The Hidden Health and Economic Burden of Rotavirus Gastroenteritis in Malaysia

An Estimation Using Multiple Data Sources

Tharani Loganathan, MD, MPH,* Chiu-Wan Ng, MBBS, MPH, PhD,* Way-Seah Lee, MBBS, FRCPCH, MD,†‡ and Mark Jit, BSc, PhD, MPH§¶

Background: Rotavirus gastroenteritis (RVGE) results in substantial mortality and morbidity worldwide. However, an accurate estimation of the health and economic burden of RVGE in Malaysia covering private, public and home treatment is lacking.

Methods: Data from multiple sources were used to estimate diarrheal mortality and morbidity according to health service utilization. The proportion of this burden attributable to rotavirus was estimated from a community-based study and a meta-analysis we conducted of primary hospital-based studies. Rotavirus incidence was determined by multiplying acute gastroenteritis incidence with estimates of the proportion of gastroenteritis attributable to rotavirus. The economic burden of rotavirus disease was estimated from the health systems and societal perspective.

Results: Annually, rotavirus results in 27 deaths, 31,000 hospitalizations, 41,000 outpatient visits and 145,000 episodes of home-treated gastroenteritis in Malaysia. We estimate an annual rotavirus incidence of 1 death per 100,000 children and 12 hospitalizations, 16 outpatient clinic visits and 57 home-treated episodes per 1000 children under-5 years. Annually, RVGE is estimated to cost US$ 34 million to the healthcare provider and US$ 50 million to society. Productivity loss contributes almost a third of costs to society. Publicly, privately and home-treated episodes consist of 52%, 27% and 21%, respectively, of the total societal costs.

Conclusions: RVGE represents a considerable health and economic burden in Malaysia. Much of the burden lies in privately or home-treated episodes and is poorly captured in previous studies. This study provides vital information for future evaluation of cost–effectiveness, which are necessary for policy-making regarding universal vaccination.

Key Words: rotavirus, gastroenteritis, burden, morbidity, mortality, cost, vaccine

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From the *Department of Social and Preventive Medicine, Julius Centre University of Malaya, and †Department of Paediatrics, Faculty of Medicine, and the ‡University Malaya Paediatrics and Child Health Research Group, University of Malaya, Kuala Lumpur, Malaysia; †Modeling and Economics Unit, Public Health England; and §Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom.

This economic evaluation is part of the SteMM Programme supported by the World Health Organization (WHO) estimated that in 2008, rotavirus resulted in 453,000 deaths in children under age 5 years worldwide and 15 deaths in Malaysia.1 In 2005, it was estimated that by the age of 5 years, 1 in 61 children will be hospitalized and 1 in 37 children will seek outpatient treatment for RVGE in Malaysia.2 The annual costs of providing inpatient care for RVGE was estimated at US$ 1.8 million in 2002.3

The WHO recommends 2 rotavirus vaccines for universal vaccination in all countries.4 However, rotavirus vaccines are expensive, particularly for middle-income countries such as Malaysia that are not eligible for multinational pooled purchasing schemes such as those initiated by Gavi, the Vaccine Alliance.5 Consequently, rotavirus vaccine introductions in middle-income countries have lagged behind those of high- and low-income countries.6,7

The problem is exacerbated by poor understanding of the true burden of RVGE in middle-income countries. In these settings, diarrheal mortality is low but the burden of cases presenting to health care is potentially high. However, the healthcare burden is difficult to estimate in countries such as Malaysia as much of healthcare provision is supplied by the private sector.8 Previous estimations of rotavirus burden in Malaysia have focused on diarrhea treated at public facilities,2,3,9 which substantially underestimate the overall burden. Hence, a comprehensive estimate of disease burden is essential for decision making around the introduction of a new vaccine, both nationally and in other similar countries.

The objective of this study is to estimate the burden of RVGE in Malaysia; which includes deaths, hospitalizations and outpatient visits to public and private facilities, home-treated episodes and the economic burden of these events to the healthcare provider and society.

Materials and Methods

Overview

Multiple data sources were used to estimate the incidence of acute gastroenteritis (AG) by health service utilization in Malaysia. The incidence of RVGE in children under-5 years was determined by multiplying the incidence of AG with estimates of the proportion of AG episodes attributable to rotavirus. The economic burden of RVGE was estimated from the healthcare provider and societal perspective (Fig. 1).

