**Author's response to reviews**

**Title:** Disease burden and related medical costs of rotavirus infections in Taiwan

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**Author's response to reviews:** see over
Dear Dr. Nelson and Dr. Stein:

Thank you both very much for the expert critiques and suggestions on our manuscript entitled "Disease burden and related medical costs of rotavirus infections in Taiwan" (MS: 188212553102107). We have revised our manuscript based on your suggestions as much as possible. Major revisions and our replies to each of the specific points you raised are explained below.

Major Revisions.

We agree with Dr. Nelson that most of the rotavirus infections occur in children <5 years old. Therefore, in the revision we presented data for children 0-16 years old in Table 1 only in order to show that acute gastroenteritis (AGE) occur mostly in <5 years old children. Subsequent analysis focused on <5 years old only. We have also re-analyzed the proportions of children with AGE attributable to rotavirus for inpatients and outpatients separately for the three hospitals. We have also redone our analysis using the ICD-9-CM codes used by Dr. Nelson and colleagues (J Infect Dis 2005, 192:S71-S79) to include 558.9 and 787.91 in addition to 001 to 009 (excluding 003.2 and 006.2-006.6).

As both of you pointed out, we recognize that by including TCH, the hospital in the east, we may be under estimating the disease burden. Therefore, the disease burden and medical cost of rotavirus were extrapolated separately for inpatients and outpatients by using ranges rather than a single percentage. For inpatients, the ARSN data (43%) published by Chen et al. (J Infect Dis 2005; 192:S44-S48.) was used as the upper limit and our own result from the three hospitals (32.9%) was used as the lower limit. Because we used a range to estimate the inpatients, we also used the range of 15-35% reviewed by Glass et al. (Lancet 2006;368:323-332) to estimate the outpatient rotavirus disease burden. Our data is comparable to this range since we found that 24% of the outpatients with AGE were attributable to rotavirus in the three hospitals studied.

Reply to Reviewer #1 (Dr. Edmund Nelson)

Major compulsory Revisions:
1. We have focused our analysis on children <5 years of age in the revision. We have also used a range to estimate the disease burden as explained above.

Since we reanalyzed the data for the hospitals for children <5 years old, now 17 (18.3%) and 12 (12.9%) of the diarrhoea admission at TCH were due to rotavirus and Shigella, respectively. Taiwan is a small mountainous island with the western and northern parts being the most developed and densely populated. The central mountainous areas, offshore islands, and eastern part are the least populated areas and can be considered “rural”. The population in these areas comprised less than 5% of the total population in Taiwan. In the eastern part where TCH is located, the population in that county comprised 1.6% of the total population.
(353,139/22,405,568) in Taiwan in 2001. Thus including the TCH data may have underestimated the total disease burden. Therefore we used the range to estimate the disease burden as you suggested.

The current study was undertaken independently from ARSN. Our data was collected and analyzed separately from that of Chen et al., although both studies involved National Taiwan University Hospital (NTUH). The study by Chen et al prospectively collected stool samples for children with AGE for a 2-year period between April 2001 and March 2003. We retrospectively reviewed AGE patient records and their laboratory data for 1 year between March 2001 and February 2002, thus there could have been overlap of some patients from NTUH. The other hospitals are different in the two studies.

2. We have redone our analysis using the ICD-9-CM codes used by Nelson et al in J Infect Dis (2005, 192:S71-S79) to include 558.9 and 787.91 in addition to 001 to 009 (excluding 003.2 and 006.2-006.6) This is explained in the Methods (pages 5-6) and discussed briefly in the Discussion section (page 12).

The sampling database is a systematic sampling of every 20 inpatient records and every 500 outpatient records from the BNHI all-patients database at the National Health Research Institutes based on statistical advice of a team working on the database. The team has previously determined that statistically this sampling strategy would provide comparable representative data to all-patients database. The sampling database was done and made available to researchers in Taiwan for research purposes because the database of all-patient records is tremendously large that even the highly advanced personal computers do not have the capacity to handle such large database and queries. In the 2001 sampling database, there were over 620,000 outpatient and 120,000 inpatient records, which we feel provide adequate sample size for our analysis.

