnancy trimester, etc, are discussed in much greater detail than is warranted when such differences are likely to be due to chance variation.

Response: We accept your comment and we have now reduced the details in the discussion section

Comment 4: The manuscript was difficult to follow and containing numerous typographical and grammatical errors. It would benefit from review by a native English speaker and use of clear, consistent terminology, particularly in regards to the primary outcomes, rubella IgG seropositivity (or protective immunity) and rubella IgM seropositivity (or recent exposure/infection).

Response: We have now tried to use terminologies consistently.

Abstract:

Comment 1: The differences in IgM seropositivity across age groups and pregnancy trimesters was not statistically significant and therefore could be simply due to chance. These two sentences should be removed and the authors should instead state that no statistically significant differences were observed across these categories.

Response: Your comment is well taken and we have now revised according to your suggestion.

Comment 2: Page 2, Line 36: define "COR".

Response: We have now defined it

Introduction

Comment 1: Page 3, line 32: "Defects are rare after 20 weeks of gestation", please clarify as follows: "Congenital anomalies are rare if infection occurs after 20 weeks of gestation..."

Response: Thanks for your suggestion and we have now revised that section.

Comment 2: Page 4, lines 39-41: "In Ethiopia, sero-surveys are limited to inform on current status of rubella..." This is unclear. Have sero-surveys been conducted in Ethiopia to determine the prevalence of rubella immunity? If so, what were the findings?

Response: We have now modified the sentence to read correctly.

Method

Comment 1: Page 5, lines 30-32: "All pregnant women who attended the antenatal care clinics...during the study period were the study population". I think the authors mean that these women were the source population (i.e., the population from which the study subjects were drawn), since not all women who attended the clinics during the study period were recruited

Response: We have now revised the manuscript according to your advice.

Comment 2: Page 5, lines 32-34: "Pregnant women in the age range 15-49 years, or those who consented to participate, or had no major sickness to be interviewed were eligible..." Presumably subjects had to meet all of the above criteria, in which case, this sentence should be corrected as follows: "pregnant women 15-49 years of age who consented to participate AND had no major sickness that would prevent them from being interviewed were eligible." Could the authors define "major sickness"?

Response: We have now taken the correction

Comment 3: Line 36-38: "However, none of the pregnant women approached..." This sentence should be moved to the results section.

Response: Your comment is well taken and revision has been made.

Comment 4: Page 5, lines 43-57: Sample size calculation: It is unclear why 50% sero-positivity rate was used as the basis for the sample size calculation when there were sero-surveys from neighboring countries showing much higher seroprevalence of rubella IgG. Those values would have provided a more accurate estimate of the sero-prevalence in Ethiopia. Did the authors try to power the study to be able to detect differences in seropositivity between subgroups (e.g., age groups)?

Response: We did not consider results from neighboring countries to estimate the sample size as we thought Ethiopian contexts may be different with respect to risk factors of rubella and vaccination status.

Comment 5: Page 6, lines 4-6: Please specify the target recruitment at each hospital site.

Response: We have now specified the target recruitment at each hospital site.

Comment 6: Page 6, line 16: please define: stillbirth, spontaneous abortion, and fetal death.

Response: We have now had subheading for “definitions” in the method section to briefly describe important terms.

Comment 7: Page 6, lines 35-36: IgG seropositivity indicates past infection/exposure to rubella, not “past or present”, please correct.

Response: Thanks, and revision has been made accordingly.

Comment 8: Page 6, lines 47-48: “the completeness of gathered data was checked immediately.” Please clarify how the data were checked.

Response: We have now rehearsed the sentence to enhance its clarity

Comment 9: Page 7, lines 11-16: Did the authors plan to do multivariable analysis? If so, what were the criteria for including variables in the multivariable models? If not, why was multivariable analysis not planned?

Response: Our plan was to perform multivariable logistic regression analysis if more than one variable was found to be significantly associated with rubella infection (p-value <0.05) in a bivariate logistic regression analysis. However, since only one variable (residence site), which showed a significant association with rubella infection, we disregard performing multivariable analysis.

