Laying the groundwork for future dengue economics research and the use of dengue vaccines

Costing Dengue Cases And Outbreaks: A Guide To Current Practices And Procedures

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Conflicts of interest

The authors do not have any conflict of interest in developing the guidelines.
Preface

These guidelines were commissioned by the Pan American Health and Education Foundation (PAHEF) as part of a regional initiative to develop sound methodologies and approaches for estimating the socio-economic costs of dengue in the Americas. Johns Hopkins University’s International Vaccine Access Center (JHU’s IVAC), in collaboration with PAHEF, would like to extend its appreciation and thanks to the participants of this initiative who are each recognized in their own country as an expert in the field.

The current document is meant to provide guidance for developing studies on estimating socio-economic costs of dengue. Because it is expected that these guidelines will continually evolve with future applications and studies, a Regional Steering Committee on Estimating Socio-economic Costs of Dengue was established. Governments and organizations that plan to undertake studies on estimating avoidable costs of dengue are invited to become members of the Regional Steering Committee.

It is hoped that these guidelines will be helpful to all countries in the Americas. When undertaking costing studies, guideline users are strongly advised to focus on a particular setting. Similarly, local dengue surveillance data in the country should be available.

For questions or information regarding the guidelines and the Regional Steering Committee on Estimating Socio-economic Costs of Dengue, please contact JHU’s IVAC at the following address:

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Abstract

An expert panel was convened to discuss and develop guidelines and standards for costing dengue so that over the next decade, local, and regional decision-makers will have access to improved information on the true cost of dengue in endemic countries of the region. In this document, we describe the outcome of the expert panel meeting, which resulted in the draft of costing guidelines. The guidelines were regional in scope. They aimed to provide an overview of the state of the field of costing dengue and a discussion of the methods used in costing dengue in a manner that should be accessible to persons with some familiarity with a cost 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. While 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, the optimal collection and valuation of unit cost data for use in multi-country settings. Beyond these core principles, several concerns remain regarding the use of sensitivity analysis in uncertainty areas, data representativeness; cost variance within and across countries.
Abbreviations

CEIS Centro de Estudios e Investigación en Salud
DALYs Disability-adjusted life years
DF Dengue fever
DHF Dengue hemorrhagic fever
DHS Demographic and health surveys
DSS Dengue shock syndrome
DVI Dengue Vaccine Initiative
ICD International Classification of Diseases
INSPI Instituto Nacional de Salud Pública de México/Mexican National Institute of Public Health
IVAC International Vaccine Access Center
GDP Gross Domestic Product
GNI Gross National Income
JHSPH Johns Hopkins School of Public Health
JHU Johns Hopkins University
JHU’s IVAC Johns Hopkins University’s International Vaccine Access Center
LAC Latin America and the Caribbean
LOS Length of stay
MAR Missing at random
MCAR Missing completely at random
MINSA Ministerio de Salud/Minister of Health
MOH Ministry of Health
MSH Management Sciences for Health
NGOs Non-government organization
NICE National Institute for Health and Clinical Excellence
PAHEF Pan American Health and Education Foundation
PAHO Pan American Health Organization
PCR Polymerase chain reaction
PPP Purchasing power parity
QALY Quality-adjusted life years
RCT Randomized controlled trial
UNAM Universidad Nacional Autónoma de México
WHO World Health Organization
WHO-CHOICE World Health Organization Choosing Interventions that are Cost Effective
# Table of Contents

Acknowledgments ............................................................... 3
Conflicts of interest ............................................................. 3
Preface ................................................................................. 4
Abstract ................................................................................ 5
Abbreviations ......................................................................... 6
Table of Contents ................................................................. 7
1. Background ......................................................................... 9
   1.1 Introduction ............................................................... 9
   1.2 Aims ........................................................................... 11
   1.3 Structure of the guidelines ........................................... 11
2. Methods ................................................................................. 12
   2.1 Overall approach ...................................................... 12
   2.2. Review of the literature ............................................. 12
   2.3 Assessment of existing guidelines ............................... 13
   2.4 Expert survey ............................................................ 14
   2.5 Guideline recommendations ....................................... 15
3. Planning the study ............................................................... 18
   3.1 Scope of Analysis ...................................................... 18
   3.2 Target Audience ....................................................... 19
   3.3 Choice of perspectives .............................................. 20
   3.4 Definition of target population .................................... 20
   3.5 Timeframe of the study .............................................. 21
   3.6 Case definition .......................................................... 21
   3.7 Sample size and sample rate calculation ..................... 22
      3.7.1 Determining the sampling rate and selecting the sample population 23
      3.7.2 Sampling: hospital ............................................. 24
      3.7.3 Sampling: ambulatory centers .............................. 25
4. Considerations for costing dengue cases ............................... 26
   4.1 Getting an overview of dengue treatment ..................... 26
   4.2 Costs associated with dengue ..................................... 26
      4.2.1 Cost components of a dengue case ....................... 33
      4.2.2 Other types of cost requirements .......................... 34
   4.3 Potential data sources ............................................... 35
   4.4 Methods for costing hospitalized dengue cases ............. 36
### 5. Considerations for costing dengue outbreaks

5.1 Definition of a dengue outbreak
5.2 Cost components of a dengue outbreak
5.3 Sources for costing a dengue outbreak
5.4 Steps for measuring outbreak costs
5.5 Discounting
5.6 Purchasing power parity conversions and official exchange rates
5.7 Data uncertainties
  5.7.1 Sensitivity analysis
  5.7.2 Univariate sensitivity analysis
  5.7.3 Multivariate sensitivity analysis
  5.7.4 Probabilistic sensitivity analysis

### 6. Methodological considerations

6.1 Perspective and research question
6.2 Resource use
6.3 Resource use data: country groupings
6.4 Financial versus economic costing
6.5 Full versus incremental costing
6.6 Treatment costs
6.7 Cost savings
6.8 Missing or incomplete cost data
6.9 Ethical considerations
6.10 Confidentiality
6.11 Informed consent

### 7. Conclusions

### 8. References

Annex 1. Cost evaluation description
Annex 2. Definition of common technical terms
Annex 3. Websites of Interest

Guidelines For Economic Evaluations
Economic Analysis
Health Literature Search And Evidence
Journals
General Sites Providing Useful Gateway To Information On The Internet
1. Background

1.1 Introduction

Limited research has been done to estimate the costs of dengue in the Latin American and Caribbean (LAC) region. In a recent review of the literature only a handful of economic studies were found in the region (1). The studies reviewed indicated a great variation in cost estimates for dengue due to differences in case classification, definition of cost categories, sampling, data sources, and other methodological challenges. Findings of the literature were not of sufficient quantity and quality. It was not always clear from these economic studies which form of treatment associated with dengue was being costed, what was included in the total cost estimates and how these estimates were calculated. Moreover, cost estimates from these studies were 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 like dengue. In the health care systems of most European countries formal systems have been set up around evaluation guideline documents. The 1996 publication of the conclusions of a working group (the Washing Panel) funded by the Public Health Service in the U.S. (2) marked an attempt to standardize the methodological approach to economic evaluation in health care. Standardization of information could address several important issues. First, if the base-case assumptions in economic model inputs were transparent, there would be a better understanding of the potential impacts of diseases on medical, public health, and economic outcomes. Standardization of information could also reduce the potential for bias in cost evaluations. In addition, standardization might allow experts to examine costs of disease earlier in the decision pipeline, thus enabling them to be better informed about conclusions from, and limitations to, the economic data at hand. Finally, standardization may facilitate comparison of information from one setting to another or between one intervention and other interventions.

On-going efforts by governments and healthcare systems to harmonize approaches to economic evaluation, however, have made little progress. In the Americas, the situation is no different. 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.

In response to the growing need for cost information for future introduction of vaccines against dengue, an expert panel was convened March 6-8 2012 to discuss and develop a standardized methodology for estimating costs of dengue in the Americas (3). Estimates of the costs of dengue constitute just one component in a range of potential economic information on dengue. Other components include information on the economic benefits of dengue control and prevention interventions (in term of cases, hospitalization and death avoided, DALYs averted, QALYs gained) and information on cost-effectiveness and budget impact analysis. Table 1 presents a summary of the potential dengue cost estimates and their possible uses.
<table>
<thead>
<tr>
<th>Type of estimate</th>
<th>Interpretation of results</th>
<th>Example of policy use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggregate costs</td>
<td>Total external costs of dengue compared with the alternative situation of no dengue</td>
<td>Indication of the size of the dengue problem</td>
</tr>
<tr>
<td>Avoidable costs</td>
<td>Potential economic benefits from dengue resulting from dengue control and prevention strategies</td>
<td>Determination of the appropriate level of resources devoted to dengue control and prevention strategies</td>
</tr>
<tr>
<td>Cost incidence</td>
<td>The distribution of the external costs of dengue among various community groupings</td>
<td>Mobilization of support from various members of the community for dengue prevention and control programs</td>
</tr>
<tr>
<td>Disaggregated costs</td>
<td>External costs of dengue disaggregated by categories</td>
<td>Economic evaluation (cost effectiveness or cost benefit analysis) of dengue prevention and control strategies</td>
</tr>
<tr>
<td>Budgetary impact</td>
<td>The impact of dengue on government expenditures and revenues</td>
<td>Indication of the impact that dengue has on a country's overall budget</td>
</tr>
</tbody>
</table>

The current document presents Guidelines that provide considerable information on estimation of what, in Table 1, are referred to as aggregate costs. However, while 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 which are potentially avoidable nor the nature of the programs and policies best suited to achieve this cost avoidance. The current Guidelines do not explicitly consider economic evaluations (cost per DALY, cost per QALY) because regional experts considered the need for dengue-specific costing guidelines a priority. Future versions of the Guidelines may address other forms of economic evidence related to dengue.

The Guidelines generated from this workshop were 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 whom have practical experience in the estimation of disease costs, was applied. Since the estimation of dengue costs is a relatively new area of research, in which there is limited published literature, few of the experts who attended the workshop had practical experience in this research area.
1.2 Aims

The aims of these Guidelines are to ensure robust assessment of the economic burden of dengue infections and to make the results of future dengue cost studies more comparable among Latin-American countries. The intended outcome of the Guidelines is a conceptual framework that would allow the differing dengue costs between countries to be understood in context and to point the way towards a general approach that might be used by the public health community to plan costing dengue studies in different country settings.

Guidelines for costing dengue are considered to have three main purposes:

(i) Economic estimates are frequently used to argue that policies on dengue control and prevention should be given a high priority on the public health policy agenda;

(ii) Economic cost studies help to identify information gaps, research needs and desirable refinements to national statistical reporting systems;

(iii) The development of improved dengue cost estimates offers the potential to provide a baseline measure to determine the cost-effectiveness of dengue policies and programs.

It is hoped that the current Guidelines will encourage and 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. Improvements in research methodology and in the areas of epidemiology and health economics suggest that regular revision of these Guidelines is needed.

1.3 Structure of the guidelines

The guidelines are divided in six main parts. Part one provides background information and lists the aims and objectives of the guidelines. Part two describes the methodology used to develop the guidelines, including a description of the overall approach. Part three provides an overview of the recommendations on how to plan the study and select the sample size for the data collection. Parts four and five provide recommendations for costing dengue cases and dengue outbreaks. The final part of these guidelines, part six, provides a discussion of methodological considerations for costing dengue.
2. Methods

2.1 Overall approach

Two key questions were central to the development of the Guidelines. These were related to the type of standard methods needed to capture the true economic cost of dengue and the type of cost information that is most useful to making public health policies to counter dengue infections. To address these questions a workshop was organized to identify methodological gaps in this area, and develop guidelines to measure the true cost of dengue.

The workshop was organized in a 2.5-day session using a mixture of self-supported material, small group discussions and formal didactic sessions. The approach was to present workshop participants with existing methodology that has previously been used to estimate costs associated with dengue and other diseases, to share this methodology with participants prior to the workshop, compare and contrast the methodology and prepare strategic options for harmonizing differences in methodology across studies.

Workshop participants were asked to share past experiences when costing dengue. If participants were planning to conduct an economic study of dengue, or were directing an economic study of dengue, they were asked to present key methodological areas being considered for their analysis. This was an opportunity for workshop participants to share their view of how individual countries are currently doing or planning to do the analysis.

Workshop participants worked in groups of four, facilitated by Johns Hopkins University’s International Vaccine Access Center (JHU’s IVAC) and the Pan American Health and Education Foundation (PAHEF) staff to allow maximum discussion of the methodology. While the structure of the workshop was novel and unique to most workshop participants, the content for the most part was drawn from existing sources. There is a wealth of materials in cost estimation upon which to draw including case studies and interactive guidelines. The preparation of the workshop involved the selection of material from existing sources and adaptation of it to the specific needs of the workshop participants. This required the writing of linking material and the development of some new background material, but the basis was published articles and texts.

Key to the success of the workshop was the development of pre-workshop material, which included a synopsis of country experiences with the design and conduct of existing dengue cost studies; a review of the literature that provided a discussion on the differences and similarities in methodology used; an assessment of existing guidelines that are publicly available; and a survey of experts conducted specifically to identify areas in dengue economics research that are considered high priority.

2.2. Review of the literature

We conducted a search of the literature to provide a critical overview of the issues related to dengue economics research and to form a background with which to address the question of costing dengue in the LAC context. To achieve these two objectives we summarized what is known about the cost of dengue. We also identified appropriate methods used in assessing the costs of dengue. Lastly, we identified gaps and pitfalls of previously published research in this area.
The papers found were obtained from the PubMed, Embase, Cochrane CENTRAL, Global Health, Biological Abstracts, Pascal BioMed, Scopus and the Web of Science databases. The regional databases of PAHO and WHO LILACS were also considered. Manual bibliographic searches revealed additional articles.

