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# Disease and economic burdens of dengue

Marcia C Castro, Mary E Wilson, David E Bloom

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# Dengue 1

# Disease and economic burdens of dengue

*Marcia C Castro, Mary E Wilson, David E Bloom*

**The burden of dengue is large and growing. More than half of the global population lives in areas with risk of dengue transmission. Uncertainty in burden estimates, however, challenges policy makers' ability to set priorities, allocate resources, and plan for interventions. In this report, the first in a Series on dengue, we explore the estimations of disease and economic burdens of dengue, and the major estimation challenges, limitations, and sources of uncertainty. We also reflect on opportunities to remedy these deficiencies. Point estimates of apparent dengue infections vary widely, although the confidence intervals of these estimates overlap. Cost estimates include different items, are mostly based on a single year of data, use different monetary references, are calculated from different perspectives, and are difficult to compare. Comprehensive estimates that decompose the cost by different stakeholders (as proposed in our framework), that consider the cost of epidemic years, and that account for productivity and tourism losses, are scarce. On the basis of these estimates, we propose the most comprehensive framework for estimating the economic burden of dengue in any region, differentiated by four very different domains of cost items and by three potential stakeholders who bear the costs. This framework can inform future estimations of the economic burden of dengue and generate demand for additional routine administrative data collection, or for systematic incorporation of additional questions in nationally representative surveys in dengue-endemic countries. Furthermore, scholars could use the framework to guide scenario simulations that consider ranges of possible values for cost items for which data are not yet available. Results would be valuable to policy makers and would also raise awareness among communities, potentially improving dengue control efforts.**

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This is the first in a Series of three papers on dengue

**Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA, USA** (M C Castro PhD, D E Bloom PhD, Prof M E Wilson MD)**; and School of Medicine, University of California, San Francisco, CA, USA** (Prof M E Wilson)

Correspondence to: Dr Marcia C Castro, Department of Global Health and Population, Harvard TH Chan School of Public Health, Boston, MA 02115, USA **mcastro@hsph.harvard.edu**

## Introduction

Dengue is a systemic infection caused by a mosquito-transmitted, single-stranded RNA virus of the genus Flavivirus. Dengue viruses exist as four related serotypes: 1–4. Infection with one serotype might confer lifelong immunity to that serotype but only transient immunity to the other three serotypes, so an individual can be infected more than once. Second infections are epidemiologically associated with increased risk for severe disease, which has been attributed to antibody-dependent enhancement of disease.[1] Specific diagnosis of dengue is made by laboratory testing. Many treatment modalities have been tested, but so far nothing has improved on the outcomes that can be achieved with attentive and experienced clinical care, and judicious fluid replacement.[2] Although mosquito transmission causes virtually all dengue infections, other routes of transmission have been documented, such as blood transfusion,[3] tissue or organ transplantation,[4] needle stick,[5] percutaneous exposure to blood from a viraemic person (eg, in a health-care setting),[6] and, possibly, breastfeeding.[7]

In 2009, WHO issued guidelines for case classification, but variation in the definition of dengue cases still occurs.[8] Signs and symptoms of dengue—fever, severe muscle aches, headache, and rash[9,10]—are non-specific and resemble those of other infections, such as malaria, chikungunya, and Zika virus disease. Symptoms begin 5–7 days (with a range of 3–10 days) after a bite from an infective mosquito; viraemia, however, can begin 1·5 days before the onset of symptoms and could persist for up to a week. A small minority of those with dengue fever (5% or less) develop severe dengue.[10] However, most dengue virus infections are asymptomatic or mild—only about one in four infections is symptomatic—and result in complete recovery. The ratio of asymptomatic to apparent infections ranges widely and depends on age, dengue serotype and genotype, previous dengue infection, presence of antibodies, and genetic factors.[11] Most patients with acute dengue fever do not need admission to hospital, but many are unable to work, attend school, or manage a household, resulting in major economic burden.[12,13]

Dengue epidemiology is inseparable from vector ecology. Transmission has distinct patterns that are seasonal (within a year) and cyclical (with outbreaks in certain years), reflecting interactions between the climate (rainfall and temperature), the mosquito, the circulating virus, and population immunity.[14,15] The primary vector for dengue, *Aedes aegypti*, is highly adapted to the urban environment and avidly attracted to human blood, entering homes and breeding in small collections of water, such as those found in discarded plastic cups and bottles, flower pots, drains, and used tyres.[16] Rapid and unplanned urban growth, often resulting in the absence of, or unreliable access to, piped water, leads people to store water in their homes in tanks, jugs, and other containers, which are ideal breeding sites. A second mosquito vector, *Aedes albopictus*, is not as strongly attracted to humans as *A aegypti*, but it can survive in cooler temperatures than *A aegypti*[17] and it can be found in forested areas, potentially expanding the areas where dengue infections can spread.[18,19]

Dengue prevention remains primarily limited to vector control, which includes the use of larvicides, adulticides, biological control, and environmental management.[8] Physical elimination of breeding sites requires intensive, sustained work and must include members of the community.[20] In rapidly developing cities, the presence of slums and areas with poor housing, absence of piped water, precarious waste collection, and unscreened windows and doors provide ideal conditions for mosquito breeding. Therefore, collaboration among government sectors (eg, health, urban planning, and education) could contribute to more effective environmental management efforts. Overall, however, vector-control programmes have not prevented the spread of dengue, even in areas with well organised public health systems.[20] New approaches are being tested, such as the genetic engineering of mosquitoes and infecting mosquitoes with *Wolbachia* spp.[21,22]

The health system does not capture asymptomatic infections, nor are they the target of current surveillance or control strategies. However, a study by Duong and colleagues[23] shows that people with asymptomatic dengue infections not only infected mosquitoes, but were more infectious to mosquitoes than people with dengue symptoms. Therefore, the epidemiological importance of asymptomatic individuals is potentially large, challenging the current framework of dengue epidemiology, surveillance, and control. In the absence of symptoms, individuals are likely to continue to work and carry out their usual activities while infected, representing a silent reservoir of the virus with crucial importance in the dynamics of dengue spread.

