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Cost of Dengue Cases in Eight Countries in the Americas and Asia: A Prospective Study

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Abstract. Despite the growing worldwide burden of dengue fever, the global economic impact of dengue illness is poorly documented. Using a common protocol, we present the first multicountry estimates of the direct and indirect costs of dengue cases in eight American and Asian countries. We conducted prospective studies of the cost of dengue in five countries in the Americas (Brazil, El Salvador, Guatemala, Panama, and Venezuela) and three countries in Asia (Cambodia, Malaysia, and Thailand). All studies followed the same core protocol with interviews and medical record reviews. The study populations were patients treated in ambulatory and hospital settings with a clinical diagnosis of dengue. Most studies were performed in 2005. Costs are in 2005 international dollars (I$). We studied 1,695 patients (48% pediatric and 52% adult); none died. The average illness lasted 11.9 days for ambulatory patients and 11.0 days for hospitalized patients. Among hospitalized patients, students lost 5.6 days of school, whereas those working lost 9.9 work days per average dengue episode. Overall mean costs were I$514 and I$1,394 for an ambulatory and hospitalized case, respectively. With an annual average of 574,000 cases reported, the aggregate annual economic cost of dengue for the eight study countries is at least I$587 million. Preliminary adjustment for under-reporting could raise this total to $1.8 billion, and incorporating costs of dengue surveillance and vector control would raise the amount further. Dengue imposes substantial costs on both the health sector and the overall economy.

INTRODUCTION

Dengue fever, a viral infection transmitted by the *Aedes aegypti* mosquito, is a rapidly growing public health problem in tropical and sub-tropical countries. A large share of the world population is at risk, as over 2.5 billion people live in affected areas,[1] and an additional 120 million people travel to affected areas annually.[2] The annual number of dengue infections is estimated at 50 to 100 million.[2–5] Cases reported to the World Health Organization (WHO) over the past four decades show an upward trend, partly resulting from an increased spread of vector mosquitoes and increases in total human population, including specific increases in urban populations at risk of dengue infection.[6] In preliminary studies, potential dengue vaccines[7] and certain vector control strategies[8] were highly cost effective, but more and better cost information are needed to evaluate preventive interventions in multiple settings.

Cost of illness studies quantify the economic value of resources lost because of disease or consumed in its prevention, treatment, and care.[9] Endemic and epidemic dengue imposes economic and social stress on health care systems, affected households, and society at large. Previous cost studies have been limited to a single country and did not address all these associated economic losses.[10–17]

The objectives of this study were to measure the cost of a dengue case (either ambulatory or hospitalized) comprehensively in several countries in Asia and the Americas, collecting data prospectively using a common protocol, which included data on lost productivity, school absenteeism, and unpaid time of caregivers. The countries participating in this collaborative study represent 64% of worldwide reported dengue cases. Therefore, this analysis provides some indication of the global costs imposed by dengue illnesses.[7,18,19]

METHODS

Study design. We conducted prospective health care facility-based studies on disease burden and cost of dengue illnesses in eight endemic countries. Five of the countries were in the Americas (Brazil, El Salvador, Guatemala, Panama, and Venezuela) and three were in Asia (Cambodia, Malaysia, and Thailand) (Figure 1).

The study population consisted of patients with febrile illness that met the WHO clinical case definition for dengue.[20] In Panama and Venezuela, only laboratory confirmed dengue cases were included. Investigators chose age groups and facilities based on dengue endemicity and access in consultation with national authorities (see Table 1). All sites included children (< 15 year of age) and five also included adults. All sites enrolled patients admitted to major provincial or national reference public hospitals. Six sites (those in urban areas) also enrolled ambulatory patients from outpatient facilities linked to the selected hospitals. In Brazil, patients attending private facilities were also recruited into the study. The studies used a core protocol under the supervision of a coordinating institution. This protocol sought to document, but not to change, patterns of visits and hospital days.

Patients were selected consecutively or systematically (where patient volume exceeded interviewer capacity). Selected patients or legal guardians (for children) were invited to participate, asked to sign an informed consent form, and then enrolled in the study. Although the number of individuals choosing not to participate in the study was minimal, no systematic effort was made to characterize these individuals. Recruitment periods varied by country, extending from

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FIGURE 1. Location of study sites.

September 2004 through January 2007, with most patients enrolled during the 2005 dengue season.

Research procedures. We developed, piloted, and translated (into Khmer, Malay, Portuguese, Spanish, and Thai) a patient questionnaire. This questionnaire documented demographic and socio-economic data for patients and other household members, characteristics of the illness episode and its effects on health status, use of medical services, work and school absences, hours of patient care provided by household members, household spending, and household income lost. We abstracted medical records of hospitalized patients to obtain clinical data, including length of hospital stay. Additionally, we used a hospital cost form to collect each facility's annual operating expenses, number of beds, occupancy rates, and number of emergency and outpatient visits for calculating unit costs.

