Overcoming data limitations: design of a multi-component study for estimating the economic burden of dengue in India

Yara A. Halasa, a Vishal Dogra, b Narendra Arora, b B.K. Tyagi, c Deoki Nandan d & Donald S. Shepard a#

a Schneider Institutes for Health Policy, Heller School, Brandeis University, Waltham, MA 02454-9110, USA.

b International Clinical Epidemiology Network (INCLEN), New Delhi, India.

c Centre for Research in Medical Entomology (Indian Council of Medical Research), 4, Sarojini Street, China Chokikulam, Madurai-625 002, Tamil Nadu, India.


Abstract

Dengue is emerging as a serious global health problem. Estimating the economic burden of dengue is crucial to inform policy-makers of the disease’s societal impact and may assist in implementing appropriate control strategies. However, developing such studies is constrained by limited data and other challenges. This paper shows how analyzing hospital records carefully can adjust surveillance data for possible under-reporting and misdiagnosis of dengue, merging information on treatment patterns with macro costing to estimate the cost of dengue episode by age and severity in various treatment settings, and combining adjusted surveillance data with cost information can estimate the aggregate cost of dengue illness in India and in other endemic countries.

Keywords: Dengue; Burden; Cost; Surveillance; Expansion, India.

Introduction

Dengue is emerging as a serious public health problem globally, with 2.5 billion people at risk and 50 million dengue infections occurring annually. Estimates of the economic burden of dengue are important in order to inform policies on dengue prevention and management, but published studies on this subject are limited. This paper presents an...
Estimating the economic burden of dengue in India

approach to estimate the economic burden of dengue illness in India. It utilizes several tools to assess the coverage of the dengue surveillance system: estimating an expansion factor to correct under-reporting and under-diagnosis, computing the average cost of a dengue illness episode, and aggregating direct and indirect costs.

Dengue is caused by four closely-related but serologically-distinct dengue viruses: DENV-1, DENV-2, DENV-3 and DENV-4. Lifetime immunity to each serotype follows an infection by that serotype. However, individuals infected with one or more serotypes remain vulnerable to infections by the other dengue serotypes.[7,8] Dengue infections affect all age groups and produce a spectrum of clinical manifestations, with varied clinical evolutions and outcomes that range from asymptomatic to a mild or non-specific viral syndrome and to a severe and occasionally fatal disease characterized by haemorrhage and shock.[3,9-11] Primary infection (the first dengue infection caused by any of the four serotypes) is often asymptomatic, but primary infections sometimes result in dengue fever, a very uncomfortable febrile illness. However, secondary dengue infections can lead to the life-threatening dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS).[12-16] Epidemiological studies have demonstrated that secondary or subsequent dengue infections contribute to higher rates of DHF in Thailand and Cuba.[17-22] Several hypotheses may explain the pathogenesis of severe dengue.[23-25]

Dengue challenge in India

Dengue is becoming a serious public health problem in India.[26-29] Although dengue infection has been endemic in India since the nineteenth century, DHF has become endemic in various parts of India since 1987, with the first major widespread epidemics of DHF and DSS occurring in 1996, involving areas around Delhi and Lucknow, Uttar Pradesh, and spreading to other regions in India.[30-33] However, the epidemics of Delhi and Pune in western India in 2006 and in Kerala state in 2008 marked the changing epidemiology of dengue infection, with all four serotypes of dengue viruses found in co-circulation, leading to an increase in secondary dengue infection and, in some cases, co-infections with DENV-1 and DENV-3, DENV-2 and DENV-3 and DENV-1, DENV-2 and DENV-3.[11-13,26,27,31,34,35] In West Bengal state, nearly 61% of dengue cases reported between 2005 and 2007 were secondary dengue infection cases.[36] Moreover, some studies revealed the evolving phylogeny (change through time) of DENV-3 and DENV-4 and their circulation in South-East Asia and India, emphasizing higher risks of DHF/DSS outbreaks.[13,37]