The disease and economic burdens of dengue are considerable. Quantifying these burdens is essential for policy makers to set priorities, allocate resources, select control and prevention strategies, and evaluate the cost-effectiveness of interventions.[13,24] Coupled with burden estimates, mathematical models can simulate the outcomes of different combinations of interventions, aiding decision making. However, the characteristics of dengue pose major challenges to quantifying these burdens. Additionally, few dengue-endemic countries have good-quality health information systems. Thus, substantial uncertainty exists in current estimates,[25] limiting the potential of these numbers to inform policy decisions.

This Series paper discusses current thinking and evidence on the nature, size, and measurement challenges of the burdens of dengue. We discuss the most recent estimates and the major sources of uncertainty, and reflect on opportunities to remedy these deficiencies, such as alternative data collection methods that leverage ongoing survey efforts in dengue-endemic countries. Lastly, we propose a framework for guiding the estimation of the economic burden of dengue that can contribute to standardisation in future estimates.

## The burden of dengue

The disease burden of dengue is often expressed as the number of infections (with or without symptoms) and as summary metrics that facilitate comparison with other diseases, such as years of life lost to premature mortality, years lived with disability, and disability-adjusted life-years—the latter being a key parameter in calculating the cost-effectiveness of interventions.

The economic burden of dengue can be conceptualised in terms of the costs that dengue infections impose on society, including costs that are directly or indirectly associated with the diagnosis, treatment, outcome, and prevention of disease. Summarising these costs into four domains—illness, surveillance and reporting, control and preventive actions, and outbreak management[13]—suggests that different stakeholders, specifically the government or a private insurer, the individual, or the household, and the broader community, incur these costs. In this context, outbreak refers to the introduction of the disease in areas with no previously reported cases or a significant increase in the number of cases (eg, two standard deviations above the mean of the past 3–5 years).[26] Additionally, the broader community refers to the administrative unit of analysis (eg, state, country) that bears the large-scale costs resulting from dengue infections in the area. Panel 1 illustrates this framework and details the types of costs to consider by domain and by cost-bearing stakeholder. Although we aim to be comprehensive in listing the costs in our proposed framework, quantifying some of these costs is challenging or not feasible, as we will discuss in the next section. Detailed guidelines for estimating some of dengue-related costs in panel 1 have been proposed in the context of Latin America and the Caribbean.[27]

Estimations of the economic burden for one particular country using the proposed framework (panel 1) could also be detailed by broad age groups and major regions. Moreover, because some countries depend heavily on external funding to conduct control strategies, breaking down health provider costs by origin of financial resources would facilitate the estimation of the fraction of the donor's economic burden. Also, comparability across countries requires a clear description of the structure of the health system in each country. For example, Brazil has a unified health system that provides health care free of charge to any individual, and which coexists with a private scheme into which individuals can opt-in. This could result in lower individual or household medical costs when compared with countries that charge a fee for medical services.

The disease burden of dengue has been estimated using different data, analytical methods, and geographical coverage. Although the burden has unquestionably increased in the past two decades, the estimates vary greatly. A commonly cited figure (used by WHO) is 50–100 million annual cases.[8] On the basis of 2010 population data and using geostatistical models, the burden of dengue infections is estimated to be 390 million (95% credible interval [CrI] 284–528) infections per year, with 96 million (95% CrI 67–136) of

**Panel 1: Types of costs by domains of the economic burden of dengue and by stakeholder**

**Domain of economic burden: illness**

*Stakeholder: health provider (public or private)*

- Personnel, equipment, and supplies
- Unit cost of ambulatory care
- Unit cost of admission to and treatment in hospital
- Unit cost of a death
- Comorbidities (diabetes, hypertension, allergy, cardiovascular disease, stroke, respiratory disease, and renal disease)
- In a public system (free services to patients): medical services, diagnostic tests, drugs, and vaccines
- Cost of screening donated blood

*Stakeholder: individual or household*

- Medical costs: co-payment, deductibles, or full payment for medical services, diagnostic tests, and drugs; payment for services at pharmacies
- Traditional medicine costs: healers, and other alternative services
- Non-medical costs: transportation, food, lodging, and other costs related to seeking and obtaining medical care (sick individual and caregiver) and to visiting patients at the hospital (caregiver); travel time; days of school and of work (formal and informal) lost (sick individual and caregiver) because of the immediate and long-term consequences of an infection (absenteeism); reduced capacity and performance at work (formal and informal) and school (presenteeism); need to hire caregivers; loss of household services; burial services; costs related to reduced quality of life such as anxiety, pain, and suffering; costs related to the loss of a family member's life; and interest paid on incurred debt to manage illness

*Stakeholder: community**

- Productivity and tax revenue loss from fatal cases
- Loss in tourism, loss in business travel, and loss in foreign and local investment

**Domain of economic burden: surveillance and reporting**

*Stakeholder: health provider (public or private)*

- Personnel, equipment, and supplies (for both epidemiological and entomological surveillance)
- Laboratory testing
- Database management
- Monitoring and dissemination of information about cases, outbreaks, and deaths

*Stakeholder: individual or household*

- N/A

*Stakeholder: community**

- N/A

**Domain of economic burden: control and preventive actions**

*Stakeholder: health provider (public or private)*

- Vector control, behaviour change campaigns, educational campaigns using different media, activities to promote community engagement, vaccination campaigns
- Personnel, equipment, and supplies
- Research and development of new technologies
- Intersectoral collaborations

