Burden of Disease Assessment: A Practical Guide

Brecht Devleesschauwer

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Preface

Disability-Adjusted Life Years (DALYs) have become a key indicator in descriptive epidemiology. DALYs represent the number of healthy life years lost due to ill health and mortality, and allow comparing the population health impact of diseases, injuries and risk factors.

Although the DALY concept has been introduced nearly 30 years ago, there is still little guidance available on their calculation. This book aims to address this gap, through a combination of theoretical sections, simplified examples, and real-life experiences.

This book is the result of interactions and collaborations within the European Burden of Disease Network (COST Action CA18218), supported by COST (cooperation in science and technology). Further information on the network is available via https://www.burden-eu.net.

Why read this book

This book is primarily intended for students, researchers and public health professionals interested in learning how to calculate DALYs.

However, it should also be noted that the **best way of learning is by doing**. We therefore hope that this book can encourage you to get started with your own calculation examples.

Structure of the book

The first part of the book is dedicated to the basic concepts of DALY calculations. Starting from simple examples, different layers of complexity will be introduced.

The second part of the book is dedicated to national burden of disease studies.

About the authors

Brecht Devleesschauwer

Some info here.

https://twitter.com/brechtdv

Part I: Calculating DALYs

Chapter 1

Introduction

The ultimate goal of public health policy is to protect and promote the population's health (Devleesschauwer et al., 2014). This requires information on the health status of the population, often referred to as the "burden of disease". In order to make relevant decisions and set appropriate priorities, policy makers need to be informed about the size of health problems in the population, the groups that are particularly at risk, and the trends in the state of health over time. In addition, an accurate estimate of the population's health status can be used for determining the expected health care use and is vital for prioritizing effective interventions and evaluating their impact and cost-effectiveness (Baltussen et al., 2003).

As public health is a multifactorial phenomenon with many facets, the disease burden of the population can be described by a variety of indicators. Typical indicators of population health are life expectancy, cause-specific mortality rates, numbers of new and existing cases of specific diseases (i.e., incidence and prevalence), perceived health, the occurrence of physical and mental limitations and disability, but also more indirect measures, such as absenteeism, incapacity of work, and the use of medical facilities and the associated costs. However, all these indicators highlight only one facet of public health, i.e., either mortality or morbidity.

Summarizing public health in terms of mortality-based indicators, such as life expectancy, dates from the time when only reliable data for mortality existed. In many countries, however, one has been confronted with ageing populations and an epidemiological transition of public health problems. The importance of early mortality due to plagues and famines has been replaced by chronic, non-communicable diseases, while communicable diseases remain a real threat, causing a "double burden" (Marshall, 2004). Cardiovascular diseases and cancers have replaced infectious diseases as the main causes of death. However, these diseases are also associated with an important morbidity component, due

to the life prolonging effect of continuously improving medical practice (Jelenc et al., 2012). Moreover, not only an extended life expectancy per se is aimed for, living these extra years in good health has become just as important (Bryant et al., 2001). As a result, current health policy requires a global overview of public health, one that combines morbidity and mortality and takes account of health-related quality of life (Robine et al., 2013).

Given the importance of combining morbidity and mortality, several summary measures of population health (SMPH) have been proposed and implemented (Murray et al. (2000); 1.1). SMPHs may be divided into two broad families: health expectancies or experiences and health gaps, but all have in common that they use "time" as the common measure for quantifying health or health loss. The most powerful SMPHs are those that are able to combine morbidity and mortality into a single figure.

Table 1.1: Classification of summary measures of population health

	Health Experience	Health Gap
Mortality	Life Expectancy	Potential Years of Life Lost(Years of Potential Life Lost)Standard Expected Years of Life Lost
Morbidity	Quality-Adjusted Life Year	Years Lived with Disability
Morbidity & Mortality	Active Life ExpectancyDisability-Free Life ExpectancyHealthy Life YearsQuality-Adjusted Life ExpectancyDisability-Adjusted Life Expectancy	Disability-Adjusted Life Year

Driven by the influential Global Burden of Disease (GBD) projects initiated in the early 1990s (Murray et al., 1996), the Disability-Adjusted Life Year (DALY) has become the dominant SMPH for quantifying burden of disease. The DALY metric has therefore been selected as key SMPH for the Belgian National Burden of Disease study. DALYs measure the health gap from a life lived in perfect health, and quantify this health gap as the number of healthy life years lost due to morbidity and mortality. Although the basic DALY formulas are rather straightforward, the calculation of DALYs, like any other SMPH, requires several assumptions, some of which are not always obvious. Furthermore, DALY-based burden of disease studies are almost always confronted by uncertainties and almost always require manipulations of epidemiological data.

