



## The Burden of Zoonoses in Nepal

## Brecht Devleesschauwer

Thesis submitted in fulfilment of the requirements for the degree of Doctor in Veterinary Sciences (UGent) and the degree of Doctor in Public Health (UCL)

Promoters: Prof. Dr. Pierre Dorny (UGent) Prof. Dr. Luc Duchateau (UGent) Prof. Dr. Niko Speybroeck (UCL)

March 2015



This PhD research was made possible with the financial support of the Ghent University Special Research Fund (BOF)

#### Brecht Devleesschauwer

The Burden of Zoonoses in Nepal

Front cover: A member of the Dum community herds *Hurra* pigs along a river in Itahari, Nepal. Free ranging of pigs is a major risk factor for parasitic zoonoses such as *Taenia solium* and *Toxoplasma gondii*.

Printed by Ryhove ISBN 978-90-5864-417-6

Data is not information. Information is not knowledge. Knowledge is not action. — after Clifford Stoll

## Jury

Chair, UGent	Prof Dr Frank Gasthuys (UGent)
Chair, UCL	Prof Dr Edwin Claerebout (UGent)
Promoters	Prof Dr Pierre Dorny (UGent, Institute of Tropical Medicine)
	Prof Dr Luc Duchateau (UGent)
	Prof Dr Niko Speybroeck (UCL)
Jury Members	Prof Dr Lieven De Zutter (UGent)
	Prof Dr Jean Macq (UCL)
	Prof Dr Herman Van Oyen (UGent, Scientific Institute of Public Health)
	Prof Dr Paul Torgerson (University of Zurich)

### Contents

List of Figures	ix
List of Tables	xi
List of Abbreviations	xiii
1 Introduction	1
2 Objectives	15
3 DALY calculation in practice: a stepwise approach	17
4 Dealing with uncertainties in DALY calculations	25
5 The DALY Calculator: a GUI for stochastic DALY calculation in R	39
6 The burden of parasitic zoonoses in Nepal	61
7 Rabies in Nepal: epidemiology, impact and control	81
8 General discussion	95
Bibliography	109
Summary	139
Résumé	143
Samenvatting	147
Curriculum Vitae	151
Acknowledgments	157

## **List of Figures**

1.1	Years Lived with Disability (YLD) and Years of Life Lost (YLL) for the alcohol use disorder example under different social weighting scenarios	7
3.1	Stepwise approach towards a DALY-based burden of disease study.	18
3.2	Generic causal chain of disease.	19
3.3	Hazard-based disease model for <i>Campylobacter</i> infection	20
4.1	Barplot of geographical areas for which burden of disease study were performed.	28
5.1	DALY Calculator main window in Ubuntu, Mac OS X 10.6, and Windows 7.	42
5.2	DALY Calculator 'File' menu	42
5.3	DALY Calculator 'Settings' menu	42
5.4	DALY Calculator 'Help' menu	42
5.5	Population of West-Cameroon, stratified by sex and age	43
5.6	DALY calculation with the DALY Calculator: setting the 'Population'	
	table (1) and the 'Life Expectancy' table (2). $\ldots$ $\ldots$ $\ldots$ $\ldots$	44
5.7	DALY calculation with the DALY Calculator: setting the 'Data' table (3), selecting the social weighting functions (4), and obtaining the results (5).	45
5.8	DALY Calculator main window, with social values set to full age	
	weighting and a $3\%$ discount rate, as applied by Praet et al	47
5.9	Epidemiological parameters for the DALY calculation of	
<b>F</b> 10	Neurocysticercosis in Cameroon, based on Praet et al.	48
5.10	Standard output of the DALY calculation for <i>Taenia solium</i>	10
5 11	Neurocysticercosis in west-Cameroon	48
5.12	Solocting columns/rows in DALY Calculator table widgets	49 50
5.12	Histogram of deaths due to Neurocysticercosis West Cameroon	53
5.14	Boxplot of YLDs YLLs and DALYs for Neurocysticercosis. West Cameroon	55
5.15	Tornado plot for Neurocysticercosis DALYs West Cameroon	57
5.16	Scenario analysis for the Neurocysticercosis DALY calculation. West	0.
	Cameroon	58
6.1	Nepal, in red, bordered by India in the south, and China in the north	65
6.2	Generic flow diagram of applied search strategy	66
6.3	Population-level (DALY[0;0] per year) versus individual-level burden	
	(DALY[0;0] per symptomatic case) in Nepal, 2006	76

7.1	Number of rabies outbreaks reported during 2000–2009 to the Veterinary
	Epidemiology Center of the Directorate of Animal Health, Department of
	Livestock Services, Ministry of Agricultural Development
7.2	Median number of dog bites reported during 2001–2012 to the
	Department of Health Services, Ministry of Health and Population 88
7.3	Estimated mean number of rabies deaths in Global Burden of Disease
	studies
8.1	Population-level (DALY[0;0] per year) versus individual-level burden (DALY[0:0] per symptomatic case) in Nepal 2000–2010 101

### **List of Tables**

1.1	Top three diseases according to different Global Burden of Disease (GBD)	4
1.2	Years Lived with Disability (YLDs), Years of Life Lost due to premature mortality (YLLs) and Disability-Adjusted Life Years (DALYs) for the alcohol use disorder example under different social value choices	4
1.3	Social value choices applied by different Global Burden of Disease (GBD) studies	7
6.1	Parasitic zoonoses considered in the Nepalese burden of disease study (in alphabetical order).	64
6.2	2006 age and sex specific population sizes used in the calculation of incident cases, deaths and DALYs.	68
6.3	Retrieved documents (total, retained)	69
6.4	Results of the qualitative assessment (in alphabetical order)	70
6.5	Quantitative assessment: Occurrence of intestinal parasites	75
6.6	Quantitative assessment: Disease impact	76
7.1	Animal rabies cases reported during 2000–2009 to the Veterinary Epidemiology Center of the Directorate of Animal Health, Department of Livestock Services, Ministry of Agricultural Development.	87
8.1	Deaths and Disability-Adjusted Life Years (DALYs) with corresponding 95% Credibility Intervals (CrI) for foodborne zoonoses in Nepal estimated by the Foodborne Disease Burden Epidemiology Reference Group	102

## List of Abbreviations

ARV	Anti-Rabies Vaccine
AVL	Anthroponotic Visceral Leishmaniosis
BPL	Beta-Propiolactone
CHERG	Child Health Epidemiology Reference Group
COPD	Chronic Obstructive Pulmonary Disease
CrI	Credible Interval
DAH	Directorate of Animal Health
DALE	Disability-Adjusted Life Expectancy
DALY	Disability-Adjusted Life Year
DFLE	Disability-Free Life Expectancy
DLS	Department of Livestock Services
DLSO	District Livestock Service Office
DoHS	Department of Health Services
DW	Disability Weight
EDCD	Epidemiology and Disease Control Division
ELISA	Enzyme-Linked Immunosorbent Assay
FBT	Foodborne Trematode
FERG	Foodborne Disease Burden Epidemiology Reference Group
GARC	Global Alliance for Rabies Control
GBD	Global Burden of Disease
GBS	Guillain-Barré Syndrome
GHE	Global Health Estimates
GUI	Graphical User Interface
HICAST	Himalayan College of Agricultural Sciences and Technology
HLY	Healthy Life Years
HMIS	Health Management Information System
HPAI	Highly Pathogenic Avian Influenza
$\mathrm{HRQoL}$	Health-Related Quality of Life
IAAS	Institute of Agriculture and Animal Sciences

IHME	Institute for Health Metrics and Evaluation
$\mathbf{JE}$	Japanese Encephalitis
KAT Centre	Kathmandu Animal Treatment Centre
MDG	Millennium Development Goal
NCC	Neurocysticercosis
NCD	Non-Communicable Disease
NHP	National Health Policy
NHSP	Nepal Health Sector Prorgamme
NZFHRC	National Zoonoses and Food Hygiene Research Centre
PEP	Post-Exposure Prophylaxis
PrEP	Pre-Exposure Prophylaxis
PSA	Probabilistic Sensitivity Analysis
$\mathbf{PZ}$	Parasitic Zoonosis
<b>RIA</b> Foundation	Rabies in Asia Foundation
RIG	Rabies Immunoglobulin
RVPL	Rabies Vaccine Production Lab
SDG	Sustainable Development Goal
SLTHP	Second Long-Term Health Plan
SMPH	Summary Measure of Population Health
VEC	Veterinary Epidemiology Center
WHO	World Health Organization
YLD	Years Lived with Disability
YLL	Years of Life Lost due to mortality

# Introduction

#### Adapted from

**Devleesschauwer B**, Maertens de Noordhout C, Smit GSA, Duchateau L, Dorny P, Stein C, Van Oyen H, Speybroeck N (2014) Quantifying burden of disease to support public health policy in Belgium: opportunities and constraints. *BMC Public Health* 14:1196.

**Devleesschauwer B**, Havelaar AH, Maertens de Noordhout C, Haagsma JA, Praet N, Dorny P, Duchateau L, Torgerson PR, Van Oyen H, Speybroeck N (2014) Calculating disability-adjusted life years to quantify burden of disease. *Int J Public Health* 59:565–9.

**Devleesschauwer B**, Ale A, Duchateau L, Dorny P, Lake R, Dhakal P, Pun SB, Pandey BD, Speybroeck N (2013) Understanding the burden of disease in Nepal: a call for local evidence. *J Nepal Health Res Counc* 11:221–4.

#### 1.1 What is burden of disease?

The main goal of public health policy is to protect and promote population health. This requires information on the health status of the population, often referred to as the "burden of disease". More than just the presence/absence of specific diseases and conditions, disease burden encompasses a comprehensive quantification of the physical and psychosocial health impact of diseases, conditions, and risk factors [1].

Evidence on the disease burden is important for decision-making processes within the health sector. 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 (e.g., by integrating them in generalized cost-effectiveness analyses [2]).

The disease burden of the population can be described by a variety of indicators. Indeed, public health is a multifactorial phenomenon with many facets and different ways to measure it. 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.

Historically, there has always been more of a focus on the collection of mortality and cause of death data. Population health has therefore traditionally been summarized in terms of mortality-based indicators, such as life expectancy. In many countries, however, one has been confronted with 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" [3]. 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 [4]. Moreover, not only an extended life expectancy per se is aimed for, living these extra years in good health has become just as important [5]. 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 (HRQoL; [6]).

Given the importance of combining morbidity and mortality, the last few decades have seen important methodological advances in so-called summary measures of population health (SMPH; [7]). By and large, SMPHs may be divided into two broad families, namely health expectancies and health gaps. Metrics of each family combine morbidity and mortality into a single figure. Health expectancy-based metrics, such as Disability-Free Life Expectancy (DFLE), Healthy Life Years (HLY), and Disability-Adjusted Life Expectancy (DALE), translate these indicators into a health-adjusted life expectancy; health gap metrics, such as the Disability-Adjusted Life Year (DALY), translate these indicators into a number of life years lost due to bad health and mortality.

Driven by the influential Global Burden of Disease (GBD) projects initiated in the early 1990s, the DALY has become the dominant SMPH [8–11]. In the next section and the remainder of this thesis, we will therefore focus on the DALY as main metric for quantifying burden of disease.

## 1.2 Calculating disability-adjusted life years to quantify burden of disease

#### 1.2.1 Introduction

In the DALY philosophy, every person is born with a certain number of life years potentially lived in optimal health. People may lose these healthy life years through living with illness and/or through dying before a reference life expectancy. These losses in healthy life years are exactly what is measured by the DALY metric. Ten DALYs, for instance, correspond to ten lost years of healthy life, attributable to morbidity, mortality, or both. On a population level, diseases with a higher public health impact will thus account for more DALYs than those with a lesser impact.

DALYs have been the key measure in the different GBD studies, each presenting a comprehensive assessment of the worldwide health impact of disease, injury and risk factors [8–11]. Table 1.1 shows the most important diseases according to the different GBD studies. Furthermore, various national and regional DALY calculations have been performed to assess and monitor local health and to set priorities within the local health sector (e.g., Melse et al. for the Netherlands [12], and Mathers et al. for Australia [13]).

GBD 1990 [8]	GBD 2001 [9]	GBD 2004 [10]	GBD 2010 [11]
Lower respiratory in- fections	Perinatal conditions	Lower respiratory in- fections	lschaemic heart dis- ease
Diarrhoeal diseases	lschaemic heart dis- ease	Diarrhoeal diseases	Lower respiratory in- fections
Perinatal disorders	Lower respiratory in- fections	Unipolar depressive disorders	Stroke

 Table 1.1: Top three diseases according to different Global Burden of Disease (GBD) studies

#### 1.2.2 Basic DALY formulae

DALYs are composed of Years Lived with Disability (YLDs) and Years of Life Lost due to premature mortality (YLLs).

YLDs, the morbidity component of the DALYs, are calculated as follows:

 $YLD = Number of cases \times Duration till remission or death \times Disability Weight$  (1.1)

The Disability Weight (DW) is a crucial component of the DALY calculation, as they translate morbidity into healthy life years lost, thus enabling comparison of morbidity and mortality. A DW, scaled from zero (perfect health) to one (worst possible health state), can be interpreted as the proportional reduction in good health due to an adverse health state. In the DALY mindset, this is set equivalent to losing the same proportion of healthy life years over the course of the disability. Living ten years with a DW of 0.10, or five years with a DW of 0.20, thus both correspond to losing one full healthy life year.

For example, a female patient develops severe alcohol use disorder at age 40 and consequently dies at age 60. This condition has a DW of 0.55 [14], and is thus assumed to cause a 55% reduction of good health, or, equivalently, a loss of 55% of the potential healthy life years lived during the 20 years of suffering from this condition. The number of YLDs for this patient (i.e., number of cases = 1) is therefore calculated as:

$$YLD = 1 \times (60 - 40) \times 0.55 = 11$$

YLLs, the mortality component of the DALYs, are calculated as follows:

 $YLL = Number of deaths \times Residual life expectancy at the age of death$  (1.2)

The first GBD studies used the life expectancy at the age of death from the Coale-

Demeny Model Life Table West. This table has a life expectancy at birth of 80 for males and 82.5 for females [15]. In the latest GBD study, a new model life table was developed, with a life expectancy at birth of 86 for both males and females (available as a supplement in [1]). Furthermore, current World Health Organization (WHO) Global Health Estimates are based on the projected frontier life expectancy for 2050, with a life expectancy at birth of 92 for both males and females [16]. Alternatively, local life tables may be used instead of standard life tables.

Continuing the aforementioned example, the residual life expectancy of a 60-year old female is 25 years in the Coale-Demeny Model Life Table West. Dying at the age of 60 will thus cause a loss of 25 full life years potentially lived in optimal health (note again that number of deaths = 1):

 $YLL = 1 \times 25 = 25$ 

DALYs are simply the sum of the YLDs and YLLs:

$$DALY = YLD + YLL \tag{1.3}$$

For our patient, this would mean 11 YLDs + 25 YLLs = 36 DALYs, which can be interpreted as a loss of 36 healthy life years. These 36 years (DALYs) are composed of the equivalent of 11 full healthy life years lost due to living in a less-than-optimal health state (YLDs), and the actual 25 healthy life years lost due to premature death (YLLs).

In population-based burden studies, average DALYs are calculated for specific age and sex strata, based on the total number of cases and deaths in each stratum, and the average duration, age at onset and age at death in each stratum. Population totals are then obtained by summing these stratum-specific DALYs.

#### 1.2.3 Social weighting

The basic formulae for YLDs and YLLs may be extended by applying so-called social weighting functions. This implies that not all life years lost will be valued equally, and social weighting is therefore not universally accepted [17, 18].

Age weighting, as used in the initial GBD study and many ensuing studies, implies that the value of life depends on age. A higher weight is given to the healthy life years lived in the (assumed) socially more important life span between 9 and 56 [15]. The standard age weighting formula is:

$$Cxe^{-\beta x}$$
 (1.4)

with x the concerned age, and C and  $\beta$  constants commonly set to 0.1658 and 0.04.

Time discounting discounts years of healthy life lived in the future at a rate of (usually) 3%. This reflects similar practices in economic assessments, and would prevent policy makers from saving resources for a future eradication program, instead of investing in currently available, but less effective, intervention measures [15].

The standard time discounting formula is as follows:

$$e^{-r(x-a)} \tag{1.5}$$

with r the discount rate, x the concerned age, and a the age to which the burden will be assigned.

Combining both social weighting functions gives the following extended YLD and YLL formulae:

$$YLD = N \times DW \times \int_{A}^{A+L} \left\{ KCx e^{-\beta x} e^{-r(x-a)} + (1-K)e^{-r(x-a)} \right\} dx$$
(1.6)

$$YLL = M \times \int_{A}^{A+L} \left\{ KCx e^{-\beta x} e^{-r(x-a)} + (1-K) e^{-r(x-a)} \right\} dx$$
(1.7)

where N equals the number of cases, M the number of deaths, and DW the disability weight. K is a modulating factor equalling one if age-weighting is applied and zero otherwise; A and L represent, respectively, the age at onset and the duration (Eq. 1.6), or the age at death and the life expectancy at the age of death (Eq. 1.7).

The subjective choices of whether or not to apply age weighting and time discounting can have important effects on the DALY estimates. Only DALYs based on the same social value choices should therefore be compared. For illustration, we calculated DALYs for our example under different scenarios (Table 1.2). Figure 1.1 visualizes these results (note that the integrals of Eq. 1.6 and Eq. 1.7 translate to areas under the curve). Table 1.3 presents the social value choices applied by the four different GBD studies.

Given the lack of consensus on social weighting, we recommend to calculate DALYs under different scenarios, denoted DALY[K; r]. By calculating at least the DALY[0;0], DALY[0;0.03], and DALY[1;0.03] scenario, comparability with most other studies is likely. **Table 1.2:** Years Lived with Disability (YLDs), Years of Life Lost due to premature mortality<br/>(YLLs) and Disability-Adjusted Life Years (DALYs) for the alcohol use disorder<br/>example under different social value choices

Scenario [K;r]	Age Weighting	Discount Rate	YLD	YLL	DALY
DALY[0;0]	No	0%	11.0	25.0	36.0
DALY[1;0]	Yes	0%	12.3	16.7	29.1
DALY[0;0.03]	No	3%	8.3	9.7	17.9
DALY[1;0.03]	Yes	3%	9.5	6.7	16.2



**Figure 1.1:** Years Lived with Disability (YLD) and Years of Life Lost (YLL) for the alcohol use disorder example under different social weighting scenarios. The top left plot represents the basic Disability-Adjusted Life Year (DALY) calculation. The bottom left plot includes age weighting; the curved black line is the age-dependent zero disability level, while the straight grey line compares the situation without age weighting. The top right plot includes a 3% time discount rate; the burden is assigned to the year of disease onset (i.e., the age of 40). The bottom right plot, finally, combines age weighting and a 3% time discount rate.

Study	Age Weighting	Discount Rate	Scenario[K;r]
GBD 1990 [ <mark>8</mark> ]	Yes	3%	DALY[1;0.03]
GBD 2001 [9]	No	3%	DALY[0;0.03]
GBD 2004 [10]	Yes	3%	DALY[1;0.03]
GBD 2010 [11]	No	0%	DALY[0;0]

Table 1.3: Social value choices applied by different Global Burden of Disease (GBD) studies

#### 1.2.4 Presenting DALYs

DALYs can be expressed as an absolute number, thereby giving an idea of the total population burden. They can also be expressed relative to the population, e.g., as the number of DALYs per 1000 population. This enables a direct comparison of the burden suffered by different populations. Finally, DALYs may also be expressed relative to the number of cases. This allows comparisons of the impact of diseases at the patient-level, instead of at the population-level.

All assumptions used in the DALY calculation should be explicitly mentioned, including DWs, life expectancy table and social weighting functions. This ensures correct interpretation of DALY estimates and reduces "error" variation between burden studies [19].

## 1.3 Understanding the burden of disease in Nepal: a call for local evidence

#### 1.3.1 Burden of Disease in Nepal

The importance of burden of disease estimates for the health policy-making process in Nepal becomes evident from recent policy documents and recommendations. A comprehensive and strategic approach towards public health is a relatively recent phenomenon in Nepal. The first National Health Policy (NHP) was adopted in 1991<sup>1</sup>, and served as a policy framework to guide the development of the health sector. The NHP was mainly focused on increasing the health status of the rural population. To this end, it included directives to establish health facilities at the Village Development Committee level and to implement decentralization throughout the health sector. Based on the NHP, the Second Long-Term Health Plan (SLTHP) 1997–2017 was drafted, which was the first document to recognize the importance of prioritizing health sector needs, motivated by the scarce human, financial and physical resources available<sup>2</sup>. In parallel with the development of the SLTHP during the late 1990s, a comprehensive analysis of health care delivery in Nepal was conducted by the World Bank, and in 2000 the results were presented in a report entitled Operational Issues and Prioritization of Resources in the Health Sector [20]. Based on a situation analysis, the report makes several recommendations for the further development of the Nepalese health sector, one of which was the establishment of priorities:

"Because Nepal lacks the institutional or financial capacity to do everything

<sup>&</sup>lt;sup>1</sup>http://mohp.gov.np/english/publication/national\_health\_policy\_1991.php

<sup>&</sup>lt;sup>2</sup>http://mohp.gov.np/english/publication/second\_long\_term\_health\_plan\_1997\_2017.php

that needs to be done immediately, health system initiatives and interventions will need to be phased in. [...] Sequenced priority interventions that have the strongest impact on health status need to be planned and given the management attention and financial resources necessary for their successful implementation."

These recommendations were carried forward in the development of the Nepal Health Sector Programmes (NHSP), short-term strategic frameworks for the further development of the health sector. Within these programmes, disease burden is recognized as one of the bases for setting programme priorities. The second NHSP Implementation Plan 2010–2015 states, for example, that the "introduction of new and under-used vaccines will be prioritised based on disease burden, financial sustainability and infrastructure" [21].

#### **1.3.2** But where is the evidence?

Notwithstanding the importance of burden of disease estimates, Nepalese DALY estimates are very scarce. The first national burden of disease study was conducted by the World Bank in the 1990s, and its results appeared as an annex to the aforementioned situation analysis report [20]. This study used mortality data from the United Mission to Nepal hospitals and morbidity data from WHO community-based studies and national vectorborne disease control programmes. Data on non-communicable diseases (NCDs) were extrapolated from NCD burden of disease estimates for rural India. The study estimated a national burden of disease for 1996 of 363 DALYs per 1000 population. The proportion of total DALYs due to communicable, maternal/perinatal and nutritional conditions was 68.5%. Non-communicable and congenital diseases accounted for 22.8% of the burden, injuries and violence for the remaining 8.7%. Based on a projected demographic shift due to decreasing fertility rates, the study team predicted the national burden to decrease to 245 DALYs per 1000 in 2011. The proportions of the different disease categories were projected to evolve to 61.4%, 28.6% and 10.0%, respectively, implying that the group of communicable diseases would remain the dominant source of disease burden.

A second source of disease burden estimates for Nepal is the 2004 update of the WHO GBD study [10]. This study estimated an overall age-standardized disease burden of 308 DALYs per 1000 in 2004, in line with the World Bank projections. In contrast to the World Bank estimates, however, the majority of the burden was attributed to non-communicable and congenital diseases (48.5%), followed by communicable, maternal/perinatal and nutritional conditions (39.9%) and injuries and violence (11.6%). An important difference between the World Bank and WHO studies is that the former was largely based on local

data, whereas the latter was mainly based on regional extrapolations. Except for tuberculosis, malaria, HIV/AIDS and childhood-cluster diseases, the WHO study reported low levels of evidence on mortality and morbidity for all other considered diseases and disabilities. The cause-of-death distribution patterns of India and the Philippines were therefore used as proxy for that of Nepal. Although Nepal is in certain aspects comparable to these countries, most notably India, it is questionable to what extent their health situations are similar. Such extrapolations must therefore be treated with caution. It is for instance not clear whether or not Nepal is undergoing its demographic and epidemiological transition at the same pace as India. A possible policy shift from communicable to non-communicable diseases based on these estimates [22], should therefore be evaluated with utmost care.

Indeed, the WHO GBD 2004 results seem to be refuted by the third and most recent source of DALY estimates for Nepal, the comprehensive GBD 2010 study [11]. This study concluded that between 1990 and 2010, the importance of communicable diseases has decreased in favour of NCDs, but that even today lower respiratory infections, diarrheal diseases, and neonatal encephalopathy (due to birth asphyxia or trauma) are still the leading causes of healthy life years lost in Nepal. However, as GBD 2010 did not provide its raw data, it remains unclear to what extent these conclusions were based on local data.

#### 1.3.3 A call for local evidence

It is clear that local and reliable evidence on the burden of disease in Nepal is of great importance in setting healthcare priorities and monitoring health trends. In this respect, it is laudable that national burden of disease studies have recently been initiated by the Nepal Health Research Council, with the support of the Ministry of Health and Population [23, 24]. A first Assessment of Burden of Diseases in Nepal project was initiated in 2007, and was based on a nation-wide sample of primary mortality data collected through the Motherhood Method [25], and complemented with secondary morbidity data. The project is reported to be completed, but results have not yet been made available. In 2009, a second Assessment of Burden of Diseases in Nepal project was launched, focusing on the Central Development Region of Nepal. The main aim of the study was to obtain mortality and cause-of-death estimates through verbal autopsy questionnaires. This project is currently reported to be nearing completion.

Notwithstanding these current efforts, there are still huge knowledge gaps with regards to Nepal's health status. More and better local information is therefore urgently needed. This can and should be achieved at the different levels of the data generation process:

- There should be an increased focus on data collection in Nepal. Investments in national community-based surveys and longitudinal studies would generate new evidence bases upon which future policies can be drafted. Nepal is currently participating in Demographic and Health Surveys [26], but these only cover a fraction of the entire health spectrum, and are mainly focused on child and maternal health.
- Existing data generation mechanisms should be further strengthened. In this respect, the efforts to improve the Health Management Information System [27, 28], the official passive surveillance system of Nepal, should continue to be actively encouraged and supported. Capacity strengthening at all levels of the decentralized data collection system will need to be an important part of these efforts.
- Existing data should be made publicly available and integrated. The health system in Nepal is multi-sectorial, with major contributions by private and NGO providers, in addition to the government. As a result, various government agencies, development partners, I/NGOs, local and international academia are actively collecting data, but these are not always made available to the general public. Difficulties in obtaining health statistics from the private sector has been recognized as an important factor limiting the evidence base in Nepal [29]. With regards to academic research, improved digital thesis libraries could help to disseminate the information produced by the various Bachelor, Master and PhD students in Nepal.
- Available data should be used in the most optimal way. Local capacity for transforming the available data into policy-relevant information, such as DALYs, should therefore be further strengthened. There are a number of international projects which can assist in the translation of incidence data into burden of disease estimates and provide context. This includes the GBD 2010 study, which performed a comprehensive and consistent revision of disability weights, a fundamental input into DALY calculations [14]. Global and regional estimates of the incidence and burden of disease by WHO initiated *Epidemiology Reference Groups* for children (CHERG) and foodborne hazards (FERG) can provide issue specific information [30].

#### 1.3.4 The way forward

By strengthening the local evidence base, we can continually improve our understanding of the burden of disease in Nepal. By effectively translating this evidence into policy, we may furthermore assure that this burden can be addressed in the most efficient way. All stakeholders, including policy makers, development partners, researchers and public health workers, should therefore join forces to accomplish these goals.

#### Appendix. Calculating DALYs in R

The following R code can be used to calculate DALYs:

```
## Helper function (calculates integral in Eq. (1.6) and (1.7))
f <-
function(x, K, C = .1658, beta = .04, r, a) {
    K * C * x * exp(-beta * x) * exp(-r * (x - a)) +
    (1 - K) * exp(-r * (x - a))
}
## Burden calculation function (Eq. (1.6) and (1.7))
burden <-
function(N, DW, A, L, K, r, a) {
    N * DW * integrate(f, lower = A, upper = A + L, K = K, r = r, a = a)$value
}</pre>
```

The following R code implements the alcohol use disorder example:

## Select any of the following scenarios
K <- 0; r <- 0 # DALY[0;0]
K <- 1; r <- 0 # DALY[1;0]
K <- 0; r <- 0.03 # DALY[0;0.03]
K <- 1; r <- 0.03 # DALY[1;0.03]</pre>

## Calculate DALY = YLD + YLL burden(N = 1, DW = 0.55, A = 40, L = 20, K = K, r = r, a = 40) + # YLD burden(N = 1, DW = 1.00, A = 60, L = 25, K = K, r = r, a = 40) # YLL

# Objectives

The introduction has identified the importance of burden quantification for guiding health policy and breaking the cycle of indifference and under-funding, especially in resourcepoor settings such as Nepal. However, although the DALY has become the key metric for quantifying disease burden, its use is hampered by a limited standardization of methodologies.

The main objective of this thesis is therefore two-fold:

#### To contribute to the standardization of the DALY metric

To achieve this objective, we will propose a general approach for conducting DALYbased disease burden studies (**Chapter 3**); review which sources of uncertainty exist and how these can be dealt with (**Chapter 4**); and develop a standardized tool for DALY calculations (**Chapter 5**).

#### To quantify the burden of zoonoses in Nepal

To achieve this objective, we will quantify the burden of parasitic zoonoses in Nepal (Chapter 6) and study the burden of rabies (Chapter 7).

## DALY calculation in practice: a stepwise approach

Adapted from

**Devleesschauwer B**, Havelaar AH, Maertens de Noordhout C, Haagsma JA, Praet N, Dorny P, Duchateau L, Torgerson PR, Van Oyen H, Speybroeck N (2014) DALY calculation in practice: a stepwise approach. *Int J Public Health* 59:571–4.

#### 3.1 Introduction

The philosophical and methodological aspects of the Disability-Adjusted Life Year (DALY) calculation have been described (and debated) in great detail [15, 31, 32], and have been summarized in the introductory chapter. The steps *preceding* the actual calculation, how-ever, remain less well documented. This Chapter tries to address this gap by presenting a general approach towards a DALY-based burden of disease study. This approach consists of five consecutive steps, and is presented in Figure 3.1.



Figure 3.1: Stepwise approach towards a DALY-based burden of disease study.

#### 3.2 Step 1: Study population definition

As a first step, the context in which the burden assessment study will take place should be clearly defined. The target population must be delineated by defining study area and time period. The latter may be one specific year, or a range of years, which can then be used to calculate the average burden of that time period.

#### 3.3 Step 2: Disease model definition

The disease model (also called outcome tree) serves as a guide through the further process of the study. Figure 3.2 presents the causal chain of disease. In general, risk factors increase the risk of disease, either directly or indirectly through facilitating exposure to biological, chemical or physical hazards. The course of disease is characterized by different health states (e.g., acute or chronic phases, short-term or long-term sequelae), possibly having different severity levels. A disease model is a schematic representation of the different health states associated with the concerned cause of disease burden, and the possible transitions between these states.


Figure 3.2: Generic causal chain of disease.

Depending on the cause of interest, i.e., the disease as such, the hazard or the risk factor, three different approaches may be distinguished:

- Outcome-based disease models represent different health states of diseases, irrespective of the possible (infectious or non-infectious) aetiologies. For example, a disease model for the burden of diarrhoea could describe different diarrhoea severity levels (mild, moderate, severe), contributing Years Lived with Disability (YLDs), and diarrhoea-related death, contributing Years of Life Lost (YLLs) [33]. Soerjomataram et al. [34] present generic outcome-based disease models for cancer, including disease progression phases and sequelae.
- Hazard-based disease models represent different health states associated with hazards such as biological or chemical agents or traumas [35]. For example, *Campylobacter* infection causes diarrhoea, but also other health states, such as Guillain-Barré Syndrome (GBS) [36]. The disease model would thus consist of the different associated symptoms (contributing YLDs), and death attributable to each symptom (contributing YLLs).
- **Risk factor-based disease models** represent different health states associated with risk factors. For example, a disease model for unsafe water would include the health effects associated with feco-oral pathogens, including *Campylobacter*, other diarrhoeal pathogens and soil-transmitted helminths [37].

A hazard-based disease model for *Campylobacter* infection is given in Figure 3.3. This model includes diarrhoea, possibly progressing from acute to chronic stages and to death;

 $\sim$ 

GBS occurring in a mild or severe form, the latter being able to cause death; and reactive arthritis. Other disease models can be constructed in a similar way. Disease models can be obtained from previous burden studies. However, new insights might indicate an updated disease model requiring data from a systematic review of relevant clinical and epidemiological aspects.



**Figure 3.3:** Hazard-based disease model for *Campylobacter* infection. GBS = Guillain-Barré Syndrome.

# 3.4 Step 3: Data collection

This step is often the most difficult and time-consuming one. It is also the most crucial one, as the quality of the final DALY estimate directly depends on the quality of the data. Ideally, the necessary data should be collected through a systematic review of peer-reviewed literature and various sources of grey literature, including government agencies, non-governmental organizations and academia. An important guide for conducting and reporting systematic reviews is the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [38]. As much as possible, collected data should be stratified by age and sex, as this will yield a more precise overall estimate and will enable to study the burden by age and sex. Further stratification by other parameters can also be useful, and could allow a breakdown of disease burden by sub-region, occupation, socio-economic status, etc.

Extrapolation models may be needed when literature searches cannot provide essential data. These models estimate parameters from data of neighbouring regions or other time periods. The external data used must thus be representative of the selected population, region and time. Where no empirical data can be identified, expert elicitation may be applied (see [39] for a guide).

In general, three groups of data need to be collected:

# 3.4.1 Demographic data

DALY calculations require the total number of males and females, per age group, of the selected area and time period. These data can be obtained from national statistical bureaux or from the United Nations Statistics Division<sup>1</sup>. A second required source of demographic data is the life expectancy table. In order to enhance comparability, the life expectancy at the age of death is generally drawn from standard life expectancy tables (Chapter 1). However, local life expectancy tables may also be used, in particular when within-country disease ranking is an important objective. Local life tables are typically available from national statistical bureaux.

### 3.4.2 Epidemiological data

The most important data for DALY calculations are the number of cases in the different health states defined by the disease model, including death. Most often, the number of incident cases is considered, although DALYs may also be calculated based on the number of prevalent cases (see [40] for a comparison). In the following, we will assume an incidence perspective.

The number of incident cases is the product of the incidence rate and the population size. Depending on data availability, there are three approaches to obtain incidences of the individual health states in the disease model:

- 1. **Direct approach:** The incidence of a health state is directly available, e.g., through a disease or mortality register. In our example (Figure 3.3), this would be the case if a prospective population-based study directly estimated the incidence of *Campylobacter*-associated GBS.
- 2. Attribution approach: The incidence of a health state is obtained from the overall incidence of the given health state (i.e., regardless of aetiology), and an attribution probability (not applicable for outcome-based disease models):

Overall incidence health state  $\times$ Proportion attributable to hazard or risk factor

<sup>&</sup>lt;sup>1</sup>http://data.un.org/

The incidence of GBS due to *Campylobacter* can for instance be obtained by multiplying the overall incidence of GBS in the population to the proportion of *Campylobacter*-attributable GBS. In risk factor-based disease models, the proportion of cases attributable to the risk factor is commonly referred to as the *Population Attributable Fraction* [41].

3. **Transition approach:** The incidence of a health state can be obtained from the previous incidence in the model. Two scenarios are possible:

```
Overall incidence burden cause ×

Probability of transition to health state

Incidence health state ×

Probability of transition to next health state
```

The first scenario would imply that we model the incidence of *Campylobacter*associated GBS on the overall *Campylobacter* incidence in the population and the probability of developing GBS after *Campylobacter* infection. The second scenario would imply, for instance, that we model the chronic diarrhoea incidence by multiplying the acute diarrhoea incidence by the probability of progressing from acute to chronic diarrhoea.

Possibly, epidemiological estimates can be derived through different approaches. In this case, cross-validation of the different estimates can be performed, which can strengthen their reliability.

#### 3.4.3 Disease severity data

DALY estimates incorporate the severity of the health states through their duration and disability weight (DW). The former can be obtained through hospital registers, literature reviews, or expert elicitation. The latter are most commonly derived from Global Burden of Disease studies [14] or the Dutch Burden of Disease study Stouthard et al. [42]. Essink-Bot & Bonsel [43] describe methods for DW derivation.

