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Costing Dengue Fever Cases and Outbreaks: Recommendations from a Costing Dengue Working Group in the Americas

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ABSTRACT

Objectives: The overall aim of this article was to present a step-by-step guideline for determining the costs associated with dengue in dengue-endemic countries of the Latin American and the Caribbean region and to illustrate how each of these steps can be applied in dengue costing studies. **Methods:** An expert panel was convened to develop standards for costing dengue so that over the next decade, decision makers will have access to improved information on the true cost of dengue in endemic countries of the Latin American and the Caribbean region. We described the outcome of the expert panel meeting, which resulted in the provision of a step-by-step dengue costing guideline that aims to provide direction to planners and program managers on how to estimate dengue economic burden studies, and provide a discussion forum of the methods used to cost dengue fever cases and outbreaks in a manner that should be accessible to persons with some familiarity

with a cost study. **Results:** The guideline includes nine sequential steps: 1) definition of the scope of the study; 2) identification of the target population; 3) description of the study perspective; 4) definition of the time horizon; 5) calculation of the sample size; 6) definition of the unit of analysis; 7) identification of the cost items; 8) measurement and valuation of the cost items; and 9) handling of uncertainty. The trade-off between accurate, patient-level cost estimates and data availability constraints is discussed. **Conclusions:** The current guideline is the result of constructive collaboration among a multidisciplinary research team to better ascertain the true economic burden of dengue across countries of the region.

Keywords: costing, dengue fever cases, dengue outbreaks.

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Background

Dengue is the vector-borne viral infection most widely and further spread in the world, representing a severe public health problem. Dengue is caused by one of four serotypes (Denv1, Denv2, Denv3, and Denv4), transmitted by several species of mosquito within the genus *Aedes aegypti*. This disease has no boundaries or limits, affecting populations of all ages and socio-economic levels. It is estimated that 390 million dengue infections are reported every year, with 70% of the 96 million clinical dengue infections reported occurring in Asia, followed by 16% in Africa and 14% in the region of Latin America and the Caribbean

[1]. The dramatic increase in dengue cases is due to a number of factors, including population growth, urbanization, and increased international travel. Dengue has a high social and economic impact, affecting not just the patient but also the family and the community in which those affected by dengue live. The true economic cost of the disease is unknown; however, it is believed to range from US \$13.5 million (Nicaragua) to US \$56 million (Malaysia) [2].

Limited research has been done to estimate the costs of dengue in the Latin American and Caribbean region. In a recent review of the literature, only a handful of economic studies were found in the region [2]. The studies reviewed indicated an

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important variation in dengue cost estimates due to differences in case classification, definition of cost categories, sampling, data sources, and other methodological challenges. In addition, the published literature shows that studies looking at dengue cost estimates are not of sufficient quantity and quality. It is not always clear from these economic studies which form of treatment associated with dengue is costed, what is included in the total cost estimation of dengue, and how these estimates are calculated. Moreover, cost estimates from these studies are of heterogeneous (mixed) quality, not generalizable to other populations, and not representative of the total economic consequences of dengue.

These methodological issues are compounded by the absence of well-established guidelines for costing diseases such as dengue. Efforts by governments and health care systems in the United States, Europe, Asia, Latin America, and the Caribbean to harmonize approaches to economic evaluation are ongoing, but the task is challenging. With governments and health care systems continuing to take an independent line on evaluation, the scientific community is left in a difficult position, given the international basis of its research activities [3]. The impetus of conducting dengue cost studies is that they can be used as inputs into cost-effectiveness analyses to provide important information about efficient resource allocation and health care financing [4–6].

Cost studies can be performed across various delivery settings, such as hospitals or primary care centers; in different geographic areas, from urban to rural hospitals and primary care centers; and in different socioeconomic settings, from high-income households to low-income households [2]. Because of the limited research that has been done to estimate dengue costs across various health care delivery settings, geographic areas, and socioeconomic settings, and to estimate the consequences of dengue in settings outside the health care system (e.g., tourism), there is little development of the necessary underlying theory of economic costs of dengue and limited data systematically collected for this purpose are available.

Many guidelines have been developed to direct the design and conduct of economic studies, comprising an analysis of the costs and effects of an intervention. Most of the guidelines are from developed countries [6–9], where data are more readily available, and are not disease-specific. From preliminary discussions with experts in the region, we found a few country-specific economic evaluation guidelines in dengue-endemic countries of the region [10–12]. The overriding constraint when costs are estimated in these settings is the lack of financial records and incomplete patient disease registers, as well as the limited expertise in conducting costing studies. These issues are compounded by the fact that there is little consensus on which guidelines to adopt to estimate the true costs of disease.

In response to the growing need for dengue cost estimates to inform future vaccine introduction, an expert panel was convened on March 6–8, 2012 to discuss and develop a standardized methodology for estimating costs of dengue in the Americas [13].

Aim and Objectives

The overall aim of this article was to present a step-by-step guideline for determining the costs associated with dengue in dengue-endemic countries of the region and to illustrate how each of these steps can be applied in dengue costing studies. The guideline is regional in scope and includes nine sequential steps: 1) definition of the scope of the study; 2) identification of the target population; 3) description of the study perspective; 4) definition of the time horizon; 5) calculation of the sample size; 6) definition of the unit of analysis; 7) identification of the cost

items; 8) measurement and valuation of the cost items; and 9) handling uncertainty. Because a cost study has many different methodological components built from extensive theoretical and operational evidence of their comprising disciplines, it is not possible to cover all the diverse dengue-related costing issues. Only areas of priority to the expert panel are highlighted in this article [13].

Methods

On the basis of a systematic review of the literature and an expert survey described elsewhere [2], we developed a framework to cost dengue cases and outbreaks in the Americas. Two key elements were central to the development of this framework: 1) the type of standard methods needed to capture the true economic cost of dengue, and 2) the type of cost information that is most useful to making public health policies to counter dengue infections. We convened a panel of experts to identify methodological gaps in this area and discuss recommendations to measure the true cost of dengue. The overall approach used to develop the guideline is discussed elsewhere [13].

In brief, the guideline was developed using a stepwise approach starting with a provisional guideline developed by a multidisciplinary group of experts who attended a workshop in 2012. The guideline was based on existing evidence and extensive small and large group discussions and formal didactic sessions. A working group was then formed to review recommendations from the guideline, address common methodological issues when costing dengue, and assess the scientific validity of the guideline. Much like the original expert panel convened for the workshop, the working group was composed of health economists from various countries in the Americas, including epidemiologists, entomologists, program managers, and policymakers with background or expertise in dengue or dengue economics.

Defining Dengue

The lack of accuracy around dengue cost estimates is in large part due to the uncertainty of what to measure. There is considerable uncertainty surrounding the case and outbreak definitions, and what definitions are known vary across countries and regions. Experts agreed about the need to be explicit and consistent about the use of the dengue case definition and to distinguish where these cases are being reported (e.g., ambulatory vs. hospitalized dengue cases) because the costs differ across settings, and to characterize how these cases are being reported (e.g., suspected dengue cases, probable dengue cases, and confirmed dengue cases). In this section, we discuss dengue case and outbreak definitions based on in-depth expert discussions and address some of the key challenges of defining dengue.