The literature review focused on English, Spanish and Portuguese language peer-reviewed publications from between 1970 and 2011. Papers were critically appraised using preset quality criteria. Of the 187 papers found in our preliminary search we narrowed the choice of literature down to 28 papers.

The current evidence suggests that the cost of dengue is substantial due to cost of hospital care and lost earnings. However, it was not always clear from the economic studies reviewed which form of treatment associated with dengue was being costed, what was included in the total cost estimates and how these estimates were calculated. Moreover, cost estimates from these studies were of heterogeneous quality, not generalizable to other populations and not representative of the total economic consequences of dengue. The review underscored the lack of consistency that exists on many methodological areas. Notwithstanding these shortcomings, there was a relatively strong mix of methodologies, evenly spread across the two geographic areas. The studies reviewed indicated great variation in cost estimates for dengue within and across countries due to differences in dengue classification, definition of cost categories, sampling, data sources, discount rates, different health care financing systems, delivery systems, and conversion into U.S. dollar values. Further research in this area will broaden our understanding of the economic impact of dengue and aid in the design and evaluation of intervention programs against dengue. The review of the literature underscores the need to develop guidelines for the estimation of costs of dengue. Detailed information about this literature review are presented elsewhere (1).

2.3 Assessment of existing guidelines

Guidelines on conducting economic evaluations were publicly available in Brazil, Colombia and Mexico (3). The intended use of these guidelines was comparable to other economic evaluation guidelines that are publicly available elsewhere. These guidelines centered on the provision of a basic set of standards for carrying out economic studies to ensure that cost and cost-effectiveness results are compatible among different settings. The focus of these guidelines, for the most part, was on costing interventions or programs, and conducting cost-effectiveness analysis of different interventions and/or programs. For the most part, Ministries of Health (MoH) from Brazil, Colombia and Mexico based their guidelines on existing guidelines (e.g. National Institute for Health and Clinical Excellence [NICE]). The targeted audience of the local guidelines was mainly the person in charge of carrying out economic evaluations, which included program managers, economists, epidemiologists and decision-makers. All guidelines contained a quality checklist for comparative economic studies, which was generally based on existing costing quality checklists.

Despite their similarities, the three guidelines differed in a number of ways. For example, we found that these guidelines disagreed on the best way to attach monetary value to resource use. There was also disagreement on the appropriate measurement and valuation method of informal caregiver time and productivity costs, and on how to measure the costs incurred in added years of life. More troubling was the limited information provided on how to translate the principles into practice. Even the guidelines published in Colombia, which were found to be more detailed than the ones...
from Brazil and Mexico, considered to be one of the most detailed guidelines, was limited in its discussion on how to translate principles into practice. In addition, limited discussion about the more practical challenges such as the trade-off between information accuracy and the costs of securing the information or how to deal with missing data was provided by the guidelines. Table 2 provides an overview of the main methodological considerations made by the authors of these guidelines.

Table 2 Guidelines considerations across countries

<table>
<thead>
<tr>
<th>Considerations</th>
<th>Brazil</th>
<th>Colombia</th>
<th>Mexico</th>
</tr>
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<tbody>
<tr>
<td>Types of economic evaluations</td>
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<td></td>
</tr>
<tr>
<td>Cost minimization analysis (CMA)</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cost effectiveness analysis (CEA)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cost utility analysis (CUA)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cost benefit analysis (CBA)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Study scope</td>
<td>✓</td>
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</tr>
<tr>
<td>Study population</td>
<td>✓</td>
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</tr>
<tr>
<td>Perspective</td>
<td>✓</td>
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<td>✖</td>
</tr>
<tr>
<td>Specification of costs</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Direct costs</td>
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<td>✓</td>
<td>✖</td>
</tr>
<tr>
<td>Indirect costs</td>
<td>✓</td>
<td>✓</td>
<td>✖</td>
</tr>
<tr>
<td>Choice of providers</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Selection of costing method</td>
<td>✓</td>
<td>✓</td>
<td>✖</td>
</tr>
<tr>
<td>Description of data used</td>
<td>✓</td>
<td>✓</td>
<td>✖</td>
</tr>
<tr>
<td>Time horizon</td>
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<td>✓</td>
<td></td>
</tr>
<tr>
<td>Discount rates</td>
<td>✓</td>
<td>✓</td>
<td>✖</td>
</tr>
<tr>
<td>Sample size calculation</td>
<td>✖</td>
<td>✖</td>
<td>✖</td>
</tr>
<tr>
<td>Case definition of disease</td>
<td>✖</td>
<td>✖</td>
<td>✖</td>
</tr>
<tr>
<td>Double counting</td>
<td>✖</td>
<td>✖</td>
<td>✖</td>
</tr>
<tr>
<td>Underreporting</td>
<td>✖</td>
<td>✖</td>
<td>✖</td>
</tr>
<tr>
<td>Nonmonetary costs</td>
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<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Generalizability</td>
<td>✓</td>
<td>✖</td>
<td>✓</td>
</tr>
<tr>
<td>Documentation of data</td>
<td>✓</td>
<td>✓</td>
<td>✖</td>
</tr>
<tr>
<td>Guidelines adapted from NICE or other guidelines</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Disease-specific guidelines</td>
<td>✖</td>
<td>✖</td>
<td>✖</td>
</tr>
<tr>
<td>Budget impact analysis</td>
<td>✖</td>
<td>✖</td>
<td>✖</td>
</tr>
</tbody>
</table>

✓ = specified  ✖ = not specified

2.4 Expert survey

Prior to the workshop, experts were asked to complete a survey to identify areas in dengue economics research that were considered high priority. The targeted audience for this survey was dengue experts and health economists in the region. Experts provided feedback to the survey based on informed opinion and past experience in conducting dengue economics research in the region.

The survey comprised a total of 17 questions that were multiple-choice or short answer questions. Categories of dengue economics research considered in the survey included: (i) scope of analysis; (ii) study duration considerations; (iii) study population; (iv) measures/indicators for dengue.
costing; (v) sample size calculations; (vi) sources of information; (vii) data collection methods; (viii) economic approaches for costing dengue; and (ix) representativeness and/or generalizability of data. The criteria used in assessing overall agreement on priority ranking was: (i) High agreement: ≥ 8 checks per box; (ii) Moderate agreement: 6-7 checks per box; and (iii) Low agreement: ≤ 5 checks per box. Results of this survey are presented elsewhere (3).

Based on discussions from the workshop, JHU’s IVAC compiled a series of recommendations, which served as the basis for the initial draft of the Guidelines for costing dengue. The panel of experts who attended the workshop and external experts reviewed several drafts of the Guidelines, which resulted in this document. In the following pages we present the recommendations on costing dengue made by the expert panel.

2.5 Guideline recommendations

The expert panel agreed that the Guidelines on costing dengue should be consistent to existing guidelines to avoid bias and allow comparisons of other methodologies when possible. In addition, the recommendations should be based on underlying economic theory.

The following pages provide the recommendations made by experts attending the workshop. Table 3 summarizes these recommendations by methodological area. The first part of the recommendations pertains to planning the study.

<table>
<thead>
<tr>
<th>Methodological area</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope of analysis</td>
<td>Criteria for defining scope of analysis: knowledge of disease burden, availability of data and reproducible tools, surveillance system in place, assessment of social impacts, and establishments of response thresholds. Scope of analysis: this depends on the study objective but generally it includes the cost to the patient, household, institution, state and others</td>
</tr>
<tr>
<td>Target audience</td>
<td>Formulary committees making reimbursement decisions, regulatory entities, professional organizations, payer-providers, public health officials, program planners, pediatricians, academics and parents</td>
</tr>
<tr>
<td>Type of provider</td>
<td>Public provider, private, social insurance and other sectors (not specified)</td>
</tr>
<tr>
<td>Choice of perspective</td>
<td>Preference: society. This will depend on the study questions.</td>
</tr>
<tr>
<td>Target populations/ geographical areas</td>
<td>Target population stratified by the following age groups: 0-4 years, 5-9 years, 10-14 years, 15-19 years, 20-59 years, &gt;60 years. This stratification reflects the burden of dengue in the region. Dengue in the LAC region is a disease of the young. This is 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.</td>
</tr>
<tr>
<td>Time horizon of analysis</td>
<td>One-year duration that includes all seasonal changes within that year. Three-year 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.</td>
</tr>
<tr>
<td>Criteria for case definition</td>
<td>Follow PAHO guidelines – use PCR, serology, culture.</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Definition of cases</td>
<td>Currently: DF &amp; DHF</td>
</tr>
<tr>
<td></td>
<td>Future:</td>
</tr>
<tr>
<td></td>
<td>- Dengue without warning signs</td>
</tr>
<tr>
<td></td>
<td>- Dengue with warning signs</td>
</tr>
<tr>
<td></td>
<td>- Severe dengue (includes severe DHF and severe dengue fever)</td>
</tr>
<tr>
<td>Sample size calculations</td>
<td>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), classification (e.g. DF, DHF). This should be independent of which sector it comes from. We need to be realistic on how many confirmed cases are reported. There should be a margin of error of 0.5 with low standard deviations. It’s more important to establish the criteria for sampling, not the actual sample size.</td>
</tr>
<tr>
<td>Identification of subjects</td>
<td>Subjects diagnosed with DF and severe dengue.</td>
</tr>
<tr>
<td>Selection of study sites</td>
<td>Sites should be representative of the country in question.</td>
</tr>
<tr>
<td>Types of resources consumed</td>
<td>Entomological surveillance, epidemiological surveillance (active/passive), prevention and control, household, management practice, death-related, intersectoral</td>
</tr>
<tr>
<td>Categories of resources consumed</td>
<td>Public sector: entomological surveillance, epidemiological surveillance, prevention and control, management practice. Private sector: epidemiological surveillance (active/ passive), management practice, death-related Social insurance sector: epidemiological surveillance (active/ passive), management practice, death-related Other: prevention and control, management practice, death-related, intersectoral</td>
</tr>
<tr>
<td>Measurement of resource consumption</td>
<td>Provide accurate description of process of treatment or program being used to monitor disease. This involves the measurement of the specific quantities of resources consumed during the process of treatment or monitoring.</td>
</tr>
<tr>
<td>Potential sources of resource use data</td>
<td>Primary data (prospectively): epidemiological surveillance, RCTs, caregiver interviews. Primary data (retrospectively): patients’ charts, household surveys. Secondary data: national administrative data, published literature.</td>
</tr>
<tr>
<td>Cost components</td>
<td>Healthcare costs &amp; Program Costs</td>
</tr>
<tr>
<td>Categories of costs</td>
<td>Hospitalized &amp; Outpatients Healthcare costs, Vector Control, Education and Community Mobilization &amp; Surveillance</td>
</tr>
<tr>
<td>Measurement of costs</td>
<td>- Development of a classification system</td>
</tr>
<tr>
<td></td>
<td>- Definition of intervention activities and cost categories within each activity</td>
</tr>
<tr>
<td></td>
<td>- Measurement of resource use data in physical units</td>
</tr>
<tr>
<td></td>
<td>- Conversion of resource data into cost data</td>
</tr>
<tr>
<td></td>
<td>- Adjustments for inflation and currency, etc.</td>
</tr>
<tr>
<td>Potential sources of cost data</td>
<td>Primary data collections for Healthcare costs and official government costs for program costs</td>
</tr>
<tr>
<td>Definition of an outbreak</td>
<td>A dengue outbreak corresponds to two standard deviations away from the mean (average) of cases (= the endemic channel); 1 case in an area where there is no case before.</td>
</tr>
</tbody>
</table>
### Cost components of an outbreak

Vector control activities, Public education/media communication, Surveillance system (increased laboratory control, Medical personnel (nurses, physicians), Tourism decreased revenue (increase government and household cost), Inter-sectoral collaborations.

### Sources of data in an outbreak

Published literature, budget from the government and states, household surveys, inter-sectoral budget

### Steps for measuring cost of outbreaks

- Confirmation of an outbreak
- Estimation # people infected during outbreak
- Multiply # people infected with the cost per case.

### Financial versus economic costs

Financial costs: expenditures for resources to implement the program; based on market prices; convenient, sometimes incomplete measure of costs (e.g. salaries for personnel, supply costs). Economic (opportunity) costs: value of the lost benefit because the resource is not available for its next best use; resource’s cost = the sacrifice necessary to obtain goods or services. Financial costs will be used from the practical standpoint, considering the variable costs. Economic (opportunity) costs will be used when data availability and time allows.

### Full versus incremental costing

The full cost considers both the fixed and variable costs without any consideration to changes in costs. The incremental cost is the change in the total costs that arises when the quantity produced changes by one unit. That is, the cost of producing one more unit of good. Average cost per case preferred, excluding capital costs. In case of vaccine introduction, incremental costs will be modeled.
3. Planning the study

3.1 Scope of Analysis

Planning a study on costing requires detailed review of local disease burden, its epidemiology, and insight knowledge of the organization of national health system under study. In addition, health outcomes and costs must be identified, and methods for measuring these need to be formulated. Other methodological issues that must be addressed include sample size requirements, suitability of study endpoints, representativeness of study data, and dealing with uncertainty. Given the controversy that surrounds many of these issues, it is important to invest time in the preplanning phase of the study to ensure production of meaningful and sound recommendations, which can be easily transferred to other settings.

The decision of which type of cost study to consider for inclusion in a Guidelines document such as this is driven primarily by the economic questions or objectives that have been formulated, the perspective(s) chosen, and the measures of resource use and costs included as target outcome measures. The scope is also driven by the availability of information (e.g. patient costs, household costs, institution costs, state-level costs), and the need to bring information together for policy.

Figure 1 describes, in a nutshell, the scope of analysis for costing dengue. The final outcome is the economic burden of dengue infections, which entails the costs associated with dengue outbreaks, the costs associated with dengue prevention and surveillance systems, and the economic impact that dengue has on tourism, education and other sectors of society.