# 3.5 Step 4: Data adjustment

Potential data biases should be critically appraised. Under-reporting and under-ascertainment are well-documented sources of bias [44]. Misclassification bias due to imperfect diagnostic

tests can be amended using various statistical techniques [45]. Finally, coherence in different epidemiological parameters for non-infectious diseases can be assessed using DisMod software [46].

# 3.6 Step 5: DALY calculation

Once all required data have been gathered, the actual DALY calculation can commence. We have provided a technical summary of DALY calculations in section 1.2 of the Introduction. In **Chapter 4**, we will provide an overview of parameter, model and methodological uncertainties related to DALY estimations, and propose ways for addressing these uncertainties. Before the start of this thesis, however, there were no DALY calculation tools available to perform stochastic DALY calculations. Indeed, most users had made their own calculation model, either in a programming language such as R, or in Microsoft Excel with add-ins enabling Monte Carlo simulation. Although flexible, these methods do not guarantee methodological transparency. To address this gap and to improve consistency in DALY calculations, we developed a free and open-source tool for stochastic DALY calculations in R. This tool, called the DALY Calculator will be introduced in **Chapter 5**.

# Dealing with uncertainties in DALY

# calculations

Adapted from

**Devleesschauwer B**, Maertens de Noordhout C, Beutels P, Bilcke J, Briggs A, Dorny P, Duchateau L, Havelaar AH, Smit GSA, Torgerson PR, Speybroeck N. Quantifying uncertainties in Disability-Adjusted Life Year calculations: a systematic review of burden of disease studies. *In preparation*.

4

# 4.1 Introduction

In recent years, the Disability-Adjusted Life Year (DALY) has become one the most important metrics for quantifying burden of disease. DALYs are defined as the number of healthy life years lost due to living with disease and/or dying before a predetermined life expectancy. Causes inferring more morbidity or mortality will therefore attribute more DALYs, making the DALY a natural currency for measuring and comparing burden of disease. DALYs may also be used as effect measure in health impact assessment and cost-utility analyses.

As with any population health metric, DALYs are 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. [47] classified uncertainty into three categories. Parameter uncertainty relates to uncertainty about the true value of the model parameters; structural or model uncertainty relates to uncertainty regarding the model structure; and methodological uncertainty relates to uncertainty due to normative or subjective modelling choices.

The aim of this paper is to explore through a systematic review of burden of disease studies how the aforementioned categories of uncertainty apply to DALY calculations, and to review how these sources of uncertainty have been dealt with in DALY calculation studies. We conclude by making recommendations on how to quantify uncertainties in DALY-based burden of disease studies.

# 4.2 Materials and Methods

A systematic review was conducted of peer-reviewed literature published from 1994 to 2013, i.e., the 20-year period following the introduction of the DALY metric. Four scholarly databases, i.e., PubMed<sup>1</sup>, Asia Journals Online<sup>2</sup>, African Journals Online<sup>3</sup> and Latin America Journals Online<sup>4</sup>, were searched using the following search terms: "DALY"; "DALYs"; "disability-adjusted life year"; "disability-adjusted life years"; "disability adjusted life years"; "YLD"; "YLDs"; "years lived with disability"; "YLL"; "YLLs"; "years of life lost". When full texts could not be retrieved online, authors were contacted by email and requested to share a full text version.

<sup>&</sup>lt;sup>1</sup>http://www.ncbi.nlm.nih.gov/pubmed

<sup>&</sup>lt;sup>2</sup>http://www.asiajol.info/

<sup>&</sup>lt;sup>3</sup>http://www.ajol.info/

<sup>&</sup>lt;sup>4</sup>http://www.lamjol.info/

After generating a set of unique titles, we screened titles, abstracts and, if needed, full texts, for eligibility. In a first step, we only retained papers that presented unique DALY calculations for the purpose of disease burden estimation. We therefore excluded papers that did not present new DALY calculations, as well as DALY-based cost-utility and health impact assessment studies. In a second step, we retained papers that presented burden of disease assessments for current populations, thus excluding patient-level studies and burden projections. We also excluded studies applying different YLL definitions than the standard expected YLL introduced by Murray [15]. Studies focusing on risk factors were also excluded as uncertainty in such studies has recently been reviewed by Knol et al. [48] and Prüss-Ustün et al. [49]. Finally, studies based on quantitative risk assessment or life cycle assessment were excluded as they apply specific methodologies and thus are not representative for burden of disease studies. Although the search terms were in English, no restrictions were placed on the language of retrieved publications. Screening was conducted independently by two researchers (BD, CMdN), and any disagreements were solved through discussion and if needed through a third researcher (NS).

For each of the eligible papers, a narrative summary was made of the sources of uncertainty, and information was extracted on how parameter, model and methodological uncertainty were dealt with. As in the screening step, data extraction was performed independently by two researchers (BD, CMdN), and any disagreements were solved through discussion and if needed through a third researcher (NS). Manuscripts written in languages not mastered by the data extractors or their colleagues were translated using Google Translate.

In addition to the systematic review, we also reviewed how uncertainties were handled in different Global Burden of Disease (GBD) studies, i.e., GBD 1990, GBD 2001, GBD 2010 and the WHO Global Health Estimates (GHE).

# 4.3 Results

### 4.3.1 Systematic review

In total, we could retain and evaluate 228 papers. The number of burden of disease studies increased exponentially from 1994 to 2013, with almost half of the papers being published in the last five years. Most of these were written in English (217), followed by Spanish (8), Chinese (7), French (2), Portuguese (2), and Dutch, Japanese, Korean, Polish and Swedish (1 each). The majority of the studies presented general burden of disease assessments (78); 74 assessed the burden of communicable diseases, 68 of non-communicable diseases and 28

of injuries. Twenty-four presented a global burden assessment; others presented a burden assessment for a single country or region, with the top five being The Netherlands, China, Spain, Australia and South Korea (Figure 4.1).



Figure 4.1: Barplot of geographical areas for which burden of disease study were performed.

# 4.3.2 Sources of uncertainty in DALY calculations

In line with the classification of Bilcke et al. [47], we distinguish between parameter uncertainty, model uncertainty and methodological uncertainty.

#### 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 (**Chapter 3**), 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. Misclassification, underreporting and under-ascertainment are typical and common sources of systematic error in epidemiological parameters such as prevalence, incidence and mortality [45, 50]. García-Fulgueiras et al. [51, 52] for instance highlight uncertainty in hepatitis C and B mortality rates due to misclassification as aids, and Ditsuwan et al. [53] discuss uncertainty in the number of deaths from road traffic accidents due to the presence of ill-defined causes (so-called "garbage codes") in vital registration data. Formally, a distinction is made between under-ascertainment, referring to cases not seeking health care, and underreporting, referring to healthcare seeking cases that do not get reported to national surveillance systems [35]. In practice, however, many authors combine both phenomena under the heading of "underreporting". Indeed, uncertainty in the level of underreporting appears to be one of the most commonly highlighted sources of uncertainty. The level of underreporting is commonly expressed as the ratio of the presumed total number of cases over the reported number [54], referred to by different authors as the underreporting factor, multiplier, expansion factor or multiplication factor.

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, instead of country-specific parameters, regional or global parameters are used 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 (**Chapter 5**).

#### 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 (**Chapter 3**). 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 [52], or post-infectious irritable bowel syndrome following giardiosis [55]. Model uncertainty in DALY calculations may also originate from health states being controversial due to ethical reservations. In this respect, Jamison et al. [56] discussed the inclusion of stillbirths in GBD assessments.

29

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.

#### Methodological uncertainty

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

The morbidity component of the DALY metric, the Years Live with Disability (YLDs), is defined as the number of incidence cases multiplied with the duration and disability weight (DW) of the health state. DWs value the loss in health-related quality of life (HRQoL) due to a given health state. Different methods exist for deriving DWs, based on either an econometric or psychometric philosophical perspective on HRQoL [57, 58]. 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. [59] for instance compared DWs for schizophrenia elicited from both patients and clinicians using different multiattribute utility instruments. Furthermore, DWs may be corrected for multimorbidity, but again, different methods have been proposed, ranging from the use of arbitrary attribution factors [60], over worst case or multiplicative approaches [1, 13], to regression models [61, 62]. 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. [63] 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.

The YLL component of DALYs is calculated as the number of deaths multiplied by the residual life expectancy at the average age of death. 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 [64–71]. Local life expectancy tables have also been used for specific population subgroups, such as ethnic minorities in Australia [72], or for future populations, such as the French population in 2020 [73]. Some authors further adapted local life expectancies to reflect reduced life expectancy in fatal cases, assuming that these cases had underlying diseases [36, 74, 75]. Matemba et al. [76] 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 oc-

curred. 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. The standard life expectancy table used in the original formulation of the DALY metric had a life expectancy at birth of 80 for males and 82.5 for females [15]. Recently, a new, synthetic standard life expectancy table was introduced in the GBD 2010 study, with a life expectancy at birth of 86 for both males and females [1]. The WHO GHE, finally, are based on a standard life expectancy table reflecting the projected life expectancy in 2050, and has a life expectancy at birth of 92 for both males and females [16].

The basic DALY formulas can be extended by including so-called social weighting functions (**Chapter 1, Section 1.2.3**). Age weighting gives different weights to healthy life years lived at different ages. Time discounting gives exponentially decreasing weights to healthy life years lived in the future. Whether or not these social weighting functions should be used remains a subjective choice, and has indeed been the subject of various discussions [17, 18]. 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 [77]. 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 [55].

The GBD 2010 study introduced a prevalence-based version of the YLD, defined as the product of number of prevalent cases and DW [1]. The possible choice between an incidence and prevalence perspective introduces a new source of methodological uncertainty.

# 4.3.3 Dealing with uncertainties in DALY calculations

Most authors seem to be aware of the uncertainty in their final DALY estimates and discuss uncertainty as an important study limitation or indicate that their estimates are conservative. However, only in 105 studies (46%) some sort of uncertainty quantification had been performed. Parameter uncertainty was quantified in 77 studies (34%), model uncertainty in 22 studies (10%), and methodological uncertainty in 60 studies (26%). Different approaches have been used to deal with these sources of uncertainty, although the nomenclature used to describe these methods was found to be heterogeneous.

#### Parameter uncertainty

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. At each iteration, the sampled values are used to calculate a DALY estimate. The combination of iterations therefore results in a distribution of DALY estimates, reflecting the joint uncertainty in the input parameters. PSA was applied in 33 studies, or 33% of studies quantifying parameter uncertainty.

Some authors included parameters in their PSA that they considered to be variable, but not uncertain. Nevertheless, it is possible to separate both processes, using second order or two-dimensional Monte Carlo [74, 78]. Zhao et al. [79] introduced the jackknife method for estimating variability around DALY estimates. They re-sampled their data by deleting one subgroup of records at a time and recalculated the DALY measures at each iteration.

A less powerful method for evaluating parameter uncertainty is scenario analysis or one-way sensitivity analysis. In this approach, one parameter is changed at a time by taking a value at the extreme of the distribution while keeping the other parameters fixed at their central value. This approach was also applied in 33 studies (33%), often as the only means of parameter uncertainty quantification, but sometimes in combination with PSA when some parameters had large uncertainty due to strongly contradicting data sources [36, 74, 80, 81].

Some authors used a substitution method for estimating DALY uncertainty intervals. In this approach, an uncertainty interval for the DALY estimate is obtained by calculating DALYs for the lower and upper confidence limit of a specific input parameter. It transposes the standard error or confidence interval of an input parameter to the DALY estimate. Although this approach is simple and appealing, it will lead to biased results if more than one parameter is considered uncertain. Also, the method requires that the DALY estimate is a monotonic function of the parameter for which the uncertainty interval is available [82].

To evaluate which uncertain parameters contribute most to the uncertainty in the final DALY estimate, variable importance analysis techniques can be applied. To add to the

confusion, these are often also called sensitivity analyses. Certain authors calculated standardized regression coefficients, by regressing the standardized input parameters against the (standardized) simulated DALYs obtained with PSA [83–86]. The resulting regression coefficients reflect the expected (standard deviation) change in DALY per standard deviation change in the respective input parameter. Other authors calculated as a measure of influence the ratio of the change in DALY observed in a scenario analysis over the baseline DALY estimate [87–90].

Most authors who assessed parameter uncertainty reported using Excel with a specific add-in for Monte Carlo simulations, such as **@RISK**, **Crystal Ball**, **PopTools** or **Ersatz**. A limited number of authors used programming languages such as **Analytica**, **SAS**, or **R**. Late versions of **DisMod-II** also appear to have been used for PSA [91, 92]. The computational framework set up for the GBD 2010 study allows propagating uncertainty through the different modelling steps [1]; however, it is not entirely clear to what extent parameter uncertainty is propagated to the end result, and at which modelling steps uncertainty is propagated or ignored.

Correlation of uncertainty was not explicitly addressed by any of the reviewed papers. Nevertheless, the manual of the DALY Calculator discusses stratification uncertainty and propose an approach for dealing with it (Chapter 5). Stratification uncertainty would occur when an obtained uncertainty distribution for parameter X relates to a general population, say both males and females, but should be used for calculating DALYs for a specific population, say males or females. If this distribution would have a variance  $\sigma^2$ , simulating independent samples from this distribution, and adding these up, i.e., ignoring stratification uncertainty, would yield a variance of  $var(X) + var(X) = \sigma^2 + \sigma^2 = 2\sigma^2$ . However, taken into account the perfect correlation, they propose to sample once from this distribution, and use the vector of sampled values twice. This would yield a variance of  $var(2X) = 4\sigma^2$ . By extending this example, it can be shown that the variance for nstrata is  $n^2\sigma^2$ , whereas it would be  $n\sigma^2$  if simulated independently. In other words, not accounting for stratification uncertainty would underestimate the overall uncertainty with a factor n.

Quantifying uncertainty resulting from extrapolation from non-representative populations or time periods is much more challenging. Torgerson & Mastroiacovo [93] modelled the uncertainty in congenital toxoplasmosis incidence in countries without data as a uniform distribution defined by the lowest and highest observed incidence in neighbouring countries. In GBD 2010, DisMod-MR is designed to extrapolate across time and space, using either mixed models or space-time regression [1].

#### Model and methodological uncertainty

Both model and methodological uncertainty can be quantified through scenario analysis, in which DALYs are calculated under different assumptions and compared. Of the 22 studies that quantified model uncertainty, 10 had performed scenario analyses to assess the effect of correcting for underreporting. Of the 60 studies that quantified methodological uncertainty, the effects of age weighting and time discounting were most commonly assessed (30 studies each), followed by different choices for DW (19) and life expectancy table (14).

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. [94] performed a PSA with a multiplication factor ranging from 0.3 to 10, thus accounting for overreporting over correct reporting to underreporting. Including or excluding a certain health state could for instance be modelled as a Bernoulli random variable with inclusion probability  $\pi$ . The resulting distribution of simulated DALY estimates will then be a combination of different disease model assumptions. This approach however has not yet been applied in burden of disease studies.

# 4.4 Discussion

Identifying and addressing uncertainties in DALY calculations is crucial for conveying the strength of evidence of the estimate and for allowing proper comparisons between studies. As a result, the validity of the estimates will be strengthened, increasing their usefulness for influencing decision-making processes. Additionally, it will help to identify knowledge gaps and provide opportunities for further research. Nevertheless, uncertainty in DALY calculations so far received little attention. To date, the most comprehensive review of uncertainty in DALY estimations focused on the environmental burden of disease, i.e., the burden attributable to environmental risk factors [48]. Other researchers focused on uncertainties in DALY calculations in the context of health impact assessments [95] and cost-utility analyses [96]. Two recent systematic reviews, on general and foodborne burden of disease studies, covered methodological choices and uncertainty analyses, but were limited in scope and detail [19, 97]. To the best of our knowledge, this systematic review therefore provides the most comprehensive and detailed assessment of uncertainty in DALY calculations for assessing burden of disease.

By reviewing the disease burden studies published in the first two decades after the introduction of the DALY metric, we observed that most authors were aware of the uncertainties inherent to DALY estimations. However, only half of the studies presented some kind of quantification of these uncertainties. Nevertheless, methods for quantifying parameter, model and methodological uncertainty are available and commonly used in other, closely related fields, such as risk assessment and health economics [98, 99]. Also, several tools already exist for quantifying and analysing uncertainty in DALY calculations, including the DALY Calculator in R (Chapter 5), Qalibra [100], and the GBD 2010 methodological framework comprising DisMod-MR [1]. However, only the DALY Calculator is available to the general public.

Our review also identified several avenues for further research. Parameter uncertainty due to extrapolating data from (spatially and/or temporally) non-representative populations is common in DALY calculations, but is difficult to quantify. So far only few authors have addressed this issue [1, 93], and further experimental research is needed to understand the performance of their proposed methods. Second, model uncertainty can only be realistically quantified if there exists a realistic set of models. Although this is a general problem, which *in fine* cannot be resolved, it is unfortunate that disease models appear to be reused without critical assessment of their accuracy or validity. Finally, to address methodological uncertainty, Briggs et al. [101] argued for the definition of a "reference case", a baseline scenario against which all methodological choices can be assessed. In the context of the DALY metric, however, this seems problematic, as methodologies have been gradually changing since its inception. The current consensus seems to be that age weighting and time discounting should no longer be part of the reference case, but less agreement exists over which DW methodology and life expectancy table to use.

Notwithstanding the above limitations, researchers should be aware of the various possible sources of uncertainty when calculating DALYs, and should, in order of importance, identify, quantify and analyse these uncertainties. We recommend researchers to quantify parameter uncertainty using PSA, if possible complemented by a variable importance analysis. Although scenario analyses could also be used, this approach is less powerful in quantifying joint uncertainty, and would lead to too many scenarios if several parameters are considered uncertain. On the other hand, we do recommend researchers to quantify model and methodological uncertainty using scenario analyses, because of practical and philosophical reasons. Indeed, model and methodological uncertainty relates to choices that need to be made, and that will be made differently by different researchers. Only scenario analyses allow comparing estimates generated uncertainty, combining a selection of choices in a PSA could be considered as a new choice and therefore even introduces new uncertainty. Finally, researchers should be aware that uncertainty can never be fully quantified. Quantifying uncertainty therefore paradoxically creates a false feeling of certainty, which can even be artificially induced if important sources of uncertainty are wilfully ignored.

# 4.5 Conclusion

Various sources of parameter, model and methodological uncertainty exist when calculating DALYs for burden of disease assessment. Identifying, quantifying and analysing these uncertainties should become a standard part of DALY calculations. We recommend PSA for quantifying parameter uncertainty and scenario analyses for quantifying model and methodological uncertainties.

# 4.6 Acknowledgments

We would like to thank Mark Spohr, Steve Begg, Ferrán Catalá-López, Machi Suka, Nadia Minicuci, Nguyen Trang Nhung and Tzu Chi Lee for providing us with full text versions of their manuscript. We also express our gratitude to Moti Yohannes Gemechu, for his help in identifying Ethiopian papers, and to Tianyu Liu, for his help in translating Chinese papers.

# The DALY Calculator: a Graphical User Interface for stochastic DALY calculation in R

Adapted from

**Devleesschauwer B**, McDonald S, Haagsma J, Praet N, Havelaar A, Speybroeck N (2014) *DALY: The DALY Calculator – A GUI for stochastic DALY calculation in R.* R package version 1.4.0. Available [http://cran.r-project.org/package=DALY].

**Devleesschauwer B**, McDonald S, Haagsma J, Praet N, Havelaar A, Speybroeck N (2014) *The DALY Calculator – A graphical user interface for stochastic DALY calculation in R. Manual version 1.3.0.* 39 pp.

# 5.1 Introduction

The Disability-Adjusted Life Year or DALY is a summary measure of population health widely used in disease burden assessment studies and cost-utility analyses (**Chapter 1**). DALYs represent the number of healthy life years lost due to a disease or disability, and do so by incorporating non-fatal and fatal health outcomes, calculated as the years of life lived with disability (YLD) and the years of life lost due to premature death (YLL), respectively. The formulas for calculating the YLLs and YLDs are presented in Murray [15] and Murray & Acharya [31], and can easily be incorporated in a spreadsheet, such as the "DALY calculation template"<sup>1</sup> prepared by the World Health Organization (WHO). This template allows the computation of YLLs and YLDs for both sexes and various age groups, which are then summarized into a single deterministic DALY measure.

The reliability of the final DALY result depends heavily on the quality of the epidemiological data, which are commonly derived from routine data collection systems, scientific literature, and expert elicitation. The estimates provided by these data sources include an inherent level of uncertainty, mainly due to sampling error, diagnostic uncertainty, and population heterogeneity (as discussed in **Chapter 4**). To reflect this stochastic nature, epidemiological parameters are often accompanied by a confidence or credibility interval, or represented as a probability distribution, rather than being represented by a single point estimate. Monte Carlo simulations have been suggested as the appropriate technique to incorporate this uncertainty in the final DALY estimate [95], which can then be presented as a point estimate with a credibility interval. This interval allows the assessment of the level of uncertainty in the total DALYs, and facilitates a more reliable comparison of the health impact of different diseases.

To our knowledge, however, there are no standardized tools available for stochastic DALY calculation. Therefore, we designed a Graphical User Interface (GUI) for calculating DALYs that allows for the incorporation of input uncertainty and the computation of a DALY credibility interval through Monte Carlo simulations. This program, the DALY Calculator, is designed to be used by a variety of users, with different levels of statistical skills, to allow maximum flexibility, and to promote consistency in the DALY uncertainty analysis.

<sup>&</sup>lt;sup>1</sup>http://www.who.int/entity/healthinfo/bodreferencedalycalculationtemplate.xls

# 5.2 Installing and running the DALY Calculator

The DALY Calculator is developed in R, an open-source environment for statistical programming and graphics [102]. The use of the DALY Calculator requires the prior installation of R, which can be freely downloaded from the Comprehensive R Archive Network (CRAN): http://cran.r-project.org/

The installation procedure under Mac OS X is somewhat more complicated. Two additional tools need to be installed:

- The X Window System (X11): if this is properly installed, the file X11.app should appear in the Utilities folder under Applications in the Finder. If not, you can install it from your Mac OS X installation disc.
- Tcl/Tk for X Windows: this can be installed by downloading and installing tcltk-8.5.5-x11.dmg from http://cran.r-project.org/bin/macosx/tools/

Linux users may need to download and install the Tktable toolkit, which can be found through http://packages.ubuntu.com/search?keywords=tk-table. Ubuntu/Debian users may download and install the toolkit directly by issuing any of the following commands from Terminal:

sudo apt-get install tk-table
sudo apt-get install libtktable2.10

The DALY package is available on the CRAN repository, and can be installed directly from the R console, by calling:

```
install.packages("DALY")
```

Finally, every time the DALY Calculator has to be used, the DALY package has to be loaded by typing the following command in the R console:

```
library(DALY)
```

This call will load and attach the DALY package, and initiate the main window of the DALY Calculator (Figure 5.1).

Ele Settings Help	Jlator	LV Calculator	
set	File Settings Help	76 DALY Calculator	- 0 X
	set	File Settings Help	
outcome 1	disease	set population	
outcome 2	outcome 1		
outcome 3	outcome 2	disease	set data
outcome 4 outcome 5	outcome 3	outcome 2	set data
outcome 6	outcome 5	outcome 3	set data
outcome 7	outcome 6	outcome 4	set data
outcome 8	outcome 7	outcome 5	set data
age weig	outcome 8	outcome 7	set data
discount r	age weig	outcome 8	set data
CALC	discountra	are weighting No.	-
	CALC	discount rate (%)	
		CALCULATE DALYs	

Figure 5.1: DALY Calculator main window in Ubuntu, Mac OS X 10.6, and Windows 7.

76 DALY Calculator	
File Settings Help	_
Load DALY data from file Save DALY data to file	
Reset DALY Calculator	
Exit	

X 76 DALY Calculator File Settings Help Life Expectancy table... Options...

Figure 5.2: DALY Calculator 'File' menu. Figure 5.3: DALY Calculator 'Settings' menu.

7	🕻 DALY Cal	culator 🗆 🗆 🗙	
	File Settin	gs Help	
		Load examples	Neurocysticercosis, Cameroon (Praet et al., 2009)
		Html help	Toxoplasmosis, the Netherlands (Kortbeek et al., 2009)
		DALY Calculator manual (PDF)	
	disea	Package description	
	outcom	e1 scroute	1

Figure 5.4: DALY Calculator 'Help' menu.

# 5.3 Getting started with the DALY Calculator

The DALY Calculator is designed to be used in an outcome-based as well as an agentbased approach. Depending on the approach, YLDs, YLLs, DALYs and incident cases and deaths can be computed for a combination of up to eight different disease categories of one outcome, or of up to eight different outcomes of one agent.

According to the original GBD studies, the incidence-based approach was favored over the prevalence-based approach. The current version of the DALY Calculator is able to calculate DALYs for a basic incidence-based disease model with well-defined incidence and/or mortality rates per disease category or outcome.

The default age groups used by the DALY Calculator are the five age groups used by the GBD 1990 study: 0-4; 5-14; 15-44; 45-59; 60+[8]. At least one combination of sex and age group has to be set in order to proceed with the DALY calculation.

To compute YLDs, YLLs, DALYs, incident cases and deaths, five steps have to be followed (as illustrated in Figure 5.6 and 5.7). These steps will be explained using one of the two built-in examples (The burden of *Taenia solium* cysticercosis in Cameroon; Praet et al. [81]). Users can load this example by selecting:

Help > Load examples > Neurocysticercosis, Cameroon (Praet et al., 2009)

# **STEP 1:** Set the population table

Clicking the set population button opens the *Population* window, where the number of males and females, per age group, can be entered. At least one combination of sex and age group has to be set.

76 Population		
{Age Group}	Male	Female
0-4	397229	408673
5-14	686600	706380
15-44	1073342	1104265
45-59	210474	216538
60+	129081	132800
	OK Can	cel

Figure 5.5: Population of West-Cameroon, stratified by sex and age.



Figure 5.6: DALY calculation with the DALY Calculator: setting the 'Population' table (1) and the 'Life Expectancy' table (2).





#### **STEP 2:** Set the life expectancy table

The default life expectancy table used by the DALY Calculator is the Coale and Demeny model life-table West, level 26 and 25, which has a life expectancy at birth of 80 for males and 82.5 for females [15]. However, the user can define his own life expectancy table, by accessing the *Life Expectancy* window through the *Settings* menu:

#### Settings > Life Expectancy

Pract et al. [81] applied the standard life expectancy table, which is the default life expectancy table of the DALY Calculator. Therefore, no action is required during this step.

#### STEP 3: Set the input parameters, per disease category or outcome

After entering the disease and outcome names, the epidemiological data and disability weights can be entered by clicking the **set data** button. For every parameter, the user can specify the distribution by selecting one of following:

- Beta-Pert (mode; min; max)
- Beta (alpha; beta)
- Gamma (shape; rate)
- Normal (mu; sigma)
- Lognormal-geometric (logmean; logsigma)
- Lognormal-arithmetic (mean; sigma)
- Uniform (min; max)
- Fixed

Next, the user has to select the specific level of stratification for every parameter. The following four stratification levels are available:

- Age and Sex: full stratification
- Age: data is stratified by age group, but not by sex
- Sex: data is stratified by sex, but not by age group
- None: no stratification, data applies to total population

For calculating the YLDs and incident cases, the following tables have to be completed:

- Incidence: number of new cases per 1,000 persons per year
- Treatment: proportion of patients receiving proper treatment; range [0-1]
- Onset of the disease: age of onset in years
- Duration of the disease: duration in years
- Disability Weight for treated cases: range [0-1]
- Disability Weight for non-treated cases: range [0-1]

For calculating the YLLs and deaths, the following tables have to be completed:

- Mortality: number of deaths per 1,000 persons per year
- Average age at death: age at death in years; based on these values, the DALY Calculator will compute the corresponding life expectancies according to the specified life expectancy table.

By default, the distributions of incidence and mortality will be set to Gamma, those of the proportion treated and the disability weights to Beta, and those of onset, duration and average age at death to Fixed; the level of stratification for all parameters is set to full stratification (i.e., Age and Sex).

Figure 5.9 shows the input parameters used for the Neurocysticercosis example.

### STEP 4: Set the social values

The default social weighting values applied by the DALY Calculator are uniform age weights (i.e., no age weighting) and a zero discount rate. However, the user is given the possibility to define the required set of social values, and to alter these values to assess their influence on the final result.



Figure 5.8: DALY Calculator main window, with social values set to full age weighting and a 3% discount rate, as applied by Praet et al. [81].

incidence:	cases/1000 pe	rsons/year	G	amma	<ul> <li>Age and Sex</li> </ul>	treatment:	proportion [0	-1]	Beta	<ul> <li>None</li> </ul>
	M.Shape	M.Rate	F.Shape	F.Rate			Alpha	Beta		
0-4	47.3	6.671	47.3	7.617			267	733		
	47.3	9.522	47.3	14.756						
15-44	47.3	17.141	47.3	28.093						
	47.3	13.321	47.3	28.574						
60+	47.3	7.617	47.3	13.321						
onset: age	n years		Fi	ked	▼ Age ▼	duration: y	ears		Fixed	<ul> <li>Age and Sex</li> </ul>
	Value						Male	Female		
0-4	2.5					0-4	1.4	1.6		
	9.95					5-14	2	3.1		
15-44	26.99					15-44	3.6	5.9		
45-59	51.94					45-59	2.8	6		
60+	73.6					60+	1.6	2.8		
DW treated	: range [0-1]		Be	:ta	▼ Age ▼	DW untreat	ed: range [0-	1]	Beta	▼ Age
	Alpha	Beta					Alpha	Beta		
0-4	1.5	35				0-4	3	27.3		
5-14	1.5	21.6				5-14	3	17		
15-44	1.5	21.6				15-44	3	17		
45-59	1.5	21.6				45-59	3	17		
60+	1.5	21.6				60+	3	17		
mortality: o	leaths/1000 p	ersons/year	G	amma	▼ None ▼	average ag	e at death: ag	e in years	Fixed	✓ Age
	Shape	Rate					Value	-	_	
	3.049	12.321				0-4	2.5			
						5-14	10			
						15-44	30			
						45-59	52.5			
						60+	77.5			
						007				

Figure 5.9: Epidemiological parameters for the DALY calculation of Neurocysticercosis in Cameroon, based on Praet et al. [81].

# **STEP 5: CALCULATE DALYs**

Clicking the CALCULATE DALYs button will read the data and compute the YLDs, YLLs, DALYs and incident cases and deaths per disease category/outcome. By default, the overall mean, median and a 95% credibility interval of these results will be printed to the R Console, and a histogram of total DALYs, with corresponding credibility interval, will be displayed (Figure 5.10).



Figure 5.10: Standard output of the DALY calculation for *Taenia solium* Neurocysticercosis in West-Cameroon, based on Praet et al. [81].

A more detailed output of the DALY calculation can be obtained by changing the output settings in the *Options* window (Figure 5.11):

Settings > Options

7%	Options 🛛 🗖 🗙
[	Iterations 20000
	Output
	Summed over age/sex classes 🔹
	Summed over outcomes 🔹
	Absolute 👻
	✓ DALY histogram
	OK Cancel

Figure 5.11: 'Options' window.

The following settings are possible:

- Age/Sex classes
  - Results summed over different age/sex classes (default)
  - Results shown per age/sex class
- Outcomes
  - Results summed over different outcomes (default)
  - Results shown per outcome
- Absolute/Relative
  - Absolute values (default)
  - Relative values, i.e., per 1000 population

More advanced output, both numerically and graphically, can be obtained by saving the DALY Calculator output to an R object, and manipulating this object in the R environment (see Section 5.5 for more details and examples).

# 5.4 Using the DALY Calculator table widgets

All tables of the DALY Calculator are built using the Tktable toolkit. The navigation and editing properties of this tabulator toolkit differ from those of common spreadsheet documents, which may cause confusion. Some clues are therefore useful to get started: വ

- Keyboard navigation is only possible through the arrow keys; pressing the RETURN (ENTER) key will not change focus to the underlying cell, but will append blank space to the currently active cell.
- To select all values of a column (row), you can click the column (row) header. Selecting all values in the table is possible by clicking the header in the top-left corner of the table. Figure 5.12 gives some examples.
- Removing the value of one or more cells can be done by selecting the corresponding cells and pressing CTRL+X (also on Mac).
- Pasting values into a table (eg, after copying them from a spreadsheet document), can be done by selecting the top-left cell of the desired range, and pressing CTRL+V (also on Mac).

7% Population	7% Population
{Age Group} Male Female 0-4 5-14 15-44 45-59 60+	(Age Group) Male Female 0-4 5-14 15-44 45-59 60+
OK Cancel	OK Cancel

Figure 5.12: Selecting columns/rows in DALY Calculator table widgets.

# 5.5 Handling DALY Calculator output in the R environment

Instead of clicking the CALCULATE DALYs button in the DALY Calculator main window, the DALY calculation process may also be invoked by calling the getDALY() function from the R console. This function initiates the Monte Carlo simulation process, and returns the simulated DALYs, YLDs, YLLs and incident cases and deaths. Of course, this will only take place if the data have been entered, as outlined before.

The getDALY() function takes two arguments, aw and dr, that specify the age weighting constant and time discount rate, respectively. If these values are not specified, they will be taken from the GUI (see Figure 5.8).

The results of the DALY calculation process can be stored in an object, say  $\mathbf{x}$ , as follows:

x <- getDALY()

Since **aw** and **dr** were not specified, these values were taken from the GUI. If one wishes to specify the social weighting values directly from the command-line, the values from the GUI will be over-ruled. For instance, one could specify to use no age weighting and a 3% time discount rate as follows:

 $x \leftarrow getDALY(aw = FALSE, dr = 0.03)$ 

#### 5.5.1 Structure of the object returned by getDALY()

The getDALY() function returns an object of class 'DALY', which inherits from class 'list'. The returned object is a list containing the following elements:

i	For each outcome $i$ , an unnamed list containing simulated
	DALYs, YLDs, YLLs and incident cases and deaths, per age/sex
	class;
pop	A matrix containing the population data;
name	The name of the disease.

Each list of simulated results for a certain outcome i contains the following six elements:

DALY	3-dimensional array of simulated DALYs;
YLD	3-dimensional array of simulated YLDs;
YLL	3-dimensional array of simulated YLLs;
cases	3-dimensional array of simulated incident cases;
deaths	3-dimensional array of simulated deaths;
name	The name of the outcome;
input	A list containing the simulated samples (arranged in
	3-dimensional arrays) from all input distributions.

The three dimensions of DALY, YLD, YLL, cases, deaths and the input elements, are, respectively, iteration, age group, and sex.

The input element is a list of eight arrays, named as follows:

- inc incidence rate;
- trt proportion treated;
- ons age at disease onset;
- dur disease duration;
- DWt disability weight for treated cases;
- DWn disability weight for non-treated cases;
- mrt mortality rate;
- dth age at death.

#### 5.5.2 Methods for objects of class 'DALY'

Six methods have been made available for the objects of class 'DALY':

<pre>print()</pre>	print results, summed over age/sex classes;
<pre>summary()</pre>	print results, per age/sex class;
aggregate()	aggregate simulations by outcome, age/sex, or both;
hist()	histogram of total DALYs, YLDs, YLLs, cases or deaths;
plot()	plot a stacked barplot of YLLs/YLDs with a DALY error bar;
<pre>scatterplot()</pre>	generate a scatterplot of population versus patient level burden.

In both the print() and summary() methods, the user can specify whether or not to print the results per outcome (argument outcome), and whether or not to print the results relative to the population (i.e., per 1000 population; argument relative). By default, outcome and relative are set to FALSE.

The argument digits of both the print() and summary() methods controls the number of decimal digits to be printed. By default, digits equals 0. The argument prob of the print() method sets the range of the printed credibility interval. By default, prob equals 0.95.