Costs were inflated to 2013 Ringgit Malaysia10 then converted to 2013 US$ using the World Bank exchange rate for 2013 of Ringgit Malaysia 3.15 to US$ 1. Analysis was conducted using Microsoft Excel Professional Plus 2013.

This study was approved by the Medical Ethics Committee, University Malaya Medical Center and the Medical Research and Ethics Committee, Ministry of Health (MOH), Malaysia (Approval numbers: 2014010690 and NMRR-14-192-19192).

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Outpatient visits for AG were classified by the facility and then reported in an aggregated form to health departments. Information on outpatient visits are routinely collected at each facility, and more recently from private hospitals, are captured in a national database by the MOH. We extracted data on children under-5 years in 2013, a Runs test was used to test for randomness of the annual under-5 years AG mortality rate from 2000 to 2008. The null hypothesis of the Run’s test is that the data sequence is produced in a random manner. As the resulting test statistic of -1.04 was less than the critical value of 1.96 (P = 0.15), we were unable to reject the null hypothesis. The mortality data vary at random around a constant mean, at the 0.05 significance level, and there is no trend component. Hence, the mean AG mortality rate for children under-5 years from 2000 to 2008 was used to estimate the diarrheal deaths in children under-5 years for 2013.

Rotavirus Detection Proportions

We conducted a systematic search to select studies conducted in Malaysia that comply with WHO recommendations for hospital-based rotavirus surveillance. A meta-analysis was conducted to obtain pooled rotavirus-detection proportions for AG hospitalizations. Detailed methods are included in Supplementary Text, Supplemental Digital Content 3, http://links.lww.com/INF/C428 and Table, Supplemental Digital Content 4, http://links.lww.com/INF/C429 for detailed comparison of our estimates with that of the 2005 rotavirus burden study. We conducted a systematic search to select studies conducted in Malaysia that comply with WHO recommendations for hospital-based rotavirus surveillance. A meta-analysis was conducted to obtain pooled rotavirus-detection proportions for AG hospitalizations. Detailed methods are included in Supplementary Text, Supplemental Digital Content 3, http://links.lww.com/INF/C428 and Table, Supplemental Digital Content 4, http://links.lww.com/INF/C429 for detailed comparison of our estimates with that of the 2005 rotavirus burden study.2

Deaths

Diarrhea-specific mortality for children under-5 years was acquired from the Department of Statistics, Malaysia, for the years 2000 to 2008. We defined diarrheal deaths as deaths that were certified by medical personnel with ICD-10 etiologic codes for diarrhea and those that were certified by lay personnel as having died of diarrhea.

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(WHO-CHOICE) and distribution of healthcare facilities were applied to local cost estimates to obtain average costs.


Direct Nonmedical Costs

The NHMS 2011 recorded healthcare consumption costs in Malaysia. Costs for 1-way travel to health facilities were provided by this survey.19 We assumed travel costs were doubled for an outpatient visit and quadrupled for a hospital admission.

Costs for extra diapers and food were obtained from the 2010 hospital-based study. An average cost of US$ 3 for extra diapers was used for all RVGE episodes regardless of severity. The cost of extra food was only applied for inpatient episodes.20

Indirect Costs

Indirect costs is defined here as productivity loss for 1 caregiver for the duration of diarrheal illness. Productivity loss was calculated by multiplying average daily wage with work-days missed. As wage-earners were assumed to work a 6-day a week, daily wage was calculated by dividing the average monthly wage in Malaysia of US$ 651 by 26.21 Average duration of diarrheal illness in children under-5 years of 2.7 days from NHMS 2006 was used to represent work-days missed for rotavirus episodes of any severity.12