Result

Comment 1: Page 7, lines 42-27: in addition to the women meeting the inclusion criteria, please indicate how many consented to participate and completed the survey. The response rate is the proportion of eligible women approached who completed the survey.

Response: We approached 422 women and all met the inclusion criteria. Giving consent to participate was considered as one of the inclusion criteria. All the women completed the survey. Thus, the response rate was 100%.

Comment 2: Page 7 lines 8-9: “The sero-positivity rate for anti-rubella IgG was 86.3%, which indicated exposure to the infection.” Positivity to either rubella IgM or IgG indicates exposure to the rubella virus. While IgM positivity indicates more recent infection (or re-infection), IgG positivity indicates distant exposure/infection with development of protective immunity. Please clarify this throughout the results and discussion sections.

Response: Thanks for your valuable inputs and the manuscript has been revised according to your suggestions.

Comment 3: Page 8, lines 13-23 and lines 36-42: The differences in seropositivity between age groups, occupation, trimester, gravidity and parity are not statistically significant and therefore any differences observed in the point estimates are likely due to chance variation. The authors should clarify that IgM and IgG seropositivity were not significantly different across these variables.

Response: We agree with your comment. We actually specified this information in the manuscript as:
A. "However, rubella sero-positivity was found to be significantly influenced only by residence site where urban dwellers had more exposure than rural dwellers (COR 6.3; 95% CI 3.29-12.14, $p < 0.001$)" to represent socio-demographic characteristics.
B. "In bivariate analysis, none of these factors was found to be significantly associated with either IgM or IgG sero-positivity status" to represent reproductive characteristics.

Comment 4: Page 8, lines 41-45: "the rates of anti-rubella IgG among women who reported a history of stillbirth..." The authors should avoid restating information from the tables in the text.

Response: We have now deleted that sentence.

Comment 5: Page 9, Table 1: anti-rubella IgG by age group – there are no data for rubella IgG positivity in women ≥ 35 years of age. What was the reference value for the crude ORs for IgG positivity by age group?

Response: Thank you so much for your comment. We have now corrected the error.

Comment 6: Table 1: under rubella IgG for single marital status, the COR is 2.0 but the 95% CI is 9.0-51.6, please correct

Response: We have now corrected the error

Comment: Tables 1 & 2: Results are reported with varying precision (i.e., to between 1 and 3 decimal places). Please ensure that all percentages/ORs/confidence limits are reported with the same precision.

Response: We have now corrected percentages/ORs/confidence limits to 1 decimal places

Discussion

Comment 1: Page 11, lines 24-25: "aimed to generate data on recent/acute and exposure to rubella..." As mentioned in point 2 under results above, this sentence should be clarified to differentiate between recent/acute exposure and past/remote exposure with development of protective immunity

Response: Your comment is well taken and a revision has been made

Comment 2: Page 12, lines 10-11: What is the 95% confidence interval for the IgM seropositivity rate? Is 0.75%, as observed in Bangladesh, statistically significantly different from the 2% observed in this study?

Response: The 95% confidence interval for the IgM seropositivity is calculated to be 1-4%. Thus, 0.75% is not within the interval.

Comment 3: Page 12, lines 36-37: The results show that women in urban areas had 6.3- fold greater odds of protective immunity to rubella, not necessarily a higher rate of exposure.

Response: Thanks for your input, and revision has now been made

Comment 4: Page 12, lines 45-48: “The rate of exposure...appears to be decreasing with increasing age” – This conclusion is not supported by the results, which show no significant difference in seropositivity by age groups

Response: Yes, we agree with your comment and have now revised that section

Comment 5: Page 13, lines 5-9: Please remove “However, the positivity rate seems higher...” as any differences observed are likely due to chance, as discussed above.

Response: We have now removed as per your advice

Comment 6: Page 14, lines 3-11: As mentioned in point 4 under methods, the authors should indicate that this study may not have been adequately powered to identify risk factors for seropositivity for rubella IgG.

Response: Your comment is well taken and we have now stated the weaker power of the study as a limitation.

Reviewer #2

Comment 1: Create space between introduction and methods.

Response: We have now addressed your comment.

Comment 2: Sample size and sampling method line 14 correct word.

