

Economic burden of cholera in Asia

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ABSTRACT

Background: The economic burden data can provide a basis to inform investments in cholera control and prevention activities. However, treatment costs and productivity loss due to cholera are not well studied. **Methods:** We included Asian countries that either reported cholera cases to the World Health Organization (WHO) in 2015 or were considered cholera endemic in 2015 global burden of disease study. Public health service delivery costs for hospitalization and outpatient costs, out-of-pocket costs to patients and households, and lost productivity were extracted from literature. A probabilistic multivariate sensitivity analysis was conducted for key outputs using Monte Carlo simulation. Scenario analyses were conducted using data from the WHO cholera reports and conservative and liberal disease burden estimates.

Results: Our analysis included 14 Asian countries that were estimated to have a total of 850,000 cholera cases and 25,500 deaths in 2015. While, the WHO cholera report documented around 60,000 cholera cases and 28 deaths. We estimated around \$20.2 million (\$74.4 million) in out-of-pocket expenditures, \$8.5 million (\$30.1 million) in public sector costs, and \$12.1 million (\$43.7 million) in lost productivity in 2015. Lost productivity due to premature deaths was estimated to be \$985.7 million (\$3,638.6 million). Our scenario analyses excluding mortality costs showed that the economic burden ranged from 20.3% (\$8.3 million) to 139.3% (\$57.1 million) in high and low scenarios when compared to the base case scenario (\$41 million) and was least at 10.1% (\$4.1 million) when estimated based on cholera cases reported to WHO.

Conclusion: The economic burden of cholera in Asia provides a better understanding of financial offsets that can be achieved, and the value of investments on cholera control measures. With a clear understanding of the limitations of the underlying assumptions, the information may be used in economic evaluations and policy decisions.

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1. Introduction

Cholera continues to be a challenge to global health. In 2015 alone, 42 countries reported more than 172,000 cases and 1300 deaths due to cholera [1]. Many countries are known to under report cholera cases to the World Health Organization (WHO) due to limitations in their surveillance systems and diagnostic capabilities, and fear of negative economic impact [1]. Considering the insufficient number of surveillance studies, efforts have been made to estimate the cholera disease burden by using modeling approaches. For example, one recent cholera global burden study

estimated that there are 2.9 million (uncertainty range: 1.3–4.0 m) cholera cases and 95,000 deaths (uncertainty range: 21,000–143,000) annually in cholera-endemic countries [2]. About 37% of all the WHO-reported cholera cases and 39.0% of estimated global cholera cases are reported from Asia. Cholera, that is known to have originated in and is endemic to Asia [3], continues to trouble the region.

Despite the known occurrence of cholera in Asia, the cost of cholera treatment to the health facilities and individual families, and the lost income resulting from the inability to work among patients and caregivers (collectively referred to as cost of illness and loss of productivity), are not well understood. Only two previous studies have measured the cost of illness by capturing expenditures borne by the government and the individual/family [4–5]. These publications represented study sites in three countries: Bangladesh, India, and Indonesia. To understand the broader and

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macro-economic impacts of cholera, several costs that account for every cholera case at the country or regional level should be aggregated: treatment cost borne by all health facilities, and out-of-pocket expenses and productivity losses borne by individual families. Such cumulative disease-related costs and loss of productivity is often referred to as economic burden. Having information on the economic burden of cholera is essential in conducting economic evaluations of the value of investments on cholera control and elimination. This multi-sectoral approach includes early detection and management of cholera cases, improving water, sanitation and hygiene (WaSH), and vaccination [6]. For example, the costs incurred through cholera illness can be offset by the cost savings generated by implementing prevention interventions. Furthermore, data on the economic burden can also serve as an advocacy tool that can help in demonstrating the need for cholera-control interventions.

Below we present data on the economic burden of cholera in Asia (as defined by the United Nations) [7], in countries where cholera has been reported in 2015 [1] or countries identified as cholera endemic in the 2015 global disease burden estimates [2].