RESULTS

Health Burden

In children under-5 years, 23,450 public hospital discharges in 2011 and 15,886 private hospital discharges in 2013 had ICD-10 codes for AG (see Table, Supplemental Digital Content 2, http://links.lww.com/INF/C427). We estimate 70,000 AG-related hospitalizations in children under-5 years annually. In 2012, there were 129,424 AG-related outpatient visits to MOH facilities among children younger than 10 years. We estimate 40,000 AG-related outpatient visits to public hospitals, 42,000 visits to public clinics and 151,000 visits to private clinics among children under-5 years annually. Annually, we estimate 1.2 million AG episodes in children under-5 years are home-treated. In 2008, a total of 60 (1.5%) of the 3887 deaths in children under-5 years were AG related. We estimate 61 AG-related deaths (95% CI, 47–75) among children under-5 years in 2013 (Table 1). We detail the systematic review of prospective hospital-based rotavirus surveillance studies in Malaysia in a PRISMA flow diagram (Fig. 2). Three studies fulfilled the eligibility criteria and were

<table>
<thead>
<tr>
<th>TABLE 1.</th>
<th>Burden of Rotavirus Gastroenteritis in Malaysia, 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Annual No. of Cases of Diarrhea</td>
</tr>
<tr>
<td></td>
<td>AG Related</td>
</tr>
<tr>
<td>Deaths</td>
<td>61</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>70,000</td>
</tr>
<tr>
<td>Outpatient visits</td>
<td>234,000</td>
</tr>
<tr>
<td>Home treated episodes</td>
<td>1,209,000</td>
</tr>
<tr>
<td>Total</td>
<td>1,515,000</td>
</tr>
</tbody>
</table>

Total population 0-4 years (both sexes combined) in 2012, is 2,550,000; Source: Department of Statistics, Malaysia.

FIGURE 2. PRISMA flow diagram on the systematic review process. Systematic review of prospective hospital-based rotavirus surveillance studies in Malaysia. EIA indicates enzyme immunoassay test.
TABLE 2. Meta-analysis of Prospective Studies to Obtain the Proportion Attributable to Rotavirus in Children Hospitalized for Acute Gastroenteritis

<table>
<thead>
<tr>
<th>Study Location</th>
<th>No. of Rotavirus Positive</th>
<th>No. of Rotavirus Detection Proportion</th>
<th>SE 95% Confidence Interval</th>
<th>SE 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsu et al21</td>
<td>Kuala Lumpur and Kuching</td>
<td>1130 2260 50.00 0.01 (47.08–2.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hung et al22</td>
<td>Kuala Lumpur</td>
<td>820 1756 46.70 0.02 (43.5–49.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hung et al23</td>
<td>Kuching</td>
<td>445 912 48.79 0.02 (44.26–53.33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al24</td>
<td>Kuala Lumpur</td>
<td>161 385 41.82 0.03 (35.36–48.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al25</td>
<td>Kuala Terengganu</td>
<td>87 273 31.87 0.03 (25.17–38.56)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results from 5 individual study sites from the 3 selected studies were pooled in the meta-analysis. Random effects model used for the pooled outcome estimate. I² statistic describes the percentage of total variation across studies because of heterogeneity; meta-analysis performed using methods described by Neyeloff et al.26

Economic Burden

Annually, RVGE is estimated to cost US$ 34 million to the healthcare provider and US$ 50 million to society, of which a third is contributed by indirect costs. Publicly, privately and home-treated episodes consist of 52%, 27% and 21%, respectively, of total societal costs. Total societal costs of rotavirus diarrhea (US$ 50 million) were divided by the population of children under-5 years (2.6 million) in Malaysia, to obtain annual societal costs of US$ 19 per-child under-5 years in Malaysia (Table 3 and Table Supplemental Digital Content 10–12, http://links.lww.com/INF/C435, http://links.lww.com/INF/C436 and http://links.lww.com/INF/C437).

DISCUSSION

This work is the most recent and complete estimation of national burden, and the only one to include data on annual discharges and outpatient visits from both public and private facilities. Only one previous estimate of rotavirus burden in Malaysia has been published, and this inadequately considered privately treated episodes.2 Detailed comparison of the current incidence estimates with the previous rotavirus burden study is in Supplementary Text, Supplemental Digital Content 3, http://links.lww.com/INF/C428.

The previous findings of 3.3 rotavirus-related hospitalizations per 1000 children may have been an underestimation. Discharge data from the newly established national database did not include private and non-MOH public hospitals. In this study, we extrapolated to account for all diarrheal discharges in Malaysia, including those not reported, by using weights of total hospital beds in the country. In addition, the ICD-10 coding of discharges at public hospital has improved, leading to more accurate data on diarrheal discharges.