For example, if one wishes to see the results of the Neurocysticercosis example expressed relative to the population size, and with 90% credibility intervals, one would call:

```
print(x, relative = TRUE, prob = 0.90, digits = 2)
##
## DALY Calculator: Neurocysticercosis
##
## Total population: 5065382
```

##					
##		Mean	Median	5%	95%
##	DALY	8.91	8.10	3.39	17.23
##	YLD	1.37	1.32	0.78	2.11
##	YLL	7.55	6.72	2.09	15.82
##	cases	3.60	3.60	3.29	3.92
##	deaths	0.25	0.22	0.07	0.52
##					
##	YLD/DAI	LY = 1	L9%		
##	YLL/DAI	LY = 8	31%		

The hist() method plots a standardized histogram of simulated results. By default, argument xval is set to "DALY", argument prob to 0.95, and argument central to "mean". The histogram shown in Figure 5.10 is a result of these default settings.

If one wishes to see a histogram of, say, the number of deaths in the Neurocysticercosis example, with an indication of the median and a 90% credibility interval, one would call:

```
hist(x, xval = "deaths", prob = 0.90, central = "median")
```



# Neurocysticercosis

Figure 5.13: Histogram of deaths due to Neurocysticercosis, West Cameroon

53

#### 5.5.3 Handling objects of class 'DALY'

The strength of the implementation of the DALY Calculator is that its results can be directly manipulated from within the R environment. This allows users to obtain virtually any possible numerical or graphical output they desire. Of course, this also requires a more advanced knowledge of the R programming language. Some examples might therefore be useful.

Each of the elements of x may be extracted using the [[ operator. Named elements may also be extracted using the \$ operator. For example, we can view the population matrix of the Neurocysticercosis example as follows:

```
x[["pop"]] # equivalent to 'x$pop'
```

##		[,1]	[,2]	
##	[1,]	397229	408673	
##	[2,]	686600	706380	
##	[3,]	1073342	1104265	
##	[4,]	210474	216538	
##	[5,]	129081	132800	

Likewise, the simulated DALYs due to epilepsy (i.e., outcome 1 of the Neurocysticercosis example), may be extracted as follows (note the double indexing):

#### x[[1]][["DALY"]]

The aggregate() method is a utility function used to sum up simulated results by outcome, age/sex, or both (controlled by argument by). This method returns a list of aggregated DALYs, YLDs, YLLs, incident cases and deaths, as well as the population matrix and disease name.

```
aggregate(x, by = "outcome") # aggregate by outcome, sum over age/sex class
aggregate(x, by = "class") # aggregate by age/sex class, sum over outcomes
aggregate(x, by = "total") # sum over outcomes and age/sex classes
```

As an example, suppose one would like to have a boxplot of total YLDs, YLLs and DALYs from the Neurocysticercosis example:

y <- aggregate(x, by = "total")
boxplot(y\$YLD, y\$YLL, y\$DALY, names = c("YLD", "YLL", "DALY"))</pre>


Figure 5.14: Boxplot of YLDs, YLLs and DALYs for Neurocysticercosis, West Cameroon

# 5.6 Sensitivity analysis

Sensitivity analysis (or variable importance analysis) studies how the uncertainty in the overall DALY estimate can be apportioned to the different sources of uncertainty in the input parameters [103]. These results can therefore help to identify those input parameters that cause significant uncertainty in the overall DALY estimate and that therefore may be the focus of further research if one wishes to reduce the uncertainty in the overall estimate.

The **sensitivity()** function implements a probabilistic global sensitivity analysis of the overall DALY estimate, in which the analysis is conducted over the full range of plausible input values (hence global), determined by the specified uncertainty distributions (hence probabilistic). Two general methods are available, i.e., based on (standardized) regression coefficients (**method** = "src") or on partial correlation coefficients (**method** = "pcc"). The **sensitivity()** function is defined as follows:

```
sensitivity(x, method = c("src", "pcc"), rank = FALSE, mapped = TRUE)
```

Specifying **method** = "src" will perform a linear regression-based sensitivity analysis. Here, the simulated overall DALY estimates will be regressed against the simulated values for the stochastic input parameters (using lm()). To facilitate comparison, the independent terms are standardized (using scale()) such that they are normally distributed with mean zero and standard deviation one. The resulting regression coefficients are therefore referred to as *standardized* regression coefficients.

Argument **rank** specifies whether the regression should be performed on the actual values (**rank** = FALSE; default) or on the ranked values (**rank** = TRUE). Rank-based

55

regression may be preferred when the relation between output and inputs is non-linear.  $R^2$  values smaller than 0.60 may be indicative of a poor fit of the default linear regression model.

If mapped = TRUE, the dependent term is not standardized, such that the resulting mapped regression coefficients correspond to the change in overall DALY given one standard deviation change in the corresponding input parameter. If mapped = FALSE, the dependent term is standardized, such that the resulting standardized regression coefficients correspond to the number of standard deviations change in overall DALY given one standard deviation change in the corresponding input parameter.

Specifying **method** = "pcc" will calculate partial correlation coefficients for each of the input variables. Partial correlation coefficients represent the correlation between two variables when adjusting for other variables. In the presence of important interactions between input variables, partial correlation coefficients may be preferred over standard-ized regression coefficients.

Argument **rank** specifies whether the correlation should be calculated between the actual values (**rank** = FALSE; default) or between the ranked values (**rank** = TRUE).

The sensitivity() function returns an object of class 'DALY\_sensitivity'. Both a print() and plot() method are available for this class, the latter generating a tornado plot of the regression or partial correlation coefficients.

For example, a sensitivity analysis of the Neurocysticercosis model, based on mapped regression coefficients, could be performed as follows:

```
sa <- sensitivity(x, method = "src", mapped = TRUE)</pre>
```

## show results of sensitivity analysis
print(sa)

```
## Mapped standardized regression coefficients:
```

##		Estimate Std.	Error	t value	Pr(> t )	
##	mrt1	21897.942	1.505	14549.977	0	***
##	DWn1.3	1725.126	1.505	1146.392	0	***
##	DWn1.2	901.396	1.505	598.937	0	***
##	DWt1.3	410.693	1.505	272.862	0	***
##	inc1.M.3	284.638	1.505	189.112	0	***
##	inc1.F.3	280.846	1.505	186.619	0	***

##	DWn1.4	237.095	1.505	157.515	0	***
##	DWt1.2	213.054	1.505	141.567	0	***
##	inc1.F.2	149.741	1.505	99.507	0	***
##	DWn1.1	146.834	1.505	97.586	0	***
##	inc1.M.2	143.994	1.505	95.687	0	***
##	DWn1.5	90.457	1.505	60.115	0	***
##	trt1	-61.807	1.505	-41.077	0	***
##	DWt1.4	54.818	1.505	36.429	2.24e-281	***
##	inc1.M.4	41.145	1.505	27.338	1.4e-161	***
##	inc1.F.4	37.730	1.505	25.069	1.38e-136	***
##	DWt1.1	31.732	1.505	21.087	1.22e-97	***
##	inc1.F.1	25.253	1.505	16.781	8.98e-63	***
##	DWt1.5	23.401	1.505	15.548	3.43e-54	***
##	inc1.M.1	20.817	1.505	13.833	2.54e-43	***
##	inc1.M.5	14.897	1.505	9.899	4.77e-23	***
##	inc1.F.5	13.275	1.505	8.822	1.21e-18	***
##						
##	Signif. coo	les: 0 '***'	0.001	'**' 0.01	'*' 0.05 '	.' 0.1 ' ' :
##						
##	Adjusted R-	-squared:	1			
##	plot torn	ado graph				

plot(sa)



Sensitivity analysis

Figure 5.15: Tornado plot for Neurocysticercosis DALYs, West Cameroon

വ

From the above results, we learn that the uncertainty in mortality rate has the highest influence on the overall uncertainty. Indeed, one standard deviation change in mortality rate would lead to a difference of more than 20,000 DALYs in the overall DALY estimate.

# 5.7 Scenario analysis

To assess the impact of methodological choices, such as the application of age weighting or the choice of the discount rate, different scenarios can be run and the results compared. Likewise, scenario analyses can be performed to assess model uncertainty.

The **DALY\_list()** function combines multiple 'DALY' objects into an object of class 'DALY\_list'. Methods exist to print the different scenario results and for producing comparative stacked barplots and scatterplots.

As an example, we will calculate DALYs for the neurocysticercosis example based on three different social weighting scenarios, i.e., no age weighting or time discounting (DALY[0;0]), no age weighting but 3% time discounting (DALY[0;0.03]), and age weighting and 3% time discounting (DALY[1;0.03]).

```
## calculate DALYs under different scenarios
ncc_00 <- getDALY(aw = FALSE, dr = 0)
ncc_03 <- getDALY(aw = FALSE, dr = 0.03)
ncc_13 <- getDALY(aw = TRUE, dr = 0.03)
## save results as 'DALY_list'
ncc <- DALY_list(ncc_00, ncc_03, ncc_13)</pre>
```

```
## barplot of different scenarios
plot(ncc, names = c("DALY[0;0]", "DALY[0;0.03]", "DALY[1;0.03]"))
```



Figure 5.16: Scenario analysis for the Neurocysticercosis DALY calculation, West Cameroon

# 5.8 Saving and loading input data

An additional feature of the DALY Calculator is the possibility to save the entered values for the epidemiological parameters to an .RData image file. This function is available through:

```
File > Save DALY data to file...
```

Thus created .RData files can be reloaded into the DALY Calculator by accessing:

File > Load DALY data from file...

Alternatively, saving and loading .RData files can be done directly from the R console:

```
saveDALYdata() # save data to .RData file
readDALYdata() # load data from .RData file
```

# 5.9 Current limitations and future work

The current version of the DALY Calculator allows basic DALY calculations and uncertainty analyses, which could be useful for a variety of users. However, certain restrictions might limit a more advanced performance. The current version of the DALY Calculator is designed to calculate a basic incidence-based disease model, with well-defined incidence and mortality rates per disease category or outcome. The incorporation of conditional probabilities or the calculation of complex disease models is currently not possible. Furthermore, the DALY Calculator only allows the simultaneous assessment of up to eight health states and up to five age groups. This is sufficient for most diseases or agents, but could be limiting for certain more complex models. Finally, there are currently only two DALY calculation examples are built-in.

Efforts are being made to resolve these limitations, and solutions should be provided in the next major releases of the DALY Calculator. Indeed, a new version of the DALY Calculator is in development, and has already been used as the basis for the computational framework of the Foodborne Disease Burden Epidemiology Reference Group, a WHO workgroup tasked with estimating the global burden of foodborne disease [104].

# The burden of parasitic zoonoses in Nepal

Adapted from

**Devleesschauwer B**, Ale A, Torgerson P, Praet N, Maertens de Noordhout C, Pandey BD, Pun SB, Lake R, Vercruysse J, Joshi DD, Havelaar AH, Duchateau L, Dorny P, Speybroeck N. (2014) The burden of parasitic zoonoses in Nepal: a systematic review. *PLoS Negl Trop Dis* 8(1):e2634.

# 6.1 Introduction

Various parasites infecting humans depend on vertebrate animals to complete their life cycle. Humans most commonly become infected with these zoonotic parasites through consumption of infected hosts or through fecal-oral contamination. The results of these infections may vary from asymptomatic carriership to long-term morbidity and even death. Although data are still scarce, it is clear that these parasitic zoonoses (PZs) present a significant burden for public health, particularly in poor and marginalized communities [105, 106]. Moreover, PZs can lead to significant economic losses, both directly, through their adverse effects on human and animal health, and indirectly, through control measures required in the food production chain [107, 108].

Estimates of the impact of diseases on public health, generally referred to as burden of disease, may be valuable inputs for decision makers when setting policy priorities and monitoring intervention programs. In Nepal, it is now recognized that health sector needs should be prioritized, and that disease burden should be considered as one of the bases for this prioritization [21]. However, disease burden estimates are not readily available. While the World Health Organization and the Global Burden of Disease (GBD) initiative have generated such estimates for Nepal, these were largely based on regional extrapolations, and, more importantly, included only a limited number of PZs [10, 11]. If disease burden estimates are to be used for priority setting, an incomplete assessment of the burden of PZs may lead to a vicious circle of under-recognition, a wrong ranking of priorities and under-funding for research, prevention and control programs [109].

To address this issue, a disease burden assessment of PZs was conducted in Nepal. Ideally, the primary data sources for such studies would be official surveillance data and death registers. In Nepal, however, these data sources have limited value in terms of PZs. The official passive surveillance system of the Government of Nepal, the Health Management Information System (HMIS), has been reported to suffer from inconsistencies, incomplete reporting, and under-reporting from mainly central-level and private hospitals [27, 28]. Active surveillance systems are in place, but only target certain vaccine-preventable diseases, and not PZs. Death registration is reported to have a completeness rate of 32% [110]. We therefore opted for a more comprehensive approach, based on a systematic review of all possible secondary data sources related to PZs in Nepal from 1990 to 2012. This comprehensive review allowed us to identify endemic and possibly endemic PZs, and, subsequently, to quantify the disease burden of those PZs for which sufficient quantitative data were available.

# 6.2 Materials and Methods

The main objective of this study was to provide a comprehensive overview of the public health impact of PZs in Nepal. To this end, a step-wise approach was taken:

- 1. Systematic review of national and international peer-reviewed and grey literature;
- 2. Qualitative assessment: classification of considered PZs according to (presumed) endemicity status and data availability; and
- 3. Quantitative assessment: quantification of health impact of endemic PZs in terms of the annual number of cases, deaths and Disability-Adjusted Life Years (DALYs), for the year 2006.

# 6.2.1 Considered PZs

The twenty PZs considered in this study are listed in Table 6.1. This selection is based on a recent review of the world-wide socioeconomic burden of PZs [105] and a review of emerging food-borne parasites [111], as many PZs may be classified as being food-borne. Seven of the considered PZs also belong to the group of neglected tropical diseases, i.e., leishmaniosis, cystic and alveolar echinococcosis, cysticercosis, food-borne trematodosis, schistosomosis and soil-transmitted helminthosis [112–114].

#### 6.2.2 Systematic review

Direct and indirect evidence on the occurrence of the considered PZs was located through a systematic search of national and international peer-reviewed and grey literature. Direct evidence was defined as any data on prevalence, incidence or mortality of the PZ in humans. Indirect evidence was defined as occurrence of the concerned parasite in animal hosts or in the environment (e.g., water, soil). If no direct or indirect evidence could be identified from Nepal (further referred to as "local" evidence), recent case reports were sought from (North) India, Nepal's largest neighbour with whom it shares an open border in the west, south and east, and from the Tibet Autonomous Region, which borders Nepal in the north (Figure 6.1).

For each PZ, we constructed a search phrase consisting of the key word "Nepal" and any element of a list containing the name of the PZ, possible synonyms, and the name(s) of the causative parasite(s). Manuscript titles were retrieved through searching PubMed, Web of Science, WHO Global Health Library, Asia Journals OnLine and MedInd. If available, the major Nepalese journals were additionally searched through their websites.

Table 6.1:	Parasitic	zoonoses	considered	in	the	Nepalese	burden	of	disease	study	(in	alpha-
	betical or	rder).										

Parasitic zoonosis	Involved species	Transmission route(s)*
Alveolar echinococcosis	Echinococcus multilocularis	Fecal-oral
Angiostrongylosis	Angiostrongylus cantonensis	Snail-borne (meat-borne, fecal-oral)
Anisakidae infections	Anisakis spp., Pseudoterranova spp.	Fish-borne
Capillariosis	Capillaria philippinensis	Fish-borne
	Capillaria hepatica	Meat-borne
	Capillaria aerophila	Fecal-oral (earthworm-borne)
Cystic echinococcosis	Echinococcus granulosus	Fecal-oral
Cysticercosis	Taenia solium	Fecal-oral
Dirofilariosis	Dirofilaria spp.	Arthropod-borne
Diphyllobothriosis	Diphyllobothrium latum	Fish-borne
Foodborne trematodoses	Fasciola spp.; Fasciolopsis buski	Plant-borne
	<i>Opisthorchis</i> spp.; <i>Clonorchis sinensis</i>	Fish-borne
	Paragonimus spp.	Arthropod-borne
	Intestinal flukes	Various
Gnathostomosis	Gnathostoma spp.	Amphibian/reptile-borne
Sparganosis	Spirometra spp.	Amphibian/reptile-borne
Taeniosis	Taenia spp.	Meat-borne
Toxocarosis	Toxocara spp.	Fecal-oral (meat-borne)
Toxoplasmosis	Toxoplasma gondii	Fecal-oral, meat-borne
Trichinellosis	Trichinella spp.	Meat-borne
Zoonotic intestinal helminth infections	Ascaris suum; Trichuris spp.	Fecal-oral
	Ancylostoma spp.; Strongyloides stercoralis	Fecal-oral, transcutaneous
Zoonotic intestinal protozoal infections	Giardia duodenalis; Cryptosporidium spp.; Blastocystis spp.	Fecal-oral
	Sarcocystis spp.	Meat-borne
Zoonotic leishmaniosis	<i>Leishmania</i> spp. (excluding <i>L. donovani</i> )	Arthropod-borne
Zoonotic schistosomosis	Schistosoma japonicum	Water-borne
Zoonotic trypanosomosis	Trypanosoma cruzi	Arthropod-borne

 $\ensuremath{^*\text{Less}}$  common transmission routes are shown in parentheses.



Figure 6.1: Nepal, in red, bordered by India in the south, and China in the north.

In addition, the thesis libraries of Tribhuvan University (Kathmandu, Nepal) and the Institute of Agriculture and Animal Sciences (Rampur, Chitwan district) were manually explored to find relevant manuscripts. Dissertations were also collected from the website of the Veterinary Public Health master course jointly organized by Chiang Mai University (Thailand) and Freie Universität Berlin (Germany), as this program has a regular intake of Nepalese students. No dissertations were sought from countries neighbouring Nepal, as we did not have prior knowledge of masters courses organized in these countries with a regular intake of Nepalese students.

In a second step, the retrieved titles were screened for eligibility by applying a set of predefined criteria to the titles and, if possible, to the abstracts and full texts. Only papers published in 1990 or later were considered eligible, and no restrictions were placed on the language of publication. For the qualitative assessment, documents were only excluded if they did not relate to the PZ in question, or if they did not pertain to Nepal or Nepalese patients. For the quantitative assessment, additional restrictions were put on the year of publication (between 2000 and 2012), the study setting and population (Nepalese patients infected in Nepal), and the type of information (quantitative, thus excluding case reports

and case series). Finally, additional titles were sought for using forward and backward reference searches (so-called "snowballing"). In the forward reference search, the titles eligible for the qualitative assessment were entered in **Google Scholar** to obtain a list of articles citing the former. The latter were then screened using the same criteria as used in the initial searches. In the backward reference search, the reference lists of the initially retrieved eligible documents were hand-searched and the same criteria were applied. The forward and backward searches were repeated until no more new information could be retrieved. Figure 6.2 presents a generic flow diagram of this applied search strategy.



Figure 6.2: Generic flow diagram of applied search strategy.

Relevant data on study setting, diagnostic methods and study results were extracted from all eligible articles, and entered in spread sheet documents for further use.

#### 6.2.3 Qualitative assessment

This initial assessment aimed at classifying the considered PZs according to their presumed endemicity status and data availability. To this end, we defined four categories:

**Probably not endemic:** there is no direct or indirect local evidence and no direct evidence from neighbouring countries;

- **Potentially endemic:** there is no direct or indirect local evidence, but there is direct evidence from neighbouring countries; or, there is some direct local evidence, but of questionable nature, thus needing further confirmation;
- **Probably endemic & non-quantifiable:** there is direct or indirect local evidence; the burden cannot be quantified due to insufficient quantitative data or uncertainty in zoonotic potential or health effects;
- **Probably endemic & quantifiable:** there is direct or indirect local evidence; the burden can be quantified.

Additionally, information regarding the zoonotic nature of potentially zoonotic parasites was considered, with respect to alternative (dominant) anthroponotic transmission.

#### 6.2.4 Quantitative assessment

Where possible, the prevalence of each PZ classified as "probably endemic & quantifiable" was modeled using a random effects meta-analysis in a Bayesian framework. In this model, it is assumed that the number of positive samples  $x_i$  in each study results from a binomial distribution with sample size  $n_i$  and a study-specific true prevalence  $\theta_i$ , which is in its turn the result of an overall true prevalence  $\pi$  and a random study effect. The study effect is assumed to be normally distributed with mean zero and variance  $\tau_2$ . The prior distribution of  $\tau_2$  is Gamma with scale and shape parameter equal to 1, while a Normal distribution with mean 0 and precision 0.001 was used as prior for the logit-transformed true prevalence. Markov chain Monte Carlo methods are used to fit the model.

If data allowed, the health impact of the concerning PZs was also quantified as the number of incident cases, deaths and DALYs. The DALY metric is a summary measure of population health, widely used in disease burden assessments and cost-effectiveness analyses [10, 11]. DALYs represent the overall number of healthy life years lost due to morbidity and mortality, hereby facilitating comparisons between diseases, and between countries and regions. Calculation of DALYs was done using the standard formulas, and implemented in a fully stochastic framework using the DALY Calculator in R (Chapter 5). We calculated undiscounted and unweighted DALYs, based on the Coale-Demeny model life table West, as our base case scenario. However, in order to enhance comparability of our estimates to estimates made by other authors, we performed scenario analyses by varying the time discount rate from 0% to 3%, by including age weighting, and by using the life expectancy table developed for the GBD 2010 study [11]. These different scenarios were denoted by DALY[K;r], with K equal to 0 for unweighted DALYs and equal to 1 for age-weighted DALYs, and with r the time discount rate. For all scenarios, results

9

were calculated at the population level (i.e., absolute number of DALYs per year) and at the individual level (i.e., relative number of DALYs per symptomatic case). Incident cases, deaths and DALYs were calculated for reference year 2006, i.e., the midpoint of the eligible publication period, 2000–2012. The total population size for 2006 was calculated as the mean of the population sizes estimated in the 2001 and 2011 censuses. The age and sex distribution of the 2006 population was derived from the 2006 Nepal Demographic and Health Survey [26]. Table 6.2 presents the resulting population sizes used in the calculations.

Age	Male	Female	Total
0-4	1,766,025	1,673,583	3,439,608
5-14	3,655,548	3,556,364	7,211,913
15-44	4,668,234	6,331,723	10,999,957
45-59	1,259,682	1,464,385	2,724,068
60+	975,636	920,471	1,896,107
All ages	12,325,126	13,946,527	26,271,653

 Table 6.2: 2006 age and sex specific population sizes used in the calculation of incident cases, deaths and DALYs.

#### 6.2.5 Ethics statement

The data collection activities required for this study were approved by the ethical review board of the Nepal Health Research Council (Ramshahpath, Kathmandu, Nepal) and of the Ghent University Hospital (Ghent, Belgium; registration number B670201111932).

# 6.3 Results

#### 6.3.1 Systematic review

For all twenty considered PZs, we identified 267 unique peer-reviewed documents and 50 unique dissertations. All identified documents were published in English. Table 6.3 summarizes the results of the systematic review for each considered PZ.

Parasitic zoonosis	l otal unique titles	Retained	titles						
		Qualitative	e assessmen	t		Quantitati	ve assessme	ent	
		Literature	Snowball	Thesis	Total	Literature	Snowball	Thesis	Total
Alveolar echinococcosis	3	1	0	0	1	0	0	0	0
Angiostrongylosis	3	0	0	0	0	0	0	0	0
Anisakidae infections	0	0	0	0	0	0	0	0	0
Capillariosis	7	2	0	4	6	0	0	0	0
Cystic echinococcosis	34	14	1	7	22	0	0	2	2
Cysticercosis	58	46	12	4	62	9	4	3	16
Diphyllobothriosis	1	0	0	3	3	0	0	0	0
Dirofilariosis	4	0	0	0	0	0	0	0	0
Foodborne trematodoses	22	2	4	5	11	0	0	0	0
Gnathostomosis	3	0	0	1	1	0	0	0	0
Sparganosis	3	1	0	0	1	0	0	0	0
Taeniosis	36	12	8	13	33	6	4	11	21
Toxocarosis	8	3	0	5	8	0	0	0	0
Toxoplasmosis	35	14	4	3	21	5	1	3	9
Trichinellosis	5	4	0	2	6	0	0	0	0
Zoonotic intestinal helminth infections	154	83	21	27	131	34	12	19	65
Zoonotic intestinal protozoal infections	114	62	24	23	109	36	12	16	64
Zoonotic leishmaniosis	242	17	1	1	19	0	0	0	0
Zoonotic schistosomosis	20	3	0	2	5	0	0	0	0
Zoonotic trypanosomosis	7	0	0	0	0	0	0	0	0

Table 6.3: Retrieved documents (total, retained)

# 6.3.2 Burden assessment

• • •

Table 6.4 presents the results of the qualitative classification of PZs. Out of the twenty considered PZs, only *Anisakidae* infections, zoonotic sleeping sickness (trypanosomosis) and zoonotic schistosomosis were classified as probably not endemic as no direct or indirect evidence was found. Seven PZs were classified as potentially endemic, i.e., alveolar echinococcosis, angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis, sparganosis and cutaneous leishmaniosis. The ten remaining PZs were considered probably endemic, and the burden of three of these, neurocysticercosis, congenital (but not acquired) toxoplasmosis and cystic echinococcosis, could be fully quantified in terms of incident cases, deaths and DALYs.

	•	· ·	,
Probably endemic & quantifiable	Probably endemic & non-quantifiable	Potentially endemic	Probably not endemic
Cystic echinococcosis	Diphyllobothriosis	Alveolar echinococcosis	Anisakidae infections
Cysticercosis	Foodborne trematodoses	Angiostrongylosis	Zoonotic schistosomosis
Toxoplasmosis	Taeniosis*	Capillariosis	Zoonotic trypanosomosis
	Toxocarosis	Dirofilariosis	
	Trichinellosis	Gnathostomosis	
	Zoonotic intestinal helminth infections*	Sparganosis	
	Zoonotic intestinal protozoal infections*	Zoonotic leishmaniosis	

<b>Table 6.4:</b> Results of the qualitative assessment	(in a	alphabetical	order)
---	-------	--------------	--------

\* For these parasitic zoonoses, prevalence estimates were available

#### Potentially endemic parasitic zoonoses

No local evidence could be found for alveolar echinococcosis, angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis, or sparganosis. However, recent case reports of these diseases in India indicate that these might be, or become, endemic in Nepal as well. Furthermore, some local evidence has been reported on zoonotic leishmaniosis, but this information remains unconfirmed. If any of these potentially endemic PZs are indeed endemic to Nepal, their burden is probably limited to a few sporadic cases.

So far, no cases of alveolar echinococcosis have been reported from Nepal, although a case of alveolar echinococcosis in a monk having traveled to Nepal, India, and Singapore has been reported [115]. However, given the considerable burden of alveolar echinococcosis in Tibetan communities [116], and the presence of putative cases from India [117–119], there are likely to be some cases in Nepal as well [120].

Human angiostrongylosis, capillariosis, dirofilariosis, gnathostomosis and sparganosis result from accidental infection with parasites that mainly have rodents, canines or felines as definitive hosts. The latter hosts are common in Nepal, and *Capillaria* eggs have already been identified in dog, cat and monkey stool samples and environmental samples [121–126], but it is unclear whether these were *C. aerophila*, or the clinically more important *C. hepatica* and *C. philippinensis*, which cause hepatic and intestinal capillariosis, respectively. Furthermore, *Spirometra* has been identified in stray dog stool samples from Kathmandu Valley [125], and Gewali [122] apparently found *Gnathostoma* eggs in water samples from Kathmandu. Human cases of these five PZs have not yet been reported from Nepal, but sporadic cases have been reported from India. Cases of eosinophilic meningitis due to Angiostrongylus cantonensis have been reported mainly from the southern Indian states [127, 128]. Only few cases of human intestinal and hepatic capillariosis have been reported from India so far [129, 130]. Ocular and subcutaneous manifestations of human dirofilariosis due to Dirofilaria immitis and Dirofilaria repens have been reported from southern states of India, but there have also been cases from the northern state of Punjab [131, 132]. Barua et al. [133] reported a case of Gnathostoma spinigerum in a patient from the northeastern Indian state of Meghalaya, while Mukherjee et al. [134] presented a case of cutaneous gnathostomosis in a female from the northeastern Indian state of Manipur. Some sparganosis case reports from India have been published, including cerebral [135], hepatic [136] and visceral manifestations, the latter in a patient from Uttar Pradesh [137].

It is widely recognized that Nepal is endemic for *Leishmania donovani*, the causative agent of anthroponotic visceral leishmaniosis (AVL), locally known as kala-azar [138–140]. Although some studies have hinted at a possible zoonotic transmission route of L. *donovani* [141–143], we considered kala-azar as a purely anthroponotic parasitic disease, and excluded it from the current study. In addition to AVL, however, several reports have presented cases of cutaneous leishmaniosis [144–149]. Although most of these cases have been imported, mostly from the Middle East, one report mentions a case of cutaneous leishmaniosis caused by *Leishmania major* in a woman not known to have lived outside Nepal [150–152]. The presence of *Phlebotomus papatasi*, a possible vector of *L. major* and *L. infantum* [141, 153–157], further suggests that Nepal might be (or become) endemic for zoonotic leishmaniosis [158].

#### Probably endemic parasitic zoonoses

Trichinellosis has been confirmed in pigs, but never in humans in Nepal. Serological and/or coprological evidence of human infections with *Toxocara*, *Diphyllobothrium*, foodborne trematodes (FBT), and *Taenia* exists, but the population impact of these PZs is probably too low to quantify, although certain groups might be at high risk. Although patent infections with intestinal helminths and protozoa are still very common, the health impact of *zoonotic* intestinal helminths and protozoa could not be assessed, due to uncertainty of zoonotic potential and health effects. On the other hand, the health impact of cysticercosis, toxoplasmosis and cystic echinococcosis was deemed quantifiable.

Trichinella infection has been serologically confirmed in pigs from Kathmandu [159, 160], although Karn et al. [161] could not find seropositives in a sample of 344 pigs slaughtered in five districts of the Central Development Region of Nepal (including Kath-

mandu). Larvae have so far not yet been found on digestion. No human cases have been reported from Nepal, although Joshi et al. [159] mention the undocumented occurrence of sporadic cases of human trichinellosis reported from medical hospitals, and a trichinellosis outbreak has been documented from the north Indian state of Uttarakhand [162].

In a serological ELISA study, a high proportion of Nepalese people ( $\sim 80\%$ ) appeared positive for *Toxocara* infection [163]. Recently, two children with eosinophilia were serodiagnosed with toxocarosis [164]. Furthermore, *Toxocara* spp. have been identified from dogs from Kathmandu [125, 165, 166], cats from Nawalparasi and Chitwan [124], and water samples from Kathmandu [122, 123].

Diphyllobothrium has been found in dog stool samples from Kathmandu [165] and in the intestine of common carp fingerlings from a fish farm near Kathmandu [167]. Thapa [168] reports finding Diphyllobothrium eggs in the stools of 18/62 (29.0%) and 2/90 (2.2%) people of the Bote and Darai ethnic communities, respectively. Both are marginalized communities from Chitwan, and mainly depend on agriculture and fishing.

Some Nepali studies have reported trematode eggs in human and animal stools. Eggs of *Fasciola* spp. have been reported from buffaloes in a number of studies [169–173]. In community-based studies conducted in Kavre and Chitwan, *Fasciola* spp. eggs were reported in human stools [174, 175]. In a study of diarrheal samples from Kathmandu, eggs resembling those of *Clonorchis sinensis* or *Opisthorchis* spp. were found [176, 177]. However, as identification was based on visual identification only, confirmation is not certain. Three out of 84 children with eosinophilia presenting at a university hospital in Kavre were serologically positive for fasciolosis [164], while in another case series on eosinophilia in children, paragonimosis was suggested as a possible cause, given that a significant proportion of patients had the habit of eating undercooked fresh water crab meat [178]. In India, human cases of *Fasciolopsis buski* have been described from the Nepal bordering states of Bihar [179, 180] and Uttar Pradesh [181].

Taeniosis, due to Taenia solium, Taenia saginata or Taenia asiatica, is commonly reported in Nepal. Different studies indicate low taeniosis prevalences in the general public and in clinical samples (<2%), although some papers hint at high prevalences in certain ethnic groups (10–50%). Higher taeniosis prevalence in certain groups is possible, as discussed by Prasad et al. [182] and Devleesschauwer et al. [183], although estimates of up to 50% are somewhat doubtful. Molecular studies have identified *T. asiatica* and *T. saginata* as causes of taeniosis [183, 184], although it is to be expected that *T. solium* also causes taeniosis in Nepal, given its presence in animal intermediate hosts [185]. Apart from rare

σ

complications such as gastrointestinal obstruction or inflammation, the health impact of taeniosis is minimal. So far, there has only been one report describing such complications in a Nepalese patient [186]. As neither the national nor the international literature give a clear view of the probability of developing such complications, it was decided that the health impact could not be quantified.

A large number of studies have assessed the prevalence of intestinal helminths and protozoa in Nepal (Table 6.5). Community-based studies mainly targeted school children, while hospital-based studies were mostly set in large urban referral hospitals. Fewer studies looked at intestinal helminthic and protozoal infestations in HIV-AIDS patients. However, a meaningful quantification of the public health impact of zoonotic intestinal helminths and protozoa was deemed impossible, due to the uncertainty regarding the extent to which these infections are truly zoonotic and the uncertainty regarding the health effects of zoonotic species [105]. Indeed, the limited available data suggest that intestinal helminth infections are mainly due to anthroponotic species. In the large study on genetic influences of helminth susceptibility in the Jirel population of Jiri, Dolakha, only Ascaris lumbricoides was reported [187, 188]. Fecal cultures to identify hookworm larvae so far only revealed the anthroponotic hookworm species Ancylostoma duodenale and *Necator americanus* [189, 190]. The zoonotic relevance of intestinal protozoa remains less clear, even though genetic characterization of *Giardia* and *Cryptosporidium* from Nepal has been performed [191–194]. The zoonotic potential of *Blastocystis* appears to be best studied [195–197], yet there is large uncertainty about the prevalence of human infection given the limited number of studies, as well as substantial doubt regarding its pathogenic nature [198].

Human cysticercosis in Nepalese people has been described since the early 1990s, mainly through reports of patients with neurocysticercosis (NCC) [199–209], ocular cysticercosis [210–214] and muscular and soft tissue cysticercosis [215–223]. Its public health impact however did not receive full attention until the 2000s. Hospital-based studies indicate NCC prevalences in seizure patients ranging from 7% to 73%. The majority of these studies applied neuro-imaging. Two studies report the prevalence of NCC in hydrocephalus patients, indicating a prevalence of 1–2% [224, 225], while a recent study indicates NCC prevalence of ~5% in patients with chronic headache [226]. A case series of three Nepalese intraventricular NCC patients molecularly identified the removed lesions as *T. solium* [227].

The majority of population-based studies on *Toxoplasma gondii* seroprevalence are from the 1990s [228–232], apart from two recent studies [233, 234]. *T. gondii* seroprevalence has also been studied in women with bad obstetric history [235–238], patients with

HIV/AIDS [237, 239–242], ocular disorders [237] and hydrocephalus [224]. Apart from a recent case description [243], however, there appears to be no direct evidence on the impact of congenital toxoplasmosis, which is likely to represent the highest population burden [105]. As a result, it is only possible to obtain an indirect view of the impact of congenital toxoplasmosis in Nepal through population-based seroprevalence data.

Cystic echinococcosis has traditionally mostly been studied in livestock [125, 244–249]. The few data in dogs indicate higher prevalence in areas where livestock is slaughtered [247, 250]. Since the 2000s, various case reports have been published on human hydatidosis [251–259]. Hospital register studies for cystic echinococcosis cases have found low incidences [245, 260, 261]. So far, genotyping studies have revealed the presence of G1, the sheep strain in humans [262], dogs and livestock [247, 263, 264], G5 (cattle strain) in livestock [263] and G6 (camel strain) in humans [263].

#### Quantitative assessment

For intestinal infestations with *Taenia* spp., helminths and protozoa, we were able to estimate prevalence based on a random effects meta-analysis (Table 6.5). For NCC, congenital toxoplasmosis and cystic echinococcosis we could estimate the number of incident cases, deaths and DALYs (Table 6.6). Figure 6.3 visualizes the estimated burden at population and individual level, taking into account the uncertainty resulting from the parameter uncertainties, as suggested by Havelaar et al. [55]. Congenital toxoplasmosis has both a high population and patient burden, while NCC is relatively less important at the patient level, but equally important at the population level. Cystic echinococcosis appears less important at both levels.

