Reviewer's report

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

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Reviewer: Edmund Nelson

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This article estimates disease and economic burden of rotavirus infection in Taiwan using data from two main sources:

1. Retrospective analysis of hospital data from 3 hospitals is used to estimate disease burden for rotavirus for BOTH inpatient and outpatient settings in all children less than 16 years.

2. National Health System data is used to provide estimates of total hospitalisations for diarrhoea and total outpatient attendance for diarrhoea in children less than 16 years. These data also provide an estimate for the cost of hospitalisation of a case of diarrhoea and the cost of an outpatient visit for a case of diarrhoea. These estimates are used to calculate the economic burden of rotavirus for the whole of Taiwan.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. A retrospective study of diarrhoea admissions to 3 hospitals. 30% had stool specimens were tested and 28.9% of these were rotavirus positive. This figure of 28.9% is then used to extrapolate disease burden estimates for the whole of Taiwan. These data included children under the age of 16 years. The authors reference but do not discuss in detail the paper by Chen et al published in JID (ref 7). This report used prospective surveillance at 4 sentinel hospitals (Apr 2001 to Mar 2003) 43% of 2600 enrolled children under the age of FIVE years were rotavirus positive. Rotavirus is a disease of YOUNG children. Therefore including data of children from 6 - 16 years is probably not desirable as the proportion of rotavirus positive cases in the older children is anticipated to be very much less. Thus it is not clear why the disease burden estimate from Chen et al is not used to make disease burden estimates for the whole of Taiwan for Hospitalised children. The authors note that 100/193 (51.8%) of diarrhoea admission at TCH were due to shigella. How many of these children with Shigella and rotavirus were under 5 years? This finding in this more rural population raises the the point that Chen et al's estimate of 43% may overestimate rotavirus disease burden in rural settings - what proportion of Taiwan would be considered "rural"?

I am also slightly confused because both Chen et al's report and the present paper utilised data from the National Taiwan University Hospital - was this a collaboration or was data collected and analysed separately?

The second very important error in the extrapolation of the retrospective disease burden estimate of 28.9%, is that it is also used for the estimates of OUTPATIENT disease burden. It is well established that rotavirus disease is more severe and more likely to result in dehydration and hospitalisation than other common causes of childhood diarrhoea. Thus the proportion of hospitalised diarrhoea cases due to rotavirus will be much higher than the proportion of diarrhoea cases seen in outpatient settings. A number of studies indicate that in outpatient settings only about 10-15% of diarrhoea cases are due to rotavirus (in children less than 5 years).

Thus I would suggest that the retrospective data for the hospitalised patients be reanalysed for those children under the age of 5 years. It is still likely to give a figure less than Chen et al's 43% but this range could be examined in the economic burden analysis. Secondly the figure for the % of hospitalised diarrhoea due to rotavirus should NOT be used to extrapolate outpatient disease burden. For outpatient estimates references could be taken from the literature (most recent reference being Glass et al. Lancet 2006;368:323-332).

2. National Health System data. The majority (97.6%) of 989,780 paediatric visits were OUTPATIENT. The authors analysed ICD9-CM codes of 001-009 with no exclusion.

When undertaking a similar analysis in Hong Kong (Nelson EAS eta al. Surveillance of childhood diarrhoeal
disease in Hong Kong, using standardized hospital discharge data. Epidemiol & Infect 2004;132:619-626), we used the following ICD9-CM codes to define diarrhoea hospitalisations: 001-005, excluding 003.2, and 008.0-008.5 (bacterial diarrhoeas); 006-007, excluding 006.2-006.6 (parasitic diarrhoeas); 008.61 (rotavirus diarrhoea); 008.6-008.8 (other viral diarrhoeas); 009.0-009.3 (diarrhoea of undetermined aetiology, including that presumed to be infectious); and 558.9 and 787.91 (other non-infectious diarrhoeas). Although children with gastroenteritis who have no pathogen isolated should be correctly coded as ICD 009.0-009.3, it was apparent that ICD codes 558.9 and 787.91 are often being used instead.

Thus by not excluding some ICD codes as indicated above, and not including other non-specific codes (558.9 and 787.91) estimates of national disease burden may be affected. As indicated in Table 3, the majority of inpatient diarrhoea (0-5yrs) is classified under 003 (salmonella), 008 (viral/rotavirus), 009 (not specified). Outpatient diarrhoea (0-5yrs) is mainly 009 (not specified). However as indicated above a much smaller percentage of these outpatient diarrhoeas are anticipated to be due to rotavirus.

Why was every 500th (outpatient) and every 20th (inpatient) visit analysed. Was this based on statistical advice or were these arbitrary figures? Was it necessary to sample or could the whole of the database have been as easily analysed?

The cost of an outpatient visit (0-5yrs) is US$ 10.5 and inpatient admission (0-5yrs) is US$ 312.6. It would be helpful for the reader to better understand in more detail how the National Health System derives these costs. It is noted that 40.6% is room charge, 18.6% pharmacy, 18.6% lab and 15.6% physician fee. Does this include nursing costs? There is mention of a co-pay system as well. Are costs derived from the National Health System full costs, or partly subsidised by government. The figure of US$ 312.6 seems somewhat less than Hong Kong (US$ 1868, ref Nelson et al JID 2005;192(suppl 1):S64-S70) and Japan (US$ 1236, ref Nakagomi T et al JID;192(suppl 1):S106-S110). This may reflect the relatively lower GNI per capital of Taiwan as suggested by the authors but also raises the possibility that the cost may not reflect the full costs to the government.

The authors make some comparisons with Hong Kong and US. In terms of the hong Kong comparision it should be noted that the economic burden estimate only referred to hospitalised cases. It should be clearly specified whether the direct medical costs refers to both inpatient or outpatient care.

In summary the National Health System data is obviously a very useful source of data from which extrapolations about national disease burden and economic burden can be made. However I think the analysis should focus only on the 0-5 year age group. For inpatient disease burden and economic burden, Chen et al's 43% estimate should also be included as an upper range in the analysis, with a lower range being obtained from a reanalysis of the retrospective data presented by the authors (restricted to 0-5yrs). More detailed explanation of exactly how the costs are derived by the National Health System will also be important.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Figure 1 could be omitted but if not it should present the data by month rather than by season.

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I have received funding and support from Merck for rotavirus surveillance studies, and I am currently principal investigator of a phase 3 rotavirus vaccine study funded by GlaxoSmithKline. I have received lecture fees and travel support from Glaxo-SmithKline. Both these companies now have licensed rotavirus
vaccines.