Figure 1. The scope of analysis for costing dengue
3.2 Target Audience

There are a number of potential audiences for health economic information in different settings, including: formulary committees making reimbursement decisions, regulatory entities, professional organizations, payer-providers, public health officials, program planners, pediatricians, academics and parents. The types of information likely to be used by each differ and as a result the findings of any economic study of this nature must provide the required information to all relevant audiences.

Types of Health Care Providers using Dengue Cost Information

The type of health care providers from the public health care sector, the private sector (insurance and out-of-pocket), the social insurance sector, and other sectors (inter-sectoral e.g. tourism) that typically use this information needs to be identified. The decision of which health care providers to include depends on the objective(s) of the costing study and the perspective(s) chosen. In this context, ‘health care provider’ connotes both clinicians and health care facilities.

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-, tertiary-level hospitals)\(^1\) and social security providers in some cases should be included. If the study objective is a cost study from the societal viewpoint\(^2\), all types of health care providers (from the private, social security and public healthcare sectors) should be considered. While the public sector is in charge of surveillance, preventative and management programs to the population as a whole, the private sector is in charge of disease management to certain sectors of the population. In some countries of the region the analysis may be limited to the public sector as including the private sector to the analysis might be challenging but necessary.

An understanding of how local health systems are organized is essential to determine the types of health service providers that are important in the treatment of dengue. For instance, if the dengue affected population is being treated in non-for-profit outpatient centers, these types of health care centers should be considered in the study sample. While it will be difficult to come up with an exact estimate of health services utilization by type of provider, efforts should be made to record the most likely picture. The proportion of dengue cases that are not taken to any health care provider for treatment should be assessed as well.

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\(^1\) According to the World Health Organization (WHO), primary-level hospitals generally contain general practitioners and/or specialties such as internal medicine, obstetrics-gynecology, pediatrics, and general surgery. These hospitals are often considered district hospitals or first level referral hospitals and have a capacity of 30 beds or less. A secondary-level hospital may have 5-10 clinical specialties and may serve as the provincial/district hospital. A tertiary-level hospital contains more specialties than the primary- and secondary-level hospitals as well as more technical equipment. A tertiary-level hospital is often a central or regional hospital located in a city.

\(^2\) The societal perspective includes the costs borne by the government, the social security system, and the household. These household costs include ambulatory visits and hospitalizations at the private level, co-payments borne by the household at the social security level, as well as transportation costs, special care costs, and productivity (income) losses for the child.
3.3 Choice of perspectives

The gold standard for the choice of perspective is that of society. This would 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, and costs associated with patient or caregiver absenteeism. The societal perspective is by far the broadest perspective as it captures all costs and all health effects, regardless of who pays for the vaccination program or who is the beneficiary of that program. (2) This perspective is preferred, particularly when costing dengue cases. Several authors that have conducted dengue economic studies have illustrated the significance of considering this perspective in their analyses. (5-14)

Most decisions about dengue prevention and control are 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 are generally concerned with direct costs as these are most indicative of their immediate budgets (5-9). In view of the fact that dengue prevention and control are generally publicly funded and there is evidence of a small dengue economic family burden in these countries, the use of alternative (narrower) viewpoints, including the health service perspective, is recommended.

3.4 Definition of target population

The definition of the target population depends on the difference in costs (cost per case, cost of outbreaks, cost of prevention and surveillance, impact on tourism, education), and can be defined by geographic area (country, region, town or high-, medium- and low-endemic areas to account for geographic variation, defined by the presence of vector, transmission and virus circulating) and age group and gender.

Geographic areas are different if the objective is to have the cost per case or the cost of outbreak or the costs associated with surveillance. For the cost per case, the geographic areas will depend on the national health care system. If no difference in cost per case exists between the areas, an endemic area should then be chosen to get access to much more dengue patients in a short time.

In terms of age groups, a modified Pan American Health Organization (PAHO) age group stratification system was recommended: 0-4 year olds, 5-9 year olds, 10-14 year olds, 15-19 year olds, 20-59 year olds, >60 year olds – based on PAHO age group stratification system. A further classification of 10-14 year olds and 15-19 year olds was recommended to account for the considerable burden of disease in these age groups in certain countries (e.g. In Mexico, the highest incidence is in the 10-15 year olds).

It is important to stratify target populations according to differences in cost per case found at the country level. If no difference in costs is expected between ages ranging from 5-9 years and 10-14 years, for example, a split in age groups would not be necessary.
3.5 Timeframe of the study

Choosing an appropriate time horizon for the evaluation of dengue costs requires consideration of the major short and long-term economic outcomes. It is important to capture not only the intended effects, but also the side effects, which may be unintended. (17) The period of analysis of the majority of dengue economic studies published thus far vary greatly among the literature. (1) The majority of the studies involved a relatively short period of analysis (0-1 year), while only a handful considered a period of analysis of 2 to 5 years, 6-10 years or over 10 years. Studies with short period of analysis did not capture the long inter-epidemic intervals or seasonal fluctuations.

The time frame for sampling 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, including dengue fever (DF) and severe dengue, then sampling should initially cover a full year and should reflect the seasonal variations. If, on the other hand, the purpose of the study is to estimate the costs of DF, data collection can 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 account for the seasonal fluctuations of disease that vary from one year to the next. During this period, data can be reviewed retrospectively (3-5 epidemic years) and modeled to estimate the average cost of dengue.

3.6 Case definition

The World Health Organization (WHO) case classification of dengue into DF, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) was originally formulated in 1974 by a Technical Advisory Committee, based on studies of disease patterns in children in Thailand in the 1960s. (18) Some modifications to this definition were made in 1997 and 2009 to account for the geographic expansion of dengue and its increased incidence in older age groups. (19-21)

The revised 2009 WHO 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 and, in 2006, the WHO Dengue Scientific Working Group recommended additional research into dengue diagnostics and triaging of patients for optimized clinical management. (22)

The 11th revision of the International Classification of Diseases (ICD-11) is considering this new classification. During this transition phase, some countries will be using the 2009 case classification and others will be adopting the new case classification.

The following possible case definitions are recommended:

- DF and DHF
- Dengue with and without warning signs and severe dengue (new WHO classification)
- Hospital and ambulatory dengue cases
- Laboratory-confirmed or clinical dengue cases.
There should not necessarily be a **standard for case definition** because the case definition depends mainly on the surveillance system in each country. One key consideration to allow robustness of the overall economic burden of dengue infections estimation (see figure 1) is to have coherence in case definition between “cost per case” and the source given the “incidence” data (surveillance or randomized controlled trials). For example, if in the surveillance system, dengue cases are classified between ambulatory and hospitalized patients, the costing studies should estimate the unit cost of ambulatory and hospitalized cases. The overall economic burden of dengue infections calculation would then be possible thanks to the multiplication between the number of ambulatory/hospitalized cases (from the surveillance system) and the cost per ambulatory/hospitalized cases.

In terms of clinical or unconfirmed dengue cases, it is not necessarily to base the case definition on laboratory confirmation as all countries have the capacity to provide laboratory-confirmed cases. The confirmation of a case could be clinical. Around the same cost per case should be obtained if we have a suspected dengue case or a confirmed dengue case. However, in order to estimate the true cost of dengue, the cost per case estimate should be multiplied by the confirmed number of dengue cases, if available. The cases can be further stratified in suspected (clinically diagnosed) and laboratory-confirmed cases. In this case, confirmed and unconfirmed cases could be costed separately.

- If a confirmed dengue case is identified, PAHO guidelines using polymerase chain reaction (PCR), serology, and culture should be used to confirming the case.
- If a clinically suspected case is identified, the PAHO classification should be used, which includes: fever plus two or more of the following symptoms and signs (arthralgia/myalgia, frontal headache, retro-orbital pain, rash, hemorrhagic manifestations, leucopenia).
- Laboratory-confirmed cases will be defined as those that have a positive result in one of the following tests: PCR, serology, culture.

It is important to be explicit and consistent about the use of the dengue definition. It is also important to distinguish between ambulatory and hospitalized dengue cases because of the difference in cost between these two categories.

### 3.7 Sample size and sample rate calculation

Calculation of sample size is of crucial importance in the design of a costing study, as it determines the ability to identify significant differences in costs between groups. (24-25) 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 significant results for the clinical endpoints. (25) Sample size requirements for economic evaluations are often larger than those for clinical trials or surveillance systems, due to the high variability in cost data associated with skewed distributions of resource use data. (25-7)

Various methods for calculating sample sizes have been advocated, including, calculating the number of subjects needed to rule out unacceptably high upper confidence limits for the cost estimates. (28-9) For practical reasons, representativeness of cost (rather than representativeness of disease) is key to any economic study. For an economic study it is essential to have a big enough sample size to explain variability, and differences in costs. The main question to address is what sample size is needed to ensure that empirical estimates are closed to the true value of the study population.
The methodology used for the sample size calculation will depend on the number of sites, settings (outpatient, inpatient), age groups, perspectives (private, public), and disease classification (e.g. DF, DHF). A sufficient number of patients per stratification should be included to ensure a statistical calculation of an average cost per case. However, WHO guidelines do not give any ‘minimum number’. 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.

Other issues to consider with sample size calculation include using averages when presenting cost data making explicit the standard deviation; being realistic about the number of dengue cases that can be used for the study; whether sampling occurs throughout the year or only during the peak of a dengue season.

### 3.7.1 Determining the sampling rate and selecting the sample population

Once the sample size has been determined, the sampling rate (k) can be calculated as the ratio of the sample size (n) and the expected number of cases ($N_0$).

$$k = \frac{n}{N_0}$$

To account for seasonal variation, data from primary or secondary data sources will be collected for a one-year period. A combination of retrospective and prospective data can be used at the investigator’s discretion (e.g. 11 months of retrospective and 1 month of prospective; 6 months retrospective and 6 months prospective; 12 months prospective). In some settings, normal hospital records may not have sufficient detail, requiring the use of prospective data collection. Some prospective data collection must be done to collect data through patient interviews.

Systematic sampling will be used to identify sick individuals. For each month of data collection from the medical records, every $k^{th}$ individual should be selected for inclusion. In addition, individuals with concomitant conditions should be excluded from the analysis. Replacement should be done for those meeting this exclusion criterion. Replacement should be done by selecting the next individual.

For out-of-pocket expenses, a prospective data collection approach should be used. If out-of-pocket expenses are expected to represent a small overall fraction of the economic burden, a lower level of precision (15%) may be acceptable. The period of prospective data collection through patient interviews can range from 1 to 12 months. The sampling rate for this component of data collection may need to be higher in order to reach the desired sample size in the shorter time period.

Care should be taken to ensure that both medical records and patient interview data are collected for some subset of individuals. This will allow investigators to explore relationships between the variables (such as the relationship between length of stay and time lost from work). The same prospective individuals should be followed for out-of-pocket as well as direct medical costs. If a 12 month prospective approach is used for both record reviews and patient interviews, than the samples may overlap completely.
3.7.2 Sampling: hospital

The decision on which hospitals to include in the sample first of all depends on the objective of the analysis and the perspective that is to be taken. If the objective is to estimate the costs of dengue treated in hospitals, only a representative selection of hospitals should be included in the sample. On the other hand, if the objective is to carry out a costing study of a preventative intervention from the point of view of the governmental health sector, only public/government health facilities should be included. If the study objective is a cost study from the societal viewpoint, a sample of all types of hospitals should be included in the sample (e.g. public, government, mixed, private).

To ensure that the sample cost estimates can be used to generate a national estimate, the number of each type of hospitals to include in the sample mainly depends on the desired precision of the analysis as well as resources available to undertake the study. Justifications for the choice of types of hospitals as well as their numbers included in the sample should always be given.

The goal is to select a sample of hospitals from each setting (between 3-5 hospitals of each sample type of provider). However, time and research budgets may be limited and complete sampling may not be feasible. Many factors can be considered when developing a reduced sample. When variation between types of hospitals is expected to be small, it may be appropriate to consider them together. If it is known that very limited variability in resource use and/or unit costs exists between the same types of hospitals in the whole country, it can be justified only to include one or two hospitals in the sample. If a hospital provides care to a small percentage of patients, extrapolation of data from other hospital types may be appropriate or ignored altogether. Ultimately the final choice of hospitals should be justified based on the above factors.

The sample size varies by hospital depending on the size of the hospital (number of beds), occupancy rate, geographic location, type of hospital (e.g. public versus private) and quality of care. When selecting hospitals or clinics within each country, certain conditions within that country (climate, population density, and variations in clinical practice, current economic, political and socio-economic climate) should be considered. Another important consideration is access of hospital information and completeness of medical records.

Once hospitals are selected, a list of patients with discharged diagnosis of interest should be obtained. The chart numbers, ages, and discharge dates are obtained for each eligible patients to generate two sampling frames, one for dengue-confirmed cases and the other for suspected cases. These cases can be sorted by their date of discharge. Individual charts are then gathered and abstracted beginning with the most recent cases and working in reverse chronological order until n equaled at least 100 (50 cases per disease).

The majority of the data collected in the hospital should be retrospective if data are considered to be sufficiently robust. A subset of 10% newly and consecutively admitted patients fulfilling the inclusion criteria are subjected to prospective data recording. Their data should be compared to those retrospectively collected to determine whether differences in the recording of resource use exist. If there are no gross differences, their data are to be summarized with a total n equal to at least 100 (90% retrospectively collected and 10% prospectively collected). If there are differences, the utilization rates should be examined to determine where the differences could be attributed. Adjustments to the sample size can be made as a result of these differences.
3.7.3 Sampling: ambulatory centers

The judgment of whether an ambulatory center is ‘representative’ is left to the discretion of the local investigators. The selection of ambulatory centers should be random within the catchment area of the hospitals being studied, depending on the number of patients presenting with dengue, and the willingness of the ambulatory center authorities to participate. Local investigators should formally select the centers that authorize access to data with the appropriate authorities.