Intestinal parasite	Datasets	Estimated prevalence (%)			
		Mean	95% Range*	Distribution	
Community-based stu	ıdies				
<i>Taenia</i> spp.	15	3.4	0.7-8.1	Beta(2.977, 84.058)	
Ascaris spp.	37	15.6	10.6-21.4	Beta(26.936, 145.189)	
Trichuris spp.	36	11.2	6.4–17.1	Beta(14.545, 115.807)	
Hookworm	35	10.4	5.9–15.9	Beta(14.476, 125.337)	
<i>Giardia</i> spp.	28	8.9	6.2-12.0	Beta(32.089, 330.444)	
Cryptosporidium spp.	12	0.6	0.2–1.4	Beta(4.165, 641.569)	
Blastocystis hominis	5	6.9	1.5-15.7	Beta(3.137, 42.457)	
Hospital-based studie	25				
<i>Taenia</i> spp.	8	0.5	0.1-1.0	Beta(4.575, 977.996)	
Ascaris spp.	25	3.4	1.8–5.5	Beta(12.621, 353.634)	
Trichuris spp.	25	1.0	0.4–2.0	Beta(5.588, 550.789)	
Hookworm	25	1.5	0.7–2.7	Beta(8.954, 577.751)	
<i>Giardia</i> spp.	28	5.5	3.8–7.6	Beta(29.778, 507.152)	
Cryptosporidium spp.	17	1.7	0.6–3.3	Beta(6.077, 352.688)	
Blastocystis hominis	7	1.2	0.0–4.5	Beta(0.948, 77.444)	
HIV-AIDS patients					
Ascaris spp.	4	2.1	0.0-9.2	Beta(0.671, 30.91)	
Trichuris spp.	4	4.3	0.1–15.5	Beta(0.935, 21.065)	
Hookworm	4	3.1	0.0-12.3	Beta(0.79, 24.688)	
<i>Giardia</i> spp.	5	5.6	1.7–11.6	Beta(4.32, 73.437)	
Cryptosporidium spp.	8	6.4	2.7-11.7	Beta(7.069, 102.905)	
Blastocystis hominis	3	2.8	0.1–9.4	Beta(1.157, 40.646)	

 Table 6.5: Quantitative assessment: Occurrence of intestinal parasites

\*Defined as the 2.5th and 97.5th percentile of the concerned distribution

Table 0.0. Quantitative assessment. Disease impact								
Metric*	Neurocysticercosis	Congenital toxoplasmosis	Cystic echinococcosis	Total				
Incident cases (95%Crl)	_	1396 (1058–1780)	145 (114–179)	_				
Incident symptomatic cases** (95%CrI)	10,618 (3304–22,296)	626 (473–813)	145 (114–179)	11,389 (4083–23,045)				
Deaths (95%CrI)	163 (39–378)	60 (27–105)	3 (0-7)	225 (93–442)				
DALY[0;0] (95%Crl)	14,268 (5450–27,694)	9255 (6135–13,292)	251 (105–458)	23,773 (14,094–37,719)				
DALY[0;0] /1000 (95%Crl)	0.543 (0.207–1.054)	0.352 (0.234–0.506)	0.010 (0.004–0.017)	0.905 (0.536–1.436)				
DALY[0;0] /symptomatic case (95%Crl)	1.581 (0.576–4.047)	14.934 (10.128–21.796)	1.741 (0.737–3.243)	_				
DALY[1;0.03] (95%Crl)	10,924 (4270–21,301)	3964 (2648–5653)	204 (116–323)	15,092 (8215–25,546)				
DALY[0;0.03] (95%Crl)	8916 (3569–17043)	3553 (2359–5098)	174 (96–277)	12,642 (7046–20,791)				
DALY[0;0][GBD2010 LE] (95%Crl)	14,994 (5668–29,273)	9673 (6347–14,017)	263 (106–486)	24,930 (14,706–39,702)				

Table 6.6:	Quantitative	assessment:	Disease	impact
	Quantitative	assessment.	DISEase	mp

\*Scenarios are denoted as DALY[age weighting constant; discount rate]; CrI: Credibility Interval; GBD2010 LE: Global Burden of Disease 2010 Life Expectancy table

\*\*Incident symptomatic cases are the sum of all clinical manifestations across all incident cases



**Figure 6.3:** Population-level (DALY[0;0] per year) versus individual-level burden (DALY[0;0] per symptomatic case) in Nepal, 2006. The scatterplots represent 1000 random samples from each distribution, with the black symbol representing the centroid; both axes are on a log10 scale.

# 6.4 Discussion

As disease burden estimates are of increasing importance for policy making and evaluation, the need for such estimates becomes eminent. In the late 1990s, the World Bank commissioned a comprehensive analysis of health care delivery in Nepal. Several recommendations were made for the further development of the Nepalese health sector, one of which was the establishment of priorities [20]. These recommendations were carried forward in the development of the Nepal Health Sector Programmes (NHSP), short-term strategic frameworks for the further development of the health sector. Since then, disease burden is recognized as one of the bases for setting program priorities [21]. However, when routine surveillance systems are performing poorly and baseline epidemiological studies are rare, these estimates are not readily available ([265]; **Chapter 1**). In this paper, we present the first comprehensive systematic review of the burden of PZs in Nepal. Information was sought from the international and national peer-reviewed scientific literature, and an important source of information was found in dissertations. The information found allowed qualitative assessment of the twenty PZs considered. However, quantitative estimates of prevalence or disease burden were possible for only a few.

Nepal is considered endemic for at least ten PZs, and might be endemic for seven others. Most of these diseases probably only have a small public health impact. However, NCC and congenital toxoplasmosis are likely to impose an important burden to public health. Indeed, if we compare with the three "major" infectious diseases, we see that the estimated burden due to major clinical manifestations of three PZs, with in total 0.57 DALY[1;0.03] per 1000 people, is higher than that of the WHO 2004 GBD estimate for malaria (0.05 DALY[1;0.03] per 1000), comparable to that for HIV/AIDS (0.74 DALY[1;0.03] per 1000), but substantially lower than that for tuberculosis (5.45)DALY[1:0.03] per 1000) [10]. These comparisons suggest that greater attention for PZs in Nepal is warranted. Toxoplasmosis is for instance not reported in any official Nepalese data collection system, and cysticercosis and toxoplasmosis were not considered in the WHO 2004 GBD update [10]. As a result, the incidence of congenital toxoplasmosis remains a critical data gap, and considerable uncertainties remain regarding the epilepsy prevalence and proportion of NCC-associated epilepsy. Data on the zoonotic potential of intestinal helminths and protozoa and their health effects are lacking, although these infections may represent a considerable additional health burden.

In our study, certain methodological choices were made with as a consequence certain limitations. First, instead of applying strict inclusion/exclusion criteria, we aimed at collecting as much relevant information as possible. Inherently, this led to large heterogeneity in the collected quantitative data. As a result, our burden estimates have large uncertainty intervals, making it for instance impossible to statistically distinguish the burden of NCC and congenital toxoplasmosis. For congenital toxoplasmosis, as no direct evidence was available, we estimated the incidence based on a single age-specific seroprevalence study. Clearly, this puts an important constraint on the representativeness of our resulting burden estimate. Direct evidence on the incidence of congenital toxoplasmosis (e.g., through serological studies on newborns), preferably obtained through a multi-center study, is therefore needed to confirm our burden estimate.

Second, uncertainty was introduced by the selection and valuation of the clinical outcomes for the three diseases. We based our disease models on published studies [64, 80, 81, 266], but note that other authors applied alternative ones. For instance, Bhattarai et al. [85] also included severe headaches in their assessment of the burden of NCC in Mexico, whereas this was deemed infeasible in our study. Likewise, the disability weights assigned to the different included clinical outcomes were derived from earlier studies [64, 80, 81, 266], in order to enhance comparability with those studies. Nevertheless, other studies, including the GBD studies, are less transparent about their applied disease models and disability weights, impeding unambiguous comparisons. For instance, the GBD 2010 study estimated the number of DALY[0;0] in Nepal to be 667 [141–2073] for "echinococcosis" and 4220 [2786–6022] for cysticercosis [11]. Given a lack of knowledge on the disease models, disability weights and data behind these estimates, it is difficult to assess the reason for any differences or similarities with our estimates. Toxoplasmosis and other PZs appear to be absent from the GBD 2010 study.

Third, subjective methodological choices regarding the calculation of DALYs may lead to further uncertainty. We tried to deal with this source of uncertainty by calculating DALYs under different common sets of normative assumptions, i.e., no discounting and age weighting, 3% time discounting and no age weighting, 3% time discounting and age weighting; and by calculating DALYs based on both the Coale-Demeny model life table West and the new GBD 2010 life expectancy table. As expected, time discounting led to smaller burden estimates. The difference between both life tables was minimal.

In addition, this study focused on the population burden of PZs. Some PZs, however, might have an important individual burden, even though their population burden is negligible or small. Likewise, the burden suffered by specific sub-populations (e.g., caste or ethnic groups), might be much higher than average population burden [183].

Finally, due to a lack of time and resources, we had to place restrictions on the nature

of the diseases to be studied, and on the nature of the burden estimates to be generated. Indeed, this study only focused on the burden of parasitic zoonoses. However, as means for interventions are poor, future integrated control could be packaged by, for instance, simultaneously controlling cystic echinococcosis, brucellosis and rabies. This analysis should therefore be extended to the burden of bacterial and viral zoonoses in Nepal. By quantifying the burden in terms of incidence, mortality and DALYs, we also focused on the *health* impact of the concerned diseases. Some PZs might have an important economic impact, for example in terms of livestock health, or might reduce psycho-social wellbeing in a way not captured by the applied metrics. Truly evidence-informed priority setting and decision making should take into account all these aspects of disease burden, implying that our estimates should be complemented by others.

Despite these limitations, this study has identified the most important PZs for Nepal, as far as existing data allowed. The quantitative estimates of disease burden for three of these diseases suggest that PZs deserve greater attention and more intensive surveillance. As population and disease transmission dynamics change over time, disease burden changes dynamically as well. Therefore, the presented results should be updated regularly, and this exercise should be extended to other groups of neglected diseases or even to a full national burden of disease study. We therefore hope that this study will stimulate further research, so that the overall human health burden in Nepal can be better characterized. In the long term, however, continued efforts to improve surveillance and database system at the local level should enable truly monitoring of disease burden over time.

# Rabies in Nepal: epidemiology, impact and control

Adapted from

**Devleesschauwer B**, Aryal A, Ale A, Declercq A, Depraz S, Gaire TN, Karki S, Pandey BD, Pun SB, Sharma B, Duchateau L, Dorny P, Speybroeck N. Rabies in Nepal: epidemiology, impact and control. *In preparation*.

# 7.1 Introduction

Rabies is a neglected zoonotic disease caused by an RNA virus of the family Rhabdoviridae, genus Lyssavirus. All mammals can be infected with the rabies virus, but dogs and dog bites are the most important source of human rabies. Although the necessary evidence and tools are in place to control and eliminate rabies, the virus still has a worldwide distribution and is causing a significant health and economic burden to mainly developing countries in Africa and Asia [84].

Rabies is a vaccine-preventable disease. Modern cell culture-based and embryonated egg-based anti-rabies vaccines (ARV) have proven to be safe and effective in preventing rabies [267]. Earlier nerve tissue ARV could induce severe adverse reactions and were less immunogenic. As a result, the production and use of nerve tissue ARV has been discouraged by the World Health Organization (WHO) since 1984 [268]. Pre-exposure prophylaxis (PrEP) is recommended to individuals coming in close contact with (specimens of) rabid animals, such as laboratory technicians and veterinarians. Once exposed to a rabid animal, timely post-exposure prophylaxis (PEP) can be lifesaving. The WHO-recommended PEP protocol consists of immediate primary wound management, accompanied by a recommended course of ARV and, for high risk exposures, administration of rabies immunoglobulin (RIG). Intradermal administration of ARV is recommended over intramuscular administration, as it reduces the volume used and thus the direct cost of the vaccine by 60-80%, without compromising on safety or immunogenicity [268].

Although proper implementation of PrEP and PEP can significantly reduce the burden of human rabies, it is not a sustainable approach for controlling rabies. Indeed, prophylaxis alone does not reduce the rabies transmission and can induce an unbearable economic burden on households, communities and governments. The *Partners for Rabies Prevention*, an international group of agencies and experts involved in rabies, developed a blueprint for rabies prevention and control [269]. The main intervention strategy in the dog rabies control blueprint is mass dog vaccination, possibly complemented with dog population management measures. However, proper planning and evaluation are equally crucial components of the blueprint. In the planning phase, information should be gathered on the local rabies epidemiology and the extent of the dog population. Also, awareness should be created and support elicited from both the local population and the relevant governmental agencies. Once a programme is in place, the change in epidemiological, economic and social impact of the disease needs to be monitored to evaluate the effectiveness of the programme. Reliable baseline data and effective rabies surveillance are inevitable to accomplish this goal.

82

This chapter focuses on the rabies situation in Nepal. Landlocked between India and China, Nepal has a surface of 147,000 km<sup>2</sup> and a population of approximately 29 million. Geographically the country can be divided in three ecological belts, i.e., the northern Himalayas, the central hills, and the southern Terai plains. Due to a concurrent history and an open border, Nepal has similar socioeconomic conditions as India, the country with the largest rabies burden worldwide [84]. Nevertheless, little is known about the actual status of rabies in Nepal. This review summarizes current knowledge on epidemiology, impact and control of rabies in Nepal, and ends with recommendations for a way forward.

# 7.2 Materials and methods

We used a variety of sources to search for information on rabies in Nepal. We performed a systematic review of scientific literature indexed in PubMed, Web of Knowledge and Nepal Journals Online<sup>1</sup>, complemented by manual searches of main Nepalese journals, the Journal of the Association for Prevention and Control of Rabies in India<sup>2</sup> and the conference proceedings of the Rabies in Asia (RIA) foundation<sup>3</sup>. We searched for the following key words: ("rabies" OR "rabid" OR "dog") AND "nepal", and excluded items that did not pertain to rabies in Nepal. Further grey literature was collected through browsing the websites of the WHO and the National Zoonoses and Food Hygiene Research Centre (NZFHRC). We also searched **Google** and **Google Scholar** for additional documents, but acknowledge that these searches are not replicable, due to the continuous updating of the Google databases and the user-specific ranking of database items.

Additionally, we reviewed websites and documents from relevant government agencies. Rabies surveillance in Nepal is passive and based on a decentralized data collection system. The Veterinary Epidemiology Centre (VEC), resorting under the Directorate of Animal Health (DAH), Department of Livestock Services (DLS), Ministry of Agricultural Development, is the national focal point for animal disease surveillance, including rabies. Passive surveillance for human rabies is comprised in the Health Management Information System (HMIS), managed by the Department of Health Services (DoHS), Ministry of Health and Population. The Zoonotic Disease Sub-section of the DoHS Epidemiology and Disease Control Division (EDCD) is responsible for prevention and control of rabies and other zoonotic diseases.

<sup>&</sup>lt;sup>1</sup>http://www.nepjol.info/

<sup>&</sup>lt;sup>2</sup>http://apcrijournal.org/

<sup>&</sup>lt;sup>3</sup>http://www.rabiesinasia.org/riacon.html

Finally, we searched news items on rabies in Nepal from the archives of The Himalayan Times, a large English-language Nepalese daily, and ProMED, a global electronic reporting system for outbreaks of infectious and other diseases. We acknowledge that these data sources do not provide reliable quantitative information, but believe that they are useful sources of qualitative information on the rabies situation in Nepal.

# 7.3 Results

#### 7.3.1 Data sources

Little original research has been conducted on the epidemiology and impact of rabies in Nepal. From the systematic review, we retained a total of 22 documents. The further online searches revealed another 38 documents.

We obtained a dataset from the VEC containing reported data for the period 2000–2009. The same dataset has been, in total or partly, discussed by Gongal [270] and Karki & Thakuri [271]. The VEC receives a monthly *Animal Disease Epidemiological Report* in a specified format from all 75 District Livestock Service Offices (DLSO). Each DLSO, in its turn, receives animal health and disease data from the animal health technicians working in the various Village Development Committees, the lowest administrative level in the Nepalese system [270]. Further information on rabies in Nepal was available from two DAH Annual Technical Reports [272, 273].

Since 1994, the DoHS publishes Annual Reports which analyse the performance of different programmes and present information collected by the HMIS<sup>4</sup>. In fiscal year 2012/13, all 75 District (Public) Health Offices, 82.9% of public hospitals, 95.4% of Primary Health Care Centres, 98.4% of Health Posts, 96.3% of Sub Health Posts reported to HMIS [274]. A total of 441 NGO and 669 private health institutions also reported to HMIS that year. The Annual Report contains information on the number of dog bites and other animal bites, by district, reported to the concerned health centres. It also contains hospital inpatient data on rabies morbidity and mortality, based on the ICD codes A82 (Rabies) and A82.8 (Rabies, unspecified). We obtained DoHS Annual Reports for fiscal years 2001/02 to 2012/13, the latest issue available.

<sup>&</sup>lt;sup>4</sup>http://dohs.gov.np/

### 7.3.2 Epidemiology

Rabies in Nepal occurs in two interrelated epidemiological cycles: an urban cycle involving domesticated dogs and a sylvatic cycle involving wildlife [275]. The urban cycle is the predominant source of human rabies, with more than 96% of rabies patients reported during 1991–2000 showing a history of rabid dog exposure [276]. Nevertheless, overlap between both cycles does occur. Indeed, spill-over between cycles has recently been demonstrated by the isolation of a virus from a human rabies case that showed 100% identity over the studied region to viruses previously isolated from two dogs and a mongoose (family *Herpestidae*) in Nepal [277].

The urban cycle is maintained by the stray and community dog population, with spillovers to pet dogs adding to the human rabies burden. There is little current information on the extent of the stray dog population in Nepal. According to a dog census carried out by the NZFHRC in 1998, there would be nearly 2 million dogs in Nepal [278]. However, most other surveys have been conducted in the Kathmandu Valley of Nepal, comprising the Kathmandu, Bhaktapur and Lalitpur districts. In 1989, Bögel & Joshi [279] estimated a dog population of 12,500 in Lalitpur city, or 700 per km<sup>2</sup>. In October 1997, a much higher stray dog density of 2,930 dogs per km<sup>2</sup> was established in Kathmandu [280]. With an area of just over 50 km<sup>2</sup>, this would correspond to a total of nearly 150,000 stray dogs. More recently, animal welfare organizations have undertaken several dog population surveys in the Kathmandu Valley. Within the Ring Road area, the estimated dog population was 31,000 in 2006, dropping to 22,500 in 2010 and 22,300 in 2012 [281, 282].

One cause of this problematic size is the religious adoration of the dog [279]. The culmination of dog worship takes place on *Kukur Tihar*, the second day of *Tihar*, the festival of lights, on which dogs are worshipped with garlands, tika and food. However, more important factors for the sustenance of the stray dog population are probably the bad garbage policy and open slaughter facilities, especially in the Kathmandu Valley [283]. The decline in the vulture population since the 1990s also implied the loss of a competitor for food [284]. Finally, the rapid urbanization and the growth of slum areas further create favourable conditions for the sustenance of stray dog populations [285, 286].

The sylvatic cycle is maintained by wild carnivores living in forest zones, national parks, or wildlife reserves, such as mongooses (family *Herpestidae*), jackals (*Canis aureus*), foxes (*Vulpes* spp.), wolves (*Canis lupus*) and tigers (*Panthera tigris*) [276]. In Nepal, the direct importance of this cycle is thought to be less important, although it probably has a significant indirect importance as continuous source of infection for the urban cycle [275, 277].

Rhesus macaques (*Macaca mulatta*) are abundant in certain temple areas inside and outside of the Kathmandu Valley. Although these temple monkeys can become infected through the urban and sylvatic cycle, their role in rabies transmission is unclear. Nevertheless, monkey bites or scratches are reported to occur frequently in tourists and expats staying in Kathmandu [287, 288], and in India, a rhesus macaque is believed to have transmitted rabies to a 10-year-old Australian boy [287, 289]. Furthermore, monkeys are occasionally reported to menace the local population, although it is not always clear if this is due to rabies infection.

The risk of rabies infection is believed to be highest in the southern Terai plains, which are densely populated agricultural areas and contain various wildlife areas [270, 276]. Nevertheless, animal and human rabies is reported from nearly all 75 districts of the country. Figure 7.1 shows the distribution of rabies outbreaks reported to the VEC during 2000–2009. The districts with the highest number of outbreaks were Surkhet (193), Nawalparasi (189), Makwanpur (140) and Jhapa (139). No outbreaks were reported from six mountain districts (Bajhang, Bajura, Manang, Mugu, Mustang, Sindhupalchowk) and three hill districts (Gulmi, Myagdi, Ramechap).



**Figure 7.1:** Number of rabies outbreaks reported during 2000–2009 to the Veterinary Epidemiology Center of the Directorate of Animal Health, Department of Livestock Services, Ministry of Agricultural Development.

# 7.3.3 Impact

#### Animal rabies

Thakuri et al. [290] observed 34 rabies cases in cattle during 1985–1990 at the veterinary hospitals of four hill districts in Eastern Nepal. The only recent epidemiological data on animal rabies in Nepal stem from the VEC. Table 7.1 shows the number of affected, dead, vaccinated and treated animals as reported to the VEC during 2000–2009. During that period, a total of 1692 animals were reported dead and 88,002 vaccinated. Cattle and buffalo appeared to be the most affected livestock species. However, the reporting of animal rabies cases is probably dependent on the economic value of the affected species [270].

**Table 7.1:** Animal rabies cases reported during 2000–2009 to the Veterinary EpidemiologyCenter of the Directorate of Animal Health, Department of Livestock Services,Ministry of Agricultural Development.

Species	Affected	Dead	Vaccinated	Treated
Dog	3,927	551	79,528	837
Cat	0	0	2	0
Cattle	1,187	600	3,266	542
Buffalo	681	377	2,222	149
Goat	440	128	1,192	158
Sheep	45	5	1,210	34
Horse	20	8	209	2
Pig	62	23	205	7

Molecular identification of animal rabies virus has identified both the Indian subcontinent lineage and the Arctic lineage to occur in animals in Nepal [291].

#### Human rabies

Epidemiological data on human rabies are available from the Annual Reports of the DoHS. The total number of reported dog bites showed a steady increase, from 15,000 in 2001 to 35,000 in 2012. Figure 7.2 shows the apparent distribution of dog bites in Nepal. Nearly 5% of all dog bites occurred in the districts of the Kathmandu Valley. The number of other animal bites stayed constant at around 2,000 per year. Inpatient morbidity cases ranged between 1 and 28 per year, while inpatient mortality cases ranged between 0 and 6 per year. However, data from the EDCD showed that there were nearly 100 rabies deaths each year [274].

Further information on the rabies burden in Nepal is available from the global burden

of disease studies conducted by the WHO and the Institute for Health Metrics and Evaluation (IHME) (Figure 7.3). The available estimates indicate an important decrease in the annual number of rabies deaths, converging to 200–400 deaths in recent years. The burden of rabies, expressed in Disability-Adjusted Life Years (DALYs), was estimated by IHME at 21,643 for the year 2010 [11] and by WHO at 18,587 for the year 2012 [16].



**Figure 7.2:** Median number of dog bites reported during 2001–2012 to the Department of Health Services, Ministry of Health and Population.



Figure 7.3: Estimated mean number of rabies deaths in Global Burden of Disease studies. WHO: World Health Organization Global Health Estimates [292]; GBD2010: Global Burden of Disease 2010 Study [293]; GBD2013: Global Burden of Disease 2013 Study [294].

#### 7.3.4 Control

#### Prophylaxis

Production of ARV in Nepal started in 1970 and continues to date. ARV production is managed by the Central Rabies Vaccine Production Lab (RVPL), which falls under the DAH, DLS, Ministry of Agricultural Development [272, 273]. Distribution of ARV is handled via the five regional veterinary laboratories, which serve as rabies vaccine banks [295]. Initially, the RVPL produced phenolized 20% sheep brain ARV for pet immunization and phenolized 5% sheep brain ARV for livestock immunization. In 1983/84, the RVPL started production of Beta-Propiolactone (BPL) inactivated 5% sheep ARV for human use, and was able to meet the national demand by 1994 [296, 297]. Following the WHO recommendations, the production of nerve tissue ARV has now been phased out in favour of tissue or cell culture ARV. The veterinary authority phased out the production of phenolized 5% nerve tissue ARV for human use has been phased out in 2006 [272].

To replace the nerve tissue vaccines, the RVPL worked with the Japan International Cooperation Agency to set up cell culture ARV production facilities [272, 298]. A first trial batch of cell culture ARV for animal use was produced in 2002 [297], and after further development the first commercial batch was released in the market in 2006 under the trade name "NeJaRab". However, with a current target of 50,000 doses per year, the production of NeJaRab does not meet national demand, necessitating the import of additional ARV for animal use [295, 299]. Further in 2006, a first trial batch of a Vero cell culture-based ARV for human use was produced, and in 2009, a first trial batch of hyper-immune serum from sheep was produced [297]. Today, the productions of cell culture ARV and RIG for human use are still reported to be in trial phase [299]. Nepal is also reported to be in the process of introducing intradermal rabies vaccination schedules [300].

The Government of Nepal is providing free ARV for human use at government hospitals and health centres since 2007 [296, 301]. Despite the progress made in ARV production capacity, Nepal is 100% dependent on import for covering its PrEP and PEP need. For the three-year period 2013–2015, the Government of Nepal with support from the World Bank purchased 900,000 ARV vials from an Indian manufacturer, at a total cost of 220 million NRs (1.8 million Euro). This would be sufficient to provide PEP to 30–40,000 people per year [274]. Nevertheless, media reports show that the availability and supply of government-provided ARV is sometimes insufficient, in the best case forcing people to resort to the private market for more expensive vaccines or, in the worst case, depriving people of PEP. Furthermore, equine or human RIG is available only in clinics in Kathmandu, and due to the high cost, mainly used by tourists and expats [276, 302].

#### **Rabies control programmes**

Over the past decades, various state and non-state actors have been involved in rabies control activities in Nepal. The driving force behind many of these projects appears to have been Dr Durga Datt Joshi, who served various government positions in the health and agriculture sector, including that of Chief Zoonotic Diseases Control Section. In 1995, he founded the NZFHRC, a research-oriented NGO which he chaired until his demise in 2013. In recent years, various animal welfare organizations have started engaging in dog population management and rabies control activities. The most notable such organization is the Kathmandu Animal Treatment (KAT) Centre, which has been active in animal birth control and dog rabies vaccination in Kathmandu since 2004.

The first reference to a rabies control programme in Nepal appears in the CV of Dr DD Joshi [303]. In 1970, he was member of the coordination committee for a rabies control programme in street and pet dogs of Kathmandu. However, further information on this project is lacking. The next historical reference is given in Bögel & Joshi [279] and Kappeler & Wandeler [304]. In the early 1980s, Dr DD Joshi and Dr Konrad Bögel, then Chief of the WHO Veterinary Public Health unit, worked out plans for rabies control projects in Nepal, including a four-year period vaccination campaign, starting with a pilot project in Lalitpur City. Funds for the pilot project were assured by Vétérinaires sans Frontières, and in June–July 1989, an intensive dog vaccination campaign was conducted in Lalitpur town, eventually vaccinating around 8400 dogs. This pilot study was preceded by an *Intercountry Practical Training Course on Dog Population Management*, organized in 1986 in Kathmandu by the WHO Regional Office for South-East Asia, and several extensive dog population studies conducted in 1986 and 1989 [279, 304]. Despite encouraging results, however, we could not retrieve any information pointing to a continuation of the project beyond the pilot phase.

In 2000–2008, the NZFHRC engaged in free dog rabies vaccination campaigns supported by the Donative Unit for Rabies Vaccine to Nepal, Tokyo, Japan. Mass dog vaccination and awareness programmes were organized in 24 municipalities across the country, in collaboration with the respective local governments. Over the eight-year period, a total of 18,973 dogs and cats were reported to be vaccinated [305–307].

Since 2001, faculty and students at the Cummings School of Veterinary Medicine, Tufts University, have been involved in rabies control activities in Nepal [308, 309]. Partnerships have been set up with the NZFHRC, the KAT Centre, the Himalayan College of Agricul-
tural Sciences and Technology (HICAST), and the Chitwan-based Institute of Agriculture and Animal Science (IAAS). Based on a workshop organized in April 2001 in Kathmandu, a concept for a *Nepal National Rabies Control Programme* was developed, aiming for the control of rabies in Nepal over a ten-year period. Since 2002, however, Tufts' efforts have been refocused on dog sterilization and rabies vaccination capacity building and student exchanges at IAAS and the KAT Centre<sup>5</sup>.

In April 2007, the NZFHRC organized a Workshop for Consensus Building amongst National Alliance Partners to Eliminate Canine Rabies in Nepal and Development of the National Strategic Plan [310]. Supported by WHO, the aim of the workshop was to develop a National Rabies Control Plan towards control of rabies by 2012 and elimination by 2027. Following the workshop, an Alliance Group for Rabies Control in Nepal was established in 2008, comprising the NZFHRC, the KAT Centre, the Veterinary Public Health Division of the DLS, and the Department of Public Health and Social Welfare of Kathmandu Metropolitan City. Since then, the Alliance Group has mainly been involved in dog vaccinations in Kathmandu, including the vaccination of 10,000 stray and community dogs in 2009 [272]. They are also involved in the annual promotion of World Rabies Day in Kathmandu, an initiative launched by the Global Alliance for Rabies Control (GARC) in 2007. During this day, free dog vaccination and awareness campaigns are organized. Currently, World Rabies Day is marked all across Nepal, with the support of various animal welfare and students organization.

Although the Government of Nepal has been involved in most of the aforementioned rabies control activities, it lacks a comprehensive and realistic national rabies control strategy. There are currently no legal requirements regarding the vaccination of pet animals or livestock. Moreover, the EDCD is currently still supplying free strychnine sulfate to local governments, leading to the elimination of around 20,000 stray dogs each year [305].

Regional and international rabies control initiatives are emerging, which could help Nepal in its control efforts [311]. The institution of World Rabies Day by the GARC is just one example, but other initiatives are being launched by the WHO Regional office for South-East Asia [114, 300], the South Asian Association for Regional Cooperation [275], and the RIA Foundation [311, 312].

<sup>&</sup>lt;sup>5</sup>http://vet.tufts.edu/idgh/ivm/projects/rabies\_control.html

## 7.4 Discussion

A proper understanding of the epidemiology and impact of rabies is crucial for planning, implementing and evaluating rabies control programmes. In this review, we tried to generate the best possible summary of data on animal and human rabies in Nepal. Per year, rabies is reported to kill about 100 livestock and 100 humans, while about 9,000 animals and 35,000 humans are reported to receive rabies PEP. However, these estimates very likely represent serious underestimations of the true rabies burden. Indeed, underreporting is very likely to occur in both the animal and human passive surveillance systems [265]. Illustrative for these problems are the discrepancies in human rabies deaths between the DoHS Annual Reports and the EDCD reports and the lack of inpatient data from three districts since the last four years. Further perturbation is introduced by putative cases typically being diagnosed based on history and symptoms, and not on lab confirmation. Laboratory confirmation of rabies is currently limited to the Central Veterinary Laboratory, Kathmandu, which sees around 15 human and animal samples a year [291, 299]. Underreporting of human rabies cases may further result from the fact that rabies patients sometimes prefer to visit traditional healers or prefer to stay home when rabies symptoms have appeared.

Rabies is estimated to cause around 20,000 DALYs per year (WHO; [11]). This is in line with the total burden of the three major parasitic zoonoses in Nepal (i.e., cysticercosis, toxoplasmosis, cystic echinococcosis; [313]), showing that rabies still is a major zoonosis in Nepal. However, in absence of reliable data, the burden estimates generated by WHO and IHME are based on extrapolations from neighbouring countries, warranting cautious interpretation. Only with more reliable local data can these estimates be further refined.

Significant progress has been made in the production of ARV and RIG. The abandonment of nerve tissue vaccines has been successfully mitigated by the production of cell culture vaccines. Efforts are ongoing to produce ARV and RIG for human use. Nevertheless, availability and supply of vaccine remains a matter of concern, especially in remote areas. Furthermore, it should be clear that prophylaxis alone is not sufficient to control rabies. Unfortunately, much less success has been made in the implementation of effective rabies control programmes. Rabies control programmes appear to have been initiated since the 1970s. Although some individual projects reported successes, the overall impact has probably been limited due to limited duration and geographical coverage. Different state and non-state actors have been involved in rabies control over the years, but collaboration between these different groups has been limited. Illustrative of this is that most projects included awareness and mass dog vaccination, but lacked dog population management activities such as animal birth control or waste management. Canine rabies control programmes could further be complemented with praziquantel treatment against *Echinococcus granulosus*, another endemic dog-borne zoonosis [313]. Finally, with 80% of all rabies occurring in the South Asian region [84], several regional control efforts are emerging, providing new opportunities for rabies control in Nepal.

## 7.5 Conclusion

Limited data indicate that rabies still is a major zoonosis in Nepal. However, more and better data are needed, especially from rural areas, to estimate the true burden of animal and human rabies and to plan, implement and evaluate rabies control programmes. The current control of rabies is hampered by insufficient vaccine availability across the country. The way forward for effective rabies control programmes lies in more collaboration, both within the country and within the region. To accomplish all of these recommendations, high-level political commitment is required. Making rabies the model zoonosis for successful control may be a powerful step towards achieving this.

# General discussion

The main objective of this thesis was to unravel the burden of zoonoses in Nepal and to quantify this burden using the Disability-Adjusted Life Year (DALY) metric. To achieve this goal, we contributed to a further standardization of the DALY metric. First, we proposed a stepwise approach for conducting a DALY-based burden of disease study, thereby defining important concepts such as the disease model (**Chapter 3**). Next, we studied sources of uncertainty inherent to DALY calculations and proposed guidelines for quantifying parameter, model and methodological uncertainty (**Chapter 4**). Finally, we developed a free and open-source tool for calculating DALYs and quantifying related uncertainties (**Chapter 5**). Based on the guidelines and tools developed in these first chapters, we then went on to accomplish the main objective of the thesis. We reviewed the occurrence of parasitic zoonoses in Nepal, and quantified the disease burden due to cystic echinococcosis, neurocysticercosis, and congenital toxoplasmosis (**Chapter 6**). In addition, we reviewed the epidemiology, burden and control of rabies in Nepal (**Chapter 7**).

In this chapter we will place our findings in a broader perspective, discuss the main limitations of the thesis and present avenues for future research.  $\infty$ 

## 8.1 Towards a standardization of the DALY metric

With the advent of the Global Burden of Disease (GBD) 2013 study, the DALY metric will continue to play a central role in global health. In addition, individual DALY-based disease burden studies continue to emerge. However, comparability of estimates across studies is not guaranteed, leading to "error" sources of variability. Our work contributed to identifying these sources of methodological variability, but definitely did not manage to resolve the lack of comparability across studies. Moreover, it is not likely that this problem will be solved in the near future. Indeed, even though the GBD 2013 study will include nearly 300 causes of ill health, there will still be many diseases and conditions not covered, including important zoonoses such as toxoplasmosis. Furthermore, even though the GBD 2013 estimates will have a high degree of internal consistency, their external validity is not guaranteed. The large discrepancy in rabies death estimates between the GBD 2010 and GBD 2013 studies for instance indicates that GBD estimates are highly dependent on the applied data sources and methodologies and cannot be considered as gold standard. Independent disease burden studies will therefore continue to be required. Ideally, the findings from **Chapter 4** could lead to the development of a reporting guideline for these different studies, in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews and meta-analyses [38] or the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies [314]. Such a check list of assumptions would not resolve comparability issues, but would at least increase methodological transparency. The DALY Calculator presented in Chapter 5 should be further developed, allowing for more complex disease models. Developing a user-friendly online interface to the DALY Calculator would allow the tool to gain a much wider audience.

DALYs were introduced over 20 years ago [15]. However, there has been relatively little methodological research on the DALY metric and its assumptions and data needs. Two issues deserve special attention, i.e., the problem of multimorbidity and the extrapolation of health statistics. In addition, it is important to acknowledge some inherent limitations of the DALY metric and of summary measures of population health (SMPH) in general.

