Title: The burden of rotavirus gastroenteritis and nosocomial rotavirus gastroenteritis among children aged <6 years in Japan: A multi-hospital, retrospective, epidemiological survey

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Author's response to reviews: see over
Dear Editorial Team,

Please find enclosed our manuscript entitled “The Burden of Rotavirus Gastroenteritis and Hospital-acquired Rotavirus Gastroenteritis among Children aged <6 Years in Japan: A Multi-hospital Retrospective Epidemiological Survey” which we have revised, taking into consideration comments from the peer reviewers. We sincerely appreciate your review and consideration for publication of the revised manuscript in BMC Pediatrics.

This manuscript reports the burden of rotavirus gastroenteritis (RVGE), focusing on the hospital burden in pre-vaccine era in Japan. Given that there have been no multi-hospital epidemiological studies addressing the burden of laboratory confirmed RVGE in Japan, the study results will be of importance to estimate vaccine impact in the near future. We showed that RV infection was the primary cause of hospitalization due to acute gastroenteritis and also was one of the primary causes of hospitalization compared to other vaccine-preventable diseases such as influenza. In addition, the occurrence of RV nosocomial infection, and its related medical cost were estimated. Risk factors for nosocomial infection were analyzed using a multiple logistic regression model. We observed that hospitals with higher nurse allocation and children with chronic medical condition and longer duration of hospitalization, and at the youngest age group experienced more nosocomial infection.

The Instructions for Authors provided on the BMC Pediatrics Journal website have been followed and all named authors have agreed to this submission. This manuscript was previously rejected by the PIDJ Journal and was revised for submission to BMC Pediatrics. All the comments and suggestions of the reviewers received through PIDJ and BMC Pediatrics have been considered and incorporated into this manuscript. Point-by-point responses to peer reviewers’ comments have been given below. We hope that BMC Pediatrics will find our manuscript relevant for its readers and will consider our revised manuscript for publication. We look forward to hearing from you on the outcome of the review process.

On behalf of all authors,

Yours sincerely,

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Responses to peer reviewers’ comments

Reviewer 1: Jonathan Gubbay

Question 1: Page 8, Line 3: It is stated that RVGE was to be “preferably confirmed by RV diagnostic kits” – it should be stated what alternative diagnostic tests were considered acceptable e.g. PCR, electron microscopy. Most importantly, for study purposes there has to have been laboratory confirmation of all cases included in the study.

Answer: In Japan, rapid diagnostic test using immune-chromatography test is used to confirm RV positivity, the rest of the children in this study had ICD code for RVGE meaning that those kids most probably were tested in clinics or other health care facilities before being hospitalized. Sentence modified to “confirmed by RV diagnostic tests”. The term “preferably was used earlier to indicate for subjects who were transferred from other hospitals and the medical records were not available in the hospital database (Page 8, Line 4 – Methods-Study design).

Question 2: p8: At end of 2nd paragraph data on underlying medical conditions is given. The actual data should be presented in the Results section, not methods. In methods section would just state that data on underlying conditions was gathered.

Answer: The population data for children with underlying medical conditions have been moved to the results section (Page 12, Line 22 – Results- Risk factors of hospital-acquired RVGE).

Question 3: page 10, 2nd paragraph, line 2. How were the ICD10 designated cases confirmed to be valid? It appears that 20 cases (665-645) were diagnosed using ICD10 alone without laboratory testing, which doesn’t seem appropriate.

Answer: That is indeed correct, 645 cases were confirmed by both RV rapid tests and ICD codes. But, the inclusion criteria from the present study states inclusion of a subject with confirmed RVGE (either by ICD codes or RV rapid tests). Even though all participating hospitals routinely conducts RV diagnosis test, in case the subjects have RV-positive test result which was done in other clinics or hospitals before hospital admission, or in case subjects’ siblings are already diagnosed as RVGE, it is indeed possible that the doctors do not repeat the same test to lessen parents’ financial burden. This point was added to the manuscript as possible variance of diagnosis intensity depends on subjects, but not as diagnosis intensity variance among participating hospitals (Page 8, line 8-10). Our results are therefore reported on 665 cases.

Question 4: p12: 2nd last paragraph. Please check this sentence, which begins with “Among all RVGE hospitalisations…..” It is not clear what is being communicated here.

Answer: Sentence modified (Page 12, Line 20 - Results- Risk factors of hospital-acquired RVGE).

