

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Recent trends in seroprevalence of rubella in Korean women of childbearing age: a cross-sectional study
<b>AUTHORS</b>	Choi, Rihwa; Oh, Yejin; Oh, Youngju; Kim, Sung Ho; Lee, Sang Gon; Lee, Eun Hee

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Alberto E Tozzi Bambino Gesù Children's Hospital Rome, Italy
<b>REVIEW RETURNED</b>	11-May-2019

<b>GENERAL COMMENTS</b>	<p>Adding new data to the puzzle of world rubella seroprevalence is important. This study offers a view from a geographical area rarely represented in epidemiological studies with a very large sample. The manuscript is clear and straightforward. However I would suggest to clarify minor points that can be useful to the reader:</p> <ol style="list-style-type: none"><li>1. I am not very clear on the population based approach of the study. The Authors may better explain how the private laboratory network involved in the study can represent the general population. Moreover, some information about any potential selection of the population included in the study may be useful for better interpreting the results;</li><li>2. Since I understand that the sample included in the study is not the entire population, I would recommend to add 95% confidence intervals of the proportions in the results;</li><li>3. Since Table 2 offers seroprevalence from the total population, it would be more interesting to propose the same data in a figure together with rubella incidence from surveillance (although I understand that no peaks were observed over time);</li><li>4. Likewise, data on historical immunization coverage in children may be helpful to interpret the data;</li><li>5. I think the Authors can give more emphasis to the cohort analysis. This approach seems from figure S1 to suggest that all the strategies in place were very stable. Yet, the proportion of negative women should be discussed more in deep to come out with concrete recommendations to increase vaccine coverage?</li><li>6. It would be interesting to know which prevention policy for rubella is currently adopted in Korea and if there is any promotion of lab screening in the pre-conceptional period free of charge and consequent active offer of immunization.</li></ol>
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<b>REVIEWER</b>	Yajuan Wang Beijing Children's Hospital, Capital Medical University, Beijing, China
<b>REVIEW RETURNED</b>	12-May-2019

<b>GENERAL COMMENTS</b>	<p>This study was involved Korean women of childbearing age (15-49 years) in order to investigate the epidemiology of rubella using the serologic status of rubella-specific IgG antibodies (anti-rubella IgG). It has certain clinical significance, but there are some questions:</p> <ol style="list-style-type: none"> <li>1. Between 2010 and 2017, 329,707 tests from 327,637 Korean women age 15-49 years who had visited obstetric private clinics. At least 70 sera were performed twice, and if duplicate sera samples should be excluded?</li> <li>2. Could you explain why? "Over the 8-year study period, the rate of unimmunized women ranged from 7.8-9.7%. Over the study period, the rate of women who were IgG+ (from 81.0% in 2010 to 73.0% in 2017) decreased". The possible explanations? Or expressed as a percentage of the population base, the results may vary.</li> <li>3. The paper should require specialist statistical help to fully represent the data.</li> <li>4. Language needs to touch up. For example, "The overall rate of women that were anti-rubella IgG- and defined as 'unimmunized' was 7.8-9.7%. Over the 8-year study period, the rate of unimmunized women ranged from 7.8-9.7%."</li> </ol>
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<b>REVIEWER</b>	Manoj Murhekar National Institute of Epidemiology, Chennai, India
<b>REVIEW RETURNED</b>	15-May-2019