Dengue Cases

Measurement of the local burden of disease is an essential component of dengue cost evaluations. When data on disease burden are lacking, policymakers may perceive that the disease is not important and the benefits of prevention and control strategies (e.g., vector control and vaccines) will not be appreciated. To estimate the burden of dengue, key outcomes of infection need to be identified. Difficulties arise because of inconsistencies in case definitions for dengue, overlapping clinical features with other illnesses, nonspecific and/or expensive diagnostic tools, and reliance on verbal autopsy to estimate mortality figures.

Although population-based studies provide the best current estimates of dengue burden in the region, more comprehensive information on the amount of dengue is likely to be provided by phase III efficacy trials. It is possible that, as is the case with many clinical trials, results of previous studies will prove to be significant underestimates of the true burden of dengue. Furthermore, disease burden may be underestimated in the vaccine trial because of the high specificity of case definitions.

Ideally, data on disease burden should be available from all countries to ensure that decision makers appreciate the true economic consequences of dengue and the potential benefits of control and prevention strategies in their setting. In reality, however, given the difficulties that exist in establishing disease surveillance, this is unlikely to ever be the case. It is therefore important that surveillance be instituted on a regional basis and that case definitions used in clinical trials be standardized to facilitate transfer of results.

Over recent decades, there has been extensive debate regarding dengue case definitions. The World Health Organization (WHO) case classification of dengue fever, dengue hemorrhagic fever, and dengue shock syndrome was originally formulated in 1974 by a technical advisory committee on the basis of studies of disease patterns in patients in Thailand in the 1960s [14]. Some modifications to this definition were made in 1997 [14], and in 2006, the WHO Dengue Scientific Working Group recommended additional research into dengue diagnostics and triaging of patients for optimized clinical management [15].

A revised guideline was proposed in 2009 following the 2006 modifications to account for the geographic expansion of dengue and its increased incidence in older age groups [16,17], and current practices in case treatment, hospital laboratory, and dengue diagnostic methods [14]. The revised 2009 WHO dengue case definitions classified the illness into dengue with and without warning signs and severe dengue. Although the 2009 revisions were more sensitive to the diagnosis of severe dengue, and beneficial to triage and case management, this classification system was not universally applicable for appropriate clinical management [18–25].

The 11th revision of the *International Classification of Diseases* [25] is considering the inclusion of this new classification. During this transition phase, some countries of the region plan to use the previous classification (revised 2009 WHO case definition); others will adopt the new classification (2011 WHO case definition) or a modified version of this definition. It is unclear, however, how these countries will adapt these case definitions into their ongoing surveillance programs. The Pan-American Health Organization (PAHO), through the Dengue Regional Program, supports member states in the implementation of the Integrated Management Strategy for the Prevention and Control of Dengue [26] in which case definition is part of the integrated strategy for the surveillance of and preparedness for dengue cases and outbreaks.

Given that the dengue classification is changing, the expert panel recommends that the approach for costing dengue cases should be explicit to discriminate at least two types of dengue cases: cases that are treated in ambulatory settings and cases that are treated in hospital settings. In addition, dengue cases should be further stratified into suspected (clinically diagnosed) cases, probable cases, and laboratory-confirmed cases. Considerations need to be made, however, when stratifying dengue into suspected, probable, and laboratory-confirmed cases: 1) not all countries have adopted the WHO/PAHO case definition or agree with the new case definition, and 2) not all countries have the capacity to provide laboratory confirmation; therefore, a standard for case definition should not be based solely on laboratory confirmation but on clinical observation as well. All experts agreed that the old definition of dengue hemorrhagic fever

should not be used and that confirmed and unconfirmed cases should be costed separately.

Dengue Outbreaks

The International Research Consortium on Dengue Risk Assessment, Management and Surveillance [27] has been seeking consensus on the technical definition of an outbreak with the intent to use the definition for discovery, epidemiologic, or diagnostic purposes in the absence of confirmatory laboratory tests. In the absence of a clear definition, the expert panel defined a dengue outbreak as the number of cases representing two standard deviations (SDs) away from the mean of cases. The WHO uses a similar definition when describing the process of triggering an outbreak alert where it tracks the occurrence of current (probable) cases and compares them with the average number of cases by week (or month) of the preceding 5 to 7 years, with confidence intervals set at two SDs above and below the average (± 2 SD) [24]. This is sometimes referred to as the “endemic channel,” in which an outbreak alert is triggered if the number of cases reported exceeds two SDs above the endemic channel in weekly or monthly reporting. This, however, is not an official dengue outbreak definition.

The expert panel agreed that a dengue outbreak can also mean the confirmation of one or more locally acquired dengue cases. In this case, one case in an area where no other case has been reported could be considered an outbreak. Many countries in the region have used this definition, but the number of locally acquired confirmed dengue cases differs by country and currently there is no standard definition of a dengue outbreak. Dengue outbreaks range from a few cases in an urban area through to large-scale outbreaks with hundreds of cases across the region. The approach for costing dengue outbreaks should be similar to the one applied for costing dengue cases—that the process of defining a dengue outbreak should be explicit. There are, however, important differences between suspected cases of dengue occurring during an outbreak and probable dengue cases and confirmed dengue cases occurring during an outbreak.

Systematic Approach to Estimate the Socioeconomic Costs of Dengue

The impetus for cost studies is to inform the community about the economic consequences of dengue. Although the number of published economic studies has increased substantially over the past two decades, the quality of these studies has been questioned [2], and their influence on program implementation remains uncertain. Furthermore, many endemic countries do not have the resources or finances needed to perform detailed cost studies. Thus, it is important to promote the use of generalized approaches to conducting these studies.

Guidelines for estimating costs can be used to plan various aspects of a cost study including the selection of the sample frame for data collection and the target population; the collection of resource utilization and unit cost data; the estimation of the national economic burden of a disease; and the incorporation of these data into a cost-effectiveness analysis of preventive interventions, in particular dengue vaccination and vector-control strategies. Developing guidelines for the purpose of estimating costs of dengue is an empiric process. Although it is helpful to consider certain core principles in deriving guidelines, the application of these principles is a complex process that requires innovative approaches to tackling the myriad of potential factors involved. Central to the development of costing guidelines is a clear understanding of the terminology used in costing, cost

categories, and study designs used to document the cost impact of diseases and disease interventions. The following is a discussion of this process.

Costs and Cost Categories

The terminology used in costing can often be confusing. In much of the existing literature, the terms “direct,” “indirect,” and “intangible” have been used to classify the costs (and benefits) associated with an intervention. The term “direct” generally refers to changes in resource use (and health) attributable to the intervention. The term “indirect” is commonly used to denote time and productivity lost or gained because of the intervention. Other definitions of costs have been used, including direct medical costs (savings), referring to those resources used (averted) because of the intervention, such as treatment costs averted; direct nonmedical costs (or non-health care) refer to costs that are associated directly with provision of medical services but are non-medical, including travel, and childcare costs. In view of inconsistencies in definitions used across studies and differing interpretation across professional fields, the expert panel recommended the use of the following terminology: costs of disease (health care, non-health care costs), costs associated with an intervention, and costs associated with foregone productivity.

