Dengue fever is caused by a mosquito-borne virus, which has four serotypes.1,2 The disease has a wide range of clinical manifestations. A patient with classic dengue fever will typically experience fever, headache, pain in the muscles, joints and bones, nausea, and vomiting and develop a rash.3,4 Although most dengue infections can be characterized as mild,2,5 some cases will present as dengue hemorrhagic fever (DHF). The latter is characterized by hemorrhagic manifestations and excessive capillary permeability. Approximately 33% of patients with DHF will experience serious circulatory failure, known as dengue shock syndrome (DSS).5 The fatality rate for those patients with DSS can be between 12% and 44%,5 although infusions of fluids, electrolyte management, and use of oxygen can reduce the fatality rate to less than 1%.3

Cases of dengue fever were described more than 200 years ago,2 and histories of dengue and dengue epidemics have been written.2,3,6–10 After the Second World War, populations of the most important mosquito vector, Aedes aegypti, were suppressed in Latin America. The control campaigns, however, were abandoned in the early 1970s and the vector re-established itself in virtually all of the countries that had vector control campaigns as well as expanding into a few new areas, such as the Amazon basin. This re-establishment and expansion of the vector has resulted in the dengue viruses spreading rapidly around the globe. In 1980, it was estimated that at least 1.5 billion people live in areas with dengue activity.10 In 1995, this estimate was increased to 2.5 billion,11 as residents in several additional countries became newly infected with dengue. Most of these newly infected countries are in Africa, South and Central America, and the Caribbean.11 The number of cases have led researchers to describe the incidence of dengue and DHF as pandemic.6–8,10 Illustrating the rate of increase is the fact that globally, there were 25,000–30,000 reported cases of DHF per year from 1956 to 1980. For the period 1981–1985, an average of 137,504 cases of DHF/DSS per year were reported, and for 1986–1990, the average number of reported DHF/DSS cases per year increased to 267,692.12 Given problems of diagnosis and reporting, it is likely that these figures are conservatively low. It has been estimated that there were more than 1.3 million cases of DHF in the period 1986–1990.12 The reasons for the geographic spread and increased incidence of dengue and DHF have been described,2,6,8,11,13–15 and include an increase in international trade, rapid urbanization without concurrent improvements in sanitation, and a decrease in the effective control of the vectors. The rapid spread of dengue and DHF and the large numbers of people afflicted have resulted in dengue being classified by national and international public health authorities as an emerging, or re-emerging, infectious disease.8,11,16,17

Curiously, despite the large number of victims, there are few estimates of the economic impact of dengue. Estimates of the total direct and indirect costs from the 1977 epidemic in Puerto Rico range from US $6.1 million to $15.6 million (approximately $26–$31 per clinically ill case).18 The 1981 epidemic in Cuba, which had a total of 344,203 reported cases, cost about US $103 million (approximately $299 per reported case).19 An outbreak in 1980 in Thailand was estimated to cost a minimum of US $6.8 million (approximately
The lack of estimates of the impact of endemic dengue is important because such estimates are needed by policy planners to help allocate resources for research, prevention, and control activities. The World Bank recently sponsored a study that evaluated the global burden of more than 200 infectious diseases. The most recent World Bank-sponsored study on infectious diseases can be used by international health organizations and donor countries to objectively prioritize funding and support for dengue programs. Prior to this analysis, data allowing dengue to be objectively prioritized with other infectious diseases have been lacking.

**MATERIALS AND METHODS**

**Number of cases.** The impact of dengue in Puerto Rico over time was analyzed for the period 1984–1994. The time period was chosen because of data availability and because it encompasses two notable epidemics that occurred in 1986 and 1994. The number of reported cases of dengue (confirmed and suspected), the number of reported hospitalized cases, the percentage of reported cases that had one or more hemorrhagic manifestations, and the number of laboratory-positive deaths from dengue were obtained from data bases maintained at the San Juan Laboratories, Centers for Disease Control and Prevention (CDC) (Table 1).