<b>GENERAL COMMENTS</b>	<p>Recent trends in seroprevalence of rubella in Korean women of childbearing age</p> <p>The manuscript describes the sero-prevalence of rubella among &gt;300,000 women of childbearing age, who attended 1438 obstetric private hospitals in Korea during 2010 to 2017. The overall susceptibility to rubella was 7.8% to 9.7%. While the findings of study would be useful for strengthening rubella prevention activities in Korea, I have the following comments/suggestions:</p> <ol style="list-style-type: none"> <li>1. Page 5, Line 83: Authors mention that their aim was to investigate the epidemiology of rubella. However, what they have studied is immunity against rubella. Please consider revising this sentence.</li> <li>2. Page 6, Line 110-11: Individuals with IgG levels of <math>\geq 10</math> IU/ml could be due to rubella vaccination as well as due to clinical/sub-clinical infection. Consider categorizing such individuals as "Immune" rather than "Immunized".</li> <li>3. Page 6, Line 111-12: What was the lab protocol for individuals with equivocal results? Were these samples re-tested?</li> <li>4. Line 7, Lines 130-152: The trend of rubella seroprevalence (as well those with equivocal results) was found to have a declining trend. Authors should also mention that trend of sero-negativity was not statistically significant (not mentioned in the manuscript).</li> <li>5. Important findings of the study is that the rubella susceptibility (sero-negativity) in the study was higher than the 5% recommended threshold and this the need for strengthening</li> </ol>
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	<p>rubella vaccination program. However, in absence of a declining trend of rubella sero-negativity, authors could consider mentioning that this has been the situation since last 8 year.</p> <p>6. Authors need to clearly state in the discussion that the declining trend of rubella sero-positivity was because of increasing trend of rubella equivocal results and not due to increasing trend of sero-negativity. In fact the published and unpublished data indicate that the rates of negative or equivocal results for RV IgG is higher in vaccinated populations.</p> <p>7. Page 8, Line 180: To say that 23.6% (negative + equivocal) women susceptible might not correct. Authors may review the study by Bouthry et al (JCM, 2016) in which they have suggested considering equivocal results as positive and consider re-analyzing their data.</p> <p>8. Increasing trend of % results with equivocal results in fact has an implication on lab testing protocol. Maybe by repeat testing such samples with same or another IgG assay.</p> <p>9. One limitation of the study could be that data was from private sector only. What proportion of pregnant women in Korea attend public health facilities? Are there any differences (with respect to socio-demographics, as well as rubella vaccine coverage) among population seeking health care from private and public sector?</p> <p>10. Also, is the proportion of pregnant women (as well as general population) seeking care from private sector different across provinces?</p>
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<b>REVIEWER</b>	Nicolas Gilbert Public Health Agency of Canada
<b>REVIEW RETURNED</b>	16-May-2019

<b>GENERAL COMMENTS</b>	<p>This is a study of seroprevalence of rubella antibodies in Korean women of reproductive age (15-49 years). The results are broken down by birth cohort categories based on temporal changes in rubella vaccination programs. The paper is well written.</p> <p>Line 53: "so-called German measles" is useless, given this is old terminology.</p> <p>Lines 67-68: Here, the authors should describe a paragraph summarizing the incidence of rubella and congenital rubella syndrome in Korea, and in WHO Western Pacific Region.</p> <p>Line 68-69. Rewrite the sentence: "In Korea, a rubella vaccination program using the measles, mumps in rubella (MMR) vaccine has been included..."</p> <p>Line 74 Are there national guidelines in Korea regarding ascertainment of rubella immunity (through serological testing or documentation of past vaccination) in pregnant women, or post-partum vaccination of non-immune women? If yes, please describe them, and if not, please state there none.</p> <p>Lines 102-103: Please explain why results were "prone to ascertainment bias".</p> <p>Line 138:</p>
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	<p>Rewrite: "Rubella immunity in Korean women of childbearing age"</p> <p>Lines 139-140: Rewrite: "The overall proportion of IgG-negative women who were defined as 'unimmunized' was 8.7%, and the overall proportion of IgG-positive women was 76.4%."</p> <p>Lines 193. Here the authors should describe the guidelines in force in Korea, if any, or specify there is no guideline.</p> <p>Table 2 and Figure 1 present the same information. Authors should keep only one of them</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Alberto E Tozzi

Institution and Country: Bambino Gesù Children's Hospital

Rome, Italy

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Adding new data to the puzzle of world rubella seroprevalence is important. This study offers a view from a geographical area rarely represented in epidemiological studies with a very large sample. The manuscript is clear and straightforward. However I would suggest to clarify minor points that can be useful to the reader:

1. I am not very clear on the population based approach of the study. The Authors may better explain how the private laboratory network involved in the study can represent the general population. Moreover, some information about any potential selection of the population included in the study may be useful for better interpreting the results;

Reply: Thank you for your valuable comments. The authors agree with your comments and included the sentences about the above in the revised manuscript according to your recommendations (lines 99-108; lines 265-272).