Costs of disease include the costs directly related to treatment (e.g., physician services, ambulatory and hospital care, antibiotic therapy, laboratory and diagnostic studies, surgical procedures, nursing, and supplies). These costs are also referred to as direct health care costs or direct medical costs. Also included in this category are care costs for parents of sick children attending the hospital or clinic, transport costs to and from the hospital or clinic, costs of over-the-counter medications, and home care costs. These are referred to as direct non-health care costs or direct nonmedical costs.

Costs associated with an intervention include the intervention costs, costs to participants of the intervention, and costs associated with side effects (or adverse events) of the intervention. The costs of the intervention comprise the price of the intervention, supplies and equipment, facilities, and storage. The costs to participants include all out-of-pocket expenses and productivity losses resulting directly from the intervention. Finally, the costs associated with side effects are related to the intervention itself.

Costs associated with foregone productivity resulting from an intervention and its consequences can be considered, as well as the cost of personal care to patients and their families, travel or informal care, and fixed intervention costs resulting from the intervention and its consequences. Loss of productivity that can arise from reduced productivity of working parents of individuals who have dengue should also be considered as are costs associated with lost or impaired ability to work or enjoy other activities or days absent from preschool due to disease. Commonly, this important component is omitted in the calculation of disease costs because it is more difficult to calculate than production losses. There are often problems associated with the estimation of indirect costs. These difficulties are partly attributable to the fact that indirect costs are borne by the individuals and their families whereas direct (medical) costs are generally incurred by public agencies and hence are more readily valued and measurable. Despite difficulties in estimating indirect costs in cost studies, it is a worthwhile process at the very least to establish the order of magnitude of such costs.

A related issue, probably of importance in some countries, is the inclusion of benefit payments for disability or sickness. These are generally considered to be “transfer payments” and not economic costs from a broad societal perspective. They may,

however, be important from a government regulatory perspective. The importance of obtaining information on different cost categories and/or benefit payments in individual countries, by means of a further side study of a subsample of infants and young children, should be considered when costing dengue as part of a country requirement.

The order of magnitude of the costs (disease-related, intervention-related, and costs of productivity foregone) varies widely. Some differences may be accounted for by the fact that cost studies are conducted in different settings and different cost components are considered for diseases such as dengue. Cost differences can also be attributable to their exclusion of some or all disease and/or intervention costs and possible exclusion of important costs associated with foregone productivity. This raises the issue of what costs to include in cost studies. Although in theory all relevant costs should be included, in practice there is a limit to what can be identified and measured. The choice of which type of costs to include in the evaluations is country-specific; therefore, categories of costs specific to each country need to be developed. In addition, guidelines should be developed to value these cost categories differently.

Financial Costs and Economic Costs

In cost studies, costs should be considered at their opportunity value. Cost in economic terms is defined as the value of resources that have been foregone for alternative uses. Economic costs include the true costs of a disease. The use of economic (opportunity) cost is optimal because this is the most accurate way of valuing resource use. There are, however, major challenges in estimating the opportunity costs. In contrast, financial costs (charges or shadow prices [prices that have been adjusted to yield economic costs]) are generally considered in the absence of opportunity costs.

There are important differences between financial costs and economic costs. Financial costs represent the actual expenditure on goods and services purchased and are therefore described in terms of how much money has been paid for the resources used, whereas economic (opportunity) costs are values of the lost benefit because the resource is not available for its next best use. Using cost data that are financial in nature may be practical though care must be taken to be clear when financial data are used. The expert panel recommends the use of financial cost data from a practical standpoint (when opportunity costs are not available). They also recommend the use of the economic (opportunity) costs when data availability and time allow.

Marginal and Average Costs

There are important differences between marginal (incremental) costs and average costs. The marginal (incremental) cost is the change in the total costs that arises when the quantity produced changes by one unit; that is, the additional cost of producing one more unit of good. Many difficulties can stem from the estimation of marginal costs because costs of intervention programs and annual increases of resources are often unknown.

The average cost considers both the fixed and variable costs without any consideration to changes in costs. Average costs typically include the total costs of an intervention, regardless of pre-existing structures or levels of provision, divided by the number of persons affected by the intervention. Such costs are generally higher than marginal costs because they do not account for preexisting structures or levels of provision common to intervention programs. The expert panel recommends the use of the incremental costing and the use of the average cost per

case (rather than the total cost) because they recognize that obtaining fixed costs can be difficult.

Economic Study Methods

A number of techniques focus on disease, intervention, and productivity foregone cost estimations. These include cost consequence analysis, cost minimization analysis, and cost-of-illness (COI) study. These techniques differ in the extent to which they measure and value disease, intervention, and productivity foregone costs. The cost consequence analysis is a form of economic evaluation that presents the costs and consequences of interventions in a natural unit of effect but are reported separately (costs and consequences are not combined). Another form of economic evaluation is a cost minimization analysis, and the aim of this evaluation is to find the least costly program among those shown or assumed to be of equal benefit. The COI study identifies and evaluates the direct and sometimes indirect and intangible costs of a particular disease or risk factor. The expert panel discussed the methodology of the COI study specifically because of its relevance to the guidelines.

COI studies estimate the total costs attributable to a particular disease rather than a particular intervention. The aim of COI studies is to establish the true level of the economic burden imposed by a particular disease so that informed choices can be made regarding health care resource allocation. This form of study identifies those elements of cost that might be reduced by more effective new treatment. In diseases such as dengue, in which treatment prevents or controls the number of infections transmitted, the effect of new treatment may be to reduce disease episodes or disease severity.

One of the benefits of COI studies is identifying the illnesses that consume the most health care resources and broader societal perspectives. This form of study introduces an estimate of the scale of medical problems in terms of the amount of spending. COI studies, however, have often been criticized for not addressing the value for money question. In addition, these studies do not provide any indication of how to improve the economic value of disease intervention; they do not compare alternative uses of resources. Instead, they consider the costs of resources consumed in an intervention or disease. In particular, a high proportion of direct costs used are often in areas that would not be affected by new treatments; that is, COI does not identify the potential to achieve gains. Nevertheless, it is important to be aware of the costs attributable to dengue, particularly if potential cost savings could be realized through new and innovative interventions.

There are two distinct approaches to undertaking a COI study: the prevalence approach and the incidence approach. These approaches refer to the manner in which costs are attributed to a particular disease. The prevalence-based cost would estimate the costs attributable to all individuals suffering from dengue in a given year. In contrast, an incidence-based cost study would estimate the present value of the lifetime costs of all individuals newly diagnosed with dengue in a given year. The incidence approach is more precise but has more information needs and is more costly to perform. This approach is generally used to cost infectious diseases because of their short duration and fluctuation of incidence. The key difference in these two approaches is the choice of variables or model parameters and outcomes measured.