Question 5: Table 3. For “Age at the time of hospitalization”, why is the Crude RR 0.41, but adjusted RR 2.16? It appears that 20 cases (665-645) were diagnosed using ICD10 alone without laboratory testing, which doesn’t seem appropriate.

Answer: Corrected. Source: Table 66 (Clinical study report) (Table 3)

Question 6: p14: paragraph 2, 3rd line. Change “years” to “months”.

Answer: Changed (Page 15, Line 16 - Discussion).

Question 7: p.14: The following texts (2nd and 3rd sentences) seem contradictory, and should be revised: “As determined from the present study, the mean duration of RVGE hospitalizations was 5.3 days. This is a longer period of hospitalization than those previously published [6,15]. Previous findings have also shown a similar duration of hospitalization for RVGE (5.2 days) [6].”

Answer: Paragraph revised (Page 15, Line 7).

Question 8: P16, line 2: Delete “the” from the text: “may need more attention from the caregivers” so reads “may need more attention from caregivers…..”

Answer: Deleted (Page 15, Line 22).

Question 9: It is suggested not to use abbreviations in the abstract.

Answer: All abbreviations from the abstract have been removed (Please refer to the Abstract).

Question 10: p14 2nd paragraph. Other previous studies have found that the rate of nosocomial rotavirus gastroenteritis decreased as nurse to patient ratios went up, and with provision of isolation
rooms. This study found the opposite (although was not significant when an adjusted RR was done for patient isolation. Can you suggest any explanation for this finding?

**Answer:** To fulfill the requirement of nurse 7 allocation more nurses should be hired and allocated to paediatric wards. We suppose that if many nurses take care of children with acute GE and any of them fails to obey the standard precautions as well as appropriate hygienic measures to reduce contact transmission, it seems likely to spread RV to other inpatient children through cares given by those nurses. Therefore, increase in frequency of nurse contact to patients might lead to increased frequency of hospital-acquired infections. Our tentative speculation is as follows: if the number of nurse will be more; it can also increase frequency of contact to the patient (Explanation provided, not included in the manuscript)

**Question 11:** P18. Line 1 of Conclusion - Suggest change “largest” to “large”

**Answer:** Changed (Page 18, line 1).

**Reviewer 2: Martin Petric**

**Question 12:** Results, paragraph 3, line 7: change table 2 to figure 2

**Answer:** Changed (Page 10, line 18).

**Question 13:** Discussion, paragraph 2, line 3: change years to months.

**Answer:** Changed (Page 15, Line 16 – Discussion).

**Question 14:** The seasonal incidence does not differ from that reported over the past several decades. It would have been interesting had there been any difference shown for seasonal incidence from north to south

**Answer:** We have looked for seasonal incidence among the eight hospitals that participated in this study. As a result, there was no difference in the seasonal incidence among those hospitals. Thus the data on seasonal incidence from north to south is not included in the revised manuscript. Additionally, it is the perspective of the authors that they do not see any value to divide 8 participating hospitals from north to south to observe regional difference of RVGE incidence, because hospital location per latitude does not reflect similar temperature, similar seasonal virus circulation, similar geographical characteristics etc., which may influence on ‘seasonal’ incidence that the reviewer would like to see. Of course we can divide the 8 hospitals according to routine administrative boundary, however, we think that it is impossible to divide them to enable all natural factors which likely influence on ‘real’ circulation of viruses to reflect on ‘seasonal’ incidence precisely (Explanation provided, not included in the manuscript).

**Reviewer 3: Julie A Bettinger**

**Question 15:** The number and proportion of cases with underlying disease should be presented in the results, not the methods section.

**Answer:** We revised accordingly (Page 12, Line 22 – Results: Risk factors of hospital-acquired RVGE).

**Question 16:** Typo in the 2nd paragraph of the discussion: study was not done in children <18 years of age.

**Answer:** Corrected (Page 15, Line 16 – Discussion).

**Question 17:** Healthcare or Hospital acquired infections is the preferred term to nosocomial infections. (See Coffin SE, Zaoutis TE. Healthcare-associated Infections. In: Long SS, Pickering LK, Prober CG. Principles and Practice of Paediatric Infectious Diseases. 3rd ed. Churchill Livingstone; 2008: chap 101)

**Answer:** We revised accordingly (Throughout the manuscript).

**Question 18:** Please include the approximate percentage of the paediatric population covered by the hospitals participating in the study (i.e. their paediatric catchment).