2. Since I understand that the sample included in the study is not the entire population, I would recommend to add 95% confidence intervals of the proportions in the results;

Reply: Thank you for your valuable comments. The authors added the statistical analysis in this study and included 95% confidence intervals for the proportions in the results according to you and other reviewers.

3. Since Table 2 offers seroprevalence from the total population, it would be more interesting to propose the same data in a figure together with rubella incidence from surveillance (although I understand that no peaks were observed over time);

Reply: Thank you for your valuable comments. The authors provided rubella incidence from surveillance data available from the Korean Centers for Disease Control and Prevention and Healthcare Bigdata Hub by the Health Insurance Review and Assessment Service with the data in the revised Figure 1.

4. Likewise, data on historical immunization coverage in children may be helpful to interpret the data;

Reply: Thank you for your valuable comments. The authors included about historical immunization coverage in the Discussion section (lines 224-233).

5. I think the Authors can give more emphasis to the cohort analysis. This approach seems from figure S1 to suggest that all the strategies in place were very stable. Yet, the proportion of negative women should be discussed more in depth to come out with concrete recommendations to increase vaccine coverage?

Reply: Thank you for your valuable comments. The authors included discussion about the cohort analysis and vaccine coverages in the revised manuscript (lines 224-233).

6. It would be interesting to know which prevention policy for rubella is currently adopted in Korea and if there is any promotion of lab screening in the pre-conceptional period free of charge and consequent active offer of immunization.

Reply: Thank you for your valuable comments. The authors included the prevention policy, including lab screening for rubella control and prevention in South Korea, in the revised manuscript (lines 240-244).

Reviewer: 2

Reviewer Name: Yajuan Wang

Institution and Country: Beijing Children's Hospital, Capital Medical University, Beijing, China

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This study was involved Korean women of childbearing age (15-49 years) in order to investigate the epidemiology of rubella using the serologic status of rubella-specific IgG antibodies (anti-rubella IgG). It has certain clinical significance, but there are some questions:

1. Between 2010 and 2017, 329,707 tests from 327,637 Korean women age 15-49 years who had visited obstetric private clinics. At least 70 sera were performed twice, and if duplicate sera samples should be excluded?

Reply: Thank you for your valuable comments. The authors reviewed the raw data for anti-rubella IgG test results and duplicated test results were all excluded. The exclusion criteria for this study were data from unknown age, sex, and geographic regions, and duplicated test results. The authors clarified the exclusion criteria in the revised manuscript (lines 126-128).

2. Could you explain why? "Over the 8-year study period, the rate of unimmunized women ranged from 7.8-9.7%. Over the study period, the rate of women who were IgG+ (from 81.0% in 2010 to 73.0% in 2017) decreased". The possible explanations? Or expressed as a percentage of the population base, the results may vary.

Reply: Thank you for your valuable comments. The authors included additional statistical analysis including multivariate logistic regression and deleted the sentence with the results of this study in the revised manuscript.

3. The paper should require specialist statistical help to fully represent the data.

Reply: Thank you for your valuable comments. The authors performed additional statistical analysis to represent the data of this study and revised the manuscript per your recommendations (lines 157-162).

4. Language needs to touch up. For example, "The overall rate of women that were anti-rubella IgG- and defined as 'unimmunized' was 7.8-9.7%. Over the 8-year study period, the rate of unimmunized women ranged from 7.8-9.7%."

Reply: Thank you for your valuable comments. The authors revised the sentence according to your recommendations and attached please find a certificate for professional English language editing.