The previous findings of 5.5 rotavirus-related outpatient visits per 1000 children under-5 years did not include private facilities. An accurate estimation of privately treated rotavirus is important in Malaysia because a substantial portion of the population utilize private healthcare. The NHMS 2006 found that among children under-5 years with a recent illness, 64% of those seeking outpatient treatment and 15% of those hospitalized were treated privately.12 Our findings of 12.2 rotavirus-related hospitalizations per 1000 children per-year in Malaysia is within the range of results of a 2012 systematic review estimating 2.1 to 20.0 episodes per 1000 children per-year in Asia.25 Our estimates of 16.2 rotavirus-related outpatient visits per 1000 children under-5 years in Malaysia annually, are similar to findings for Asia (5.6 to 45.3 per 1000 children),25 India (15.0 per 1000 children), Philippines (12.1 per 1000 children) and China (20.1 per 1000 children).25 Likewise, our estimate of 27 rotavirus-related deaths in children under-5 years in 2012 are consistent with those estimated for Malaysia by the Child Health Epidemiology Reference Group for WHO and United Nations Children's Emergency Fund of 55 diarrheal deaths included in the meta-analysis.2,22,23 A total of 5586 stool samples were tested, with rotavirus-detection proportions ranging from 32% to 50% at each individual study sites (see Table, Supplemental Digital Content 9, http://links.lww.com/INF/C434). A random effects model was applied to account for heterogeneity (I² = 81%). The pooled estimate of the rotavirus-detection proportion in children under-5 years hospitalized for AG was 44.5% (95% CI, 39.6–49.4; Table 2). Please refer to Supplementary Text, Supplemental Digital Content 5, http://links.lww.com/INF/C430, for detailed results. In Malaysia, we estimate that 27 rotavirus-related deaths occur annually. RVGE is estimated to result in 31,000 hospitalizations, 41,000 outpatient visits and 145,000 home-treated episodes, annually. The annual incidence of rotavirus among children under-5 years was estimated at 1 death per 100,000 children, 12 hospitalizations per 1000 children, 16 outpatient clinic visits per 1000 children and 57 home-treated cases per 1000 children (Table 1). This means that by the age of 5 years, 1 in 19,000 children will die, 1 in 16 will be hospitalized, 1 in 12 will have an outpatient visit and 1 in 4 will be treated at home for RVGE.

TABLE 3. Economic Burden of Rotavirus Gastroenteritis in Malaysia, 2013

<table>
<thead>
<tr>
<th>Rotavirus episodes (’000)</th>
<th>Direct Medical Costs (US$ ’000)</th>
<th>Direct Nonmedical Costs (US$ ’000)</th>
<th>Indirect Costs (US$ ’000)</th>
<th>Total Costs (US$ ’000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public hospital inpatients</td>
<td>23</td>
<td>22,350</td>
<td>450</td>
<td>1570</td>
</tr>
<tr>
<td>Public hospital outpatients</td>
<td>7</td>
<td>430</td>
<td>80</td>
<td>480</td>
</tr>
<tr>
<td>Public clinic inpatients</td>
<td>7</td>
<td>30</td>
<td>40</td>
<td>500</td>
</tr>
<tr>
<td>Private hospital inpatients</td>
<td>8</td>
<td>8890</td>
<td>160</td>
<td>530</td>
</tr>
<tr>
<td>Private clinic outpatients</td>
<td>27</td>
<td>1820</td>
<td>180</td>
<td>1800</td>
</tr>
<tr>
<td>Home treated</td>
<td>145</td>
<td>—</td>
<td>470</td>
<td>9820</td>
</tr>
<tr>
<td>Total</td>
<td>217</td>
<td>33,520</td>
<td>1380</td>
<td>14,700</td>
</tr>
</tbody>
</table>

All costs are in 2013 US$.
In 2010\textsuperscript{49} and slightly higher than the WHO estimate of 15 rotavirus deaths in 2008.\textsuperscript{3}
We estimated 145,000 home-treated episodes of RVGE annually, resulting in US$ 10 million in indirect and direct non-medical costs, or 21% of the societal burden. This considerable hidden burden has not previously been explored in Malaysia.