TABLE 1
Dengue epidemiologic and economic indicators for study countries and sites*

	Americas						Asia	
Characteristics	Brazil	EI Salvador	Guatemala	Panama	Venezuela	Cambodia	Malaysia	Thailand
Currency name	Real	US$	Quetzal	US$	Bolivar	Riel	Ringgit	Baht
Exchange rate used	2.53	1.00	7.93	1.00	2150	4000	3.80	39.00
GDP, US$/capita	3,460	2,450	2,400	4,630	4,810	380	4,960	2,750
GDP, I$/capita	8,230	5,120	4,410	7,310	6,440	2,490	10,320	8,440
Ratio: GDP I$/US$	2.38	2.09	1.84	1.58	1.34	6.55	2.08	3.07
Minimum daily wage, I$ (US$)	12.8 (5.4)	14.4 (6.9)	9.2 (5.0)	17.3 (11.0)	13.2 (9.8)	12.3 (1.9)	11.4 (5.5)	11.0 (3.6)
Cost per day of school, I$ (US$)	4.4 (1.9)	2.4 (1.2)	1.0 (0.3)	3.6 (2.3)	3.3 (2.4)	0.8 (0.1)	9.6 (4.6)	5.8 (1.9)
Characteristics of study site								
Location	Goiânia City	San Salvador City	Guatemala City	Panama Province	Falcon State	Takeo Province	Klang Valley Region	Khon Kaen Province
Population (millions)	1.20	2.20	2.50	1.61	0.87	0.87	5.60	1.70
Main year of recruitment for study	2005	2005	2006	2005	2005	2005	2005	2005
Reported dengue cases in site	9,033	4,472	3,513	4,043	3,254	705	39,686	746
Children (0–14 years), %	15%	55%	38%	17%	60%	99%	22%	78%
Adults (15 plus years), %	85%	45%	62%	83%	40%	1%	78%	22%
Circulating dengue serotypes	1,2,3	2,4	1,2,4	1,2	1,2,3,4	1,2,3,4,	1,2,3	1,2,3,4
Predominant	3	2	1	1	3	2	1	4
Unit costs in participating facilites†								
Per inpatient bed day, I$ (US$)	193.7 (81.4)	160.0 (76.5)	82.3 (44.8)	173.8 (110.1)	91.1 (68.1)	30.0 (4.6)	453.9 (218.1)	263.9 (86.0)
Per ambulatory visit, I$ (US$)	29.1 (12.2)	24.0 (11.5)	12.3 (6.7)	26.1 (16.5)	13.7 (10.2)	4.5 (0.7)	68.1 (32.7)	39.6 (12.9)

* GDP = gross domestic product; US$ = U.S. dollars; I$ = international dollars.
† Participating hospitals in the Americas:
Brazil's major participating hospitals: Hospital de Doencas Tropicais (state and country's public reference hospital for tropical infectious diseases); Hospital Santa Helena (state's private reference hospital for infectious diseases); EI Salvador: Children Hospital Benjamin Bloom (country's pediatric reference public hospital); Guatemala: Roosevelt Hospital (country's pediatric reference hospital); Zacapa Regional Hospital (regional reference public hospital); Panama: Santo Thomas Hospital (country's reference public hospital); Venezuela: Coro Hospital (state's reference public hospital).
Participating hospitals in Asia:
Cambodia: Daun Keo Referral Hospital (provincial's reference public hospital); Malaysia: University of Malaya Medical Center (state and country's reference hospital); Thailand: Khon Kaen Provincial Hospital (provincial's reference public hospital).

Data collection and management. Patients were interviewed by a trained health interviewer using the patient questionnaire. Each study participant had a final interview around or after the time of his/her recovery. In six countries, an additional interview was administered during the acute stage of illness. All patients received at least one in-person interview (at the health facility or the patient's home or workplace). The additional interviews, when performed, were conducted either in-person or by telephone. Data were entered into a Microsoft Access database (2003, Microsoft Corp, Redmond, WA). To standardize data accession, quality control, analytical procedures, and training of interviewers, site investigators participated in at least one of three international workshops, received site visits, accessed a list serve from the coordinating unit, and conferred regularly with the coordinating unit via e-mail and phone. Missing data were generally imputed from other items from the same household (e.g., missing transportation cost was imputed of other household members).

Analytic framework. The unit of analysis is a dengue case, defined as a documented acute febrile illness with a clinical diagnosis of dengue. This study examined all dengue illnesses, regardless of severity, using the WHO case definition.[20] In countries located in the American hemisphere, the diagnosis of dengue syndromes complied with the Pan-American Health Organization (PAHO) case definition,[21] whereas in Asian countries the WHO case definitions of dengue fever and dengue hemorrhagic fever were used.[22] However, the case definitions between the two regions are very similar and the minor differences, which lie in the criteria for dengue shock syndrome, were not consequential for this study. Although dengue laboratory confirmation was a condition for enrollment only in Panama and Venezuela, the majority of the patients enrolled in all the other countries, except Thailand, had dengue laboratory testing. Dengue testing was based on IgM capture enzyme-linked immunosorbent assay (ELISA) performed in provincial or national reference laboratories, which followed WHO guidelines.[20] In addition, four countries (Cambodia, Guatemala, Panama, and Malaysia) also performed virus isolation on appropriately timed samples. Among recruited and interviewed patients, we excluded from analysis in all countries except Panama patients discharged from the hospital with a non-dengue diagnosis or patients whose first interview was later than 30 days after the onset of symptoms. In Panama, where laboratory testing took unexpectedly longer, we extended this period to 60 days. We estimated the economic cost of a case by summing direct medical costs, direct non-medical costs, and indirect costs borne by government, households, and employers during the entire illness episode.