Reviewer: 3

Reviewer Name: Manoj Murhekar

Institution and Country: National Institute of Epidemiology, Chennai, India

Please state any competing interests or state 'None declared':None declared

Please leave your comments for the authors below

Recent trends in seroprevalence of rubella in Korean women of childbearing age

The manuscript describes the sero-prevalence of rubella among >300,000 women of childbearing age, who attended 1438 obstetric private hospitals in Korea during 2010 to 2017. The overall susceptibility to rubella was 7.8% to 9.7%. While the findings of study would be useful for strengthening rubella prevention activities in Korea, I have the following comments/suggestions:

1. Page 5, Line 83: Authors mention that their aim was to investigate the epidemiology of rubella. However, what they have studied is immunity against rubella. Please consider revising this sentence.  
 Reply: Thank you for your valuable comments. The authors revised the sentence according to your recommendations (lines 109-110).
2. Page 6, Line 110-11: Individuals with IgG levels of  $\geq 10$  IU/ml could be due to rubella vaccination as well as due to clinical/sub-clinical infection. Consider categorizing such individuals as "Immune" rather than "Immunized".  
 Reply: Thank you for your valuable comments. The authors revised the sentence according to your recommendations (lines 147-149).
3. Page 6, Line 111-12: What was the lab protocol for individuals with equivocal results? Were these samples re-tested?  
 Reply: Thank you for your valuable comments. During the 8 years of the study period, the lab protocol was maintained without any changes and samples with equivocal results for anti-rubella IgG were not re-tested. The lab protocol for rubella using sample re-tests was only applied to anti-rubella IgM tests. The authors included information about the re-test lab protocols in the Methods section for readability (lines 143-144).
4. Line 7, Lines 130-152: The trend of rubella seroprevalence (as well those with equivocal results) was found to have a declining trend. Authors should also mention that trend of sero-negativity was not statistically significant (not mentioned in the manuscript).  
 Reply: Thank you for your valuable comments. The authors included multiple factors associated with rubella immunization status in the statistical analysis and there was no sero-negativity trend although there were significant differences in sero-negativity rates in different tested years. The authors mentioned that trend of sero-negativity was not statistically significant (lines 179-181).
5. Important findings of the study is that the rubella susceptibility (sero-negativity) in the study was higher than the 5% recommended threshold and this the need for strengthening rubella vaccination program. However, in absence of a declining trend of rubella sero-negativity, authors could consider mentioning that this has been the situation since last 8 year.  
 Reply: Thank you for your valuable comments. Although there was no declining trend for rubella sero-negativity, the odds of being immune to rubella were statistically significantly lower from 2011 to 2017 compared with 2010 (Table 2).
6. Authors need to clearly state in the discussion that the declining trend of rubella sero-positivity was because of increasing trend of rubella equivocal results and not due to increasing trend of sero-negativity. In fact the published and unpublished data indicate that the rates of negative or equivocal results for RV IgG is higher in vaccinated populations.

Reply: Thank you for your valuable comments. The authors performed statistical analysis focused on sero-negativity (not immune to rubella) and revised the manuscript according to your recommendations (lines 199-201).

7. Page 8, Line 180: To say that 23.6% (negative + equivocal) women susceptible might not correct. Authors may review the study by Bouthry et al (JCM, 2016) in which they have suggested considering equivocal results as positive and consider re-analyzing their data.

Reply: Thank you for your valuable comments. The authors performed statistical analysis focused on sero-negativity (not immune to rubella) and revised the manuscript according to your recommendations (lines 199-201).

8. Increasing trend of % results with equivocal results in fact has an implication on lab testing protocol. Maybe by repeat testing such samples with same or another IgG assay.

Reply: Thank you for your valuable comments. The authors included sentences about lab testing protocols and which re-test was not performed in the Methods section according to your recommendations (lines 143-144).

9. One limitation of the study could be that data was from private sector only. What proportion of pregnant women in Korea attend public health facilities? Are there any differences (with respect to socio-demographics, as well as rubella vaccine coverage) among population seeking health care from private and public sector?

Reply: Thank you for your valuable comments. The authors included statistical data about private and public health facilities available in South Korea in the Introduction section. However, exact proportions and differences among populations seeking health care in the private and public sectors were not available and the authors included discussion of these factors as a limitation of this study in the Discussion section (lines 99-108; lines 265-272).

10. Also, is the proportion of pregnant women (as well as general population) seeking care from private sector different across provinces?