**Multiplication factors.** For several reasons, the number of reported cases, confirmed or otherwise, is only a proportion of actual cases. For example, a serologic survey conducted between August and December 1982 in Manatí, Puerto Rico, found a 12% incidence of dengue infection (defined by a four-fold increase in titer). The 1990 census estimated the Manatí population at approximately 39,000. If one allows for a 1% per annum growth rate, the 1982 population would have been approximately 36,000. When a uniform attack rate of 12% is assumed, it is calculated that 4,320 dengue infections occurred in Manatí in 1982. Only 65 cases, however, were reported; thus, the maximum ratio of actual to reported cases is 66:1. This ratio is unlikely to be realistic since not every infection results in a symptomatic case. Other studies, however, also point to large differences between actual and reported cases. Von Allmen and others calculated that during the 1977 epidemic, there were between 196,652 and 584,354 clinical cases of dengue in Puerto Rico. Yet, only 11,840 cases were reported (CDC, San Juan Laboratories, 1995), giving minimum and maximum ratios of actual to reported cases of 17:1 and 49:1, respectively. Another study, which used data from the 1963 epidemic in Puerto Rico, estimated that the ratio of actual to reported cases could have been as high as 60:1 in the Guaynabo township, which is part of metropolitan San Juan. However, it was felt that this figure “... seems excessive,” and the investigators used data from a small house-
ECONOMIC IMPACT OF DENGUE IN PUERTO RICO

267

TABLE 2
Age-based distribution of laboratory-diagnosed cases of dengue, 1991 (n = 3,595)*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Percent of all cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–14</td>
<td>32</td>
</tr>
<tr>
<td>15–29</td>
<td>32</td>
</tr>
<tr>
<td>30–44</td>
<td>20</td>
</tr>
<tr>
<td>45–59</td>
<td>10</td>
</tr>
<tr>
<td>≥60†</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

* Source: Centers for Disease Control and Prevention, Dengue Branch. Dengue Surveillance Summary No. 64, 1992, 2.
† ≥60-year-old age group includes unknown, equal to 3% of all cases.

to-house survey to calculate a factor of 17 or 21, depending upon whether or not it was assumed that reported cases were also recorded in the survey. During the 1986 epidemic in Puerto Rico, cohort studies of 5–9-year-old school children in three cities in Puerto Rico showed that there were 36 infections (as detected by serologic tests) for every reported case in that age-group (CDC, San Juan Laboratories, unpublished data). Obviously, not every infected case was symptomatic.

Multiplying the number of reported cases by a set factor to obtain an estimate of actual cases is complicated by the fact that there is an age-related factor affecting the number of symptomatic cases. Halstead,10 examining data from Thailand for children less than 14 years old, found a positive correlation between age and prevalence of dengue-specific antibodies, and a negative correlation between age and hospitalization rates for DHF. In a study of school children 4–15 years old, Burke and others30 found that depending on immune status, 8–16% who were infected during the course of the study were symptomatic. The remainder were asymptomatic or “minimally” symptomatic.

These data from Thailand suggest that for the 0–15-year-old age group, the proportion of reported cases should be less than the proportion of those 0–15 years of age in the total population of Puerto Rico. However, those 0–14 years of age accounted for 32% of all reported cases in Puerto Rico (Table 2), while accounting for approximately 27% of the total population in Puerto Rico.31 We hypothesized that probably due to parental influence, there is a greater probability of a case of dengue being reported in the 0–15-year-old age group than in other age groups. To model both the age-differentiated susceptibility to developing a symptomatic disease (lost time, ability, or activity). Based on results of two surveys conducted in Puerto Rico to determine some of the impacts of dengue,29, 34 the number of days lost because of a case of dengue fever was set at four days. The baseline values for the days lost because of dengue with hemorrhagic manifestations and cases requiring hospitalization were set at 10 and 14 days, respectively.29, 39 Patients with dengue fever can be bedridden for more than four days.35 For example, in a study of patients admitted to a hospital in Bangkok for DHF, patients spent 1–7 days with symptoms before admission, and between one and nine days in the hospital.20 Thus, the estimates of days lost from dengue fever can be considered as being conservatively low.

Estimating DALYs. The DALYs estimate the amount of time, ability, or activity lost by an individual from disability or death because of disease.22, 23 This loss is then adjusted to account for age of onset, severity of disability, and length of disability. Adjusting for the age of onset reflects the idea that 10 days sick in bed is not the same loss for an infant as for a 30-year-old man. To adjust for the severity of the disability, the DALY methodology uses 1 to represent loss from premature death. Disabilities are then classified into six categories or grades, with each grade allocated a preset proportion of 1. The lower the proportion, the less impact the disability has on a person’s life. The disability weighting considers the loss of time or ability to perform in one or more of the following areas: recreation, education, procreation, and occupation.22