We estimated direct medical costs as a sum of the products of the quantity of services used (ambulatory or inpatient) by sector (public or private) times their respective average unit costs. We calculated unit costs of uninsured private medical care by dividing household payments by numbers of visits, as providers needed to recover their costs from users. In Malaysia, where panel doctors were paid directly by employers, we assumed the payment equaled 80% of average out-of-pocket payments for private consultations on the assumption that panel doctors agreed to a volume discount. In Brazil, where the major private insurer (Uniao Medios) (UNIMED) paid negotiated fees, we used these reimbursements as proxies for unit costs for both private and public facilities. In all other countries, unit costs were based on the cost of an average hospital day in the participating hospitals following a macro-costing approach, dividing the hospitals' expenses by their weighted units.[23] This macro-costing approach found that the average cost of a hospital outpatient visit ranged from 12–60% of the cost of inpatient day, with an average of 32%.[23] As dengue visits require few medicines or procedures, we assumed that its cost would be 20% of the cost of an inpatient day (i.e., in the lower half of this range). Furthermore, as less sophisticated health facilities tend to have lower unit costs,[24] we assumed that the average unit cost of all public-sector outpatient visits (which include health centers and dispensaries, as well as hospitals) would be 75% of the cost of the hospital outpatient visit. In Brazil, where the reimbursement prices paid by the public health insurance, Sistema Único de Saúde (SUS, Unified Health System) generally do not cover the full economic costs of care,[25,26] we used private sector reimbursement rates. Table 1 summarizes the unit cost of health services provided by the studied public facilities by country as well as the country–specific economic indicators used for other cost calculations.

Direct non-medical costs included patients' out-of-pocket payments for transportation, food, lodging, and miscellaneous expenses associated with seeking and obtaining medical care and/or household members visiting patients at the hospital. Indirect costs were the monetary values of 1) days of school lost, 2) lost days of work for pay, and 3) other days lost by either the patient or any other household member who provided care to the patient during an illness episode. The personal and societal cost of school absence is difficult to value.[27,28] Because all countries fund primary education publicly, the economic value of a day of school must be at least equal to the cost of providing a day of public primary school. Being conservative, we assumed that this economic was equal to the cost of schooling, as shown in Table 1.[29] We then calculated the economic loss attributed to school days lost as the product of the daily cost times the number of school days lost. We valued a day of work lost to the worker or to the employer[30] as the higher of the reported daily loss or the country–specific minimum daily wage (Table 1),[3–5] and then calculated the total economic costs of work days lost as the product of this average daily loss times the number of work days lost. To value "other" days (caregiver and patient days lost other than for school or work) we used a country's daily minimum wage for patients or household members 15 years of age or above. Household total days affected are the sum of school, work, and other days lost. As there were no deaths in our cohorts, the economic costs of premature deaths were not incorporated into the facility-based estimates of cost per case, but are included subsequently under aggregate national and multi-country estimates.

Standardization of costs across countries. To standardize measurements of economic impact across countries and facilitate comparisons and interpretations, we expressed all direct and indirect costs in 2005 international dollars (I$), which adjust for purchasing power parity (PPP), using the ratio of the gross domestic product (GDP) per capita in I$ to the GDP per capita in US dollars (US$) at the market exchange rate (see Table 1). Specifically, WHO describes I$ as "the costs in local currency units converted to international dollars using PPP exchange rates. The PPP exchange rate is the number of units of a country's currency required to buy the same amount of goods and services in the domestic market as the US$ would buy in the United States."[31]

In addition, we expressed total cost in US$ to facilitate within-country interpretation. To compare dengue costs with economic costs calculated for previous studies of dengue and other acute infectious diseases in low- and middle-income countries, we also expressed costs in days of GDP per capita (per capita GDP divided by 365).

Statistical analysis for cost per dengue case. We conducted separate analyses for each country by type of care—ambulatory (participants without any hospitalization) and hospitalized (participants with a hospital stay of at least one day). Using SPSS,[32] we calculated unweighted means and standard deviations for continuous variables and cross tabulated categoric variables, which provide a natural weighting for all the participants. We could also have used the true number of treated dengue cases by setting in a country as the weighting factor if known, but such data were not available. To our knowledge, no two patients came from the same household, and no patient had repeat dengue episodes during the study period. We treated each patient as an independent observation.

Aggregate national and regional dengue cost estimates. To help the reader quantify the magnitude of dengue costs, we also constructed a preliminary economic model. It estimates the average annual aggregate cost of dengue by country and region based on 2001–2005 dengue cases and deaths officially reported to the WHO,[33] with updates from participating countries. Because neither WHO nor standard surveillance reports provided the breakdown by setting, we requested supplementary data. The actual shares hospitalized (mean ± standard error) were available for Brazil (which includes both ambulatory and hospitalized patients) for 2001–2005 (11.7% ± 2.4%), Malaysia (which includes primarily hospitalized patients) for 2005–2006 (95% ± 1.9%), and Thailand (which also includes primarily hospitalized patients) for 2002–2005 (83.0% ± 1.7%). The share for Cambodia (98% ± 2.0%) resulted from the structure of its reporting system, which is almost exclusively based on hospitalizations. For the remaining American countries, following expert opinion, we used Brazilian rates. On the basis of epidemiologic similarities, we used the annual average age at death (mean ± standard error) for 2001–2005 of Brazil (38.6 ± 1.1) as the proxy for other American countries and Malaysia, and of Thailand (7.6 ± 2.0) for Cambodia.

The model's country–specific inputs were dengue cases, percentage of cases by setting (ambulatory and hospitalized), cost of a dengue case by setting, number of deaths by age, and GDP per capita.

