Author's response to reviews

Title: The burden of rotavirus gastroenteritis and hospital-acquired rotavirus gastroenteritis among children aged less than 6 years in Japan: A retrospective, multicenter 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 less than 6 Years in Japan: A retrospective, multicenter 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 has been few multicenter hospital epidemiological studies addressing the burden of 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 hospital-acquired RV infection and its related medical costs were estimated. We observed that in children with chronic medical conditions and those hospitalized for longer durations and in the youngest age group proportions of hospital-acquired RV infection were higher.

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 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: Julie A Bettinger

Major compulsory revisions

Question 1: Methods lines 3-5. While the authors may not be able to provide the catchment areas for the hospital they should provide the population of children <6 years of age in the regions where the hospitals are located and that proportion of the entire population of children <6 years of age this represents. Without this information, one cannot judge the representativeness or generalizability of the results.

Answer: Based on the National Population Statistics and the annual inpatients data for all hospitals the number of children below 6 years of age and the proportion of the entire population of children below 6 years are 5,982 and 4.6% for Hospital 1, 7,231 and 5.6% for Hospital 2, 4,608 and 4.0% for Hospital 3, 7,598 and 5.2% for Hospital 4, 5,203 and 4.8% for Hospital 5, 8,094 and 5.2% for Hospital 6, 3,386 and 5.7 % for Hospital 7, 7,400 and 5.7 % for Hospital 8, respectively. In total the eight hospitals cover a population of 49,502 <6 years of age in their regions. According to the reported annual numbers of children who contract rotavirus infection and the proportion of patients who need hospitalization for rotavirus gastroenteritis in Japan, the expected number of inpatients with RVGE in the eight hospitals were estimated as follows; 49,502×(a/(b)×(c/100) = 604 cases. This estimated number, 604, is regarded to be in the close range of the observed number, 665 in our study. This result gives some degree of reliability to estimated populations <6 years of age that each hospital covers.

a: annual population with rotavirus infection <6 years of age in Japan, 1.99 million [1, 2]
b: population of <6 years of age in Japan, 6.36 million [3]
c: proportion of admission due to RVGE <6 years of age, 3.9% [4]

Question 2: Methods and table 3: The logistic regression models were intended to model the risk of hospital acquired infection. However, with a total N of 13767 the authors did not remove the acute gastroenteritis or the community acquired cases from the logistic regression models. Clearly these children were not at risk for hospital acquired infection and the risk estimates are not correct. In their risk estimates, the authors should control for underlying health status and season, two variables which their descriptive analysis and the literature indicate are important. The authors also should show the number of hospitals with 7 nurses per patient, the number with 10 nurses per patient, the number with < 30 beds, the number with >= 30 beds and the number with and without isolation rooms. The authors need to use a model that will account for the hospital effects in their estimates as they are using individual level variables and hospital level variables. Without significantly more development (adding important other covariates, adjusting for hospital effects, etc.) the risk estimates are the weakest part of this paper and the authors should remove them. Given the limited variables included (especially without an adjustment for the various types of underlying health conditions) they do not provide much useful information. Moreover, the interpretation of the estimates in the discussion is not correct.

Answer: Risk estimates derived from logistic regression model have been removed from the manuscript. Proportions of hospital-acquired RVGE by hospital and patient characteristics with exact confidence intervals have been reported instead. Please refer to Table 3; Results, page 12, lines 8-17; Discussion, page 14, lines 10-23, page 15, line 1-2. The number of hospitals for each hospital characteristic is shown in footnote of Table 3.

Question 3: The authors still have not provided the mean or median and range for duration of stay for patients with hospital acquired infection. They are only providing their calculation of additional days. The reader still cannot judge how they derived neither this number nor the outliers that may be influencing this calculation. This information should be added given its use in the discussion to derive costs estimates. In addition, the authors need to describe the original conditions which caused the admission or the underlying health status of this group in order to understand the characteristics of these HA cases. The authors should also examine whether or not the length of stay for HA infections and the proportion of HA infections differs by the centers in their study.

Answer: Median duration of hospitalization due to hospital-acquired RVGE was 10.0 days (range: 2.0–133). This has been included in the results (page 11, lines 20-21). The numbers and proportions of underlying conditions in for the different subject groups i.e. acute GE, RVGE and hospital-acquired...
RVGE are reported (Table 1; results page 10, lines 13-15). Median durations of hospitalization by underlying medical conditions and center are described in the results section. Ranges of the median duration of hospitalization and proportions of hospital-acquired RVGE by center are described to allow the reader to see the variation in proportion by center and presence of medical condition. Please refer to results, page 11, lines 21-22, page 12, lines 1-7.