In the following pages we present a step-by-step guide for estimating dengue. This guide provides considerable information on the estimation of aggregate costs. Although aggregate costs are extremely valuable for a number of purposes, as an indicator of the overall economic burden borne by the community as a result of dengue, they indicate neither the proportion of such costs that are potentially avoidable nor the nature of the

programs and policies best suited to achieve this cost avoidance. The current step-by-step guide does not explicitly consider economic evaluations because regional experts considered the need for dengue-specific costing guidelines a priority. Future versions of the guideline may address other forms of economic evidence related to dengue. [Table 1](#) describes the steps of the dengue costing guideline.

Step-by-Step Guide

The expert panel agreed that the step-by-step guide should be based on existing recommendations and should be disease-specific. This is to avoid bias and allow comparisons of other methodologies when possible. In addition, the guide should be practical to apply in settings with limited data availability, incomplete patient disease registers, and limited expertise or experience in conducting costing studies. The following text describes the step-by-step recommendations that include nine sequential steps.

Step 1: Defining the Scope of the Analysis

The first step to conducting a cost study is to frame the analysis. Framing the analysis involves defining the problem and the scope and adopting a research strategy. Decisions made at this stage will determine which costs are considered relevant and should therefore be included in the analysis. Planning a disease-specific costing study requires detailed review of local disease burden, its epidemiology, and knowledge of the decision space. The definition of the scope of the study is driven primarily by the decision problem. For example, if a local stakeholder wants to have an understanding of the true economic burden of dengue in his or her country, country-specific estimates of dengue cases and outbreaks may need to be estimated for at least 1 year. The perspective(s) chosen in this case would be the societal perspective to include the health care costs and the costs outside the formal health care. The measures of resource use and costs would be in accordance with the perspective chosen. The public sector, as well as the private, social insurance, and intersectoral sectors, should be considered in the analysis to allow for various cost components to be estimated. For example, in the intersectoral sector, it would be important to consider the costs associated with prevention and control strategies, tourism costs, and other industries. The scope of the study is also defined by the availability of information (e.g., patient costs, household costs, institution costs, and state-level costs) and the need to bring information together for policy.

Step 2: Identifying the Target Population

The target population should be the population exposed to dengue disease, which can be defined by geographic area; age group; and the presence of vectors, transmission, and virus circulation. Geographic areas can be different if the objective is to have an estimate of the cost per case, the cost per outbreak, or the cost associated with a surveillance program. For example, for the cost per case, the geographic areas will depend on the national health care system. If no difference in cost per case exists across geographic areas, an endemic area should then be chosen to capture an adequate number of dengue cases in a defined time period.

In terms of age groups, a modified PAHO age group stratification system should be considered. The following stratification was proposed by experts: 0- to 4-year-olds, 5- to 9-year-olds, 10- to 19-year-olds, 20- to 59-year-olds, and those older than 60 years. A further classification of 10- to 14-year-olds and 15- to 19-year-olds should also be considered to account for the sizeable burden of disease in these age groups in certain countries (e.g., in

Table 1 – Step-by-step guideline for costing dengue cases and outbreaks.

Steps	Recommendations
Step 1: Define scope of analysis	Criteria: knowledge of disease burden, availability of data and reproducible tools, surveillance system in place, assessment of social impacts. Public sector: entomological surveillance, epidemiological surveillance, prevention and control, management practice. Private sector: epidemiological surveillance (active/passive), management practice. Social insurance sector: epidemiological surveillance (active/passive), management practice, death-related. Intersectoral sector: prevention and control, tourism, finance, death-related. Scope of analysis depends on the study objective but generally includes the cost to the patient, household, institution, state, and others.
Step 2: Identify target population	Target population stratified: 0–4 y, 5–9 y, 10–14 y, 15–19 y, 20–59 y, >60 y, reflecting on disease burden, based on PAHO age stratification. Geographic areas defined by areas of transmission, high incidence, and historic trends. Stratify by low-, medium-, and high-transmission to account for geographic variations.
Step 3: Define study perspective	Preference: society, which is the broadest perspective because it captures all costs and all health effects, regardless of who pays for dengue treatment or who is the beneficiary of that treatment. This will depend on the decision problem.
Step 4: Define time horizon	Preference: 1-y duration that includes all seasonal changes within that year. Alternatively, 3-y projections to evaluate the cost of preventive program and to account for seasonal variations from year to year. Study should be conducted during a period of substantial transmission in a particular country.
Step 5: Calculate sample size	Representativeness of data is key. Distinction between the sample size of an observational study and an economic study is important. Methodology will depend on the number of sites, settings (outpatient, inpatient), age groups, perspectives (private, public), and 2009 revised WHO dengue case classification (e.g., DF and DHF). This should be independent of which sector it comes from. A margin of error of 0.5 with low SDs should be considered. Establish criteria for sampling.
Step 6: Define the unit of analysis	Health care resources: hospitalized patients and outpatients. Program resources: vector control, education, community mobilization, and surveillance. Productivity-related resources: missed work, education, and community mobilization. Multisectoral resources: tourism, foreign direct investment, long-term fatigue and depression, outbreak control, and surveillance spending.
Step 7: Identify cost items	A “menu” of cost components for dengue cost evaluations. These include 1) health care activities, 2) program activities, 3) activities related to productivity, and 4) intersectoral activities.
Step 8: Measure and value cost items	Accurate description of the process of treatment or the program being used to monitor disease needed. This involves the measurement of the specific quantities of resources consumed during the process of treatment or monitoring: development of a classification system; definition of intervention activities and cost categories within each activity; measurement of resource use data in physical units; and conversion of resource data into cost data. Differentiate between average vs. marginal costs; opportunity costs vs. hospital charges, center-specific costs vs. average costs. Adjustments need to be made for inflation and currency including discounting, inflation, and purchase power parity. The common currency used is international dollars.
Step 9: Handle uncertainty	Need to consider four different types of uncertainty: 1) data sources; 2) generalizability; 3) extrapolation; and 4) analytic method. Inadequate sample sizes, skewed cost data, discount rates, and unit costs may introduce additional uncertainty. Extensive sensitivity analysis needs to be performed to deal with these uncertainties.
DF, dengue fever; DHF, dengue hemorrhagic fever; PAHO, Pan-American Health Organization; WHO, World Health Organization.	

Mexico, the highest incidence is in the 10–15-year-olds). One important caveat when stratifying the target population is to determine whether there are any differences in cost per case found at the country level. If no differences in costs are expected for ages ranging from 5 to 9 years and 10 to 14 years, for example, a split in age groups should not be considered. Other considerations include geographic areas defined by areas of transmission and historic trends in incidence and mortality.