#### 8.1.1 Accounting for multimorbidity

The co-occurrence of two or more medical conditions in the same individual is not uncommon, especially in the elderly [315]. In medical literature, this phenomenon is called *multimorbidity*. When there is an underlying index disease resulting in multimorbidity, one typically uses the term *comorbidity* [315]. In DALY calculations, multimorbidity may lead to an overestimation of the morbidity component, the Years Lived with Disability (YLD). Assume, for instance, a patient with both a moderate osteoarthritis of the shoulder (DW = 0.114) and a moderate Chronic Obstructive Pulmonary Disease (COPD; DW = 0.192) [14]. Without correcting for multimorbidity, the DW for this patient would implicitly be calculated as the sum of both DWs, i.e., 0.144 + 0.192 = 0.336. However, assuming that DWs, and thus reductions in Health-Related Quality of Life (HRQoL), add up, is not necessarily correct. Furthermore, additivity could lead to a multimorbid DW that is larger than 1, i.e., a situation "worse than death".

Different methods have been described to account for multimorbidity and overcome the limitations of the additive approach [316]. In the maximum limit or worst case approach, the multimorbid DW is set equal to the highest DW of the individual conditions. For our patient, this would result in a DW of 0.192, i.e., that of COPD. In the multiplicative approach, the multimorbid DW is calculated as  $1 - \prod (1 - DW_i)$ , with DW<sub>i</sub> the individual DWs. For our patient, this would result in a DW of 1 - (1 - 0.114)(1 - 0.192) = 0.284. Other researchers used a regression approach to decompose the effects of multimorbidity on HRQoL [61, 62]. Similar decomposition methods have been used to examine the contribution made by causes of disability to differences in healthy life expectancy [317] or disability prevalence [318]. Unlike the classical DALY approach, these methods allow for a "background" burden, i.e., disability in subjects without a reported disease. Unfortunately, decomposition methods only allow to study the contribution of multiple causes to overall health, but do not allow to obtain a DW for an arbitrary set of conditions.

Although these possible correction methods result in theoretically sound DWs, i.e., bounded between 0 and 1, their practical validity remains unclear. Indeed, in a comparison of theoretical and observed multimorbid DWs, measured using the EQ-5D questionnaire, the maximum limit model appeared to perform worst, while both the maximum limit and multiplicative approach provided a bad fit in the case of mild to moderate pre-existing disease [316]. As it is not realistic that all possible multimorbid DWs can be obtained through health surveys, further research is needed to develop appropriate methods for estimating DWs for an arbitrary set of conditions.

In addition to the appropriate multimorbid DW, calculating YLDs also requires data on the prevalence or incidence of the multimorbid condition. Ideally, this information should come from a population-based health survey. However, due to the large number of possible causes of ill health, it is practically impossible to measure all possible diseases and conditions in a population sample [319]. In absence of such information, one has to estimate the prevalence or incidence of multimorbidity from the prevalence or incidence of the individual diseases. In the GBD 2010 and GBD 2013 studies, the prevalence of multimorbidity was estimated by assuming independence between the prevalence of the individual diseases [1, 320]. In our example, this would mean that the prevalence of the given multimorbidity would equal the product of the prevalence of moderate shoulder arthritis and the prevalence of moderate COPD. Murray et al. [1] argue that the error associated with the independence assumption is minimal when this assumption is applied within each specific age–sex group. However, there is little evidence to support this assumption. Furthermore, there has been no research on methods for estimating the *incidence* of multimorbid conditions from the individual incidences or prevalences.

#### 8.1.2 Estimating health statistics

In disease burden studies, it is often necessary to extrapolate data from populations and time periods that are not necessarily comparable to the concerned population and reference year. Obviously, this is not only a problem for DALY-based disease burden studies. Nevertheless, there has been little research on the extrapolation of health statistics and the related uncertainties. In general, we can distinguish two approaches for filling gaps in health statistics, i.e., statistical, top-down models, and mechanistic, bottom-up models.

Statistical models use available data to estimate missing data. Maertens de Noordhout et al. [321] for instance used a random effects model to extrapolate available listeriosis incidences to countries that lacked such data. The random effect used was World Health Organization subregion, assuming that countries within a given subregion have a similar incidence of listeriosis. Further extending such models by including covariates or fixed effects would lead to mixed effects models. Such models were frequently used in the GBD 2010 and GBD 2013 studies [1, 320]. Rabies mortality, for instance, was modelled based on the covariates "health system access" and "population density". In addition, for its overall mortality estimates, the GBD 2010 and GBD 2013 studies applied a three-stage approach consisting of non-linear mixed effects regression, spatial-temporal smoothing of residuals, and Gaussian process regression [294]. Despite the underliably large impact of these models on the resulting health estimates, there has been little research on their performance. Recently, McDonald et al. [322] compared Bayesian random and mixed effects regression models for imputing missing country-level incidence rates, and found that the inclusion of informative covariates could improve model performance, but that results should be appraised carefully. Further research, e.g., through simulation studies, is needed to better understand the performance of statistical models and the reliability of the resulting health estimates.

Mechanistic models, sometimes referred to as bottom-up or *a priori* models, provide an alternative means of estimating health statistics. These models are based on an understanding of the disease dynamics, and predict disease occurrence from information on the presumed drivers of disease. Kanobana et al. [323] for instance proposed an agent-based model for human toxocarosis. Based on information on environmental contamination with *Toxocara* spp. eggs, larvation of eggs and age-related contact with eggs, the model predicted *Toxocara* antibody positivity in children. To our knowledge, however, such models and their estimated health statistics have not yet been used in disease burden studies.

# 8.1.3 General limitations of DALYs and summary measures of population health

The DALY metric has been developed to compare disease-specific burdens across populations or time periods. As a result, when DALYs are generated for one or a selected group of diseases, as was the case in our work, comprehensive comparisons are not possible. Indeed, the thus obtained DALYs only help to prioritize among the considered diseases, but ignore the overall importance (or lack thereof) of the group of considered diseases. Ideally, DALYs should therefore be calculated within an internally consistent framework covering the entire disease spectrum and multiple time points, allowing for trends over time to be assessed. Unfortunately, such studies are currently lacking in most countries, including Nepal. Likewise, as a disease-specific measure, the DALY is less well suited to provide an overview of the general health status of a population. Indeed, quantifying the total disease burden of a population would require DALYs to be calculated for an exhaustive set of diseases. Other SMPH, such as the Disability-Free Life Expectancy, have been developed to quantify and monitor general population health, and may therefore be more suitable when disease-specific burdens are not of prime interest. Finally, as the DALY was developed to combine morbidity and mortality in a single estimate, it avoids the question of whether improvements in morbidity rather than mortality should be pursued. A recent study by the Belgian Health Care Knowledge Centre (KCE) showed that the Belgian general population prefers improvements in quality of life over extensions of life expectancy [324]. Whether or not the same preferences prevail in countries with lower life expectancy, such as Nepal, remains unclear.

Certain limitations of the DALY metric are common to the larger group of SMPH. As synthetic measures, the calculation of SMPH is more complex, involving the combination of multiple input parameters. When one of these input parameters is biased, the SMPH will therefore also be biased. A crucial component in most SMPH is the weighting factor for quality of life, or loss thereof. As quality of life is a phenomenon that cannot be measured directly, different estimation methods have been proposed, inherently leading to different values. Haagsma et al. [57] review methodologies for deriving disability weights for DALY calculations. Furthermore, SMPH reflect by definition only the health impact of diseases. Especially for zoonotic diseases, however, the economic impact may also be significant, as not only health-related costs add to the economic burden, but also costs related to impaired animal health and prevention and control in the veterinary sector. The negligible global health impact of trichinellosis, for instance, is in sharp contrast to the significant economic losses due to surveillance in pigs [325]. From an economic point of view, public health policy should aim at maximizing population health and welfare with the healthcare resources available [326]. SMPH may assist in achieving allocative efficiency, i.e., the optimal mixture of healthcare programmes that maximizes overall population health and welfare. They do not assist in achieving technical efficiency, i.e., the optimal physical relation between available resource inputs and a given health outcome.

## 8.2 Burden of zoonoses in Nepal

This thesis contributed to an improved understanding of the epidemiology and burden of zoonoses in Nepal. The work also demonstrated that even without comprehensive and efficient surveillance systems, it is possible to unravel the burden of neglected diseases and break the vicious cycle of neglect. In this respect, the current work has served as a guiding example for the Country Studies Task Force of the WHO's Foodborne Disease Burden Epidemiology Reference Group (FERG), which aims to provide guidance for conducting national foodborne disease burden assessments [327].

Figure 8.1 shows the combined results of **Chapter 6** and **Chapter 7**, highlighting the importance of rabies, both at the population-level and the patient-level.

However, our work has been limited by the fact that only the health burden was quantified, and not the economic burden. The economic impact of zoonoses may be significant, as it not only results from expenses in the medical sector, but also from productivity losses and treatment and control costs in the veterinary sector [105, 108]. The high cost related to the purchase of anti-rabies vaccines (**Chapter 7**) suggests that zoonoses do impose a significant economic burden to the Nepalese society. Further research on the economic impact of zoonotic diseases is therefore encouraged.

In addition, by only focusing on parasitic zoonoses and rabies, we only covered one part of the large spectrum of zoonotic diseases. Indeed, over 800 pathogens have been defined as zoonoses, and it is believed that over 60% of all emerging infectious diseases are of



zoonotic nature [112, 328]. This Section aims to provide a more comprehensive picture of the burden of zoonoses in Nepal, by drawing upon the GBD and FERG studies.

**Figure 8.1:** Population-level (DALY[0;0] per year) versus individual-level burden (DALY[0;0] per symptomatic case) in Nepal, 2000–2010.

#### 8.2.1 Foodborne zoonoses

In 2006, the World Health Organization (WHO) launched the *Initiative to Estimate the Global Burden of Foodborne Disease*. One year later, FERG was established, a group of experts that were tasked with carrying forward the *Initiative* [329]. FERG established task forces for quantifying the burden of foodborne diseases due to parasitic agents, bacterial and viral enteric agents, and chemical and toxic hazards. Several of these agents are entirely or partly of zoonotic nature. Table 8.1 shows the number of deaths and DALYs estimated by FERG for different foodborne zoonoses in Nepal. According to these estimates, the highest burden is imposed by non-typhoidal salmonellosis and campylobacteriosis. There further appears to be a large uncertainty on the burden of brucellosis and listeriosis [330]. *Cryptosporidium* spp. is the parasite with the highest burden, although this burden is probably largely due to anthroponotic transmission, as discussed in **Chapter 6**. The burden of congenital toxoplasmosis is significantly lower than our estimate, but this is mainly because stillbirths were not included in the FERG estimates [331].

**Table 8.1:** Deaths and Disability-Adjusted Life Years (DALYs) with corresponding 95% Cred-<br/>ibility Intervals (CrI) for foodborne zoonoses in Nepal estimated by the Foodborne<br/>Disease Burden Epidemiology Reference Group

Zoonosis	Deaths	(95% Crl)	DALYs	(95% Crl)
Parasitic foodborne zoonose	es			
Cryptosporidiosis*	248	(128–504)	18,885	(8628–41,720)
Cysticercosis	149	(89–230)	11,816	(8475–15,825)
Toxoplasmosis, acquired	0	(00)	8193	(5597–11,086)
Ascarosis*	18	(0-85)	5065	(3247–10,330)
Toxoplasmosis, congenital	7	(3–13)	2387	(1224–4081)
Giardiosis*	0		428	(60–1237)
Cystic echinococcosis	4	(1-8)	320	(157–570)
Fasciolosis	0		19	(6–47)
Paragonimosis	0		18	(5–47)
Alveolar echinococcosis	0.2	(0-0.5)	6	(1–21)
Trichinellosis	0		0.20	(0.07–0.35)
Bacterial foodborne zoonos	es			
Salmonellosis, non-typhoidal	544	(331–1039)	38,274	(20,604–82,567)
Campylobacteriosis	244	(109–508)	22,102	(10,106–45,484)
Brucellosis	152	(0–986)	9672	(2–64,153)
Listeriosis	26	(0–149)	968	(0–5538)
Bovine tuberculosis	8	(3–16)	470	(192–902)
STEC infection**	2	(0-8)	184	(10–678)

\*Not 100% foodborne

\*\*STEC: Shiga-toxin producing Escherichia coli

#### 8.2.2 Vector-borne zoonoses

In recent years, vector-borne zoonoses have emerged or re-emerged in many geographical regions, partly driven by habitat and climate changes [332]. In Nepal, Japanese Encephalitis (JE) appears to be the best-studied vector-borne zoonosis. JE is caused by a mosquito-borne flavivirus and transmitted by *Culex tritaeniorhynchus* and related mosquitoes that lay eggs in rice paddies and other open water sources. Pigs and aquatic birds are the main vertebrate amplifying hosts. JE mainly affects children, and induces an encephalitis that may lead to neurological sequelae or even death [333]. JE was first recorded in Nepal in 1978. Nepal launched an extensive laboratory-based JE surveillance in 2004 and introduced mass immunizations in 2005 [334]. Anti-JE vaccination is also included in the National Immunization Programme, reaching a coverage of 87% [274]. In 2006, there were nearly 300 recorded JE cases, dropping to nearly 200 in 2010 and 129 in 2012/13 [274, 334]. Likewise, the number of recorded JE deaths dropped from 42 in 2006 to 1 in 2010 [334]. JE is not included in the GBD 2010 and GBD 2013 studies. Earlier WHO Global Health Estimates however did include JE: for the year 2004, the WHO estimated 174 JE deaths and 10,708 DALY[1;0.03]<sup>1</sup>.

Information on other vector-borne zoonoses is very limited. Murine typhus, due to *Rickettsia typhi*, and scrub typhus, due to *Orientia tsutsugamushi*, appear to be common causes of febrile illness in Nepalese [335–338]. Recently, the first three cases of chikungunya fever have been reported, indicating that this zoonosis may be emerging in Nepal [339].

#### 8.2.3 Other zoonoses

Case reports and hospital-based studies indicate the presence of various other zoonoses in Nepal. However, the available information is typically insufficient to give a clear idea of their actual impact on population health. From June 2009 to March 2010, pandemic (H1N1) 2009 virus was confirmed in 172 respiratory samples submitted to the National Public Health Laboratory [340], and till May 2010, three deaths were reported [341]. Leptospirosis was confirmed in nearly 10% of hepatitis and febrile illness cases [335, 336, 342], and has been recognized as an important differential diagnosis of acute encephalitis syndrome [343]. Hepatitis E Virus has been studied as a cause of morbidity and death during pregnancy [344, 345] and as a cause of hepatitis in travellers [346]. Kimura & Ohnishi, finally, reported a patient with Q fever who had recently visited rural areas in Nepal and Tibet [347].

#### 8.2.4 Conclusion

The available information shows that several zoonotic diseases are endemic to Nepal. The zoonoses with the highest public health burden are non-typhoidal salmonellosis, campy-lobacteriosis, toxoplasmosis, cysticercosis and rabies. Except for cysticercosis, however, there has been relatively little research on the epidemiology and burden of these zoonoses. There is a need for more comprehensive burden studies, generating comparable burden estimates. The inclusion of non-typhoidal salmonellosis, campylobacteriosis and toxoplasmosis in the GBD studies would be an important step towards achieving this. Furthermore, it is also important to note that the Millennium Development Goals (MDGs) and other global health initiatives have had an important impact on the better measurement of population health [348]. With the deadline for the MDGs in sight, the international

 $\infty$ 

<sup>&</sup>lt;sup>1</sup>http://www.who.int/healthinfo/global\_burden\_disease/estimates\_country\_2004\_2008/en/

community is currently preparing the post-2015 development agenda. An Open Working Group under the aegis of the United Nations drafted a list of 17 Sustainable Development Goals (SDGs)<sup>2</sup>, which will be proposed for adoption at the SDG Summit in September 2015. SDG 3 aims to "ensure healthy lives and promote well-being for all at all ages", and specifically addresses zoonotic and other neglected diseases in subgoal 3.3:

"by 2030 end the epidemics of AIDS, tuberculosis, malaria, and neglected tropical diseases and combat hepatitis, water-borne diseases, and other communicable diseases"

When endorsed, the SDGs might therefore provide an impetus for improving the measurement of the zoonoses burden in Nepal and other endemic countries. Nevertheless, discussion is still ongoing on the targets and indicators to be used in the SDG monitoring framework for most neglected tropical diseases [349].

## 8.3 Control of zoonoses in Nepal

The ultimate aim of disease burden estimates is to inform decision makers on setting the right research and control priorities. In this section we summarize recent zoonoses control activities in Nepal and discuss the contribution of our and other burden estimates.

#### 8.3.1 Zoonoses control activities

The Zoonotic Disease Sub-section of the Epidemiology and Disease Control Division (EDCD), Department of Health Services, Ministry of Health and Population, is responsible for the prevention and control of zoonotic diseases. The Sub-section was established in 1979 as "Veterinary Public Health" Section [350]. The main activities of the Sub-section are related to the purchase and distribution of anti-snake venom serum and anti-rabies vaccines, which are both distributed free of charge through government hospitals [274]. Rabies control activities are discussed in more detail in **Chapter 7**. The EDCD further managed to control JE through mass vaccination campaigns and the inclusion of JE in the National Immunization Programme [274, 334].

The main legislations related to zoonoses control are the Animal Health and Livestock Services Act 1998 and the Animal Slaughterhouse and Meat Inspection Act 1999. These acts and their rules and regulations make provisions related to animal quarantine, slaughter of animals, sale of animal products, etc. The Animal Slaughterhouse and Meat

 $\infty$ 

<sup>&</sup>lt;sup>2</sup>https://sustainabledevelopment.un.org/focussdgs.html

Inspection Act, for instance, states that all slaughter animals and meat should be examined by a meat inspector [283]. However, despite its promulgation more than 15 years ago, the Act has not yet been officially enforced. Unstable governments due to continuous political transitions, along with insufficient public awareness and deficiencies in the Act itself are believed to be the main reasons for its non-implementation [351, 352].

Since 2007, Nepal has been granted two World Bank projects to support its zoonoses control activities. The Avian Influenza Control Project<sup>3</sup> ran from January 2007 to July 2011, aiming to increase capacity to respond to a potential pandemic of highly pathogenic avian influenza (HPAI). In the spirit of a "One Health" approach, the project was managed collaboratively by the Department of Livestock Services (DLS) and the Department of Health Services (DoHS). The project established an effective system for identifying and controlling outbreaks of HPAI in birds, but had only a modest impact on preparedness for human influenza epidemics and pandemics [353]. From April 2012 to March 2014, a follow-up World Bank project was run, entitled the Zoonoses Control Project<sup>4</sup>. One of the main outcomes of this project was the definition of a set of "priority zoonoses" for Nepal. Based on certain criteria, such as food safety, morbidity, mortality, risk of emergence, and nationally available financial resources for control, the following eight zoonoses were identified as priority zoonoses: HPAI, brucellosis, leptospirosis, toxoplasmosis, cysticercosis, cystic echinococcosis, (bovine) tuberculosis and rabies. Further outputs included the establishment of a One Health Hub<sup>5</sup> between representatives of the DLS and the DoHS, and the redefinition of the National Avian Influenza Information Committee to National Zoonoses Information Committee [354].

#### 8.3.2 Impact of burden estimates on policy

Although our work has been picked up by certain media<sup>6,7</sup>, we have no evidence that our work managed to inform decision makers. Moreover, we see a clear disconnect between the recent prioritization of zoonoses by the Government of Nepal and our findings. For four of the eight priority zoonoses, we either found a low burden or insufficient data to estimate the burden. On the other hand, FERG identified two non-prioritized zoonoses, i.e., non-typhoidal salmonellosis and campylobacteriosis, as major foodborne zoonoses. In the report of a WHO Regional Meeting on Zoonotic Diseases [355], this disconnect

105

<sup>&</sup>lt;sup>3</sup>http://www.worldbank.org/projects/P100342/avian-influenza-control-project?lang=en

<sup>&</sup>lt;sup>4</sup>http://www.worldbank.org/projects/P130089/zoonoses-control-project-zcp?lang=en <sup>5</sup>http://www.hubnet.asia/sites/nepalonehealthhub

<sup>&</sup>lt;sup>6</sup>http://www.thehimalayantimes.com/fullNews.php?headline=Better+zoonoses+surveillance+ stressed&NewsID=408443

<sup>&</sup>lt;sup>7</sup>http://www.scidev.net/south-asia/health/news/animal-borne-parasites-plague-nepal. html

between evidence and policy was phrased as follows:

"It was difficult to understand how hydatidosis, toxoplasmosis, brucellosis and leptospirosis were considered as priority zoonoses in Nepal when the magnitude of the disease problem and socioeconomic impact of selected diseases were not known."

The limited impact of our work can perhaps be seen as the main limitation of this thesis. We therefore strongly recommend to include capacity building and knowledge transfer activities in similar, future projects. In our case, this could have been through a workshop with relevant stakeholders, during which we could have introduced the DALY metric and presented our burden estimates. Nevertheless, when placing knowledge transfer in a broader perspective, we must acknowledge that incorporating scientific evidence in the policy cycle is not a straightforward undertaking [356]. Even if we would have presented our results directly to the concerned stakeholders, our findings would not necessarily have been translated into policy. Indeed, although evidence-based policy making is an important aspirational goal, only a small proportion of research has the policy impact it might have [357]. The complexity of DALYs and other synthetic measures of population health may make them less intuitive for policy makers to use. Different methodologies for generating DALYs and different ways of presenting DALY estimates (e.g., population versus patient level, uncertainty intervals), might further impede appreciation by the concerned policy makers. Capacity building, i.e., generating an understanding and appreciation of the metric by health officials, is therefore an important driver of policy transfer. Exemplary of this link is the current importance of DALYs for health policy in the Netherlands, which is driven by an early adoption of the metric by scientists working at the Dutch National Institute for Public Health and the Environment [12]. In addition to the complexity of the metric, DALYs only tell one part of the story, while prioritizations in the health sector are ideally guided by a variety of inputs, including economic impact and availability of effective control measures. In practice, however, decisions often have to be made in absence of such information, or are influenced by personal interests of decision makers and stakeholders. On the other hand, burden estimates are sometimes merely demanded by decision makers to back up current control activities [358]. Notwithstanding the possible disconnect between burden estimates and policy, we do believe that it is of paramount importance to continue generating disease burden estimates. Only then can we gain the knowledge that is required to take the right actions.

## 8.4 Perspectives

This thesis highlighted the following avenues for further research:

- **Development of a reporting guideline for DALY-based disease burden studies.** In line with the PRISMA or STROBE statements, a checklist of assumptions would increase methodological transparency in DALY-based disease burden studies.
- **Development of a user-friendly DALY calculation tool.** A user-friendly online interface to the DALY Calculator would allow the tool to gain a wider audience.
- **Improved estimation of the burden of multimorbid conditions.** Appropriate methods are required to estimate disability weight, prevalence and incidence of an arbitrary set of conditions.
- **Improved estimation of health statistics.** More evidence is needed on the performance of statistical models and the possible use of mechanistic models for filling gaps in health statistics.
- **Economic burden of zoonoses in Nepal.** Information on financial losses in both the medical and veterinary sector are needed to inform decision makers.
- **Comparable burden estimates.** Comprehensive burden studies are needed to assess and monitor the burden of the identified top zoonoses.
- Capacity building and knowledge transfer. Future projects should emphasize the transfer of skills and knowledge to the concerned stakeholders, such that burden estimates can truly be used to guide policy.

## **Bibliography**

- Murray CJ, Ezzati M, Flaxman AD, Lim S, Lozano R, Michaud C, Naghavi M, Salomon JA, Shibuya K, Vos T, et al.: GBD 2010: design, definitions, and metrics. *The Lancet* 2012, 380(9859):2063–2066.
- [2] Edejer TTT: Making Choices in Health: WHO Guide to Cost-Effectiveness Analysis, Volume 1. World Health Organization 2003.
- [3] Marshall SJ: Developing countries face double burden of disease. Bulletin of the World Health Organization 2004, 82(7):556–556.
- [4] Jelenc M, Van Hoof E, Albreht T, Meglič M, Seljak M, Krnel SR: Joint action European partnership for action against cancer. Archives of Public Health 2012, 70:24.
- [5] Bryant LL, Corbett KK, Kutner JS: In their own words: a model of healthy aging. Social Science & Medicine 2001, 53(7):927–941.
- [6] Robine JM, Cambois E, Nusselder W, Jeune B, Van Oyen H, Jagger C: The joint action on healthy life years (JA: EHLEIS). Archives of Public Health 2013, 71:1–5.
- [7] Murray CJ, Salomon JA, Mathers C: A critical examination of summary measures of population health. Bulletin of the World Health Organization 2000, 78(8):981–994.
- [8] Murray CJ, Lopez AD: The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Harvard School of Public Health 1996.
- [9] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ: Measuring the Global Burden of Disease and Risk Factors, 1990–2001, Volume 1. Oxford University Press 2006.
- [10] Mathers C, Fat DM, Boerma J: The Global Burden of Disease: 2004 Update. World Health Organization 2008.
- [11] Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, et al.: Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2013, 380(9859):2197–2223.

- [12] Melse JM, Essink-Bot ML, Kramers P, Hoeymans N: A national burden of disease calculation: Dutch disability-adjusted life-years. Dutch Burden of Disease Group. American Journal of Public Health 2000, 90(8):1241.
- [13] Mathers CD, Vos ET, Stevenson CE, Begg SJ: The burden of disease and injury in Australia. Bulletin of the World Health Organization 2001, 79(11):1076–1084.
- [14] Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, Begum N, Shah R, Karyana M, Kosen S, et al.: Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. The Lancet 2013, 380(9859):2129–2143.
- [15] Murray CJ: Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bulletin of the World Health Organization 1994, 72(3):429.
- [16] WHO: WHO Methods and Data Sources for Global Burden of Disease Estimates, 2000-2011. Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2013.4. Department of Health Statistics and Information Systems, World Health Organization 2013, [http://www.who.int/healthinfo/statistics/GlobalDALYmethods\_ 2000\_2011.pdf].
- [17] Barendregt JJ, Bonneux L, Van der Maas P: DALYs: the age-weights on balance. Bulletin of the World Health Organization 1996, 74(4):439.
- [18] Arnesen T, Kapiriri L: Can the value choices in DALYs influence global priority-setting? *Health Policy* 2004, 70(2):137–149.
- [19] Polinder S, Haagsma JA, Stein C, Havelaar AH: Systematic review of general burden of disease studies using Disability-Adjusted Life Years. *Population Health Metrics* 2012, 10:21.
- [20] World Bank: Nepal—Operational Issues and Prioritization of Resources in the Health Sector. Kathmandu, Nepal: World Bank Publications 2000, [http://documents.worldbank.org/curated/en/2000/06/437178/ nepal-operational-issues-prioritization-resources-health-sector].
- [21] MoHP: Nepal Health Sector Programme—Implementation Plan (NHSP-IP 2) 2010-2015. Ministry of Health and Population, Nepal 2010, [http://www.nhssp.org. np/health\_policy/Consolidated%20NHSP-2%20IP%20092812%20QA.pdf].
- [22] Engelgau MM, El-Sahary S, Kudesia P, Rajan V, Rosenhouse S, Okamoto K: Capitalizing on the Demographic Transition: Tackling Noncommunicable Diseases in South Asia. World Bank Publications 2011.
- [23] NHRC: Annual Report: Fiscal Year 2064/65 (17 July 2007-15 July 2008). Kathmandu: Nepal Health Research Council 2009, [http//nhrc.org.np/files/ download/61b4b7d89095e0f].
- [24] NHRC: Annual Report: Fiscal Year 2067/68 (17 July 2010-16 July 2011). Nepal Health Research Council 2012.

- [25] Maskey MK, Baral KP, Shah R, Shrestha BD, Lang J, Rothman KJ: Field test results of the motherhood method to measure maternal mortality. The Indian Journal of Medical Research 2011, 133:64–69.
- [26] Ministry of Health and Population (MOHP) [Nepal], New ERA, ICF International Inc: Nepal Demographic and Health Survey 2011. Kathmandu: Ministry of Health and Population, New ERA, and ICF International, Calverton, Maryland 2012, [http://dhsprogram.com/pubs/pdf/FR257/FR257%5B13April2012%5D.pdf].
- [27] Trägård A, Shrestha IB: System-wide effects of Global Fund investments in Nepal. Health Policy and Planning 2010, 25(suppl 1):i58–i62.
- [28] NHSSP: Workshop on Strengthening Health Management Information System (HMIS): Report Outlining Workshop Findings, Recommendations for Government & NHSSP Support. Kathmandu: Nepal Health Sector Support Programme 2011, [http://www.nhssp.org.np/monitoring/HMIS%20Workshop%20Report.pdf].
- [29] Dhillon PK, Jeemon P, Arora NK, Mathur P, Maskey M, Sukirna RD, Prabhakaran D: Status of epidemiology in the WHO South-East Asia region: burden of disease, determinants of health and epidemiological research, workforce and training capacity. International Journal of Epidemiology 2012, 41(3):847–860.
- [30] Stein C, Kuchenmüller T, Hendrickx S, Prüss-Üstün A, Wolfson L, Engels D, Schlundt J: The global burden of disease assessments—WHO is responsible? *PLoS Neglected Tropical Diseases* 2007, 1(3):e161.
- [31] Murray CJ, Acharya AK: Understanding DALYs. Journal of Health Economics 1997, 16(6):703–730.
- [32] Anand S, Hanson K: Disability-Adjusted Life Years: a critical review. Journal of Health Economics 1997, 16(6):685–702.
- [33] Lamberti LM, Walker CLF, Black RE: Systematic review of diarrhea duration and severity in children and adults in low-and middle-income countries. BMC Public Health 2012, 12:276.
- [34] Soerjomataram I, Lortet-Tieulent J, Ferlay J, Forman D, Mathers C, Parkin DM, Bray F: Estimating and validating disability-adjusted life years at the global level: a methodological framework for cancer. BMC Medical Research Methodology 2012, 12:125.
- [35] Mangen MJJ, Plass D, Havelaar AH, Gibbons CL, Cassini A, Mühlberger N, van Lier A, Haagsma JA, Brooke RJ, Lai T, et al.: The pathogen- and incidencebased DALY approach: An appropriated methodology for estimating the burden of infectious diseases. *PLoS ONE* 2013, 8(11):e79740.
- [36] Havelaar A, De Wit M, Van Koningsveld R, Van Kempen E: Health burden in the Netherlands due to infection with thermophilic *Campylobacter* spp. *Epidemiology and Infection* 2000, 125(03):505–522.

- [37] Prüss A, Kay D, Fewtrell L, Bartram J: Estimating the burden of disease from water, sanitation, and hygiene at a global level. *Environmental Health Perspectives* 2002, **110**(5):537–542.
- [38] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P, et al.: Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine 2009, 6(7):e1000097.
- [39] Cooke RM: Experts in Uncertainty: Opinion and Subjective Probability in Science. Oxford Univ Press 1991.
- [40] Schroeder SA: Incidence, prevalence, and hybrid approaches to calculating disability-adjusted life years. *Population Health Metrics* 2012, 10:19.
- [41] Perez L, Künzli N: From measures of effects to measures of potential impact. International Journal of Public Health 2009, 54:45–48.
- [42] Stouthard ME, Essink-Bot ML, Bonsel GJ: Disability weights for diseases A modified protocol and results for a Western European region. The European Journal of Public Health 2000, 10:24–30.
- [43] Essink-Bot ML, Bonsel GJ: Summary Measures of Population Health, Geneva: World Health Organization 2002 chap. How to derive disability weights, :449–465.
- [44] Lake R, Adlam S, Perera S, Campbell D, Baker M: The disease pyramid for acute gastrointestinal illness in New Zealand. Epidemiology and Infection 2010, 138(10):1468–1471.
- [45] Speybroeck N, Devleesschauwer B, Joseph L, Berkvens D: Misclassification errors in prevalence estimation: Bayesian handling with care. International Journal of Public Health 2013, 58(5):791–795.
- [46] Barendregt JJ, Van Oortmarssen GJ, Vos T, Murray CJ: A generic model for the assessment of disease epidemiology: the computational basis of DisMod II. Population Health Metrics 2003, 1:4.
- [47] Bilcke J, Beutels P, Brisson M, Jit M: Accounting for methodological, structural, and parameter uncertainty in decision-analytic models a practical guide. *Medical Decision Making* 2011, 31(4):675–692.
- [48] Knol AB, Petersen AC, Van der Sluijs JP, Lebret E: Dealing with uncertainties in environmental burden of disease assessment. Environmental Health 2009, 8:21.
- [49] Prüss-Ustün A, Vickers C, Haefliger P, Bertollini R: Knowns and unknowns on burden of disease due to chemicals: a systematic review. *Environmental Health* 2011, 10:9.
- [50] Gibbons CL, Mangen MJJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, Peterson KL, Stuurman AL, Cassini A, Fèvre EM, et al.: Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. *BMC Public Health* 2014, 14:147.

- [51] García-Fulgueiras A, García-Pina R, Morant C, García-Ortuzar V, Genova R, Alvarez E: Hepatitis C and hepatitis B-related mortality in Spain. European Journal of Gastroenterology & Hepatology 2009, 21(8):895–901.
- [52] García-Fulgueiras A, García-Pina R, Morant C, Fernández de Larrea-Baz N, Alvarez E: Burden of disease related to hepatitis C and hepatitis B in Spain: a methodological challenge of an unfolding health problem. Journal of Viral Hepatitis 2011, 18(10):e453–e460.
- [53] Ditsuwan V, Veerman LJ, Barendregt JJ, Bertram M, Vos T: The national burden of road traffic injuries in Thailand. Population Health Metrics 2011, 9(2):1–9.
- [54] Toljander J, Dovärn A, Andersson Y, Ivarsson S, Lindqvist R: Public health burden due to infections by verocytotoxin-producing *Escherichia coli* (VTEC) and *Campylobacter* spp. as estimated by cost of illness and different approaches to model disability-adjusted life years. *Scandinavian Journal of Public Health* 2012, 40(3):294–302.
- [55] Havelaar AH, Haagsma JA, Mangen MJJ, Kemmeren JM, Verhoef LP, Vijgen S, Wilson M, Friesema IH, Kortbeek LM, van Duynhoven YT, et al.: Disease burden of foodborne pathogens in the Netherlands, 2009. International Journal of Food Microbiology 2012, 156(3):231–238.
- [56] Jamison DT, Shahid-Salles SA, Jamison J, Lawn JE, Zupan J: Global Burden of Disease and Risk Factors, World Bank Publications 2006 chap. Incorporating deaths near the time of birth into estimates of the global burden of disease.
- [57] Haagsma JA, Polinder S, Cassini A, Colzani E, Havelaar AH: Review of disability weight studies: comparison of methodological choices and values. *Population Health Metrics* 2014, 12:20.
- [58] Wiedermann W, Frick U: Using surveys to calculate disability-adjusted lifeyears. Alcohol Research: Current Reviews 2014, 35(2):128.
- [59] Phanthunane P, Vos T, Whiteford H, Bertram M, Udomratn P: Schizophrenia in Thailand: prevalence and burden of disease. *Population Health Metrics* 2010, 8:24–31.
- [60] Mathers CD, Vos ET, Stevenson CE, Begg SJ: The Australian Burden of Disease Study: measuring the loss of health from diseases, injuries and risk factors. The Medical Journal of Australia 2000, 172(12):592–596.
- [61] Cuijpers P, Smit F, Unger F, Stikkelbroek Y, ten Have M, de Graaf R: The disease burden of childhood adversities in adults: a population-based study. *Child Abuse & Neglect* 2011, 35(11):937–945.
- [62] Lokkerbol J, Adema D, de Graaf R, ten Have M, Cuijpers P, Beekman A, Smit F: Non-fatal burden of disease due to mental disorders in the Netherlands. Social Psychiatry and Psychiatric Epidemiology 2013, 48(10):1591–1599.

