Author’s response to reviews

Title: Rubella seroprevalence among pregnant women in Beijing, China

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Author’s response to reviews:

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Dear Dr. Drews,

Thank you very much for your special consideration of our work. We deeply appreciate the thoughtful comments by the three reviewers.

According to the reviewers' suggestions, we have revised the manuscript. A point-by-point response to the comments from the two reviewers has been addressed as following, and modified contents in manuscript have been labeled in red.
We hope this revised manuscript could be evaluated again for publication in BMC Infectious Diseases.

Thank you very much for your consideration.

Best regards,

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Point-by-point response

Olatunji Kolawole (Reviewer 1)

This is a good and well-designed research addressing the need to prevent an avoidable outbreak of rubella virus and its associated effects on pregnant women and the baby. However, the research depth is superficial.

The study didn’t consider risk factors which might provide information about its transmission.

Response: Thank you for your careful comments. The protective immunity to rubella was analyzed by a series of patient factor, including age, gravidity, parity, birth place, residence place, education and occupation. The analyses indicated that there were no statistically significant correlations between rates of protective rate and age (P=0.99) (Table 1), gravidity (P=0.84), parity (P=0.84) (Table 2), birth place (P=0.16), residence area (P=0.58), education
(P=0.40) or occupation (P=0.65) (Table 3). The description was added into the revised manuscript.

There is need to include IgM result if available to provide incidence information of the virus thereby strengthening the need for preventive measures such as vaccine for unprotected women. Furthermore, the result would proffer evidence based deduction for the IgG equivocal subject if it remains so after second assay.

Response: Thank you for your careful comments and suggestions. The main purpose of this research is to find the immune (protective) and non-immune (susceptible) rate for rubella. Furthermore, researchers have stressed that it is important to consider the guidelines used as an index of positivity, the cut off value of 10 IU/ml was used for most. According to previous reports, the individuals with anti-rubella IgG ≥10 IU/ml were defined as protected against rubella in our research. It was not the objective of this study to diagnose the current rubella infection. Therefore, the result of IgM had not been included in this research.

For further studies, there should be a molecular result to differentiate the presence of vaccine strain from wild-type which will avoid miss-interpretation of prevalence.

Response: This is a retrospective study. In fact, the routine rubella vaccine immunization was not performed in this population involved in the present study. Only serum samples were collected, and there was no throat swabs to analyze molecular characteristics of rubella virus. We could not provide the molecular information.

Conclusively, please attend to all highlighted sections of the manuscript.

Response: Thank you for your careful comments and suggestions. We have revised the manuscript as the reviewer’s suggestions. Because the modifications are so many that we do not enumerate them here.
Ashrafun Nessa (Reviewer 2)

Title: Title should be more specific. A total of 324 participants are taken from a single hospital of Beijing and it is not mentioned in the methodology whether they representing different geographical location of China. So, they do not represent the total Chinese pregnant women. It is better to mention the name of the city or in a tertiary level hospital of China.

Response: The reviewer’s suggestion makes the title clear, so that we adopted it and revised it as following:

“Webumella seroprevalence among pregnant women in Beijing, China”.

Abstract: Abstract should be modified based on the suggested correction.

Response: Thank you for your careful comments and suggestions. We have revised the manuscript as the reviewer’s suggestions.

Background: The background information is inadequate. China is a country of WHO Western Pacific Region. Current status of immunization program for Rubella and CRS control in China is not stated here. The importance of rubella antibody among pregnant mother in CRS prevention is not highlighted properly. Investigators should enrich and elaborate the background section.

Response: Thank you for your careful comments and suggestions. We have enriched and elaborated the background section as the reviewer’s suggestions.