If comprehensive medical records are held at the ambulatory center, these are used to estimate information on ambulatory care for patients with dengue. However, in many ambulatory settings, the recording of information is frequently incomplete and, in the case of dengue, many may be unreported (or misreported). To counteract these difficulties, the application of prospective data collection tools is considered to observe ambulatory care for dengue. Actual observation of ambulatory centers provides information on the process of treating dengue. But issues of bias (Hawthorne effect) or time (too time-consuming) may arise.

Once ambulatory centers are selected, sampling of patients with dengue (suspected and confirmed) is performed. A sample size of at least 100 per country and per ambulatory center is required. Discharge logbooks are used to identify patients. The names, ages, chart numbers and dates of admission are obtained for each eligible patient with the diagnosis.

A systematic sampling of individuals should be performed to avoid any potential seasonal biases. This should comprised the following steps: (i) determine the total number ‘n’ in the sampling frame; (ii) decide on the size ‘s’ of the sample; (iii) calculate the ratio (s/n) = k. Select every k’th (round off to the nearest whole number) item on the list, starting at any point.

Replacement should be done if the individual initially selected did not fulfill any of the inclusion criteria or was lost to follow-up. The next individual in the list is selected until the required sample size (n = at least 100 country, per setting) is obtained.

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3 Since a prospective approach is being considered for data collection, additional constraints on the sample size may arise. To avoid problems resulting from restricted sample size, collection of data on resource use and indirect costs should be implemented in the initial stages of data collection.

4 Hawthorne’s effect occurs when individual behavior is altered because of being watched or studied. The effect refers specifically to the increase in worker productivity by the psychological stimulus of being singled out and made to feel important. The effect was first noticed in 1927.

5 The sample size of 100 per case and ambulatory center are chosen as the minimum value for the same practical reasons as that of the hospital dataset.
4. Considerations for costing dengue cases

4.1 Getting an overview of dengue treatment

Understanding where patients seek treatment for dengue is an important consideration. For instance, if most patients are being treated in non-for-profit outpatient centers, these types of healthcare centers should be included in the sample. Table 4 provides a summary of where patients seek treatment for dengue. While it may be difficult to come up with an exact estimate of health service utilization according to provider, efforts should be made to record the most representative list of resource utilization. It should moreover be assessed what proportion of dengue cases are not taken to any health care provider for treatment.

Table 4. Categories of resources consumed

<table>
<thead>
<tr>
<th>Private sector provider</th>
<th>Social security provider</th>
<th>Public sector provider</th>
<th>Other sector provider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entomological surveillance (passive/active)</td>
<td>Epidemiological surveillance (passive/active)</td>
<td>Epidemiological surveillance (passive/active)</td>
<td>Prevention and control (individuals)</td>
</tr>
<tr>
<td>Treatment (resource use)</td>
<td>Treatment (resource use)</td>
<td>Treatment (resource use)</td>
<td>Treatment (resource use)</td>
</tr>
<tr>
<td>Mortality-related costs (resource use)</td>
<td>Mortality-related costs (resource use)</td>
<td>Mortality-related costs (resource use)</td>
<td>Mortality-related costs (resource use)</td>
</tr>
</tbody>
</table>

Information on where patients are treated for dengue can be collected from a number of sources. Demographic and Health Surveys (DHS), which are undertaken periodically in a number of countries, normally include a section on the treatment of infectious diseases like dengue. In this section, data is usually available on the percentage of cases taken to a health facility or provider. Data on the proportion of patients receiving hospital treatment compared to outpatient services can be difficult to estimate, as well as the public versus private facility choice. Likely sources for this information include health care utilization surveys, interviews with doctors, nurses and/or Ministry of Health (MoH) officials, published papers from neighboring or comparable countries.

4.2 Costs associated with dengue

The types of resource use and costs included in a dengue costing study depend on the perspective taken. If the perspective of a health care provider is considered, only those costs and effects for which the health care provider is accountable for are included. If a societal perspective is taken, all costs and consequences are taken into account regardless of whose budget is affected or where in society they occur.

Table 5 provides a ‘menu’ of cost components. There are two main components that should be considered in a dengue cost study: (i) healthcare costs (hospital-related costs, outpatient-related costs) and (ii) program costs (prevention and control, including vector control, costs, education and community mobilization costs, and surveillance costs).
• For the healthcare costs, the unit of analysis for this component is a dengue case recruited in a healthcare facility. In order 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 complexity of 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 in a period of time including a high and low transmission season. The aim of these evaluations is to get the annual costs for each component. Capital costs should not be included in these studies (see economic explanation).

Table 5. A proposed ‘menu’ for cost components

<table>
<thead>
<tr>
<th>Mandatory cost components</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospitalized patients</strong></td>
</tr>
<tr>
<td>Medical Direct (Number and type Stratified by level of assistance including Public and Private Sector)</td>
</tr>
<tr>
<td>Medical Visits, Nurse Visits, Tests / Exams, Drugs, Hospital cost</td>
</tr>
<tr>
<td>Medical Non Direct (Number and type)</td>
</tr>
<tr>
<td>Food, Lodging, Transportation, Treatment by patient (out-of-pocket)</td>
</tr>
<tr>
<td>Indirect</td>
</tr>
<tr>
<td>Absenteeism (work / school) for patient and caregiver</td>
</tr>
<tr>
<td><strong>Outpatient patients</strong></td>
</tr>
<tr>
<td>Medical Direct (Number and type Stratified by level of assistance including Public and Private Sector)</td>
</tr>
<tr>
<td>Medical Visits, Nurse Visits, Tests / Exams, Drugs, Monitoring/Observation</td>
</tr>
<tr>
<td>Medical Non Direct (Number and type)</td>
</tr>
<tr>
<td>Food, Lodging, Transportation, Treatment by patient (out-of-pocket)</td>
</tr>
<tr>
<td>Indirect</td>
</tr>
<tr>
<td>Absenteeism (work / school) for patient and caregiver</td>
</tr>
<tr>
<td><strong>Prevention strategies</strong></td>
</tr>
<tr>
<td>Vector Control</td>
</tr>
<tr>
<td>Routine Activities</td>
</tr>
<tr>
<td>Recurrent cost - Field work personnel, supplies (larvicides/insecticides, traps, protective clothing and uniforms, office supplies, equipment, entomology lab, information system)</td>
</tr>
<tr>
<td>Operational costs (fuel and vehicle, per diems and food, spare parts, maintenance of equipment, training)</td>
</tr>
<tr>
<td>Capital means – equipment (lab and spraying equipment)</td>
</tr>
<tr>
<td><strong>Outbreak control</strong></td>
</tr>
<tr>
<td>Education and Community Mobilization</td>
</tr>
<tr>
<td>Recurrent cost – personnel, office supplies</td>
</tr>
<tr>
<td>Operational costs – media costs (production and promotion), flyers and posters, fuel and vehicle, per diems</td>
</tr>
<tr>
<td>Surveillance</td>
</tr>
<tr>
<td>Recurrent cost – personnel (including lab), office supplies</td>
</tr>
<tr>
<td>Operational costs – information system, fuel and vehicle, per diems, laboratory surveillance (culture and other tests), training</td>
</tr>
<tr>
<td>Capital costs – equipment (lab and spraying equipment), furniture</td>
</tr>
</tbody>
</table>
Table 6 contains a list of data requirement for costing dengue. A description of a dengue costing study can be found in Annex 1. Definitions of common technical terms and a list of websites of interest can be found in Annexes 2 and 3, respectively.

**Table 6. Data requirements for costing dengue**

<table>
<thead>
<tr>
<th>Data Requirements</th>
<th>Description of Data</th>
<th>Numbers Needed</th>
<th>Data Sources</th>
<th>Type of Analysis</th>
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<tbody>
<tr>
<td><strong>Resource use and costs associated with medical care</strong></td>
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<tr>
<td>▪ <strong>Hospitalization:</strong></td>
<td>Costs of hospitalization are the sum of hospital events. Hospital cost is calculated as the product of the LOS for patient and corresponding per diem cost (including personnel and hotel hospital costs), number and cost of diagnostic tests, number and cost of medications, number and cost of services.</td>
<td>Variable depending on completed resource use forms ~100 cases per country/region/sites depending on the variation of costs among the country (based on expert panel recommendation)</td>
<td>▪ Patient Data Abstraction Form ▪ Country-specific costing exercise</td>
<td>▪ Mean length of stay ▪ Mean cost of inpatient care ▪ Mean cost of an hospitalized case of dengue</td>
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<tr>
<td>  ▪ <strong>Intensive care unit</strong></td>
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<td>  ▪ <strong>Observation unit</strong></td>
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<td>  ▪ <strong>Other</strong></td>
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<tr>
<td>▪ <strong>Outpatient visits</strong></td>
<td>Costs of outpatient visits are calculated as the sum of outpatient events. Outpatient events are calculated by combining patient information on resource use and unit cost measures of outpatient visits, tests, medications, and special services.</td>
<td>Variable depending on completed resource use forms ~100 cases per country/region/sites depending on the variation of costs among the country (based on expert panel discussion)</td>
<td>▪ Patient Data Abstraction Form ▪ Country-specific costing exercise</td>
<td>▪ Mean number of disease-related outpatient clinics ▪ Mean cost per outpatient visit ▪ Cost of disease-related visits averted</td>
</tr>
<tr>
<td>▪ <strong>Medications:</strong></td>
<td>Costs of medications are calculated by combining patient information on resource use and unit cost measures of medications, by type of medication, dose, mode of administration, frequency; duration and amount spent.</td>
<td>Variable depending on completed resource use forms ~100 cases per country (based on expert panel recommendation)</td>
<td>▪ Patient Data Abstraction Form ▪ Country-specific costing exercise</td>
<td>▪ Mean number of disease-related medications ▪ Mean cost of medication ▪ Mean cost (incremental) of treating disease</td>
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<tr>
<td>  ▪ <strong>Antipyretics</strong></td>
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<tr>
<td>  ▪ <strong>Other drugs</strong></td>
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### Data Requirements

<table>
<thead>
<tr>
<th>Resource use and costs associated with typical management</th>
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<tr>
<td><strong>Hospitalization:</strong>&lt;br&gt; Intensive care unit&lt;br&gt; Observation unit&lt;br&gt; Other</td>
</tr>
<tr>
<td>Costs of hospitalization are the sum of hospital events. Hospital cost is calculated as the product of the LOS for patient and corresponding per diem cost (including personnel and hotel hospital costs), number and cost of diagnostic tests, number and cost of medications, number and cost of services.</td>
</tr>
<tr>
<td><strong>Outpatient visits:</strong></td>
</tr>
<tr>
<td><strong>Medications:</strong>&lt;br&gt; Antipyretics&lt;br&gt; Other drugs</td>
</tr>
<tr>
<td>Costs of medications are calculated by combining patient information on resource use and unit cost measures of medications, by type of medication, dose, mode of administration, frequency; duration and amount spent.</td>
</tr>
<tr>
<td><strong>Diagnostic tests and procedures:</strong>&lt;br&gt; Blood test&lt;br&gt; Blood culture&lt;br&gt; Other tests and procedures</td>
</tr>
<tr>
<td>Costs of diagnostics and procedures are calculated by combining patient information on resource use and unit cost measures of diagnostic tests and procedures by level of care, setting (hospital and outpatient clinic, public and private), duration, and amount spent.</td>
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<tr>
<td>Data Requirements</td>
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<tr>
<td>-----------------------------------------</td>
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<tr>
<td>Resource use and costs associated with</td>
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<tr>
<td>surveillance and vector-control programs</td>
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<tr>
<td>▪ Human resources</td>
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<tr>
<td>Nurses</td>
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<tr>
<td>Auxiliaries</td>
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<tr>
<td>Drivers</td>
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<tr>
<td>Administrative staff</td>
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<tr>
<td>Supervisors, other</td>
</tr>
<tr>
<td>▪ Physical resources</td>
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<tr>
<td>surveillance centers</td>
</tr>
<tr>
<td>Storage</td>
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<tr>
<td>Other</td>
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<tr>
<td>▪ Equipment</td>
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<tr>
<td>Refrigerators</td>
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<tr>
<td>Transportation</td>
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<tr>
<td>Transport boxes</td>
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<tr>
<td>Other</td>
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<tr>
<td>▪ Supplies</td>
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<tr>
<td>Vector-control</td>
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<tr>
<td>Other</td>
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<tr>
<td>▪ Operations-related</td>
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<td>Telephone / fax</td>
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<td>Paper</td>
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<tr>
<td>Equipment maintenance</td>
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<tr>
<td>Transport</td>
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<tr>
<td>Storage, other</td>
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<tr>
<td>Data Requirements</td>
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<td>--------------------------------------------------------</td>
</tr>
</tbody>
</table>
| **Resource use and costs associated with surveillance and vector-control programs** | - Promotion activities  
  Advertisement  
  Campaigns  
  Training, other  
  Costs of promotion activities are calculated by combining information on resource use and cost measures of promotion activities by personnel time, by type, frequency, duration, and amount spent. | Variable, depending on expert interviews conducted | - Expert Interviews  
  - Surveillance and vector-control program  
  - Country-specific costing exercise | - Type of promotion activities  
  - Cost of surveillance and vector-control program |
| **Parent expenses**                                      | - Over-the-counter drugs and other medical resource items (e.g. laboratory exams, medical consultations) Costs of over-the-counter drugs and other expenses are calculated by combining information on resource use and unit cost measures of over-the-counter medications and others associated with dengue event. The number and cost of over-the-counter medications will be by days of use, type, route, frequency, and amount spent | Variable, depending on caregiver responses ~100 responses per country (based on expert panel recommendations) | - Caregiver questionnaire  
  - Country-specific costing exercise | - Out-of-pocket expenses by parents of sick children |
|                                                        | - Transportation Travel costs include initial cost of taking the child to the hospital or doctor, the number of trips taken by family to visit child, the cost of each one-way trip to the hospital or outpatient clinic. Transport costs are calculated by type, frequency, distance, duration of use, and amount spent | Variable, depending on caregiver responses ~100 responses per country (based on expert panel recommendations) | - Caregiver questionnaire  
  - Country-specific costing exercise | - Transportation cost incurred by parents of sick children |
|                                                        | - Productivity loss Indirect costs are based on lost time from work for the family and the marginal productivity of labor in the country, including the number of days lost from productive work by the family resulting from hospitalizations. Productivity loss are estimated by type, duration, frequency, and amount lost | Variable, depending on caregiver responses ~100 responses per country (based on expert panel recommendations) | - Caregiver questionnaire  
  - Country-specific costing exercise | - Lost time from work for parents who care for their sick children |
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<tr>
<td>Household expenses</td>
<td>Costs of over-the-counter drugs and other expenses are calculated by combining information on resource use and unit cost measures of over-the-counter medications and others associated with dengue event. The number and cost of over-the-counter medications will be by days of use, type, route, frequency, and amount spent</td>
<td>Variable, depending on caregiver responses ~100 responses per country (based on expert panel recommendations)</td>
<td>Caregiver questionnaire Country-specific costing exercise</td>
<td>Out-of-pocket expenses by parents of sick children</td>
</tr>
<tr>
<td>▪ Over-the-counter drugs and other medical resource items (e.g. laboratory exams, medical consultations)</td>
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<tr>
<td>▪ Transportation</td>
<td>Travel costs include initial cost of taking the child to the hospital or doctor, the number of trips taken by family to visit child, the cost of each one-way trip to the hospital or outpatient clinic. Transport costs are calculated by type, frequency, distance, duration of use, and amount spent</td>
<td>Variable, depending on caregiver responses ~100 responses per country (based on expert panel recommendations)</td>
<td>Caregiver questionnaire Country-specific costing exercise</td>
<td>Transportation cost incurred by parents of sick children</td>
</tr>
<tr>
<td>▪ Productivity loss</td>
<td>Indirect costs are based on lost time from work for the family and the marginal productivity of labor in the country or school absentee, including the number of days lost from productive work by the family resulting from hospitalizations. Productivity loss are estimated by type, duration, frequency, and amount lost</td>
<td>Variable, depending on caregiver responses ~100 responses per country (based on expert panel recommendations)</td>
<td>Caregiver questionnaire Country-specific costing exercise</td>
<td>Lost time from work for parents who care for their sick children</td>
</tr>
</tbody>
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4.2.1 Cost components of a dengue case