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Chapter 3

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Chapter 7

Quantifying uncertainty

7.1 Sources of uncertainty

Nearly every DALY estimation is subject to data uncertainty and modelling choices. The resulting DALY estimate is thus hardly ever a single, fixed value, defined with perfect accuracy and precision. In a practical guide on accounting for uncertainty in decision-analytic models, Bilcke et al. (2011) classified uncertainty into three categories: parameter uncertainty (uncertainty regarding the true value of the model parameters); structural or model uncertainty (uncertainty regarding the model structure); and methodological uncertainty (uncertainty due to normative or subjective modelling choices).

7.1.1 Parameter uncertainty

Parameter uncertainty relates to a lack of knowledge on the true value of model parameters. DALY calculations require demographic, epidemiological, and severity parameters, each of which can be uncertain. Severity parameters, such as duration and disability weight, relate to individual patients and can therefore also be variable. Variability, sometimes referred to as stochasticity or first order uncertainty, distinguishes itself from uncertainty in that it is an inherent property of populations, and cannot be reduced by gaining more information, e.g., by increasing the sample size.

In general, parameter uncertainty results from sampling error and/or systematic error or bias. Sampling error is well known and well-studied by statisticians. It arises when a parameter is inferred from a representative sample of the population of interest. It can be modelled directly, for instance by assuming a Binomial distribution for a prevalence estimate obtained by testing a certain population sample. At a different level, when parameters are modelled from a

statistical model, the resulting standard errors also reflect this sampling error. Systematic error, on the other hand, is less well-studied, but is potentially much more important. In DALY calculations, systematic error is very often related to the extrapolation of parameter values from non-representative populations or time periods. The most extreme form of extrapolation occurs when there is a complete lack of data, a common situation in global or regional burden of disease studies. It is not clear to what extent these alternative settings are representative for the concerned setting, and different alternative settings may provide different parameter values, related to different levels of bias. Ill-defined coding, misclassification and underestimation are typical and common sources of systematic error in epidemiological parameters such as prevalence, incidence and mortality (see section 3.1).

A specific problem related to parameter uncertainty arises when uncertainty is correlated. This may be the case if DALYs are calculated per age and sex group, but parameters are only available at a less granular level. In GBD studies, this problem occurs when regional or global parameters are used instead of country-specific parameters and applied to each of the concerned countries. Such issues may be described as stratification uncertainty: uncertainty arising because the level of detail required in the DALY calculations does not match the level of stratification in the data (Devleesschauwer et al., 2016).

7.1.2 Model uncertainty

DALY calculations follow a disease model or outcome tree, i.e., a schematic representation of health states that are causally related to the risk factor, hazard or disease of interest (Devleesschauwer et al., 2014c). Uncertainty in this disease model may arise when there is insufficient or conflicting evidence on the causal relation of certain symptoms. Such uncertainty is common for long-term outcomes of infections, such as cirrhosis and hepatocellular carcinoma following hepatitis C and B infection (García-Fulgueiras et al., 2011), or post-infectious irritable bowel syndrome following giardiosis (Havelaar et al., 2012). Model uncertainty in DALY calculations may also originate from health states being controversial due to ethical reservations. In this respect, Jamison et al. (2006) discussed the inclusion of stillbirths in GBD assessments.

A second source of model uncertainty can be linked to the epidemiological data used in the DALY calculations. Often the available data come with a lot of restrictions, and several assumptions need to be made to transform these into useable numbers. Whether or not data should be corrected for underreporting or misclassification may for instance become a source of model uncertainty.

7.1.3 Methodological uncertainty

The DALY metric encapsulates various methodological choices, often referred to as value choices. All of these choices are normative and thus subjective, as there is no intrinsically correct choice. As a result, different choices are being made, and contested, in literature.

The different methodological choices that need to be made when calculating DALYs have been outlined in section 2 of the manual. Here we provide some examples of how these choices can lead to uncertainties.