With these epidemiological developments, dengue infection changed its manifestation in India from the infection’s asymptomatic and benign form to its severe forms of DHF and DSS, with increasing frequency of outbreak, morbidity and mortality.[10,11,27,30-33,36,38-45] Although dengue is considered an urban and semi-urban disease, in recent years, due to water storage practices and large-scale development activities in rural areas, dengue has become endemic in rural areas of India as well, increasing the scale of the dengue challenge in the country.[36,45-48]
After the 1996 dengue haemorrhagic fever epidemic in Delhi, dengue was declared a dangerous disease under sections 2(9) (b) of the Delhi Municipal Corporation (DMC) Act, 1957 (Delhi Gazette Notification dated April 25 1997). Under this Act, all private practitioners, nursing homes and government hospitals are required to notify suspected dengue cases to the Municipal Health Officer.[29] However, under-diagnosis and under-reporting of dengue cases persist in India, where reported cases underestimate the real burden of the disease.[49-51] Similar to studies in Nicaragua and Thailand, a strict application of WHO criteria resulted in the omission of many cases of DHF in India.[11] The WHO 1997 classification makes use of symptoms and signs that are often not present in the first few days of illness and thus are not a sufficient guide for early diagnosis without expensive laboratory investigations such as RT-PCR or NS1; lack of these tools is likely to lead to under-diagnosis and under-reporting of severe manifestations of dengue.[39,52] For example, during the 2010 dengue outbreak in Delhi, the number of dengue cases was likely under-reported as platelet counts were not performed immediately, nor were they followed by serological screening.[49,53] Additionally, medical and public health professionals had less familiarity with investigating and managing dengue than their counterparts in other countries where the disease is more endemic.[53] Access to routine public laboratory testing of dengue (based on IgM antibodies) is limited to patients treated in large public hospitals. This diagnostic tool is applicable only to samples obtained six or more days after the onset of fever, and may still yield false negative results.[4] While tests based on viral replication in cell culture, molecular investigations, immunofluorescence or immunohistochemistry may be more accurate,[53-56] they are not generally feasible for routine use.[23]

Several studies have addressed the burden of dengue illness in India. These studies were facility-based, focused on tertiary care hospitals, and, in most cases, limited to one location and a single outbreak study.[10,11,27,30-33,38-45,57] Moreover, only a handful of them examined the economic cost of dengue in the country. While a useful start, these studies were limited by examining only one sector (public or private), reliance on data from other countries (mainly Thailand) for expansion factors, or a single geographical area.[58-62] With dengue’s changing epidemiology, a broader study is needed to estimate the overall economic burden of the disease in India. This paper sets forth a method designed to meet this need.

**Proposed approach**

**Conceptual framework**

In order to estimate the economic burden of dengue, ideally, data should be compiled from multiple sources in the health system at different levels. At the national, regional and state levels, surveillance data and expansion factors are needed to correct the under-reporting and under-diagnosis of dengue cases. First, to address the variability of dengue, surveillance data are needed for several years for all regions in India, preferably broken down by the setting from which the case is reported, dengue classification or severity, and the patient’s
Estimating the economic burden of dengue in India

age. Second, an expansion factor is needed to adjust surveillance data to under-reporting and provide reasonable estimates of dengue cases according to setting, severity and age. At the facility and household levels, data are needed to estimate the overall economic cost of a dengue episode according to treatment setting (hospitalized vs ambulatory) by a patient’s age and case severity. The economic cost includes direct medical cost, direct non-medical cost (i.e. transportation, meals and lodging), and indirect costs associated with the illness episode (value of work, school or leisure time lost due to illness or care-giving). To estimate the economic cost of dengue we compute the weighted average cost of dengue according to care setting and patient’s age group. The figure below presents the proposed methodology to overcome data limitations and respect time constraints. These steps are simple in concept but challenging in practice due to lack of systematically compiled data.

**Figure:** Conceptual framework of the economic burden of dengue in India study

Study setting

This study represents a collaboration among academic and government institutions in India and overseas. The participating institutions are: Brandeis University (Waltham, Massachusetts, USA), the National Institute of Health and Family Welfare (New Delhi, India), the Centre for Research in Medical Entomology of the Indian Council of Medical Research (Madurai, India), and the International Clinical Epidemiology Network (INCLEN) (New Delhi, India). This collaboration combines local knowledge and experience in vector transmission, virology...
Facility and household data: estimating the average cost of a hospitalized dengue episode

For this study, India will be divided into five regions (south, north, west, east and central) to capture the diversity among different regions in the country. Two states will be selected from each region. One selected state in each region will represent a state in that region with a relatively high incidence rate of reported dengue cases and the second selected state will represent a state in that region with a relatively low incidence rate of reported dengue cases. The incidence rates will be obtained from national, regional or state surveillance systems and the official statistics of the Ministry of Health and Family Welfare starting with the year 1996, when dengue reporting became mandatory. From each of these ten selected states, one medical college hospital will be selected based on the availability of electronic medical data, willingness to participate, and ability to meet the study timeline and the quality requirement for this research.