The DALYs lost by each case of dengue (reported + estimated) in Puerto Rico for the period 1984–1994 were estimated by using the following formula:22

$$-\frac{DCe^{-br}}{(b+r)}[e^{-(b+r)L}a(1+(b+r)(L+a))-(1+(b+r)a)]$$

where $D$ is the disability weight ($D = 1$ for premature death, 0 for perfect health); $C$ and $b$ are parameters from an age weighting function; $a$ is the age at onset of the disease (distributed as in Table 2); $L$ is the duration of the disability or years of life lost due to premature death; and $r$ is the social discount rate. The age-weight function that defines the values of $C$ and $b$ is $Cxe^{-r}$, where $x$ is the age in years at onset.22 The values used in the model are presented in Table 3. To allow direct comparison with the DALYs estimated to be lost to other diseases, the values used for $C$, $b$, and $r$ are the same as those used in the World Bank study.21, 22 The DALY formula was entered into a computer-based spreadsheet (Excel 5.0; Microsoft Corp., Redmond, WA). The DALYS for each age-specific category and degree of severity were multiplied by the number of cases in each year, then summed to give annual totals. These totals were then divided by the estimated population to give DALYS per million population per year, which are the units used in the World Bank report.21, 22

Severity of dengue. Following the methodology used in studies of outbreaks of dengue,30, 31 we divided cases of dengue into three categories of increasing severity. These three categories can be described as dengue fever (classic dengue), dengue with manifestations more severe than classic dengue, such as evidence of hemorrhage (but not requiring hospitalization), and cases requiring hospitalization. It was assumed that increasing severity translated into longer episodes of disease (lost time, ability, or activity). Based on results of the impacts of dengue,29, 34 the number of days lost because of a case of dengue fever was set at four days. The baseline values for the days lost because of dengue with hemorrhagic manifestations and cases requiring hospitalization were set at 10 and 14 days, respectively.29, 39 Patients with dengue fever can be bedridden for more than four days.35 For example, in a study of patients admitted to a hospital in Bangkok for DHF, patients spent 1–7 days with symptoms before admission, and between one and nine days in the hospital.20 Thus, the estimates of days lost from dengue fever can be considered as being conservatively low.
The disability weights (D) were assumed to be the same for each level of severity, with a base rate of 0.81, which is Class 5 in the World Bank classification. The rationale for using this rate is that even if a patient has dengue fever for only two days, that person’s abilities and activities are as effectively curtailed as a person who spends two days in a hospital because of dengue. The difference between the two cases is that the hospitalized person will have a longer total time of curtailed activities. This assumption effectively states that the symptoms produced by dengue fever can incapacitate a person, leaving her or him unfit for almost all usual daily activities.

In the few laboratory confirmed deaths directly attributed to dengue in Puerto Rico (Table 1), the average age of death was approximately 33 years (SD = 27 years) (CDC, San Juan Laboratories, unpublished data). The average life expectancy of a person 33 years of age in 1990 was approximately 44 years, and this was the amount assumed lost for each death.

Sensitivity analysis. It is obvious that the baseline results obtained depend on the values used for some critical parameters. For example, the multiplication factors used for the two broad-based age groups depend on interpretations of rather scant data, and the actual values could change, especially over time and with different virus strains. The number of days lost by each category of severity is another set of values that have a marked effect on the total DALYs estimated, as is the value used for the disability weighting (D).

To analyze the potential impact of changes in one or more of these values, a multivariate sensitivity analysis was conducted by using Monte-Carlo-type techniques. To use this methodology, a probability distribution of potential values is specified for each parameter that will be investigated in the sensitivity analysis. A computer algorithm then runs the model for several iterations. For each iteration, the algorithm uses a preset sampling methodology to choose, from the probability distribution, a value for each parameter. After the final run, the model provides estimates of the means, maximums, minimums, and distributions of the output variables. The sensitivity analysis for this model was run with a computer algorithm (@Risk; Palisade Corp., Newfield, NY), set for 1,000 iterations, with the probability distributions sampled using a Latin-hypercube methodology. The ranges for the values of the six inputs used for the sensitivity analysis are given in Table 3. Two Monte-Carlo-type sensitivity analyses were run, one assuming triangular distributions (distribution is defined using minimum, maximum, and most likely values), and one assuming uniform distributions (using only minimum and maximum values). Finally, a step-wise regression was run with the average DALYs per million population as the dependent variable and the six input variables used in the sensitivity analysis as the independent variables (Table 3). The standardized coefficients from these regressions were used to identify the six variables that were the most influential in determining the size of the output value.