Assuming that the distribution of cost per case by setting in our study was representative of the country's dengue cases, we estimated each country's aggregate cost by multiplying its average annual reported cases by its cost per case. To estimate the economic cost associated with reported dengue deaths, we used official 2001–2005 reports on the number of dengue deaths by age, and calculated the years of premature life lost as the remaining life expectancies at the ages of death based on the country–specific life tables.[34] To adjust for standard time preferences, we discounted years lost at an annual rate of 3%. On the basis of the conservative "livelihood" approach,[35] we then multiplied the discounted years lost by the country's 2005 GDP per capita. The livelihood approach is considered the lower bound for the economic value of a discounted year of life lost.[33,36]

Countries exhibited variations by year in the number of reported cases, setting of care, number of deaths, and ages at death. Therefore, we used Monte Carlo simulation methods to analyze the effect of variations in these inputs on aggregate costs.[37] Because each input could be skewed to the right and had to be non-negative, we fitted lognormal distributions, commonly used in economic models, to each input. We used the means and standard errors of historic data of reported cases and deaths (from national data) and costs per case from our study. Combining Crystal Ball version 7.3[38] and Excel 2003 software,[39] we then ran a simulation with 200,000 iterations to generate precise estimates of standard deviations. Each iteration randomly drew values from the distribution of each input. From the resulting empirical distributions, we obtained means and standard deviations of the average annual aggregate cost of dengue in the study countries and the weighted (combining hospitalized and ambulatory cases and deaths) mean cost per reported case.

Ethical considerations. The study protocol was approved by Institutional Review Boards at Brandeis University, participating sites, and the sponsor.

Role of the funding source. One author (SBH) directs a different program sponsored by the funding source. In addition, other officers at the funding source read an early draft of this manuscript and suggested clarifications.

RESULTS

Demographic and illness characteristics. Of the 1,796 patients recruited and interviewed, 1,695 dengue cases in eight countries met the inclusion criteria for analysis. Table 2 summarizes demographic and illness attributes of study cases. Overall, 55% were treated in ambulatory settings, 45% were hospitalized for at least one day, 86% were treated in the public sector, 54% were females, 48% were < 15 years of age, and 83% were from urban areas. Study participants spanned the full range of socio-economic strata based on the household maximum level of education. No participants died during the study.

On average, ambulatory patients reported 11.9 days of illness, including 5.0 days with fever, and 78% had dengue documented by laboratory testing. On average, hospitalized participants reported 11.0 days of illness, including 5.9 days with fever. The majority of this cohort had evidence of bleeding (73%), leakage (vasculopathy, 62%), and laboratory documentation of dengue (75%).

Use of medical services. Table 3 shows the burden placed by an ambulatory or hospitalized dengue case on the health system and patients' households. The proportion of patients who were studying or working at the time of the illness varies considerably by site, reflecting their target populations. Ambulatory and hospitalized patients averaged 4.2 and 4.6 ambulatory care visits, respectively, with country means ranging from 2.8 (Guatemala) to 6.3 (El Salvador) among ambulatory patients, and from 2.0 (El Salvador) to 7.1 (Malaysia) among hospitalized patients. The average hospitalized patient spent 3.8 days in the hospital, with country means ranging from 2.8 days (Malaysia) to 6.4 (Guatemala). Although no patients outside of Brazil were enrolled from private facilities, interview data found that visits to private facilities during the course of illness were not uncommon; they accounted for 30%

Table 2
Participants' and illness characteristics by study site

Characteristics	Americas					Asia			All countries
	Brazil	El Salvador	Guatemala	Panama	Venezuela	Cambodia	Malaysia	Thailand	
All cases									
Number of participants	550	189	85	136	200	127	235	173	1695
Hospitalized, %	25%	47%	25%	4%	35%	100%	55%	100%	45%
Recruited in public sector, %	56%	100%	100%	100%	100%	100%	100%	100%	86%
Females, %	63%	48%	53%	62%	56%	53%	40%	46%	54%
Age group									
0–14 years, %	14%	100%	41%	12%	63%	98%	30%	99%	48%
15 plus years, %	86%	0%	59%	88%	37%	2%	70%	1%	52%
Urban residence, %	100%	100%	84%	87%	89%	13%	98%	30%	83%
Maximum level of education in household									
Primary school or less, %	33%	33%	61%	19%	13%	40%	8%	49%	29%
Secondary school, %	39%	40%	21%	33%	65%	55%	59%	31%	44%
Vocational, college, or more, %	28%	27%	18%	48%	22%	5%	33%	20%	27%
Interviews: days from onset to:									
First interview, mean ± SD	14.6 ± 5.6	6.2 ± 2.6	4.4 ± 3.1	38.5 ± 9.6	10.9 ± 4.8	6.3 ± 1.3	6.4 ± 1.7	5.2 ± 2.4	11.9 ± 10.0
Second interview, mean ± SD	–	14.0 ± 4.1	14.3 ± 8.3	–	17.8 ± 4.4	15.0 ± 2.1	15.0 ± 2.1	18.1 ± 3.1	14.8 ± 5.0
Ambulatory cases									
Dengue confirmed,* %	73%	59%	50%	100%	100%	NA	79%	NA	78%
Days of fever, mean ± SD	4.8 ± 2.5	4.9 ± 2.9	6.1 ± 2.2	6.1 ± 5.3	3.6 ± 1.3	NA	5.5 ± 1.6	NA	5.0 ± 3.0
Days of illness, mean ± SD	12.3 ± 5.2	8.7 ± 2.9	11.0 ± 4.2	19.6 ± 12.3	8.6 ± 1.8	NA	8.6 ± 2.4	NA	11.9 ± 6.9
Any reported bleeding, %	22%	11%	22%	17%	9%	NA	16%	NA	18%
Hospitalized cases									
Dengue confirmed,* %	78%	87%	71%	100%	100%	97%	95%	24%	75%
Days of fever, mean ± SD	6.7 ± 2.6	5.0 ± 1.7	10.9 ± 4.5	8.5 ± 1.0	5.8 ± 1.6	3.7 ± 1.3	7.1 ± 1.2	6.0 ± 3.5	5.9 ± 2.8
Days of illness, mean ± SD	13.3 ± 5.0	10.6 ± 3.1	13.9 ± 10.4	18.8 ± 5.7	11.1 ± 2.3	6.3 ± 1.3	12.6 ± 2.3	10.8 ± 5.0	11.0 ± 4.7
Any bleeding, %	67%	74%	52%	100%	86%	54%	68%	89%	73%
Any leakage, %	29%	74%	29%	50%	51%	79%	75%	66%	62%