A mixed approach will be used to obtain the economic cost of dengue, combining retrospective and prospective data collection. The retrospective abstraction of data from inpatient medical records and a prospective survey of ambulatory patients suspected of having dengue, combined with a macro-costing analysis will be used to obtain the cost of dengue according to treatment setting, age and severity for the year 2010. The reference years for the retrospective component will be the last five years with available data, years 2006 through 2010, to cover a cyclical pattern in the number of cases across years, as well as seasonal variation. Study participants will be drawn from three populations: (1) patients with a clinical discharge diagnosis of dengue (ICD10 code A90); (2) patients with discharge diagnosis of any of the following febrile illnesses: chikungunya (A92.0), Khysanur forest disease (A98.2), influenza-like illnesses or influenza and pneumonia (J09-J18), malaria (B52), typhoid (Z22) and fever with rash and haemorrhage (A98.4-A99), who were hospitalized during the dengue season starting 1 July through 30 November during the specified study years; and (3) patients with a discharge diagnosis of fever or pyrexia of unknown origin (R50.9) hospitalized during the dengue seasons mentioned above. A systematic random sample of 7500 medical records is planned. The sample will consist of 150 hospitalized cases in each of 10 medical colleges for each of five years. Each year’s sample consists of three strata reflecting the three categories of the study population, each with 50 patients. If there are 50 patients or fewer we will enroll all these patients in the study. If there are more than 50 patients, a systematic random sample will be selected from that category after recording the sample frame. Based
on a previous multi-country study, we project that this sample will give accuracy in cost per case of 9.3% for hospitalized cases. This level of precision will be adequate for measuring trends or comparing regions.\cite{63}

Using the definition of dengue febrile illnesses adopted by publications of the World Health Organization in 1999 and 2011 (referring to the detection of dengue virus in patients with two days of fever irrespective of severity of illness),\cite{3,9,64-66} an evidence-based triage strategy will be used to develop a prediction model to identify individuals likely to have dengue infection, but have been misdiagnosed for another febrile disease. A data abstractor, a professional with a medical or paramedical background, will review signs, symptoms, notes and lab tests to see whether they are consistent with a diagnosis of dengue as stated by the WHO-recommended surveillance standards 1999 classification of DF, DHF and DSS.\cite{66} Based on the type of information available, such cases will be classified as confirmed dengue, suspected dengue, indeterminate or non-dengue. Based on probability theory with a dichotomous outcome, the sample size for each illness category should be proportional to the variance in the expected number of cases in that category, \( n[p(1-p)]^{1/2} \), where ‘n’ is the number of admissions in that category, and ‘p’ is the estimated probability that an admission in that category is ‘suspected’ or ‘confirmed’ dengue. Data will be extracted from medical records, with a careful review of laboratory and clinical records used to classify which cases should be considered dengue. These data will be compiled to assess the probability of a dengue case being misdiagnosed. These data will also be used to estimate the expansion factor for institutions with good dengue reporting systems and an expansion factor for institutions with weaker dengue reporting systems. The average of these two factors should be a reasonable proxy for the national expansion factor for India.

The results will be tabulated to calculate arithmetic and weighted means, standard deviations and standard error of the mean, t-tests, ANOVA and Chi-square tests with alpha level of significance at 0.05. Sensitivity analyses will test the variation in the economic costs among years and regions in India.

**Facility and household data: estimating the average cost of an ambulatory dengue episode**

The prospective outpatient study will focus on dengue cases that received ambulatory care only and will be implemented during the dengue season (July through November). This component will be carried out in ambulatory facilities affiliated with one or two of the participating medical college hospitals (those in Mumbai and Delhi are recommended, for they have the most sophisticated laboratory capabilities and the highest proportions of routine ambulatory patients with fever tested for dengue). The sample frame will consist of all patients with acute febrile illness and clinically diagnosed dengue cases seeking treatment during the study period. A field-trial approach using commercial dengue NS1 antigen-capture for early laboratory confirmation of acute dengue will be utilized to obtain a sample of 100
confirmed dengue cases and 150 patients with fever or pyrexia of unknown origin. The sample size is based on the previous multi-country study of dengue burden and costs. This level of precision will be adequate for measuring trends.