3. After we reanalyzed the data for <5 years old children only, the medical cost now is US$ 10.8 per outpatient and US$ 336.0 per inpatient. Since the implementation of a single-payer, publicly administered universal national health insurance program in 1995, expenses of medical care are reimbursed by the Bureau of National Health Insurance (BNHI). By December 2000, over 96% of Taiwan’s 22.3 million (22,276,672) population was covered. The database contained health care related information, including registration files, original claim data (diagnosis, treatments, etc.) and reimbursement data (medical costs). The medical costs include BNHI reimbursements, co-payments, and all governmental subsidies for certain subpopulation. We did not include the registration fee of US$ 1.5-3.0 for each outpatient visit in our estimate. The BNHI reimbursements for AGE hospitalization typically include hospital room charge and nursing fee (40.7%), pharmacy and treatment-related charges (29.3%), laboratory services (14.6%), and physician fee (15.4%). The reason for the lowered cost per case is very likely due to that medical cost for healthcare in Taiwan is lower in general. However, the economic burden per hospitalized diarrhoea patient due to rotavirus infection is higher in Taiwan than that of USA and Hong Kong when the direct medical cost is normalized with GNI. This comparison is done on inpatient care only.

Minor Essential Revisions. Figure 1 has been deleted.
Reply to Reviewer #2 (Dr. Ken Stein)

1. The methods for estimating costs are explained in more details on pages 5 and 6 of the revised manuscript. Briefly, the medical costs include the Bureau of National Health Insurance (BNHI) reimbursements, co-payments, and all governmental subsidies for certain subpopulation. The BNHI reimbursements for AGE hospitalization typically include hospital room charge and nursing fee (40.7%), pharmacy and treatment-related charges (29.3%), laboratory services (14.6%), and physician fee (15.4%). The medical costs estimate for rotavirus infection took into account all these items. Please also see our reply to Dr. Nelson above (point #3).

2. (a). Because very few rotavirus AGE were coded in the BNHI database, the uncertainty of the precision of our estimates is inevitable. However, we have tried to get at a more precise estimate using ranges rather than single percentage by incorporating data from our three hospitals and data published by Chen et al (for inpatients) and Glass et al (for outpatients) (please see Major Revision above for details). We believe that our estimates based on the three hospitals we studied and the BNHI database provides a good estimate of rotavirus disease burden in Taiwan. The inpatient and outpatient data we obtained from the three hospitals are also comparable to previous studies done in Taiwan and other countries. (b) We used the BNHI data of medical cost estimations. This is very reliable because BNHI is the single payer of the healthcare system in Taiwan and medical costs are almost fully reimbursed by BNHI. The co-payments and subsidies from the government were all included in the BNHI database. Detailed information is provided on pages 5, 6, and 8. Also, by using a range rather than single percentage, we feel that we have obtained a reasonable estimate for medical costs.

3. The limitation of the study is discussed in more detail in the revised manuscript with emphasis on: (1) the difficulties in determining the proportion of all AGE attributable to rotavirus infections. (2) The rationale of using the ranges for estimations. (3) The limitation of estimating the total medical costs by extrapolating from data obtained in three different hospitals has been added in the Discussions.

4. The BNHI database is very comprehensive. This is because that since the implementation of a single-payer, publicly administered universal national health insurance program in 1995, expenses of medical care are reimbursed by the Bureau of National Health Insurance (BNHI) in Taiwan, and by December 2000, over 96% of Taiwan’s 22.3 million (22,276,672) population was covered. Thus the database contained health care related information, including registration files, original claim data (diagnosis, treatments, etc.) and reimbursement data (medical costs) on over 96% of Taiwan’s population.

5. The sampling database is a systematic sampling of every 20 inpatient records and every 500 outpatient records from the BHNI all-patients database at the National Health Research Institutes based on statistical advice of a team managing the database. The team has previously determined that statistically this sampling strategy would provide comparable representative data to all-patients database. The sampling database was done and made available to researchers in Taiwan for research purposes because the database of all-patient
records is tremendously large that even the highly advanced personal computers do not have the capacity to handle such large database and queries. In the 2001 sampling database, there were over 620,000 outpatient and 120,000 inpatient records, which we feel provide adequate sample size for our analysis.

6. We recognized that by including TCH, the hospital in the east, we might be underestimating the national rotavirus disease burden. Therefore we have amended this by using ranges to estimate the rotavirus disease burden as explained in details in Major Revisions above.

7. There was no mortality documented resulting from rotavirus infections in Taiwan. This is probably due to easy accessibility to health care in Taiwan. The morbidity of rotavirus is reflected by the cases numbers seeking medical cares. The medical costs we estimated included all the medical expenditures in the BNHI database, which includes BNHI reimbursements, co-payments, and all governmental subsidies for certain subpopulation (please see reply to Dr. Nelson point 3 also).

We thank you both again for your valuable time and all the helpful constructive critiques. We look forward to hearing your comments and decision on our revised manuscript soon.

Sincerely,

Chun-Yi Lu and Tsai-Ling Lauderdale