*Stakeholder: individual or household*

- Participation in community activities for vector control
- Use of screens, mosquito repellent, insecticides, and air-conditioning as protective measures

*Stakeholder: community**

- N/A

**Domain of economic burden: outbreak management**

*Stakeholder: health provider (public or private)*

- Same as illness domain, plus: community mobilisation; extra personnel, equipment, and supplies; degradation of treatment quality at overloaded health facilities; increase in morbidity from other illnesses because of overloaded health facilities; delays in processing and reporting laboratory results; increased stress in health providers; and increase in nosocomial infections because of crowded facilities
- Intersectoral collaborations

*Stakeholder: individual or household*

- Same as illness domain

*Stakeholder: community**

- Same as illness domain

*Administrative unit of analysis (eg, state, country) that bears the large-scale costs resulting from dengue infections in the area

those causing clinical symptoms.[28] Thus, the estimated number of apparent cases is close to the high end of WHO estimates. Asia, with its large, densely populated areas, is estimated to bear 70% of the burden (67 million infections annually). These numbers are much larger than the figures that countries officially report, leaving it unclear whether the modelling approach is overestimating or underestimating dengue infections.[29]

The Global Burden of Disease Study 2013[30] estimated 58·4 million (95% uncertainty interval 23·6–121·9) apparent dengue cases in 2013, resulting in about 10 000 deaths annually. The number of symptomatic cases lies at the low end of WHO estimates and is much lower than the 2010 estimates by Bhatt and colleagues.[28] Considering the overlap in the wide uncertainty intervals of the two most recent estimates,[28,30] the results are not significantly different, despite the disparity between the point estimates. The Global Burden of Disease Study 2013 also estimates the temporal trend in the burden of dengue, with the number of apparent cases more than doubling each decade between 1990 and 2013.[30] With regard to children in particular, not only is the burden of symptomatic infections high, but a significant fraction of these infections result in hospital admission (ranging from 4·9% to 45·5% in ten Asian and Latin American countries[31]). With regard to deaths, however, the estimates seem low and do not accompany the increasing trend observed in the apparent cases.[25,30] Considering summary metrics, the Global Burden of Disease Study 2013 estimates that dengue was responsible for 1·14 million disability-adjusted life-years in 2013, a 61% increase from 1990.[30,32] Yet many dengue-endemic countries with large populations have insufficient data about deaths.[30] Analysis using data from a surveillance system from Puerto Rico recorded the highest dengue mortality rate ever detected (1·05 per 100 000 people), with particularly high rates among adults (1·66 per 100 000 people aged 65 years or older), and among those with comorbidities.[33] These numbers, however, are still underestimated.

With regard to the economic burden of dengue, only two studies[34,35] produced global estimations of the burden. Using disease burden estimates by Bhatt and colleagues,[28] combined with costs of dengue treatment (provided by WHO) and costs due to lost productivity (provided by the International Monetary Fund), the global economic cost of dengue was estimated to be US$39·3 billion (about $414 per symptomatic case) for 2011.[34] A study by Shepard and colleagues[35] combined data from varied sources (including the Global Burden of Disease Study 2013, household data, expert panel surveys, and empirical cost data) in a modelling exercise that produced the first worldwide estimation of the economic burden of dengue, comparable across countries and regions.[35] The global health burden was estimated to be 58·4 million symptomatic cases, resulting in an estimated global cost of $8·9 billion (95% uncertainty interval 3·7–19·7).[35] Although not without limitations, these studies are needed to support advocacy efforts for intensified and concerted dengue control efforts.[36]

Individual country-level or region-level estimates of the economic burden often vary in several aspects: types of costs considered, number of years of data used, decisions on how to extrapolate the data, choice of cost analysis perspective (provider or societal), geographical coverage, and monetary reference. These differences cause major impediments in comparing the results from studies; nevertheless, estimates of the economic burden show that middle-income and low-income tropical countries, those most affected by dengue, face an enormous burden. A large fraction (50–60%) of the estimated economic costs of dengue relate to productivity losses,[37–39] and vector control is one of the most important burdens on health systems (40–72% of the estimated cost).[24,40,41] The costs of dengue in 12 countries in southeast Asia are comparatively higher than those of other conditions, such as Japanese encephalitis, upper respiratory infections, and hepatitis B infections.[38] Also, the daily cost of illness of a dengue case in India is estimated to be twice the cost per day of illness for a tuberculosis case,[42] and in the Americas the economic burden of dengue surpassed that of other viral diseases, such as human papillomavirus.[37]

Some country-level studies have revealed the substantial economic burden of dengue from the patient's perspective. An assessment of the economic cost of dengue in Puerto Rico[39] showed that households incurred 48% and employers 7% of the total dengue illness cost, whereas the government bore 24% and insurers 22% of the cost. Detailed by setting, households incurred 90% of the cost associated with fatal cases; 21% and 37% of the costs for hospital admission of a child and an adult, respectively; and 51% and 63% of the costs for ambulatory child and adult cases, respectively. Also, estimates of the direct medical costs in India,[42] a country estimated to bear about a third of the global disease burden of dengue,[28] suggest that private sources, mostly households, bore 80% of the cost. As mentioned previously, the burden could vary by country, depending on the finance structure of the health care system. Disentangling the estimates by cost-bearing stakeholders facilitates the assessment of eventual catastrophic medical costs incurred by families.[43]

Uncertainties in the estimation of the burden of dengue reflect problems with data availability and quality, but also raise important points: the burden is without question large and growing; uncertainties in estimating disease burden (ie, infections and deaths) carry over into the estimation of the economic burden of disease; and the larger the uncertainty in estimates, the more serious are the challenges that policy makers face in setting priorities, allocating resources, and planning for interventions.