Direct medical and non-medical costs are defined as the costs of resources incurred for the treatment of a disease. Typically, these will include the cost of hospital stay, diagnostic tests, prescribed pharmaceuticals, and medical staff time. Hospital inpatients are considered patients who are admitted to a hospital for an overnight stay. The operational definition can be adjusted to suit the needs of the specific study. In order to estimate direct medical costs at the tertiary and secondary level, it is necessary to provide an accurate description of the process of treatment. This endeavors to measure the specific quantities of resources consumed during the process of treatment: the number and type of diagnostic tests, and the quantity and type of drug, and so forth. Non-medical direct cost estimates include the cost of transportation to and from the medical facility, childcare, home care, time waiting for care and time undergoing care. Household direct expenses included additional caregiver costs, and the costs of travelling to receive medical care. Given the relative lack of information on these costs and their limited use in decision-making, these costs per event are generally based on secondary data sets.

Indirect costs are based on patient or caregiver productivity losses that may occur due to illness or death. While productivity loss is generally substantial, it does not always translate into a financial loss. For this reason, productivity should be valued in different ways: workdays lost, school days lost, and waiting time (e.g., travel time, waiting time to receive treatment, and time during treatment). Intangible costs are costs related to pain and suffering occurring because of illness or treatment. Gold and contributors (2) argued that although their inclusion in economic evaluations is generally accepted, issues related to the type and way in which these costs should be included remain unresolved. Also included should be the costs associated with lost or impaired ability to work or enjoy other activities or days absent from regular activities due to disease. Indirect costs associated with lost time from paid work were calculated for the parents or caregivers of both hospitalized children and ambulatory children. The first step is to calculate the proportion of caregivers who lose any time from paid work. The average number of hours lost per caregiver is calculated by multiplying the proportion that lost time from paid work by the mean (or median in the case of ambulatory children) number of hours lost. The average indirect cost is then estimated by multiplying the mean number of hours lost per caregiver by the mean hourly wage that was country and gender-specific, assuming an eight-hour shift.

Total costs are the sum of total hospital medical costs, direct non-medical costs, and indirect costs. Limited data are generally available for this variable in each of the countries.

The choice of which type of costs to include in the costing study is country-specific; therefore, costs specific to each country need to be developed.

ductivity by the psychological stimulus of being singled out and made to feel important. The effect was first noticed in 1927.

7 The sample size of 100 per case and ambulatory center are chosen as the minimum value for the same practical reasons as that of the hospital dataset.

8 It is currently recommended that analysts should describe the method chosen for a particular study, and report the indirect costs separately to allow readers to assess the importance of these costs themselves. (15, 24)
### 4.2.2 Other types of cost requirements

Various types of information may be used to aid in the estimation of the overall dengue economic burden (see Figure 1). These include entomological surveillance, epidemiological and laboratory-based surveillance, cost of outbreaks, impact of epidemics in tourism or educational level, etc.

- **Entomological surveillance**: This type of information may be used to determine changes in the geographical distribution and density of the vector, evaluate control programs, obtain relative measurements of the vector population over time and facilitate appropriate and timely decisions regarding interventions. It may also serve to identify areas of high-density infestation or periods of population increase. Selection of appropriate sampling methods depends on the surveillance objectives, levels of infestation, available funding and skills of personnel. A number of methods are available (e.g. larval and pupae survey, adult mosquito population survey, collection of resting mosquitoes, insecticide susceptibility) but were not discussed in any great detail at the workshop.

- **Epidemiological and laboratory-based surveillance**: This information is required to monitor and guide dengue prevention and control programs. Reporting of dengue is not standardized currently. Epidemiological and laboratory data are often collected by different institutions and reported in different formats, and are therefore difficult to collate. DengueNet, a central data management system developed by WHO, can be used to collect and analyze standardize epidemiological and virological data. Nonetheless, the epidemiological surveillance can be performed from the institutional perspective (public sector or MoH perspectives) in each country as a baseline.

- **Resource utilization surveys**: This is necessary to provide an accurate description of the process of treatment. Data on hospital resource use and outpatient resource use are typically collected from a sample of patients. A data abstraction form can be used to collect the following data: inpatient days, outpatient visits, medications, laboratory tests and other procedures. The following information is recommended for confirmed dengue cases: demographic data, disease characteristics, and treatment received due to illness.

- **Household surveys**: A household survey can be used to estimate caregiver and out-of-pocket costs. For direct medical and non-medical costs, the costs can be ascertained through the administration of a questionnaire to all caregivers. This type of tool can be used to inquire about the out-of-pocket costs incurred through ambulatory and emergency room utilization prior to consultation or hospitalization, then daily expenditures for those caregivers whose patient has been hospitalized and one-off expenditures for follow-up consultation fees.

In order to measure the days of time needed to care for a patient with dengue, a short questionnaire can be administered which will gauge the amount of time spent away from productive activities (changes in cash or non-cash production). An estimate of the number of days required to care for a sick individual should be assessed. For the valuation of lost earnings borne by caregivers, these should be calculated according to the nature of productivity lost, i.e., market or non-market, cash or non-cash, agricultural or non-agricultural. For each category of lost productivity, the associated selling price, or estimated value, per unit should be combined with the quantity of each unit of production lost (number of days required to care for the sick patient).
4.3 Potential data sources

Data on disease 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 disease are rarely present in a single source. Data must therefore be taken from a number of different sources, and synthesized using analytical structures called models.

For healthcare costs, primary data collection (data obtained from empirical studies) should be the gold standard to evaluate costs. Secondary data may be used whenever available. The main sources of secondary data are official health information systems, hospital records and payments. The main advantage of relying on primary data collection is to obtain more reliable information regarding the cases. The drawback is the cost and time consumed to conduct the cost study.

In terms of program costs, the official government data should be the main source of cost data at local, regional and national level. The main advantage of using official government data is that countrywide Information may be available, although in different institutions or level of government. The drawback is that data may not be easily available in time, or not sufficiently detailed and may be difficult to be checked for completeness. Access to cost data may be limited in certain contexts.

Resource use data can be collected from a number of sources such as demographic and health surveys (DHS), which are undertaken periodically in a number of developing countries; interviews with physicians, nurses and/or ministry of health officials; published papers from neighboring or comparable countries; national administrative data (e.g. from the ministry of health); hospital data; household surveys; physician surveys; and published literature.

Other alternatives of sources of cost estimates are likely to be available in each country. These alternatives include:

- **National price lists**: Many countries maintain price lists for medications used by public hospitals and clinics. Since these prices are based on volume government purchases, the prices may approximate the actual economic costs. If the government subsidizes these prices, then they may not be an appropriate source of information. Price lists should be available from hospital or clinic administrators. This source is likely to be most useful if laboratory procedures are routinely done outside of the hospital or clinic in a separate laboratory.

- **Private laboratory price**: If standardized national prices are not available, the price of tests in private laboratories may be used as a substitute. Actual purchase prices may still be used. For each item, private lab prices should be determined for the sample of laboratories. Prices should include any discounts. Private laboratory prices are likely to be an overestimate of the true economic cost of the procedures. As a result, they are most appropriate when national price lists are not available or to complement standardized international cost estimates.

- **Standardized international price lists**: As a part of its WHO-CHOICE project the WHO has developed cost estimates for many common laboratory tests. These cost estimates are based on resources used for each procedure and the cost of the inputs in a range of countries. Cost estimates from a sample of countries can then used to estimate costs for other countries based on the income levels.
- **Purchase price:** If standardized national prices are not available, actual purchase prices may be used. For each item, purchase prices should be determined for the sample of facilities used. Prices should include any discounts and delivery/shipping charges.

- **Management Sciences for Health (MSH) International Drug Price Indicator Guide** ([http://erc.msh.org](http://erc.msh.org)): In absence of a national price list or reliable data on purchase prices, standardized international prices lists may be used. These lists include many common medications and reflect economic costs. Information is available online.

- **A household survey can be used to estimate caregiver and out-of-pocket costs.** For direct medical and non-medical costs, the costs can be ascertained through the administration of a questionnaire to all caregivers. This type of tool can be used to inquire about the out-of-pocket costs incurred through ambulatory and emergency room utilization prior to consultation or hospitalization, then daily expenditures for those caregivers whose patient has been hospitalized, and one-off expenditures for follow-up consultation fees.

In order to measure the days of time needed to care for a patient with dengue, a short questionnaire can be administered which will gauge the amount of time spent away from productive activities (changes in cash or non-cash production). An estimate of the number of days required to care for a sick individual should be assessed. For the valuation of lost earnings borne by caregivers, these should be calculated according to the nature of productivity lost, i.e., market or non-market, cash or non-cash, agricultural or non-agricultural. For each category of lost productivity, the associated selling price, or estimated value, per unit should be combined with the quantity of each unit of production lost (number of days required to care for the sick patient).

The selection of an information source for a dengue costing study should be based on the extent to which it represents an estimate of the economic cost of the item and the acceptability of the source within the country (i.e. if the national price list is a common tool for medical professionals).

### 4.4 Methods for costing hospitalized dengue cases

The purpose of the section is to describe alternative approaches for estimating the unit cost of hospital visits. Separate estimates may be developed for public and private facilities, as well as facilities in different regions (for example urban and rural). A similar approach may be used to estimate the costs associated with care in the outpatient setting.

Several approaches can be used for estimating the cost of each type of visit. These methods differ in their intensity (financial and time resources required to carry them out) as well as the accuracy of the estimates they produce. The method used in a particular study will be selected based on the purpose of the study and the needs of decision makers. The alternative methods described below are presented in order of increasing intensity.

As a part of its WHO-CHOICE project the WHO has developed estimates of the economic cost of a hospital bed day in different settings. Regional and country estimates are developed using empirical data from a sample of countries of varying economic income levels. Country data are then used to develop a predictive model that estimates the per diem hospitalization cost of different types. Regional and country estimates are based on Gross Domestic Product (GDP), type of hospital, and the level of capacity utilization. These estimates are given in international dollars, which can be converted to local currency. Online estimates are available for each region based on...
the mortality strata, utilization rate, and hospital type (www.who.int/whosis/cea/prices/). Country specific estimates can be developed using the attached accompanying spreadsheet.

For some countries and health care centers, existing estimates of hospitalization cost may already exist. These estimates may be from published literature, administrative sources, or previous costing activities. In order to be used for the cost per bed day estimates in this study, these costs should include all relevant cost components (facilities, equipment, maintenance, administration, and personnel). These estimates are likely to be most useful when they are considered generally acceptable to decision makers. They may also be useful as a complement to WHO-CHOICE estimates. If data are collected from more than one hospital of the same type, then a weighted average should be used based on the expected number of dengue patients treated.

The simple direct estimation of per diem cost is an approach that uses administrative, cost, and healthcare utilization information from selected facilities to estimate the per diem hospitalization cost of different types of facilities. If data are collected from more than one hospital of the same type, then a weighted average should be used based on the expected number of dengue patients treated.