Response: We have now addressed your comment

Comment 3: Data collection space.

Response: We have now given space

Comment 4: somewhere in the discussions, a sentence to describe the risk factors should be included clearly before now talking about the risk factors

Response: We are not clear with this comment

Comment 5: The abstract conclusion should be rephrased

Response: We have now revised it

VERSION 2 – REVIEW

REVIEWER	Karina Top Dalhousie University Canada
REVIEW RETURNED	02-Jul-2017

GENERAL COMMENTS	<p>The authors have addressed most of the comments adequately, with the exceptions noted below. It is somewhat surprising that 422/422 women approached for the study were both eligible, consented, and completed the survey. There are still numerous grammatical errors and the manuscript would benefit from careful proofreading and editing.</p> <p>Abstract</p> <p>1. Page 2, Line 5: “recent/acute and exposure to rubella virus infection”. It seems like a word is missing: “recent/acute and past exposure to rubella virus”.</p> <p>2. Page 2 Line 23: “past or exposure to rubella” – “or” should be removed – please correct this throughout the manuscript. IgG seropositivity indicates past exposure to rubella. IgM seropositivity indicates recent exposure to rubella.</p> <p>Methods</p> <p>1. Regarding the response to comment 9 in which the authors indicated that they had planned to do multivariable analysis but only one variable was significantly associated with the outcome at the $p < 0.05$ level. Generally, a higher p-value (e.g., $p = 0.1$ or $p = 0.2$) is used to select variables to be included in a multivariable model to avoid missing potential predictors or confounders. The significance of those variables as independent predictors of the outcome is then assessed based on an alpha level (p) of 0.05. It may be helpful to indicate in the methods or results that multivariable analysis was planned but was not done for the reasons stated.</p> <p>Results</p> <p>1. Regarding the response to comment 1: “We approached 422 women and all met the inclusion criteria. Giving consent to participate was considered as one of the inclusion criteria. All the women completed the survey. Thus, the response rate was 100%.” It is indeed surprising that 100% of women who were approached consented to participate. It is also surprising that the total sample size of 422 is exactly $\frac{1}{2}$ of the number of women expected to be seeing the two ANC clinics over 3 months.</p> <p>2. Page 8, lines 40-43: “The exposure rate to rubella was higher among urban residents, were merchants, attended a primary level education, and were married.” This sentence is unclear and grammatically incorrect, please correct. – e.g., “The exposure rate to rubella was higher among urban residents, merchants, women with a primary level education, and women who were married.”</p> <p>Discussion:</p> <p>1. Page 11, lines 16-17: “aimed to generate data on recent and exposure to rubella...” As indicated in the previous review and in point 1 under the abstract, IgM and IgG seropositivity allow one to differentiate between recent and past exposure to rubella. Please correct throughout the manuscript.</p>
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	<p>2. In regards to the authors' response to comment 2 "the 95% confidence interval for the IgM seropositivity is calculated to be 1-4%. Thus, 0.75% (the result in Bangladesh) is not with in the interval." What was the 95% confidence interval for the Bangladesh result (i.e., the 95% CI around the 0.75%)? It is quite possible that the 95% CI's for this study and for the Bangladesh studies overlap, in which case the two results are not different.</p> <p>3. Page 12, lines 9-12: "It was observed that 8 of the 9 IgM cases were tested positive for IgG" – Please clarify if these 8/9 cases are referring to IgM positive cases identified in the case surveillance. For improved clarity, suggest rewording to: "it was observed that 8 cases were IgM positive and IgG positive and only one case was IgM positive and IgG negative."</p> <p>4. Page 12, lines 50-52: "This agrees with a study done in Nigeria..." – it is unclear what "this" is referring to. Please clarify which result is consistent with the findings of the Nigerian study cited.</p> <p>5. Page 12 lines 52-53: "reported a higher rate in the second trimester" – it is not clear if the higher rate refers to the rate of positive rubella IgM or the rate of vertical transmission. Please clarify.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Comment: The authors have addressed most of the comments adequately, with the exceptions noted below. It is somewhat surprising that 422/422 women approached for the study were both eligible, consented, and completed the survey.