**Answer:** It is difficult to ascertain the percentage of paediatric population covered by the participating hospitals of this study due to the approach in health-seeking behaviour. Every patient is free to visit any doctor, clinic or hospital at any time; therefore, it is very difficult to estimate the appropriate catchment population in this case.
Question 19: Please clarify whether all cases were included or only those providing consent.
Answer: The Japanese ethical guideline for epidemiological research does not request to collect informed consent form in case of database study. Authors clarified this in the manuscript (Page 8, line 18).

Question 20: There are multiple places where the data are presented both in the text and tables or figures. Please present data either in the text or tables/figures, but not both places. The reader can be referred to the table without a summary of what is included in the table. For example, table 1 include demographic characteristics of the study population rather than describing the median age of cases, which is also shown in the table. Figure 2 is not needed. Either report data in the text or figure; don’t include both. There are other instances of this duplication throughout the manuscript. Please revise.
Answer: Results section and tables have been modified to report these numbers, while all redundancies have been removed. Table 1 modified. Figure 2 retained. Numbers in both text and figures/tables have been revised to avoid repetitions.

Question 21: The discussion refers to outbreaks of rotavirus. What is the definition for these outbreaks? How are they determined to be outbreaks? It is well-known that rotavirus exhibits a seasonal pattern with increases in late winter to early spring. Please clarify why this is being referred to as an outbreak.
Answer: The term “outbreak” was used in a general context. We agree with your point. Definition for RV outbreak is not officially decided based on its reproduction number or disease infectiousness. We have revised accordingly (Page 14, line 11-16).

Question 22: There is evidence from North American studies demonstrating rotavirus occurs in the spring. This is not a new finding. The authors should place this finding in the context of what is known in the literature.
Answer: This is indeed not a new finding. However, our statement in the discussion was for Japan. This is a new finding in Japan; however, seasonality of the disease has not been well examined previously as done in our multihospital nationwide surveillance. We have now placed our findings in the context of what is known in the literature for Japan (Page 14, line 11-16).

Question 23: The literature review is fairly cursory and would benefit from including some of the major North American studies on this subject especially in sections where the disease burden is discussed.
Answer: We added the following two articles in the Background and Discussion section. The first one is to show the inevitable limitation of all retrospective surveillance in the Discussion section (Page 16, Line 22). The latter is to show that RVGE can be severe in Background section (Page 5, Line 9).


Question 24: It is not appropriate to compare the burden in developing countries to the results in this study (reference 19). Again, there are many other studies that have examined the burden of both community and hospital acquired rotavirus in developed countries that would be more appropriate to use.
Answer: As done and published in Fischer et al’s literature review, it is acceptable to put down with the data from developed and developing countries as far as it is not blurred into each other; however, authors revised the manuscript accordingly. Reference 19 for developing nations deleted. Updated the present reference with a reference for developed countries – Forster et al (12) and Gleizes et al (19) (Page 14, line 20, 22)

Question 25: Without population based surveillance data, the authors cannot know that the number of hospital acquired cases missed is low. This should be revised as a limitation in the discussion.
Answer: Sentence “However, the number of these cases is expected to be low” deleted (Page 17, line 8).
Question 26: The statistical analyses used in the manuscript are not transparent.

Answer: Additional details have been provided in the methods section. Statistical methodology has been re-written to ensure clarity (please refer to endpoints and statistical analyses).

Question 27: It is unclear why the total number of community and hospital acquired cases is not provided in the tables, but rather the percentages of total admissions.

Answer: Results section and tables have been modified to report these numbers, while all redundancies have been removed. Community-acquired RVGE (n =584) and hospital-acquired RVGE (n =81) are included in the text (Results, Page 10, Characteristics of acute GE and RVGE hospitalizations and Table 1).

Question 28: More details need to be provided on how the risk ratios were calculated. What regression model was used? What logical tests and data validity checks were used and what were the results of these. Given the very small numbers in some of the categories (N=3) multiple regression may not be appropriate, but without additional information this cannot be determined. Because the risk factor data is not adequately presented the arguments in the discussion about these data are not well supported. If these data do not support multivariate regression then the discussion should be modified as well.

Answer: Included. The model included all variables as all of them are considered important and the model assessed risk in an exploratory manner. Since the model converged, the fit is good for the data. The risk ratios were computed from estimates from logistic regression using PROC GENMOD, keeping log link function for binomial distribution. Considering the prognostic importance of covariates, all risk factors were included in the model, though few covariates were not significant. The parameters were estimated by maximum likelihood estimation through an iterative fitting process.