6

- [63] LaBeaud AD, Bashir F, King CH: Measuring the burden of arboviral diseases: the spectrum of morbidity and mortality from four prevalent infections. *Population Health Metrics* 2011, 9:1.
- [64] Budke CM, Deplazes P, Torgerson PR: Global socioeconomic impact of cystic echinococcosis. Emerging Infectious Diseases 2006, 12(2):296–303.
- [65] Chapman G, Hansen KS, Jelsma J, Ndhlovu C, Piotti B, Byskov J, Vos T: The burden of disease in Zimbabwe in 1997 as measured by disability-adjusted life years lost. Tropical Medicine & International Health 2006, 11(5):660–671.
- [66] Ahmadi-Abhari S, Moayyeri A, Abolhassani F: Burden of hip fracture in Iran. Calcified Tissue International 2007, 80(3):147–153.
- [67] Gkogka E, Reij MW, Havelaar AH, Zwietering MH, Gorris LG: Risk-based estimate of effect of foodborne diseases on public health, Greece. *Emerging Infectious Diseases* 2011, 17(9):1581.
- [68] Jayatilleke N, Pashayan N, Powles J: Burden of disease due to cancer in England and Wales. Journal of Public Health 2012, 34(2):287–295.
- [69] Plass D, Chau PY, Thach TQ, Jahn HJ, Lai PC, Wong CM, Kraemer A: Quantifying the burden of disease due to premature mortality in Hong Kong using standard expected years of life lost. BMC Public Health 2013, 13:863.
- [70] Mousavi B, Moradi-Lakeh M, Karbakhsh M, Soroush M: Years of life lost among Iranian people killed in the Iraq–Iran war: the 25-year perspective. International Journal of Injury Control and Safety Promotion 2014, 21(4):382–387.
- [71] Wu VK, Poenaru D, Poley MJ: Burden of surgical congenital anomalies in Kenya: A population-based study. Journal of Tropical Pediatrics 2013, 59(3):195–202.
- [72] Costilla R, Tobias M, Blakely T: The burden of cancer in New Zealand: a comparison of incidence and DALY metrics and its relevance for ethnic disparities. Australian and New Zealand Journal of Public Health 2013, 37(3):218– 225.
- [73] Lapostolle A, Lefranc A, Gremy I, Spira A: Sensitivity analysis in summary measure of population health in France. The European Journal of Public Health 2008, 18(2):195–200.
- [74] Havelaar A, Van Duynhoven Y, Nauta M, Bouwknegt M, Heuvelink A, De Wit G, Nieuwenhuizen M, Van de Kar N: Disease burden in The Netherlands due to infections with Shiga toxin-producing *Escherichia coli* O157. *Epidemiology* and Infection 2004, 132(03):467–484.
- [75] Wielders C, van Lier E, Van't Klooster T, van Gageldonk-Lafeber A, van den Wijngaard C, Haagsma J, Donker G, Meijer A, van der Hoek W, Lugner A, et al.: The burden of 2009 pandemic influenza A (H1N1) in the Netherlands. The European Journal of Public Health 2012, 22:150–157.

- [76] Matemba LE, Fèvre EM, Kibona SN, Picozzi K, Cleaveland S, Shaw AP, Welburn SC: Quantifying the burden of *rhodesiense* sleeping sickness in Urambo District, Tanzania. *PLoS Neglected Tropical Diseases* 2010, 4(11):e868.
- [77] Yang BH, Bray FI, Parkin DM, Sellors JW, Zhang ZF: Cervical cancer as a priority for prevention in different world regions: an evaluation using years of life lost. *International Journal of Cancer* 2004, **109**(3):418–424.
- [78] Tariq L, Haagsma J, Havelaar A: Cost of illness and disease burden in The Netherlands due to infections with Shiga toxin-producing *Escherichia coli* O157. *Journal of Food Protection* 2011, 74(4):545–552.
- [79] Zhao Y, Condon JR, Guthridge S, You J: Living longer with a greater health burden-changes in the burden of disease and injury in the Northern Territory Indigenous population between 1994–1998 and 1999–2003. Australian and New Zealand Journal of Public Health 2010, 34(s1):S93–S98.
- [80] Havelaar A, Kemmeren J, Kortbeek L: Disease burden of congenital toxoplasmosis. Clinical Infectious Diseases 2007, 44(11):1467–1474.
- [81] Praet N, Speybroeck N, Manzanedo R, Berkvens D, Nforninwe DN, Zoli A, Quet F, Preux PM, Carabin H, Geerts S: The disease burden of *Taenia solium* cysticercosis in Cameroon. *PLoS Neglected Tropical Diseases* 2009, 3(3):e406.
- [82] Daly LE: Confidence limits made easy: interval estimation using a substitution method. American Journal of Epidemiology 1998, 147(8):783–790.
- [83] Meltzer MI, Rigau-Perez JG, Clark GG, Reiter P, Gubler DJ: Using disabilityadjusted life years to assess the economic impact of dengue in Puerto Rico: 1984–1994. The American Journal of Tropical Medicine and Hygiene 1998, 59(2):265–271.
- [84] Knobel DL, Cleaveland S, Coleman PG, Fèvre EM, Meltzer MI, Miranda MEG, Shaw A, Zinsstag J, Meslin FX: Re-evaluating the burden of rabies in Africa and Asia. Bulletin of the World Health Organization 2005, 83(5):360–368.
- [85] Bhattarai R, Budke CM, Carabin H, Proaño JV, Flores-Rivera J, Corona T, Ivanek R, Snowden KF, Flisser A: Estimating the non-monetary burden of neurocysticercosis in Mexico. *PLoS Neglected Tropical Diseases* 2012, 6(2):e1521.
- [86] Verhoef L, Koopmans M, van Pelt W, Duizer E, Haagsma J, Werber D, Van Asten L, Havelaar A: The estimated disease burden of norovirus in The Netherlands. *Epidemiology and Infection* 2013, 141(03):496–506.
- [87] Krishnamoorthy K, Harichandrakumar K, Krishna Kumari A, Das L: Burden of chikungunya in India: estimates of disability adjusted life years (DALY) lost in 2006 epidemic. *Journal of Vector Borne Diseases* 2009, 46:26–35.
- [88] Siddiqi AeA, Ebrahim SH, Soucie JM, Parker CS, Atrash HK: Burden of disease resulting from hemophilia in the US. American Journal of Preventive Medicine 2010, 38(4):S482–S488.

115

σ

- [89] Carrasco LR, Lee LK, Lee VJ, Ooi EE, Shepard DS, Thein TL, Gan V, Cook AR, Lye D, Ng LC, et al.: Economic impact of dengue illness and the costeffectiveness of future vaccination programs in Singapore. *PLoS Neglected Tropical Diseases* 2011, 5(12):e1426.
- [90] Jia T, Sun L, Hong Q, Deng Y, Zhang G, Wang H, Yi P, Guo J, Zhou X: [Burden of disease in schistosomiasis *japonica*. I. Calculation and evaluation of years lived with disability of chronic schistosomiasis]. *Chinese Journal of Schistosomiasis Control* 2011, 23(3):243–248.
- [91] Katzenellenbogen JM, Begg S, Somerford P, Anderson CS, Semmens JB, Codde JP, Vos T: Disability burden due to stroke in Western Australia: new insights from linked data sources. International Journal of Stroke 2010, 5(4):269–277.
- [92] Katzenellenbogen JM, Vos T, Somerford P, Begg S, Semmens JB, Codde JP: Burden of stroke in indigenous Western Australians a study using data linkage. *Stroke* 2011, 42(6):1515–1521.
- [93] Torgerson PR, Mastroiacovo P: The global burden of congenital toxoplasmosis: a systematic review. Bulletin of the World Health Organization 2013, 91(7):501–508.
- [94] Luz P, Grinsztejn B, Galvani A: Disability adjusted life years lost to dengue in Brazil. Tropical Medicine & International Health 2009, 14(2):237–246.
- [95] de Vocht F, Higgerson J, Oliver K, Verma A: Incorporating uncertainty in aggregate burden of disease measures: an example of DALYs-averted by a smoking cessation campaign in the UK. Journal of Epidemiology and Community Health 2011, 65(9):751–756.
- [96] Fox-Rushby J, Hanson K: Calculating and presenting disability adjusted life years (DALYs) in cost-effectiveness analysis. *Health Policy and Planning* 2001, 16(3):326–331.
- [97] Haagsma JA, Polinder S, Stein CE, Havelaar AH: Systematic review of foodborne burden of disease studies: Quality assessment of data and methodology. International Journal of Food Microbiology 2013, 166:34–47.
- [98] Briggs AH, Claxton K, Sculpher MJ: Decision Modelling for Health Economic Evaluation. Oxford university press 2006.
- [99] Gray AM, Clarke PM, Wolstenholme JL, Wordsworth S: Applied Methods of Costeffectiveness Analysis in Healthcare. Oxford University Press 2010.
- [100] Hart A, Hoekstra J, Owen H, Kennedy M, Zeilmaker MJ, de Jong N, Gunnlaugsdottir H: Qalibra: A general model for food risk-benefit assessment that quantifies variability and uncertainty. Food and Chemical Toxicology 2013, 54:4–17.
- [101] Briggs AH: Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000, 17(5):479–500.

- [102] R Core Team: R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria 2014, [http://www.R-project. org/].
- [103] Vose D: Risk analysis: A Quantitative Guide. John Wiley & Sons 2008.
- [104] Devleesschauwer B, Haagsma J, Angulo F, Bellinger D, Cole D, Döpfer D, Fazil A, Fèvre E, Gibb H, Hald T, Kirk M, Lake R, Maertens de Noordhout C, McDonald S, Pires S, Speybroeck N, Thomas M, Torgererson P, Wu F, Havelaar A, Praet N: Methodological framework for WHO estimates of the global burden of foodborne disease (in preparation).
- [105] Torgerson PR, Macpherson CN: The socioeconomic burden of parasitic zoonoses: global trends. Veterinary Parasitology 2011, 182:79–95.
- [106] Hotez PJ, Alibek K: Central Asia's hidden burden of neglected tropical diseases. PLoS Neglected Tropical Diseases 2011, 5(9):e1224.
- [107] Torgerson PR: One world health: Socioeconomic burden and parasitic disease control priorities. Veterinary Parasitology 2013, 195(3):223–232.
- [108] Murrell KD: Economic losses resulting from food-borne parasitic zoonoses. The Southeast Asian Journal of Tropical Medicine and Public Health 1991, 22(suppl):377–81.
- [109] Vanderelst D, Speybroeck N: Quantifying the lack of scientific interest in neglected tropical diseases. *PLoS Neglected Tropical Diseases* 2010, 4:e576.
- [110] Thapa A: *Current situation in mortality statistics in Nepal.* Kathmandu, Nepal: Ministry of Health and Population 2007.
- [111] Dorny P, Praet N, Deckers N, Gabriel S: Emerging food-borne parasites. Veterinary Parasitology 2009, 163(3):196–206.
- [112] WHO: The Control of Neglected Zoonotic Diseases: a Route to Poverty Alleviation: Report of a Joint WHO/DFID-AHP Meeting, 20 and 21 September 2005, WHO Headquarters, Geneva, with the Participation of FAO and OIE. Geneva: World Health Organization 2006.
- [113] WHO: Working to overcome the global impact of neglected tropical diseases: First WHO Report on Neglected Tropical Diseases. Geneva, Switzerland: World Health Organization 2010, [http://whqlibdoc.who.int/publications/2010/ 9789241564090\_eng.pdf].
- [114] WHO: Sustaining the Drive to Overcome the Global Impact of Neglected Tropical Diseases: Second WHO Report on Neglected Tropical Diseases. World Health Organization 2013.
- [115] Huang J, Wu YM, Liang PC, Lee PH: Alveolar hydatid disease causing total occlusion of the inferior vena cava. Journal of the Formosan Medical Association 2004, 103(8):633–636.

- [116] Craig PS, Li T, Qiu J, Zhen R, Wang Q, Giraudoux P, Ito A, Heath D, Warnock B, Schantz P, et al.: Echinococcoses and Tibetan communities. *Emerging Infectious Diseases* 2008, 14(10):1674.
- [117] Taneja K, Gothi R, Kumar K, Jain S, Mani R, et al.: Peritoneal Echinococcus multilocularis infection: CT appearance. Journal of Computer Assisted Tomography 1990, 14(3):493–494.
- [118] Shaw M, Gambhir R, Chaudhry R, Jaiswal S: *Ecchinococcus multilocularis* causing alveolar hydatid disease liver: a rare occurrence in Indian subcontinent. *Tropical Gastroenterology* 2010, 31(2):119–120.
- [119] Tyagi DK, Balasubramaniam S, Sawant HV: Primary calcified hydatid cyst of the brain. Journal of Neurosciences in Rural Practice 2010, 1(2):115.
- [120] Torgerson PR, Keller K, Magnotta M, Ragland N: The global burden of alveolar echinococcosis. PLoS Neglected Tropical Diseases 2010, 4(6):e722.
- [121] Rai S, Uga S, Ono K, Rai G, Matsumura T: Contamination of soil with helminth parasite eggs in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 2000, 31(2):388–393.
- [122] Gewali L: Bacteriological and helminthological assessment of the drinking water quality of Ward-19, KMC. *Msc dissertation*, Tribhuvan University, Kathmandu, Nepal 2002.
- [123] Thapa S: Assessment of biological contamination and waterborne helminthic parasites in drinking water sources of Ward no 20, KMC. *Msc dissertation*, Tribhuvan University, Kathmandu, Nepal 2002.
- [124] Khanal B: Studies on some intestinal helminth parasites of *Felis catus* (Linnaeus, 1758) from Nawalparasi and Chitwan districts of Nepal. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2004.
- [125] Manandhar S, Hörchner F, Morakote N, Kyule MN, Baumann M: Occurrence of hydatidosis in slaughter buffaloes (Bos bubalis) and helminths in stray dogs in Kathmandu Valley, Nepal. Berliner und Munchener Tierarztliche Wochenschrift 2005, 119(7-8):308–311.
- [126] Dhoubhadel M: Prevalence of intestinal helminth parasites in Rhesus monkey (Macaca mulatta) of Swoyambhu and Nilbarahi area of Kathmandu Valley. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2007.
- [127] Malhotra S, Mehta D, Arora R, Chauhan D, Ray S, Jain M: Ocular angiostrongyliasis in a child: first case report from India. Journal of Tropical Pediatrics 2006, 52(3):223-225.
- [128] Panackel C, Cherian G, Vijayakumar K, Sharma R, et al.: Eosinophilic meningitis due to Angiostrongylus cantonensis. Indian Journal of Medical Microbiology 2006, 24(3):220.

- [129] Vasantha P, Girish N, Leela KS: Human intestinal capillariasis: A rare case report from non-endemic area (Andhra Pradesh, India). Indian Journal of Medical Microbiology 2012, 30(2):236.
- [130] Nabi F, Palaha H, Sekhsaria D, Chiatale A: Capillaria hepatica infestation. Indian Pediatrics 2007, 44(10):781.
- [131] Gautam V, Rustagi I, Singh S, Arora D: Subconjunctival infection with Dirofilaria repens. Japanese Journal of Infectious Diseases 2002, 55(2):47–48.
- [132] Chopra R, Bhatti S, Mohan S, Taneja N: *Dirofilaria* in the anterior chamber: a rare occurrence. *Middle East African Journal of Ophthalmology* 2012, 19(3):349– 351.
- [133] Barua P, Hazarika N, Barua N, Barua C, Choudhury B, et al.: Gnathostomiasis of the anterior chamber. Indian Journal of Medical Microbiology 2007, 25(3):276.
- [134] Mukherjee A, Ahmed N, Samantaray J, Mirdha B: A rare case of cutaneous larva migrans due to Gnathostoma sp. Indian Journal of Medical Microbiology 2012, 30(3):356–358.
- [135] Rengarajan S, Nanjegowda N, Bhat D, Mahadevan A, Sampath S, Krishna S: Cerebral sparganosis: a diagnostic challenge. *British Journal of Neurosurgery* 2008, 22(6):784–786.
- [136] Khurana S, Appannanavar S, Bhatti HS, Verma S: Sparganosis of liver: a rare entity and review of literature. BMJ Case Reports 2012, 2012:bcr2012006790.
- [137] Duggal S, Mahajan R, Duggal N, Hans C, et al.: Case of sparganosis: a diagnostic dilemma. Indian Journal of Medical Microbiology 2011, 29(2):183.
- [138] Stauch A, Sarkar RR, Picado A, Ostyn B, Sundar S, Rijal S, Boelaert M, Dujardin JC, Duerr HP: Visceral leishmaniasis in the Indian subcontinent: modelling epidemiology and control. *PLoS Neglected Tropical Diseases* 2011, 5(11):e1405.
- [139] Pun SB, Pandey K, Shah R: A series of case reports of autochthonous visceral leishmaniasis, mostly in non-endemic hilly areas of Nepal. The American Journal of Tropical Medicine and Hygiene 2013, 88(2):227-229.
- [140] Uranw S, Meheus F, Baltussen R, Rijal S, Boelaert M: The household costs of visceral leishmaniasis care in south-eastern Nepal. PLoS Neglected Tropical Diseases 2013, 7(2):e2062.
- [141] Burniston I, Roy L, Picado A, Das M, Rijal S, Rogers M, Coosemans M, Boelaert M, Davies C, Cameron M: Development of an enzyme-linked immunosorbent assay to identify host-feeding preferences of *Phlebotomus* species (*Diptera: Psychodidae*) in endemic foci of visceral leishmaniasis in Nepal. Journal of Medical Entomology 2010, 47(5):902–906.
- [142] Khanal B, Picado A, Bhattarai NR, Van der Auwera G, Das ML, Ostyn B, Davies CR, Boelaert M, Dujardin JC, Rijal S: Spatial analysis of *Leishmania dono*vani exposure in humans and domestic animals in a recent kala azar focus in Nepal. Parasitology 2010, 137(11):1597–1603.

- [143] Bhattarai NR, Van der Auwera G, Rijal S, Picado A, Speybroeck N, Khanal B, De Doncker S, Das ML, Ostyn B, Davies C, et al.: Domestic animals and epidemiology of visceral leishmaniasis, Nepal. Emerging Infectious Diseases 2010, 16(2):231.
- [144] Karki P, Parija S, George S, Das M, Koirala S: Visceral leishmaniasis with cutaneous ulcer or cutaneous leishmaniasis in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 1997, 28(4):836–837.
- [145] Parija S, Jacob M, Karki B, Sethi M, Karki P, Koirala S: Cutaneous leishmaniasis in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 1998, 29:131–132.
- [146] Joshi A, Agrawal S, Garg VK, Thakur A, Agarwalla A, Jacob M: Severe mucosal involvement in a patient with cutaneous leishmaniasis from Nepal. International Journal of Dermatology 2000, 39(4):312–320.
- [147] Pandey BD, Babu E, Thapa S, Thapa LB: First case of cutanous leishmaniasis in Nepalese patient. Nepal Medical College Journal: NMCJ 2006, 8(3):213–214.
- [148] Neupane S, Sharma P, Kumar A, Paudel U, Pokhrel D: Cutaneous leishmaniasis: report of rare cases in Nepal. Nepal Medical College Journal: NMCJ 2008, 10:64–67.
- [149] Kayastha B, Shrestha P, Shrestha R, Jahan R: Cutaneous leishmaniasis: a case report. Nepal Journal of Dermatology, Venereology & Leprology 2009, 8:27–30.
- [150] Kumar R, Ansari NA, Avninder S, Ramesh V, Salotra P: Cutaneous leishmaniasis in Nepal: Leishmania major as a cause. Transactions of the Royal Society of Tropical Medicine and Hygiene 2008, 102(2):202–203.
- [151] Kalra N, Arya S: Comment on: Cutaneous leishmaniasis in Nepal: Leishmania major as a cause. Transactions of the Royal Society of Tropical Medicine and Hygiene 2008, 102(6):618.
- [152] Kumar R, Ansari NA, Avninder S, Ramesh V, Salotra P: Reply to comment on: Cutaneous leishmaniasis in Nepal: Leishmania major as a cause. Transactions of the Royal Society of Tropical Medicine and Hygiene 2008, 102(6):618–619.
- [153] Joshi A, Banjara M, Pokhrel S, Jimba M, Singhasivanon P, Ashford R: Elimination of visceral leishmaniasis in Nepal: Pipe-dreams and possibilities. *Kathmandu University Medical Journal (KUMJ)* 2006, 4(4):488–496.
- [154] Pandey K, Pant S, Kanbara H, Shuaibu MN, Mallik AK, Pandey BD, Kaneko O, Yanagi T: Molecular detection of *Leishmania* parasites from whole bodies of sandflies collected in Nepal. *Parasitology Research* 2008, 103(2):293–297.
- [155] Hamarsheh O, Presber W, Yaghoobi-Ershadi MR, Amro A, Al-Jawabreh A, Sawalha S, Al-Lahem A, Das M, Guernaoui S, Seridi N: Population structure and geographical subdivision of the *Leishmania major* vector *Phlebotomus papatasi* as revealed by microsatellite variation. Medical and Veterinary Entomology 2009, 23:69–77.

- [156] Gidwani K, Picado A, Rijal S, Singh SP, Roy L, Volfova V, Andersen EW, Uranw S, Ostyn B, Sudarshan M, et al.: Serological markers of sand fly exposure to evaluate insecticidal nets against visceral leishmaniasis in India and Nepal: a cluster-randomized trial. *PLoS Neglected Tropical Diseases* 2011, 5(9):e1296.
- [157] Bhandari G, Angdembe M, Rijal S, Boelaert M: Will visceral leishmaniasis be eliminated from Nepal? A review of recent (1994-2006) control efforts. Nepal Medical College Journal: NMCJ 2011, 13(3):220-225.
- [158] Schwarz D, Andrews J, Gauchan B: Visceral leishmaniasis in far western Nepal: another case and concerns about a new area of endemicity. The American Journal of Tropical Medicine and Hygiene 2011, 84(3):508–508.
- [159] Joshi D, Moller L, Maharjan M, Kapel CMO: Serological evidence of trichinellosis in local pigs of Nepal. Veterinary Parasitology 2005, 132:155–157.
- [160] Sapkota B, Hörchner F, Srikitjakarn L, Kyule M, Baumann M, K N: Seroprevalence of *Trichinella* in slaughter pigs in Kathmandu Valley, Nepal. *The Southeast Asian Journal of Tropical Medicine and Public Health* 2006, 37(6):1078– 1082.
- [161] Karn SK, Hörchner F, Srikitjakarn L, Baumann M, Nöckler K: Cross-sectional study of *Trichinella* spp. in pigs in CDR, Nepal using pepsin digestion and ELISA serology. *The Southeast Asian Journal of Tropical Medicine and Public Health* 2008, **39**(5):795–799.
- [162] Sethi B, Butola K, Kumar Y, Mishra J: Multiple outbreaks of trichinellosis with high mortality rate. Tropical Doctor 2012, 42(4):243.
- [163] Rai SK, Uga S, Ono K, Nakanishi M, Shrestha HG, Matsumura T: Seroepidemiological study of *Toxocara* infection in Nepal. *The Southeast Asian Journal* of Tropical Medicine and Public Health 1996, 27(2):286–290.
- [164] Shrestha S, Singh SD, Shrestha N, Shrestha R: Clinical and laboratory profile of children with eosinophilia at Dhulikhel Hospital. Kathmandu University Medical Journal (KUMJ) 2013, 10(2):58–62.
- [165] Ghimire K: Prevalence of intestinal parasites in humans and dogs of KMC particularly in Ward no 19, KMC. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2002.
- [166] Karki S: Prevalence of intestinal parasites in humans and dogs of KMC particularly in Ward no 20, KMC. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2003.
- [167] Rai P: Study on the fish parasites of exotic fished (rainbow trout and carp) and their control measures in different culture systems. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2002.
- [168] Thapa R: Prevalence of intestinal helminth parasites in general and *Taenia* spp in detail, particularly in Bote and Darai communities of Vyash

σ

Muncipality-5, Kumaltari, Tanahun district of Nepal. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2000.

- [169] Pandey K: Prevalence of fasciolosis in buffaloes in relation to Fasciola larvae infection in Lymnaea snails in Dev Bhumi Baluwa VDC of Kavre district. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2001.
- [170] Mahato S, Harrison L: Control of fasciolosis in stall-fed buffaloes by managing the feeding of rice straw. Tropical Animal Health and Production 2005, 37(4):285–291.
- [171] Gurung B: Prevalence of eggs of three trematode genera (*Fasciola* spp, *Dicrocoelium* spp and *Schistosoma* spp) in buffaloes of Satungal slaughter house, Kathmandu. *Msc dissertation*, Tribhuvan University, Kathmandu, Nepal 2007.
- [172] Mukhia G: A study on the intestinal helminth parasites of buffaloes brought to Satungal (KTM) for slaughter purpose. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2007.
- [173] Shrestha A: Prevalence of fascioliasis present in buffaloes of slaughter house in Kirtipur Municipality. *Msc dissertation*, Tribhuvan University, Kathmandu, Nepal 2010.
- [174] Yong TS, Sim S, Lee J, Ohrr H, Kim MH, Kim H: A small-scale survey on the status of intestinal parasite infections in rural villages in Nepal. The Korean Journal of Parasitology 2000, 38(4):275–277.
- [175] Hamano S, Kobayashi S, Ogaki T, Koga M, Kawasaki M, Ito K, Saito A, Tsuji M, Tsuji S, Sharma S: A survey on helminthic infections in two rural communities in Nepal. Japanese Journal of Tropical Medicine and Hygiene 1999, 27(4):511–515.
- [176] Uga S, Rai SK, Kimura K, Ganesh R, Kimura D, Wakasugi M, Miyake Y, Ishiyama S, Rajbhandari TP: Parasites detected from diarrheal stool samples collected in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 2004, 35:19–23.
- [177] Kimura K, Rai SK, Rai G, Insisiengmay S, Kawabata M, Karanis P, Uga S: Study on Cyclospora cayetanensis associated with diarrheal disease in Nepal and Loa PDR. The Southeast Asian Journal of Tropical Medicine and Public Health 2005, 36(6):1371–1376.
- [178] Shrestha S, Timila D, Karki U, Shrestha A, Bhandary S: Clinical profile of children with moderate-to-severe eosinophilia presenting to a tertiary hospital in Nepal. Tropical Doctor 2012, 42(4):232–234.
- [179] Kumari N, Kumar M, Rai A, Acharya A: Intestinal trematode infection in North Bihar. Journal of Nepal Medical Association 2006, 45(161):204–206.
- [180] Rai S, Wadhwa V, Kharbanda P, Uppal B: A case of poly-parasitism involving a trematode and four different nematodes in a migrant from Bihar. Indian Journal of Medical Microbiology 2007, 25:62.

- [181] Mahajan RK, Duggal S, kumar Biswas N, Duggal N, Hans C: A finding of live Fasciolopsis buski in an ileostomy opening. The Journal of Infection in Developing Countries 2010, 4(06):401–403.
- [182] Prasad KN, Chawla S, Jain D, Pandey CM, Pal L, Pradhan S, Gupta RK: Human and porcine *Taenia solium* infection in rural north India. *Transactions of* the Royal Society of Tropical Medicine and Hygiene 2002, 96(5):515–516.
- [183] Devleesschauwer B, Aryal A, Joshi DD, Rijal S, Sherchand JB, Praet N, Speybroeck N, Duchateau L, Vercruysse J, Dorny P: Epidemiology of *Taenia solium* in Nepal: is it influenced by the social characteristics of the population and the presence of *Taenia asiatica*? *Tropical Medicine & International Health* 2012, 17(8):1019–1022.
- [184] Nkouawa A, Sako Y, Nakao M, Nakaya K, Ito A: Loop-mediated isothermal amplification method for differentiation and rapid detection of *Taenia* species. Journal of Clinical Microbiology 2009, 47:168–174.
- [185] Joshi DD, Maharjan M, Johnsen MV, Willingham AL, Gaihr Y, Sharma M: Taeniasis/cysticercosis situation in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 2004, 35:252–258.
- [186] Chakrabarti I, Gangopadhyay M, Bandopadhyay A, Das N: A rare case of gangrenous appendicitis by eggs of *Taenia* species. *Journal of Parasitic Diseases* 2014, 38:135–137.
- [187] Criscione C, Anderson J, Raby K, Sudimack D, Subedi J, Rai D, Upadhayay R, Jha B, Williams-Blangero S, Anderson T: Microsatellite markers for the human nematode parasite Ascaris lumbricoides: development and assessment of utility. The Journal of Parasitology 2007, 93(3):704–708.
- [188] Criscione CD, Anderson JD, Sudimack D, Subedi J, Upadhayay RP, Jha B, Williams KD, Williams-Blangero S, Anderson TJ: Landscape genetics reveals focal transmission of a human macroparasite. PLoS Neglected Tropical Diseases 2010, 4(4):e665.
- [189] Navitsky R, Dreyfuss M, Shrestha J, Khatry S, Stoltzfus R, Albonico: Ancylostoma duodenale is responsible for hookworm infections among pregnant women in the rural plains of Nepal. The Journal of Parasitology 1998, 84(3):647–651.
- [190] Rai SK, Shrestha HG, Nakanishi M, Kubo T, Ono K, Uga S, Matsumura T: Hookworm Infection Recorded at an University Teaching Hospital in Kathmandu, Nepal Over One Decade Period. Japanese Journal of Tropical Medicine and Hygiene 1997, 25(2):81–84.
- [191] Singh A, Janaki L, Petri WA, Houpt ER: Giardia intestinalis assemblages A and B infections in Nepal. The American Journal of Tropical Medicine and Hygiene 2009, 81(3):538–539.

123

δ

- [192] Wu Z, Nagano I, Boonmars T, Nakada T, Takahashi Y: Intraspecies polymorphism of *Cryptosporidium parvum* revealed by PCR-restriction fragment length polymorphism (RFLP) and RFLP-single-strand conformational polymorphism analyses. *Applied and Environmental Microbiology* 2003, 69(8):4720–4726.
- [193] Wu Z, Nagano I, Boonmars T, Takahashi Y: Further evidence that genotype I and genotype II of Cryptosporidium parvum are distinct. Tropical Medicine & International Health 2004, 32:5–14.
- [194] Feng Y, Raj Karna S, Dearen TK, Singh DK, Adhikari LN, Shrestha A, Xiao L: Common occurrence of a unique *Cryptosporidium ryanae* variant in zebu cattle and water buffaloes in the buffer zone of the Chitwan National Park, Nepal. Veterinary Parasitology 2012, 185(2):309–314.
- [195] Yoshikawa H, Wu Z, Pandey K, Pandey BD, Sherchand JB, Yanagi T, Kanbara H: Molecular characterization of *Blastocystis* isolates from children and rhesus monkeys in Kathmandu, Nepal. Veterinary Parasitology 2009, 160(3):295– 300.
- [196] Lee I, Tan T, Tan P, Nanthiney D, Biraj M, Surendra K, Suresh K: Predominance of *Blastocystis* sp. subtype 4 in rural communities, Nepal. *Parasitology Research* 2012, 110(4):1553–1562.
- [197] Lee LI, Chye TT, Karmacharya BM, Govind SK: *Blastocystis* sp.: waterborne zoonotic organism, a possibility. *Parasites & Vectors* 2012, 5:130.
- [198] Coyle CM, Varughese J, Weiss LM, Tanowitz HB: Blastocystis: To treat or not to treat. Clinical Infectious Diseases 2012, 54:105–110.
- [199] Heap B: Cerebral cysticercosis as a common cause of epilepsy in Gurkhas in Hong Kong. Journal of the Royal Army Medical Corps 1990, **136**(3):146–149.
- [200] Fegan D, Glennon J: Epilepsy and disappearing lesions: adopting a wait and see policy. BMJ: British Medical Journal 1991, 302(6789):1402.
- [201] Prasad R, Taparia S: Lateral sinus thrombosis with neurocysticercosis. Indian Pediatrics 2004, 41:1074–1075.
- [202] Prasad R, Singh R, Joshi B: Lateral sinus thrombosis in neurocysticercosis. Tropical Doctor 2005, 35(3):182–183.
- [203] Sundarka M: Bilateral ptosis due to neurocysticercosis in the midbrain. Nepal Journal of Neuroscience 2005, 2:137.
- [204] Gurung G, Shrestha B, Shah T: Unusual presentation of neurocysticercosis: report of two cases. Nepal Journal of Neuroscience 2005, 2:185–189.
- [205] Mamkin I, Sood N, Ramanan SV: *Taenia solium* neurocysticercosis. New England Journal of Medicine 2007, 357(16):1666–1667.
- [206] Shrestha R, Adhikari L: Sequel of ring enhanced lesion on computerized tomographic scans of brain of patients presenting with seizure. Nepal Journal of Neuroscience 2009, 6:12–14.

- [207] Patnaik MM, Rajasingham R, Deshpande A, Parmar G, Stauffer W: The Nepalese shepherd. Journal of Travel Medicine 2009, 16:68–71.
- [208] Azzopardi L, Quirk J: An acquired source of seizures. BMJ: British Medical Journal 2012, 344:e2991.
- [209] KC I, Rana K, Joshi R, Mandal A, Bhhatarai S: Multiple parenchymal neurocysticercosis: a case report. Medical Journal of Shree Birendra Hospital 2012, 10:44–45.
- [210] Rauniyar R, Thakur S, Panda A: CT in the diagnosis of isolated cysticercal infestation of extraocular muscle. *Clinical Radiology* 2003, 58(2):154–156.
- [211] Wong Y, Goh K, Choo C, Seah L, Rootman J: An unusual cause of acquired horizontal diplopia in a young adult. The British Journal of Ophthalmology 2005, 89(3):390.
- [212] Shariq S, Adhikari B: Managing cysticercosis in anterior chamber of eye: a case report. *Kathmandu University Medical Journal (KUMJ)* 2007, 5(2):240–242.
- [213] Shrestha J, Paudel P, Karmacharya P: Spontaneous extrusion of subconjunctival cysticercous cyst: a case report. Nepal Medical College Journal: NMCJ 2008, 10(2):139–140.
- [214] Yadav S, Winter I, Singh S: Management of intra-vitreal cysticercosis. Nepalese Journal of Ophthalmology 2009, 1(2):143–145.
- [215] Amatya BM, Kimula Y: Cysticercosis in Nepal: A histopathologic study of sixty-two cases. The American Journal of Surgical Pathology 1999, 23(10):1276.
- [216] Sah S, Jha P, Gupta A, Raj G: An incidental case of breast cysticercosis associated with fibroadenoma. Indian Journal of Pathology and Microbiology 2001, 44:59.
- [217] Smiti S, Sripathi H, Naik L: Unusual location of *Cysticercus* lesions in soft tissue-report of three cases. *Indian Journal of Radiology and Imaging* 2003, 13(2):157.
- [218] Bhandary S, Singh R, Karki P, Sinha A: Cysticercosis of tongue—diagnostic dilemma. Pacific Health Dialogue 2004, 11:87–88.
- [219] Adhikari R, Aryal G, Jha A, Pant A, Sayami G: Diagnosis of subcutaneous cysticercosis in fine needle aspirates: a study of 10 cases. Nepal Medical College Journal: NMCJ 2007, 9:234–238.
- [220] Agarwal A, Murty O, Jain M: Fine needle aspiration cytology in the diagnosis of cysticercosis cases. Asian Pacific Journal of Tropical Medicine 2009, 2:49–53.
- [221] Lakhey M, Hirachand S, Akhter J, Thapa B: Cysticerci in palpable nodules diagnosed on fine needle aspiration cytology. Journal of Nepal Medical Association 2009, 48(176):314–317.