NA = not available.
* Most unconfirmed dengue cases did not have laboratory testing. Panama and Venezuela study sites included only laboratory-confirmed cases.

of all visits in the ambulatory cohort in Guatemala and 42% in the hospitalized cohort in Cambodia.

Dengue illness episodes affected school attendance and other productive activities of patients and household members. Patients in school at the time of the illness comprised 40% of the ambulatory cohort and 65% of the hospitalized cohort. They lost an average of 4.2 and 5.6 days of school, respectively. Similarly, patients who were working for pay at the time of the illness, constituting 43% of ambulatory and 18% of hospitalized cases, lost an average of 6.6 and 9.9 days of work, respectively. The burden on household members in addition to the patient was substantial. This impact represented 30% and 73% of work days lost in the ambulatory and hospitalized cohorts, respectively.

Economic costs of a dengue case. Table 4 summarizes the costs of ambulatory and hospitalized dengue cases by country and overall. Cost varied greatly within each country, as reflected by the relatively large standard deviations (about 60% of the respective means). In the ambulatory group, indirect costs represented the largest share (overall 72%) of case costs in all countries except Malaysia. For hospitalized cases, direct costs represented the largest share of total costs. Expressed in terms of days of GDP per capita, the total cost of an ambulatory case ranged from 12 days in Venezuela to 31 days in Brazil and from 45 days in Venezuela to 110 days in Cambodia for a hospitalized case. The mean unweighted cost per case was I$514 for ambulatory patients and I$1,394 for hospitalized patients in our cohorts.

Aggregate national, regional, and global cost of officially reported cases in eight countries. The yearly reported dengue cases by these eight countries for 2001–2005 averaged 574,000, but ranged from 253,000 to 1,020,000, reflecting variations in outbreaks by year.[33] On average, during the same years there were 399 reported deaths (range 260 to 596) leading to 10,283 discounted years of life lost. Based only on these officially reported cases and deaths, the estimated annual total cost associated with dengue illness was I$587 million (range: I$448 to I$768 million). About 89% and 11% of this cost was imposed by dengue morbidity and dengue mortality, respectively. Dengue in Brazil and Thailand was responsible for 94% and 60% of the aggregate cost in the American and Asian study countries, respectively. The mean cost of a dengue reported case, weighted by the official numbers of deaths and cases by setting, was I$1,031 in the eight countries, but 2.7 times larger (I$2,005 versus I$759) in Asia than in the Americas.

DISCUSSION

This was a prospective study in which dengue patients were identified using WHO case definition guidelines.[20–22] A high rate of serologic confirmation of recent dengue infection was achieved. Reflective of the real world, a marked heterogeneity of demographic and socio-economic characteristics in these studies demonstrates the diversity in treatment sites, disease expression, or in disease descriptions in different country settings. Although some deaths might have been expected in this cohort of 1,695 patients, none were observed. Using the overall case fatality rates implicit in Table 5 in the Americas (0.014%) and Asia (0.27%), we would have expected two deaths. This absence of deaths may reflect chance or slight