(1) YLD perspective

The GBD 2010 study introduced a prevalence-based version of the YLD, defined as the product of number of prevalent cases and DW (Murray et al., 2012). Both perspectives are equally valid, but have a different interpretation. The choice between an incidence and prevalence perspective therefore remains a normative choice.

(2) Disability weights

Different methods exist for deriving DWs, based on either an econometric or psychometric philosophical perspective on health-related quality of life (Haagsma et al., 2014; Rehm and Frick, 2010). Also, subjective choices need to be made on which population's values to use: those of patients, lay people, or disease experts? Phanthunane et al. (2010) for instance compared DWs for schizophrenia elicited from both patients and clinicians using different multi-attribute utility instruments. Furthermore, DWs may be corrected for comorbidity, but again, different methods have been proposed, ranging from the use of arbitrary attribution factors (Mathers et al., 2000), over maximum limit or multiplicative approaches (Mathers et al., 2001; Murray et al., 2012), to regression models (Cuijpers et al., 2011; Lokkerbol et al., 2013). Finally, when DWs are not available for specific health states, "proxy" DWs are commonly derived by mapping the concerned health state to alternative health states for which DWs are available. LaBeaud et al. (2011) for instance present a set of proxy DWs for arbovirus-related long-term sequelae, showing the uncertainty induced by the need to map to analogous health states.

(3) Residual life expectancy table

Different possibilities exist regarding the choice of the life expectancy table. The use of local (e.g., national) life expectancy tables has been propagated to reflect the local epidemiological situation (Plass et al., 2013). Local life expectancy tables have also been used for specific population subgroups, such as ethnic minorities in Australia (Costilla et al., 2013), or for future populations, such as the French population in 2020 (Lapostolle et al., 2008). Some authors further adapted local life expectancies to reflect reduced life expectancy in fatal cases, assuming that these cases had underlying diseases (Wielders et al., 2012). Matemba et al. (2010) used the opposite approach, by adapting the local life

expectancy table to estimate the burden of sleeping sickness if the HIV/aids epidemic had not occurred. In addition to these local life expectancy tables, the use of so-called "standard" life expectancy tables has been promoted to ensure comparability across populations. To date, however, there are three different "standard" life expectancy tables in use (Appendix A).

(4) Social weighting

The basic DALY formulas can be extended by including age weighting and time discounting functions (Devleesschauwer et al., 2014b). Whether or not these social weighting functions should be used remains a subjective choice, and has indeed been the subject of debate (Barendregt et al., 1996). Furthermore, there is no consensus on the exact parameterization of these social weighting functions. Although age weighting commonly follows the original formulation, some authors proposed alternative formulations that better reflected their local situation (Yang et al., 2004). When discounting time, the standard choice has been to apply a 3% discount rate, but certain national instances propose different weights, e.g., 1.5% in The Netherlands and 3.5% in the United Kingdom (Havelaar et al., 2012).

7.2 Dealing with uncertainties

7.2.1 Probabilistic sensitivity analysis

By far the most powerful method to deal with parameter uncertainty is probabilistic sensitivity analysis (PSA), sometimes also called uncertainty analysis or uncertainty propagation. In PSA, the uncertain parameters are represented by uncertainty distributions, thereby following the Bayesian definition of probability as a degree of belief instead of a long-term frequency. PSA uses Monte Carlo simulations, or parametric bootstrap, to sample random values from the specified uncertainty distributions (Fig 7). At each iteration, the sampled values are used to calculated a DALY estimate. The combination of iterations therefore results in an empirical distribution of DALY estimates, reflecting the joint uncertainty in the input parameters (Fig 8). This resulting distribution can be summarized by its mean and a 95% uncertainty interval defined as the 2.5th and 97.5th percentile. PSA is typically used to propagate uncertainty, thereby ignoring variability. Nevertheless, it would be possible to simulate both processes using second order or two-dimensional Monte Carlo simulations (Havelaar et al., 2004).

Fig 7. Monte Carlo simulation. Top: red dots represent seven simulated values from a normal(0;1) distribution. Bottom: as the number of Monte Carlo simulations increases, the histogram of simulated values becomes an increasingly better approximation of the target distribution (in blue).