2. Methods

2.1. Country selection

We first listed the countries categorized as Asia by the United Nations [7]. Then, we analyzed the WHO cholera reports [1] for the countries that reported cholera cases in 2015 and referenced the updated global burden of cholera [2] to verify which of the countries in Asia are considered cholera endemic and have an estimated number of cholera cases. Any country in Asia that either; (1) reported cholera cases to the WHO in 2015, or (2) was defined as a cholera-endemic country in the global burden of disease study, and listed as Low and Middle Income Country (LMIC) by the World Bank [8], was included in the analysis. The global burden of disease study defines cholera endemicity based on a spatial regression that predicts the occurrence of cholera in three of previous five years. For all included countries, we extracted the number of cases reported or estimated for 2015 from the respective reports (Fig. 1).

2.2. Identification of economic costs

To derive unit costs for this study, we looked at the data on cost of illness studies conducted in Asian countries in the past 15 years (since 2000). There were only two studies published from Asia, which were identified through a recent systematic literature review on the costs of the illness of cholera [9]. One study was from Mirpur, Bangladesh, which estimated the cost of illness in 394 hospitalized cases at the Dhaka hospital of the International Center for Diarrheal Research, Bangladesh (icddr,b) in 2011 [5]. Households of discharged cholera cases were interviewed to collect direct medical costs, direct non-medical costs, and indirect costs to patients and caregivers. The study did not include the outpatient setting nor the costs to the health facility. The other was a multi-country study that included sites in India, Bangladesh, and Indonesia and reported costs in US\$2005 [4]. This study included 277 hospitalized cases from Matlab, Bangladesh; 176 hospitalized and 140 outpatient cases from North Jakarta, Indonesia; and 66 hospitalized and 38 outpatients cases from Kolkata, India. We extracted three sets of data from the multi-country study; (1) number of workdays lost due to illness by patients, caregivers, and substitute laborers; (2) cost per case to the public health system for hospitalized cases; and (3) out-of-pocket costs to patients and households. Due to the limited availability of data, we modelled the cost data from these three countries to all Asian countries after accounting for gross domestic product per capita, and the data uncertainty represented by confidence intervals (CI).

2.3. Lost productivity due to illness

The lost productivity due to cholera cases was estimated based on the number of workdays lost by patients, caregivers, and substitute laborers. From the multi-country study [4], we were able to estimate the average number of workdays lost to patients and caregivers separately. The study from Bangladesh [5] did not present the number of workdays lost. The number of workdays lost was then multiplied by the gross domestic product (GDP) per capita per day for 2015 (annual GDP per capita/365, based on World Bank data [10] for each of the 14 countries, to estimate the lost

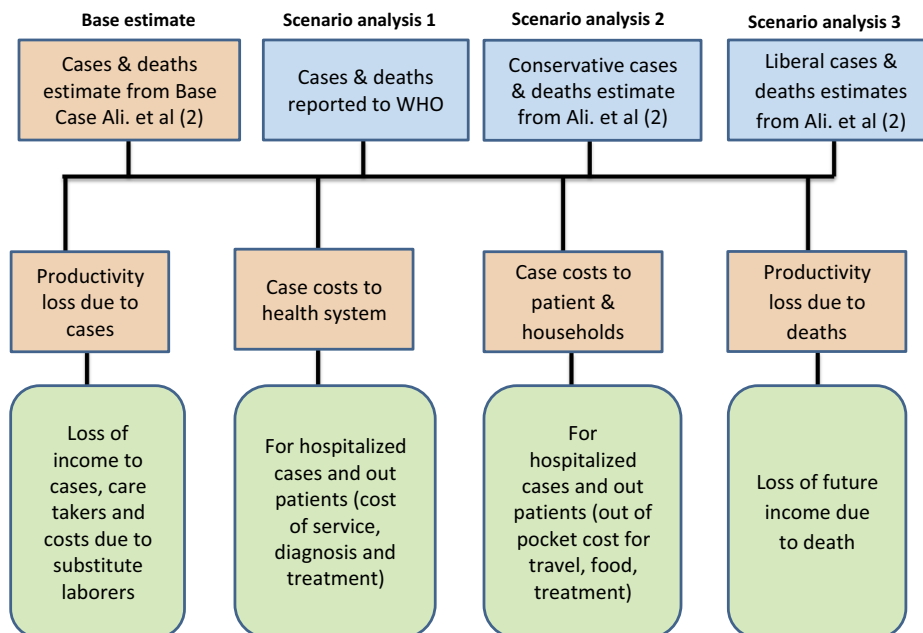


Fig. 1. Economic burden estimation method.