Step 3: Defining the Study Perspective

Decisions regarding the perspective of a costing dengue study need to be made in the planning phase of the study. Although in many ways, the scope includes the study perspective, the Costing Dengue Working Group felt that it was necessary to list this and step 1 as distinct steps so that appropriate attention could be drawn to the two steps. The decision problem of a dengue costing study relates to the resource requirements of providing dengue

control and prevention care in the hospital and ambulatory centers. This decision problem determines the study perspective. The perspective that is taken determines which costs to include, as well as how to value these costs.

The societal perspective is by far the broadest perspective because it captures all costs and all health effects, regardless of who pays for dengue treatment or who is the beneficiary of that treatment. The adoption of a societal perspective would therefore be advisable because data can be disaggregated and analyzed from a number of viewpoints. Costs from the societal perspective include the costs associated with dengue management and prevention and the household costs before, during, and after a dengue occurrence, costs associated with surveillance and program prevention at municipal, state, and country levels, costs associated with patient or caregiver absenteeism, and intersectoral costs that relate to costs outside the health care sector. Adopting a societal perspective is challenging; the valuation of productivity losses is difficult when a large proportion of the

population affected by dengue is involved in unpaid or informal work. Assigning a value to long-term disabilities and estimating costs outside the health care sector is also difficult. Data availability constraints are also important impediments to adopting a societal perspective in a dengue costing study.

Most decisions about dengue prevention and control may be taken from the health service perspective or the perspective of the Ministry of Health. Even though their decisions have a bearing on society at large, decision makers in these countries may generally be concerned with direct costs because these are most indicative of their immediate budgets. In view of the fact that dengue prevention and control are generally publicly funded and there is evidence of a small economic family burden of dengue in these countries, the use of alternative (narrower) viewpoints, including the health service perspective, is also recommended. If the objective is to carry out a cost study of a dengue intervention program from the point of view of the government health sector, only public health providers (e.g., clinics and primary-, secondary-, and tertiary-level hospitals) and social security providers, in some cases, should be included.

Step 4: Defining the Time Horizon

Choosing an appropriate time horizon for the evaluation of dengue costs requires consideration of the major short- and long-term economic outcomes resulting from dengue prevention and control interventions. It is important to capture not only the intended costs, but also the costs associated with side effects of interventions, which may be unintended. The period of analysis of most of the dengue economic studies published thus far vary greatly among the literature [2]. Most of the studies involve a relatively short period of analysis (0–1 year), whereas only a handful consider a period of analysis of 2 to 5 years, 6 to 10 years, or more than 10 years. Studies with a short period of analysis do not capture the long dengue interepidemic intervals or seasonal fluctuations.

The time frame of the study depends on the specific objectives of the study. In some countries, dengue exhibits a seasonal pattern, with a peak typically occurring in the “rainy” months. If the purpose is to estimate the overall costs of dengue, the study should initially cover a full year and should reflect the seasonal variations. If, however, the purpose of the study is to estimate the costs of dengue or the cost of a specific outbreak, data collection should focus on the patients treated during the highest incidence of dengue. Further projections should be made for additional periods of time (3–5 years) to take into account the seasonal fluctuations of dengue that vary from one year to the next and the long-term fatigue due to dengue. During this period, data can be reviewed retrospectively (3–5 epidemic years) and modeled to estimate the average cost of dengue.

As part of the valuation of costs, all future costs in a cost evaluation should be stated in terms of their present value. To convert the costs associated with dengue, which may be incurred at different points in time, to a present value, a process called discounting is recommended. In discounting, costs (and benefits) are reduced to their present values by a process of deflating future costs and benefits by an increasing proportion.

There is a bit of controversy surrounding the issue of what discount rate to use or how to convert future health care benefits using discounting as the basis. Current guidelines recommend using a discount rate of both 3% and 5%; however, it is also recommended that data should be provided undiscounted to allow recalculation by the reader at any rate. The controversy surrounding the issue of what discount rate to use or how to convert future health care costs using discounting as the basis was discussed during the workshop. A discount rate of both 3% and 5% for future costing evaluations should be considered. The

undiscounted costs should be presented when the discounted costs are reported.

Step 5: Calculating the Sample Size

The sample size calculation in a costing study determines the ability to identify significant differences in costs between groups. When economic studies are conducted alongside clinical trials or surveillance systems, sample sizes are commonly determined by the requirements of the trial or surveillance program to demonstrate the statistical significance of the results for the clinical end points. In this case, sample size requirements for costing studies are often larger than those for clinical trials or surveillance systems, due to the need to capture the high variability in cost data associated with skewed distributions of resource use data.

Various methods for calculating sample sizes were advocated by the expert panel, including calculating the number of subjects needed to rule out unacceptably high upper confidence limits for the cost estimates. Experts agreed that the representativeness of cost estimates is a key to determining the study sample. The main question to address is what sample size is needed to ensure that empirical estimates are close to the true value of the study population. Overall, the sample size should depend on the size of the country, the disease burden by some disaggregated information, if possible, such as age, severity, region, availability, and quality of data within the country, and the study question.

The methodology used for the sample size calculation will depend on the variables that contain the different type of costs such as the number of sites, settings (outpatient or inpatient), age groups, perspectives (private or public), and disease classification (e.g., dengue fever and dengue hemorrhagic fever). Some experts in the panel felt that the inclusion of around 100 patients per stratification should give a robust estimation of the cost per case with a low SD, as seen in previous studies (e.g., in Vietnam). A sufficient number of patients per stratification should be included to ensure a statistical calculation of an average cost per case. Experts did not agree on what the “minimum number” should be.

One of the key issues about the sampling question is the issue of what is an acceptable point estimate that is of sufficient evidence for adoption of the intervention under question. The data used in the evaluation should be considered to provide a measure of the precision of the cost estimate in light of sampling uncertainty. Some of the more common measures of sampling uncertainty include confidence intervals around cost estimates, confidence intervals for net monetary benefit, and acceptability curves. Other issues to consider with sample size calculation include using averages when presenting cost data, making the SD explicit; being realistic about the number of dengue cases that can be used for the study; and whether sampling occurs throughout the year or only during the peak of a dengue season. [Annex 1](#) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.vhri.2015.06.001> describes the steps for sampling calculations.

Step 6: Defining the Unit of Analysis

The next step is to define the unit of analysis that relates to the resources used for the treatment of a dengue case or outbreak and its associated costs. The unit of analysis is determined by the decision problem. For example, the unit of analysis for health care costs is a dengue case recruited in a health care facility. For each hospitalized case, a clinical pathway or management practice (e.g., health care service activities) based on daily clinical practice in the hospital should be identified. This includes information about days in the hospital, consultation, tests, and drug treatments. If, however, the decision problem relates to dengue outbreak control and surveillance spending, the unit of analysis would then be dengue outbreak. Different cost

components of an outbreak (e.g., vector control, surveillance, education, and communication before, during, and after an outbreak) would need to be considered. The sources collecting cost data during an outbreak will be primarily government-based, but there will be other sources including household surveys and surveys to outbreak response personnel that should be considered.