Moreover, we have clarified that the median duration of hospitalization was estimated based on this definition – “The duration of additional hospitalization for hospital-acquired RVGE (in days) was estimated as the difference between the usual average number of days spent in hospital due to the specific medical condition and the number of days the child actually spent in hospital.” (Methods, page 8, lines 10-13).

In the discussion we have clarified that - However, duration of additional hospitalization was estimated as zero if medical chart review revealed that RV was unlikely to have had any impact on hospitalization duration (e.g. duration of hospitalization due to primary diagnoses was too long and hospital-acquired RVGE occurred in the middle of hospitalization for initial diagnoses etc.) (Discussion, page 17, lines 2-6).

**Question 4:** Results page 11 lines 12-16. It is difficult to track the numbers in each group and this section should be rewritten to explain1) number and % hospitalized with acute GE 2) number % hospitalized with rotavirus and 3) number % hospitalized with HA rota. Once those numbers have been presented the testing patterns should be explained. The discussion mentions 32% of cases did not have a rapid test. This needs to be explained in the methods and results (see comment 9).

**Answer:** The methods and results sections have been modified to report numbers followed by % hospitalized for acute GE and then RVGE as suggested (Results, page 10, lines 6-15). Our eligibility criteria for study inclusion (diagnosis and testing) are described in the methodology (Methods, page 7 line 13-19). This proportion i.e. 68.0% has been reported in the results and we have compared the proportions – 68.0% and 32.0% (not tested; but confirmed by ICD 10th revision) to published literature in the discussion (Results, Page 10, lines 9-11, Discussion, page 13, lines 5-6, page 15, lines 17-19, page 16, lines 5-7).

**Question 5:** Page 14 line 4: This sentence should reflect the % due to rotavirus GE (4.8%) not all GE given the focus of this manuscript is rotavirus and the costs associated with rotavirus infection

**Answer:** The proportion has been changed, reported 4.8%. Discussion, page 13, line 4-5.

**Question 6:** Page 15 lines11-21: The interpretation of the risk estimate is incorrect. If estimates are not significant in the adjusted model then the risk is not higher. If the estimate and CI is above0 then the risk is increased

**Answer:** Risk estimates have been removed from the manuscript. Proportions of hospital-acquired RVGE by hospital and patient characteristics with exact confidence intervals have been reported instead. Please refer to table 3.

**Question 7:** Page 17 line 3: please describe in the methods and results the % of patient without a RV rapid test. How was the rotavirus diagnoses determined for these cases? This is different than the information already presented in the methods and results.

**Answer:** In the methods the eligibility criteria are described – RVGE or hospital-acquired were diagnosed based on either of the following two – ICD 10 codes or RV rapid test. In the results, we have reported proportions on 665 (total RVGE diagnosed by either ICD10 or RV rapid testing). For the ones with no RV test available, diagnosis was confirmed on ICD codes 10th revision only. I have revised the wording in the methods (Methods, page 7 lines 13-19) and results (according to your suggestion in comment 4).

**Question 8:** Table 1 should present the % of underlying health conditions found in each group. And whether the types of conditions differed by group (Acute GE, RVGE and HA RVGE).

**Answer:** The proportions of underlying health conditions found in each group are given in the text and Table 1. The numbers and proportions by different medical conditions for each of the groups are given in Table 1 (Results, page 10, lines 6-15/Table 1).

**Minor revisions**

**Question 1:** Figure 2: the figure legends should read hospital acquired rather than nosocomial

**Answer:** We have modified the legends. Please refer to Figure 2.
Question 2: Page 11 and page 12 lines 21-22: the reference to figure 2 should be removed. These data are not shown in Figure 2.
Answer: Removed the reference to Figure 2. Results, page 10, line 20.

Question 3: Results page 11-12 lines 22-2. Please clarify whether or not this is a mean or median. By using the word average this implies a mean. Given the range of values and the outliers a median is the appropriate measure to present.
Answer: It is the median duration. This has now been indicated in the text. Results, page 11, line 1-2.