Table 3

Utilization of health services and impact per dengue case by study site

Type of service	Americas: Brazil	El Salvador	Guatemala	Panama	Venezuela	Asia: Cambodia	Malaysia	Thailand	All cases
Ambulatory									
Number of participants	410	100	64	130	130	0	105	0	939
Studying, %	28%	72%	39%	28%	74%	–	31%	–	40%
Working, %	52%	0%	38%	59%	19%	–	62%	–	43%
Health services utilization									
Ambulatory visits, mean ± SD	3.6 ± 2.7	2.0 ± 0.2	2.5 ± 1.4	4.1 ± 2.2	6.5 ± 1.9	–	7.1 ± 2.3	–	4.2 ± 2.7
Share in private sector, %	49%	5%	30%	22%	24%	–	19%	–	31%
Patient impact									
If studying, days of school lost, mean ± SD	5.2 ± 3.9	3.9 ± 2.6	2.0 ± 2.0	3.1 ± 3.1	4.7 ± 2.6	–	3.2 ± 2.3	–	4.2 ± 3.2
If working, days of work lost, mean ± SD	7.1 ± 5.1	NA	5.6 ± 3.6	6.2 ± 7.4	3.1 ± 2.3	–	7.2 ± 2.6	–	6.6 ± 5.2
Household impact									
Days of school lost, mean ± SD	1.8 ± 4.0	3.3 ± 3.5	1.2 ± 2.4	1.0 ± 2.3	4.0 ± 3.5	–	1.0 ± 2.0	–	2.0 ± 3.6
Borne by patient, %	83%	84%	65%	87%	86%	–	97%	–	84%
Work days lost, mean ± SD	4.8 ± 6.2	1.8 ± 3.3	3.2 ± 4.4	4.5 ± 7.6	1.7 ± 2.2	–	6.0 ± 4.2	–	4.0 ± 5.6
Borne by patient, %	77%	1%	66%	80%	35%	–	74%	–	70%
Total days affected, mean ± SD*	15.0 ± 8.4	16.4 ± 6.1	11.7 ± 5.5	20.8 ± 13.5	11.6 ± 3.6	–	11.2 ± 4.2	–	14.8 ± 8.6
Borne by patient, %	84%	54%	86%	93%	73%	–	78%	–	80%
Hospitalized									
Number of participants	140	89	21	6	70	127	130	173	756
Studying, %	36%	60%	33%	50%	81%	66%	51%	100%	65%
Working, %	50%	0%	19%	33%	6%	0%	42%	0%	18%
Health services used									
Ambulatory visits, mean ± SD	4.0 ± 2.7	6.3 ± 2.5	2.8 ± 1.5	6.0 ± 3.8	4.1 ± 1.8	3.7 ± 0.8	5.6 ± 1.6	4.2 ± 2.0	4.6 ± 2.2
Share in private sector, %	45%	27%	17%	25%	9%	42%	33%	13%	29%
Hospital days, mean ± SD	3.0 ± 1.8	3.4 ± 1.8	6.4 ± 4.0	5.2 ± 3.8	5.3 ± 1.7	3.3 ± 1.3	2.8 ± 1.5	4.9 ± 3.3	3.8 ± 2.5
Share in private sector, %	47%	0%	0%	19%	0%	0%	1%	0%	7%
Patient impact									
If studying, days of school lost, mean ± SD	6.8 ± 5.4	3.8 ± 2.1	6.1 ± 2.6	5.7 ± 5.1	6.9 ± 2.2	6.8 ± 1.7	4.1 ± 2.1	5.5 ± 3.4	5.6 ± 3.3
If working, days of work lost, mean ± SD	10.7 ± 5.2	NA	9.0 ± 4.4	18.0 ± 8.5	6.5 ± 0.6	NA	8.8 ± 2.7	NA	9.9 ± 4.5
Household impact									
School days lost, mean ± SD	2.9 ± 4.8	2.8 ± 3.1	2.2 ± 3.3	2.8 ± 4.5	8.3 ± 5.5	6.5 ± 6.4	2.2 ± 2.6	5.5 ± 3.4	4.4 ± 4.8
Borne by patient, %	84%	82%	96%	100%	68%	69%	93%	100%	83%
Work days lost, mean ± SD	7.0 ± 7.4	4.5 ± 4.4	3.8 ± 5.5	8.8 ± 9.3	3.1 ± 3.3	14.4 ± 8.0	6.7 ± 5.1	3.9 ± 5.0	6.8 ± 7.0
Borne by patient, %	76%	0%	48%	68%	17%	1%	57%	0%	27%
Total days affected, mean ± SD*	17.4 ± 8.4	18.3 ± 6.9	16.3 ± 11.3	22.3 ± 9.6	20.0 ± 6.0	23.4 ± 9.5	16.2 ± 6.7	18.6 ± 10.4	18.9 ± 8.9
Borne by patient, %	79%	58%	80%	85%	56%	29%	75%	59%	59%

NA = not available.
* Includes work days lost, school days lost, and other days lost.

under enrollment of severely ill patients. As all facilities, which range from ambulatory clinics and small provincial hospitals to major university hospitals, were predominant providers in their catchment areas, they were collectively representative of treatment locations for dengue across these countries. Although in three countries (Cambodia, El Salvador, and Thailand) patients were enrolled only from pediatric locations, the majority of reported cases from those countries were in children. Furthermore, the study did not appear to influence care, as the majority of medical providers were involved in the research.

This study incorporated empirical values for most of the components of health services used, and most of their unit costs. Furthermore, it examined actual medical practice, rather than the more expensive setting of a formal prospective clinical study of laboratory confirmed dengue infections.[40]

Not surprisingly, hospitalized patients had more severe illness than ambulatory patients, as evidenced by their higher incidence of bleeding phenomena, longer duration of fever, and more days affected. Within the six countries in which ambulatory and hospitalized cohorts were included, the total cost of a hospitalized case averaged 3.7 times that of an ambulatory case. This relationship could help estimate the cost of ambulatory cases, where direct costs are not available.

The variations in costs among countries might reflect many factors, such as the case-mix of the study participants, the type of facility at which they were enrolled, the cost of health services, patterns of treatment, the country's wage rates, and cost of living. Nevertheless, as the cost per case in days of GDP per capita varied less than threefold across countries within ambulatory and hospitalized cohorts, the economic burden of dengue per case was fairly similar across the sites.