Regional experts advocate the use of the framework developed by Bärnighausen et al. [28,29] when defining the unit of analysis because dengue affects the economy and health systems of endemic countries in various ways and across various sectors of the population. Although this framework was developed to assess the broader economic benefits of vaccination (as opposed to estimating costs), we need to think about a broader perspective when costing dengue to ensure the full range of costs associated with dengue is accounted for. When adopting this broader perspective, we will capture the true costs that accrue over the lifetime of an individual with dengue. These include the costs incurred during the acute phase of the illness and costs that accrue over time when multiple episodes of dengue occurred or during dengue outbreaks. The recommendation from the experts is thus to include the health care costs (e.g., hospitalized and outpatient costs), program costs (e.g., vector control, education and community mobilization, and surveillance), productivity costs (costs associated with missed work and reduced capacity and/or productivity at work), and multisectoral costs (e.g., income from tourism, foreign direct investment flows, long-term fatigue and depression costs, outbreak control, and surveillance spending) to inform decision making regarding dengue control and prevention interventions.

Step 7: Identifying Cost Items

Once the unit of analysis is defined, the next step is to identify all the activities that relate to dengue control and prevention. Table 2 provides a “menu” of cost components for dengue cost evaluations and these include 1) health care activities, 2) program activities, 3) activities related to productivity, and 4) intersectoral activities. Each activity comprises different cost items such as

staff, equipment, and consumables. The number of cost items contained within an activity will vary depending on the level of detail desired or available.

For health care costs, the unit of analysis for this component is a dengue case recruited in a health care facility (hospital, outpatient). To have representativeness of the local health system, data on costs should be collected in all subsystems (public, private, and other sectors) and in different levels of health services (primary, secondary, and tertiary). For program costs, the assessment of the dengue program global costs should include the following three components: vector control, education and community mobilization, and surveillance. These costs should be obtained during high- and low-transmission seasons. Costs associated with loss of productivity are long-term and include caretaker wages lost or school absence resulting from dengue-related illness, productivity losses that occur because of premature death, and productivity losses that occur because of disability as a result of dengue. Costs associated with intersectoral activities include income from tourism, foreign direct investment flows, long-term fatigue and depression costs, outbreak control, and surveillance spending.

Estimating costs decisions need to be made regarding the level of precision required. The spectrum of precision ranges from a bottom-up costing approach, in which individual components of resource use are identified and measured, to a top-down costing approach, in which larger intermediate products such as a hospital day are used. The choice between bottom-up and top-down costing depends on how sensitive the results of the costing study are likely to be to the individual cost estimates and on the degree of precision required in the analysis and the time and resources required to produce a detailed breakdown of unit costs. Benefits of a bottom-up costing approach include the precision and detail of the data, as well as the transparency of results, allowing analysts in other settings to determine how relevant the resource use patterns are to their situation. Conversely, top-down costing allocates a total budget to specific services (e.g., staff salary for vaccination). The choice ultimately depends on how accurate cost estimates need to be given the study perspective. The least precise estimates are likely to be based on top-down

Table 2 – A proposed “menu” for cost components.

Health care costs	<ul style="list-style-type: none"> • The unit of analysis for this component is a dengue case recruited in a health care facility. • To have representativeness of the local health system, data on costs should be collected in <ul style="list-style-type: none"> ◦ All subsystems (public, private, and other sectors); ◦ Different levels of complexity of services (primary, secondary, and tertiary). • The cost per case estimated is multiplied by the number of cases (coming from the surveillance system or epidemiological studies) to obtain the economic burden of health care consumption. • Medical direct (number and type stratified by level of assistance including public and private sector): medical visits, nurse visits, tests/examinations, drugs, monitoring/observation, hospital cost. • Medical nondirect (number and type): food, lodging, transportation, treatment by patient (out-of-pocket). • Indirect: absenteeism (work/school) for patient and caregiver.
Program costs	<ul style="list-style-type: none"> • The assessment of these costs should include the following three components: <ul style="list-style-type: none"> ◦ Vector control; ◦ Education and community mobilization; ◦ Surveillance. • These costs should be obtained in a period of time including a high- and low- transmission season to estimate the annual costs for each component.
Productivity loss	<ul style="list-style-type: none"> • This relates to long-term costs and includes <ul style="list-style-type: none"> ◦ Caretaker wages lost or school absence resulting from dengue-related illness; ◦ Productivity losses that occur because of premature death; ◦ Productivity losses that occur because of disability as a result of dengue.
Multisectoral costs	<ul style="list-style-type: none"> • Income from tourism; • Foreign direct investment flows; • Long-term fatigue and depression costs; • Outbreak control and surveillance spending.

costing, and the most precise estimates are likely to be based on bottom-up costing. [Annex 2](http://dx.doi.org/10.1016/j.vhri.2015.06.001) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.vhri.2015.06.001> describes the data requirements for costing fever cases and outbreaks.

Methods of controlling for costs include the use of modeling through decision analysis, the exclusion of resource use attributable to the study, and modifying the study in selected centers. Each of these methods has its own advantages and disadvantages; however, none obviates the need for information on resource utilization outside the study setting. Where existing data are scarce, various techniques can be used to obtain such information, including the use of medical records, expert panels, observational studies, and prospective data collection. The use of medical records to collect data retrospectively may prove problematic in low- and middle-income countries; hence, the use of either expert consultation or prospective data collection is likely to provide information that is more accurate. Expert opinion can be obtained using physician interviews, Delphi panels, nominal group processes, or expert roundtables; however, there are currently no formal guidelines on their use. Similarly, there is little consensus on the numbers and types of facilities that need to be included if data are collected prospectively.

Data on costs can be obtained from various sources including clinical trials, observational studies, meta-analysis, case reports, databases, expert panels, and administrative records. In practice, the evidence required to evaluate the costs of medical interventions and related resources is rarely present in a single source. The expert panel recommends that cost data be taken from a number of different sources, and synthesized using analytical structures called models.

Steps 8: Measuring and Valuing Cost Items

To calculate the total costs of disease or an intervention, quantities of resources used are multiplied by an assigned value. This value is called a unit cost. The costs associated with dengue to the health care system can be estimated by combining the number of each type of event (e.g., hospitalized dengue and ambulatory dengue) with information on the costs associated with the event. For hospital and ambulatory events, these can be partitioned into the cost of the visit (including facilities and personnel) and the cost of the resources used for treatment (specific tests and medications). The valuation of resource use in monetary units must be consistent with the perspective of the analysis. If the perspective of a health care provider is considered, only those costs for which the health care provider is accountable for should be included. If a societal perspective is taken, all costs are taken into account regardless of whose budget is affected or where in society they occur.

Experts recommend using a mixed costing methodology to address the issue of data availability constraints that are common in dengue-endemic countries of the region. A mixed costing methodology would entail minimizing data collection in areas where a small share of total costs exists and maximizing the ability to measure the difference in costs between patients in areas where there is a large share of total costs. For example, when estimating the cost of a dengue outbreak, the bottom-up costing approach should be applied to estimate the costs associated with surveillance and vector-control programs and indirect costs that include loss of working hours because these are known to be key cost components of a dengue outbreak. In contrast, a top-down costing approach should be used when estimating the direct costs that include laboratory, technical services, drugs, consumables, fees, and other resources because these are drivers of the cost of an outbreak.