## Challenges in measuring the burden of dengue

The challenges of measuring the burden of dengue often result in uncertain estimates and hamper cross-country comparisons. Two studies[26,29] discuss in detail several of those challenges and recommend ways to improve dengue burden estimates, particularly the economic burden. We propose a framework to add insights to the discussion (panel 1). We group common challenges into four categories: quantifying the true number of cases, quantifying heterogeneous costs, quantifying cyclical variations, and aiming for a comprehensive assessment of the burden.

The official number of dengue cases and deaths that endemic countries report is often an underestimate for several reasons, including limited availability of information from private health practice;[29] surveillance gaps that fail to detect dengue in symptomatic patients seeking care;[44] individual decisions regarding health-care-seeking behaviour (delaying or avoiding care results in underestimation of cases, but could also lead to complications, severe cases, and death);[45] restricted access to primary health care; insufficient access to sensitive and specific diagnostic tests; failure to recognise

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symptoms and make a diagnosis of dengue;[29] absence of a national health information system (and thus reliance on paper records); and absence of regulations that make dengue a disease of mandatory notification. Calculations of the disease burden of dengue use expansion factors to circumvent this problem.[24,37,38,46] However, applying a constant factor in a country or extrapolating factors from one country to another could lead to estimation problems, because the evidence indicates that the expansion factor varies by age,[47] by the intensity of transmission[44] and transmission season,[48] by disease severity and treatment setting,[49,50] by levels of access to health care,[50] and across countries.[29] Using data from a few areas and generalising for a country could also introduce bias if substantial spatial differences in transmission exist. Also, comparability among countries requires uniformity in case definition,[29] which could be improving as the adoption of the 2009 WHO guidelines[8] expands across dengue-endemic regions.

Differences in purchasing power among countries requires the use of a standardised monetary unit to facilitate comparisons,[37] and results should be analysed in light of the finance structure of the specific health system. Also, compiling data on costs that are heterogeneous in nature is intrinsic to estimating the economic burden of dengue. Doing so requires combining medical costs with vector control expenses, with some monetary measure of productivity loss and reduced quality of life.[24] Some medical costs can be more straightforward to measure if standard fees are charged for services in the public system (not likely in case of private practice), and if governmental dengue-related expenses are distinguished in itemised accounts.

In countries where other vector-borne diseases are endemic, disentangling vector control costs by disease could be impossible,[40] since they target multiple diseases transmitted by the same vector. This is currently the case in Brazil and other countries in the Americas and Asia that are simultaneously dealing with dengue, chikungunya, and Zika viruses, and where *A aegypti* vector control activities might have intensified on an emergency basis to curb the Zika virus epidemic, which could also affect the transmission of dengue and chikungunya, if effective.

Measuring the effect of dengue on productivity is not trivial. Information about the number of days lost at work or at school is not routinely collected. Although self-reported information collected through household surveys can obtain these data, recall bias is possible. Estimates of the cost of a lost day of work can be derived using the human capital approach (based on the gross earnings of an individual) or the friction cost method (based on the cost of hiring replacement labour).[51] However, additional assumptions are needed to estimate costs related to individuals working in the informal sector of the economy. The cost of a day lost at school is sometimes assumed to be the amount spent per child per day in public schools, on the basis of information in the education budget and school enrolment.[39] Even more challenging is estimating the cost of reduced performance at work due to fatigue and other short-term and longer-term consequences of dengue (eg, presenteeism).[52] Although some reports indicate long-term symptoms of dengue, observed only among individuals who had a symptomatic infection, their frequency, duration, and intensity are largely unknown.[38,53] A 2016 study[54] found a substantial burden of persistent dengue symptoms; when considered in burden estimations for Mexico, the economic burden increased by 13% when compared with previous estimates, and the disease burden was 43% higher.

A time series of data is crucial to capture the common cyclical pattern of dengue transmission, facilitating the burden calculation during both endemic and epidemic periods (panel 2).[13,24,37,40] Failure to obtain data for multiple years is likely to result in overestimation or underestimation of the burden of dengue, depending on the epidemiological characteristics of the years considered in the analysis. Additionally, a time series allows for quantifying if, and how, the share of the burden incurred by health providers, households, and society as a whole varies during endemic and epidemic cycles. However, quantifying costs during outbreak years can be difficult for at least two reasons: additional financial resources might be disbursed on an emergency basis, without detailed allocation to specific activities, making categorising the different cost components difficult, and additional costs that are likely to occur during outbreaks are not easily quantifiable through routinely collected data, such as strains on health care from the high volume of patients and associated deterioration of service quality. Indeed, a review by Costenla and colleagues[55] indicated that less than half of studies that estimated the economic burden of dengue considered the costs of outbreaks.

**_Panel 2:_ Comprehensive calculation of the economic burden of dengue**

- Use a time series of data to capture the common cyclical pattern of dengue transmission
- Adopt a common framework that:
    - Decomposes the cost estimate by who bears the burden: the government or a private insurer; the individual, the household, or both; and the broader community
    - Summarises costs in four domains: illness, surveillance and reporting, control and preventive actions, and outbreak management
- Use existing survey efforts (eg, Demographic and Health Surveys) to collect standardised information on dengue, facilitating cross-country comparisons

A comprehensive account of the economic burden of dengue would require considering components not often included in burden estimates. Data availability hinders estimates of the effect of dengue on tourism, mass events like the World Cup and the Olympic Games, business travel, and foreign or local investment. Although statistics on tourists visiting a country might be available, assumptions regarding the nature and duration of the effect would have to be made, such as if the effect on tourism only occurs after outbreaks and, in that case, the length of the effect; and if the effect occurs in any dengue-endemic area, but is larger after outbreaks and during the months of transmission peak. Unless the statistics on tourists include the reason for the travel (eg, work and leisure), estimating the effect of dengue on travel would be quite challenging.