The absence of universal laboratory testing on all cases of suspected dengue reflected the standard practices at the participating institutions. A clinical diagnosis of dengue without laboratory confirmation is usual in ambulatory settings and in some hospitals, such as those in Thailand, where clinicians have extensive experience with dengue.[41] In a few instances, laboratory diagnosis was not possible because properly spaced sera were not obtained for laboratory testing. Although 22%

Table 4
Means (± standard deviations) of cost components per dengue case by study site*

Component	Americas: Brazil	El Salvador	Guatemala	Panama	Venezuela	Asia: Cambodia	Malaysia	Thailand	All participants	Cost share %
Ambulatory cases										
Direct cost, I$										
Medical cost	89 ± 61	47 ± 7	34 ± 38	100 ± 66	78 ± 25	–	406 ± 151	–	116 ± 126	23%
Non-medical cost	32 ± 39	4 ± 10	14 ± 28	32 ± 53	12 ± 13	–	41 ± 34	–	26 ± 38	5%
Sub-total	121 ± 86	51 ± 12	48 ± 61	132 ± 108	90 ± 30	–	447 ± 171	–	142 ± 145	28%
Indirect cost, I$	579 ± 790	133 ± 88	110 ± 93	399 ± 334	128 ± 87	–	219 ± 102	–	372 ± 576	72%
Grand total cost, ambulatory case										
In I$,	699 ± 805	184 ± 89	158 ± 130	531 ± 377	218 ± 92	–	666 ± 220	–	514 ± 601	100%
In US$	291 ± 336	88 ± 43	88 ± 72	332 ± 235	168 ± 71	–	317 ± 105	–	248 ± 261	
In days of GDP/ capita	31 ± 36	13 ± 6	13 ± 11	27 ± 19	12 ± 5	–	24 ± 8	–	24 ± 26	
Hospitalized cases										
Direct cost, I$										
Medical cost	696 ± 368	679 ± 308	588 ± 313	895 ± 530	569 ± 166	183 ± 150	1,578 ± 723	1,436 ± 902	915 ± 761	66%
Non-medical cost	87 ± 65	111 ± 87	63 ± 42	294 ± 246	41 ± 17	210 ± 118	161 ± 204	186 ± 129	142 ± 137	10%
Sub-total	782 ± 382	790 ± 342	651 ± 324	1,190 ± 559	611 ± 172	393 ± 205	1,739 ± 776	1,621 ± 998	1,058 ± 811	76%
Indirect cost, I$	840 ± 967	170 ± 124	102 ± 118	515 ± 303	204 ± 113	363 ± 194	249 ± 136	137 ± 99	337 ± 502	24%
Grand total cost, hospitalized case										
In I$,	1,622 ± 1,039	960 ± 388	752 ± 359	1,704 ± 766	815 ± 216	756 ± 309	1,988 ± 817	1,758 ± 1,079	1,394 ± 926	100%
In US$	676 ± 433	457 ± 185	418 ± 199	1,065 ± 478	627 ± 166	115 ± 47	947 ± 389	573 ± 351	571 ± 407	
In days of GDP/ capita	72 ± 46	68 ± 28	62 ± 30	85 ± 38	46 ± 12	111 ± 45	70 ± 29	76 ± 47	76 ± 43	

* I$ = international dollars; US$ = U.S. dollars; GDP = gross domestic product; NA = not applicable.

of study patients did not have confirmatory laboratory tests, we found no statistically significant overall differences in their clinical characteristics or cost between suspect dengue cases with or without laboratory confirmation. For costs, the relationships between the confirmed and non-confirmed cases were variable. The only significant difference was the ambulatory cohort in Brazil, where confirmed cases cost 40% more than unconfirmed cases (I$756 versus I$540), respectively. Possible reasons include the small sample size for cases without confirmatory tests and reliance on length of stay for calculating hospital costs. Although dengue secondary infections tend to be more severe than primary infections[42,43] and some serotypes or sequences may be more severe than others,[16,44–46] the necessary laboratory tests for these distinctions were not part of routine care and were not available in this study.

Previous research on the economic impact of dengue has been limited to single-country studies and using less comprehensive costing methods.[10–17] Cost per case in these studies, translated to days of GDP per capita, varied from 8 days[14] to 56 days.[13] Earlier estimates of the cost of dengue illnesses were below those estimated in our study. For example, previous studies found costs per case of $44 in Kampaeng Phet, Thailand in 2001,[14] $120 and $140 for Suphan Buri and Bangkok regions of Thailand, respectively, in 1994,[10] and $121 for Venezuela from 1997 to 2003.[15] Less comprehensive analysis of government subsidies for public services and valuation of indirect costs, inflation, and use of US$ instead of I$ were major reasons for the lower estimates.

We compared the total cost of inpatient dengue cases with those for other acute infectious diseases, such as influenza,

Table 5
Estimation of average annual national cost of dengue morbidity and mortality associated with 2001–2005 official reports*

