Author's response to reviews

Title: Identification of Congenital Rubella Syndrome in Sudan

Authors:

Omer Adam (omerhadi@yahoo.com)
Ahmed K.M. Ali (altom.ahmed@gmail.com)
Judith M. Hübschen (judith.huebschen@crp-sante.lu)
Claude P. Muller (claude.muller@crp-sante.lu)

Version: 3  Date: 22 May 2014

Author's response to reviews: see over
Authors’ Reply to Reviewer 1: Pawel Stefanoff

Comment #1 The manuscript "Identification of Congenital Rubella Syndrome in Sudan" was considerably improved and all my suggestions were addressed appropriately.

Reply from authors:

We take the opportunity to thank you for your valuable comments and suggestions.

Comment #2 Below are just few (minor) suggestions for improvement:

1. Page 2, line 28: The vaccine is not available on the market or is not included in the childhood immunization schedule? It could be stated more clearly.

Reply from authors:

This sentence has been modified as follows (lines 27-28):

“Epidemiological data about congenital rubella syndrome (CRS) are scarce and rubella vaccine is not yet included in the childhood immunization schedule in Sudan.”

2. Page 2, line 28: "Determine the epidemiology" is not too meaningful. A more appropriate aim would be "to identify and describe CRS cases among Sudanese infants [...]"

Reply from authors:

We have modified that sentence as follows (lines 28-30):

“This study aimed to identify and describe CRS cases among Sudanese infants with congenital eye or heart defects.”

3. Page 14: In the table you could remove CRI definition as it is not used in this study...

Reply from authors:

This is not correct. Infant number 1 in Table 2 is classified as a CRI case as the child did not fulfill the criteria for a clinically-confirmed CRS case, but has nevertheless laboratory evidence of infection with rubella virus. The definition of CRI is therefore needed.
Authors’ Reply to Reviewer 2: Pat Tookey

Comment #1 Thank you for responding to my earlier comments. However, I still feel the study methods are unclear, as is the relationship between the study group and the general population. I would also like to see further in Author response to my comment 1.

Reply from authors:

We have included additional information in the methodology section related to your previous comment 1. Please find this information in the “Study participants” section (lines 87-102).

You state that the 98 infants were identified by qualified physicians, and that at the five hospitals all infants matching the inclusion criteria and presenting in the 7 month period were included. But it is still unclear what the inclusion/exclusion criteria were, and how the 'qualified physicians' determined whether or not infants were eligible. The issue is not so much who was included, but who was not. Were all infants with congenital eye and/or heart defects included? Did the physicians identify the cases on the basis of routinely reported admissions data, in-patient data, or discharge summaries? You do address this partially in your response to Comment 5 from the other reviewer, but it's unclear whether the 'birth defect logs' you mention were only for the paediatric hospitals. Were patients classified according to WHO case definitions before being enrolled in the study (meaning that was the inclusion criteria), or after? You do provide some information in the response to reviewers about the population and the study hospitals, but more of this could be included in the paper itself for the benefit of all readers.

Reply from authors:

In the current version, we have clearly stated the study inclusion/exclusion criteria. The inclusion criteria were based on the WHO case definitions for suspected and clinically confirmed CRS (lines 88-89), while we excluded children more than 12 months old or those having congenital defects not compatible with CRS (lines 95-96). We also indicated that the physicians were provided with the study inclusion/exclusion criteria before the start of the study (lines 89-90).

All infants who met the inclusion criteria and presented with congenital eye and/or heart defects during the study period in the selected hospitals were asked to participate in the study (lines 93-95).

The physicians identified the cases according to the specialty of the hospital (lines: 92-93). If they detected either congenital cataract, glaucoma, retinopathy or heart defects in an up to 12
months old child, the child was included. Then they looked at his/her medical records (if any) and asked his/her parents for any other compatible CRS signs. All these data were transferred to the questionnaire (lines: 96-102).

We used the WHO case definition of suspected and clinically confirmed CRS for the enrollment of the subjects to the study. The final case classification was done after laboratory testing. IgM positive clinically confirmed cases were classified as laboratory confirmed cases and suspected CRS cases with a positive IgM result were classified as congenital rubella infection cases. Infants positive for IgG and ≥ 6 months were considered as potential cases and were classified as suspected or clinically confirmed CRS cases based on the detected symptoms and according to the WHO case definitions (lines 151-160).

The paragraph “Study participants” has been modified as follows (line 87-102):

“Study participants
The initial selection of the study subjects was based on the WHO case definitions [13] and both suspected and clinically-confirmed CRS cases were included (Table 1). Physicians were provided with the study inclusion/exclusion criteria before the start of the study. A total of 98 infants aged up to 12 months who matched these case definitions were recruited during the study period and their samples were tested for laboratory confirmation. The clinical examination of these cases was done by qualified physicians according to the specialty of the hospital. As hearing loss was not evaluated in this study, we included infants who presented either with congenital eye defects, heart defects or both. Children aged more than 12 months or presenting with congenital defects not compatible with the CRS case definition were excluded. At the ophthalmology hospitals and the echocardiography unit all infants matching the inclusion criteria and presenting during the 7-months study period were included. For the paediatrics hospitals the research team was called upon by hospital staff when patients matching the inclusion criteria were presented. Clinical symptoms compatible with CRS detected during medical examination, extracted from the infants’ medical records or described by their parents were recorded.”