Another important component is the additional cost associated with comorbidities. Evidence exists of an association between dengue haemorrhagic fever and several comorbidities, including diabetes, hypertension, allergy, cardiovascular disease, stroke, respiratory disease, and renal disease.[56–58] Insofar as dengue promotes greater incidence and severity of comorbid diseases and complicates their treatment, the cost of dengue will also increase.

Decomposing the cost estimate by who bears the burden (panel 1) sensitises both the government, which must identify the best strategies to control the disease, and the community, which must engage in control and preventive efforts and be aware of the most appropriate behaviour to avoid proliferation of mosquito-breeding habitats.

## Discussion

Rapid and unplanned urbanisation, global trade and travel, and environmental changes have created a contemporary environment that is extraordinarily well suited to *A aegypti* and thus to transmission of the dengue virus, particularly in tropical and subtropical regions. Currently, more than half of the global population lives in areas with risk of dengue transmission. With no specific drugs for treatment and with vector control efforts unable to curb dengue expansion, the burden of the disease is daunting, irrespective of the uncertainty in estimates.

Thoughtful recommendations have been put forth to mitigate some of the challenges in burden estimation.[26,29] However, information that is not routinely collected (eg, productivity loss) must be assembled through surveys or set on the basis of assumptions that are sometimes highly uncertain. A few cohort studies have been launched in dengue-endemic areas (some connected to vaccine trials), particularly in Asia and Latin America.[41,50,59–63] However, those tend to be costly and are still scarce.[64] With few exceptions, dengue-endemic countries do not have good quality vital registration systems (that could provide numbers on deaths by cause), and have yet to implement national health information systems capable of capturing real-time data on outpatient, inpatient, and laboratory results. This information gap is a major challenge to address; the task, however, demands technical expertise, organised health systems, and financial resources. Although this takes time to be accomplished, it must be initiated now rather than later.

Until the information gap is overcome, nationally (or regionally) representative surveys would be an ideal temporary solution, but, again, many dengue-endemic countries do not have the resources to undertake them. In such a scenario, an alternative is to use the successful model applied for malaria, which used existing survey efforts; since the year 2000, a special module has been added to the Demographic and Health Surveys conducted in malaria-endemic countries. This module gathers data to monitor the progress toward disease control and thus to reduce both morbidity and mortality and facilitate comparative analysis across countries. Similarly, a special module could be designed to gather essential information to estimate the burden of dengue. We argue that a lengthy module would not be needed, but an essential set of questions addressing variables related to productivity loss, community engagement in vector control, health-seeking behaviour (use of private or public health services to treat febrile conditions in children and adults), persistent symptoms of dengue infections, and household arrangements for managing and paying for dengue illness. The inadequate access to sensitive and specific diagnostic tests for dengue and the increasing epidemiological importance of other diseases that are clinically similar to dengue and transmitted by *A aegypti* (eg, chikungunya and Zika viruses) call for better and standardised data collection. This would certainly contribute to a more accurate estimation of disease and economic burdens, and thus better policy decisions and evaluation of interventions.

Some estimates of the disease burden of dengue include assumptions about asymptomatic cases, so that numbers reflect infections, detailed by apparent and non-apparent disease. Quantifying asymptomatic dengue infections requires assumptions and ideally should be informed by cohort studies that conduct serological surveys. Although on average only about one in four infections is symptomatic, this factor varies widely by age, transmission intensity, type of dengue virus, and location.[65–68] Estimates of the economic cost of dengue, however, do not include asymptomatic cases, because those are invisible to the system: asymptomatic individuals do not alter their daily life routine and those infections do not translate into inpatient or ambulatory care. Nevertheless, asymptomatic individuals are more infectious to mosquitoes[23] and thus are epidemiologically important, an aspect that must be addressed in behaviour change and communication campaigns to sensitise the community.

For symptomatic cases, data are often under-reported because of incomplete coverage in case notification and failure in diagnosis (as detailed previously), requiring the

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use of expansion factors for burden estimation. The existence of good health information systems would not resolve this problem, and alternative data sources (such as the Demographic and Health Surveys) would be needed. A comparison between different data sources indicated that passive surveillance provides a better measure of incidence trends (albeit likely to overestimate cases late in the transmission season); sentinel surveillance better captures seasonal outbreaks; and cohort surveys might not necessarily capture a population with similar characteristics to the surveillance data.[48] Thus, combining different data sources, but also using nationally representative data, could offer opportunities to identify correlates of expansion factors that can inform modelling exercises to improve burden estimations (panel 2).

Vector control represents a substantial portion of governmental dengue-related costs. Currently, these costs are for control of *A aegypti* and thus are not uniquely dengue related. Diseases transmitted by *A aegypti* (eg, dengue, Zika, and chikungunya viruses) are likely to present a similar epidemiological curve. Thus, one possibility is to estimate the economic burden of diseases transmitted by *A aegypti* in which the health provider and the community components are consolidated for all diseases, but in which the individual or household is broken down by disease type (to the extent that this is feasible). Additionally, despite the limited efficacy shown so far, environmental management strategies for vector control must persist, but actions should not be under the sole responsibility of ministries of health. Intersectoral collaboration is crucial to increase the return of vector control investments. For example, effective control will never be achieved without widespread access to safe sanitation and the provision of infrastructure and practices that guarantee a steady supply of safe water. Intersectoral collaboration should be considered in the economic burden estimation (panel 1), but like vector control it would also affect other diseases.