productivity per cholera case per country. Finally, we multiplied the number of cholera cases in each country to the average lost productivity per case (productivity losses to patients and caregivers) to estimate the lost productivity at the country level. As productivity loss is dependent upon the one's daily income, multiplying the number of productive days lost due to cholera by the average income per capita (represented by GDP per capita) is a reasonable method to estimate productivity loss at the population level without accounting for complex work classes and varying income levels.

2.4. Cost to health system

The public health system spends money on service delivery to provide treatment for cholera cases. The service delivery costs consist of expenses related to health manpower, medicines, diagnostics, and other goods, such as infrastructure, beds, equipment, and utilities for which patients do not pay out-of-pocket. If any of these expenditures are paid for by the patient or family, they are counted as out-of-pocket expenditures. The multi-country publication [4] provided public health system costs for hospitalized cases for three sites in three countries. We applied the average of the public health system costs per case from this study to the other Asian countries, where such costs were not available after accounting for data uncertainty represented by confidence intervals.

The same multi-country study also provided the proportion of cholera cases hospitalized [4]. To estimate the number of hospitalized cases in Asia, we applied the average rate of hospitalization from the study with three study sites that included both hospitalized and outpatient cases. As these publications did not estimate health system costs in the outpatient setting (except for Indonesia), we used the WHO estimate of service delivery costs at health centers from the WHO CHOICE database [11]. This is a conservative estimate because the service delivery costs do not include diagnostic costs and are estimated at the lowest service delivery point (Health Center). To estimate total service delivery costs, we multiplied the number of hospitalized and outpatient cholera cases by country to the respective service delivery costs in that same country.

2.5. Out-of-pocket costs

The out-of-pocket costs to patients and households were also derived from the two Asian studies [4–5]. These costs were collected by administering surveys to cholera-confirmed cases using standard micro-costing questionnaires. The out-of-pocket costs were available separately for hospitalized and outpatient cases, and included direct medical and non-medical costs. Direct medical costs are expenditures related to medicines, intravenous fluids, diagnostics, and any other costs directly related to treatment. Direct non-medical costs included costs related to travel, food, accompanying persons, and any other consequential non-medical costs. The average out-of-pocket expenditure for hospitalized and outpatient cases from these studies were directly applied to cholera cases in the other Asian countries after converting it to US \$2015 and accounting for data uncertainty represented by the CI, then multiplied by the respective number of cholera cases in each country to estimate total out-of-pocket expenditures.

2.6. Productivity loss due to premature deaths

The mean age of cholera incidence used in our models was based on estimates from a population-based study in Kolkata, India [12]. Based on this study, the reported mean age of cholera cases was assumed to be mean age of death with a specified uncertainty

range determined by age range of cases (Table 1). The number of years of lost productivity was estimated by subtracting the mean age of death from life expectancy at birth for each country. The World Bank data on life expectancy at birth for each country was used [13]. The GDP per capita per year was multiplied by the number of premature deaths and the number of productive years lost per death by country to obtain lost productivity due to premature deaths. Future costs were presented with (3%) and without (0%) discounting based on health economic principles.

2.7. Unit of costs

All costs were estimated in United States Dollars (US\$) 2015 and International Dollars (I\$) 2015 using World Bank data [10]. The I\$ is used for comparison between countries because it represents the local value of goods and services that can be purchased in the country by US\$1 in the United States. The costs reported in different financial years were converted to US\$ 2015 after adjusting for country specific inflation rates in local currency units and then converting to US\$ 2015 [14].