The full costing activity for estimating per diem costs approach is the most detailed and resource intensive. The approach uses detailed administrative, cost, and healthcare utilization data from a statistically selected sample of facilities. The approach should be used only after other methods have been utilized to develop preliminary estimates. It should only be considered when more precise estimates are needed and worth the additional required resources. If data are collected from more than one hospital of the same type, then a weighted average should be used based on the expected number of dengue patients treated.
5. Considerations for costing dengue outbreaks

5.1 Definition of a dengue outbreak

Although there is no clear agreement on the definition of a dengue outbreak, an outbreak may be defined as one case in an area where no other case has been reported, or the number of cases representing two standard deviations away from the mean (average) of cases.

5.2 Cost components of a dengue outbreak

The number of people infected with dengue will increase during an outbreak, resulting in an increase in the costs associated with vector control activities (increased government and household cost); public education/media communication (increase government cost); surveillance system (increased laboratory control that increased government cost); medical personnel (nurses, physicians); tourism decreased revenue; and inter-sectoral collaborations (outside the health sector).

5.3 Sources for costing a dengue outbreak

The sources for costing dengue outbreaks include published literature; budget sources from the government and states; household interviews to know the resources consumed during an outbreak; inter-sectoral budget, including municipalities to mitigate the impact on tourism. If no data are available, other countries’ estimation should be used.

5.4 Steps for measuring outbreak costs

The steps for measuring outbreak costs are: (i) confirmation of an outbreak; (ii) estimation of the number of people infected during an outbreak; (iii) the number of the outbreak cases times the cost per outbreak case; (iv) gather information on budget impact (e.g. vector control strategies, surveillance, media campaigns, tourism impact and medical personnel) from government officials at all relevant levels; (v) investigation of complete budget expenses by individuals or their families in response to an outbreak (e.g. vector control program, tourism impact).

5.5 Discounting

It is generally agreed that all future costs and health consequences should be stated in terms of their present value. (27) In order to convert costs and benefits, which may be incurred at different points in time, to a present value (to account for time preference9) (2, 30), a process called discounting is used. 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 quite a bit of controversy surrounding the issue of what discount rate to use or how to convert future health care costs using discounting as the basis. The problems involved in the

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9 Time preference is used to define people’s preference for present over future outcomes and future costs over present costs.
measurement of costs and in deciding which rate to use have been documented extensively (2, 30), particularly in the context of costing treatment. Current guidelines recommend using a discount rate of both 3% and 5% (15, 31-2); however, it is also recommended that data should be provided undiscounted to allow recalculation by the reader at any rate. (33)

For the present guidelines, the recommendation is that all future cost estimates be discounted at a rate of 3%.

5.6 Purchasing power parity conversions and official exchange rates

Cross-country comparisons of health care costs have attracted considerable attention in the last two decades, particularly in the context of costing studies (34-5). Two methods are generally used to make cross-country comparisons. 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.

There are prices (rates) at which currencies are bought and sold on the international market. International comparisons based on market exchange rates can greatly over- 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 only reflect the equalization of prices for internationally traded goods and not the prices of non-traded 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 to other alternative methods (36).

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.\(^{10}\) 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 U.S. 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. (36) Although they are an improvement on exchange rate conversions, a number of measurement problems have been recognized with the use of PPP conversion factors. (36) This is partly because PPP conversions make comparisons of aggregate expenditure across countries, rather than of the prices of health care interventions. (37) 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 values that individuals in different countries attach to different components of health care or to differences in the composition of that basket. (36) Moreover, PPP conversion factors are only estimated every five years and health-specific PPPs are measured on a very small sample of items. (36) In addition, there is a bias towards pharmaceutical prices with health-specific PPPs. This makes the quality of the data at more detailed level (such as health) poor, particularly for developing countries. (36)

\(^{10}\) PPP-adjusted Gross Domestic Product (GDP) or Gross National Income (GNI) values are the values converted from local currency unit into USD. They are converted into USD because the US can be used as the base country.
5.7 Data uncertainties

There are four main areas where data uncertainty may be encountered in a costing study. These include: (i) data sources; (ii) generalizability; (iii) extrapolation; and (d) analytic method. (37-8) Additional areas that add to uncertainty include: inadequate sample sizes, skewed cost data, discount rates and unit costs may introduce additional uncertainty. These uncertainties are generally described by Manning and collaborators (39) as parameter uncertainty and modeling uncertainty.

Parameter uncertainty refers to the numerical values of the parameters that are unknown, and entail uncertainties in the estimates of: disease epidemiology, response to treatment, and vaccine efficacy. These parameters may be uncertain due to sampling variation, disagreement about the appropriateness of the range of plausible values that are used, lack of information regarding disease epidemiology, and disease costs. (39). 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.

Manning and colleagues (39) relate modeling uncertainty to the structure of the model 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 in order to make better inferences about the true level of uncertainty. (2)

A clear hierarchy of uncertainty is found between the two sources of uncertainty such that parameter uncertainty may be dependent on the model structure, and the model structure dependent on the modeling process. (40). In many of these areas, uncertainty is unavoidable. According to Briggs and Sculpher (38), uncertainties can be minimized by identifying potential areas where uncertainty may arise early in the planning phase and applying sound and transparent methods to data collection and costing. Briggs (39) recommends the use of sensitivity analysis to deal with these uncertainties: one-way or multi-way analysis, threshold analysis, analysis of extremes and probabilistic sensitivity analysis.

5.7.1 Sensitivity analysis

Sensitivity analysis is a method that is used to deal with uncertainty in economic evaluations where the effect of ranges in clinical or costing variables on the overall result of the evaluation is explored. (41) Drummond and collaborators (30) and Gold and collaborators (2) point out a few limitations with sensitivity analysis, which include: selection bias resulting from individuals choosing at their own discretion variables and alternative values to vary; arbitrary interpretation of a sensitivity analysis due to lack of guidelines for interpreting results; and underestimation or overestimation of parameter uncertainty. The following section describes the approach used in developing sensitivity analysis as a way of dealing with parameter uncertainty in the dengue costing model.
As previously indicated, sensitivity analysis is conducted to test the impact on results of changes in uncertain or unfixed parameters and assess the robustness of the cost estimates to changes in assumptions and the values of the input variables. Sensitivity analysis involves three steps. These are clearly outlined by Drummond and colleagues (30) and include: (i) identifying the uncertain parameters for which sensitivity analysis is required; (ii) specifying the plausible range over which uncertain factors are thought to vary; and (iii) calculating study results based on combinations of parameters varied.

5.7.2 Univariate sensitivity analysis

Univariate (or one-way) sensitivity analysis can be used when presenting cost estimates. This is the simplest and most common form of sensitivity analysis (2, 31), and serves as a precursor for other types of sensitivity analysis (e.g., multivariate analysis). Despite providing some indication of how sensitive the results are to a change in the parameter, univariate analysis is limited. For example, univariate analysis does not recognize that more than one parameter is uncertain and that each could vary within its specified range (2, 30). Moreover, by treating one variable at a time, univariate analysis provides an incomplete estimate of how uncertain the cost-effectiveness ratio is. This may lead to underestimating the overall variability in the cost estimate. (2) Singly combining the extreme values of parameters to gain an overall best or worst estimate may have the opposite effect in terms of overstating the uncertainty.11 According to Manning et al. (39), three related problems need to be considered when using univariate sensitivity analysis. First, the incremental costs depend not just on one but also on multiple parameters (i.e., the numerator depends on the sum of hospitalizations, office visits, drugs and supplies). Secondly, the interaction of certain factors may imply that the cost estimate may be quite different from the sum of individual contributions. Thirdly, the cost estimate may be derived from uncertain numbers and the uncertainty in the ratio may be substantially larger than that of either of its elements.

5.7.3 Multivariate sensitivity analysis

Multivariate sensitivity analysis provides a more complete picture of the level of uncertainty in the cost-effectiveness ratio and is thus a more sophisticated approach to dealing with uncertainty. With this approach, multiple parameters are varied at a time. Due to the uncertainty of how variables are related or linked with one another12, the application of multivariate sensitivity analysis may be limited. The use of this form of sensitivity analysis may be restricted due to the existence of many uncertain parameters, which would lead to various unknown combinations. A large number of combinations of these parameters would make this form of sensitivity analysis unfeasible. (30)

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11 The latter approach is only useful when the results are insensitive to the combination of parameter values considered which is not the case for the current intervention.
12 The relationships can include correlations among uncertain estimates of variables or the possible effects of any nonlinearities or interactions in the model.
5.7.4 Probabilistic sensitivity analysis

To compensate for the limitations of univariate and multivariate sensitivity analyses, a third approach can be considered to deal with multiple sources of uncertainty – probabilistic sensitivity analysis. (39). This is a method of decision analysis in which more than one variable is changed to simulate random error. With this type of sensitivity analysis, probability distributions are specified for each uncertain parameter (e.g., mortality rate, hospital and outpatient incidence rates, direct medical costs and indirect costs, vaccine efficacy against mortality, hospitalization and ambulatory visits). Various techniques can be used to address this uncertainty, including Monte Carlo simulation and bootstrapping techniques.

For national disease burden variables, distributions (ranges) can be used to characterize the cumulative incidence of illness outcomes (hospitalization, ambulatory visits, and death) in each country and the proportion due to dengue. Wider distributions can be used for countries for which the estimates were extrapolated from foreign data.
6. Methodological considerations

6.1 Perspective and research question

Decisions regarding the perspective of a costing dengue study in the Americas need to be made in the planning phase of the study. The perspective that is taken determines the costs and effects to include, as well as how to value these costs and effects. Adoption of a societal perspective in economic evaluations is widely advocated in both national guidelines (31-2) and the published literature. (2, 15) By adopting this broad perspective, data can be disaggregated and analyzed from a number of viewpoints. (15)

Costs associated with dengue in the Americas are likely to be of interest to a number of groups, including the local government, provider institutions, international donors, health workers, and the general population. Furthermore, failure to include all relevant costs and benefits may result in underestimation of the true value of dengue. Adoption of a societal perspective would therefore be advisable. However, a number of difficulties exist with this approach. The main difficulty lies in valuing productivity losses when a large proportion of the population affected by dengue is involved in unpaid or informal work. Other problems may arise with detecting long-term disabilities and assigning a value to the associated loss of future earnings or productivity.

6.2 Resource use

Individuals affected by dengue are likely to make extensive use of health and social services because of their condition and for other medical reasons. In many circumstances, it is not possible to clearly distinguish resource use that is attributable to dengue (or its consequences), from resource use attributable to other causes. To address this issue, patient-level data is recommended.

The advantages of prospectively collecting resource use data alongside a surveillance system are many, including the ability to perform statistical tests for significant differences between vaccinated and placebo groups. In addition, a framework for data collection for the purposes of surveillance is already well established, so the task of collecting resource use items would be relatively easy.

When resource use data are collected within a surveillance study, health economists generally recommend that all study subjects should be included. For practical reasons, however, it may be necessary to restrict data collection to children included in morbidity surveillance of the more representative study sites. Another important issue to consider is whether data should be collected for resource use independent of the underlying cause, or restricted to resources used for illnesses due to dengue. Advantages of the second approach include ease of data collection, and reduced variability in cost data; however, problems may arise when disease conditions are multifactorial. In addition, by restricting data collection to suspected dengue-related events, it is possible that other wide-ranging effects of the disease which are not yet known, may not be detected.
6.3 Resource use data: country groupings

A study being conducted in many sites and in many countries presents difficulties about how to aggregate and analyze resource use 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 or not 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. Most economic guidelines consider these data of low transferability.

Country groupings (if any) of resource use can be established following interim evaluation. These groupings may reflect geographically or culturally similar areas in which resources used to treat dengue appears to be similar. Criteria for grouping countries are established at an early stage, and groupings determined ‘blindly’, using interim data undivided by treatment group, so that the risk of selection bias in groups was minimized.

6.4 Financial versus economic costing

There are important differences between financial costs and opportunity costs. On one hand, financial costs are expenditures for resources to implement the program; based on market prices; convenient, sometimes incomplete measure of costs (e.g. salaries for personnel, supply costs). On the other, opportunity costs: value of the lost benefit because the resource is not available for its next best use; resource’s cost is the sacrifice necessary to obtain goods or services (e.g. volunteer time, donated space). It includes the true costs of a disease, the opportunity costs.

The use of opportunity cost is optimal but there are major challenges to overcome when estimating the opportunity costs. Using cost data that is financial in nature may be practical though care must be taken to be clear when financial data is used. Financial costs, on the other hand, will be used from the practical standpoint, considering the variable costs. Economic (opportunity) costs will be used when data availability and time allows.

6.5 Full versus incremental costing

For costing dengue, the full cost should be ideally considered. The full cost considers both the fixed and variable costs without any consideration to changes in costs; however, it will be difficult to collect fixed costs related dengue diseases. The incremental cost is the change in the total costs that arises when the quantity produced changes by one unit. That is, the cost of producing one more unit of good. This type of costing should not be modeled if the question is only about costing dengue.

6.6 Treatment costs

For collection of cost data, decisions need to be made regarding the level of precision required. The spectrum of precision ranges from a micro-costing approach, where individual components of
resource use are identified and measured, to a gross-costing approach, where larger intermediate products such as a hospital day are used.\textsuperscript{13} (43) The choice between micro- and gross-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 micro-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. (44)

Costs not directly associated with childcare could be estimated using a gross-costing approach, with cost per hospital day or cost per ambulatory visit as the component events. An alternative option would be to use gross costing for all resources used. Cost of a typical hospital admission or ambulatory visit for a particular diagnosis could be made. An advantage of this approach would be simplicity of data collection; however, problems may arise in the Americas, where detailed records of departmental expenditures are often lacking.