Question 29: The mean and median stay for hospital acquired rotavirus should be provided in the results, not just the additional days over community acquired infection. This mean and median length of stay (LOS) for hospital acquired cases can be tested for significant difference against the mean and median for community acquired cases. Furthermore, the calculation for the additional median hospital days due to hospital acquired rotavirus is not appropriate. Using an estimate of days usually spent in hospital determined by doctors based on their professional experience is not an objective measure. If the authors are unable to determine the mean and median LOS for hospital acquired cases this should be stated as a limitation and this portion of the results and discussion should be removed.

Answer: As for the first part of the revision request (i.e. significant difference test between hospital acquired vs. community acquired), authors do not recognize the unquestioning value of this additional test from the following three reasons; 1) it is not our objective to examine the difference of disease burden between hospital- vs. community- acquired, 2) Those subjects whose hospital stay was very long due to chronic disease should be removed from both population, but it is difficult to define which disease should be excluded from the analyses. 3) It is not requested by all other reviewers.

As for the second part of the revision request (i.e. additional days estimation based on doctors’ professional judgment), authors admit up to a point that this method may be objective; however, estimation was done by carefully examining each medical chart of all possibly hospital-acquired subjects, which means that this method is rather conservative not to overestimate and underestimate the disease burden of hospital-acquired RVGE (medians + ranges provided – page 10, line 18-22, Page 11, line 20-22). Finally, we feel that this method was indeed possible because the number of hospital-acquired infection cases was small in each hospital.

Question 30: The finding that the longest mean hospital stay was among children 5-6 months is likely influenced by outliers. The median would be more appropriate in this instance. The sample size for cases in this age group should be provided.

Answer: Median has been provided (Page 20, line 21, 22).

Question 31: All demographic and risk factor variables that were measured should be provided in table 1 for both the community and hospital acquired cases.

Answer: Included. Demographic characteristics for community-acquired acute GE included in Table 1. Risk factor N, n and % values provided in Table 3. Redundancies in demographic characteristics in text and table removed (Table 1).

Question 32: Greater detail on the laboratory testing patterns and admission criteria at each hospital should be provided. Just over half the defined cases actually had a rotavirus test. Why were the other
cases not tested? How the testing is applied at each hospital? If a hospital only had 15 paediatric beds what criteria are used to determine who gets admitted? As we found in our surveillance, testing and admitting patterns can vary widely among hospitals and in order to accurately interpret the data an understanding of these patterns is necessary.

Answer: Even though all participating hospitals routinely conducts RV diagnosis test, in case the subjects have RV-positive test result which was done in other clinics or hospitals before hospital admission, or in case subjects’ siblings are already diagnosed as RVGE, it is indeed possible that the doctors do not repeat the same test to lessen parents’ financial burden. This point was added to the manuscript as possible variance of diagnosis intensity depends on subjects, but not as diagnosis intensity variance among participating hospitals (page 8, line 8-10). Additionally, the authors believe that as per health care practice in Japan anyone can get admitted at any hospital at any time, meaning that although we standardized our methodology across these eight hospitals we could not control for factors specific to each participating centre.

Question 33: The incidence of hospital acquired rotavirus differed significantly each year of the study. The authors should attempt to explain this difference. As well, the number and proportion of cases attributable to community and hospital-acquired rotavirus should be provided for each year.

Answer: As for the first point, we believe that as far as we study infectious diseases, such differences from one year to the next are observed. The difference between 2008 and 2009 are related to the seasonal distribution of community-acquired infections RVGE. We speculate that the larger number of RVGE patients (high circulation) in 2008 year is linked with the higher numbers of hospital-acquired infections. We do not see the value of adding this explanation in the manuscript because it will be no more than speculation. Additionally, please refer to Figure 3 and attached file (from The National Institute of Infectious Diseases). Although the data is available on file, these numbers and proportions by calendar year were not the endpoints of our study and therefore have not been reported.

Question 34: The information in the discussion related to costs does not match that from the study referenced. The costs were for a hospital stay of 5.4 days and the authors of the referenced study caution extrapolation. Furthermore, the total number of rotavirus cases Ito et al. determined was 30,000. Regardless of the errors, more rigorous cost estimate studies have already been done in Japan and this current study was not designed to estimate costs therefore

Answer: Considering that the other reviewers accepted the value of the HE analysis, the authors would like to retain this part as it is. This is the first estimation based on larger scale multi-hospital survey in Japan because Ito et al. is just based on Nantan Hospital, thus we believe our estimate is more robust.