Question 4: Page 12 line 10 the reference to table 1 should be removed. These data are not described in table 1 and the characteristics of HA cases in table 1 have already been referred to on page 11 line 10.
Answer: Removed the reference to Table 1. Results, page 11, line 9.

Question 5: Page 13 lines 3-4. The authors cannot say infants in intensive care are more likely (than whom?) to acquire hospital infection based on these data. They have not compared these infants to other groups. Also they have not indicated to which ward these infants were admitted.
Answer: We have removed the term intensive care units. Results, page 11, lines 17-19.

Question 6: Page 14 line 8: add hospitalized before RVGE.
Answer: Added hospitalized before RVGE, Discussion, page 13, line 9.

Question 7: Page 14 line 16: the proportion of HA RVGE is 0.6% NOT 12.2%. Please change.
Answer: Changed to 0.6% which is the proportion of HA RVGE among all hospitalizations. Discussion, page 13, lines 16-17.

Question 8: Page 14 line 20-21: please add in “the incidence of 1.0 per 1,000 hospital days of HA RVGE reported in our study...” and “reported in Europe by Forster.”
Answer: The sentence has been modified according to your suggestion. Discussion, page 14, lines 1-3.

Question 9: Page 15 line 1 please change “high standard of care” to “infection control procedures”. Japan does not have a higher standard of care than Europe.
Answer: Replaced high standard of care to infection control procedures. Discussion, page 13, line 20.

Question 10: Page 15 lines 5 and 6: Unless these studies measured transmission dynamics, you cannot determine who is more likely to acquire HA RVGE. Please reword.
Answer: Sentences revised. Discussion, page 14, lines 2-6.

Question 11: Page 15 line 9: Is 4.7 the average duration of hospitalization or the mean additional days of hospitalization? Please clarify.
Answer: It is the mean duration of hospitalization. This has been clarified in the text (Discussion, page 14, lines 7-8).

Question 12: Page 16 lines 3-4: what is the duration of a single hospitalization from which the $1,888 is derived? Please make this clear.
Answer: It is 5.4 days. This has now been included in the text. Discussion, page 15, lines 3-4.

Question 13: Page 13 line 13: these results cannot be applied to the general population. They may be generalizable to Japanese children < 6 years of age hospitalized for acute GE. Please reword.
Answer: Sentence modified according to your suggestion. Discussion, page 15, lines 13-14.

Question 14: Table 3: the N in the title is incorrect.
Answer: In Table 3 risk estimates have been removed. Only proportions of HA RVGE by different hospital characteristics with exact 95% CI are reported. N value corrected to 13767 (Please refer to Table 3).

Discretionary revisions

Question 1: Methods line 7 typo.
**Answer:** Cannot find the typo. However, we have reviewed and revised the methods section for tenses, grammar and spelling.

**Question 2:** Methods Lines 3-23: verb tenses change throughout please correct.  
**Answer:** Revised the methods section.

**Question 3:** Table 2: Please reorganize the age group to < 2 years; 2-<5 years and 5-<6 years and total (<6 years).  
**Answer:** We have data available only for <2 years, 2-<4 years, 4-<6 years and <6 years. These have been included in Table 2. Please refer to Table 2.

**Question 4:** Results page 11 lines 16-17. The data on children < 5 can be presented in the table (with the relevant footnote as to why these data are being presented) but should not be presented in the text. It is confusing to switch back and forth between <5 and <6.  
**Answer:** Data on children <5 years deleted from the text. Data on <5 years retained in the tables.

**Question 5:** Figure 3 is not necessary. The data are nicely summarized in the text.  
**Answer:** Figure 3 deleted.

**Question 6:** Page 12 lines 14-17: these data can go into table 2.  
**Answer:** These data have been added to Table 2.

**Question 7:** Page 15 line 1 The authors should consider commenting on the difference in infection control procedures practiced at the hospitals in this study compared to hospitals in Europe.  
**Answer:** We have added the following statement - “found that the proportion of hospital-acquired RVGE among all hospitalizations of children aged less than six years was 0.6% and was associated with median additional hospitalization of 3 days. This proportion was lower than that observed for similarly aged children in developed countries in the European Union (31−87%) [20] and could be due to different infection control procedures in the Japanese healthcare system [21]. However, no differences between Japan and European hospitals exist and the reason for this apparent difference remains to be unknown.” Please refer to the Discussion, Page 13, lines 16-22.

**References**