Issues surrounding the representativeness of resource use data collected within a surveillance study are central to the value of cost-effectiveness estimates. Biased estimates may arise because of the facilities included, characteristics of the surveyed population, and costs. Furthermore, parents’ out-of-pocket expenses are likely to be minimal within the surveillance setting, and therefore not representative of the usual situation. Resource use data needs to reflect service utilization patterns throughout the country, at the primary, secondary and tertiary levels. Services provided by Non-Government Organizations (NGOs) and private facilities should also be considered in a societal perspective. In addition, a distinction may need to be made between urban and rural areas, and seasonal patterns of illness may need to be considered when timing data collection.

Methods of controlling for costs include the use of modeling through decision analysis, 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 obviate the need for information on resource use patterns 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 Latin American countries; hence, 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 round tables; however, there are currently no formal guidelines on their use. Similarly, there is little consensus on the numbers and types of facilities which need to be included if data are collected prospectively.

\textsuperscript{13} Aggregate costs or micro-costing can be calculated from detailed “bottom-up” costing exercises, but are more usually the result of “top-down” allocation of costs or gross costing to case-mix groups. In the latter approach, costs for the elements of service directly attributable to a procedure are combined with an allocation of overhead costs based on an accounting convention. The total is then divided by an activity rate to produce an average procedure cost. Pure bottom-up costing is based on costing the detailed listing of items (disposables and consumables), laboratory tests, and drugs used in the procedure and the medical staff time. Accounting methods (similar to the above) are used to allocate the per patient cost for equipment used and the department allocation for the space.
6.7 Cost savings

Cost savings are likely to accrue primarily from changes in patterns of health resource utilization. Identification of the relevant resources to include requires knowledge of current healthcare utilization patterns and an understanding of treatment practices in a range of facilities. For the Latin American setting, it is important to distinguish between urban and rural areas, as well as resource use at the primary, secondary and tertiary levels. It may also be necessary to consider whether resource utilization in non-government organizations and private health facilities differs from that in government facilities.

Resources utilized include hospital care, investigations, medications, oxygen, intravenous fluids, blood transfusions, and child transport. When a societal perspective is taken, health provider as well as parents' out-of-pocket costs should be considered. In addition to costs associated directly with childcare, other costs including ancillary services (laboratory, pharmacy, radiology), administration (accounts, personnel, medical records), and support services (cleaning, laundry, maintenance, sterilization) need to be included.

Costs should be identified in the early stages of planning, in order to employ appropriate methods for controlling for the bias that may be introduced. The increased number of investigations performed can themselves lead to further costs, resulting from changes in antibiotic use, oxygen use and duration of admission, as a consequence of identification of disease states which would otherwise have gone undiagnosed.

6.8 Missing or incomplete cost data

Methods to handle missing data have been an area of statistical research for many years. Several approaches for missing data imputation have been presented in the literature. In most situations, a common way for dealing with missing data is to discard records with missing values and restrict the attention to the completely observed records. This approach relies on the restrictive assumption that missing data are Missing Completely At Random (MCAR). In other words, that the missingness mechanism does not depend on the value of observed or missing attributes. This assumption rarely holds and, when the emphasis is on prediction rather than estimation, discarding the records with missing data is not an option. An alternative and weaker version of the MCAR assumption is the Missing at Random (MAR) condition. Under a MAR process the fact that data are missing depends on observed data but not on missing data themselves. While the MCAR condition means that the distributions of observed and missing data are indistinguishable, the MAR condition states that the distributions differ but missing data points can be explained (and therefore predicted) by other observed variables. In principle, a way to meet the MAR condition is to include completely observed covariates that are highly related to the missing ones. The most popular conditional mean method employs least squares regression but it can be often unsatisfactory for nonlinear data and biased if model misspecification occurs. Other methods include traditional multiple imputation and multiple imputation (data augmentation) through a Bayesian analysis via a Gibbs sampler. For the first method, the imputation is carried out by generating missing values from the conditional multivariate normal distribution, taking into account the family structure. This imputation is completed \( x \) times to produce \( x \) complete data sets to analyze. From these \( x \) analyses, the final point estimate would be the mean of the \( x \) estimates. The second method is more complex. The Gibbs sampler is a particular Markov
chain algorithm that is useful when working with high dimensional problems. In addition to the 
traditional use of the Gibbs sampler, an imputation step can also be added to impute missing 
values. A multiple imputation scheme can be implemented by having an imputation step at the 
beginning of the Gibbs sampler. In order to overcome the shortcomings of the conditional mean 
imputation method, it is proposed that one way of reducing the problem of missing or incomplete 
(resource use) data is to learn patterns of disease to allow interpretation of clinical records.

6.9 Ethical considerations

A number of specific ethical issues may arise when costing dengue, including informed consent 
and the issue of confidentiality. There are generally two main areas of concern related to the 
safeguard of subject's privacy: (i) collection of clinical data and treatment from medical records of 
children, and (ii) informed consent to conduct parent interviews. There are various ethical issues 
that need to be considered when constructing and using cost estimates, including: what costs 
should be accounted for; what discount rate should be applied to costs; how to aggregate costs. 
Much work remains to be done before it will be even be possible to integrate complex ethical 
concerns into these types of studies. There is no consensus on how complex ethical concerns 
should be integrated in these. However, different answers may be appropriate for a particular issue 
in the different contexts in which economic studies are used.

6.10 Confidentiality

The key ethical consideration in this area is keeping the identification or identifiers of the subjects 
protected at all times. The search for possible subjects who meet the criteria for inclusion in the 
data collection phase required the search of medical records in the hospitals. For this reason, 
appropriate institutional consent and compatibility with institutional requirements should be 
sought. Once subjects are identified, the information is gathered in a database where name and 
other identifiers are protected through a coding system. Names and other sources of identification 
are removed from the forms.

6.11 Informed consent

Many costing studies will require that data on cost of treatment be collected. This information may 
be obtained from different clinical settings (public and private sector, hospitals of different levels, 
health centers) and from individuals with different clinical characteristics and different severity 
and outcomes) thus providing the diverse variables for the costing study. Ethical approval should 
be sought for each country.

A letter of invitation and summary details of the aims, methods, anticipated benefits and potential 
disadvantages of the interview should be prepared in advance. Parental informed consent forms 
should be sought in writing prior to the interview, by participating clinicians. Measures should be 
taken to safeguard the privacy of the parent and minimize the impact of the study on the 
caregiver’s ability to respond. Caregivers should be advised that they are free to abstain from 
participation in the study and that they are free to withdraw their consent to participation at any 
time. Their refusal to participate in the interviews should not interfere in any way with their 
individual’s ability to receive care.
7. Conclusions

While 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 multi-country 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.

These Guidelines were produced by a group of experts, all of whom are or have been involved in costing dengue. The evidence on dengue is continually evolving. Future versions of these Guidelines will be necessary in the future.
8. References


Annex 1. Cost evaluation description

The following pages provide a more detailed description of dengue costing studies.

Cost types
Patient-level data on resource use and unit cost data will be combined to estimate total economic cost per patient (Cost_Total) as the primary outcome measure. Different sub-categories of cost will also be estimated per patient. These include medical cost (Cost_Med), non-medical direct costs (Cost_NMDir), and indirect costs (Cost_Indir).

For each category, the mean and standard error should be estimated for each facility and for the sample as whole, when possible. Costs should be analyzed from the societal, healthcare system, and household perspectives. Household costs include only the direct or indirect costs borne by the families of patients with dengue. The healthcare system perspective includes those medical costs borne by public provider, social security, and the private healthcare system. The societal perspective includes all categories of costs (direct and indirect, medical and non-medical) regardless of who bears the cost.

Calculation of costs\(^{14}\)
For each patient, total costs for the visit (whether inpatient or outpatient) will be estimated as follows.

**Hospital Costs**
The total costs of hospitalized patients for patient \(i\) at facility \(j\) (Cost_Total\(_{ij}\)) are calculated as the sum of medical costs (Cost_Med\(_{ij}\)), non-medical direct costs (Cost_NMDir\(_{ij}\)), and indirect costs (Cost_Indir\(_{ij}\)).

\[
\text{Cost}_\text{Total}_{ij} = \text{Cost}_\text{Med}_{ij} + \text{Cost}_\text{NMDir}_{ij} + \text{Cost}_\text{Indir}_{ij}
\]

For hospitalized patients, the medical cost of patient \(i\) at facility \(j\) is calculated by combining patient information on resource use and unit cost measures of hospital stay, tests, medications, and special services.

\[
\text{Cost}_\text{Med}_{ijk} = \text{LOS}_{ik} \times \text{C}_\text{Perdm}_{jk} + \text{N}_\text{Diag}_{is} \times \text{C}_\text{Diag}_{s} + N_\text{Med}_{it} \times C_\text{Med}_{t} + N_\text{Serv}_{iu} \times C_\text{Serv}_{u}
\]

Where LOS\(_{ik}\) is the length of stay for patient \(i\) in ward \(k\), C_Perdm\(_{jk}\) is the per diem cost of hospitalization in ward \(k\) at facility \(j\), N_Diag\(_{is}\) is the number of diagnostic tests of type \(s\) performed for patient \(i\), C_Diag\(_{s}\) is the cost of diagnostic test type \(s\), N_Med\(_{it}\) is the number of medications of type \(t\), C_Med\(_{t}\) is the cost of that medication, N_Serv\(_{iu}\) is the number of services of type \(u\) performed on patient \(i\), and C_Serv\(_{u}\) is the cost of the service \(u\).

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\(^{14}\) This pertains to the costs associated with dengue cases. A similar approach would be used for the calculation of dengue outbreaks where surveillance and other outbreak-related activities take place.
For each resource use category (medications, diagnostic tests, and special services) a unique index should be assigned to each distinct item (for medication). Where inputs differ by dose a separate index is assigned. For each patient, resource use data is collected through the patient healthcare utilization abstraction form. The unit cost of each item should be determined as described above in the section on Unit Costs. Unit costs do not vary between individuals.

Non-medical direct costs include travel costs or other non-medical out-of-pocket expenses encountered by households. For this study non-medical direct costs include only travel costs for household members and other specific items identified by respondents. Only costs encountered prior to the time of discharge are included.

\[ \text{Cost}_{\text{NMDir}}_{ij} = \text{C}_{\text{TravInit}}_{ij} + \text{C}_{\text{Trip}}_{ij} \times N_{\text{Trips}}_{ij} + \text{C}_{\text{OtherNMD}}_{ij} \]

Where \( \text{C}_{\text{TravInit}}_{ij} \) is the initial cost of taking the child to the facility, \( N_{\text{Trips}}_{ij} \) is the number of trips taken by family members to visit the child during the stay, \( \text{C}_{\text{Trip}}_{ij} \) is the cost of each one way trip to the hospital, and \( \text{C}_{\text{OtherNMD}}_{ij} \) is the total of other non-medical out-of-pocket expenses identified by the patient’s caregiver. The cost of initial and subsequent trips varies between patients. Its calculation depends on the mode of transport used (as described in the caregiver survey). If the caregiver paid directly for transportation then the out-of-pocket expenditure per trip should be used (based on their response). If the trip was not paid for directly (e.g., family auto, walking) then the cost is estimated based on the distance from home to the facility and standard per kilometer costs based.

Indirect costs associated with each hospitalization should be estimated based on lost time from work for the family and the marginal productivity of labor in the country.

\[ \text{Cost}_{\text{Indir}}_{ij} = N_{\text{Dlost}}_{ij} \times \text{C}_{\text{Labor}} \]

Where \( N_{\text{Dlost}}_{ij} \) is the number of days lost from productive work by the family as a result of the hospitalization, and \( \text{C}_{\text{Labor}} \) is the marginal productivity of labor for each country.

**Outpatient Visit Costs**

The total costs of patients treated in outpatient facilities should be calculated as the sum of medical costs, non-medical direct costs, and indirect costs.

\[ \text{Cost}_{\text{Total}}_{ij} = \text{Cost}_{\text{Med}}_{ij} + \text{Cost}_{\text{NMDir}}_{ij} + \text{Cost}_{\text{Indir}}_{ij} \]

For outpatients, the medical cost of patient \( i \) at facility \( j \) should be calculated by combining patient information on resource use and unit cost measures of visit, tests, medications, and special services.

\[ \text{Cost}_{\text{Med}}_{ij} = \text{C}_{\text{Visit}}_{ijk} + N_{\text{Diag}}_{is} \times \text{C}_{\text{Diag}}_{is} + N_{\text{Med}}_{it} \times \text{C}_{\text{Med}}_{it} + N_{\text{Serv}}_{iu} \times \text{C}_{\text{Serv}}_{iu} \]

Where \( \text{C}_{\text{Visit}}_{jk} \) is the cost of an outpatient visit of type \( k \) (ER, day room, etc) for patient \( i \) at facility \( j \), \( N_{\text{Diag}}_{is} \) is the number of diagnostic tests of type \( s \) performed for patient \( i \), \( \text{C}_{\text{Diag}}_{is} \) is the cost of diagnostic test type \( s \), \( N_{\text{Med}}_{it} \) is the number of medications of type \( t \), \( \text{C}_{\text{Med}}_{it} \) is the cost of that medication, \( N_{\text{Serv}}_{iu} \) is the number of services of type \( u \) performed on patient \( i \), and \( \text{C}_{\text{Serv}}_{iu} \) is the cost of the service \( u \).
Annex 2. Definition of common technical terms

Cost comparisons across countries and regions are hindered by the lack of clarity in technical terms and cost concepts, and the inconsistent use of these terms. The following pages\textsuperscript{15} provide some clarity to some of the concepts with which the user of these guidelines should be familiar.