Comment #2 Thank you for providing further information on the lab tests.

Reply from authors:

We thank the reviewer for the recommendation.

Comment #3 With reference to the study limitations (my previous comment 3). Another potential explanation for the low numbers identified is that rubella is not only seasonal but also has an epidemic cycle (generally 5 or 6 years). So it could be that because infants were all identified in the short time span Feb-Sept 2010, therefore born 2009-2010, this was not a birth cohort which had been exposed to much circulating rubella. Is there any
other data which might cast light on this? If not, would you consider this to be another potential limitation of the study?

Reply from authors:

We considered your explanation in the text although the first reviewer advised us to less concentrate on the justification of obtained numbers and why the frequency of CRS was low. We added some data about the number of rubella cases in Sudan during 2009 and 2010 (lines 179-181):

“This hypothesis is supported by rubella surveillance data from Sudan for 2009 and 2010, which showed that only about 300 rubella cases were identified per year (343 cases in 2009 and 302 in 2010) [23].”

Comment #4 My previous comment 4. Thank you for providing further information on the presenting symptoms. It’s a shame that there is no information on hearing loss in these children - are they going to be reviewed at an older age to establish the proportion with hearing loss? It is still unclear from your response how many of the 24 children with clinically confirmed CRS had both eye and heart defects. You indicate that 20 had eye and 11 heart defects, so was it 7 with both? If so, 2 of the 7 appeared in your 7 confirmed/potential cases, compared with 5/91 with single defects. Would it be worth commenting on this?

Reply from authors: We agree that it would have been better testing our subjects for hearing loss, but the audiometry instruments were unavailable in the selected hospitals. That is also why we are not planning to review those children at an older age to determine the proportion with hearing loss.

A total of 7 infants had both eye and heart defects. This information has been added in the results section (lines 141-146):

“At presentation, 24.5% of the infants were classified as clinically-confirmed CRS cases (median age 4 months; 13 cases had congenital eye defects, 4 infants had congenital heart defects and 7 children had both eye and heart defects) and 75.5% as suspected CRS cases (median age 6 months; 74 cases with congenital eye defects, none had congenital heart defects) according to the WHO case definitions [13].”

The overall number of confirmed cases is quite low and even more importantly, nearly 90% of the participants were recruited in the eye hospitals. That is why we think it is probably too speculative to assume based on our data that the combination of eye and heart defects is a better predictor for CRS than multiple eye defects (we can of course not compare clinically-confirmed to only suspected cases).
Comment #1 This is a well-written, concise paper of important findings on the occurrence of congenital rubella syndrome in Sudan. I believe the findings add to the scientific body of evidence. However, the conclusion is wrong and may divert what is actually needed for a public health response.

Reply from authors:

Thank you for your comment. A new study conclusion has been added both to the main text and the abstract (lines 39-40 and 220-222):

“This study documented the presence of CRS in Sudan and highlighted the importance of rubella vaccine introduction for preventing future CRS cases in the country.”

“This study again documented the presence of CRS in Sudan. It also highlighted the importance of rubella vaccination for the interruption of rubella virus transmission to prevent future CRS cases in Sudan.”

Comment #2 Major compulsory revisions:

1) The conclusion advocates for strengthening surveillance of CRS. CRS is totally preventable by excellent vaccines. CRS signals rubella virus transmission which can be interrupted using the available safe and effective vaccines. Interruption of rubella virus transmission would prevent future cases of CRS. This well-documented in the experience of the WHO Region of the Americas.

Reply from authors:

Please see our answer to comment 1.

2) The authors do not acknowledge successful rubella and congenital rubella syndrome elimination efforts in other parts of the world. CRS surveillance was not a critical factor. Surveillance of rash and fever is much more important in eliminating measles and rubella virus transmission. The authors do not acknowledge the role of rash and fever surveillance. A reference to consider is: Andrus JK, de Quadros CA, Castillo-Solorzano C, Roses Periago M, Henderson DA. Measles and rubella eradication in the Americas. Vaccine 2011:29S;D91-D96.

Reply from authors:
In the Introduction, we now acknowledge the successful rubella and CRS elimination efforts in the Americas and emphasize the role of surveillance of rash and fever in eliminating measles and rubella virus transmission (lines 59-61). The above reference has been added.

“Effective rubella vaccination programs as well as high-quality surveillance of rash/fever diseases have been implemented in the Americas and resulted in rubella and CRS elimination in those countries since 2010 [5, 6].”

3) Focusing solely on strengthening of CRS surveillance diverts scarce resources when rubella and measles containing vaccine introduction should be the priority coupled with a focus on rash and fever surveillance. Sentinel site surveillance of CRS when affordable can add value, but is not a central component of the public health intervention. A suggested reference would be: Andrus JK, de Quadros CA. Perspectives on the role of surveillance in eliminating rubella and congenital rubella syndrome from the Americas. Expert Rev Vaccines 2013;12(9):989-93.

Reply from authors:

We clearly stated that rubella vaccine is cost-effective in comparison with the treatment of CRS cases and recommended its introduction in Sudan. As Sudan is currently far from measles and rubella elimination, strengthening of the existing surveillance system would be an important achievement. Besides the modification of the conclusions in both the main text and the Abstract, we have added a recommendation to strengthen disease surveillance (lines 215-217):

“Strengthening of the currently existing measles and rubella surveillance system and eventually its extension to rash/fever disease surveillance would further support disease control efforts.”