Reply: Thank you for your valuable comments. The authors included statistical data about private and public health facilities available in South Korea in the Introduction section. However, exact proportions and differences among pregnant women (as well as the general population) seeking health care in the private and public sectors were not available, and the authors included information about these factors in the study limitations in the Discussion section (lines 99-108; lines 265-272).

Reviewer: 4

Reviewer Name: Nicolas Gilbert

Institution and Country: Public Health Agency of Canada

Please state any competing interests or state 'None declared':None declared

Please leave your comments for the authors below

This is a study of seroprevalence of rubella antibodies in Korean women of reproductive age (15-49 years). The results are broken down by birth cohort categories based on temporal changes in rubella vaccination programs. The paper is well written.

Line 53: "so-called German measles" is useless, given this is old terminology.

Reply: Thank you for your valuable comments. The authors removed the phrase in the revised manuscript according to your recommendations.

Lines 67-68:

Here, the authors should describe a paragraph summarizing the incidence of rubella and congenital rubella syndrome in Korea, and in WHO Western Pacific Region.

Reply: Thank you for your valuable comments. The authors described a paragraph summarizing the incidence of rubella and congenital rubella syndrome in Korea, and in the WHO-defined Western Pacific Region in the revised manuscript according to your recommendations (lines 73-80).

Line 68-69.

Rewrite the sentence: "In Korea, a rubella vaccination program using the measles, mumps in rubella (MMR) vaccine has been included..."

Reply: Thank you for your valuable comments. The authors rewrote the sentence according to your recommendations (line 81).

Line 74

Are there national guidelines in Korea regarding ascertainment of rubella immunity (through serological testing or documentation of past vaccination) in pregnant women, or post-partum vaccination of non-immune women? If yes, please describe them, and if not, please state there none.

Reply: Thank you for your valuable comments. The authors included information about the national guidelines in Korea regarding ascertainment of rubella immunity and vaccination recommendations according to your recommendations (lines 87-91).

Lines 102-103: Please explain why results were "prone to ascertainment bias".

Reply: Thank you for your valuable comments. The authors included information about the possible ascertainment bias of this cross-sectional study in the Discussion section according to your recommendations (lines 265-268).

Line 138:

Rewrite: "Rubella immunity in Korean women of childbearing age"

Reply: Thank you for your valuable comments. The authors rewrote the subtitle according to your recommendations (line 175).

Lines 139-140:

Rewrite: "The overall proportion of IgG-negative women who were defined as 'unimmunized' was 8.7%, and the overall proportion of IgG-positive women was 76.4%."

Reply: Thank you for your valuable comments. The authors rewrote the sentence according to your recommendations (lines 176-177).

Lines 193.

Here the authors should describe the guidelines in force in Korea, if any, or specify there is no guideline.

Reply: Thank you for your valuable comments. The authors describe the guidelines in force in Korea according to your recommendations (lines 240-244).

Table 2 and Figure 1 present the same information. Authors should keep only one of them.

Reply: Thank you for your valuable comments. The authors performed additional statistical analyses and revised the Tables 1 and 2 and Figure 1 according to you and other reviewers' recommendations.



## VERSION 2 – REVIEW

<b>REVIEWER</b>	Yajuan Wang' Department of Neonatal Unit, Beijing Children's Hospital, Capital Medical University, Beijing, China
<b>REVIEW RETURNED</b>	20-Aug-2019
<b>GENERAL COMMENTS</b>	1. This is a cross-sectional study about recent trends in seroprevalence of rubella in Korean women of childbearing age. The results could be as a kind of suggestion for strengthening disease control, prevention of rubella, and immunization program. 2. The introduction was a little bit long.
<b>REVIEWER</b>	Manoj Murhekar ICMR National Institute of Epidemiology, Chennai, India
<b>REVIEW RETURNED</b>	24-Aug-2019
<b>GENERAL COMMENTS</b>	Authors have incorporated all the suggestions. The manuscript may be accepted for publication
<b>REVIEWER</b>	Nicolas Gilbert Public Health Agency of Canada
<b>REVIEW RETURNED</b>	01-Aug-2019
<b>GENERAL COMMENTS</b>	All my comments on the first version have been addressed. In my opinion, this revised version is acceptable for publication.