**Analytic Horizon:** The time over which benefits and costs of a given treatment or program are measured as accruing.

**Average Cost:** The total cost divided by the total output. This gives the average cost per item produced.

**Average Cost-Effectiveness Ratio (ACER):** A cost-effectiveness ratio calculated with respect to a hypothetical zero-cost, zero-life-expectancy scenario. The US Panel cautions against reporting the ACER since it is potentially confusing to readers. Other recommendations have been more favorable to ACERs.

**Base Case:** The primary results reported in a CEA study around which sensitivity analyses are often performed and reported. (Note: It is possible for the base case to be different from the reference case).

**Comparator:** Economic evaluations must compare alternatives. Usually this is the standard of care or what is currently common practice. There may be multiple comparators if the cost-effectiveness analysis involves more than two options.

**Contingent Valuation:** A method to assess individuals' willingness to pay. Respondents are asked to consider hypothetical scenarios and to think about the contingency of an actual market existing for a program or health benefit and to reveal the maximum they would be willing to pay for such a program or benefit.

**Cost Benefit Analysis:** In CBA the outcomes are valued monetarily. CBA often includes net benefits from a particular treatment or program for a more robust (net) costing picture.

**Cost Effectiveness Analysis:** CEA can use natural outcomes such as death or morbidity.

**Cost Utility Analysis:** CUA uses health utilities such as the QALY or DALY as outcomes.

**Cost Minimization Analysis (CMA):** A form of cost-effectiveness analysis in which the effectiveness of comparator interventions are presumed to be equal. Such an analysis would be focused solely on costs.

**Cost to charge ratios:** Proportion developed based on cost accounting system data that converts charges for medical services to the true economic costs. Hospitals, for example,

\textsuperscript{15} Adapted from the Centre of Health Economics (CHE) Research Paper 7, 2005.
charge more than they are actually paid. Using the charges listed from a hospital would overinflate the calculated cost of a program.

**Decision Tree Model:** A model used to represent a sequence of chance events and decisions over time. Each chance event is assigned a probability and each path through the decision tree, which represents one unique sequence of chance and decision events, is associated with a unique set of costs and effects (i.e., utilities).

**Deterministic Model:** A decision analytic model that assumes certainty in its parameters.

**Direct medical costs:** Direct medical costs are defined as the costs of resources incurred for the treatment of a disease. Typically, these will include the cost of hospital stay, diagnostic tests and prescribed pharmaceuticals.

**Direct non-medical costs:** When borne by patients and/or caregivers, these costs are also commonly defined as ‘out-of-pocket’ expenditure. In addition, direct non-medical costs include transportation to and from health care facilities, household costs to accommodate the needs of the affected person, and social services.

**Disability-Adjusted Life-Years (DALYs):** Developed by the WHO, the DALY is conceptually similar to the QALY with several notable exceptions:

1) Unlike the QALY, the life expectancy used in the DALY is constant and is set at the greatest reported national life expectancy;
2) The disability weights in the DALY, unlike the QALY, are not preferences but are person trade-off scores from an expert panel who met in Geneva in 1995;
3) The default DALY calculation uses age weights that give lower weight to years of the young and elderly.
4) DALYs are to be avoided rather than to be gained.

**Discounting:** Makes current costs and benefits worth more than those occurring in the future. Spending money now means you cannot invest it in something else (the opportunity cost) and there is desire to enjoy benefits now rather than in the future. The reason why current spending incurs an opportunity cost is that a monetary investment yields a real rate of return and therefore there is a cost to spending money in the present. The calculation is similar to interest calculation in finance. The standard rate at which the future is discounted in US studies is 3% implying that cost savings in 24 years would have to be double costs today to offset the costs.

**Dominated Alternative:** When comparing interventions or options, those that are more costly and less effective are said to be “dominated” by those interventions that are less costly and more effective.

**Economic cost:** This is the value of the lost benefit because the resource is not available for its next best use. A resource’s cost is the sacrifice necessary to obtain goods or services. It usually exceeds the financial (accounting) costs of production because economic costs include both explicit accounting costs and implicit costs. Examples of economic costs are volunteer time or donated space.
**Externality**: When a decision affects more than those who are involved in the transaction. A common example in health care is immunization: if a parent decides not to vaccinate their child, the externality is when the kids who are not vaccinated spread disease to their peers. Pollution is another commonly used example of externalities.

**Financial cost**: Financial cost or accounting cost is expenditure for resources that are used to implement the program based on market prices. Financial costs are often in the budget proposal and they are convenient, sometimes incomplete measure of costs. Examples include salaries for project personnel, supply costs, computer purchases.

**Fixed Cost**: Cost that does not change with the quantity of output. Examples include the building of a health clinic or a hospital.

**Friction Costs (associated with productivity changes)**: Direct, non-healthcare costs associated with the replacement of a worker. For example, if substitute labor is not as productive as the labor it replaces and the difference in productivity is not fully captured by wage rates, then the discrepancy is a friction cost.

**Health Economics**: A branch of economics that primarily looks at how healthcare resources are and should be allocated within a constrained budget environment. It also uses economic theory to provide guidance selection of intervention options based on costs, benefits, effectiveness and efficiencies.

**Health Related Quality of Life**: An outcome measure used within the context of healthcare evaluation. HRQoL is typically associated with measures for monitoring changes in a patient’s health status, usually self-reported, due to an intervention.

**Health Utility**: The preferences people have for living in certain health states under the condition of uncertainty. You may not now live with a broken arm, but if you did, how would you rate your quality of life? The health utility indexes pool these preferences across a population of people to get a single value for the quality of life in a certain health state. Health Utilities are the foundations of QALYs and DALYs.

**Human Capital Approach**: This is a way of calculating productivity losses. This values people’s wages or time spent working at home to assess the full value of the illness beyond medical expenses.

**Incremental Cost Effectiveness Ratio (ICER)**: Ratio of change in costs to the change in effects when comparing 2 or more intervention options.

**Incremental cost**: Additional cost incurred by one program over another

**Indirect costs**: Indirect costs, or productivity losses, are costs borne by patients and caregivers. They are borne by patients through morbidity and premature mortality due to a disease, and are borne by caregivers during the period that caregivers, generally members of family, spend taking their child to health care facilities and whilst at home caring for their child.
**Marginal Costs:** The cost of producing one additional unit. For healthcare, it’s the change in total healthcare costs that arise when the quantity of “health” produced through an intervention changes by one unit.

**Markov Model:** One type of decision analytic model that incorporates a series of “states” to and from which individuals or a cohort of individuals may transition. “States” may be defined according to disease stage, treatment status, or a combination of the two. Transitions occur from one state to another at defined recurring intervals according to transition probabilities.

**Monte Carlo Simulation:** Repeated sampling of possible values from the probability distributions of variables in the CE model. This would be used in probabilistic sensitivity analysis.

**Multivariate Sensitivity Analysis:** Varying multiple parameters in the model to see how the ICERs change. This could change the conclusions policy makers draw from your analysis if the model is not robust to changes in one or more variables.

**Opportunity Cost:** The highest-valued alternative that is forgone as a result of making a decision.

**Perspective:** The frame used to conduct the analysis. This helps determine which costs and outcomes to use in the analysis. The societal perspective is commonly recommended but it is not clear how decision makers would use this perspective.

**Probabilistic Sensitivity Analysis (PSA):** Sensitivity analysis in which probability distributions are applied to the specified ranges for key model parameters and samples drawn at random from these distributions are used to generate an empirical distribution of cost-effectiveness results.

**Productivity Cost:** Time working or doing other such activities like housework lost to illness or taking time away for treatment.

**Reference Case:** For those following the guidelines of the US Panel on Cost Effectiveness in Health and Medicine, then there is an established reference case (follow a strict set of rules on how to perform the analysis) to improve the comparability between studies.

**Revealed Preference:** A method to determine individuals’ preferences and willingness to pay based on actual consumer choices. For example, it is possible to examine preferences for Lasik eye surgery by looking at what consumers have paid for the service.

**Standard Gamble:** A way of calculating health utilities. This is usually formatted as a series of choices for how you might value different health states over time.

**Stated Preference:** This is similar to willingness-to-pay. These methods ask consumers about their preferences for various services, aspects of technologies, etc.

**Stochastic (Probabilistic) Model:** A decision analytic model that explicitly incorporates parameter uncertainty into its calculations.
**Threshold analysis:** A univariate sensitivity analysis on one specific parameter to assess the impact of a range of values on the models output. In such analysis, it is possible to determine the “threshold” value at which the main conclusion of the model may change.

**Time Frame:** The time over which the treatment or intervention is applied.

**Time Trade-off:** A method for determining health utilities. This method attempts to assess how people value living with an illness compared with living in perfect health. This will result in valuations where living with an illness for six-months has the same utility as living in perfect health for one year.

**Univariate Sensitivity Analysis:** Varying one parameter at a time to test the sensitivity of the model. This process helps determine which factors are most important in swaying the ICER.

**Variable Costs:** Costs that change according to how much output is produced.

**Visual Analogue Scale:** A way of calculating health utilities. Patients are presented with a scale from 0 to 100, for example, and they rate the health state on the scale.

**Willingness-to-pay:** The maximum amount an individual says they will pay for a good
Annex 3. Websites of Interest

Guidelines For Economic Evaluations

Brazil

Colombia
http://www.minproteccionsocial.gov.co/salud/Documents/Gu%C3%ADa%20Metodol%C3%B3gica%20para%20elaboraci%C3%B3n%20de%20gu%C3%ADas.pdf

Mexico

Economic Analysis

CHOosing Interventions that are Cost Effective (WHO-CHOICE):
http://www.who.int/choice/en/
- WHO-CHOICE assembles regional databases on the costs, impact on population health and cost-effectiveness of key health interventions. It also provides a contextualization tool, which makes it possible to adapt regional results to the country level.

Cost Effectiveness Analysis (CEA) Registry:
http://www.tufts-nemc.org/cearegistry/index.html
- Public electronic access to a comprehensive database of cost-effectiveness ratios in the published literature. Its goals are to find opportunities for targeting resources to save lives and improve health and to move towards standardization of cost-effectiveness methodology in the field.

NHS Economic Evaluation Database (NHS EED):
http://www.york.ac.uk/inst/crd/nhsdfaq.htm
- NHS EED has been funded by the Departments of Health of England and Wales to assist decision-makers by systematically identifying and describing economic evaluations, appraising their quality and highlighting their relative strengths and weaknesses. NHS EED saves decision-makers time that might have been spent searching for studies in databases such as MEDLINE and EMBASE.
Health Literature Search And Evidence

BIREME (the Latin America and Caribbean Center on Health Sciences Information):
http://www.bireme.br

BVS – Virtual Health Library:
www.bvsalud.org/
- BIREME’s objective is the promotion of technical cooperation in scientific and
technical health information with the countries and among the countries of the Latin
America and the Caribbean (REGION), aiming to develop the means and the
capacities for the provision and the equitable access to the relevant and up-to-date
scientific and technical health information.

SciELO (Scientific Electronic Library Online):
http://www.scielo.org
- SciELO - Scientific Electronic Library Online provides an efficient way to assure
universal visibility and accessibility to their scientific literature, contributing to
overcome the phenomena known as "lost science". In addition, the SciELO model
comprises integrated procedures for the measurement of usage and impact of
scientific journals. It is a product of a partnership among FAPESP – the State of São
Paulo Science Foundation, BIREME (http://www.bireme.br) - the Latin America and
Caribbean Center on Health Sciences Information, as well as national and
international institutions related to scientific communication and editors. Since
2002, the Project is also supported by CNPq (http://www.cnpq.br) - Conselho
Nacional de Desenvolvimento Científico e Tecnológico.

PubMed:
- PubMed was developed by the National Center for Biotechnology Information (NCBI)
at the National Library of Medicine (NLM), located at the U.S. National Institutes of
Health (NIH). PubMed provides access to citations from biomedical literature
through bibliographic information that includes MEDLINE. MEDLINE is the NLM's
premier bibliographic database covering the fields of medicine, nursing, dentistry,
veterinary medicine, the health care system, and the preclinical sciences. MEDLINE
contains bibliographic citations and author abstracts from more than 4,800
biomedical journals published in the United States and 70 other countries. Coverage
is worldwide, but most records are from English-language sources or have English
abstracts.

SUMsearch:
http://sumsearch.uthscsa.edu/
- SUMSearch is a unique method of searching for medical evidence by using the
Internet, combining meta-searching and contingency searching in order to automate
searching for medical evidence.
Free Online Medical Journals:
http://www.freemedicaljournals.com/
- The Free Medical Journals Site was created to promote the free availability of full text medical journals on the Internet. 1450 Journals are available, sorted by language of publication, title of journal and specialty. Over the next few years, many important medical journals will be available online, free and in full-text. The unrestricted access to scientific knowledge will have a major impact on medical practice.

Cochrane Collaboration:
http://www.cochrane.org/
- The Cochrane Collaboration is committed to summarizing and providing evidence on the effects of interventions using systematic review methods, focusing on reviews of the effects of health care interventions.

**Journals**

Bulletin of the World Health Organization, special issue on economics of immunization:
Volume 82, Number 9, September 2004, 639-718
http://www.who.int/bulletin/volumes/82/9/en/index.html

The BMJ series of Economics Notes:
http://bmj.bmjournals.com/cgi/content/full/320/7229/246

Cost-Effectiveness and Resource Allocation (periodico en línea):
http://www.resource-allocation.com/home/

Medical Decision-Making:
http://mdm.sagepub.com/

Commission on macroeconomics and health:
http://www.cmhealth.org/
- Discussion papers summarizing evidence on cost-effectiveness of health interventions in low/middle income countries

**General Sites Providing Useful Gateway To Information On The Internet**

The International Health Economics Association (iHEA):
www.healtheconomics.org

The Health Economics Resources Centre:
www.york.ac.uk/res/herc/

Health Economics Research Centre, University of Oxford, Institute of Health Sciences:
http://www.herc.ox.ac.uk/