Several issues regarding the valuation of resource use data exist, including the use of average versus marginal costs,

opportunity costs versus hospital charges, center-specific versus average costs, as well as methods of valuing productivity changes. For example, marginal cost refers to the change in total costs when producing an additional unit of input, and the marginal cost of an activity depends on the time frame of the analysis. As an approximation, it is quite common to estimate marginal cost using average costs. This is done because average cost is generally easier to measure. In the long run, average costs will be a good approximation to marginal costs because all inputs, including labor/capital, become variable, but average costs are generally not good approximation in the short run where costs are fixed and only a few may be variable. Staff time (and associated costs) may be fixed in the short run, whereas drug costs will generally be variable.

For each country, baseline cost estimates can be generated using resource use information from multicenter hospital-based or community-based observational study and facility-specific cost data. Two additional simpler approaches can also be used: physician interviews and extracting estimates from the WHO-CHOICE project (Universidad Nacional Autónoma de México, personal communication, 2012). The first approach offers the advantage of using empirical methods to reflect costs (direct medical, nonmedical, and indirect costs). The step-down costing method can be used here to measure unit (average) costs. This method was preferred in the present analysis because of the careful description of hospital and ambulatory costs. The responses of local physicians can also be used to augment the estimation of resource utilization and unit cost data. The third and last approach uses generalized unit cost data derived from local and national sources and secondary data to estimate direct medical costs of dengue.

The steps for measuring outbreak costs include 1) confirmation of an outbreak; 2) estimation of the number of people infected during an outbreak; 3) calculation of the outbreak cases times the cost per outbreak case; 4) gathering of information on budget impact (e.g., vector-control strategies, surveillance, media campaigns, tourism impact, and medical personnel) from government officials at all relevant levels; and 5) investigation of complete budget expenses by individuals or their families in response to an outbreak (e.g., vector-control program and tourism impact). Additional recommendations regarding the steps for measuring outbreak costs include the following: 1) be systematic about the scope, scale, perspective, and measurement approach used; 2) understand the health care system where the outbreak occurs; 3) account for differences in the design and conduct of these studies; 4) focus data collection for future costing on disease that is considered to be the most costly but also the most frequent; and 5) understand that small changes in costs can produce large fluctuations in economic burden and target efforts on getting those costs accurately assessed.

Information on where patients are treated for dengue can be collected from a number of sources. Demographic and health surveys, which are undertaken periodically in a number of countries, normally include a section on the treatment of infectious diseases such as dengue. Data are usually available on the percentage of cases taken to a health facility or provider. Other likely sources for this information include health interviews with doctors, nurses, and/or Ministry of Health officials and published articles from neighboring or comparable countries. A detailed list of these sources is provided in [Annex 3](http://dx.doi.org/10.1016/j.vhri.2015.06.001) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.vhri.2015.06.001>.

A study being conducted in many sites and in many countries presents difficulties in aggregating and analyzing cost data. The analyst is faced with a choice of whether the cost data should be country-specific or pooled across countries. A further consideration is important here: namely, whether to combine local unit costs with local resource use data or combine local unit costs

with resource use data from a wider pooling of countries, possibly including the entire study cohort. Estimates of average resource use (and the cost of such resource use) based on information from a single country are subject to uncertainty, with wide confidence intervals. Using resource use data from the entire study may suffer from the potential lack of representativeness of these data for an individual country of interest. Access and use of health services, treatment patterns, and costs vary greatly among countries. These are considered to be data of low transferability. A description of a dengue costing evaluation can be found in [Annex 4](#) in Supplemental Materials found at <http://dx.doi.org/10.1016/j.vhri.2015.06.001>.

Two methods are generally used to make cross-country comparisons of health care costs. These comprise purchasing power parity (PPP) conversion factors and official exchange rates. These methods have been used widely to convert values of different countries into a common denominator. The agreed definition of official exchange rates is that they are prices (rates) at which currencies are bought and sold on the international market. International comparisons based on market exchange rates can greatly overestimate or underestimate the value of the economic activity of a country. Because many goods and services are not traded in international commerce, market-based exchange rates may not reflect the relative values of goods. They may reflect only the equalization of prices for internationally traded goods and not the prices of nontraded goods such as health care. Hence, a given sum of money converted into different currencies using official exchange rates may not necessarily buy the same quantity of goods and services in all countries. In this way, exchange rates fail to address the issue of comparability arising from differences in price levels between countries, and their applicability in economic studies may be limited and only for the purpose of comparing it with other alternative methods.

In contrast, PPP conversion factors are virtual exchange rates; they are the numbers that are used to compare the standard of living of two countries. PPP-adjusted gross domestic product or gross national income values are the values converted from local currency unit into US dollars because the United States is used as the base country. They estimate the units of a country's currency that would be required to purchase the same baskets of goods that a dollar would buy in the US market, thus eliminating the differences in price levels between countries. The average country is based on a composite of all participating countries, so no single country acts as the base country. Although they are an improvement on exchange rate conversions, a number of measurement problems have been recognized with the use of PPP conversion factors. This is partly because PPP conversions make comparisons of aggregate expenditure across countries, rather than of the prices of health care interventions. PPP conversion factors do not account for health care-specific weights, which are likely to be different from the relative weights within the basket of goods used to construct PPP conversions.

An even bigger problem is related to the value that individuals in different countries attach to different components of health care or to differences in the composition of that basket. Moreover, PPP conversion factors are estimated every 5 years only and health-specific PPPs are measured on a very small sample of items. In addition, there is a bias toward pharmaceutical prices with health-specific PPPs. Two hundred and twenty-eight prices out of 294 prices for health PPPs are based on pharmaceutical prices. This makes the quality of the data at more detailed level (such as health) poor, particularly for developing countries. Given all these caveats, the expert panel recommends that all monetary figures should be reported in their local currency and international dollars for consistency purposes and to enable cross-country comparisons.

Step 9: Handling Uncertainty

There are two main areas of uncertainty in a costing study: parameter uncertainty and modeling uncertainty. Sources of data, extrapolation, and analytic methods contribute substantially to parameter uncertainty. Inadequate sample sizes, skewed cost data, discount rates, and unit costs may introduce additional parameter uncertainty.

Parameter uncertainty refers to the numerical values of the parameters that are unknown and entail uncertainties in the estimates of disease epidemiology, treatment interventions, and costs associated with treatment. These parameters may be uncertain because of sampling variation, disagreement about the appropriateness of the range of plausible values that are used, lack of information regarding disease epidemiology, and disease costs. The implications of these uncertainties are particularly important in the assessment of potential health care policy options, for example, with respect to the selection of control and prevention strategies for dengue. A few countries have developed methodologies to deal with this type of uncertainty. Mexico, for example, developed a Program, Actions, Activities, Tasks and Inputs methodology to deal with model uncertainty by comparing the costs derived from standard methodology with real cost estimates (Universidad Nacional Autónoma de México, personal communication, 2012).