2.8. Uncertainty analysis

The input data on costs are uncertain and therefore vary by person, place, and other circumstances. Thus, it was important to specify a range of costs in our economic burden model. We used the beta-PERT distribution for cost inputs, which is a type of uniform distribution that uses a three-point estimation technique, consisting of the following values: the minimum, maximum, and mode (which indicates the peak of the distribution) [15]. The various cost parameter inputs used in the uncertainty analysis are presented in Table 1. We did a Monte Carlo simulation based on 5000 random draws from each of the cost input distributions to conduct probabilistic multivariate sensitivity analysis and to estimate 95% CI for key cost outputs using Ersatz (Version 1.31, Epi-gear International, Brisbane, Australia) [16].

2.9. Scenario analysis

Because the actual data on cholera disease burden is not known, the estimated number of cases varies widely based on the underlying assumptions (e.g., using the WHO-reported case numbers which are an underestimate). Considering these unknowns, in addition to a base case analysis, we analyzed three additional scenarios. In the base case analysis, we used the global burden of disease study from 2015 as the primary estimate of cases and deaths [2]. In this estimation, the annual number of cholera cases was estimated by multiplying the population at-risk with cholera incidence from population-based studies [12,17–18]. The population at-risk for cholera was determined using the percentage of the population without access to sanitation. In Scenario 1, we used the number of cases and deaths as reported to the WHO in 2015 [1]. Scenario 2 is similar to the base case, with the exception that the population at-risk was estimated using the fraction of the population without sustainable access to improved water [2], making it a more conservative estimate than the base case (low estimate). Scenario 3 is also similar to the base case, but the population at-risk was assumed to be the entire population of India and Indonesia [2], making it the most liberal estimate (high estimate).

As cholera disproportionately affects people with poor water and sanitation, and those individuals' incomes are likely lower than the average population, we considered alternate scenarios to account for possible variations in costs related to premature deaths. In addition to valuing 100% of GDP per capita per day for

Table 1
Input parameter assumptions used in uncertainty analysis.

Input parameter	Mean value	Minimum value	Maximum value	Source
Number of days with loss of income – cholera cases	1.63 days	0.10 days	4.70 days	[4]
Number of days with loss of income – caregivers	2.10 days	0.10 days	11.81 days	[4]
Proportion of cases hospitalized	0.53	0.22	0.99	[4]
Public health service delivery costs for hospitalized cases	26.70 US\$	8.79 US\$	47.14 US\$	[4]
Public health service delivery costs for outpatient cases	3.85 US\$	0.99 US\$	14.06 US\$	[10]
Out-of-pocket costs to patient and family for hospitalization	54.40 US\$	9.04 US\$	180.48 US\$	[4–5]
Out-of-pocket costs to patient and family for outpatient cases	15.80 US\$	3.17 US\$	26.99 US\$	[4]
Age of death due to cholera	16.93 years	1.00 year	75.00 years	[11]

productivity loss resulting from premature deaths, we also estimated productivity loss at 75%, 50%, and 25% of GDP per capita per day.

3. Results

Of the 35 LMIC Asian countries, only 14 countries were either reported cholera cases to the WHO in 2015, or were defined as cholera endemic countries in the global burden of disease study from 2015. These 14 countries were included in the analysis. The countries included were (as per United Nations definition of Asia) Afghanistan, Bangladesh, Bhutan, India, Iran, Nepal, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, and Timor-Leste. Out of these countries, four were not listed as cholera-endemic countries in the global burden of disease study from 2015 (Iran, Malaysia, Myanmar, and Thailand) and seven did not report any cases to the WHO in 2015 (Bangladesh, Bhutan, Cambodia, Indonesia, Laos, Philippines, and Timor-Leste). The total estimated number of cholera cases in these countries was 851,396 and the number of deaths was 25,482 (Annexe 1), while 59,591 cholera cases and 28 deaths were reported to the WHO at the same time (Annexe 2).