A lab technician will make the first contact with outpatients sent to the affiliated hospital laboratory for a dengue panel of tests (NS1 or IgM, platelets, haematology, packed cell volume and haematocrit) or to investigate fever or pyrexia of unknown origin, to screen and explain the objectives of the study to them and invite them or their proxy to participate and sign a consent form. A second contact will occur when patients seek the results of the test and physician’s diagnosis. At this point, patients will be divided into two groups. The first group will consist of patients with positive dengue diagnosis. The second group will consist of patients who are negative for dengue and diagnosed with fever or pyrexia of unknown origin. This group will be randomized based on their outpatient department medical record number, where those with even numbers will be retained in the study. The rationale of including these patients is based on the inconclusiveness of the NS1 test to rule out dengue after 3-5 days of infection with dengue virus. A model will be developed to compare the symptoms of patients with dengue and patients with fever or pyrexia of unknown origin to determine the likelihood of dengue infection in this category of patients.

Two weeks after the initial screening, where we hypothesize that the illness episode will be over, all patients remaining in the study will be asked to complete a survey. A standardized survey instrument will be used. It includes a section from the World Health Survey and EuroQol (visual scale) to measure the quality of life. The survey will ascertain the clinical characteristics of the patient’s illness such as days of fever, days of overall illness, perceived severity and quality of life, and care-seeking behaviour, as well as an assessment of the socioeconomic impact on the patient and his/her household. Cost-related domains include the cost associated with the use of medical services, days of schooling lost, loss in work productivity and income, leisure time lost due to illness or care-giving, and out-of-pocket spending. To complement the clinical information obtained from the patients during the interviews, medical records will be reviewed at the selected ambulatory facility to extract relevant clinical data (e.g. days of fever, clinical manifestations such as vomiting, diarrhoea, etc.) and laboratory data (e.g. platelet and white cell count, hematocrit, radiological results, etc.) associated with that illness episode.

A full economic analysis from a societal perspective will be conducted by combining the three major cost categories: direct medical, direct non-medical and indirect costs. To compute the direct medical costs for each patient, we will sum the type and amount of services received by ambulatory setting and by provider and multiply this by their respective unit costs. We will use each patient’s actual out-of-pocket payments for costing private medical services. To calculate direct non-medical costs we will aggregate the out-of-pocket payments by the patients and their household and care-givers for transportation, food, lodging and related miscellaneous expenses.
To estimate the indirect cost for the dengue episode, we will compute the monetary values of the time lost due to days of school missed; days of work lost (paid and unpaid); and leisure time lost due to illness or care-giving. The economic loss attributed to school days lost will be calculated by multiplying the cost of a school-day in a public school by the number of school days lost. The societal value of a day of work lost and leisure time lost will be valued as the larger of the worker’s reported income lost per day or India’s daily minimum wage. The total economic costs of work days lost will be calculated as the product of this average daily loss and the number of work days lost. Finally, the total cost of a dengue case will be calculated for each patient as the sum of all his or her direct (medical and non-medical) and indirect costs.

The cost will focus only on one episode of illness and all the treatment and cost associated with that episode. The results will be reported as means and standards deviations for continuous variables and frequencies for categorical variables. T-test and Chi square test with alpha level of significance at 0.05 will be performed for key analyses.

To estimate the economic cost of the medical care provided by medical college hospitals, a macro-costing approach will be used. It entails three stages. First, using admissions, length of stay and numbers of ambulatory visits in the selected facilities, we can estimate the hospital’s annual number of hospital-day equivalents. This estimation will be computed by multiplying the annual number of admissions by the average length of stay and the number of hospital outpatient visits by 0.25, based on the observation that the cost of a hospital outpatient visit was one fourth of a hospital day. Second, to calculate the average cost of a hospital day, we will divide the hospital’s total annual expenses by the total number of hospital-day equivalents. Third, as we assume that the public ambulatory care will be provided not only by selected ambulatory facilities but also by other health centres and dispensaries, we expect that the cost of a public ambulatory visit would be 60% of the cost of a hospital outpatient visit.