As the reviewer’s suggestion, we added “There is no specific treatment for rubella and CRS, but they can be prevented by immunization. With the implementation of rubella vaccination strategies, endemic rubella transmission has been interrupted in the Americas since 2009. However, Japan and other countries have been confronted with rubella outbreaks because of the partial vaccination strategy. The MMR (measles-mumps-rubella) vaccine contains live, attenuated viruses for measles, mumps and rubella. To avoid the theoretical risk for fetal complications, MMR vaccine was not administered for pregnant women. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommended that non-pregnant women of child-bearing age without evidence of rubella immunity should receive 1 dose of MMR.”
In China, the national immunization program was first established in 1978, however, only 4 basic vaccines against 6 contagious diseases (tuberculosis, diphtheria, neonatal tetanus, whooping cough, poliomyelitis, and measles) was included. In order to control rubella epidemics, two types of rubella vaccine, including a domestic MMR vaccine containing rubella vaccine strain BRDII and an imported MMR vaccine containing rubella vaccine strain RA27/3, were used in several large cities in eastern China since the 1990s. As recipients had to pay for the vaccine by themselves, the rubella vaccine coverage in children was low at that time until 2007. Since 2008, the rubella vaccine was formally introduced to the national Expanded Program on Immunization (vaccine recipients free vaccination), and a two-dose vaccine schedule is administrated to infants at 8 months of age (Measles-Rubella vaccine, MR) and at 18–24 months of age (MMR) into the revised introduction section (Page 4-5, line 60-82). Therefore, the description about “Current status of immunization program for Rubella and CRS control in China” and “The importance of rubella antibody among pregnant mother in CRS prevention” are both included in the new manuscript.

Methodology:

It is a very important study but the methodology section is too short.

Response: Thank you for reminding us to give more details in methodological decisions. We have enriched and elaborated the methodology section as the reviewer’s suggestions. The details about power calculation, inclusion and exclusion criteria details are added into the revised manuscript. The patient information, including age, gravidity, parity, birth place, residence place, education and occupation, was also added into the revised manuscript.

Study participant selection is not clear. Socio-demographic data like economic status, education level, residence (rural/urban), trimester of pregnancy, parity etc are not stated.

Response: The reviewer’s suggestion makes the manuscript more integrated. The socio-demographic like birth place (Beijing or other city), residence area (urban or rural), education (Non-educated/ Primary school/ Junior high school/ Senior high school/ College or higher) and occupation (Unemployed/ employed/), and the fertility information about gravidity (one pregnancy or more) and parity (one delivery or more) were all stated in the revised manuscript. The analyses about the relationship between protective rate and these patient factors were also added into the revised result section as following:
“There were no statistically significant correlations between protective rate and gravidity (P=0.84), parity (P=0.84), birth place (P=0.16), residence area (P=0.58), education (P=0.40) or occupation (P=0.65) (Table 2 and 3).” (Page 10, line 164-166)

Patient selection: It is not mentioned why the 35 weeks of pregnancy only included in this study. Pregnancy other than 35 weeks are not included should be justified.

Response: We are sorry for the fuzzy words. Not only the 35 weeks of pregnancy included, and pregnancy other than 35 weeks are also included in this study. From June 2016 through March 2017, 324 pregnant women who were about to deliver their baby in the Shunyi Women and Children’s Hospital of Beijing Children’s Hospital were included in this study. However, to reduce unnecessary blood collection, a routinely blood sample obtained at 35 weeks of gestational age was used. To make it clear, we have revised the manuscript as following:

“This is a cross-sectional and hospital-based study. From June 2016 through March 2017, 324 pregnant women who were about to deliver their baby in the Shunyi Women and Children’s Hospital of Beijing Children’s Hospital were included in this study.

…….. Written informed consent was obtained from all pregnant women at the time of enrollment for their blood to be used for research on maternal/infant infectious diseases. After obtaining informed consent, a routinely maternal blood sample was obtained at 35 weeks of gestational age.” (Page 7-8, line 100-124)

Rubella vaccination history is not taken. It is mentioned in discussion that self-supported rubella vaccination has started from 1990s. So, vaccination history is very important.

Response: Thank you for your careful comments and suggestions. The Chinese immunization program has a long history, and a national immunization program first established in 1978 was a routine immunization schedule that included 4 basic vaccines against 6 contagious diseases (tuberculosis, diphtheria, neonatal tetanus, whooping cough, poliomyelitis, and measles). Hepatitis B vaccine was added into the routine immunization schedule in 2002, and in 2008, the national immunization schedule was expanded from 5 vaccines against 7 contagious diseases to 14 vaccines against 15 infectious diseases, and rubella vaccine was introduced into the national immunization schedule at this opportunity. As recipients had to pay for the vaccine by themselves, the rubella vaccine coverage in children was low at that time until 2007. Meanwhile, the national rubella and CRS surveillance has not yet been established, there was also a lack of
detailed information on population coverage of rubella vaccine. The pregnant women in this study were born in 1971-1990. According to some published paper, the rubella vaccine coverage in children was low than 50% before 2007. In fact, it is one of the limits in our study.

The antibody results were expressed in international units per mini-liter (IU/ml). Please verify whether it is mili-liter or mini-liter.