We estimated around \$20.2 million (\$74.4 million; 49%) in out-of-pocket expenditures, \$8.6 million (\$30.1 million; 21%) in public health costs, and \$12.2 million (\$43.7 million; 30%) in lost productivity in 2015. Lost productivity due to premature deaths was estimated to be \$946.0 million (\$3,491.3 million), (Table 2). About 96% of the overall economic burden was due to lost productivity as a result of premature death. The maximum economic burden was estimated in India, followed by Bangladesh, Nepal, and Afghanistan (Annexe 1). The cost of illness per case ranged from US\$41.4 in India to US\$122.2 in Indonesia with a mean value of US\$48.2 in Asia (Annexe 1).

3.1. Uncertainty analysis

The probabilistic multivariate sensitivity analysis is based on the Monte Carlo simulation using 5,000 random draws from each of the cost inputs provided 95% CIs for various economic burden parameters (Table 2). The Tornado plots in Fig. 2 show which input

parameters affect the economic burden estimates most and orders them based on Spearman's rank correlation coefficient. Hospitalization costs, the proportion of cases hospitalized, and lost productivity to patients were the most sensitive parameters that drove the economic burden due to illness. Because India had 79% of total cholera cases in Asia, these three parameters from India drove the costs for the whole region (Fig. 2). Lost productivity due to premature death was the predominant (96%) cost for the overall economic burden, driven by the mean age of death.

3.2. Scenario analysis

In the scenario analysis, the number of cholera cases ranged from 60,000 to 1.2 million in 2015, and deaths ranged from 28 to 36,000 (Annexe 2). Using the WHO-reported cholera cases, deaths, and economic burden resulted in the lowest cost estimate (Scenario 1). The economic burden, excluding lost productivity due to premature deaths, ranged from US\$4 million (\$13 million) to US\$57 million (\$210 million) (Fig. 3). When future costs of premature death are undiscounted, the total economic burden of cholera in the base case increased by 1.7 times (\$987 million vs. \$1,715 million).

When productivity loss due to premature mortality loss was accounted at 75%, 50%, and 25% of GDP per capita per day, the lowest economic burden was US\$278 million in the base case scenario and US\$5 million in the WHO report-based estimate (Annexe 3).

4. Discussion

We estimated the economic burden of cholera in endemic and cholera-reporting countries in Asia for 2015. Using assumptions derived from data available from peer-reviewed studies, our economic model finds that the estimated economic burden of cholera illness in Asia is \$41 million (95% CI: \$26.5 million to \$65.9 million). Of this \$41 million, about \$29 million is due to direct costs borne by the health system and individual family members. This translates to roughly \$0.01 per capita in expenditures in these 14 countries (with a population of 2.2 billion). When lost productivity due to premature deaths is accounted for, the \$41 million figure increases to \$987.1 million (95%CI: \$522.9 to \$1,142.4 million),

Table 2
Economic burden of cholera in Asian countries.

Economic burden	US\$ 2015 (in millions)			I\$ 2015 (in millions)		
	Mean	95%LCI	95%UCI	Mean	95%LCI	95%UCI
Lost productivity due to illness	\$12.2	\$6.5	\$18.5	\$43.7	\$22.6	\$67.1
Public health system costs	\$8.6	\$5.8	\$14.2	\$30.1	\$19.8	\$51.6
Out-of-pocket costs	\$20.2	\$8.8	\$43.2	\$74.4	\$31.2	\$162.7
Subtotal economic burden	\$41.0	\$26.5	\$65.9	\$148.2	\$93.1	\$243.9
Lost productivity due to premature deaths	\$946.0	\$478.4	\$1099.3	\$3491.3	\$1758.4	\$4059.2
Total economic burden	\$987.1	\$522.9	\$1142.4	\$3639.5	\$1919.9	\$4216.1

LCI = lower confidence interval; UCI = Upper confidence interval.