A promising tool against dengue is the use of a vaccine, and more accurate burden estimates would lead to better planning of vaccination campaigns and better evaluation of their cost-effectiveness. Even a partially effective vaccine would affect the burden of dengue, reducing the number of new infections and thus reducing many of the costs associated with illness from the perspective of health providers, individuals or households, and society (panel 1). An effective vaccine would be a welcome addition to the limited tools currently available to reverse the growing burden of dengue.[69] A live recombinant tetravalent dengue vaccine that requires three doses is licensed in seven countries (Brazil, Mexico, the Philippines, Indonesia, Costa Rica, Paraguay, and El Salvador) for use in individuals aged 9–45 years. Results from phase 3 trials in Asia and Latin America showed reductions in numbers of severe dengue cases and the need for hospital admission among some groups,[62,70,71] but protective efficacy varied by serotype and presence of antibodies from previous infection at the time of vaccination. Trial results also suggest possible disease enhancement in younger children.[62,72] Research continues with other vaccine candidates.[73–76]

### Search strategy and selection criteria

We found references for this Series paper by searching PubMed, Embase, and Virtual Health Library for articles published until May, 2016, with the terms "dengue", "cost of illness", "dengue/economics", "hospitalization/economics", "public health/economics", "public sector/economics", "costs", "cost analysis", "health expenditures", "health care costs", and "severe dengue/economics". Articles resulting from this search and relevant references cited in those articles were reviewed. Articles published in English and Spanish were included.

**Contributors**

MCC, MEW, and DEB conceptualised the article. MCC and MEW prepared the first draft. All authors provided critical feedback and edits to finalise the manuscript.

**Declaration of interests**

MCC and MEW declare no competing interests. DEB reports grants from Sanofi-Pasteur outside the submitted work.

**References**

1 Halstead SB, O'Rourke EJ. Dengue viruses and mononuclear phagocytes. I. Infection enhancement by non-neutralizing antibody. *J Exp Med* 1977; **146:** 201–17.
2 Simmons CP, McPherson K, Van Vinh Chau N, et al. Recent advances in dengue pathogenesis and clinical management. *Vaccine* 2015; **33:** 7061–68.
3 Tambyah PA, Koay ES, Poon ML, Lin RV, Ong BK. Dengue hemorrhagic fever transmitted by blood transfusion. *N Engl J Med* 2008; **359:** 1526–27.
4 Punzel M, Korukluoğlu G, Caglayik DY, et al. Dengue virus transmission by blood stem cell donor after travel to Sri Lanka; Germany, 2013. *Emerg Infect Dis* 2014; **20:** 1366.
5 de Wazières B, Gil H, Vuitton DA, Dupond J-L. Nosocomial transmission of dengue from a needlestick injury. *Lancet* 1998; **351:** 498.
6 Chen LH, Wilson ME. Transmission of dengue virus without a mosquito vector: nosocomial mucocutaneous transmission and other routes of transmission. *Clin Infect Dis* 2004; **39:** e56–60.
7 Barthel A, Gourinat A-C, Cazorla C, Joubert C, Dupont-Rouzeyrol M, Descloux E. Breast milk as a possible route of vertical transmission of dengue virus? *Clin Infect Dis* 2013; **57:** 415–17.
8 WHO. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization and the Special Programme for Research and Training in Tropical Diseases, 2009.
9 Guzman MG, Harris E. Dengue. *Lancet* 2015; **385:** 453–65.
10 Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. *N Engl J Med* 2012; **366:** 1423–32.
11 Reiner RC, Stoddard ST, Forshey BM, et al. Time-varying, serotype-specific force of infection of dengue virus. *Proc Natl Acad Sciences USA* 2014; **111:** E2694–E702.
12 Gubler DJ. The economic burden of dengue. *Am J Trop Med Hyg* 2012; **86:** 743–44.
13 Suaya JA, Shepard DS, Beatty ME. Dengue burden of disease and cost of illness. In: Report of the Scientific Working Group meeting on dengue. Geneva: World Health Organization, 2006: 35–49.
14 Descloux E, Mangeas M, Menkes CE, et al. Climate-based models for understanding and forecasting dengue epidemics. *PLoS Negl Trop Dis* 2012; **6:** e1470.
15 Liu-Helmersson J, Stenlund H, Wilder-Smith A, Rocklöv J. Vectorial capacity of *Aedes aegypti*: effects of temperature and implications for global dengue epidemic potential. *PLoS One* 2014; **9:** e89783.