Comparison of impact. The DALYs estimated to be lost because of dengue in Puerto Rico were compared with previously estimated DALYs lost to other infectious diseases or disease groups in the Latin American and Caribbean region (calculated using 1990 data). In that region, infectious and parasitic diseases account for approximately 60% of the burden from communicable, maternal, and perinatal diseases or injuries, and 25% of the burden caused by all diseases and injuries. To facilitate comparisons, the losses attributed to a specific disease or disease group were calculated as both a logarithm (base 10) and as a percentage of the total estimated DALYs lost to all infectious and parasitic diseases in the region.

RESULTS

In the baseline model, the annual DALYs lost per million people ranged from 145 (1984) to 1,492 (1994), with an 11-year average of 658 (SE = 114). As seen in Figure 1, the three-year moving average, which smooths year-to-year variation to reveal overall trends, indicated an upward trend for the period studied. Because of the influence of the epidemics in 1986 and 1994 (Table 1), the standard errors of the means are larger at the beginning and end of the period studied than the middle of the period (1987–1989 through 1990–1992).

For the sensitivity analyses, the simulation that used the triangular distributions had an average DALYs lost/year/million population of 580. The maximum calculated average was 1,021 DALYs and the minimum was 240 DALYs. The means, maximums, minimums, and 5th and 95th percentiles for each year are plotted in Figure 2. The maximum values were approximately 3.5–4 times greater than the minimum values, and the 95th percentiles were approximately 2–2.25 times greater than the 5th percentile values. Similar results were obtained by using the uniform distributions.

The step-wise regression had an R² value of approximately 0.98, indicating a good fit. The standardized coefficient for the time lost in days because of a classic case of dengue was 0.86. The coefficients for the five other input variables used in the sensitivity analysis were all less than 0.5. Thus,
the variable that most influenced the calculation of the DALYs lost was the time lost because of classic dengue fever.

The annual DALYs lost to dengue in Puerto Rico are equivalent to 1–4% of all DALYs lost to infectious and parasitic diseases in Latin America and the Caribbean (Table 4). The average of 658 DALYs/ year/ million population from all types of dengue is three orders of magnitude greater than the two DALYs/year/million population lost to DHF in Latin America and the Caribbean (Table 4). The range of DALYs lost per million population to dengue is similar to the annual losses attributed to any one of the following diseases or disease clusters; the childhood cluster (primarily pertussis, polio, measles, tetanus), meningitis, hepatitis, or malaria (Table 4). In addition, the average impact of dengue calculated for 1984–1994 is within the same order of magnitude of impact as any one of the following diseases or disease clusters; tuberculosis, sexually transmitted diseases (excluding human immunodeficiency virus [HIV]), the tropical cluster (primarily Chagas’ disease and schistosomiasis), or intestinal helminths (primarily roundworm, whipworm, and hookworm) (Table 4).

**DISCUSSION**

Within the period studied, the losses attributed to dengue have increased over time (Figure 1). Although the losses occurring in the 1986 and 1994 epidemics are noticeably larger than other years studied (Figure 2), dengue continues to extract a substantial toll even during nonepidemic years. The DALYs calculated depended directly on the number of reported cases (Table 1). A key question arises: is the increase in reported cases because of an increase in the percentage of cases being reported (perhaps owing, in part, to better surveillance), or was there a genuine increase in den-
Table 4
Disability-adjusted life years (DALYs) lost to dengue in Puerto Rico compared to losses from other infectious and parasitic diseases in Latin America and the Caribbean*