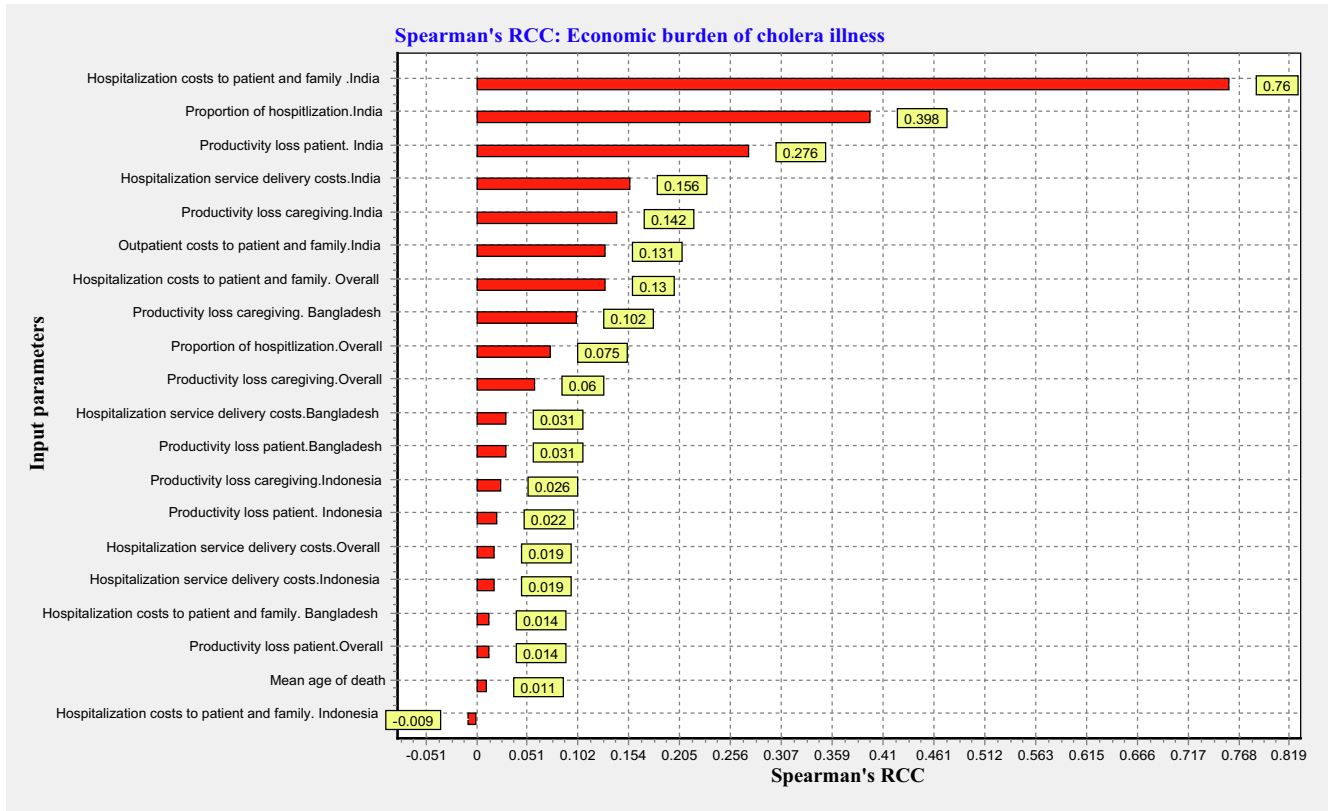


Fig. 2. Tornado plots showing Spearman's rank correlation coefficient between model input parameters and cholera economic burden in Asia (excluding productivity loss due to premature death).