16 Suwonkerd W, Mongkalangoon P, Parbaripai A, et al. The effect of host type on movement patterns of *Aedes aegypti* (Diptera: Culicidae) into and out of experimental huts in Thailand. *J Vector Ecol* 2006; **31:** 311–18.
17 Rochlin I, Ninivaggi DV, Hutchinson ML, Farajollahi A. Climate change and range expansion of the Asian tiger mosquito *Aedes albopictus* in northeastern USA: implications for public health practitioners. *PLoS One* 2013; **8:** e60874.
18 Kraemer MU, Sinka ME, Duda KA, et al. The global compendium of *Aedes aegypti* and *Ae albopictus* occurrence. *Sci Data* 2015; **2:** 150035.
19 Lambrechts L, Scott TW, Gubler DJ. Consequences of the expanding global distribution of *Aedes albopictus* for dengue virus transmission. *PLoS Negl Trop Dis* 2010; **4:** e646.
20 Achee NL, Gould F, Perkins TA, et al. A critical assessment of vector control for dengue prevention. *PLoS Negl Trop Dis* 2015; **9:** e0003655.
21 Ritchie SA, Townsend M, Paton CJ, Callahan AG, Hoffmann AA. Application of *w*MelPop *Wolbachia* strain to crash local populations of *Aedes aegypti*. *PLoS Negl Trop Dis* 2015; **9:** e0003930.
22 Lambrechts L, Ferguson NM, Harris E, et al. Assessing the epidemiological effect of wolbachia for dengue control. *Lancet Infect Dis* **2015:** 862–66.
23 Duong V, Lambrechts L, Paul RE, et al. Asymptomatic humans transmit dengue virus to mosquitoes. *Proc Natl Acad Sci USA* 2015; **112:** 14688–93.
24 Carrasco LR, Lee LK, Lee VJ, et al. Economic impact of dengue illness and the cost-effectiveness of future vaccination programs in Singapore. *PLoS Negl Trop Dis* 2011; **5:** e1426.
25 Wilder-Smith A, Byass P. The elusive global burden of dengue. *Lancet Infect Dis* 2016; **16:** 629–31.
26 Armien B, Arredondo J, Carabali M, et al. Costing dengue cases and outbreaks: a guide to current practices and procedures. Baltimore: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health, 2012.
27 Constenla D, Armien B, Arredondo J, et al. Costing dengue fever cases and outbreaks: recommendations from a costing dengue working group in the Americas. *Value Health Reg Issues* 2015; **8:** 80–91.
28 Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. *Nature* 2013; **496:** 504–07.
29 Shepard DS, Undurraga EA, Betancourt-Cravioto M, et al. Approaches to refining estimates of global burden and economics of dengue. *PLoS Negl Trop Dis* 2014; **8:** e3306.
30 Stanaway JD, Shepard DS, Undurraga EA, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis* 2016; **16:** 712–23.
31 L'Azou M, Moureau A, Sarti E, et al. Symptomatic dengue in children in 10 Asian and Latin American countries. *N Engl J Med* 2016; **374:** 1155–66.
32 Hotez PJ, Alvarado M, Basáñez M-G, et al. The Global Burden of Disease Study 2010: interpretation and implications for the neglected tropical diseases. *PLoS Negl Trop Dis* 2014; **8:** e2865.
33 Tomashek KM, Rivera A, Torres-Velasquez B, et al. Enhanced surveillance for fatal dengue-like acute febrile illness in Puerto Rico, 2010–2012. *PLoS Negl Trop Dis* 2016; **10:** e0005025.
34 Selck FW, Adalja AA, Boddie CR. An estimate of the global health care and lost productivity costs of dengue. *Vector Borne Zoonotic Dis* 2014; **14:** 824–26.
35 Shepard DS, Undurraga EA, Halasa YA, Stanaway JD. The global economic burden of dengue: a systematic analysis. *Lancet Infect Dis* 2016; **16:** 935–41.
36 Jit M. The economic burden of dengue: no longer invisible or unavoidable. *Lancet Infect Dis* 2016; **16:** 873–74.
37 Shepard DS, Coudeville L, Halasa YA, Zambrano B, Dayan GH. Economic impact of dengue illness in the Americas. *Am J Trop Med Hyg* 2011; **84:** 200–07.
38 Shepard DS, Undurraga EA, Halasa YA. Economic and disease burden of dengue in southeast Asia. *PLoS Negl Trop Dis* 2013; **7:** e2055.
39 Halasa YA, Shepard DS, Zeng W. Economic cost of dengue in Puerto Rico. *American J Trop Med Hyg* 2012; **86:** 745–52.
40 Castañeda-Orjuela C, Díaz H, Alvis-Guzman N, et al. Burden of disease and economic impact of dengue and severe dengue in Colombia, 2011. *Value Health Reg Issues* 2012; **1:** 123–28.
41 Undurraga EA, Betancourt-Cravioto M, Ramos-Castaneda J, et al. Economic and disease burden of dengue in Mexico. *PLoS Negl Trop Dis* 2015; **9:** e0003547.
42 Shepard DS, Halasa YA, Tyagi BK, et al. Economic and disease burden of dengue illness in India. *Am J Trop Med Hyg* 2014; **91:** 1235–42.
43 Beatty ME, Beutels P, Meltzer MI, et al. Health economics of dengue: a systematic literature review and expert panel's assessment. *Am J Trop Med Hyg* 2011; **84:** 473–88.
44 Silva MMO, Rodrigues MS, Paploski IAD, et al. Accuracy of dengue reporting by national surveillance system, Brazil. *Emerg Infect Dis* 2016; **22:** 336.
45 Elsinga J, Lizarazo EF, Vincenti MF, et al. Health seeking behaviour and treatment intentions of dengue and fever: a household survey of children and adults in Venezuela. *PLoS Negl Trop Dis* 2015; **9:** e0004237.
46 Suaya JA, Shepard DS, Siqueira JB, et al. Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. *Am J Trop Med Hyg* 2009; **80:** 846–55.
47 Meltzer MI, Rigau-Pérez JG, Clark GG, Reiter P, Gubler DJ. Using disability-adjusted life years to assess the economic impact of dengue in Puerto Rico: 1984–1994. *Am J Trop Med Hyg* 1998; **59:** 265–71.
48 Olkowski S, Stoddard ST, Halsey ES, Morrisson AC, Barker CM, Scott TW. Sentinel versus passive surveillance for measuring changes in dengue incidence: evidence from three concurrent surveillance systems in Iquitos, Peru. Feb 19, 2016. http://www.biorxiv.org/content/early/2016/02/18/040220 (accessed Dec 8, 2016).
49 Undurraga EA, Halasa YA, Shepard DS. Use of expansion factors to estimate the burden of dengue in southeast Asia: a systematic analysis. *PLoS Negl Trop Dis* 2013; **7:** e2056.
50 Wichmann O, Yoon IK, Vong S, et al. Dengue in Thailand and Cambodia: an assessment of the degree of underrecognized disease burden based on reported cases. *PLoS Negl Trop Dis* 2011; **5:** e996.
51 WHO. WHO guide for standardization of economic evaluations of immunization programmes. Geneva: World Health Organization, 2008.
52 Bärnighausen T, Bloom DE, Cafiero ET, O'Brien JC. Valuing the broader benefits of dengue vaccination, with a preliminary application to Brazil. *Semin Immunol* 2013; **25:** 104–13.
53 García G, González N, Pérez AB, et al. Long-term persistence of clinical symptoms in dengue-infected persons and its association with immunological disorders. *Int J Infect Dis* 2011; **15:** e38–43.
54 Tiga DC, Undurraga EA, Ramos-Castaneda J, Martinez-Vega RA, Tschampl CA, Shepard DS. Persistent symptoms of dengue: estimates of the incremental disease and economic burden in Mexico. *Am J Trop Med Hyg* 2016; **94:** 1085–89.
55 Constenla D, Garcia C, Lefcourt N. Assessing the economics of dengue: results from a systematic review of the literature and expert survey. *Pharmacoeconomics* 2015; **33:** 1107–35.
56 Figueiredo MA, Rodrigues LC, Barreto ML, et al. Allergies and diabetes as risk factors for dengue hemorrhagic fever: results of a case control study. *PLoS Negl Trop Dis* 2010; **4:** e699.
57 Pang J, Salim A, Lee VJ, et al. Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study. *PLoS Negl Trop Dis* 2012; **6:** e1641.
58 Toledo J, George L, Martinez E, et al. Relevance of non-communicable comorbidities for the development of the severe forms of dengue: a systematic literature review. *PLoS Negl Trop Dis* 2016; **10:** e0004284.
59 Endy TP, Yoon I-K, Mammen MP. Prospective cohort studies of dengue viral transmission and severity of disease. In: Rothman LA, ed. Dengue virus. Berlin, Heidelberg: Springer Berlin Heidelberg; 2010: 1–13.
60 Comach G, Blair PJ, Sierra G, et al. Dengue virus infections in a cohort of schoolchildren from Maracay, Venezuela: a 2-year prospective study. *Vector Borne Zoonotic Dis* 2009; **9:** 87–92.
61 Restrepo BN, Piedrahita LD, Agudelo IY, Parra-Henao G, Osorio JE. Frequency and clinical features of dengue infection in a schoolchildren cohort from medellin, Colombia. *J Trop Med* 2012; published online Dec 13. DOI:10.1155/2012/120496.
62 Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *N Engl J Med* 2015; **373:** 1195–206.
63 Sarti E, L'Azou M, Mercado M, et al. A comparative study on active and passive epidemiological surveillance for dengue in five countries of Latin America. *Int J Infect Dis* 2016; **44:** 44–49.