Estimation of home treatment is inherently uncertain because these episodes are not captured by health records and can only be derived by examining healthcare utilization patterns. Incidence of home-treated episodes was estimated based on health utilization patterns from the one community-based study in Malaysia.\textsuperscript{13} Parashar et al\textsuperscript{48} estimated that for every child requiring medical attention for RVGE, an additional 3 to 5 children develop illness that requires only home treatment. Our findings of 141,000 home-treated episodes are within this range of estimates (124,000–206,000). Also, Bilcke et al\textsuperscript{40} estimated the global incidence of symptomatic rotavirus infections at 0.31 (0.19–0.50) per-person per-year in children under-2 years. Our estimate of 217,000 symptomatic rotavirus episodes annually in children under-5 years in Malaysia, is well below the Bilcke et al\textsuperscript{40} estimate of 315,000 (193,000–509,000) symptomatic rotavirus episodes in children under-2 years annually in Malaysia.

Our estimation of the economic burden of RVGE on the health system in Malaysia is higher than the 2002 estimation of US$ 1.8 million.\textsuperscript{3} This was based on average direct medical costs per-episode of rotavirus hospitalization, obtained from 1 university hospital. Our current estimation is more robust and accounts for direct medical costs for inpatient and outpatient care, at public and private facilities in Malaysia.

Annual societal costs of US$19 per-child under-5 years in Malaysia are similar to estimates for upper-middle income countries of US$ 15 per-child in 2013 US$.\textsuperscript{36} Our estimation of direct medical costs per hospitalized rotavirus episode of US$ 1000 are comparable with costs in high-income Asian countries, such as Japan (US$ 1500–2000),\textsuperscript{31–33} Taiwan (US$ 330–760)\textsuperscript{34–36} and Hong Kong (US$ 2500).\textsuperscript{37}

This study has several limitations. First, as there are no official unit costs for healthcare facilities in Malaysia, we estimated costs based on top-down costing methods.\textsuperscript{17,18,36} Our estimation is robust as it uses local data from annual reports of 5 tertiary-level hospitals, costing studies of 6 primary-level hospitals and 11 health clinics.

Second, our estimation of outpatient attendances to public health facilities is conservative. Data from MOH captures outpatient attendances to MOH hospitals and primary healthcare clinics, but does not capture treatment for childhood diarrhea given by nurses or midwives at maternal and child health clinics. We assume that these children have mild illness; therefore, do not seek medical attention from a medical officer.

Since all except 1 rotavirus study in Malaysia were hospital based, the rotavirus-detection proportion at outpatient clinics and for home-treated episodes were obtained from the only community-based rotavirus study.\textsuperscript{13} The rotavirus-detection proportion at outpatient clinics in Malaysia of 18% is comparable with a 2012 pooled estimate of outpatient-based rotavirus studies in Asia of 23%.\textsuperscript{24} In addition, the rotavirus-detection proportion for home-treated episodes in Malaysia (12%) is similar to the results of a community-based study conducted in Thailand (12.2%).\textsuperscript{89}

Our estimation of societal costs are conservative as workdays missed were assumed to be equal for all diarrheal episodes, regardless of severity. In addition, the emotional impact of caring for a child with diarrhea is not captured here. The stress and anxiety of caring for an ill child could translate to higher economic costs beyond the loss of income and is an avenue for future research.

In line with the 4th Millennium Development Goal, there have been sustained international efforts to reduce diarrheal deaths, including the development of the rotavirus vaccines. Remarkably, as of July 1, 2015, only 77 countries including 24 from non-Gavi eligible, middle-income countries, have introduced rotavirus vaccines universally. Among Asian countries, only the Philippines and recently Thailand have introduced the vaccines on a limited basis.\textsuperscript{8}

With the anticipated availability of more affordable rotavirus vaccines,\textsuperscript{40} an accurate estimation of disease burden is necessary when considering the benefits of preventing illness. Our study demonstrates the considerable burden of rotavirus episodes treated privately and at home, which has not been well captured in previous studies. This provides vital information for future evaluation of cost-effectiveness and the broader economic impacts of vaccination, which are necessary for policy-making regarding universal vaccination.

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