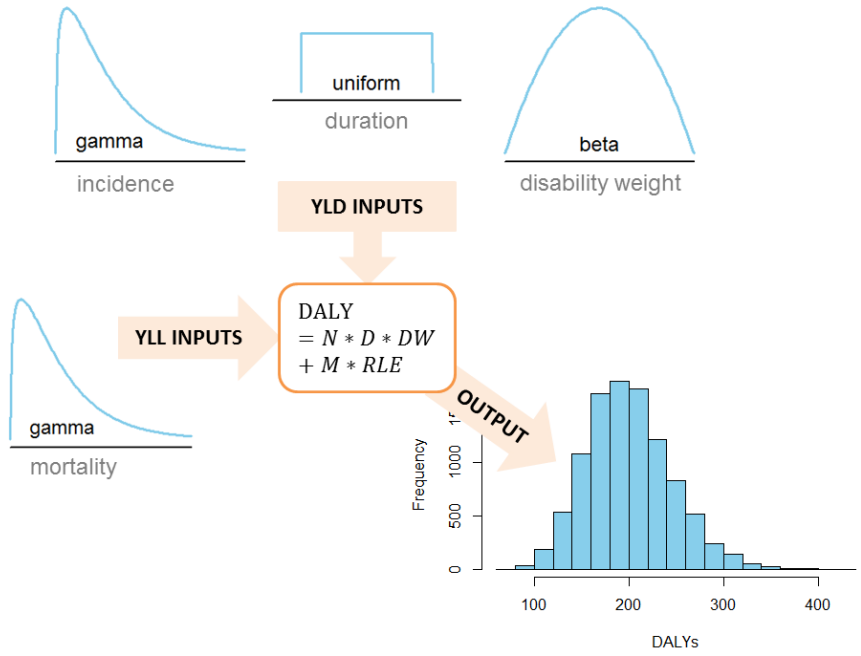

Figure 7.1: Probabilistic sensitivity analysis applied to DALY calculations. Probability distributions are specified to reflect the uncertainty in the input parameters; random values are simulated from these distributions and used to calculate DALYs, resulting in an empirical distribution of the joint uncertainty in the DALY estimate.

7.2.2 Variable importance analysis

To evaluate which uncertain parameters contribute most to the uncertainty in the final DALY estimate, variable importance analysis techniques can be applied. These techniques are often also called sensitivity analyses, adding to the confusion. A common approach is to calculate standardized regression coefficients, by regressing the standardized input parameters against the (standardized) simulated DALYs obtained with PSA (Verhoef et al., 2012). The resulting regression coefficients reflect the expected (standard deviation) change in DALY per standard deviation change in the respective input parameter. Alternatively, partial correlation coefficients may be calculated, which do not assume a linear relationship between inputs and output. For both methods, the resulting variable importance coefficients may be represented in a tornado graph, which sorts, from top to bottom, the input variables in order of their importance (Fig 9).

Fig 9. Tornado graph showing the results of a variable importance analysis in a study on the burden of neurocysticercosis-epilepsy in Tanzania (Trevisan et al. 2016). E: epilepsy; NCC: neurocysticercosis.

7.2.3 Scenario analyses

Scenario analyses imply that DALYs are calculated under different assumptions and compared. These analyses are the method of choice for quantifying model and methodological uncertainty. Fig 10 shows an example.

Fig 10. Scenario analysis of the disease burden of toxoplasmosis in the Netherlands (Havelaar et al., 2007). The evaluated scenarios include alternative incidence data, the inclusion of time discounting, the exclusion of fetal losses, and the use of alternative disability weights

In theory, model and methodological uncertainty may also be assessed through PSA, by parameterizing the uncertain model elements or the methodological choices. Whether or not underreporting should be corrected for, could for instance be parameterized by specifying an uncertainty distribution on the underreporting factor with a minimum of one and a certain maximum. Indeed, Luz et al. (2009) performed a PSA with a multiplication factor ranging from 0.3 to 10, thus accounting for over-reporting, over correct reporting, to underreporting, with a stronger emphasis on the former. Including or excluding a certain health state could for instance be modelled as a Bernoulli random variable with inclusion probability . The resulting distribution of simulated DALY estimates will then be a combination of different disease model assumptions, which in itself can be regarded as a new scenario. Furthermore, parameterization would prevent decision makers to identify the results that correspond to their model choice or methodological preference.

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