64 Harpham T, Huttly S, Wilson I, Wet T. Linking public issues with private troubles: panel studies in developing countries. *J Int Dev* 2003; **15:** 353–63.

65 Yap G, Li C, Mutalib A, Lai Y-L, Ng L-C. High rates of inapparent dengue in older adults in Singapore. *Am J Trop Med Hyg* 2013; **88:** 1065–69.

66 Gordon A, Kuan G, Mercado JC, et al. The Nicaraguan Pediatric Dengue Cohort Study: incidence of inapparent and symptomatic dengue virus infections, 2004–2010. *PLoS Negl Trop Dis* 2013; **7:** e2462.

67 Endy TP, Chunsuttiwat S, Nisalak A, et al. Epidemiology of inapparent and symptomatic acute dengue virus infection: a prospective study of primary school children in Kamphaeng Phet, Thailand. *Am J Epidemiol* 2002; **156:** 40–51.

68 Chastel C. Eventual role of asymptomatic cases of dengue for the introduction and spread of dengue viruses in non-endemic regions. *Front Physiol* 2012; **3:** 70.

69 Rodriguez-Barraquer I, Mier-y-Teran-Romero L, Schwartz IB, Burke DS, Cummings DA. Potential opportunities and perils of imperfect dengue vaccines. *Vaccine* 2014; **32:** 514–20.

70 Capeding MR, Tran NH, Hadinegoro SR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* 2014; **384:** 1358–65.

71 Villar L, Dayan GH, Arredondo-García JL, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015; **372:** 113–23.

72 Simmons CP. A candidate dengue vaccine walks a tightrope. *N Engl J Med* 2015; **373:** 1263–64.

73 Durbin AP, Kirkpatrick BD, Pierce KK, et al. A single dose of any of four different live attenuated tetravalent dengue vaccines is safe and immunogenic in flavivirus-naive adults: a randomized, double-blind clinical trial. *J Infect Dis* 2013; **207:** 957–65.

74 Osorio JE, Huang CYH, Kinney RM, Stinchcomb DT. Development of DENVax: A chimeric dengue-2 PDK-53-based tetravalent vaccine for protection against dengue fever. *Vaccine* 2011; **29:** 7251–60.

75 Coller B-AG, Clements DE, Bett AJ, Sagar SL, Ter Meulen JH. The development of recombinant subunit envelope-based vaccines to protect against dengue virus induced disease. *Vaccine* 2011; **29:** 7267–75.

76 Beckett CG, Tjaden J, Burgess T, et al. Evaluation of a prototype dengue-1 DNA vaccine in a phase 1 clinical trial. *Vaccine* 2011; **29:** 960–68.