Response: As health settings in Ethiopia do not provide a routine rubella screening service for pregnant women, they usually considers participating in such study as good opportunity to get rubella screening free of charge. Moreover, since most pregnant women provide blood for other laboratory investigations/screenings, they usually do not refuse to participate in a study that use aliquot of blood withdrawn for other testing purposes.

Comment: There are still numerous grammatical errors and the manuscript would benefit from careful proofreading and editing.

Response: The manuscript has now been edited by native English language speaker.

Abstract

Comment 1. Page 2, Line 5: "recent/acute and exposure to rubella virus infection". It seems like a word is missing: "recent/acute and past exposure to rubella virus". Page 2 Line 23: "past or exposure to rubella" – "or" should be removed – please correct this throughout the manuscript. IgG seropositivity indicates past exposure to rubella. IgM seropositivity indicates recent exposure to rubella.

Response: Thanks, we have now revised the manuscript according to your advice.

Methods

Comment 1. Regarding the response to comment 9 in which the authors indicated that they had planned to do multivariable analysis but only one variable was significantly associated with the outcome at the $p < 0.05$ level. Generally, a higher p-value (e.g., $p = 0.1$ or $p = 0.2$) is used to select variables to be included in a multivariable model to avoid missing potential predictors or confounders. The significance of those variables as independent predictors of the outcome is then assessed based on an alpha level (α) of 0.05. It may be helpful to indicate in the methods or results that multivariable analysis was planned but was not done for the reasons stated.

Response: We agree with your comment of considering a higher p-value to select variables for multivariable model. However, we considered variables with $p < 0.05$ in bivariate analysis to be a candidate for multivariable model as past exposure to rubella occurred with uniform high rate in almost all categories to appreciate differences in multivariable model.

Results

Comment 1. Regarding the response to comment 1: "We approached 422 women and all met the inclusion criteria. Giving consent to participate was considered as one of the inclusion criteria. All the women completed the survey. Thus, the response rate was 100%." It is indeed surprising that 100% of women who were approached consented to participate. It is also surprising that the total sample size of 422 is exactly $\frac{1}{2}$ of the number of women expected to be seeing the two ANC clinics over 3 months.

Response: We have now specified the possible reasons for high response rate in your above mentioned comment. We were able to recruit 422 women in a period more than three months (March to June), which was different from our expectation.

Comment 2. Page 8, lines 40-43: "The exposure rate to rubella was higher among urban residents, were merchants, attended a primary level education, and were married." This sentence is unclear and grammatically incorrect, please correct. – e.g., "The exposure rate to rubella was higher among urban residents, merchants, women with a primary level education, and women who were married."

Response: Thank you for this input, we have now edited that section

Discussion:

Comment 1. Page 11, lines 16-17: "aimed to generate data on recent and exposure to rubella..." As indicated in the previous review and in point 1 under the abstract, IgM and IgG seropositivity allow one to differentiate between recent and past exposure to rubella. Please correct throughout the manuscript.

Response: We have now corrected it

Comment 2. In regards to the authors' response to comment 2 "the 95% confidence interval for the IgM seropositivity is calculated to be 1-4%. Thus, 0.75% (the result in Bangladesh) is not with in the interval." What was the 95% confidence interval for the Bangladesh result (i.e., the 95% CI around the 0.75%)? It is quite possible that the 95% CI's for this study and for the Bangladesh studies overlap, in which case the two results are not different.

Response: Your comment is well taken and we have now revised the specified section.

Comment 3. Page 12, lines 9-12: “It was observed that 8 of the 9 IgM cases were tested positive for IgG” – Please clarify if these 8/9 cases are referring to IgM positive cases identified in the case surveillance. For improved clarity, suggest rewording to: “it was observed that 8 cases were IgM positive and IgG positive and only one case was IgM positive and IgG negative.”

Response: Thanks, we have revised it according to your suggestions

Comment 4. Page 12, lines 50-52: “This agrees with a study done in Nigeria...” – it is unclear what “this” is referring to. Please clarify which result is consistent with the findings of the Nigerian study cited.