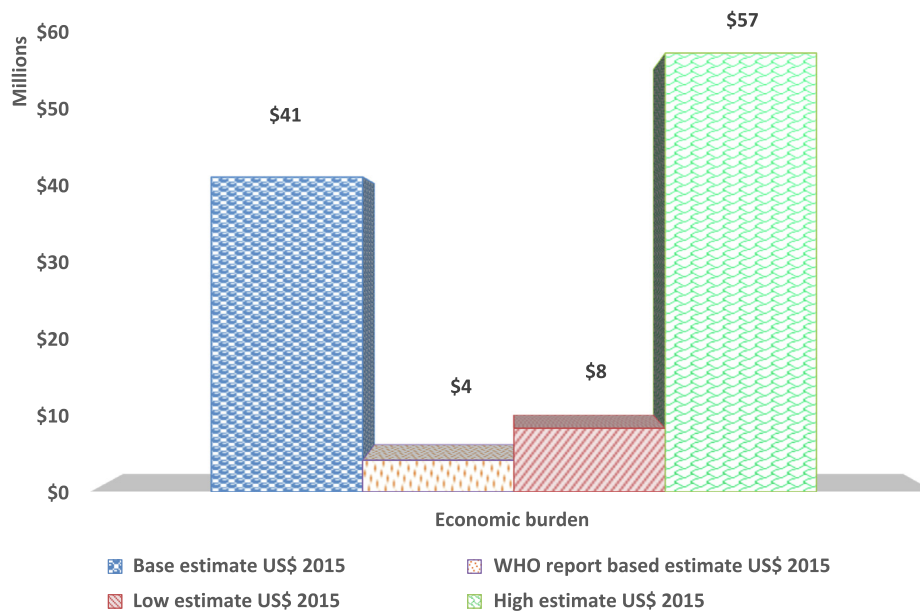


Fig. 3. Economic burden of cholera in Asia under various scenario analyses excluding productivity loss due to premature deaths.

which raises per capita expenditures/lost productivity to 46 cents. However, because the true burden of cholera may vary widely, our scenario analyses (low, high, and using the WHO-reported cases) finds that the economic burden (excluding mortality costs) may vary from US\$4 million to US\$57 million in 2015, depending on disease burden numbers. The countries that contribute the greatest to the cholera disease burden have the largest economic burden

(i.e., India and Bangladesh). The mean cost of illness that included lost productivity was US\$48.2 (95% CI: US\$41.4 to US\$122.2). To our knowledge, these estimates are the first available for Asia.

Recently, the Global Task Force on Cholera Control (GTFFC), a diverse partnership of 50 UN and international agencies, academic institutions, and non-governmental organizations, has proposed an ambitious strategy to reduce cholera by 90% by 2030 [19]. The

strategy highlights the need for an integrated approach with multi-sectoral partnerships and synchronization of efforts by all players to work on improving water, sanitation and hygiene services, cholera treatment and emergency management, and vaccination. As cholera is considered a disease that spreads in endemic hotspots where predictable outbreaks occur [19], interventions need to be targeted on the right spot and at the right time. To achieve this goal, a stronger understanding of the economic burden of cholera is critical for raising awareness and advocating for control interventions, such as vaccination and improvements in water and sanitation. Availability of data on the economic burden of cholera can give a better idea of the amount of health system resources that can be reallocated for other purposes, and can also provide an estimate of productivity losses averted by controlling or eliminating cholera. The validity of the economic burden results is dependent upon the accuracy of the underlying assumptions, uncertainties of parameters used, and study limitations described below. Considering these limitations, the results may be used in economic evaluations to understand the value and return on investment of cholera-control activities, and therefore for making policy decisions related to cholera control within the context of other diseases and priorities.

There are some studies that examined the economic burden of cholera at global or regional levels. Notably, Kirigia et al. has estimated the economic burden of cholera within the African WHO region from 2005 to 2007 [20]. Depending upon the life expectancy assumption used in their model, they estimated that economic losses due to cholera in 2006 ranged from \$92 million to \$156 million. Kirigia et al. modeled an estimated cost of illness using standard cost data inputs, while we use published field-based information and extrapolated it to other countries. Three other recent reviews have summarized health economic studies regarding cholera that includes cost of illness studies [9,21–22]. These studies identified only two field-based cost of illness studies in Asia, both of which we used in this analysis.

5. Limitations

In the current study, we estimated the economic burden of cholera in Asia using the latest information available for the region. However, we acknowledge that the assumptions, data used, and methodology have many limitations.

Modeling the economic burden of Asia is most limited by the dearth of disease burden data. Half of the 14 countries included in the analysis did not report any cases to the WHO in 2015 and 29% (4/14) of the countries were not considered cholera endemic by the global disease burden study. Thus, only three (21%) countries contributed to cholera cases in both scenario sources. 92% of cases in Asia were estimated to be occurring in India and Bangladesh based on the global disease burden study, while India reported only 1.5% of total WHO cases in 2015 and Bangladesh none. This unknown and uncertain cholera disease burden has the greatest impact on our economic burden estimates.