Item	Americas: Brazil	EI Salvador	Guatemala	Panama	Venezuela	Asia: Cambodia	Malaysia	Thailand	American subtotal	Asian subtotal	Both regions
Offical dengue reports											
Cases (thousand)											
Mean ± SE	387 ± 114	11 ± 3	8 ± 0.5	2 ± 1	44 ± 10	11 ± 1	31 ± 4	81 ± 20	452 ± 117	122 ± 17	574 ± 132
Deaths											
Mean ± SE	54 ± 25	5 ± 2	3 ± 1	1 ± 1	6 ± 2	151 ± 19	86 ± 11	93 ± 25	70 ± 25	330 ± 34	399 ± 59
Estimations											
Aggregate cost, mean ± SD											
In I$ (million)	322.1 ± 93.4	3.6 ± 0.8	2.2 ± 0.2	1.4 ± 0.7	13.7 ± 3.0	18.2 ± 1.2	79.4 ± 8.2	146.9 ± 32.0	343.0 ± 93.5	244.5 ± 33.0	587.4 ± 99.2
In US$ (million)	135.2 ± 39.2	1.7 ± 0.4	1.2 ± 0.1	0.9 ± 0.4	10.2 ± 2.2	2.8 ± 0.2	38.2 ± 3.9	47.8 ± 10.4	149.3 ± 39.3	88.8 ± 11.1	238.1 ± 40.9
Mean cost per reported case (including fatal cases), mean ± SD											
In I$	835 ± 44	326 ± 25	266 ± 23	847 ± 117	310 ± 17	1733 ± 128	2585 ± 140	1839 ± 127	756 ± 40	2016 ± 104	1031 ± 59
In US$	351 ± 18	156 ± 12	144 ± 12	536 ± 74	231 ± 13	265 ± 20	1234 ± 67	599 ± 41	330 ± 16	733 ± 45	417 ± 21
Mortality cost share	3%	15%	14%	17%	7%	56%	25%	14%	4%	21%	11%

* I$ = international dollars; US$ = U.S. dollars.

bronchitis, pneumonia, rotavirus, or typhoid fever, requiring inpatient care in low- or middle-income countries in The Americas and Asia. Of the examples found, only a few studies examined both direct and indirect costs.[47–51] The wide range in total costs measured in terms of days of GDP per capita, from 4 days[47] to 112 days,[50] mainly reflects variations in methodologies and study scope (e.g., household versus societal perspective) rather than differences in impact among the diseases. Nevertheless, the range for these diseases overlaps substantially with the range for dengue, indicating that the economic cost of a dengue case is comparable to that of other infectious diseases.

A limitation of our research is that in the three Asian study countries, dengue cases were included from only a single institution. Nevertheless, this is the most comprehensive study of dengue costs published to date and the first to develop comparable data across two hemispheres, and comprises an important step to documenting the global burden of dengue. Earlier comparative economic evaluations across countries for other diseases, such as for rotavirus, encountered challenges in data interpretation because of methodologic differences among studies.[52]

Although it may be premature to extrapolate these preliminary data, we appreciated the interest in generating preliminary estimates of dengue costs using currently available case reporting data. The I$587 million estimate for the average annual cost of dengue in the eight study countries was based only on the officially reported dengue cases for the 2001–2005 periods. The validity of our estimate relies on our assumption that the distributions of cost per case in our study are representative for the country. On the basis of other studies,[24] our estimate may be too high for countries where our site was a national referral hospital (such as in El Salvador and Malaysia), and too low where it was a small provincial hospital (such as Cambodia and Venezuela). These effects may tend to offset one another for the eight-country aggregate. The American countries bore only 17% of the reported dengue deaths, but 79% of the reported cases and 58% of the estimated total cost of dengue. These contrasts are a result of regional differences in both epidemiology[53] and reporting of dengue.[53] In the Americas, where dengue usually occurs as dengue fever (DF),[53] patients generally receive care in ambulatory settings, which are included in dengue surveillance and reporting systems. In Asia, by contrast, more dengue cases are believed to develop dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS), and death,[53] and surveillance and reporting systems are mainly limited to hospitalizations.[53] For example, because Cambodia had the highest average annual death rate (151 deaths out of 11,000 reported cases, or 1.4%) it had one of the highest resulting average costs per case (I$1,733).

Our estimate of the eight-country cost of dengue illness is conservative. Official reports substantially underestimate the true number of cases and highlight the need for expansion factors to adjust for this underreporting.[6] Previous research indicates expansion factors from 1.6 to 3.2 for hospitalized dengue,[54,55] from 10 to 27 for ambulatory dengue,[11] and 6 for all dengue cases.[56] As a preliminary illustration, an overall expansion factor of 3 would suggest a cost of dengue illness in these eight countries averaging I$1.8 billion per year, but ranging from I$1.3 to I$2.3 billion. With expansion factors of 2 or 6, the eight-country costs would range from I$1.2 to I$3.6 billion. Further analysis of the performance of each country's treatment reporting system would be needed to refine unit costs and expansion factors and project trends.

Furthermore, these estimates also exclude the substantial costs associated with dengue surveillance and vector control programs. For example, Brazil's budget for vector control in 1997 was US$0.6 billion, equivalent to I$1.2 billion in 2005 prices.[57] Panama, with a population of only 3.2 million people, spent US$5.0 million, equivalent to I$7.9 million in 2005.[56] Mass larviciding efforts against the dengue vector *A. aegypti* in two urban areas of Cambodia with a population of 2.9 million people between 2001 through 2005 had an annual average gross cost of US$ 568,000 in 2005 US$, or US$ 0.20 (I$ 1.31) per person covered.[8]

In summary, this study shows that dengue poses a heavy economic cost to the health system and society, that the cost varies by setting (ambulatory and hospitalized), that improved surveillance and reporting efforts are necessary to include ambulatory patients from at least sentinel sites (mainly in Asia), to officially report cases by setting, and to reduce underreporting. The study also suggests the potential economic benefits associated with promising dengue prevention interventions, such as dengue vaccines and vector control innovations.

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