National- and state-levels surveillance data and expansion factors

The dengue surveillance system in India consists of 330 facilities supported by 14 apex laboratories across the country. The system is designed to monitor outbreaks and guide responses. The current surveillance system does not currently capture all dengue cases. To address the under-reporting dilemma in India, a structured communication technique for interactive forecasting known as the “Delphi method” will be used to estimate the expansion factors for various settings, age groups and regions in India. Information from different sectors will be gathered prior to this meeting to assist the process. Supplementary information, such as the number of dengue test kits distributed by type and year for the two most widely used types of initial test (Mac Elisa IgM and NS1), can assist in estimating the number of dengue cases by state. Using an individual test as a unit of measure, this component will create two inventories of supplies reflecting domestic and foreign wholesale suppliers, including both public and private suppliers, to estimate the average number of units by year and type of
supplier. Using inventory and reported data we can compute the number of suppliers of each type and their average volume by type. Multiplying these two estimates will give the number of tests by year. Since few patients get both types of tests and these tests are generally not repeated, the sum of the two types of data will be used to estimate the total number of patients tested by year.

In order to determine the number of dengue patients treated by year in the formal health system in the selected states, an inventory of health facilities by type for the year 2010 will be generated. The average number of dengue patients per year by type of facility will be estimated using a sample of at least two facilities of each type (inpatient and outpatient).

The Delphi process can be conducted in two or more stages. In the first stage, key experts in various areas related to dengue from governmental, academic and private sectors will jointly share their knowledge and experience in a one- or two-day workshop, and answer preset questions related to the epidemiology of dengue and the quality of the surveillance system in India when it comes to reporting mechanisms from all settings (hospital vs ambulatory; public vs private; municipality vs state vs national surveillance system; rural vs urban). The second stage will take place two weeks after the workshop. A report, with the suggested estimates, will be sent to the experts and they will be asked to refine their own estimates, if needed, according to the workshop discussions and the results generated from the first round. The experts can collectively share their knowledge about dengue treatment patterns in the public and private sectors and the process of recording dengue illness to estimate the completeness of reporting in each setting.

National-, regional- as well as state-levels dengue surveillance data will be collected and compared. A special instrument will be developed to collect data at the national level (National Centre for Disease Control, Directorate General of Health Services), state level with special emphasis on the selected hospitals’ catchment areas, and at the district level for the selected hospital areas. The data collected will include: number of suspected dengue cases and the number of laboratory-confirmed dengue cases tabulated according to year, state, region, severity, fatality rate, reported site (private or public, hospital or ambulatory, location), age, gender and type of dengue virus and infection type (primary vs secondary), if possible.

**Aggregate cost of dengue in India**

Combining the information from surveillance systems (reported dengue cases by age, year and region) with the expansion factors generated through the Delphi process can give the projected numbers of dengue cases in India. Accordingly, we will compute the aggregate cost of hospitalized cases by multiplying the average number of hospitalized cases by the average cost of a hospitalized episode (with disaggregation according to setting and age if the data allows); the same approach will be used to compute the ambulatory services cost. The overall cost will be computed using the weighted average cost of child and adult patients.
Estimating the economic burden of dengue in India

Discussion

The methodology discussed in this paper should be helpful in generating data and information to support dengue policies in India. The investigators will estimate the proportion of patients with dengue misdiagnosed at discharge as febrile illnesses other than dengue. In addition, we will compute the in-hospital dengue case-fatality rate and the seasonal variation of dengue infection by year for all the sites and for individual sites. And, finally, this methodology can help build a mathematical model of the burden of dengue in different regions of India using the proportion of the population served in each site, and the estimated proportion of population seeking admission in the study’s selected medical college hospitals.

Acknowledgments

The authors thank Vivek Adish, Rohit Arora, Jeremy Brett, Meenu Maheshwari and Josemund Menezes for their valuable comments on the study design during a planning workshop in New Delhi; Josemund Menezes and Eduardo Undurraga for important background information on dengue; and Clare Hurley for editorial assistance.

References


Estimating the economic burden of dengue in India


Estimating the economic burden of dengue in India


[34] Kumaria R. Correlation of disease spectrum among four dengue serotypes: a five years hospital based study from India. *Brazilian Journal of Infectious Diseases.* 2010; 14(2): 141-146.


Estimating the economic burden of dengue in India


Estimating the economic burden of dengue in India