Response: we are sorry for this mistake. It was corrected to mili-liter in the revised manuscript. (Page 8, line 128)

Discussion:

Current status of Chinese EPI program and their strategic plan for Rubella elimination and CRS control are not focused here properly; it should be elaborated with reference. Importance of adolescent and adult vaccination in CRS control should be more detail.

Response: According to the reviewer’s suggestion, the description of “Current status of immunization program for Rubella and CRS control in China” is enriched and moved to the third paragraph in the introduction section.

As the reviewer’s suggestion, we added “the strategic plan for Rubella elimination and CRS control in china” into the revised manuscript as following:

“CRS is an important cause of birth defects in countries where rubella is endemic. To control rubella and prevent CRS, the WHO Regional Office for the Western Pacific (WPR) set a target for rubella of less than 10 cases per million populations by 2015.

Since 2005, the WPR formally declared regional measles elimination a goal with a target date set for 2012. Measles and rubella are similar diseases, both characterized by a rash that may be difficult to differentiate clinically. Therefore, the WHO has decided to include laboratory testing for rubella in the measles surveillance system. During the measles elimination campaign in China, particularly in 2009, the large numbers of suspected measles turn out to be rubella cases. Therefore, it is crucial to eliminate rubella during measles eradication campaigns for China, and then the sentinel CRS surveillance was established in China in 2010-2011. However, national
rubella and CRS surveillance has not yet been established. And there is a lack of detailed information on population coverage of rubella vaccine. In fact, both high vaccine coverage and high-quality surveillance are needed for rubella and measles elimination.” (Page 11, line 168-184)

We also added more detail about “importance of adolescent and adult vaccination in CRS control” into the revised manuscript as following:

“The strategy of adult women vaccination may prevent CRS but does not control rubella. Meanwhile, it still has a long way to implement 100% adult women vaccination. Therefore, a strategy of adolescent vaccination also should be considered to control rubella. As comprehensive measles elimination program had been established in China, rubella and CRS prevention programs may benefit from the established measles control campaigns. It is more feasible to conduct an adolescent MR immunization program in students because of the mandatory education system in China. The rationale for vaccinating adolescent is twofold - to prevent the spread of rubella (at the present now) and additionally to reduce the risk of CRS in the future.” (Page 13-14, line 227-236)

More literature review should be done to show comparisons or consistencies with other studies.

Response: Thank you for your careful comments and suggestions. It is important to consider the guidelines used as an index of positivity. According to previous reports, the cut off value of 10 IU/ml was used for most. More literature review has been collected. However, we just show comparisons or consistencies with other studies with the same cut off value. To make it clear, we revised the manuscript as following:

“De Paschale et al. stressed that it is important to consider the guidelines used as an index of positivity. Adopting the cut off value of 10 IU/ml, our prevalence is comparable with the 85.8% and 87.5% seroprevalence reported in southern Italy and Osogbo, respectively. However, it is lower than the prevalence recorded in Burkina Faso, Ontario, Haiti, and Jeddah with seroprevalence of 93.3%, 90%, 92.8% and 91.6%, respectively.” (Page 12, line 192-198)
Muhammad Sohail Afzal, PhD (Reviewer 3)

The manuscript entitled "Rubella seroprevalence among Chinese pregnant women" by Meng et al. showed the prevalence of Rubella infection in pregnant women in Beijing. The study was carried out from June 2016 through March 2017, and included 324 study participants. The manuscript highlighted the need of vaccination in Chinese women at child bearing age because 16.7% of pregnant women were susceptible to rubella. Although the study covers a very good topic and relevant to the public health, however there are some observations; 1. Background is too short, add some more data to cover the topic. 2. Manuscript should be rechecked for English language corrections and typing errors. Hence I suggested minor revision of the manuscript.

Response: Thank you for your careful comments and suggestions. The reviewer’s suggestion makes the manuscript more integrated. We have enriched and elaborated the background section as the reviewer’s suggestions (Page 4-6, line 51-98). While, the socio-demographic like birth place (Beijing or other city), residence area (urban or rural), education (Non-educated/ Primary school/ Junior high school/ Senior high school/ College or higher) and occupation (Unemployed/ employed/), and the fertility information about gravidity (one pregnancy or more) and parity (one delivery or more) were all stated in the revised manuscript. The analyses about the relationship between protective rate and these patient factors were also added into the revised manuscript (Page 10, line 164-166).

We are ashamed for our unsatisfactory English and thank you very much for your careful correction. After receiving your email, we spent a lot of time to improve the English expression. Because the minor modifications are so many that we do not enumerate them.