<table>
<thead>
<tr>
<th>Disease or disease group</th>
<th>DALYs lost per million population</th>
<th>Log base 10 of DALYs/1000 infectious and parasitic disease cases</th>
<th>% of all infectious and parasitic disease cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dengue in Puerto Rico</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average (baseline case, 1984–1994)</td>
<td>658</td>
<td>2.818</td>
<td>1</td>
</tr>
<tr>
<td>Maximum single year estimate (1994)</td>
<td>1,492</td>
<td>3.174</td>
<td>3</td>
</tr>
<tr>
<td>Maximum three-year average estimate (1992–1994)</td>
<td>933</td>
<td>2.970</td>
<td>2</td>
</tr>
<tr>
<td>Maximum from sensitivity analysis (1994)</td>
<td>2,153</td>
<td>3.333</td>
<td>4</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All infectious and parasitic diseases</td>
<td>58,184</td>
<td>4.765</td>
<td>100</td>
</tr>
<tr>
<td>Dengue hemorrhagic fever (DHF)</td>
<td>2</td>
<td>0.301</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>5,782</td>
<td>3.762</td>
<td>10</td>
</tr>
<tr>
<td>Sexually transmitted diseases (except human immunodeficiency virus)</td>
<td>5,409</td>
<td>3.733</td>
<td>9</td>
</tr>
<tr>
<td>Human immunodeficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>virus infection</td>
<td>9,982</td>
<td>3.999</td>
<td>17</td>
</tr>
<tr>
<td>Diarrheal diseases</td>
<td>13,243</td>
<td>4.122</td>
<td>23</td>
</tr>
<tr>
<td>Childhood cluster</td>
<td>3,612</td>
<td>3.558</td>
<td>6</td>
</tr>
<tr>
<td>Meningitis</td>
<td>1,603</td>
<td>3.205</td>
<td>3</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>360</td>
<td>2.556</td>
<td>1</td>
</tr>
<tr>
<td>Malaria</td>
<td>984</td>
<td>2.993</td>
<td>2</td>
</tr>
<tr>
<td>Tropical cluster</td>
<td>6,731</td>
<td>3.828</td>
<td>12</td>
</tr>
<tr>
<td>Leprosy</td>
<td>149</td>
<td>2.173</td>
<td>0.3</td>
</tr>
<tr>
<td>Trachoma</td>
<td>248</td>
<td>2.394</td>
<td>0.4</td>
</tr>
<tr>
<td>Intestinal helminths</td>
<td>5,388</td>
<td>3.731</td>
<td>9</td>
</tr>
</tbody>
</table>

* DALYs lost from diseases in Latin America and Caribbean calculated from Murray et al., except the value for DHF from Murray and others.
† Log (base 10) allows for quick comparison of differences of orders of magnitude.
‡ Percentages for Latin America and the Caribbean do not add up to 100% because some diseases are excluded from the list (see Murray and others).
§ Percentages are rounded to nearest whole number, except for leprosy and trachoma.

When comparing the impact of dengue to other diseases, it is important to first note that the impact of all types of dengue is significantly larger than the impact of DHF alone (Table 4). Thus, using only cases of DHF as a measure to compare the impact of dengue will seriously underestimate the economic burden imposed by dengue. In using DALYs to compare the impact of different diseases, the most important differences are those of an order of magnitude or larger (Murray C, 1995, unpublished data). When that criterion is used, the logarithm (base 10) values in Table 4 show that only diarrheal diseases and HIV infection have a truly greater impact per year per million population than dengue. Even this distinction fades away when the maximum calculated impact of dengue (1994) is considered. When comparing the impact of dengue to the burden of the childhood cluster as measured in 1990 (Table 4), it is important to note that in September 1994 the Americas were certified as free of cases due to wild polio virus, although vaccine-based cases of acute polio still occur. Also, the number of reported cases of measles in the Americas has reached an all-time low. Even with these caveats regarding the comparison of the impact of dengue to the childhood cluster, this study has confirmed that dengue has become a disease of considerable impact, as suggested by others. In terms of DALYs, the majority of this impact is borne by those victims who suffer a classic case of dengue fever lasting approximately four days. Since 50% of the families in Puerto Rico have an income of $10,000 per year or less (1989 data), it is logical to suggest that the largest portion of the burden imposed by dengue in Puerto Rico is borne by those in the lower socioeconomic strata. Such people can ill-afford the four or more days of productivity lost from dengue.

The policy implications from these results are obvious and important. These results suggest that when governments and international funding agencies allocate resources for infectious disease research, prevention, and control, dengue must be given a priority equal to many other diseases that receive more resources for prevention and control (Table 4).

Authors’ addresses: Martin I. Meltzer, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C-12, 1600 Clifton Road, Atlanta, GA, 30333. Jose G. Rigau-Pérez, Gary G. Clark, and Paul Reiter, Dengue Branch, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, San Juan Laboratories, 2 Calle Casia, San Juan, PR 00921-3200. Duane J. Gubler, Division of Vector-Borne Infectious Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, PO Box 2087, Fort Collins, CO 80522.

Reprint requests: Martin I. Meltzer, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Mailstop C-12, 1600 Clifton Road, Atlanta, GA, 30333.

REFERENCES