- [222] Sharma P, Neupane S, Shrestha M, Dwivedi R, Paudel K: An ultrasonographic evaluation of solitary muscular and soft tissue cysticercosis. Kathmandu University Medical Journal (KUMJ) 2010, 8(2):257–260.
- [223] Rai B: The cysticercosis in muscles is one of the causes of lumps in human. Health Renaissance 2012, 10(2):160–161.
- [224] Mukhida K, Sharma MR, Shilpakar SK: Management of hydrocephalus with ventriculoperitoneal shunts: review of 274 cases. Nepal Journal of Neuroscience 2004, 1(2):104–112.
- [225] Karmacharya B, Kumar P: A study on complications of ventriculoperitoneal shunt surgery in Bir Hospital, Kathmandu, Nepal. Nepal Journal of Medical Sciences 2012, 1(2):119–122.
- [226] Subedee A: Evaluation of chronic headache by computed tomography: a retrospective study. Journal of Nobel Medical College 2012, 1(2):64–71.
- [227] Pant B, Devleesschauwer B, Shrestha P, Shrestha I, Praet N, Dorny P: Intraventricular *Taenia solium* neurocysticercosis: a report of three cases. *JNMA Journal of Nepal Medical Association* 2011, 51(184):192–195.
- [228] Rai S, Shibata H, Sumi K, Kubota K, Hirai K, Matsuoka A, Kubo T, Tamura T, Basnet S, Shrestha HG: Seroepidemiological study of toxoplasmosis in two different geographical areas in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 1994, 25(3):479–484.
- [229] Rai SK, Kubo T, Yano K, Shibata H, Sumi K, Matsuoka A, Uga S, Matsumura T, Hirai K, Upadhyay MP, et al.: Seroepidemiological study of *Toxoplasma* infection in central and western regions in Nepal. *The Southeast Asian Journal* of Tropical Medicine and Public Health 1996, 27(3):548–553.
- [230] Rai S, Shibata H, Sumi K, Rai G, Rai N, Manandhar R, Gurung G, Ono K, Uga S, Matsuoka A, Shrestha H, Matsumura T: *Toxoplasma* antibody prevalence in Nepalese pregnant women and women with bad obstetric history. *The Southeast Asian Journal of Tropical Medicine and Public Health* 1998, 29(4):739–743.
- [231] Rai SK, Kubo T, Yano K, Shibata H, Sumi K, Matsuoka A, Uga S, Matsumura T, Shrestha H: *Toxoplasma gondii* infection in Eastern Nepal: a seroepidemiological study. Journal of Infectious Diseases and Antimicrobial Agents 1998, 15:105–109.
- [232] Rai SK, Matsumura T, Ono K, Abe A, Hirai K, Rai G, Sumi K, Kubota K, Uga S, Shrestha HG: High *Toxoplasma* seroprevalence associated with meat eating habits of locals in Nepal. Asia-Pacific Journal of Public Health 1999, 11(2):89–93.
- [233] Ray R: Seroprevalence of IgM and IgG antibodies against the agents of TORCH infections among the patients visiting Om Hospital and Research Center. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2010.
- [234] Imura S, Ono K, Rai S, Yanagida JI, Ashitaka Y: Seroprevalence of Toxoplasma gondii infection in Nepal. Bulletin of Kobe Tokiwa University 2012, 5:9–14.
- [235] Rai SK, Upadhyay MP, Shrestha HG: Toxoplasma infection in selected patients in Kathmandu, Nepal. Nepal Medical College Journal: NMCJ 2003, 5(2):89–91.
- [236] Kafle P: Seroprevalence of TORCH in Nepalese women of childbearing age and evaluation of biochemical parameters. *Msc dissertation*, Tribhuvan University, Kathmandu, Nepal 2004.
- [237] Lamichhane S, Malla S, Basnyat S, Khanal S, Dumre S, Maharjan L, Shrestha P: Seroprevalence of IgM antibodies against the agents of TORCH infections among the patients visiting National Public Health Laboratory, Teku Kathmandu. Journal of Nepal Health Research Council 2007, 5(2):21–25.
- [238] Kumari N, Morris N, Dutta R: Is screening of TORCH worthwhile in women with bad obstetric history: an observation from eastern Nepal. Journal of Health, Population, and Nutrition 2011, 29:77.
- [239] Graham L, Flynn P, Patterson V: Teleneuroradiology: a case from Nepal with clinical and educational benefit. Journal of Telemedicine and Telecare 2002, 8(6):356–358.
- [240] Ghimire P, Sapkota D, Manandhar SP: Cryptosporidiosis: opportunistic infection in HIV/AIDS patients in Nepal. The Journal of Tropical Medicine and Parasitology 2004, 27:7–10.
- [241] Sapkota D, Ghimire P, Manandhar S: Enteric parasitosis in patients with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) in Nepal. Journal of Nepal Health Research Council 2004, 2:9–13.
- [242] Lamichhane G, Shah D, Sharma S, Chaudhary M: Ocular manifestations in HIV/AIDS cases in Nepal. Nepalese Journal of Ophthalmology 2010, 2:45–50.
- [243] Rai S, Sharma A, Shrestha R, Pradhan P: First case of congenital toxoplasmosis from Nepal. Nepal Medical College Journal: NMCJ 2011, 13:64–66.
- [244] Maharjan M: Incidence of zoonotic disease: Echinococcosis/hydatidosis in water buffaloes slaughtered for meat in Western part of Kathmandu. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 1996.
- [245] Joshi D, Joshi A, Joshi H: Epidemiology of echinococcosis in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 1997, 28:26–31.
- [246] Khatri P: Study on prevalence of echinococcosis/hydatidosis in different livestock slaughtered in Banepa, Panauti and Dhulikhel municipalities of Kavre Palanchowk district and tis impact on public health. Msc dissertation, Tribhuvan University, Kathmandu, Nepal 2003.

- [247] Manandhar S: Occurence of echinococcosis/hydatidosis in slaughter buffaloes and *Echinococcus granulosus* in stray dogs in Kathmandu Valley, Nepal. *Msc dissertation*, Chiang Mai University and Freie Universität Berlin, Chiang Mai, Thailand and Berlin, Germany 2005.
- [248] Sharma A: Prevalence of cystic echinococcosis in buffaloes slaughtered in Kirtipur Municipality and its impact on public health. Bsc dissertation, Tribhuvan University, Institute of Agriculture and Animal Sciences, Rampur, Nepal 2008.
- [249] Yadav N: Investigation of diagnostic indicators of echinococcosis in slaughtering buffaloes of Chitwan District, Nepal. Msc dissertation, Tribhuvan University, Institute of Agriculture and Animal Sciences, Rampur, Nepal 2009.
- [250] Baronet D, Waltner-Toews D, Craig P, Joshi D: *Echinococcus granulosus* infections in the dogs of Kathmandu, Nepal. Annals of Tropical Medicine and Parasitology 1994, 88(5):485–492.
- [251] Sah S, Agrawal C, Khan I, Rani S: Hydatid cyst presenting as a breast lump. The Southeast Asian Journal of Tropical Medicine and Public Health 2000, 31:185– 186.
- [252] Biswas R, Dhakal B, Das R, Shetty K: Resolving diagnostic uncertainty in initially poorly localizable fevers: a prospective study. International Journal of Clinical Practice 2004, 58:26–28.
- [253] Gupta D, Sharma M, Shilpakar S: Giant hydatid cyst of brain. Nepal Journal of Neuroscience 2007, 4:77.
- [254] Khan JA, Devkota P, Acharya B, Pradhan NM, Shreshtha S: Bony hydatid disease of superior pubic ramus with extension into pelvis and proximal thigh. JNMA Journal of Nepal Medical Association 2007, 47(171):139–141.
- [255] Bhandari RS, Shrestha M, Shrestha G, Shrestha P, Singh K: Abdominal lump: a diagnostic dilemma. Journal of Nepal Medical Association 2009, 48(173):75–77.
- [256] Mondal S, Sengupta S: Hydatid cyst of radial bone. JNMA Journal of Nepal Medical Association 2009, 48(176):321–323.
- [257] Joshi LSA, Shrestha K: Infected hydatid cyst: various presentations. Post-Graduate Medical Journal of NAMS 2011, 11:59–61.
- [258] Subedi P, Niyaf A, Sharma M, Shilpakar S: Surgical management of parasitic lesions of the central nervous system: our experience. Nepal Journal of Neuroscience 2012, 9:21–28.
- [259] Rauniyar R, Sharma U, Baboo S: Isolated extra hepatic hydatid cyst of para spinal muscle—unusual presentation: a case report. Nepalese Journal of Radiology 2012, 2:31–34.
- [260] Bashyal K: Case study of echinococcosis/hydatidosis in different hospitals of Kathmandu. *Msc dissertation*, Tribhuvan University, Kathmandu, Nepal 2003.

- [261] Gautam B: Prevalence of cystic echinococcosis/hydatidosis in slaughtered buffaloes of Kathmandu metropolitan city and assessment of its impact on public health. *Bsc dissertation*, Tribhuvan University, Institute of Agriculture and Animal Sciences, Rampur, Nepal 2009.
- [262] Ito A, Okamoto M, Ishiguro T, Ma L, Suzuki H, Yasui A, Shigeta H, Matsuura T, Hosokawa T, Chai JJ: Short report: An imported case of cystic echinococcosis in Japan diagnosed by imaging and serology with confirmation of *Echinococcus granulosus*-specific DNA sequences. The American Journal of Tropical Medicine and Hygiene 1998, 58(6):790–792.
- [263] Zhang L, Joshi D, McManus D: Three genotypes of *Echinococcus granulosus* identified in Nepal using mitochondrial DNA markers. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000, 94(3):258–260.
- [264] Joshi D, Yamasaki H: Histopathological and molecular confirmation of porcine cystic echinococcosis (CE)/hydatidosis in Nepal. Journal of Institute of Medicine 2010, 32(3):54–58.
- [265] Devleesschauwer B, Ale A, Duchateau L, Dorny P, Lake R, Dhakal P, Pun SB, Pandey BD, Speybroeck N: Understanding the burden of disease in Nepal: a call for local evidence. Journal of Nepal Health Research Council 2013, 11(24):221–224.
- [266] Kortbeek L, Hofhuis A, Nijhuis C, Havelaar A: Congenital toxoplasmosis and DALYs in the Netherlands. Memórias do Instituto Oswaldo Cruz 2009, 104(2):370–373.
- [267] WHO: Rabies vaccines: WHO position paper. Weekly Epidemiological Record 2007, 82:425–436.
- [268] WHO: WHO Expert Consultation on Rabies. Second report. In World Health Organization Technical Report Series, 982, World Health Organization 2013:139.
- [269] Lembo T, Partners for Rabies Prevention: The blueprint for rabies prevention and control: a novel operational toolkit for rabies elimination. PLoS Neglected Tropical Diseases 2012, 6(2):e1388.
- [270] Gongal G: The epidemiological trend of animal rabies in Nepal and future control strategy. APCRI Journal 2006, 8.
- [271] Karki S, Thakuri KC: Epidemiological situation of animal rabies and its control strategy in Nepal. In Proceedings of the 9th Conference of Nepal Veterinary Association, Kathmandu, Nepal 2010:105–110, [http://www.docstoc.com/ docs/72179558/Epidemiology-of-Rabies-in-Nepal].
- [272] DAH: Annual Technical Report (2065-2066). Kathmandu, Nepal: Directorate of Animal Health, Department of Livestock Services, Ministry of Agriculture and Cooperatives, Government of Nepal 2009, [http://www.docstoc.com/docs/132879787/ ANNUAL-TECHNICAL-REPORT-065-66---Directorate-of-Animal-Health].

- [273] DAH: Annual Technical Report (2067-2068). Kathmandu, Nepal: Directorate of Animal Health, Department of Livestock Services, Ministry of Agriculture Development, Government of Nepal 2011, [http://ahd.gov.np/wp-content/uploads/ 2013/08/Annuanl-Technical-Report-206768.pdf].
- [274] DoHS: Annual Report 2069/70 (2012/2013). Department of Health Services, Ministry of Health and Population, Government of Nepal 2014, [dohs.gov.np/ wp-content/uploads/2014/04/Annual\_Report\_2069\_70.pdf].
- [275] Gongal G, Wright AE: Human rabies in the WHO Southeast Asia Region: forward steps for elimination. Advances in Preventive Medicine 2011, 2011:383870.
- [276] Gongal GN, Rai JN: Human rabies in Nepal. In Rabies Control in Asia, John Libbey Eurotext 2001:231.
- [277] Pant GR, Horton DL, Dahal M, Rai JN, Ide S, Leech S, Marston DA, McElhinney LM, Fooks AR: Characterization of rabies virus from a human case in Nepal. Archives of Virology 2011, 156(4):681–684.
- [278] Joshi DD, Heron BR: Epidemiology of rabies and echinococcosis in Nepal. In Proceedings of the 9th Symposium of the International Society for Veterinary Epidemiology and Economics, Breckenridge, Colorado, USA 2000.
- [279] Bögel K, Joshi DD: Accessibility of dog populations for rabies control in Kathmandu valley, Nepal. Bulletin of the World Health Organization 1990, 68(5):611–617.
- [280] Kato M, Yamamoto H, Inukai Y, Kira S: Survey of the stray dog population and the health education program on the prevention of dog bites and dog-acquired infections: a comparative study in Nepal and Okayama Prefecture, Japan. Acta Medica Okayama 2003, 57(5):261–266.
- [281] Kakati K: Street Dog Population Survey, Kathmandu 2010. Final Report to the World Society for the Protection of Animals 2010, [http://www.katcentre.org. np/about/2010\_Kathmandu\_Dog\_Survey\_Report.doc].
- [282] Kakati K: Street Dog Population Survey, Kathmandu 2012. Final Report to the World Society for the Protection of Animals 2012, [http: //awnnepal.org/pdf/DogSurvey,Kathmandu2012.FinalReport%28April15, 2012%29.K.Kakati\_3.pdf].
- [283] Devleesschauwer B, Pruvot M, Joshi DD, Craeye SD, Jennes M, Ale A, Welinski A, Lama S, Aryal A, Victor B, Duchateau L, Speybroeck N, Vercruysse J, Dorny P: Seroprevalence of zoonotic parasites in pigs slaughtered in the Kathmandu Valley of Nepal. Vector-Borne and Zoonotic Diseases 2013, 13(12):872–876.
- [284] Shultz S, Baral HS, Charman S, Cunningham AA, Das D, Ghalsasi G, Goudar MS, Green RE, Jones A, Nighot P, et al.: Diclofenac poisoning is widespread in declining vulture populations across the Indian subcontinent. Proceedings of the Royal Society of London. Series B: Biological Sciences 2004, 271(Suppl 6):S458–S460.

- [285] Gongal: Anti-rabies drive in Nepal. In Proceedings of Medicine and Health in the Tropics, Marseille, France 2005:45.
- [286] Muzzini E, Aparicio G: Urban Growth and Spatial Transition in Nepal: An Initial Assessment. World Bank Publications 2013.
- [287] Pandey P, Shlim DR, Cave W, Springer MFB: Risk of possible exposure to rabies among tourists and foreign residents in Nepal. Journal of Travel Medicine 2002, 9(3):127–131.
- [288] Boggild AK, Costiniuk C, Kain KC, Pandey P: Environmental hazards in Nepal: altitude illness, environmental exposures, injuries, and bites in travelers and expatriates. *Journal of Travel Medicine* 2007, 14(6):361–368.
- [289] Centers for Disease Control (CDC): Imported human rabies–Australia, 1987. MMWR. Morbidity and Mortality Weekly Report 1988, 37(22):351–353.
- [290] Thakuri K, Mahato S, Thakur R: Diseases of cattle and buffaloes in the Koshi hills of Nepal. A retrospective study. Veterinary Review (Kathmandu) 1992, 7(2):41–46.
- [291] Pant G, Bhatta D: Molecular characterization of rabies virus of Nepal. Journal of Institute of Medicine 2011, **33**(2):5.
- [292] WHO: WHO Methods and Data Sources for Country-level Causes of Death 2000-2012. Global Health Estimates Technical Paper WHO/HIS/HSI/GHE/2014.7. Geneva, Switzerland: Department of Health Statistics and Information Systems, World Health Organization 2014, [http://www.who.int/healthinfo/global\_ burden\_disease/GlobalCOD\_method\_2000\_2012.pdf].
- [293] Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al.: Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 2013, 380(9859):2095–2128.
- [294] Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, Vollset SE, Ozgoren AA, Abdalla S, Abd-Allah F, et al.: Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. The Lancet 2014.
- [295] Pant GR: Rabies control strategy in SAARC member countries. In Proceedings of the Inception Meeting of the OIE/JTF Project for Controlling Zoonoses in Asia under One Health Concept, Tokyo, Japan 2013 [http://www.oie.int/doc/ ged/d12940.pdf].
- [296] Gongal GN: Anti-rabies drive in Nepal: opportunities and challenges. APCRI Journal 2004, 6, [http://rabies.org.in/rabies-journal/rabies-06/ ContSpecialArticle2.htm].

- [297] Pant GR: Production and use of anti-rabies vaccine in Nepal. In Proceedings of a Workshop on Snake Envenoming and Rabies, Kathmandu, Nepal, Kathmandu, Nepal: Nepal Health Research Council 2009:52-55, [http://e-library. nhrc.org.np/nhrc/collect/workshop/index/assoc/HASH01d0.dir/doc.pdf].
- [298] Ide: Rabies vaccine production in tissue culture. In JICA Nepal Office Newsletter, Volume 37, Kathmandu: JICA Nepal Office 2005:3, [http://www. jica.go.jp/nepal/english/office/others/pdf/newsletter\_37.pdf].
- [299] Fox CB: Modern Vaccines/Adjuvants Formulation Session 6: Vaccine & Adjuvant Formulation & Production 15-17 May 2013, Lausanne, Switzerland. Human Vaccines & Immunotherapeutics 2013, 9(9):2007–2008.
- [300] WHO: Strategic Framework for Elimination of Human Rabies Transmitted by Dogs in the South-East Asia Region. New Delhi: World Health Organization, Regional Office for South-East Asia 2012.
- [301] Singh S, Shreshta KB: Rabies in Nepal. In Proceedings of the RIA-SAARC Intercountry Meet on Rabies, Mysore, India 2011:71–74.
- [302] Ranney M, Partridge R, Jay GD, Rozzoli DE, Pandey P: Rabies antibody seroprotection rates among travelers in Nepal: "rabies seroprotection in travelers". Journal of Travel Medicine 2006, 13(6):329–333.
- [303] NZFHRC: Zoonoses and Food Hygiene News, 19(4). National Zoonoses and Food Hygiene Research Centre 2013, [http://www.nzfhrc.org.np/page/news/V19N4. docx].
- [304] Kappeler A, Wandeler AI: Dog Population Studies Related to a Vaccination Campaign Against Rabies in Lalitpur City, Nepal, May 31 to July 05, 1989. Geneva, Switzerland: World Health Organization 1991, [http://apps.who.int/iris/ bitstream/10665/69473/1/Kappeler\_Wandeler\_Nepal\_Report\_1989\_eng.pdf].
- [305] Sharma M: Knowledge and attitude of dog owner's towards the dog anti rabies vaccination. Journal of Nepal Health Research Council 2005, 3:11–16.
- [306] Joshi DD: Rabies situation and control programme in Nepal. In Proceedings of the 1st International Conference of Rabies in Asia (RIA) Foundation, Bangalore, India 2007:22–23.
- [307] NZFHRC: Zoonoses and Food Hygiene News, 14(1), Volume @articleklijs2011contribution, title=Contribution of chronic disease to the burden of disability, author=Klijs, Bart and Nusselder, Wilma J and Looman, Caspar W and Mackenbach, Johan P, journal=PloS one, volume=6, number=9, pages=e25325, year=2011, publisher=Public Library of Science. National Zoonoses and Food Hygiene Research Centre 2011, [www.nzfhrc.org.np/page/news/V14N1.doc].
- [308] Kaufman G: Controlling rabies in Nepal: An international collaborative research and service program at Tufts Cummings School of Veterinary Medicine. In Proceedings of Tufts University, Research Days 2009-2010, Global Health and Infectious Disease, Poster Presentations 2009:48.

- [309] Kaufman GE, Lindenmayer JM: Academia's role in rabies prevention and Control: Tufts Cummings School, a case study. In Proceedings of the 3rd Annual Merial World Rabies Day Symposium, North Grafton, MA, USA 2010[http://www.docstoc.com/docs/80131901/ Academia-Role-in-Rabies-Prevention-Control-Tufts-Cummings].
- [310] Joshi DD: Development of rabies short-term, mid-term and longterm control plan in Nepal. In Proceedings of a Workshop on Snake Envenoming and Rabies, Kathmandu, Nepal: Nepal Health Research Council 2009:56-68, [http://e-library.nhrc.org.np/nhrc/collect/workshop/index/ assoc/HASH01d0.dir/doc.pdf].
- [311] Dodet B: An important date in rabies history. Vaccine 2007, **25**(52):8647–8650.
- [312] Lembo T, Attlan M, Bourhy H, Cleaveland S, Costa P, De Balogh K, Dodet B, Fooks AR, Hiby E, Leanes F, et al.: Renewed global partnerships and redesigned roadmaps for rabies prevention and control. Veterinary Medicine International 2011, 2011:923149.
- [313] Devleesschauwer B, Ale A, Torgerson P, Praet N, de Noordhout CM, Pandey BD, Pun SB, Lake R, Vercruysse J, Joshi DD, Havelaar AH, Duchateau L, Dorny P, Speybroeck N: The burden of parasitic zoonoses in Nepal: a systematic review. PLoS Neglected Tropical Diseases 2014, 8:e2634.
- [314] Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Preventive Medicine 2007, 45(4):247-251.
- [315] van den Akker M, Buntinx F, Knottnerus JA: Comorbidity or multimorbidity: what's in a name? A review of literature. European Journal of General Practice 1996, 2(2):65–70.
- [316] Haagsma JA, van Beeck EF, Polinder S, Toet H, Panneman M, Bonsel GJ: The effect of comorbidity on health-related quality of life for injury patients in the first year following injury: comparison of three comorbidity adjustment approaches. *Population Health Metrics* 2011, 9:10.
- [317] Nusselder WJ, Looman CW: Decomposition of differences in health expectancy by cause. *Demography* 2004, **41**(2):315–334.
- [318] Klijs B, Nusselder WJ, Looman CW, Mackenbach JP: Contribution of chronic disease to the burden of disability. *PLoS ONE* 2011, 6(9):e25325.
- [319] van den Akker M, Buntinx F, Roos S, Knottnerus JA: Problems in determining occurrence rates of multimorbidity. Journal of Clinical Epidemiology 2001, 54(7):675–679.
- [320] Institute for Health Metrics and Evaluation: GBD 2013: Global Burden of Diseases, Injuries, and Risk Factors: Protocol 2013, [http://www.healthdata.org/sites/ default/files/files/GBD\_2013\_Protocol.pdf].

133

- [321] Maertens de Noordhout C, Devleesschauwer B, Angulo FJ, Verbeke G, Haagsma J, Kirk M, Havelaar A, Speybroeck N: The global burden of listeriosis: a systematic review and meta-analysis. The Lancet Infectious Diseases 2014, 14(11):1073–1082.
- [322] McDonald SA, Devleesschauwer B, Speybroeck N, Hens N, Praet N, Torgerson P, Havelaar A, Wu F, Tremblay M, Amene E, Döpfer D: Data-driven methods for imputing national-level incidence rates in global burden of disease studies. Bulletin of the World Health Organization 2015, in press.
- [323] Kanobana K, Devleesschauwer B, Polman K, Speybroeck N: An agent-based model of exposure to human toxocariasis: a multi-country validation. *Parasitology* 2013, 140(8):986–998.
- [324] Cleemput I, Devriese S, Kohn L, Devos C, van Til J, Groothuis-Oudshoorn K, Vandekerckhove P, Van de Voorde C: Incorporating societal preferences in reimbursement decisions: Relative importance of decision criteria according to Belgian citizens. KCE Reports 234. D/2014/10.273/91. Brussels, Belgium: Belgian Health Care Knowledge Centre (KCE) 2014.
- [325] Devleesschauwer B, Praet N, Speybroeck N, Torgerson PR, Haagsma JA, Smet KD, Murrell KD, Pozio E, Dorny P: The low global burden of trichinellosis: evidence and implications. International Journal for Parasitology 2015, 45(2– 3):95–99.
- [326] Palmer S, Torgerson DJ: Definitions of efficiency. BMJ: British Medical Journal 1999, 318(7191):1136.
- [327] Lake R, Devleesschauwer B, Nasinyama G, Havelaar A, Kuchenmüller T, Haagsma J, Jensen H, Jessani N, Maertens de Noordhout C, Angulo F, Ehiri J, Molla L, Friday A, Aungkulanon S, Kumagai Y, Speybroeck N: National studies as a component of the World Health Organization initiative to estimate the global and regional burden of foodborne disease (in preparation).
- [328] Jones KE, Patel NG, Levy MA, Storeygard A, Balk D, Gittleman JL, Daszak P: Global trends in emerging infectious diseases. *Nature* 2008, 451(7181):990– 993.
- [329] Havelaar AH, Cawthorne A, Angulo F, Bellinger D, Corrigan T, Cravioto A, Gibb H, Hald T, Ehiri J, Kirk M, Lake R, Praet N, Speybroeck N, de Silva N, Stein C, Torgerson P, Kuchenmüller T: WHO Initiative to Estimate the Global Burden of Foodborne Diseases. The Lancet 2013, 381:S59.
- [330] Kirk M, Pires S, Black R, Caipo M, Crump J, Devleesschauwer B, Döpfer D, Fazil A, Fischer-Walker C, Hald T, Hall A, Keddy K, Lake R, Lanata C, Torgerson P, Havelaar A, Angulo F: World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal and viral diseases, 2010 (in preparation).
- [331] Torgerson P, Devleesschauwer B, Praet N, Speybroeck N, Willingham AL, Kasuga F, Rokni M, Zhou XN, Fevre E, Sripa B, Furst T, Budke CM, Carabin H, Kirk M,

Angulo F, Havelaar A, de Silva N: WHO Foodborne Disease Burden Epidemiology Reference Group (FERG) 2010 estimates of the global and regional disease burden of eleven foodborne parasitic diseases (in preparation).

- [332] Harrus S, Baneth G: Drivers for the emergence and re-emergence of vectorborne protozoal and bacterial diseases. International Journal for Parasitology 2005, 35(11):1309–1318.
- [333] Campbell GL, Hills SL, Fischer M, Jacobson JA, Hoke CH, Hombach JM, Marfin AA, Solomon T, Tsai TF, Tsu VD, et al.: Estimated global incidence of Japanese encephalitis: a systematic review. Bulletin of the World Health Organization 2011, 89(10):766–774.
- [334] Dumre SP, Shakya G, Na-Bangchang K, Eursitthichai V, Grams HR, Upreti SR, Ghimire P, Khagendra K, Nisalak A, Gibbons RV, et al.: Dengue virus and Japanese Encephalitis virus epidemiological shifts in Nepal: a case of opposing trends. The American Journal of Tropical Medicine and Hygiene 2013, 88(4):677–680.
- [335] Murdoch DR, Woods CW, Zimmerman MD, Dull PM, Belbase RH, Keenan AJ, Scott RM, Basnyat B, Archibald LK, Reller LB: The etiology of febrile illness in adults presenting to Patan hospital in Kathmandu, Nepal. The American Journal of Tropical Medicine and Hygiene 2004, 70(6):670–675.
- [336] Blacksell SD, Sharma NP, Phumratanaprapin W, Jenjaroen K, Peacock SJ, White NJ, Pukrittayakamee S, Day NP: Serological and blood culture investigations of Nepalese fever patients. Transactions of the Royal Society of Tropical Medicine and Hygiene 2007, 101(7):686–690.
- [337] Zimmerman MD, Murdoch DR, Rozmajzl PJ, Basnyat B, Woods CW, Richards AL, Belbase RH, Hammer DA, Anderson TP, Reller LB: Murine typhus and febrile illness, Nepal. Emerging Infectious Diseases 2008, 14(10):1656.
- [338] Pradhan R, Shrestha U, Gautam SC, Thorson S, Shrestha K, Yadav BK, Kelly DF, Adhikari N, Pollard AJ, Murdoch DR: Bloodstream infection among children presenting to a general hospital outpatient clinic in urban Nepal. PLoS ONE 2012, 7(10):e47531.
- [339] Pun SB, Bastola A, Shah R: First report of Chikungunya virus infection in Nepal. The Journal of Infection in Developing Countries 2014, 8(06):790–792.
- [340] Kandel N, Shrestha JM, Upadhyay B, Shrestha A, Shakya G: Pandemic (H1N1) 2009 cases in Nepal. JNMA Journal of Nepal Medical Association 2012, 52(188):201–204.
- [341] Adhikari BR, Shakya G, Upadhyay BP, KC KP, Shrestha SD, Dhungana GR: Outbreak of pandemic influenza A/H1N1 2009 in Nepal. Virology Journal 2011, 8:133.
- [342] Myint KSA, Murray CK, Scott RM, Shrestha MP, Mammen MP, Shrestha SK, Kuschner RA, Joshi DM, Gibbons RV: Incidence of leptospirosis in a select population in Nepal. Transactions of the Royal Society of Tropical Medicine and Hygiene 2010, 104(8):551–555.

σ

- [343] Kandel N, Thakur G, Andjaparidze A: Leptospirosis in Nepal. JNMA Journal of Nepal Medical Association 2012, 52(187):151–153.
- [344] Bista K, Rana A: Acute Hepatitis E in pregnancy: study of 16 Cases. JNMA Journal of Nepal Medical Association 2006, 45(161):182–185.
- [345] Shrestha P, Bhandari D, Sharma D, Bhandari B: A study of viral hepatitis during pregnancy in Nepal Medical College Teaching Hospital. Nepal Medical College journal: NMCJ 2009, 11(3):192–194.
- [346] Scott R, Pandey P, Shlim DR: Etiology of enterically-transmitted hepatitis among foreigners in Nepal. The Southeast Asian Journal of Tropical Medicine and Public Health 2009, 40(4):731–737.
- [347] Kimura K, Ohnishi K: Two patients with acute Q fever. The Journal of the Japanese Association for Infectious Diseases 1999, 73(12):1236–1240.
- [348] Murray CJ: Towards good practice for health statistics: Lessons from the Millennium Development Goal health indicators. The Lancet 2007, 369(9564):862–873.
- [349] WHO: Towards a monitoring framework with targets and indicators for the health goals of the post-2015 Sustainable Development Goals. Geneva: World Health Organization 2015, [http://www.who.int/healthinfo/indicators/hsi\_ indicators\_sdg\_targetindicators\_draft.pdf?ua=1].
- [350] Joshi DD: Organisation of veterinary public health in the south Asia region. Revue Scientifique et Technique de l'Office International des Épizooties 1991, 10(4):1101–1129.
- [351] Joshi DD, Maharjan M, Johansen MV, Willingham AL, Sharma M: Improving meat inspection and control in resource-poor communities: the Nepal example. Acta Tropica 2003, 87:119–127.
- [352] Karna V: Implementation status of SMIA (Slaughterhouse & Meat Inspection Act) (1999) in Kathmandu. Msc dissertation, North South University, Dhaka, Bangladesh 2010.
- [353] World Bank: Project Performance Assessment Report: Nepal Avian Influenza Control Project (IDA-H2680). World Bank Publications 2013, [http: //ieg.worldbankgroup.org/Data/reports/PPAR-78317-P100342-Nepal\_ Avian\_Influenza\_Control.pdf].
- [354] World Bank: Implementation Completion and Results Report: Nepal Zoonoses Control Project. World Bank Publications 2014, [http://documents.worldbank.org/ curated/en/2014/09/20263585/nepal-zoonoses-control-project].
- [355] WHO: Report of the Regional Meeting on Zoonotic Diseases, 20-22 August 2013. Chiang Mai, Thailand: World Health Organization Regional Office for South-East Asia 2014, [http://www.searo.who.int/entity/emerging\_diseases/sea\_ cd\_291.pdf].

- [356] Kuchenmüller T, Abela-Ridder B, Corrigan T, Tritscher A: World Health Organization initiative to estimate the global burden of foodborne diseases. Revue Scientifique et Technique de l'Office International des Épizooties 2013, 32(2):459–467.
- [357] Brownell KD, Roberto CA: Strategic science with policy impact. The Lancet 2015, in press.
- [358] Snow RW: Sixty years trying to define the malaria burden in Africa: have we made any progress? *BMC Medicine* 2014, **12**:227.

### Summary

Chapter 1 provided the background for this thesis.

The main goal of public health policy is to promote, enhance and protect population health. This requires information on the health status of the population, often referred to as the "burden of disease". Population health is a multifactorial phenomenon with many facets. As a result, the disease burden of a population can be described by a variety of indicators. As current health policy requires a global overview of public health, combining morbidity and mortality and taking into account health-related quality of life, so-called summary measures of population health (SMPH) are gaining wider importance.

Driven by the influential Global Burden of Disease projects initiated in the early 1990s, the Disability-Adjusted Life Year (DALY) has become the dominant SMPH. The DALY is a health gap measure, reflecting the number of healthy life years lost due to disease and death. In the DALY philosophy, every person is born with a certain number of life years potentially lived in optimal health. People may lose these healthy life years through living with illness and/or through dying before a reference life expectancy.

The importance of burden of disease estimates for health policy in Nepal becomes evident from recent policy documents and recommendations. The Second Long-Term Health Plan 1997–2017 was the first document to recognize the importance of prioritizing health sector needs, motivated by the scarce human, financial and physical resources available. Notwithstanding the importance of disease burden estimates, Nepalese DALYs are scarce and not rooted in local data. Especially for zoonotic and other neglected diseases, this may lead to a vicious cycle of indifference, under-recognition and under-funding.

**Chapter 2** introduced the rationale and objectives of this thesis. The main objective of this thesis was to unravel the burden of zoonoses in Nepal and to quantify this burden using the DALY metric. To achieve this goal, we contributed to a further standardization of the DALY metric.

Although the philosophical and methodological aspects of the DALY calculation have been described (and debated) in great detail, the steps *preceding* the actual calculation remained less well documented. In **Chapter 3**, we therefore proposed a stepwise approach for conducting a DALY-based disease burden study, consisting of the following five consecutive steps: Study population definition; Disease model definition; Data collection; Data adjustment; and DALY calculation.

Nearly every DALY estimation is subject to data uncertainty and modelling choices. The resulting DALY estimate is therefore hardly ever a single, fixed value, defined with perfect accuracy and precision. In **Chapter 4**, we studied sources of uncertainty inherent to DALY calculations through a systematic review of DALY-based disease burden studies. Of the 228 studies published between 1994 and 2013, only 105 (46%) had performed some sort of uncertainty quantification. Identifying, quantifying and analysing uncertainties should become a standard part of DALY calculations. We recommend probabilistic sensitivity analysis for quantifying parameter uncertainty and scenario analyses for quantifying model and methodological uncertainties.

To our knowledge, there are no standardized tools available for stochastic DALY calculation. We therefore designed a free and open-source tool for calculating DALYs that allows for the incorporation of input uncertainty and the computation of DALY credibility intervals through Monte Carlo simulations. **Chapter 5** provides an overview of the functionalities of this tool, called the DALY Calculator. Further work is needed to increase the flexibility and user-friendliness of the tool.

Based on the guidelines and tools developed in these first chapters, we then went on to accomplish the main objective of the thesis. In **Chapter 6**, we reviewed the occurrence and burden of parasitic zoonoses in Nepal. Between 2000 and 2012, the highest annual burden was imposed by neurocysticercosis and congenital toxoplasmosis, followed by cystic echinococcosis. Nepal is endemic for several other parasitic zoonoses, but these probably have a much lower population burden. We identified several critical data gaps and highlighted the need for enhanced surveillance of the identified endemic parasitic zoonoses.

In addition, we reviewed the epidemiology, burden and control of rabies in Nepal in **Chapter 7**. Limited data indicate that rabies still is a major zoonosis in Nepal. However, more and better data are needed, especially from rural areas, to estimate the true burden of animal and human rabies. The current control of rabies is hampered by insufficient vaccine availability across the country and limited collaboration, both within the country and within the region. To overcome these hurdles, high-level political commitment is required. Making rabies the model zoonosis for successful control may be a powerful step towards achieving this.

In **Chapter 8**, finally, we placed our findings in a broader perspective, discussed their main limitations and presented avenues for future research.

Our work contributed to identifying sources of methodological variability in DALY estimations, but did not manage to resolve the lack of comparability across studies. The development of a checklist of assumptions, based on our work, could increase methodological transparency in DALY-based disease burden studies. Further methodological research needs to focus on the problem of multimorbidity and the extrapolation of health statistics.

Our work also contributed to an improved understanding of the epidemiology and burden of zoonoses in Nepal and highlighted the importance of rabies, both at the populationlevel and the patient-level. However, our work has been limited by the fact that only the health burden was quantified, and not the economic burden. Furthermore, by focusing on parasitic zoonoses and rabies, we covered only one part of the large spectrum of zoonotic diseases. Further evidence on the burden of foodborne zoonoses in Nepal is available from the WHO Foodborne Disease Burden Epidemiology Reference Group. Combining all available evidence shows that the zoonoses with the highest disease burden in Nepal are non-typhoidal salmonellosis, campylobacteriosis, toxoplasmosis, cysticercosis and rabies.