Second, our cost of illness data comes from three countries, whose estimates were modelled to other Asian countries due to lack of available data from those countries. Health care seeking behavior, public health service delivery costs, out-of-pocket costs, and lost productivity are likely to vary across the different countries. While we account for this by specifying an uncertainty range for public health service delivery costs and out-of-pocket costs in our uncertainty analysis, field data from these countries would be critical to better inform the model and its estimates. The number of workdays lost was adjusted to GDP per capita per day for each country, which should mediate some variations in cost, though ultimately country-specific lost productivity data is needed.

Third, there is likely an underestimation bias in the assumptions, and thus, our estimate is likely an underestimate of the true economic burden. It is known that cholera is not reported completely due to various reasons described herein. Therefore, the WHO-reported cholera cases are an underestimate [1]. The global disease burden study estimated cholera cases in cholera-endemic countries and the decision of endemicity was made based on cholera reports. Countries that did not report cholera cases may have been classified as non-endemic and may not be accounted for in the disease burden estimation [2], thus resulting in a lower number of estimated cases and a lower economic burden. The WHO CHOICE outpatient service delivery costs do not include diagnostic costs. The service delivery costs used in the analysis are at the primary health center representing lowest cost level which implies underestimation of costs per out-patient as well as the overall costs. Intangible costs that are not measured in monetary terms, such as reduced quality of life or emotional sufferings, are not accounted for in the available field data and thus not incorporated in our model. Similarly, productivity loss did not account for the number of school days lost as it only accounted for workdays lost among adults. We did not account for other sector costs, such as loss of income to tourism and export industries during outbreaks. Finally, we did not account for costs related to outbreak control.

Fourth, some assumptions used in the modeling may have overestimated the true economic burden. As cholera tends to affect children and socio-economically disadvantaged populations disproportionately, the productivity losses resulting from premature mortality estimated based on GDP per capita method may be an overestimate. We assume that all people who die of cholera have future earning potential by discounting (3%) the value of their future earning potential. Some of these people may not be in the workforce currently or may drop out of the workforce in the future and may not have any earnings, which may potentially overestimate the costs. To understand the overestimate, we conducted scenario analyses to account for productivity loss resulting from premature mortality at 75%, 50%, and 25% of GDP per capita. In some situations, ill workers may be simply replaced by healthy workers, which would only affect household income. In this case, although people may have fallen sick and are unable to work the economy would be unaffected on balance. In reality, the income loss resulting from illness in LMICs affects households and may not always affect the country. Finally, if we had used minimum wage as an alternative for GDP per capita we would have arrived at a different economic burden estimate, likely lower than the estimate presented in our study.

6. Conclusions

We have estimated the economic burden of cholera in Asia using the most recent evidence available to construct our economic model. Although cost data are extrapolated from three countries to 14 Asian countries, the study uses actual data collected from health facilities and patients. The high economic burden demonstrates the gravity of cholera in Asian countries. Especially in India and Bangladesh, countries with a particularly high burden of disease, the economic burden is alarmingly high. If we further consider the intangible costs associated with this burden, it further highlights the necessity for action to reduce the cholera burden.

Although long-term investments to improve water and sanitation systems are ultimately necessary for cholera elimination, vaccination is a good choice for cholera control in the short and medium term, and is a strategy recommended by the WHO [23]. There is adequate experience available on vaccination campaigns [24] and related costs [25,26], and there is notable evidence on

vaccine effectiveness, impact [27–28], and cost-effectiveness as well Hsiao et al., 2018; Mogasale et al., 2013;382 [9,29]. Despite the limitations of assumptions used, the economic burden data is needed for performing economic evaluations that quantify the value of cholera-control interventions to help decision-making in Asian countries. Further research should focus on improving disease burden data and collecting disease-related costs data from field settings.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.09.099>.

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