Modeling uncertainty relates to the structure and process of the model. Model structure uncertainty exists when there is ambiguity about the correct method for combining model parameters. In contrast, model process uncertainty is introduced by the combination of decisions made by the analyst. Limited studies discuss the importance of addressing modeling uncertainty in costing models to make better inferences about the true level of uncertainty.

Although the use of modeling is often unavoidable, there are certain concerns about costing models that require attention. First, bias can be introduced when data from sources with inadequate sample sizes, poor methodology, and confounding variables are incorporated into a model. Second, models rely on a number of assumptions regarding the underlying disease process, relationships between risk factors and clinical outcomes, and extrapolation of data into final end points. Third, models are often criticized for their lack of transparency regarding the inputs, outputs, and key assumptions that have been incorporated.

Selection bias can be introduced in the design of the costing model. In this instance, factors that are likely to be the chief dependents of outcomes and the size or degree of such dependent on outcomes may be unknown. Models rely on a number of assumptions regarding the underlying disease process, relationships between risk factors and clinical outcomes, and extrapolation of data into final end points. In the trial setting, for example, treatment is randomly assigned across the patient population. Within the context of modeling design, however, it is determined by other influencing factors, such as patient attributes, disease characteristics, or sometimes the preference of the prescribing physician. Selection bias occurs when treatment choice is no longer the only differentiating factor between patients.

Selection bias can also be introduced when data from sources with inadequate sample sizes, poor methodology, and confounding variables are incorporated into a model. Selection bias affecting who received or did not receive an intervention may limit the value and generalizability of cost data collected. Information about the costs of medical and nonmedical interventions is not always collected on a trial-based study and secondary data sources, such as a claims database, may be used to fill additional information needed for the study. Other resource use items that can be overlooked include out-of-pocket expenses, time waiting for treatment, informal caregiver time, and loss in productivity.

Selection bias is considered to be one of the most difficult hurdles to overcome when interpreting the results of cost studies, and it is compounded by the fact that any one of several factors, including age, sex, indication, and severity, can interact to confuse or distort the outcome of treatment (confounding bias). One simple way to account for confounding bias is to include the likely “confounding” factors (e.g., age, sex, etc.) in a regression model in which the treatment costs can be corrected for the other variables. Although this is a relatively simple and straightforward process, cost calculations can become quite complex if adjustments must be made for many variables. An alternative to this approach is to match patients according to one or more variables, or, in cases in which there are many possible covariates, applying propensity scores can be helpful.

Sensitivity analysis and other statistical techniques are performed to test the impact on results of changes in uncertain or unfixed parameters and models and assess the robustness of the cost estimates to changes in assumptions and the values of the input variables. Sensitivity analysis involves three steps: 1) identifying the uncertain parameters for which sensitivity analysis is required; 2) specifying the plausible range over which uncertain factors are thought to vary; and 3) calculating study results based on combinations of parameters varied. In addition to providing an overall assessment of confidence in the cost estimates, sensitivity analysis provides a method for identifying variables that are likely to affect significantly final estimates of the economic burden of disease.

Discussion

As with many economic concepts, cost is not uniquely defined. This is of particular importance in estimating the costs of disease because such studies are context-specific. Dengue costing studies must be designed to reflect the scope of the study, study perspective, time horizon, and target population, among other methodological issues.

A true estimate of the overall cost of dengue can be used for three major purposes and types of analysis:

- Raising awareness of the economic burden of dengue: By demonstrating the economic impact of dengue, politicians, leaders, and policymakers can become convinced of the problem and be encouraged to engage in dengue prevention and control strategies.
- Planning and budgeting for dengue prevention and control: An estimate of the resources used to treat dengue can be used in an analysis of health sector expenditures and priorities.
- Cost-effectiveness analysis of interventions for prevention and control of dengue: Treatment costs and indirect costs of dengue can be saved if effective interventions are introduced to prevent and reduce the severity of dengue. The cost estimate is thus an integral part of a cost-effectiveness analysis of potential interventions, such as
 - Promotion of vector-control strategies;
 - Dengue immunization;
 - Improving environmental conditions in urban and rural areas; and
 - Promoting personal and domestic hygiene.

In this article, we presented a step-by-step guide for estimating the cost of dengue in endemic countries of the region. The guideline for costing dengue is the result of a collaborative effort, drawing on the direct input of local experts attending the workshop. The combined experience of the local experts from a range of countries in the Americas (Brazil, Colombia, Jamaica, El Salvador, Mexico, Panama), all of which have practical experience in the

estimation of disease costs, was applied. Experts agreed that the identification, measurement, and valuation of costs associated with dengue fever should be consistent with the perspective in question.

Cost studies will vary depending on the context in which the study is conducted and the decision problem addressed. Health care costs, non-health care costs, and broader economic costs should be considered in the costing study. Validated sources should be used for the unit costs, and standardized proxies for unit cost can be used when needed. Measurement of resource use should be done by means of observations (e.g., surveillance studies) or derived from national surveillance databases or the literature.

Key points raised by experts when costing dengue cases and outbreaks include the ability to be systematic about the scope, scale, perspective, and measurement approach used, to account for differences in the design and conduct of these studies, to focus data collection on future costing on disease that is considered to be the most costly but also the most frequent, and to understand that small changes in costs can produce large fluctuations in economic burden and target efforts on getting those costs accurately assessed.

The guidelines discussed previously are intended to be regional in scope. They aim to provide an overview of the state of the field of costing dengue and a discussion of the methods used in cost study in a manner that should be accessible to persons with some familiarity with a COI study. Because such a study has many different methodological components built from extensive theoretical and operational evidence of their comprising disciplines, a number of issues cannot be dealt with in depth. For this reason, areas of priority to workshop participants were highlighted. Although there is no single theoretically correct approach to developing guidelines for costing dengue, experts generally adhered to certain principles including the adoption of a societal perspective; the inclusion of all relevant costs and effects; the use of an adequate sample size; and the optimal collection and valuation of unit cost data for use in multicountry settings. Beyond these core principles, several concerns remain regarding the use of sensitivity analysis in uncertainty areas, data representativeness, and cost variance within and across countries.

Conclusions

Costing evaluations provide a critical input into economic evaluations. The recommendations presented in this article can be used to estimate the cost of dengue cases and outbreaks in endemic countries of the region. Through this guideline the expectation is to facilitate the development of dengue cost studies in various countries of the region, leading to the provision of better information for the determination of regional public health policies to counter dengue. Over time, the underlying estimation methodologies will improve and expand to include other economic evidence of dengue. We believe that the current guideline will help to improve the quality of dengue costing studies and permit comparison of dengue cost estimates across the countries of the region.

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Supplemental Materials

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2015.06.001 or, if a hard copy of article, at <http://www.valueinhealthjournal.com/issues> (select volume, issue, and article).

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