Response: Thank you so much for detecting errors and helping us take corrections

Comment 5. Page 12 lines 52-53: “reported a higher rate in the second trimester” – it is not clear if the higher rate refers to the rate of positive rubella IgM or the rate of vertical transmission. Please clarify.

Response: We have now revised it

VERSION 3 – REVIEW

REVIEWER	Karina Top Dalhousie University, Canada
REVIEW RETURNED	12-Aug-2017

GENERAL COMMENTS	<p>The authors have addressed the prior comments adequately. Following correction of the minor syntax errors outlined below, this manuscript will be suitable for publication.</p> <p>Minor comments</p> <ol style="list-style-type: none"> 1. page 4, lines 12-13: “5% seropositivity rate... among women of reproductive age, indicating the risk of having CRS”: This should be changed to: “indicating the risk of having an infant with CRS”. 2. Page 4, lines 22-24: “clinical features of rubella may not be the same or may satisfy the case definition of measles”: This sentence doesn’t quite make sense. Do the authors mean that the clinical features of rubella may NOT satisfy the case definition of measles? 3. Page 8, lines 46-48: “Women who reported histories of stillbirth, spontaneous abortion... were 8.8%, 17.5%, and 5.7%, respectively”: This sentence is unclear, please correct, for example: “Histories of stillbirth, spontaneous abortion... were reported by 8.8%, 17.5%, and 5.7% of participants, respectively”. 4. Page 8, lines 48-53: “The sero-positivity rate of anti-rubella IgM was higher among women in their first trimester (4.2%), primigravida (3.7%), and nulliparous (3.1%).” it seems like the sentence is incomplete – suggest, “higher among women WHO WERE in their first trimester (4.2%), primigravida (3.7%), and nulliparous (3.1%).” 5. Page 12, line 24: “This finding is supported with reports...”: “With” is incorrect in this context. Please change “with” to “by” (supported by reports). 6. Page 12, line 57: “at an early age of life” – please correct to “at an early age” 7. Page 12 line 57, to page 13, line 5: “Thus, the immunity produced as a result of natural infection diminishes the role of factors in exposing people to rubella in childbearing age.” It is not clear what point the authors are making. Consider removing this sentence.
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VERSION 3 – AUTHOR RESPONSE

We thank the reviewer for their useful comments and suggestions. We have now taken correction on the manuscript according the suggestions by the reviewer.

Minor comments

Comment 1. page 4, lines 12-13: “5% seropositivity rate... among women of reproductive age, indicating the risk of having CRS”: This should be changed to: “indicating the risk of having an infant with CRS”.

Response: Corrected

Comment 2. Page 4, lines 22-24: “clinical features of rubella may not be the same or may satisfy the case definition of measles”: This sentence doesn’t quite make sense. Do the authors mean that the clinical features of rubella may NOT satisfy the case definition of measles?

Response 3. Corrected

Comment 3. Page 8, lines 46-48: “Women who reported histories of stillbirth, spontaneous abortion... were 8.8%, 17.5%, and 5.7%, respectively”: This sentence is unclear, please correct, for example: “Histories of stillbirth, spontaneous abortion.... were reported by 8.8%, 17.5%, and 5.7% of participants, respectively”.

Response: Corrected

Comment 4. Page 8, lines 48-53: “The sero-positivity rate of anti-rubella IgM was higher among women in their first trimester (4.2%), primigravida (3.7%), and nulliparous (3.1%).” it seems like the sentence is incomplete – suggest, “higher among women WHO WERE in their first trimester (4.2%), primigravida (3.7%), and nulliparous (3.1%). “

Response: Corrected

Comment 5. Page 12, line 24: “This finding is supported with reports...”: “With” is incorrect in this context. Please change “with” to “by” (supported by reports).

Response: Corrected

Comment 6. Page 12, line 57: “at an early age of life” – please correct to “at an early age”

Response: Corrected

Comment 7. Page 12 line 57, to page 13, line 5: “Thus, the immunity produced as a result of natural infection diminishes the role of factors in exposing people to rubella in childbearing age.” It is not clear what point the authors are making. Consider removing this sentence.

Response: Corrected