The ultimate aim of disease burden estimates is to inform decision makers on setting the right research and control priorities. However, we have no evidence that our work managed to inform decision makers. Future, similar projects should therefore emphasize capacity building and knowledge transfer. Notwithstanding the possible disconnect between burden estimates and policy, we do believe that it is of paramount importance to continue generating disease burden estimates. Only then can we gain the knowledge that is required to take the right actions.

# Résumé

#### Le Chapitre 1 fournit le contexte de cette thèse.

L'objectif principal de la politique de santé publique est de protéger et promouvoir la santé de la population. Ceci nécessite des informations sur le statut de santé de la population, communément appelé « le fardeau de la maladie ». La santé de la population est un phénomène multifactoriel qui comprend énormément de facettes. En réponse à ceci, le fardeau de la maladie d'une population peut être décrit à l'aide d'une variété d'indicateurs. Ainsi, comme la politique de santé actuelle requière une vue d'ensemble de la santé publique combinant morbidité et mortalité et prenant en compte la qualité de vie liée à la santé, les mesures synthétiques de la santé publique gagnent en importance.

Le « Disability-Adjusted Life Year » (DALY) a été créé au début des années nonante par les projets d'évaluation du fardeau mondial des maladies et est actuellement la mesure synthétique la plus utilisée. Le DALY est une mesure de l'écart de santé, reflétant le nombre d'années de vie en bonne santé perdues à cause d'une maladie ou d'un décès. Dans la philosophie du DALY, chaque personne est née avec un certain nombre d'années de vie potentiellement vécues dans une santé optimale. Les personnes peuvent perdre ces années de vie en bonne santé suite à une maladie et/ou un décès avant l'espérance de vie attendue. L'importance des estimations du fardeau de la maladie pour la politique de santé au Népal devient manifeste depuis la publication de récents documents et recommandations politiques. Le deuxième projet de santé à long terme de 1997-2017 était le premier document à reconnaitre l'importance de prioriser les besoins de santé sectoriels, motivé par la rareté des ressources humaines, financières et physiques. Malgré l'importance des estimations du fardeau de la maladie, les DALYs népalais sont rares et non ancrés dans les données locales. Particulièrement pour les zoonoses et les autres maladies négligées, ce qui peut mener à un cercle vicieux d'indifférence, de sous-reconnaissance et de sousfinancement.

Le **Chapitre 2** introduit le rationnel et les objectifs de cette thèse. L'objectif principal de cette thèse était d'éclaircir le fardeau des zoonoses au Népal et de quantifier ce fardeau en utilisant le DALY comme mesure. Afin d'atteindre cet objectif, nous avons contribué à une meilleure standardisation du DALY.

Malgré que les aspects philosophiques et méthodologiques du calcul de DALY ont été décrits (et débattus) en détails, les étapes précédant le calcul même restaient moins bien documentées. Dans le **Chapitre 3**, nous avons donc proposé une approche par étapes pour élaborer une étude de fardeau de la maladie basée sur les DALYs comprenant les cinq étapes suivantes: Définition de la population d'étude; Définition du modèle de la maladie; Collecte des données; Ajustement des données; et calcul des DALYs.

Presque chaque estimation de DALY est sujette à une incertitude dans les données et à des choix de modélisation. L'estimation de DALY résultant de ces choix n'est donc presque jamais une valeur fixe définie avec une précision et une exactitude parfaite. Dans le **Chapitre 4**, nous avons étudié les sources d'incertitudes inhérentes aux calculs de DALY à l'aide d'une revue systématique des études du fardeau de la maladie basées sur le DALY. Sur les 228 études publiées entre 1994 et 2013, seulement 105 (46%) avaient réalisé une sorte de quantification de l'incertitude. Identifier, quantifier et analyser les incertitudes devraient devenir une étape standard dans les calculs de DALY. Nous recommandons une analyse de sensibilité probabiliste pour étudier l'incertitude d'un paramètre et des analyses de scénarios pour quantifier les incertitudes du model et de la méthodologie.

A notre connaissance, il n'existe aucun outil standard pour le calcul stochastique des DALYs. Nous avons donc créé un outil gratuit et open source pour le calcul des DALYs qui permet d'ajouter des données d'incertitude et de calculer les intervalles de crédibilité à l'aide des simulations de Monte Carlo. Le **Chapitre 5** fournit une vue d'ensemble des fonctionnalités de l'outil, appelé le « DALY Calculator ». Du travail supplémentaire est encore nécessaire pour améliorer la flexibilité et la convivialité de l'outil.

A l'aide des lignes directrices et des outils développés dans ces premiers chapitres, nous avons ensuite atteint l'objectif principal de la thèse. Dans le **Chapitre 6**, nous avons passé en revue la survenue et le fardeau des zoonoses parasitaires au Népal. Entre 2000 et 2012, le fardeau annuel le plus élevé était attribué à la neurocysticercose et la toxoplasmose congénitale, suivies ensuite par l'échinococcose kystique. Le Népal est endémique pour plusieurs autres zoonoses parasitaires, mais celles-ci pèsent probablement un plus faible fardeau sur la population. Nous avons identifié un certain nombre de lacunes en termes de données et souligné la nécessité de renforcer la surveillance des zoonoses parasitaires endémiques.

De plus, nous avons passé en revue l'épidémiologie, le fardeau et le contrôle de la rage au Népal dans le **Chapitre 7**. Les données restreintes indiquent que la rage reste une zoonose majeure au Népal. Cependant, des données supplémentaires et de meilleure qualité sont

nécessaires, particulièrement dans les régions rurales, pour estimer le véritable fardeau de la rage animal et humaine. Le contrôle actuel de la rage et entravé par la disponibilité insuffisante de vaccins à travers le pays et la faible collaboration, à la fois au sein du pays et dans la région. Afin de remédier à ces obstacles, un engagement politique de haut niveau est requis. Faire de la rage un modèle de contrôle de zoonose réussi pourrait être une étape puissante vers l'accomplissement de ceci.

Finalement dans le **Chapitre 8**, nous avons placé nos résultats dans une perspective plus large, discuté leurs principales limitations et présenté des pistes pour de futures recherches.

Notre travail a contribué à identifier les sources de variabilité méthodologiques dans les estimations de DALY mais n'a pas réussi à résoudre le problème du manque de comparabilité entre les études. La mise en place d'une checklist d'hypothèses, basée sur notre travail, pourrait augmenter la transparence méthodologique des études de fardeau de la maladie basées sur le DALY. D'autres recherches méthodologiques doivent se concentrer sur le problème de multimorbidité et sur l'extrapolation des statistiques de santé.

Notre travail a également contribué à améliorer la compréhension de l'épidémiologie et du fardeau des zoonoses au Népal et a souligné l'importance de la rage, à la fois au niveau de la population qu'au niveau du patient. Cependant, notre travail a également été limité par le fait que seul le fardeau de la santé a été quantifié et non le fardeau économique. De plus, en se focalisant sur les zoonoses parasitaires et la rage, nous avons uniquement couvert une petite partie du spectre très large des maladies zoonotiques. D'autres informations concernant le fardeau des maladies zoonotiques d'origine alimentaire au Népal sont également disponibles via le « Foodborne Disease Burden Epidemiology Reference Group » de l'OMS. En combinant toutes les données disponibles, nous pouvons affirmer que la salmonellose non typhique, la campylobactériose, la toxoplasmose, la cysticercose et la rage sont les zoonoses ayant le plus gros impact sur le fardeau des maladies au Népal.

Le but ultime des estimations du fardeau de la maladie est d'informer les décideurs des bonnes priorités à établir dans le domaine de la recherche et du contrôle des maladies. Cependant, nous n'avons aucune preuve que notre travail a réussi à informer les décideurs. Dans le futur, d'autres projets similaires devraient donc mettre l'accent sur le développement des capacités et le transfert des connaissances. Malgré le possible décalage entre les estimations de fardeau et la politique, nous croyons qu'il est primordial de continuer à générer des estimations de fardeau de la maladie. Alors seulement nous pouvons acquérir la connaissance nécessaire pour prendre des mesures appropriées.

# Samenvatting

#### Hoofdstuk 1 schetste de achtergrond van deze thesis.

De hoofddoelstelling van het volksgezondheidsbeleid is om de gezondheid van de bevolking te beschermen en te bevorderen. Hiervoor is informatie nodig over de gezondheidsstatus van de bevolking, ook gekend als de "ziektelast". Volksgezondheid is multifactorieel en kent verschillende facetten. Hierdoor kan de ziektelast in een populatie beschreven worden met verschillende indicatoren. Aangezien het hedendaagse volksgezondheidsbeleid nood heeft aan een globaal beeld van de gezondheid van de populatie, dat zowel ziekte als sterfte omvat en de levenskwaliteit mee in rekening brengt, winnen zogenaamde synthetische ziektelastindicatoren aan belang.

Onder impuls van de invloedrijke *Global Burden of Disease*-projecten die begin jaren '90 werden geïnitieerd, is de *Disability-Adjusted Life Year* (DALY) uitgegroeid tot de belangrijkste synthetische ziektelastindicator. De DALY is een gezondheidskloofindicator, en reflecteert het aantal gezonde levensjaren dat verloren is door ziekte en sterfte. In de DALY-filosofie wordt iedere persoon geboren met een zeker aantal levensjaren dat in volle gezondheid geleefd kan worden. Personen kunnen deze gezonde levensjaren verliezen door te leven met ziekte en/of te sterven voor een bepaalde optimale levensverwachting.

Het belang van ziektelastindicatoren voor het gezondheidsbeleid in Nepal blijkt uit recente beleidsdocumenten en -aanbevelingen. Het Second Long-Term Health Plan 1997– 2017 was het eerste document dat het belang erkende van de prioritering van behoeften binnen de gezondheidssector, en dit gemotiveerd door de schaarse personele, financiële en fysieke middelen. Niettegenstaande het belang van ziektelastindicatoren, zijn Nepalese DALYs eerder schaars en slechts in beperkte mate gesteund op lokale gegevens. Vooral voor zoönotische en andere verwaarlossde ziekten kan dit leiden tot een vicieuze cirkel van onverschilligheid, onderwaardering en onderfinanciering.

Hoofdstuk 2 introduceerde de motivering en doelstellingen van dit proefschrift. De hoofddoelstelling van het proefschrift was de ziektelast te wijten aan zoönotische ziekten in Nepal te ontrafelen en te kwantificeren aan de hand van de DALY-parameter. Om deze doelstelling te bereiken, hebben we eerst bijgedragen aan een verdere standaardisatie van de DALY-parameter.

Hoewel de filosofische en methodologische aspecten van de DALY-berekening in detail beschreven (en bediscussieerd) zijn, zijn de stappen *voorafgaand* aan de eigenlijke berekening minder goed gedocumenteerd. In **Hoofdstuk 3** hebben we daarvoor een stapsgewijze aanpak voorgesteld voor een op DALYs gebaseerde ziektelaststudie, bestaande uit de volgende vijf stappen: Definitie van de studiepopulatie; Definitie van het ziektemodel; Verzamelen van de nodige gegevens; Correctie van de gegevens; en DALY-berekening.

Bijna elke DALY-berekening is onderhevig aan onzekerheid in de gegevens en subjectieve keuzes in de modellering. De resulterende DALY-schatting is daarom zelden één vaste waarde met perfecte nauwkeurigheid en precisie. In **Hoofdstuk 4** hebben we bronnen van onzekerheid inherent aan DALY-berekeningen bestudeerd aan de hand van een systematische review van op DALYs gebaseerde ziektelaststudies. Van de 228 studies gepubliceerd tussen 1994 en 2013, had slechts 105 (46%) enige kwantificering van onzekerheid uitgevoerd. Het identificeren, kwantificeren en analyseren van onzekerheden moet een standaard onderdeel van DALY-berekeningen worden. Wij raden probabilistische gevoeligheidsanalyse aan voor het kwantificeren van parameteronzekerheid en scenarioanalyses voor het kwantificeren van het model- en methodologische onzekerheden.

Voor het begin van dit doctoraat waren er geen gestandaardiseerde tools beschikbaar voor stochastische DALY-berekeningen. Daarom hebben we een gratis en open-source tool voor de berekening van DALY's ontwikkeld die het mogelijk maakt om via Monte Carlosimulaties de onzekerheid in de gegevens om te zetten naar DALY-onzekerheidsintervallen. **Hoofdstuk 5** geeft een overzicht van de functionaliteiten van deze tool, die we de DALY Calculator genoemd hebben. Verdere aanpassingen zijn nodig om de flexibiliteit en gebruiksvriendelijkheid van de tool te verbeteren.

Op basis van de richtlijnen en tools ontwikkeld in deze eerste hoofdstukken, hebben we vervolgens de hoofddoelstelling van dit proefschrift verwezenlijkt. In **Hoofdstuk 6** hebben we het voorkomen en de ziektelast van parasitaire zoönosen in Nepal bestudeerd. Tussen 2000 en 2012 waren neurocysticercose en congenitale toxoplasmose verantwoordelijk voor de belangrijkste ziektelast, gevolgd door cystische echinococcose. Nepal is endemisch voor verschillende andere parasitaire zoönosen, maar deze hebben waarschijnlijk een veel lagere impact op de volksgezondheid. We identificeerden een aantal kritische lacunes in de gegevens en wezen op de noodzaak van een betere surveillance van de geïdentificeerde endemische parasitaire zoönosen.

Daarnaast hebben we in **Hoofdstuk 7** de epidemiologie, ziektelast en controle van hondsdolheid in Nepal bestudeerd. De beperkte gegevens wijzen erop dat hondsdolheid

nog steeds een van de belangrijkste zoönosen in Nepal is. Er zijn echter meer en betere gegevens nodig, vooral vanuit rurale gebieden, om de ware impact van hondsdolheid op dier en mens te kunnen schatten. De controle van hondsdolheid wordt momenteel belemmerd door onvoldoende beschikbaarheid van vaccins in het hele land, en door de beperkte samenwerking, zowel binnen het land als binnen de regio. Om deze hindernissen te overwinnen, is politiek engagement op hoog niveau vereist. Hondsdolheid uitroepen tot model voor een succesvolle controle van zoönosen zou een krachtige stap kunnen zijn om dit te bereiken.

In **Hoofdstuk 8**, tot slot, hebben we onze bevindingen in een breder perspectief geplaatst, hun belangrijkste tekortkomingen besproken, en mogelijkheden voorgesteld voor verder onderzoek.

Ons werk heeft bijgedragen aan het bepalen van de methodologische variabiliteit in DALY-schattingen, maar slaagde er niet in om het gebrek aan vergelijkbaarheid tussen studies op te lossen. De ontwikkeling van een checklist van methodologische assumpties, gebaseerd op ons werk, zou de methodologische transparantie in op DALY gebaseerde ziektelaststudies kunnen verhogen. Verder methodologisch onderzoek moet zich concentreren op het probleem van multimorbiditeit en de extrapolatie van gezondheidsindicatoren.

Ons werk heeft ook bijgedragen aan een betere kennis van de epidemiologie en de ziektelast van zoönosen in Nepal en heeft het belang benadrukt van hondsdolheid, zowel op populatieniveau als op patiëntniveau. Ons werk was echter beperkt door het feit dat alleen de impact op de volksgezondheid werd gekwantificeerd, en niet de impact op de economie. Door te focussen op parasitaire zoönosen en hondsdolheid, hebben we voorts ook slechts een deel van het brede spectrum van zoönosen aangepakt. Aanvullend bewijs over de ziektelast van door voedsel overgedragen zoönosen in Nepal werd gegenereerd door de *Foodborne Disease Burden Epidemiology Reference Group* van de Wereldgezondheidsorganisatie. De combinatie van alle beschikbare schattingen toont aan dat niet-tyfoïde salmonellose, campylobacteriose, toxoplasmose, cysticercose en hondsdolheid, de zoönosen met de belangrijkste ziektelast in Nepal zijn.

Het uiteindelijke doel van ziektelastschattingen is om beleidsmakers te helpen bij het stellen van de juiste prioriteiten voor onderzoek en controle. We hebben echter geen bewijs dat ons werk er ook effectief in geslaagd is om beleidsmakers te informeren. Toekomstige, soortgelijke projecten moeten daarom meer aandacht besteden aan capaciteitsopbouw en kennisoverdracht. Niettegenstaande de mogelijke discrepantie tussen ziektelastschattingen en beleid, menen we dat het van het groot belang is om ziektelastschattingen te blijven genereren. Alleen dan kunnen we de kennis genereren die nodig is om de juiste acties te kunnen ondernemen.

# **Curriculum Vitae**

Brecht Devleesschauwer was born in Ronse on 9 September 1986. After completing secondary school in mathematics-sciences at the KSO Glorieux in Ronse, he obtained the Master degree in Veterinary Medicine from Ghent University in 2010 with greatest distinction, and received the prize of the Faculty of Veterinary Medicine for best academic results. His master thesis was awarded with the Pfizer Animal Health Award for best research thesis. In 2014, Brecht also obtained the Master degree in Statistics from KU Leuven with great distinction.

In 2010, Brecht was granted a PhD scholarship from the Ghent University Special Research Fund, which allowed him to pursue a joint PhD in Veterinary Sciences and Public Health, jointly organized by Ghent University and the Université catholique de Louvain.

During this PhD, Brecht conducted research on methods for estimating burden of disease and true prevalence, and applied these methods to public and animal health problems in Nepal, Belgium, and worldwide. He also assisted in teaching practical sessions in biostatistics, and gave guest lectures on tropical veterinary medicine and epidemiology.

Brecht is (co) promoter of 17 graduate and undergraduate students, (co) author of 24 papers published in international journals, and has served as reviewer for journals in the fields of parasitology, tropical medicine and public health. In 2013-2014, Brecht worked for six months as a technical consultant to the World Health Organization to develop a computational framework for estimating the global burden of foodborne disease. He has also served as an expert for the Codex Alimentarius Committee on Food Hygiene and the Belgian Federal Agency for the Safety of the Food Chain.

#### Publications

[25] McDonald SA, **Devleesschauwer B**, Speybroeck N, Hens N, Praet N, Torgerson PR, Havelaar AH, Wu F, Tremblay M, Amene EW, Döpfer D (2014) Data-driven methods for imputing national-level incidence rates in global burden of disease studies. *Bull World Health Org*, in press

[24] Gabriel S, Johansen MV, Pozio E, Smit S, **Devleesschauwer B**, Allepuz A, Dorny P (2015) Human migration and pig/pork import in the European Union: what are the implications for *Taenia solium* infections? *Vet Parasitol*, in press

[23] Levecke B, Anderson RM, Berkvens D, Charlier J, **Devleesschauwer B**, Speybroeck N, Vercruysse J, Van Aelst S (2015) Mathematical inference on helminth egg counts in stool and its applications in mass drug administration programmes to control soil-transmitted helminthiasis in public health. *Adv Parasitol* 87:193-247

[22] Speybroeck N, **Devleesschauwer B**, Depoorter P, Dewulf J, Berkvens D, Van Huffel X, Saegerman C (2015) Needs and expectations regarding risk ranking in the food chain: a pilot survey amongst decision makers and stakeholders. *Food Control* 54:135-143

[21] Devleesschauwer B, Praet N, Speybroeck N, Torgerson PR, Haagsma JA, De Smet K, Murrell D, Pozio E, Dorny P (2015) The low global burden of trichinellosis: evidence and implications. Int J Parasitol 45:95-99

[20] Tromme I, Devleesschauwer B, Beutels P, Richez P, Leroy A, Baurain JF, Cornélis F, Bertrand C, Legrand N, Degueldre J, Thomas L, Legrand C, Haagsma JA, Speybroeck N (2014) Health related quality of life in melanoma patients expressed as index values and disability weights: a Belgian study. Br J Dermatol 171:1443-1450

[19] Devleesschauwer B, Maertens de Noordhout C, Smit GSA, Duchateau L, Dorny P, Stein C, Van Oyen H, Speybroeck N (2014) Quantifying burden of disease to support public health policy in Belgium: opportunities and constraints. *BMC Public Health* 14:1196

[18] Tromme I, **Devleesschauwer B**, Beutels P, Richez P, Praet N, Sacré L, Marot L, Van Eeckhout P, Theate I, Baurain JF, Thomas L, Speybroeck N (2014) Selective use of digital dermoscopy allows a cost reduction in the melanoma detection process: a Belgian study of patients with a single or a small number of atypical nevi. *PLOS One* 9:e109339

[17] Maertens de Noordhout C, Devleesschauwer B, Angulo FJ, Verbeke G, Haagsma J, Kirk M, Havelaar A, Speybroeck N (2014) The global burden of listeriosis: a systematic review and meta-analysis. *Lancet Infect Dis* 14:1073-1082

[16] Coral-Almeida M, Rodríguez-Hidalgo R, Celi-Erazo M, García HH, Rodríguez S, Benítez-Ortiz W, **Devleesschauwer B**, Dorny P, Praet N (2014) Incidence and transmission dynamics of human cysticercosis in a *Taenia solium* Ecuadorian endemic area: implications for disease burden assessment and control. *PLoS Negl Trop Dis* 8:e2887

[15] Devleesschauwer B, Havelaar AH, Maertens de Noordhout C, Haagsma JA, Praet N, Dorny P, Duchateau L, Torgerson PR, Van Oyen H, Speybroeck N (2014) DALY calculation in practice: a stepwise approach. *Int J Public Health* 59:571-574

[14] **Devleesschauwer B**, Havelaar AH, Maertens de Noordhout C, Haagsma JA, Praet N, Dorny P, Duchateau L, Torgerson PR, Van Oyen H, Speybroeck N (2014) Calculating disability-

adjusted life years to quantify burden of disease. Int J Public Health 59:565-569

[13] Henrard S, **Devleesschauwer B**, Beutels P, Callens M, De Smet F, Hermans C, Speybroeck N (2014) The health and economic burden of haemophilia in Belgium: a rare, expensive and challenging disease. *Orphanet J Rare Dis* 9:39

[12] Ale A, Victor B, Praet N, Gabriël S, Speybroeck N, Dorny P, **Devleesschauwer B** (2014) Epidemiology and genetic diversity of *Taenia asiatica*: a systematic review. *Parasit Vectors* 7:45

[11] Devleesschauwer B, Ale A, Torgerson P, Praet N, Maertens de Noordhout C, Pandey BD, Pun SB, Lake R, Vercruysse J, Joshi DD, Havelaar AH, Duchateau L, Dorny P, Speybroeck N (2014) The burden of parasitic zoonoses in Nepal: a systematic review. *PLoS Negl Trop Dis* 8:e2634

[10] **Devleesschauwer B**, Pruvot M, Joshi DD, De Craeye S, Jennes M, Ale A, Welinski A, Lama S, Aryal A, Victor B, Duchateau L, Speybroeck N, Vercruysse J, Dorny P (2013) Seroprevalence of zoonotic parasites in pigs slaughtered in the Kathmandu Valley of Nepal. *Vector Borne Zoonotic Dis* 13:872-876

[9] Speybroeck N, Van Malderen C, Harper S, Müller B, **Devleesschauwer B** (2013) Simulation models for socioeconomic inequalities in health: a systematic review. *Int J Environ Res Public Health* 10:5750-5780

[8] Speybroeck N, **Devleesschauwer B**, Joseph L, Berkvens D (2013) Misclassification errors in prevalence estimation: Bayesian handling with care. *Int J Public Health* 58:791-795

[7] Kanobana K, **Devleesschauwer B**, Polman K, Speybroeck N (2013) An agent-based model of exposure to human toxocariasis: a multi-country validation. *Parasitology* 140:986-998

[6] **Devleesschauwer B**, Ale A, Duchateau L, Dorny P, Lake R, Dhakal P, Pun SB, Pandey BD, Speybroeck N (2013) Understanding the burden of disease in Nepal: a call for local evidence. *J Nepal Health Res Counc* 11:221-224

[5] Devleesschauwer B, Aryal A, Tharmalingam J, Joshi DD, Rijal S, Speybroeck N, Gabriël S, Victor B, Dorny P (2013) Complexities in using sentinel pigs to study *Taenia solium* transmission dynamics under field conditions. *Vet Parasitol* 193:172-178

[4] Speybroeck N, Williams CJ, Lafia KB, **Devleesschauwer B**, Berkvens D (2012) Estimating the prevalence of infections in vector populations using pools of samples. *Med Vet Entomol* 26:361-371

[3] **Devleesschauwer B**, Aryal A, Joshi DD, Rijal S, Sherchand JB, Praet N, Speybroeck N, Duchateau L, Vercruysse J, Dorny P (2012) Epidemiology of *Taenia solium* in Nepal: is it influenced by the social characteristics of the population and the presence of *Taenia asiatica*? *Trop Med Int Health* 17:1019-1022

[2] Charlier J, Levecke B, Devleesschauwer B, Vercruysse J, Hogeveen H (2012) The economic effects of whole-herd versus selective anthelmintic treatment strategies in dairy cows. J Dairy Sci 95:2977-2987

[1] Pant B, **Devleesschauwer B**, Shrestha P, Shrestha I, Praet N, Dorny P (2011) Intraventricular *Taenia solium* neurocysticercosis: a report of three cases. *JNMA J Nepal Med Assoc* 51:192-195

#### **Oral presentations**

[13] **Devleesschauwer B**, Torgerson P, Charlier J, Levecke B, Praet N, Roelandt S, Smit S, Dorny P, Berkvens D, Speybroeck N (2014) Bayesian estimation of true prevalence from apparent prevalence in R: Introducing the "prevalence" package. Presented at the *Berliner Kolloquium—Statistische Methoden in der Empirischen Forschung*; 9 Dec 2014; Berlin, Germany.

 [12] Devleesschauwer B (2014) Unravelling the burden of zoonoses in Nepal. Presented at the University of Florida, Emerging Pathogens Institute, Seminar Series; 18 Nov 2014; Gainesville, FL, USA.

[11] **Devleesschauwer B**, Speybroeck N (2014) Understanding, interpreting and calculating Disability-Adjusted Life Years. Presented at the *Scientific Institute of Public Health (WIV-ISP)*, *Seminar Series*; 11 Mar 2014; Brussels, Belgium.

[10] **Devleesschauwer B**, Praet N, Dorny P, Duchateau L, Speybroeck N (2013) DALY calculation in practice: a stepwise approach. Presented at the 6th European Public Health Conference (EUPHA 2013): Health in Europe, are we there yet?; 14-16 Nov 2013; Brussels, Belgium.

[9] Maertens de Noordhout C, **Devleesschauwer B**, Angulo FJ, Haagsma JA, Havelaar AH, Speybroeck N (2013) Global burden of listeriosis. Presented at the 6th European Public Health Conference (EUPHA 2013): Health in Europe, are we there yet?; 14-16 Nov 2013; Brussels, Belgium.

[8] Speybroeck N, Van Malderen C, Harper S, Müller B, Devleesschauwer B (2013) Simulation models for socioeconomic inequalities in health: a systematic review. Presented at the 6th European Public Health Conference (EUPHA 2013): Health in Europe, are we there yet?; 14-16 Nov 2013; Brussels, Belgium.

[7] Praet N, **Devleesschauwer B**, Dorny P, Duchateau L, Speybroeck N (2013) What are disability-adjusted life years? Presented at the 6th European Public Health Conference (EU-PHA 2013): Health in Europe, are we there yet?; 14-16 Nov 2013; Brussels, Belgium.

[6] **Devleesschauwer B**, Dorny P, Duchateau L, Speybroeck N (2013) Unravelling the burden of parasitic zoonoses in Nepal. Presented at the *Joint NVP/BSP scientific meeting 2012: Challenges for the control of parasites*; 19 Oct 2013; Antwerp, Belgium.

[5] Charlier J, **Devleesschauwer B**, van der Voort M, Vercruysse J (2013) Can we develop farmspecific models for assessing the cost/benefits of TST approaches? Presented at the *GLOWORM* 2nd General Assembly/Scientific Meeting; 16-18 Sep 2013; Dublin, Ireland.

[4] **Devleesschauwer B** (2013) DALY's and burden of disease. Presented at the *Institute of Tropical Medicine, Methodological Seminar Series*; 7 Jun 2013; Antwerp, Belgium.

[3] Henrard S, Hermans C, **Devleesschauwer B**, Speybroeck N (2012) Assessment of the health and the economic burden of haemophilia in Belgium: a rare, very expensive and largely unknown disease with multiple public health challenges. Presented at the 5th European Public Health Conference (EUPHA 2012): All Inclusive Public Health; 8-10 Nov 2012; Portomaso, St. Julian's, Malta.

[2] Devleesschauwer B, Dorny P, Duchateau L, Speybroeck N (2012) Élucidation du fardeau des zoonoses parasitaires au Népal. Presented at the 5ième Congrès international d'Épidémiologie (ADELF-EPITER): Épidémiologie et santé mondialisée; 12-14 Sep 2012; Brussels, Belgium.

[1] Charlier J, Levecke B, **Devleesschauwer B**, Vercruysse J, Hogeveen H (2011) The economic effects of blanket versus selective anthelmintic treatment strategies in dairy cows. Presented at the 23rd international conference of the World Association for the Advancement of Veterinary Parasitology; 21-25 Aug 2011; Buenos Aires, Argentina.

#### **Poster presentations**

[4] van de Velde N, **Devleesschauwer B**, Decraeye S, Barnett J, Begeman L, Brownlow A, Davison N, Ijzer J, Jauniaux T, Hiemstra S, Siebert U, Dorny P (2014) *Toxoplasma gondii* in marine mammals. Presented at the 28th Annual Conference of the European Cetacean Society: Marine mammals as sentinels of a changing environment; 5-9 Apr 2014; Liège, Belgium.

[3] **Devleesschauwer B**, Havelaar A, Haagsma J, Praet N, Dorny P, Duchateau L, Speybroeck N (2012) Le « DALY Calculator » : une interface graphique pour le calcul des DALYs en R. Presented at the 5ième Congrès international d'Épidémiologie (ADELF-EPITER): Épidémiologie et santé mondialisée; 12-14 Sep 2012; Brussels, Belgium.

[2] Nalon E, Maes D, **Devleesschauwer B**, Millet S, Van Riet M, Janssens G, Tuyttens F (2012) Assessment of mechanical nociception thresholds in lame versus non-lame sows with two methods. Presented at the 4th European symposium of Porcine Health Management; 25-27 Apr 2012; Bruges, Belgium.

[1] **Devleesschauwer B**, Dorny P, Duchateau L, Speybroeck N (2011) Unravelling the burden of parasitic zoonoses in Nepal. Presented at the *Journée des doctorants: école doctorale thématique: santé publique, santé et société*; 17 Nov 2011; Brussels, Belgium.

## Acknowledgments

So maybe you are wondering, why on earth go to Nepal to look for parasites in pigs, but end up studying human health?

Well, it started in 2006, when Prof Vercruysse was bragging about his projects in the tropics. Apparently, the Lab of Parasitology was continuously looking for students to help in these projects. But, he stressed, this did not mean laying on the soft grass under a palm tree by the beach. As I had already been to Nepal before, he recommended me to meet Prof Dorny. Apparently he was running a project on the epidemiology of the pork tapeworm in India and Nepal, and might have some interesting research topics for me.

In the summer of 2007, I set off to Nepal, for the first of many scientific trips. Together with Waldo and Mathieu, I was welcomed by Dr DD Joshi, Meena, Minu, Arjun, Anita and many others working at the National Zoonoses and Food Hygiene Research Centre. After having collected some hundreds of pig samples, I went back in 2008 and 2009 to continue my tapeworm quest. And I indeed found my tapeworm, but also a nice girl who happened to stay with her aunt, Meena, at that same initial moment back in 2007.

Back in Belgium, I took my samples to the Institute of Tropical Medicine, where I had the pleasure to get assistance in the lab from Anke and Bjorn and several others. I also met other nice people, such as Dirk, Nicolas, Niko and Sarah, who I, as it turned out, would be seeing much more in the future.

Thanks to my life as a parasitologist, I had the chance to interact, discuss and go on various lab trips with my colleagues at the Lab of Parasitology. A special word of appraisal goes out to my fellow epidemiologists/modellers/economists, Bruno, Johannes, Mariska, Sien and Suzanne.

After completing my Masters I wanted to start a PhD, preferably with a lot of field work in Nepal, for obvious reasons. As the tapeworm project had finished, we had to look for something new. Pierre pointed me to Niko, then post-doc at the ITM and avid modeller. Hidden behind a wall of books and under a king-size headphone, Niko started talking about R, DALYs, disease models, data collection systems, and many other things I had no clue existed. But eventually, we managed to work out a project proposal together, which after some years resulted in the thesis you now have in front of you.

Not long after the start of my PhD, however, Niko moved from Antwerp to Brussels, to become Prof Speybroeck at the UCL Faculty of Public Health. Over the years, my life as an epidemiologist introduced me to various non-veterinarians, such as Carine, Charline, Isabelle, Séverine and others.

In 2011, Niko took me to Geneva, to act as a rapporteur on one of the meetings of the Foodborne Disease Burden Epidemiology Reference Group (FERG). Although I was not allowed to say anything at that meeting, I learned a great deal by listening very carefully to all those interesting people. Over the years, my role within FERG gradually grew, culminating in my membership of the Computational Task Force, headed by Nicolas. Through FERG I also gained a new set of international colleagues, including Arie, Juanita, Paul and Scott.

Apart from my life as a parasitologist and epidemiologist, I also developed a life as a statistician. To be able to initiate my PhD, we had to seek collaboration with a full-time professor at UGent. Given the importance of data analysis in my PhD, an obvious choice was Prof Duchateau, professor in statistics. What I did not know, back then, was that this choice would be instrumental in my further development. From the very first day, I was motivated to start reading books – a skill which he believed had gone lost – and to start the Masters in Statistics at the KULeuven. Furthermore, I got the opportunity to give practical sessions in statistics to the veterinary students, and even to teach students in Ethiopia. This greatly helped me to strengthen my self-confidence, and I will always be grateful for making this possible. Last but not least, Prof Duchateau also offered me a chair at a time when there was no room at the inn. This introduced me to a new family of colleagues, this time consisting of statisticians and physiologists. It all started with Jan, not soon later followed by Christophe and Kevin. Over the years, the family of spaghetti buddies grew with Ana, Bart, Carolien, Dries, Klaartje, Mieke, and Xanthippe. Dries, thanks for making coffee for me, and thanks for making the coffee breaks the most interesting parts of my day.

Pierre, Niko, Luc, I think it is fair to say that each one of you has been crucial for this PhD, and in fact for my entire development so far. I like to believe that I have become a combination of the three of you, combining my love for parasites and zoonoses with my interest in epidemiology and statistics. It has been a pleasure to work with you, and I greatly look forward to continuing this collaboration. Pierre, we have known each other the longest. Thanks for believing in me and supporting me from the very beginning, when I was still too shy to call you Pierre. Niko, meeting you was a real enrichment, and continues to be. Thanks for all the opportunities you have given me over these past years. Luc, you have really meant a lot to me, perhaps without realizing this. I will always be grateful for your support and motivation.

Thanks to all the other people that have crossed my path these past few years, people from different parts of the world and different scientific backgrounds. In particular, I want to thank everyone I have ever co-authored a paper with. Discussing specific, but diverse problems allowed me to see connections across disciplines and strengthen my skills. My thesis students I want to thank for allowing me to learn how to supervise, guide and counsel. Finally, I want to thank all other students I have ever taught, especially those with the guts to question my knowledge.

My PhD and this thesis would not have been in their current shape without the inputs of the steering committee members and the external jury members. Thank you for your valuable comments and feedback during the different moments we met. In addition, a special word of thanks needs to go to Dirk, Isabelle, Sandrine and all the other people behind the screens, without whom there would be no PhD, no thesis, no defence, and most importantly, no reception.

Mama, papa, I know that it was not always easy for you to see me leave once again to Nepal. And that it still is not easy today. That it is why, from the bottom of my heart, I want to thank you for giving me the chance to do what I wanted to do, even though you did not always know what that exactly was.

Bimala, sorry for all those lonely evenings, but thanks for making this possible. Know that you have always been, and always will be, the most important part of my life.